CARDIOVASCULAR AND METABOLIC OUTCOMES ASSOCIATED WITH INSULIN USE IN TYPE 2 DIABETES: EVIDENCE FROM INSULIN USERS IN THE UK PRIMARY CARE.

Uchenna Chidi Anyanwagu, MB.BS, MSc

Thesis submitted to the University of Nottingham for the Degree of Doctor of Philosophy

August 2017

Abstract

In clinical use, insulin improves glycaemic control at the cost, typically, of weight gain and more hypoglycaemia – both being risk factors for cardiovascular (CV) disease mortality. The issue of the effect of exogenous insulin on CV disease meanwhile has been debated for a long time. Data on the CV outcomes associated with insulin-treated diabetes in both randomised trials and observational studies have largely been inconsistent. Thus, a balance of the positives and the negatives of insulin therapy needs to be taken into account when prescribing insulin in routine clinical practice, particularly in the context of the progressive nature of diabetes, its requirement for combination glucose-lowering therapy and the availability of novel glucose lowering agents. So, in a cohort of only insulin-users in 'real-world' condition, this thesis aims to explore the association between insulin use and CV and metabolic outcomes.

Firstly, a systematic review and meta-analysis of clinical trials that compared only insulin vs other non-insulin glucose-lowering therapies (GLTs) within the past decade was performed and the risk of CV events and important metabolic outcomes were compared between both treatment groups. Then, data from RCTs were compared with 'real-world' data (using the UK Primary Care database – The Health improvement Network (THIN)) in terms of clinical outcomes between insulin regimens. Thirdly, using THIN database, retrospective cohort studies were conducted to explore the CV outcomes associated with insulin as regards to the use of newer GLTs, concurrent use of other medications, target HbA1c outcome levels and baseline metabolic profile of insulin-users. Logistic, linear, and Cox regression models; and propensity-score matching models were fitted to explore these associations. Finally, a comparative cross-sectional study was conducted to explore clinical outcomes between the insulin users in a representative UK population database (THIN) vs the local Derbyshire integrated Diabetes service database.

A meta-analysis of RCTs first provided insight that allayed fears on the CV concerns on insulin use. It showed no difference in the risk of death and adverse CV events between insulin and non-insulin GLTs. Although insulin was associated with better glycaemic control, similar proportions of both insulin and non-insulin users attained their target HbA1c. The increase in the risks of hypoglycaemia and weight-gain seen in insulin users did not translate to adverse CV events. Furthermore, although RCTs provide superior evidence from which clinical guidelines are built, they do not mirror what happens in 'real-world'. The discrepancies in glycaemic control (which is lower in real-world) and weight (higher in RCTs) were highlighted. Thus, caution is needed in the extrapolation of RCT-derived estimates of clinical outcomes when formulating guidelines for routine clinical practice. Given the observed discrepancies between weight and HbA1c outcomes between real world and RCT, I investigated the CV and metabolic effects of insulin therapy in the context of baseline weight and insulin-induced weight gain. I observed that in a background of obesity, the use of insulin did not lead to poorer glycaemic control beyond 24 months, instead, patients who were obese experienced a significant reduction in weight and BMI. In the morbidly obese, the risk of composite adverse CV outcomes was, however, increased by 30%. Also, insulin-induced weight-gain was associated with significant reductions in HbA1c and no adverse CV outcomes and mortality.

When compared with newer GLTs like the glucagon-like peptide receptor agonists (GLP-1RA), insulin was associated with greater weight-gain and a higher risk of composite CV events and mortality; but in combination with GLP1-RA, it showed both a decrease in the risk of CV event and a reduction in weight. In the elderly insulin users with multiple comorbidities and longer duration of diabetes, extreme HbA1c targets were associated with increased mortality – representing a U-shaped relationship between mortality and HbA1c targets. Furthermore, background statin use among insulin users did not worsen glycaemic control in

the long term, but was associated with reduction in composite adverse CV events and mortality independent of the statin type. Finally, the Derby model of integrated diabetes service appeared to confer better clinical outcomes compared with the UK population in terms of the achievement of the combined National Institute for Health and Care Excellence (NICE) targets of HbA1c (<7.5%), blood pressure (<140/80) and total cholesterol (<4mmol/L).

This research highlights the important central role insulin plays in the management of T2D; and adds to the growing evidence on its safety and benefits among the high risk groups – the elderly, obese and those with longer duration of diabetes. It also highlights the benefits of the combination of insulin with newer novel GLTs; and concomitant use of other medications which modify CV risk factors. Above all, it recommends individualised treatment approach with full consideration of individual's metabolic profile and other social factors. Further trials focusing on insulin therapy combinations with newer GLTs will be invaluable in providing more water-tight evidence in insulin use.

Peer-Reviewed Publications from this Thesis

Anyanwagu U, Mamza J, Donnelly R, Idris I. Effects of Background Statin Therapy on Glycemic Response and Cardiovascular Events Following Initiation of Insulin Therapy in Type 2 diabetes: A Large UK Cohort study. *Cardiovascular Diabetology* 2017.Aug 22;16(1):107. doi: 10.1186/s12933-017-0587-6.

Anyanwagu U, Mamza J, Donnelly R, Idris I. Effects of obesity on metabolic and cardiovascular outcomes following insulin initiation in patients with Type 2 Diabetes *Obesity Research & Clinical Practice* 2017http://dx.doi.org/10.1016/j.orcp.2017.08.005

Anyanwagu U, Mamza J, Donnelly R, Idris I. Premixed vs Basal-bolus Insulin regimen in Type 2 Diabetes: Comparison of clinical outcomes from randomised controlled trials and real world data. *Diabetic Medicine* 2017. DOI: 10.1111/dme.13518

Anyanwagu U, Mamza J, Donnelly R, Idris I. Association between insulin-induced weight change and CVD mortality: Evidence from a retrospective cohort study of 18,814 patients in UK Primary Care. *Diabetes Metabolism Research and Reviews* 2017. DOI: 10.1002/dmrr.2945

Anyanwagu U, Mamza J, Donnelly R, Idris I. Effect of adding GLP-1RA on mortality, cardiovascular events and metabolic outcomes among insulin-treated patients with Type 2 Diabetes: A Large Retrospective UK Cohort Study. *American Heart Journal* 2017 DOI: http://dx.doi.org/10.1016/j.ahj.2017.10.003

Anyanwagu U, Owen K, Mamza J, Sugunendran S, Stone L, Langeland L, Idris I. Demographics, insulin use and clinical targets in type 2 diabetes insulin users: comparison of a local integrated diabetes service vs a UK-wide cohort. *Practical Diabetes* 2017; **34**(4): 123-128

Anyanwagu U, Mamza J, Donnelly R, Idris I. Comparison of cardiovascular and metabolic outcomes in people with type 2 diabetes on insulin versus non-insulin glucose-lowering therapies (GLTs): A systematic review and meta-analysis of clinical trials. *Diabetes Research & Clinical Practice*. 2016 Sep; **121**:69-85.

Anyanwagu U, Mamza J, Mehta R, Donnelly R, Idris I. Cardiovascular events and all-cause mortality with insulin versus glucagon-like peptide-1 analogue in type 2 diabetes. *Heart*. 2016 Oct 1;**102**(19):1581-7.

This thesis has also inspired these other related publications…

Anyanwagu U, Olaoye H, Jennings P, Ashton-Cleary S, Sugunendran S, Hughes D, Idris I, Wilmot EG. Continuous subcutaneous insulin infusion (CSII) therapy at Derby Teaching Hospitals: sustained benefits in glucose control. *Diabetic Medicine* 2017. DOI: 10.1111/dme.13367

Anyanwagu U, Idris I, Donnelly R. Drug-Induced Diabetes Mellitus: Evidence for Statins and Other Drugs Affecting Glucose Metabolism. *Clinical Pharmacology & Therapeutics*. 2016 Apr;**99**(4):390-400.

Presentation at Conferences:

1. Two (2) Oral and five (5) poster presentations at the Diabetes UK professional conferences in Scotland (2016) and Manchester (2017).
2. Four (4) poster presentations at the American Diabetes Association (ADA) Scientific Conferences in New Orleans (2016) and San Diego (2017).
3. Four (4) poster presentations at the European Association for the Study of Diabetes (EASD) Scientific Conferences in Stockholm (2015) and San Diego (2016).

Prize Nomination:

Best Research in Type 2 Diabetes, Diabetes UK 2017 Professional Conference, Manchester

Dedication

To

My late father, **Mazi JCU Anyanwagu**

In fulfilment of that promise made 28 years ago.
"I will be a doctor and will treat your diabetes"

And to

Kayode and **Jil,**
For inspiring hope and faith amidst all odds

Acknowledgements

First, I return all glory to GOD. He alone knows and charts the course of man. Without Him, I remain nothing. He has been my help in ages past and my hope for years to come. In Him, with Him and through Him, I move and have my being.

Secondly, I remain eternally indebted and grateful to my supervisors – Prof Richard Donnelly and Dr Iskandar Idris for their unending support and guidance throughout the course of this thesis. I cannot quantify how much they have impacted my life and my career. My experience with you was awesome. It has been a great journey. The depth of my gratitude to you is without measure.

Thirdly, I appreciate the wonderful support from my mother, Nwanne and my siblings and their spouses – Dozie and Chika; Chinne and Kay; Ndy and Chichi; Nwadi and Nedu; and Nneka and Dubem. Thanks for believing in me. To my nephews and nieces – Ella, Chuba, Nwokoroma, Dede, Rachy, Nwa, Ogueji, Ijay, Agodi, Nkume, Awelle, Nwobilo, Mkpoola and Chimvoma - you represent the promise of tomorrow, the grace of the chance at another day and my hope for a brighter future. My love for you all is beyond measure.

To the love of my life, Ify, thanks for being there these past months. Your support oiled the wheels on which this journey ran. I look forward with joy to many more years ahead with you.

Finally, to all my friends, colleagues in the research unit and the office, the PGR coordinators, and to all PGR students who gave me the opportunity to serve as their representative these past 3 years, knowing you all has been come with pleasant feelings I can't ever stop to relish.

Contents

Abstract ..... **i**

Peer-Reviewed Publications from Thesis ..... **iiv**

Dedication ..... **vi**

Acknowledgements ..... **vii**

Contents ..... **viii**

List of Figures ..... **xviii**

List of Tables ..... **xx**

Appendices ..... **xxii**

Abbreviations ..... **xxiii**

Chapter One: Introduction and Literature Review 1

1.1. Background of Diabetes Mellitus 1

1.2. GLTs and association with Cardiovascular Risk Factors 9

1.3. Insulin and Cardiovascular Outcomes 17

1.3.1. Evidence from Cardiovascular Outcome Trials (CVOTs) 19

1.3.2. Evidence from Observational Studies 30

1.4. Insulin and Metabolic Outcomes 35

1.5. Research Aim and Objectives: 36

1.6. Overview of Thesis: 40

Chapter Two: Methods.....43
2.1. Overview 43
2.2. The Health Improvement Network (THIN) Database 43
2.3. Data Management:.....45
2.4. Study Design (Cohort Study) 49
2.5. Study Population.....51
2.6. Definition of Study Variables.....52
2.6.1. Exposure.....52
2.6.2. Outcomes.....52
2.6.3. Covariates.....52
2.7. Potential Biases and Adjustments.....53
2.7.1. Biases and Adjustment strategies:.....54
2.7.2. Propensity Score (PS) Analyses:.....56
2.8. Data Analyses:.....59
2.8.1. Baseline Demographics.....59
2.8.2. Meta-analysis 61
2.8.3. Cross-sectional Study.....61
2.8.4. Linear Regression Analyses 62
2.8.5. Logistic Regression Analyses 64
2.8.6. Cox Regression Analyses.....64
2.9. Subgroup and Sensitivity Analyses 68
2.10. Statistical Software 68
2.11. Limitations.....68
2.12. Ethical approval.....69

Chapter Three: Cardiovascular and Metabolic Outcomes in people with T2DM on Insulin versus Non-Insulin GLTs – A Systematic Review and Meta-analysis 70

3.1. Summary 70

3.2. Introduction 71

3.3. Methods 72

3.3.1. Search Strategy 72

3.3.2. Study selection 73

3.3.3. Data Extraction and Risk of bias assessment 74

3.3.4. Statistical Analyses: 75

3.4. Results: 77

3.4.1. Literature Search Results: 77

3.4.2. Baseline Characteristics: 79

3.4.3. Bias Risk Assessment: 85

3.4.4. All-Cause Mortality and Cardiovascular (CV) Events: 86

3.4.5. Glycaemic Control 87

3.4.6. Changes in Weight: 90

3.4.7. Episodes of Hypoglycaemia 91

3.4.8. Reported Adverse Drug Events: 92

3.5. Discussion 94

3.6. Strength and Limitation 97

3.7. Conclusion 98

Chapter Four: Premixed vs Basal-bolus Insulin regimen: Comparison of clinical outcomes from RCTs and real-world data. 100

4.1. Summary 100

4.2. Introduction 101

4.3. Methods 102

4.4. Results 104

4.4.1. Baseline Characteristics 104
4.4.2. Change in HbA1c 109
4.4.3. Change in Weight (Kg) 110
4.4.4. Predictors of response at baseline 111
4.5. Discussion 116
4.6. Limitations 118
4.7. Conclusion 119

Chapter Five: Metabolic Profile of Insulin users and association with Cardiovascular and Metabolic Outcomes 120
5.1. Overview 120

5.2. Study 1 – Effect of baseline obesity on metabolic outcomes and major adverse cardiovascular events following initiation of insulin therapy 121
5.2.1. Summary 121
5.2.2. Introduction 122
5.2.3. Methods 124
5.2.3.1. Study Design and Data Source 124
5.2.3.2. Selection Criteria and Study Population 124
5.2.3.3. Study Exposure and Outcomes 124
5.2.3.4. Covariates 125
5.2.3.5. Statistical Methods 126
5.2.3.6. Sensitivity and Subgroup analyses 127
5.2.4. Results 127
5.2.4.1. Baseline Demographics 127
5.2.4.2. BMI vs glycaemic control 131
5.2.4.3. BMI vs changes in weight and BMI 135
5.2.4.4. Risk of Major Adverse Cardiovascular Event (MACE) 137

5.2.4.5. Subgroup Analysis 138
5.2.5. Discussion 140
5.2.6. Limitations 142
5.2.7. Conclusion 143

5.3. Study 2 – Association between insulin-induced weight change, glycemic control, cardiovascular events and all-cause mortality. 144

5.3.1. Summary 144
5.3.2. Introduction 146
5.3.3. Methods 147
5.3.3.1. Study Design and Data Source 147
5.3.3.2. Study Populations 147
5.3.3.3. Exposure 148
5.3.3.4. Outcome 148
5.3.3.5. Covariates 149
5.3.3.6. Statistical Analyses 149
5.3.3.7. Subgroup/Sensitivity Analyses: 150
5.3.4. Objective 1 - Results 150
5.3.4.1. Cases and Total Follow up: 150
5.3.4.2. Patients' Characteristics 152
5.3.4.3. Crude Event Rates: 155
5.3.4.4. Risk of Composite CV Outcomes: 156
5.3.4.5. Sensitivity and Subgroup Analyses: 158

5.3.5. Objective 2 - Results.....160

5.3.5.1. Patients' Characteristics: 160

5.3.5.2. Proportion undergoing weight change from baseline 161

5.3.5.3. Does insulin-induced weight gain affect glucose control?.....163

5.3.5.4. Relationship between weight and glycaemic control.....165

5.3.6. Discussion.....166

5.3.7. Limitation 168

5.3.8. Conclusion.....169

Chapter Six: CV Events, all-cause Mortality, and Metabolic Outcomes with Insulin vs Glucagon-like Peptide Analogues (GLP-1RA).....170

6.1. Overview 170

6.2. Summary.....170

6.3. Introduction 172

6.4. Methods 174

6.4.1. Study Design and Data Sources 174

6.4.2. Study Population 174

6.4.3. Exposures and Outcomes 175

6.4.4. Covariates.....176

6.4.5. Statistical Analyses 176

6.5. Cohort 1 - Results.....178

6.5.1. Cases and Total Follow up.....178

6.5.2. Patients' Characteristics 179
6.5.3. Crude Event Rates: 182
6.5.4. Risk of Composite Cardiovascular Outcomes and Mortality 182
6.5.5. Changes in HbA1c and Weight 186
6.6. Cohort 2 – Results 187
6.6.1. Cases and Total Follow up: 187
6.6.2. Patients' Characteristics 188
6.6.3. Crude Event Rates: 192
6.6.4. Risk of MACE, All-cause mortality, and Composite Cardiovascular Outcomes 194
6.6.5. Glycaemic Control (Change in HbA1c) and Change in Weight. 197
6.6.6. Subgroup and Sensitivity analyses: 198
6.7. Discussion 201
6.8. Conclusion 205

Chapter Seven: Target HbA1c vs All-cause Mortality in Elderly Patients 206
7.1. Summary 206
7.2. Introduction 207
7.3. Methods 208
7.3.1. Study Design and Data Sources 208
7.3.2. Study Population 208
7.3.3. Exposures and Outcomes 208
7.3.4. Covariates 209

7.3.5. Procedure 209
7.3.6. Statistical Analyses 210
7.3.7. Subgroup/Sensitivity Analyses 211
7.4. Results 211
7.4.1. Cases and Total Follow up 211
7.4.2. Patient Characteristics 212
7.4.3. Crude Event Rates 215
7.4.3. Risk of All-cause Mortality and Composite Cardiovascular Outcomes 217
7.4.4. Sensitivity and Subgroup Analyses 219
7.5. Discussion 223
7.6. Limitations 225
7.7. Conclusion 226

Chapter Eight: Background Statin Therapy vs Glycaemic Response and CV Events . 227
8.1. Summary 227
8.2. Introduction 228
8.3. Methods 229
8.3.1. Study Design: 229
8.3.2. The Health Improvement Network (THIN) Database 230
8.3.3. Study Participants 230
8.3.4. Follow-up and Endpoints 230
8.3.5. Baseline and endpoint characteristics 231

8.3.6. Statistical Analysis 231

8.4. Results 232

8.4.1. Patient Characteristics, Cases and Total Follow up 232

8.4.2. Primary Endpoints: Metabolic Outcomes 233

8.4.3. Secondary Endpoints: Risk of Major Adverse Cardiovascular Events 238

8.4.4. Subgroup and Sensitivity Analyses 240

8.5. Discussion 242

8.6. Strength and Limitations 245

8.7. Conclusion: 246

Chapter Nine: Comparison of the demographics, insulin use and clinical outcomes: UK population vs Erewash (Integrated) Diabetes Service 247

9.1. Summary 247

9.2. Introduction 248

9.3. Methods 250

9.3.1. Study Population and Design 250

9.3.2. Exposure and Outcome 251

9.3.3. Covariates 251

9.3.4. Statistical Analyses: 251

9.4. Results 251

9.4.1. Patients Characteristics: 251

9.4.2. Insulin-users with T2DM: Integrated Diabetes Service vs THIN cohort 254

9.5. Discussion 256

9.6. Limitations 259

9.7. Conclusion 259

Chapter Ten: Conclusions and Recommendation 260

10.1. Summary of Evidence and Recommendations 261

10.2. Application of Findings to Clinical Practice 267

10.3. Areas for Future Research 268

10.4. Conclusion 269

References 271

Appendices 269

List of Figures

Figure 1.1. Global Prevalence of Diabetes (WHO Regions)……..……...2

Figure 1.2. Algorithm of antidiabetic escalation therapy in T2DM management…….……..8

Figure 1.3. Intensive versus standard glycemic control ……....27

Figure 1.4. Intensive versus standard glycemic control plus ORIGIN trial……...28

Figure 2.1. The structure of THIN database ...……...……...……...46

Figure 2.2. A schematic presentation of a prospective cohort study …….……..50

Figure 2.3. Schematic representation of retrospective cohort...…….... 51

Figure 2.4. Potential Biases in the study ……...54

Figure 2.5. A schematic representation of an adjusted regression model ……...63

Figure 3.1. Flow Chart of Study Identification and selection……...……...78

Figure 3.2. Risk of bias summary…… ……..…..……..85

Figure 3.3. Forest Plot showing the risk of all-cause mortality and CV events ……..….... .87

Figure 3.4. Forest plot for the mean change in HbA1c (%) ……..…….……...89

Figure 3.5. Forest plot for the proportion attaining target HbA1c …...……...89

Figure 3.6. Forest plot for the mean change in weight …….……..……..91

Figure 3.7. Forest plot showing the risk of hypoglycaemia...…...…….... 92

Figure 3.8. Forest plot for the risk of adverse events …….……...94

Figure 4.1. Mean changes in HbA1c - RCT vs Real-world data ……...…….…….... 109

Figure 4.2. Mean changes in weight - RCT vs Real-world data……..…….……111

Figure 4.3. A and B – Glycaemic Control: in RCT vs Real-world...…….……....112

Figure 4.4. A and B - Weight-Change: RCT vs Real-world ……..115

Figure 5.1. Selection of study participants The structure of THIN database ..…..……....128

Figure 5.2. Mean Change (difference) in HbA1c……. …….……133

Figure 5.3. The mean difference in weight and BMI ...…….……..... 137

Figure 5.4. Selection of Study..…….……..151

Figure 5.5. Kaplan-Meier Curve showing the probability of survival ……..……..155

Figure 5.6. Proportion of the study participants undergoing weight change ...…….....162
Figure 5.7. Yearly mean weight ……..……...163
Figure 5.8. Association between glycaemic control and change in weight ……...164
Figure 6.1: Selection of participants in Study cohort 1 179
Figure 6.2: Kaplan Meier Survival analysis plot 182
Figure 6.3: Mean Changes in HbA1c 186
Figure 6.4: Mean Changes in weight 186
Figure 6.5: Selection of participants in study Cohort 2 188
Figure 6.6: Kaplan-Meier curves for probability of survival for composite outcome 192
Figure 6.7: Kaplan-Meier curves for probability of survival for all-cause death……193
Figure 6.8: Kaplan-Meier curves for probability of survival for CV event.....194
Figure 6.9: Glycaemic efficacy - INS+GLP-1RA vs INS+non-GLP1-RA 197
Figure 6.10: Changes in weight - INS+GLP-1RA vs INS+non-GLP1-RA.....198
Figure 7.1: Flow diagram of selection of study participants 220
Figure 7.2: Adjusted hazard ratios for mortality (A) & CV events (B) by HbA1c deciles ...220
Figure 7.3: aHR for mortality based on the different models of HbA1c deciles.....220
Figure 8.1: Selection of study participants 233
Figure 8.2: Mean difference in change in HbA1c (A) and mean HbA1c levels (B) 236
Figure 8.3: Mean diff in weight(A), SBP(B) and DBP(C) and mean HbA1c(D)…….....237
Figure 8.4: Kaplan-Meier curves showing probability of survival.....220

List of Tables

Table 1.1: Prevalence of Diabetes in the United Kingdom ..……..……..……..2

Table 1.2: WHO and ADA diagnostic Criteria for Diabetes …….…….....6

Table 1.3: GLTs and effects on HbA1c levels and CV risk factors ……...…...13

Table 1.4: CVOTs and results of epidemiological follow-up and post hoc analyses …..…..…….....25

Table 1.5: Insulin vs MACE – observational studies……..…….…… 32

Table 1.6: Insulin dose/regimen vs MACE – observational studies……..…….…… 34

Table 3.1: Baseline Characteristics of Included Trials 80

Table 3.2: Trial Interventions and Outcome measures 82

Table 3.3: Commonest reported adverse drug events 93

Table 4.1: Baseline Characteristics in real world (THIN Data) population ….…….... 106

Table 4.2: Baseline Characteristics of the Randomised Clinical Trials ….…….…….... 108

Table 5.1: Baseline Characteristics of Study participants ….…….…….... 129

Table 5.2: Proportions and odds of achieving the NICE target HbA1c of ≤7.5% …..…….... 132

Table 5.3: Mean follow-up HbA1c and mean coefficients of change in HbA1c …….... 134

Table 5.4: Mean follow-up weight and mean coefficients of change in weight …….... 136

Table 5.5: Events, rates and hazard ratios of CV events (stduy 1) .....…….. …..…….... 139

Table 5.6: Baseline characteristics of study cohort …….....153

Table 5.7: Events, Incidence Rate and Hazards of Composite Outcome ……..…….... 157

Table 5.8: Events, Incidence Rate and Hazards of component outcomes …….... 159

Table 5.9: Baseline characteristics of participants (study 2, objective 2) …..……....160

Table 5.10: Association between weight gain and glycaemic control ……..…….... 164

Table 5.11: Mean change in HbA1c and association with weight change ……..... 165

Table 6.1: Baseline Characteristics (Cohort 1) 180

Table 6.2: Events, Incidence Rate and Hazard Ratio of MACE 183

Table 6.3: Events, Incidence Rate and Hazard Ratio components of MACE 185

Table 6.4: Baseline characteristics (Cohort 2) 190

Table 6.5: Events, Crude Incidence Rates and Hazard Ratios of MACE 196

Table 6.6: Events, crude incidence rates and hazard ratios of components of MACE 200

Table 7.1: Baseline Characteristics of Study Cohort…….. 213

Table 7.2: Events, Rates and Hazards of Mortality and CV events in elderly 216

Table 7.3: Cox proportional hazard models for progression to mortality 216

Table 8.1: Baseline characteristics of study participants 235

Table 8.2: Events, Crude Incidence Rates and Hazard of Events 239

Table 8.3: Events, Crude Incidence Rates and Hazard of Events by Statin types……241

Table 9.1: Baseline characteristics of study populations 2353

Table 9.2: The proportion of patients achieving the NICE targets …… 239

Appendices

Appendix 1 (Chapter 2 – Methods: Definition of READ codes). 269

1.1. Acute Myocardial Infarction (AMI) 269

1.2. Coronary Heart Diseases (CHD) 270

1.3. Cerebrovascular Accident (Stroke) 271

1.4. Heart Failure 272

1.5. Hypoglycaemia 273

1.6. Peripheral Arterial Disease (PAD) 273

1.7. Mortality 275

1.8. Ethical Approval 277

Appendix 2 (Chapter 3 – Systematic Review and Meta-analysis) 280

2.1. Search Terms 280

2.2. Risk of Bias Graph 280

2.3. Funnel plot showing the risk of publication bias (Egger's test) 281

Appendix 3 (Chapter 5 – Metabolic Profile and CV/Metabolic Outcomes) 282

3.1. Mean follow-up BMI and mean change in BMI 282

Appendix 4 (Chapter 6 – Insulin vs GLP-1RA) 283

4.1. Mean change in HbA1c 283

Abbreviations

ACCORD	The **A**ction to **C**ontrol **C**ardi**O**vascular **R**isk in **D**iabetes trial
ADVANCE	The **A**ction in **D**iabetes and **VA**scular Disease-Preterac and Diamicro**N** Modified Release **C**ontrolled **E**valuation trial
BNF	British National Formulary
CV/CVD	Cardiovascular/Cardiovascular disease
CVOT	Cardiovascular Outcome Trials
DCCT	Diabetes Control and Complication Trial
DIGAMI	**D**iabetes Mellitus **I**nsulin **G**lucose Infusion in **A**cute **M**yocardial **I**nfarction trial
GLP-1RA	Glucagon-like peptide-1 receptor analogue
GLT	Glucose-lowering Therapy
HbA1c	Glycated Haemoglobin
HR/aHR	Hazard Ratio/Adjusted Hazard Ratio
ICD	International Classification of Diseases
LLT	Lipid-Lowering Therapy
MACE	Major Adverse Cardiovascular Event
MI/AMI	Myocardial infarction/Acute Myocardial Infarction
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
OAD	Oral antidiabetic drug
OR/aOR	Odds Ratio/adjusted Odds Ratio
ORIGIN	The **O**utcome **R**eduction with **I**nsulin **G**largine **IN**tervention trial
RCT	Randomised Controlled Trials
THIN	The Health Improvement Network
T2DM	Type 2 Diabetes Mellitus
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veteran Affairs Diabetes Trial
WHO	World Health Organisation

Chapter One: Introduction and Literature Review

1.1. Background of Diabetes Mellitus

1.1.1. Diabetes Mellitus

Diabetes mellitus is a group of chronic metabolic disorders characterised by persistent hyperglycaemia due to inefficient or defective insulin secretion and/or action.[1-3] It is associated with a wide range of symptoms and long-term complications.[1, 2] There are two basic types—Type 1 and 2 which are caused by total lack of insulin secretion as a result of autoimmune destruction of the beta-cells of the pancreas,[1, 4] or decreased insulin production and insulin resistance respectively.[5-7] Other forms of diabetes include gestational diabetes (GDM) and Maturity Onset Diabetes of the Young (MODY), and intermediate groups – Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG) – which are the borderline disorders of impaired glucose metabolism between diabetes and normal glucose level. About 70% of people in this group go on to develop diabetes.[1, 2, 8, 9]

The burden of type 2 diabetes (T2DM) is defined by its rising prevalence, direct and indirect economic cost, debilitating complications and mortality. These have grave consequences in any society.

Prevalence: T2DM has become a global pandemic – one of the most challenging health problems of the 21st century[4]. Its prevalence increases globally and is projected to double in the next one-and-half decades.[10-12] The recent global prevalence estimate of diabetes is 8.3% (from 6.4% in 2010).[7, 13] This is approximately 382 million and is predicted to rise to 592 million in 2035. The International Diabetes Federation (IDF) recent reports put China, India and the United States as the top three countries with the highest number of people with

T2DM (98.4, 65.1 and 24.4 million respectively) in 2013.[4] Though the prevalence is rising globally, it varies between the different WHO regions as shown in Figure 1.1 below:

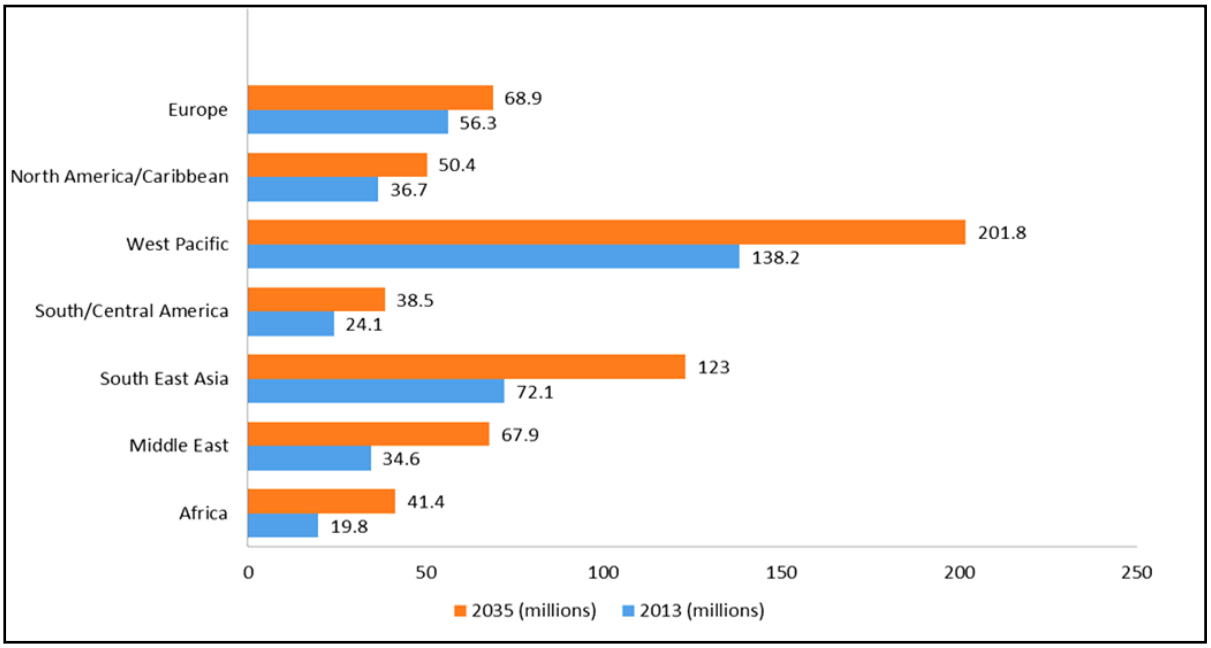


Figure 1.1. Global Prevalence of Diabetes (WHO Regions). Source of Data (WHO)[14]

In Europe, Germany has the highest prevalence of 8.9%, followed by Spain (8.1%), and France (8.1%), with UK coming a fourth (6.1%).[15] With six percent of UK citizens (totalling 3.2 million people) affected (Table 1.1); further half a million unaware of their diagnosis; 700 diagnoses made daily; and an additional 9.6 million at high risk of T2DM, it is projected that more than 5 million UK citizens will be affected by diabetes in the next decade.[6, 7, 16]

Table 1.1: Prevalence of Diabetes in the United Kingdom.[7]

Country	Prevalence	Population
England	**9.0%**	**3,8,000**
Northern Ireland	**5.3%**	**79,072**
Scotland	**5.2%**	**252,599**
Wales	**6.7%**	**173,299**

Economic Burden: T2DM places huge direct and indirect cost burden on both sufferers and the economy at large. In the UK, this cost is currently estimated to be £23.7 billion and is projected to rise in 2035 to £39.8 billion.[6, 7, 16-18] Of the £10 billion NHS budget for diabetes, the direct costs attributable to type 1 and type2 diabetes are £1 and £8.8 billion respectively. 80% (£7.7 billion) and 20% (£2.1b) of this are spent on the complications of diabetes and on treatment respectively. More than half (£4b) of the cost on complications is spent on cardiovascular diseases.[18]

Complications: The natural history of T2DM is dotted by various complications which affect almost every organ in the body. This places huge economic and social burden on the sufferers and the society at large. Complications arising from T2DM rank as the fourth leading cause of mortality in developed nations[4, 19] These life-threatening and disabling complications could be micro- or macrovascular.

Macrovascular complications include ischaemic heart disease— myocardial infarction and angina, cerebrovascular disease (stroke) and peripheral vascular disease which may lead to diabetic foot ulcers and amputation. People with T2DM have a two-fold risk of cardiovascular diseases (CVD)[20-24] and stroke[24, 25] which remain a major cause of mortality and disability in diabetes[21]. Diabetic nephropathy – a chronic complication of T2DM – is the single highest contributor of renal failure (End Stage Renal Disease (ESRD)) in UK.[26, 27] while the risk of amputation is 30 times greater in people with type 2 diabetes.[28]

Microvascular complications include diabetic nephropathy which often leads to microalbuminuria, chronic renal diseases and later to end-stage renal failure. On the other hand, diabetic retinopathy leads to blindness while neuropathy – peripheral and autonomic— affects almost half of all people with diabetes,[29, 30] and presents a plethora of debilitating symptoms as erectile dysfunction and diffuse progressive neuropathy, diabetic foot ulcer and a 24%

increased risk of sudden cardiac death.[31] Similarly, the risks of pancreatic, liver and endometrial cancers were seen to be doubled in people with T2D, with a 20 to 50% increased risk of colorectal, bladder, breast cancer and Non-Hodgkin's lymphoma.[19, 27-30]

Mortality: In 2013, diabetes accounted for 5.1 million global deaths, implying a single death every six seconds[4]. It is also responsible for 8.4% of all-cause mortality within the 20-79 age bracket, leading to a huge loss to the workforce population[4]. In the UK, people with T2DM are 37.5% more likely to die earlier than non-diabetics of similar age-groups.[32]

1.1.2. Management:

Diagnostic Criteria (The role of plasma glucose and HbA1c): Plasma glucose level is an independent predictor of CV risk.[33] The World Health Organisation (WHO) Expert Committee on the Diagnosis and Classification of Diabetes Mellitus emphasized the importance of associating glucose levels with long-term complications and recommended that glycated haemoglobin (HbA1c or A1c) should be the basic standard diagnostic measure of diabetes (Table 2).[1-3, 9, 34] This is because the measurement of glycated HbA1c in people with diabetes helps to predict the probability of the occurrence of CVD. Furthermore, a study which explored the relationship between indicators of diabetes as glucose variability, hyperglycaemia, post-prandial blood glucose and HbA1c and CVD risk factors such as BP, lipids and C-reactive protein (CRP) in people with types 1 and 2 diabetes showed that HbA1c and mean blood glucose have the strongest associations with CVD risk.[35]

The pattern of this association was further well defined by the findings of three observational studies. Firstly, a registry-based study showed a significant reduction in the risk of CVD (MI, CHD and total mortality) in patients with T2DM who had a tightly controlled HbA1c of 6.5% and BP of 130/80mmHg. Then, another observational study showed a progressive increase in

the risk of these outcomes with increasingly higher HbA1c levels;[36] while Currie et al, using a UK longitudinal database, showed a U-shaped association between HbA1c and mortality.[37]

As long-term hyperglycaemia is known to be highly predictive of diabetic complications excluding neuropathy, the establishment of specific HbA1c targets in the management of diabetes could help to prevent or delay the development of long-term complications.[38-40] So, unlike Fasting Plasma Glucose (FPG) which is a single measure of glucose level, HbA1c measures can show 2- to 3-month average plasma glucose level. In light of this, the steering committee set up by the National Glycohemoglobin Standardisation Program (NGSP) recommended an HbA1c cut off of 6.5% for the diagnosis of diabetes. Additionally, the UK consensus and the ADA statements went on to define those with an HbA1c of 6-6.4% and 5.7-6.4% respectively as the "pre-diabetes" group.[2, 41] In order to reduce the risk of CVD in the management of T2DM, they have recommended a treatment target of HbA1c levels below 7% (53mmol/mol).[42, 43] This is because this level has been validated to be effective for the prevention of microvascular though still debatable for macrovascular events.

In addition to the use of HbA1c, WHO also recommended FPG and 2-hour after75g of oral glucose load (OGTT) as basic standard diagnostic measures of diabetes.[1-3, 9, 34] These are further elucidated in Table 1.2 below. Using these criteria, a diagnosis of diabetes can be made with two readings of FPG $\geq$ 7.0 mmol/L, a 2-hour OGTT $\geq$ 11.1 mmol/L and random blood glucose of $\geq$ 11.1 mmol/L.

Table 1.2: WHO and ADA diagnostic Criteria for Diabetes and other Disorders of Glucose Metabolism[1-3]

Fasting Blood Glucose (mmol/L)	Plasma	Capillary	Whole Blood
Normal	**< 6.1**	**< 5.6**	**< 5.6**
Impaired Fasting Glucose (IFG)	**6.1 – 6.9**	**5.6 – 6.0**	**5.6 – 6.0**
Diabetes	**≥ 7.0**	**≥6.1**	**≥ 6.1**
2-hour Blood Glucose (mmol/L)			
Normal	**<7.8**	**<7.8**	**<6.7**
Impaired Fasting Glucose (IFG)	**7.8 – 11.0**	**7.8 – 11.0**	**6.7 – 9.9**
Diabetes	**≥11.1**	**≥11.1**	**≥11.1**

It is worthy to point out that there are debates on the appropriateness and reliability of the use of HbA1c over fasting plasma in diagnosing T2DM because it is reported to be less sensitive. Despite the fact that HbA1c is precisely measured as plasma glucose in some laboratories, there remains an unmet need for uniform international standardised measures of glucose irrespective of the method used. In response to this, the International Federation of Clinical Chemists (IFCC) working group recommended a reference method procedure for HbA1c, measured in mmol/mol.

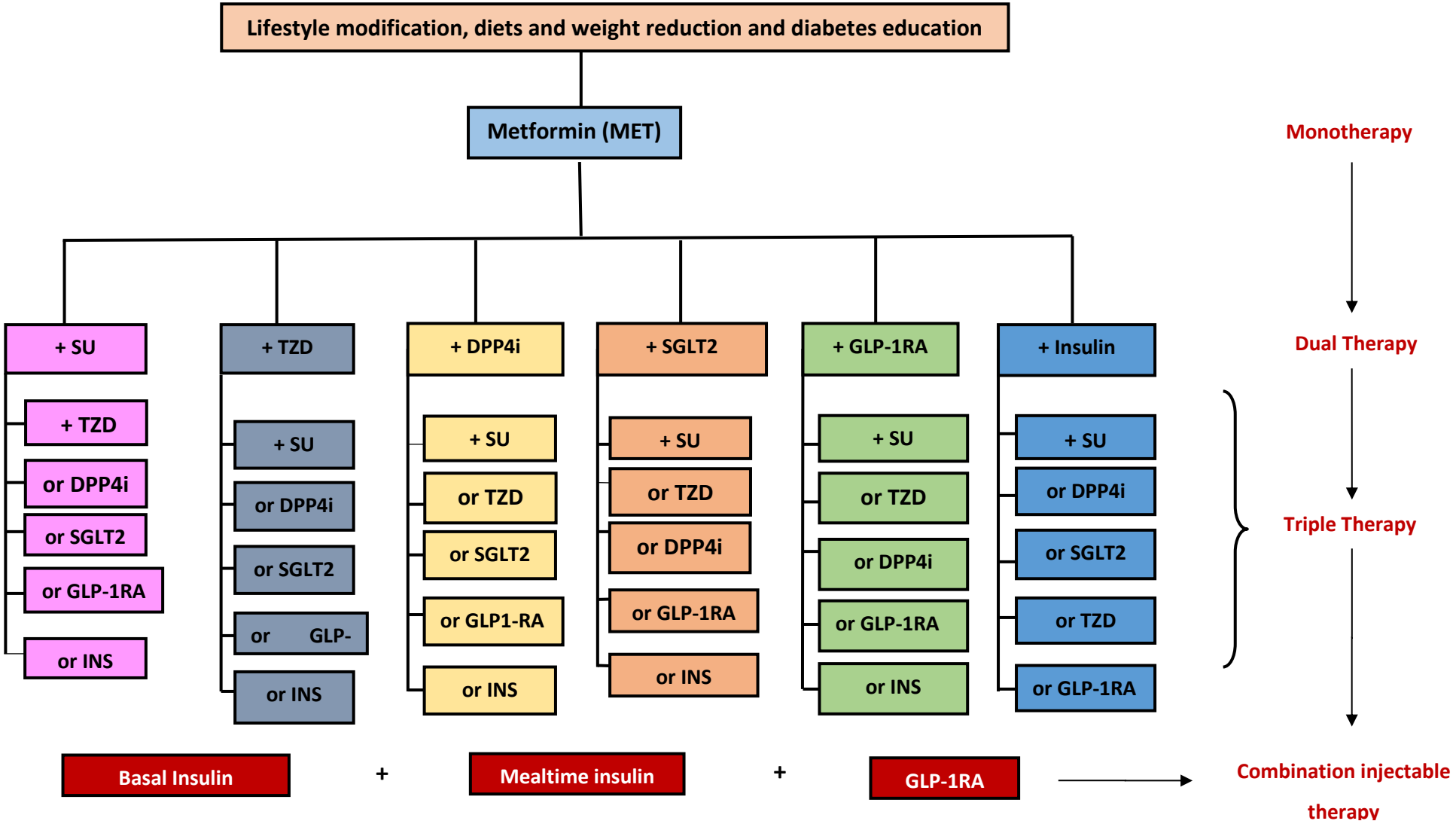
In this thesis, HbA1c will be used as the measure of glucose control. This will be measured in percentage (%) with the mmol/mol equivalence in parenthesis. Therefore, a diagnostic benchmark of 6.5% as recommended by the NGSP will be equivalent to 47.5mmol/mol or a fasting blood glucose level of 7.8mmol/L (140mg/L).

Therapeutic Management: The main therapeutic goal in the management of T2DM is improve glycaemic and other metabolic control (e.g. BP and lipids). This is important because optimal glucose control has been shown to be associated with reduced adverse micro- and macrovascular outcomes.[41] With the rapid proliferation of many therapeutic agents used in the management of diabetes; the safety issues around them; and debates and at times, controversies,

on the appropriate treatment choices and therapeutic goals in terms of glucose control level; and other comorbidities in people with T2DM; it becomes imperative to adopt a consensus approach in the management of T2DM bearing these in mind.

In response to this, most T2DM treatment guidelines advocate a gradual step-ladder increase in therapy (Figure 1.2). This starts with lifestyle modifications (good nutrition, weight loss, and exercise). Metformin (MET) is recommended as a first-line monotherapy after the failure of lifestyle modification. When optimal glucose control is not attained with MET alone, sulphonylurea (SU), where indicated and appropriate, may be added to MET. However, it must be noted that this guideline becomes complex at this point with the gradual addition of other oral glucose-lowering medications including insulin,[44, 45] because there is no conclusive evidence on the specific drug of choice for treatment intensification after MET.[46-48]

In summary, Figure 1.2 is a pictorial representation of the ADA/EASD recent algorithm for management of T2DM while Table 1.3 summarises important Glucose-Lowering Therapies (GLTs) used in the management of T2DM with their mechanisms of action, effects on HbA1c levels, benefits and associated risks.



NB: GLP-1RA: Glucagon-like Peptide 1 receptor agonist; SGLT2: Sodium-glucose co-transporter 2; DPP-4i (Dipeptidyl peptidase- 4) Inhibitors; TZD: Thiazolidinedione;

Figure 1.2: Algorithm of antidiabetic escalation therapy in T2DM management. Adapted from Inzucchi et al (2015)

1.2. Glucose-lowering Therapies (GLTs) and association with Cardiovascular Risk Factors

Glucose-lowering therapies (GLTs) were primarily developed to lower glucose levels. This reduction in blood glucose levels has been shown to be associated with reduced incidence and/or progression of many microvascular complications of diabetes as retinopathy, nephropathy.[22, 49] The management of T2D is aimed at optimising glycaemic control to deliver best treatment outcomes especially cardiovascular outcomes.

Unlike with microvascular complications, the association between this reduction in blood glucose and reduced macrovascular complications remains unclear. With the lack of evidence on CV reduction from RCTs (e.g. UKPDS and ACCORD etc.), observational studies have demonstrated a link between glycaemic control and CV risks in people with T2DM. For example, two Swedish registry-based observational studies - one among people with T2DM with tightly-controlled HbA1c (6.5%) and blood pressure (130/80mmHg) showed a significantly reduced risk of CVD, MI, stroke and coronary heart disease (CHD) compared to those without tight control after a 6-year follow-up period;[50] but the other study in a similar population, reported increasing CV risks in those with higher HbA1c levels.[36]

In spite of these, there remains concerns that adverse effects of some GLTs may reverse or counterbalance any CV benefit derived by their ability to lower blood glucose. CVD remains a major complication of T2DM and a contributor (about 65%) to deaths in people with T2DM.[51] As the main thrust of this thesis, a brief review of the effects of common GLTs on these CV risk factors and the intermediate markers of CV disease as blood pressure, weight, and lipid profile[52] is presented below and summarised in Table 1.3.

Blood Pressure (BP): The treatment of hypertension in people with T2DM is proven to reduce the risk of adverse CV events, microvascular complications and mortality.[53] This is because hypertension is a strong predictor of adverse CV events in T2DM. A meta-analysis of 45 trials in both diabetic and non-diabetic populations showed that 10mmHg reduction in SBP was associated with significant reductions in both micro- and macrovascular complications and all-cause mortality.[53] This was in concordance with the clear benefits reported in the SPRINT study in 9,361 non-diabetic population although this study was discontinued early due to the clear clinical benefits it showed.[54] In the BP sub-study (among 4,733 participants) in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, participants were allocated to intensive (<120 mmHg) vs. standard (<140mmHg) SBP targets, and the events and risk of MACE were similar between both groups, though a slight reduction was reported in the intensive group for the risk of stroke.[55]

Furthermore, in the PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) trial where 5,238 patients were randomised to pioglitazone or placebo in addition to their baseline GLTs, TZDs were shown to have a neutral to favourable effect on BP, with a significant reduction of 3mmHg in systolic BP.[56] This trend was replicated in a post-hoc analysis of this trial.[57] However, these findings were slightly different in the RECORD trial which had 4,447 participants who were randomised to rosiglitazone vs. MET+SU. The rosiglitazone group had a non-significant 1.5mmHg decrease in BP.[58]

Novel GLTs as GLP-1RA, DPP-4 inhibitors and SGLT-2 inhibitors have shown variable but favourable effects on BP. In two meta-analyses – one involving 16 trials[59] and the other 33 trials[60] – liraglutide lowered systolic BP by 5.6mmHg, and exenatide by 5.2mmHg in the first, while in the second, GLP-1RA was associated with a 2.2.mmHg reduction in systolic BP. These, however, were independent of the BP at baseline, change in weight from baseline and

baseline HbA1c. Similarly, SGLT-2 inhibitors consistently demonstrated significant reductions of 3.8 and 4.5mmHg compared to placebo in meta-analyses of 21 trials[61] and 16 trials,[62] while DPP4 inhibitors (sitagliptin) were associated with a non-significant reduction of in BP in two cross-over trials with glyburide.[63, 64]

Lipid Profile: Although there are concerns about the interplay between T2DM, abnormal lipid metabolism and the use lipid-lowering agents (LLTs) in the management of T2DM;[65] the use of statins to lower cholesterol has been demonstrated to be associated with a significant reduction in adverse CV events. In the Cholesterol Treatment Trialists' (CTT) Collaborators meta-analysis of 26 RCTs of statin therapy, a reduction of 1 mmol/mol in low-density lipoprotein (LDL) was shown to be associated with a 20% reduced risk of MACE (RR 0·80, 99% CI 0·74-0·87; p<0·0001) and a 10% reduction (RR 0·90, 95% CI 0·87-0·93; p<0·0001) in all-cause mortality in a dose-response manner.[66]

Another evidence from a meta-analysis of trials revealed that the use of DPP-4 inhibitors, compared with placebo, were associated with a reduction of 7mg/dL in total cholesterol, 17.1mg/dL in triglycerides (TG) but no change in HDL.[67] Similarly, two trials involving exenatide and liraglutide showed a similar significant trend in reductions in LDL, TG and with an increase in HDL,[68, 69] while SLGT-2i trials conversely showed modest increases in TC, LDL, and HDL with a decrease in TG.[70, 71]

Weight: Obesity is a known risk factor for T2DM and early treatment in this subgroup of patients is primarily aimed at lifestyle modification and weight loss. In spite of this, antidiabetic-induced weight gain presents a paradox in the management of T2DM. As shown in Table 1.3, different GLTs have different effects on weight – increase, loss or neutrality.

Metformin and DPP-4i have been shown to be weight-neutral. 1704 overweight and obese newly diagnosed T2D patients who were randomised to metformin in the intensive control arm

of the United Kingdom Prospective Diabetes Study (UKPDS) trial[72] had no change in weight from baseline at the end of the study. These findings were replicated in the Diabetes Prevention Program (DPP) Research Group[73] after 2.8 years of follow up of people with impaired fasting glucose who were randomised to metformin or lifestyle intervention or usual care. When compared to GLP-1RA in a review of 25 trials, sitagliptin and vildagliptin showed non-significant change in weight; but when compared to placebo, showed a significant reduction in weight.[74]

Conversely, insulin, through its action as an anabolic hormone, has consistently been shown in both RCTs and observational studies to be associated with weight-gain, especially in insulin-naïve patients. The UKPDS study showed that in a dose-dependent fashion, insulin can add 8kg in this patient-group.[75] Also, through its indirect effect of promoting insulin secretion, sulphonylurea is associated with weight gain of up to 5kg. Other GLTs associated with weight gain are TZDs and Meglitinides. TZDs have been shown to be associated with up 4kg weight gain in RCTs and this is thought to be mediated through its fluid retention ability and increased visceral fatness.[76] Finally, GLP-1RA and SGLT2 inhibitors are associated with weight loss. Through its ability to mediate and suppress food intake, GLP-1RA, in a meta-analysis of 25 trials was shown in a review of 25 trials to be associated with a 2.8kg reduction (95%CI: -3.4 to -2.3kg) in weight compared to its comparator groups.[77] This ability was independent of the GLP-1RA judging by the findings of a mixed treatment comparison and meta-analysis of 27 trials involving obese people with T2DM.[78]

Table 1.3: Summary of Glucose-Lowering Therapies (GLTs) and Estimates of their Effects on HbA1c levels and Cardiovascular Risk Factors. Adapted from Nathan et al (2009),[44] Inzucchi et al (2015)[79]and Alvarez et al (2015)[52]

Intervention	Mechanism of action	Expected HbA1c change (%)	Glucose	Weight	BP[a]	Lipid profile	Advantages	Associated Risks
Step 1: Initial therapy **Lifestyle modification**	- Reduce weight - Increase activity - Quit smoking/alcohol	1.0 – 2.0	↓↓	↓	↓	↓	- Natural - No known side-effect	- Inability to sustain glycaemic control in many after one year
Metformin	- Decreases hepatic glucose output - Increases insulin sensitivity and lowers fasting glycaemia[44, 80]	1.0 - 2.0	↓↓	↔	↔	↓LDL ↔HDL ↓Trigly[b]	- Weight stability or moderate weight loss - No hypos - ↓Cardiac events	- GI side effects - Contraindicated in renal problems - Lactic acidosis (in the presence of renal failure and hypovolaemia). - CKD, Hypoxia
Step 2: Additional Therapy **Insulin** • **Rapid-acting analogues** (Lispro, Aspart, Glulisine) • **Short-acting** (Human Regular)	- Carbohydrate metabolism - Uptake and storage of glucose by the liver and skeletal muscles	1.5 – 3.5	↓↓↓	↔	↓	↔LDL ↑↑HDL ↓↓Trigly	- Rapidly effective - Emergency treatment of hyperglycaemia	- Requires monitoring - Risks of hypoglycaemia - Weight gain - High cost - ?Mitogenic effects

• **Intermediate-acting** (Human NPH) • **Basal insulin analogues** (Glargine, Determir, degludec) • **Premix**	- Activates insulin receptors						- Improved lipid profile - Reduction in microvascular risks	- Patients' reluctance and concerns
Sulphonylureas • Chlorpropamide • Glibenclamide • Gliclazide • Glimepiride • Glipizide • Glyburide	- Enhance insulin secretion	1.0 – 2.0	↓↓	↑↑↑	↔	↓LDL ↔LDL ↓Trigly	- Rapidly effective - ↓Microvascular risk	- Weight gain - Hypoglycaemia - Blunting of myocardial ischaemic preconditioning - Low durability
Thiazolidinediones • Pioglitazone • Rosiglitazone	- Reduces peripheral insulin resistance - ↑Insulin sensitivity	0.5 – 1.4	↓↓	↑↑↑	↑	↑LDL ↑HDL Trigly ↑(Rosi) ↓(Pio)	- Improves insulin sensitivity - Improves lipid profile - No hypos - ↑Durability - ?↓CVD events	- Fluid retention, CHF - Weight gain, bone fractures - Risk of bladder cancer - ?↑risk of MI

GLP-1RA[c] agonists • Exenatide • Liraglutide • Lixisenatide • Dulaglutide • Albiglutide	- Bind and activate glucagon-like peptide (GLP-1RA) receptors to • Suppress glucagon secretion, • Increase insulin secretion and • Slow gastric emptying[80]	0.5 – 1.0	↓↓	↓↓	↓	↓LDL ↔HDL ↓Trigly	- Prevent weight gain or promote loss - No hypos - Reduce some cardiovascular risks - Reduce postprandial glucose excursions	- GI side effects - High cost - Long-term safety not established yet - ?Acute pancreatitis - Difficulty injecting it
SGLT2[d] inhibitors • Canagliflozin • Dapagliflozin • Empagliflozin	- Reversibly inhibit SGLT2 in the proximal convoluted tubules of the nephrons causing… • Decrease in glucose absorption • Increase in urinary glucose excretion[80]	0.7 – 1.3[81]	↓	↓	↓	↑LDL ↑HDL ↔Trigly	- Reduce body weight - Lowers Systolic blood pressure - No hypos - Effective at all stages of T2DM	- Genitourinary infections - Polyuria - Volume depletion, hypotension and dizziness - Transient ↑ in creatinine
DPP-4 Inhibitors[e] • Linagliptin • Saxagliptin • Sitagliptin • Vildagliptin • Alogliptin	- Inhibits DPP-4 activity - ↑postprandial active incretin - ↑Insulin secretion - ↓ production of glucagon	0.6 – 0.9	↓	↔	↔	↔LDL ↔HDL ↓Trigly	- Weight neutral - No hypos - Well tolerated	- Can interfere with immune function - Increased upper respiratory infection - Angioedema/urticaria
α-Glucosidase Inhibitors • Acarbose • Miglitol	• ↓ rate of digestion of polysaccharides • Inhibits intestinal α-Glucosidase • Lowers post-prandial glucose	0.5 – 0.8	↓↓	↔	↔	↔	- No hypos - ↓post-prandial glucose - ↓CVD events - Non-systemic	- Increased intestinal gas production - GI symptoms - Frequent dosing schedule

Amylin mimetics • Pramlintide	Synthetic analogue of amylin (β-cell hormone). Similar actions to GLP-1RA	0.5 – 0.7	↓↓	↓↓	↓	↓LDL ↔HDL ↓Trigly	- Weight loss (approx. 1- 1.5kg over 6 months) - Decreases post prandial glucose excursion	- GI side effects - Hypoglycaemia - Frequent dosing - Difficulty injecting it - Reluctance by patients
Meglitinides (glinides) • Repaglinide • Nateglinide	- Closes K-channels - ↑insulin secretions	unknown	↓↓	↑↑	↔	↔	- ↓postprandial glucose excursion - Flexibility in dosing	- Hypoglycaemia - ↑weight - Frequent dosing schedule

[a] BP: Blood Pressure. [b] Tgly: Triglyceride. [c]GLP-1RA: Glucagon-like Peptide 1 agonist. [d]SGLT2: Sodium-glucose co-transporter 2. [e]DPP-4i: Dipeptidyl peptidase- 4 Inhibitors

1.3. Insulin and Cardiovascular Outcomes

This section addresses the recent evidences involving the association between insulin use and major cardiovascular events. This includes, but not limited to, non-fatal MI, stroke, CV-deaths, hospitalisations for heart failure, etc. The first part looks at recent cardiovascular outcome trials which compared insulin to other treatment regimens or placebo; while the second part explores the recent evidences from observational studies (real-world studies) using routine clinical practice database.

Background

The therapeutic management of diabetes may on its own increase the risk of CV risk markers. This untoward effect could be due to the direct or indirect actions of the drug itself – direct through its pharmacological actions leading to side effects (e.g. hypoglycaemia), or indirect through some metabolic changes in the patient e.g. weight-gain, increased BP, etc. It is also known that these risks may not have been anticipated or immediately noticed during clinical trials due to many factors that range from the choice of trial participants to trial duration.[83] However, *post hoc* analyses of clinical trials, post-market surveys and evidence from observational studies using data from routine clinical practice have raised concerns about the CV safety of some drugs used in the management of diabetes.

Alvarez et al described insulin as the "the most potent anti-hyperglycaemic agent clinically available".[52] As the incidence and prevalence of T2DM rise globally; alongside increasing life expectancy which leads to longer duration of chronic diseases; rise in the population of the elderly; and rapid advancements in the management of diabetes; the use of insulin in the management of T2DM has continued to increase over the past 2 decades with over 30% of

people with T2DM currently on it.[52] Insulin improves glycaemic control with weight gain and incidence of hypoglycaemia as its main side effects. These are well-known risk factors for CV diseases.[84] So, as the use of insulin in the management of diabetes rises, data on the CV outcomes associated with insulin-treated diabetes have largely been inconsistent. Emerging evidences from observational studies have raised concerns about its CV safety in terms of increased mortality and morbidity in insulin users, compared to non-users.[37, 85] Additionally, this risk rises in a dose-dependent fashion.[86]

In view of the controversial publication on the adverse cardiovascular events induced by rosiglitazone,[87] the American Food and Drug Administration and Control (FDA) in 2008 mandated that, before approval of any new antidiabetic therapy, CVOTs should be carried on all GLTs in order to demonstrate their CV benefits or risks.[88] However, it can be argued that insulin therapy has up until recently not been exposed to the intense cardiovascular safety scrutiny, as has been imposed on a variety of novel glucose lowering therapies.

Below, is a brief summary of the outcomes of some major CV outcome studies which involved insulin therapy and explored major CV events and/or all-cause mortality in T2DM in the past 20 years. First, clinical trials were presented chronologically arranged according to their years of publication, followed by observational studies using routine clinical databases. Importantly, with the exception of DEVOTE, and to some extent ORIGIN, none of the other studies below has compared the cardiovascular outcomes of a specific (only) insulin therapy, compared with another.

1.3.1. Evidence from Cardiovascular Outcome Trials (CVOTs) Involving Insulin

a. The UK Prospective Diabetes Study (UKPDS)[22] - 1998

The **U**nited **K**ingdom **P**rospective **D**iabetes **S**tudy (UKPDS) was the first clinical trial to investigate CV outcomes in glucose-lowering therapies. In this trial, newly diagnosed participants with type 2 diabetes were randomised to intensive glucose control (insulin or sulphonylurea) vs standard care (diet +/- drugs if FPG > 15mmol/L). The enrolled 3867 participants were followed up period of 10 years. There was a 12% (RR: 0.88; 95%CI: 0.79 to 0.99) reduction in the risk of any diabetes-related outcome; and a 25% (RR: 0.75; 95%CI: 0.60 to 0.93) reduction in the risk of microvascular event in the intensive glucose control arm. However, the risk of macrovascular events (non-fatal MI – RR=0.79 (95%CI: 0.58-1.09) and non-fatal stroke – RR=1.07 (95%CI: 0.68-1.69)); diabetes-related death (RR=0.90; 95%CI: 0.73-1.11) and all-cause mortality (RR=0.94 95%CI: 0.80-1.10) were non-significant. Surprisingly, in a *post hoc* analysis (after a follow-up duration of 16.8years), a 15% reduction in the risk of MI (p = 0.01) was observed in the intensive arm.

The result of the UKPDS encouraged the use of intensive glucose therapy in routine clinical practice and opened a channel for further clinical trials which aimed to explore the CV outcomes of intensive glucose control.

b. The DIGAMI Trials – 1995[89] and 2005[90]

The **D**iabetes Mellitus **I**nsulin **G**lucose Infusion in **A**cute **M**yocardial **I**nfarction (DIGAMI) trials 1 and 2 aimed to test if the use of insulin glucose infusion to rapidly improve metabolic control post MI can decrease the high mortality rate in people with diabetes. Whilst DIGAMI 1 simply compared the risk of all-cause mortality in 620 patients who were randomised to insulin infusion followed by multi-dose insulin regimen (306) vs conventional therapy (314); DIGAMI 2, on the other hand, compared this same risk in 1253 who were randomised to 24-

hour insulin-glucose infusion + insulin (group 1, n = 474) vs insulin-glucose infusion + standard glycaemic control (group 2, n = 473) vs. local diabetes management protocol (group 3, n = 306).

In DIGAMI 1, intensive insulin infusion was associated with a 28% significant reduction in all-cause mortality compared to the conventional group (18.6% vs 26%; aHR: 0.72, 95%CI: 0.55 - 0.92). Later, a 20-year post follow-up confirmed the long-lasting effect of insulin-based glucose control on longevity. The median survival times were 7.0 vs 4.1years in intensive glucose control vs conventional groups respectively, with a 17% reduction in all-cause mortality compared to the conventional group (89% vs 91%, aHR: 0.83, 95%CI: 0.70-0.98).[91] Conversely, after a median follow-up period of 2.1 years, DIGAMI 2 trail failed to show any benefit in survival following the long-term use of insulin therapy after MI. Compared to group 1, the risk of all-cause death was non-significantly increased by 3% in group 1 (aHR: 1.03, 95%CI: 0.79-1.34) and 23% in group 2 (aHR: 1.23, 95%CI: 0.89-1.69).

c. The ACCORD Trial[92] - 2008

The **A**ction to **C**ontrol **C**ardi**O**vascular **R**isk in **D**iabetes trial involved 10,251 participants with T2DM and either CVD or CV risks. They were randomised to intensive therapy or standard care using different GLTs at the discretion of the physician. The baseline HbA1c was 8.3% in both arms. Only 34.9% of the participants were on insulin, while 35.2% had a history of CVD prior to the trial. The target HbA1c levels were <6.0% and 7-7.9% in the intensive and standard care arms respectively while the primary outcome was a 3-point composite of CV events of non-fatal MI or stroke and CV death. Unfortunately, the ACCORD trial was prematurely terminated after a follow-up period of 3.5years due to excess mortality in the intensive arm of the trial (CV mortality: HR: 1.35; 95%CI: 1.04 – 1.76) and all-cause mortality: HR: 1.22; 95%CI: 1.01 – 1.46). However, in spite of the recorded excess mortality, the risk of the 3-point

composite outcome was non-significantly reduced (HR: 0.90; 95%CI: 0.78 - 1.04). It was also noted that the risks of hypoglycaemia and weight gain (in excess of 10kg) were higher in the intensive arm ($p < 0.001$ for both).

These were believed to have driven the high mortality recorded in this trial but a *post hoc* analysis which explored the association between hypoglycaemia and increased mortality showed that hypoglycaemia was associated with excess mortality in both arms and in people who had just a single episode of severe hypoglycaemia, the risk of deaths was lower in the intensive arm.[93] In conclusion, this implied that hypoglycaemia may not have accounted for the excess mortality recorded. To explore the possible likely reasons, another *post hoc* analysis among all the trial participants showed that those with baseline HbA1c levels greater than 8.5% had a 65% increased risk of deaths. Coincidentally, these participants were found to be in the intensive therapy arm and did not have an improved HbA1c levels (HbA1c < 7%) throughout the trial. Also, unlike in the standard care arm, 1% increase in HbA1c in the intensive therapy arm was associated with a 66% greater risk of mortality thereby suggesting that factors which are associated with the persistence of high HbA1c may have driven the excess mortality seen in this arm.[94]

d. The ADVANCE Trial[95] - 2008

The **A**ction in **D**iabetes and **VA**scular Disease-Preterac and Diamicro**N** Modified Release **C**ontrolled **E**valuation (ADVANCE) trial involved 11,140 participants with T2DM and any macro or macrovascular disease or CV risk factors. In this trial, the participants were randomised to intensive therapy (Gliclazide + any other GLT as deemed fit by the physician) aimed at a target HbA1c <6.5% (48mmol/mol) vs standard care (any treatment as deemed fit by the physician, other than gliclazide) with a target HbA1c defined by local guidelines. It is

worthy to note that a very small proportion (1.4%) of these participants was on insulin therapy, while 32.2% had a history of macrovascular disease prior to the trial. Baseline HbA1c was 7.5% while the study outcome was a composite of micro- and macrovascular events.

Following 5 years of follow up, the outcomes were compared between the 2 groups. Whilst HbA1c was significantly lower in the intensive arm compared to the standard arm (6.5% vs 7.3%; $p < 0.05$), there were significant 10% and 14% reductions in the risks of the composite outcome and microvascular diseases in the intensive arm compared to the standard care arm (HR: 0.90; 95%CI: 0.82 – 1.06 and HR: 0.86; 95%CI: 0.77 – 0.97 respectively). Conversely, there were no significant reductions in the risks of macrovascular events (HR: 0.94; 95%CI: 0.84 – 1.06); non-fatal MI (HR: 0.98; 95%CI: 0.78 – 1.23); all-cause mortality (HR: 0.93; 95%CI: 0.83 – 1.06) and CV deaths (HR: 0.88; 95%CI: 0.74 – 1.04) but the risk of stroke was non-significantly increased by 2% in the intensive arm compared to the standard arm (HR:1.02; 95%CI: 0.85 – 1.24).

e. The VADT Trial[96] - 2009

The **V**eterans **A**ffairs **D**iabetes **T**rial (VADT) involved 1791 participants with poorly controlled T2DM, of which 97% were males. They were randomised to intensive (target of 1.5% decrease in HbA1c) vs standard care. Although the intensive arm recorded a greater reduction in HbA1c and maintained a 1.5% difference in HbA1c level throughout the study, there was no significant difference between the two arms in the risk of composite of major CV event (HR: 0.88, 95%CI: 0.74-1.05). Similarly, risks of all-cause mortality and CV deaths were similar in both arms.

f. The ORIGIN Trial[97] - 2012

The **O**utcome **R**eduction with **I**nitial **G**largine **IN**tervention (ORIGIN) trial is a very large clinical trial involving 12,537 participants with CV risk factors who had prediabetes or early T2DM. These participants were randomised to either once daily injection of insulin glargine or standard care (lifestyle modification, and/or metformin and/or sulfonylurea). After a trial duration of 12 years, with a mean follow-up period of 6.2years, it showed no statistically significant difference in a 3-point composite of MI, stroke and CV death (HR: 1.02, 95%CI: 0.94 to 1.11); or a 5-point composite which included hospitalisation for HF and revascularisation for CV death (HR 1.04; 95%CI 0.97-1.11).

The neutral outcome of the ORIGIN trial was able to douse the concerns raised on the cardiovascular safety issue raised about insulin therapy.

g. The DEVOTE Trial[98] - 2017

The DEVOTE trial results were announced at the recently concluded American Diabetes Association (ADA) conference on June 12, 2017, at San Diego, California. The trial compared the cardiovascular safety of insulin degludec vs. insulin glargine in 7637 people with T2DM, at high risk for CV events. These patients were aged 50 years above, with HbA1c $\geq$ 7.0%; and no history of acute coronary or cerebrovascular event in the previous 60days. The primary outcome was time to first occurrence of a 3-point composite major adverse of cardiovascular event (MACE) comprising cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke and secondary outcomes of severe hypoglycaemia and change in HbA1c.

After a median exposure duration of 1.83 years, a total of 325 (8.5%) vs 356 (9.3%) events were reported in the degludec vs glargine arms respectively; proving the non-inferiority of

degludec to glargine with respect to the occurrence of MACE (HR: 0.91; 95% CI: 0.78 to 1.06; p<0.001 for non-inferiority).[98]

The table below summarises the main macro- and microvascular outcomes of these trials as well as the results of their *post-hoc* analyses.

Table 1.4: Summary of outcomes of major CVOTs involving insulin and results of epidemiological follow-up and post hoc analyses

Study	Study Outcomes			Epidemiological follow-up/*post hoc* analyses		
	Microvascular outcomes	**Macrovascular outcomes**	**Effect on mortality**	**Microvascular outcomes**	**Macrovascular outcomes**	**Effect on mortality**
UKPDS	Reduced microvascular endpoint	No effect on MI*	None	Reduced microvascular disease	Reduced MI	Reduced mortality
DIGAMI-1	Not available	Not available	Reduced mortality	Not available	Not available	Reduced mortality
ACCORD	Reduced retinopathy, nephropathy, neuropathy	No effect on MACE**	Increased mortality	Reduced retinopathy	No effect on MACE	No longer increased
ADVANCE	Reduced nephropathy	No effect on MACE	None	Reduced end-stage renal disease	No effect on MACE	None
VADT	Reduced progression of albuminuria	No effect on MACE	None	Not available	Reduced MACE	None
ORIGIN	No effect	No effect on MACE	None	Not available	Not available	Not available

*** MI: Myocardial infarction**
**** MACE: Major Adverse Cardiovascular Events**

Source: Adapted from Fisher (2016)[99]

The emerging evidence from the UKPDS, ACCORD, ADVANCE, VADT and ORIGIN trials showed that intensive glucose control failed to show any benefit for major CV events compared to conventional therapy.[22, 92, 95, 96] Despite the excess mortality recorded by ACCORD study, it showed significant benefits in microvascular complications alongside the UKPDS.[22, 92] Similarly, the ADVANCE study showed a reduction in the risk of composite macro- and microvascular events but failed to show any other CV benefit.[95] On the other hand, the DIGAMI trials which focused primarily on all-cause mortality, showed no significant benefit with intensive care.[89, 90]

To explore the CV benefits or otherwise derived from these trials, a meta-analysis of the 27,049 participants in the ACCORD, ADVANCE, UKPDS and VADT trials[100] showed a 9% reduction (HR: 0.91, 95%CI: 0.84-0.99) in the risk of major CV events in the intensive therapy group compared to standard care (Figure 1.3). However, this is believed to have been driven, to a large extent, by the 15% reduction in the risk of MI (HR: 0.85, 95%CI: 0.76-0.94) in these populations because no similar significant beneficial effects were reported for stroke, CV deaths or heart failure.[100, 101, 102]

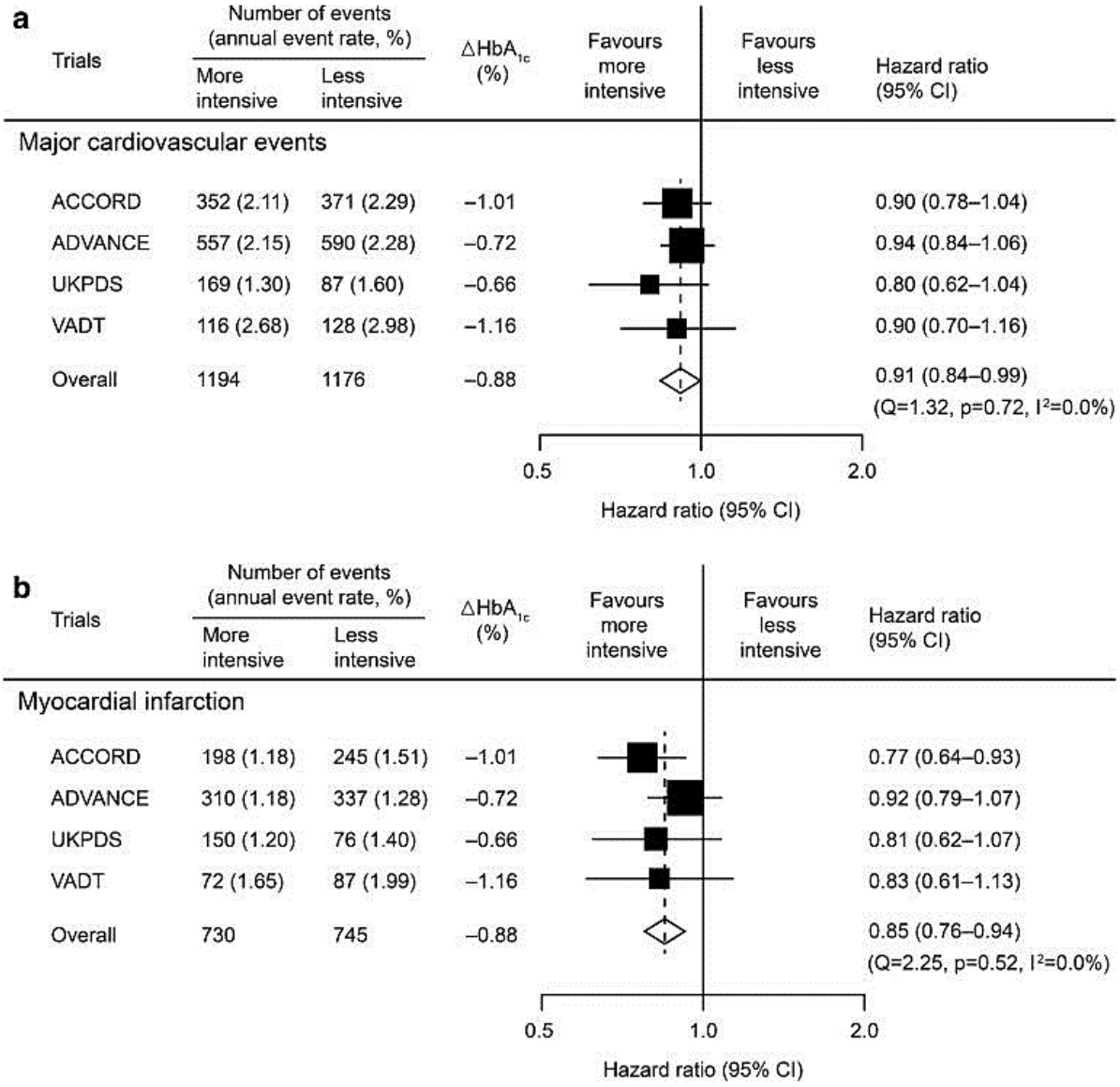


Figure 1.3: The effects of intensive versus standard glycemic control on (a) major cardiovascular events (CV death or non-fatal MI or non-fatal stroke) and (b) MI (fatal or non-fatal)

ACCORD Action to Control Cardiovascular Risk in Diabetes, ADVANCE Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation, CI confidence interval, CV cardiovascular, HbA1c glycated hemoglobin, MI myocardial infarction, UKPDS United Kingdom Prospective Diabetes Study, VADT Veteran Affairs Diabetes Trial

Source: Turnbull et al, (2009)[100]

Currently, there is no meta-analysis of these trials which included the findings of the ORIGIN study. As stated above, the ORIGIN was the first CVOT which compared only insulin vs others, and whose primary outcome was CV events. In this large trial, 12,537 participants with

CV risk factors were randomised to either once daily injection of insulin glargine or standard care (lifestyle modification, and/or metformin and/or sulfonylurea). Therefore, with the inclusion of the ORIGIN trial (see Figure 1.4), I have shown that the overall effect remained slightly non-significantly changed. The risk of major CV event was only slightly reduced from 9 to 5% (HR: 0.95, 95%CI: 0.88 – 1.03).

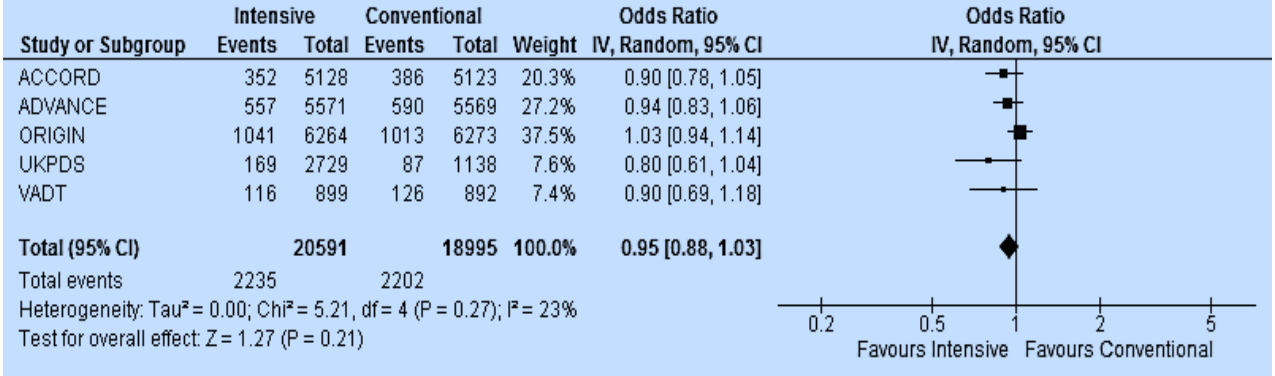


Figure 1.4: The effects of intensive versus standard glycaemic control on major cardiovascular events (CV death or non-fatal MI or non-fatal stroke) including the ORIGIN Trial[96]

Over the years, attention has been focused on the possible explanation to the variations underpinning the inability of these trials to report any clear CV benefit. This lack of concordance between these trails can be accounted for by the following: First, the different follow-up periods: the mean follow-up duration in ACCORD was 3.5years while the median/mean follow-up durations for ORIGIN, UKPDS, ADVANCE, DIGAMI and VADT trials were 6.2, 10.0, 5, 2.1 and 5.6 years respectively. The short follow up duration in some trials could not have been enough to explore the biological plausibility of the outcomes recorded. Secondly, there were variations in the study populations e.g. the duration of diabetes ranged from zero in UKPDS to up to 10 years in ACCORD and VADT. Thirdly, the presence of other comorbidities and risk factors differed in these populations. For instance, 32% of the

ADVANCE trial study population had CV disease at the background, 40% in VADT, and 35% in ACCORD; while more than half of the participants (58.8%) in ORIGIN. Fourthly, there were minor variations in age (range: 53.3 to 66 years) and use of other non-GLTs. fifthly, the target outcome in these trials were non-individualised. As the management of diabetes is individualised and patient-centred, the trials were unable to take into account individual variations and unmet needs in treatment. In addition to this, there was the lack of consideration on the different mechanisms of action of the GLTs beside their already known effects on glucose control. Finally, there was lack of uniformity or consensus on what constitutes the intensive and standard therapy arms of these trials; differences in the definition of the primary outcome and its components; differences in criteria for allocation to a treatment regimen.[52, 102-105]In summary, judging by the proportion of patients with background CV diseases in these trials, it was thought this could have influenced the effect of intensive therapy. To explore this, a sub-study of VADT showed that intensive glycaemic control was associated with reduced CV events in those with no background history of CV (e.g. atherosclerosis).[106] This implied that early initiation of intensive therapy in those with no CV history was associated improved CV outcomes. This was supported by Turnbull et al[100] in a meta-analysis of ACCORD, ADVANCE, UKPDS and VADT trials, showed a significant benefit in major CV events in the intensive therapy arm in those without a background CV diseases and shorter duration of diabetes (HR: 0.84, 95% CI: 0.75 – 0.94) vs those with CV diseases and longer duration of diabetes (HR: 1.0, 95% CI: 0.89 – 1.13). Perhaps, more importantly, a sub-analysis on the ACCORD study by Riddle et al[94] showed that mortality outcome increased in patients whose HbA1c levels increased despite allocation to the intensively controlled arm. This suggests that factors like insulin resistance (obesity as a surrogate marker) may also play an important role.

1.3.2. Evidence from Observational Studies

In spite of the high-ranking evidence from RCTs, there has been greater need for more observational studies using data from routine clinical data. This is because although RCTs meet regulatory and scientific standards, they do not necessarily reflect what happens in real world, and thus may not always provide healthcare professionals the best practical evidence for their practice. Additionally, participants in RCTs are not always representative of the population seen in routine clinical practice.

This following section focuses first on a few observational studies which explored the association between insulin use and major CV events and all-cause mortality; then the association between insulin dose and duration of use and major CV events; and finally the association between insulin regimen and major CV outcomes.

a. The use of Insulin and CV Outcomes

Observational studies which explored the association between the use of insulin and CV outcomes also produced inconsistent and inconclusive evidence. These are partly accounted for the differences between the study population in terms of definition of study exposures and outcomes. For instance, the definition of the components of a composite outcome like MACE markedly varied between studies. Others include age, use of anti-diabetic medications, comorbidities and concurrent use of other medications. An observational study which compared the risk of congestive heart failure between people with diabetes vs a matched cohort of non-diabetes reported a two-and-half fold increase in people with diabetes.[107] However, among the diabetic cohort, insulin users had above two-fold risk of CHF compared to sulphonylurea (2.33) and metformin (2.66) users[108] (Table 1.5). This was also similar for the risk of non-fatal MI among 63,579 people with type 2 diabetes, where which insulin users had

20% greater risk compared to OADs (aHR:1.20, 95%CI: 1.1 - 1.3). Also, for mortality, insulin use among newly diagnosed diabetics was associated with a 2.3-fold (aHR: 2.32; 95% CI: 1.96-2.73) increase in the risk of mortality compared to non-insulin.[109]

However, an interesting dimension to this trend was seen in an observational study by Hall et al,[110] where 22,113 poorly controlled diabetics on oral antidiabetic drugs (OADs) who intensified treatment with/without insulin were grouped according to their baseline OADs before intensification, and followed up for 5 years. After a mean follow-up period of 3.5 years, it reported treatment intensification with insulin was not associated with increased risk of major CV events compared to OADs.

When compared to sulphonylurea following metformin failure in routine clinical practice, Roumie et al[85] showed that insulin was significantly associated with an increased risk of both major CV events (aHR: 1.30; 95% CI: 1.07 - 1.58) and all-cause mortality (aHR: 1.44; 95% CI: 1.15-1.79). In a similar study of 5238 persons with T2DM after metformin + sulphonylurea dual therapy failure in routine clinical care; our research group showed that the risk of a composite of major CV events was 2.6-fold higher (aHR: 2.6; 95% CI: 1.9 - 3.4) following insulin intensification vs DPP4 inhibitors and this was more marked in the obese subgroup (aHR: 3.6; 95% CI: 2.3 – 5.6).[111] Similar results were shown in another class of GLTs - the thiazolidinedione – pioglitazone which was associated with a 56% reduction in the risk of composite CV events (aHR: 0.44; 95 % CI: 0.39 - 0.50) compared to insulin;[112] and same as with the GLP-1RA - exenatide.[113]

Table 1.5 summarises the association between insulin vs other GLTs and the risk of major adverse cardiovascular outcomes and all-cause mortality in T2DM in some selected studies using routine care databases.

Table 1.5: Summary of selected studies on the association between the use of Insulin and the risk of major adverse cardiovascular outcomes and all-cause mortality in T2DM using routine care databases

Study (year)	Comparator	Hazard Ratio [95% CI]	
		Major CV events	All-cause mortality
Nichols et al (2005)[108]	Sulphonylurea	2.33 [1.79 – 3.04][a]	NR[b]
	Metformin	2.66 [2.09 – 3.40][a]	NR
Margolis et al (2008)[114]	OADs[c]	1.20 [1.10 – 1.30]	NR
Gamble et al (2010)[109]	Non-users	NR	2.30 [1.96 – 2.73]
Currie et al (2010)[37]	OADs	1.31 [1.22 – 1.42]	1.46 [1.34 – 1.59]
Hall et al (2012)[110]	OADs at baseline (one)	0.53 [0.42 – 0.69]	
	2 OADs	0.85 [0.70 – 1.04]	NR
	3 OADs	1.07 [0.50 – 2.30]	
Currie et al (2013)[115]	Metformin	1.74 [1.44 – 2.09]	2.20 [1.98 – 2.43]
Vallarino et al (2013)[112]	Pioglitazone	2.27 [2.00 – 2.56]	NR
Roumie et al (2014)[85]	Sulphonylurea	1.30 [1.07 – 1.58]	1.44 [1.15 – 1.79]
Nijjar et al (2014)[116]	None	1.25 [1.13 – 1.39]	1.31 [1.17 – 1.47]
Paul et al (2015)[113]	Exenatide twice daily	2.00 [1.26 – 3.12]	NR
Holden et al (2016)[117]	INS+MET[d,e]	0.75 [0.62 – 0.91]	0.60 [0.52 – 0.68]
Mamza et al (2017)[111]	DPP4 inhibitors	2.60 [1.90 – 3.40]	3.70 [2.70 – 5.20]
Nystrom et al (2017)[118]	DPP4i + SGLT2i[e]	0.85 [0.73 – 0.99]	0.56 [0.49 – 0.64]
	Dapagliflozin[e]	0.51 [0.30 – 0.86]	0.44 [0.28 – 0.70]
	DPP4 inhibitors[e]	0.87 [0.75 – 1.01]	0.59 [0.51 – 0.67]

[a] Risk of congestive heart failure (CHF).
[b] NR: Not reported
[c] OAD: Oral Antidiabetic Drug
[d] INS: Insulin and MET: Metformin
[e] Results compared to insulin

b. Insulin Dose and Duration of use (Dose-response Effect) and CV Outcomes

Emerging evidences from observational studies seem to suggest that the risk of the adverse CV outcomes seen in insulin users compared to non-users[37, 85] rises in a dose-dependent fashion.[86] As a result of this, a retrospective cohort study in Canada,[109] which used the administrative databases of Saskatchewan Health, compared the association between the dose of insulin exposure vs all-cause and CV mortalities in people with newly-diagnosed diabetes aged above 30. Having categorised the yearly average cumulative duration of exposure thus: low (<3dispensations/year); moderate (3-12 dispensations/year or <1vial/month) and high (≥12 dispensations/year >1vial/month), they reported a graded risk of all-cause mortality of 75% with increasing insulin exposure (P for trend = 0.042) (Table 1.6).

An updated observational follow-up study in UK[119] in filling the inherent gaps in the Canadian study, categorised the definite dose of insulin and reported that for a unit/kg/day increase in insulin dose, the risk of all-cause mortality increased by 54% (aHR: 1.54, 95%CI: 1.32-1.78) and 37% (aHR: 1.37; 95%CI: 1.05-1.81) for major CV events. When compared to those on insulin dose of ≤0.5 units/kg/day, there was no significant difference in the risk of all-cause mortality for the <0.5 to ≤1.0 and >1.0 to ≤1.5 groups; but the risk of all-cause mortality almost doubled (aHR: 1.90; 95%CI: 1.50 - 2.40) in the high dose group (>1.5units/kg/day) as can be seen in Table 1.6. This was collaborated by another UK study in which the daily insulin dose was graded. This study reported that all-cause mortality rates were higher with increasing doses of insulin. So, compared to the reference category of < 25 units per day, the hazards of all-cause death were 41% higher in the 25 to <50 units per day group (HR: 1·41; 95% CI: 1·12–1·78); 37% higher in the 50 to <75 units per day group (HR: 1·37; 95%CI: 1·04–1·80); 85% in the 75 to <100 units per day group (HR:1·85; 95%CI: 1·35–2·53) and above 2-folds in the ≥100 units per day group (HR: 2·16; 95%CI: 1·58–2·93).

The above studies suggest that adverse CV events follow a dose-response trend – increases with increasing dose of insulin. Similarly, to explore the impact the duration of insulin use may have on these outcomes, irrespective of insulin dose, an earlier UK study[114] showed that increasing duration of insulin-use was associated with higher risks of myocardial infarction, with almost a three-fold increase after a duration of 6 months (Test for trend p-value <0.001).

Table 1.6: Association between insulin dose, regimen and duration and major CV events and all-cause mortality

Study/year	Comparator	Hazard Ratio [95% CI]	
		Major CV events	**All-cause Mortality**
Gamble et al (2010)[109]	Non-insulin users	*None users: ref Low : 1.65 [0.82 - 3.32] Moderate: 1.71 [1.17 – 2.50] High: 2.51 [1.81 – 3.50]	None users: ref Low : 1.75 [1.96 - 3.32] Moderate: 2.18 [1.82 – 2.60] High: 2.79 [2.36 – 3.30]
Holden et al (2014)[119]	Lowest dose	Not assessed	≤ 0.5units/kg/day: ref >0.5 to ≤ 1.0: 0.90 [0.78 – 1.04] >1.0 to ≤ 1.5 : 1.19 [0.99 – 1.44] >1.5 1.90 [1.50 – 2.40]
Gamble et al (2017)[120]	Lowest dose	Not assessed	< 25units/day: ref 25 to < 50: 1.41 [1.12 – 1.78] 50 to < 75: 1.37 [1.04 – 1.80] 75 to < 100: 1.85 [1.35 – 2.53] ≥ 100 2.16 [1.58 – 2.93]
Margolis et al (2008)[114]	Non-insulin users	None users: ref 1 - 5months: 2.0 [1.52 – 2.60] 6 – 11months: 2.9 [2.00 – 4.20] ≥ 12 months: 2.9 [2.10 – 3.90]	Not assessed

**Here, the outcome is CV-mortality.*
P-value for trend <0.05 in all studies except Gamble et al (2017)

The above studies highlight both the paucity and lack of conclusive evidence from observational studies on the CV safety of insulin despite the fact that insulin use in routine clinical care is very common. A major missing link here is that these studies failed short in galvanising the clinical outcomes in insulin users as relates to the management of diabetes in this special group. Rather, they focused mainly on treatment intensification with insulin in comparison to other GLTs. Be that as it may, with the rapid introduction of newer novel GLTs (known for its cardio-protective effects like the GLP-RA), there is now the need to explore their benefits or otherwise with insulin. For example, GLP-1RA-insulin combination formulations (e.g. IDegLira® and LixiLan® which are fixed dose combinations of GLP-1RA and long acting insulin) are increasingly being used in routine clinical care in the UK. This seems to be a good therapeutic synergy to modify or totally eliminate any effect of insulin on CV risk markers. Currently to my knowledge, there is very limited evidence from observational data on this, thus creating a gap in knowledge that may inform future clinical practice.

1.4. Insulin and Metabolic Outcomes

The association between insulin-use and metabolic outcomes (glycaemic control – defined by change in HbA1c levels; change in weight, episodes of hypoglycaemia and adverse events) have been presented in Chapter 3, in a meta-analysis of clinical trials which compared these outcomes between insulin and other GLTs.

1.5. Research Aim and Objectives:

Despite the plethora of emerging evidence from the above studies and clinical trials on the CV and metabolic outcomes associated with insulin use, little emphasis has been placed on the insulin-users with T2DM. This, perhaps, explains why clinical trials fall short in generating conclusive/uniform evidence on the best clinical practices or management guideline for insulin users.

This special class of people requires special consideration for many reasons. First, the use of insulin can be a marker of disease severity. This implies that those on insulin could be sicker than other people with T2DM and may not be the ideal participants for clinical trials due to ethical concerns. No doubt, this limits the generalisation of the evidence from clinical trials on this group. Secondly, insulin is often not the first or second-line treatment in the management of T2DM. Many treatment guidelines emphasise the need for other GLTs before insulin. Also, there are widespread reports on clinical inertia in initiating or intensifying treatment with insulin.[121-123] Resultantly, insulin-users usually have failure with many other antidiabetic medications before commencing insulin.[124] Thirdly, Mannucci et al opined that the prescription of insulin could be driven by the presence of other comorbidities[124] and this may translate to the use of many other medications whose actions or side effects may confound the effect of insulin therapy. Finally, insulin users may be older; or have/be at a greater risk of insulin resistance which may lead to the use of higher doses of insulin and its attendant CV risks.[86, 109, 117, 120]

Resultantly, there has been a surge in the use of healthcare databases for pharmaco-epidemiological studies[125-127] despite the well-known fact that evidence from randomised controlled trial (RCT) and meta-analysis of RCTs is considered to be the gold standard. The

reasons for this are - first, observational studies (using longitudinal data from routine clinical practice) mirror the "the real-world" picture and a true reflection of what obtains in clinical practice. Secondly, clinical trials require time to conduct and its results not readily available while real-world data are easily accessible, involve larger populations which translate to greater sensitivity, and save time. Furthermore, unlike RCTs, they are more flexible; can be used to study rare outcomes and for multiple studies. Nonetheless, it is very prone to biases which will be discussed in full details in the next chapter.

In this review, in spite a few conflicting reports, most observational studies and clinical trials affirm that insulin may be associated with adverse CV outcomes compared to other non-insulin glucose-lowering therapies. As plausible these findings may seem, they should be interpreted with caution due to the potential biases inherent in them such as selection and channelling bias in observational studies but one;[115] improper definition of the time to event, index date and study exposure, leading to immortal time bias.[128, 129] Another important observation is that these studies failed to focus on insulin users but insulin-use, thereby creating the need for a more comprehensive study to explore the clinical dynamics and features of insulin users and how this impact on the outcomes observed among them.

The aim of this thesis therefore is to explore the real-world cardiovascular and metabolic outcomes associated with the use of exogenous insulin in cohort insulin-users in the UK with type 2 diabetes, using the UK Primary Care database. This will be met through attaining the following objectives:

Objectives:

1) To systematically review and summarise clinical evidences from RCTs which compared the cardiovascular and metabolic outcomes associated with insulin vs non-insulin therapy.

2) To explore the gaps between clinical outcomes from RCTs and real-world data in terms of the effect of insulin regimen on metabolic outcomes as glycaemic control and weight.

3) To investigate the impact of metabolic profile of insulin users on metabolic outcomes and cardiovascular risk.

4) To estimate the time to Major Adverse Cardiovascular Events (MACE) and all-cause mortality following treatment intensification with insulin versus, or in combination with, newer GLTs (e.g. Glucagon like peptide-1 (GLP-1RA) analogue) following dual/triple therapy failure.

5) To evaluate the association between HbA1c levels and composite MACE in elderly people (aged 65 and above) and to establish if any association was independent of the diabetes treatment regimen.

6) To explore the effect of concurrent use of other medications which modify cardiovascular risks (e.g. statins) on glycaemic control and MACE and all-cause mortality among insulin users.

7) To characterise and compare the local demographics of insulin users with a representative national data.

1.6. Overview of Thesis:

Chapter 2 describes the methods applied on the data to answer the research questions. This begins with the methods employed in the extraction and organisation (including imputation of missing data) of the data from the UK Primary Care database – The Health Improvement Network (THIN); to a brief description of THIN; the justification for its use for this study; identification and definition of our study cohort (study population); definitions of our exposure, outcome and confounding variables; identification of potential biases and methods employed to minimise or completely eliminate them. It ends with a general overview of the statistical analytical methods employed e.g. Cox, logistics and Linear regression analyses.

Chapter 3 sets out to systematically search, analyse and summarise recent evidence from selected RCTs carried out in the past decade, which compared important cardiovascular (e.g. non-fatal MI, stroke, heart failure, CV mortality and all-cause mortality) and metabolic outcomes (e.g. weight, HbA1c, Lipid profile, episodes of hypoglycaemia and adverse drug events) between insulin and non-insulin glucose-lowering therapies. In a meta-analysis of these outcomes, the recent evidence about the CV and metabolic safety of insulin is highlighted and summarised.

Chapter 4 is aimed at exploring the differences and gaps between important clinical outcomes from RCTs and real-world (observational data) as it relates insulin regimens. It is believed that RCT outcomes do not always mirror the true clinical picture in real-world. So, here, a comparison between glycaemic control and weight-change was made between the two most popular insulin regimes – Premixed (Biphasic) vs Basal-bolus Insulin regimen, highlighting the differences or otherwise in these outcomes between RCTs and the UK Primary Care database.

Chapter 5 then x-rays the metabolic profile of insulin users and their association with insulin with CV events and metabolic outcomes. First, it looked at the relationship between baseline obesity and glycaemic control and CV events; later examined the association between insulin-induced weight-change and CV mortality; and finally, looked the impact of weight-change on glycaemic control.

Chapter 6 compares the time to a composite of major CV outcomes and all-cause mortality between insulin and a newer novel glucose-lowering drugs - GLP-1RA. Reports from clinical trials have shown that GLP-1RAs have favourable effects on weight reduction and low risks of hypoglycaemia. So, it is speculated that when used alone or in combination with insulin in intensification following dual- or triple therapy failure may have favourable CV outcome compared to insulin. Also, analysis was conducted to determine their comparative efficacy in glycaemic control and weight change.

Chapter 7 focuses on the optimal glycaemic control for elderly insulin-treated persons (aged 65 and above) with T2DM. Although treatment guidelines emphasise individualised care, there is no conclusive evidence on the target HbA1c range in this high-risk group of patients on insulin therapy. So, this chapter sets out to identify the HbA1c target ranges that can be associated with the least adverse outcome, drawing strength from the reports from other observational studies in other categories of people with T2DM which associated extremes of glycaemic target with worse CV outcomes and mortality.

In Chapter 8, the association between insulin-use and concomitant administration of other non-antidiabetic medications was explored using statins as an example. Evidence from randomized controlled trials shows that although statin therapy reduces the risk of CV events in patients

with T2DM; it also has modest adverse effects on glucose and insulin metabolism, e.g. increasing the risk of new-onset diabetes or worsening glycaemic control, especially in higher doses and with the more potent statins. So, after a 5-year follow-up period, the effects of background statin use on glycaemic control and CV outcomes following commencement of insulin therapy was explored and highlighted in order to allay fears of clinicians on its use.

In Chapter 9, the demography, insulin-use patterns, and clinical outcomes of insulin users with T2DM within our local environment – The Erewash (Integrated) Diabetes Service was compared with those of the UK population. This was to identify the proportion of patients achieving the relevant NICE targets with a view to identifying local differences for audit and improved clinical practice in our area.

Finally, Chapter 10 summarises the entire research project, relating the outcomes in the chapter to the already highlighted research aims and objectives outlined in Chapter 1. It highlights the clinical importance of the findings of this thesis and recommends further researches to bridge any identified gap or advance further knowledge in the thesis.

Chapter Two: Methods

2.1. Overview

This chapter broadly describes all the methodological approaches employed to answer the research questions in this thesis. It begins by describing the healthcare data sources used and then goes on to explain the data management principles applied. Furthermore, it describes the study population and designs; and defines the study exposure and outcome variables, alongside other important covariates. It also provides an overview of some of the inherent potential biases associated with the study and methods used to minimise or eliminate them e.g. multiple imputation and propensity-score matching. Finally, it describes the statistical analytical methods used in this thesis e.g. systematic review and meta-analysis; Cox, Linear, and Logistic regression analyses.

Due to the different statistical methods used for different study objectives, a brief overview of the statistical methods will be presented here. Further details on the methodological design specific to each objective/chapter will be contained in the subsequent chapters.

2.2. The Health Improvement Network (THIN) Database

The rapidly evolving information technology (IT) age has witnessed a rise in the volume and quality of electronically-collected data. This helped to "define primary care as a specialty", and placed in the hands of researchers, large volume of data for easy analysis and processing.[130] This is however not limited to medical researches alone. In the United Kingdom for example,

there are many electronic medical records which house many databases like The Health Improvement Network (THIN);[131] Clinical Practice Research Datalink ((CPRD) which was formerly known as GPRD)[132] and many others which are increasingly being used for epidemiological studies.

THIN is a large longitudinal database of anonymised primary care records of General Practices (GP Surgeries) in the United Kingdom. It was created in 2002 by Epidemiology and Pharmacology Information Core (EPIC) in partnership the In Practice Systems (IPS), London. EPIC recruited Primary Care practices that began data collection in 2003 and still regulates the participating practices by setting, upgrading and monitoring adherence to stipulated standards on data collection, quality, handling and storage in line with National Health Service (NHS) guidelines.[131, 133, 134] Currently, THIN is a collaboration between INPS and Cegedim Healthcare software (which writes its data collection software).[135]

Information in THIN is entered in a non-interventional manner by physicians and healthcare workers in the participating practices. These include patients' demography, lifestyle characteristics (as alcohol intake and smoking status), past and current medical diagnoses (both acute and chronic, using READ codes[136]), laboratory results, drug prescriptions (coded using the British National Formulary (BNF) codes), specialist referrals, hospital admissions, immunisations, clinical measures (e.g. height and weight) and Townsend deprivation scores[137, 138]. Recently, ethnicity, religion and languages have been added.[131] On entering the database, all identifiable or traceable information is removed from the patients' records and a unique patient-code and practice identification code assigned to them. This ensures the anonymity of the patients to both the database managers and the researchers.

As at January 2014 (when this study dataset was obtained), THIN contained details of over 12.4 million patients which are derived from the currently participating 587 general practices.

Of this, 3.61 million are currently active. Annually, only 3% of patients are lost to follow-up due to death or transfer out of practice following migration.[137, 138]

Validation

THIN covers about 4-5% of the UK population and has been shown to be demographically representative of the dynamics of the UK population in terms of the prevalence of major chronic diseases and mortality rates. As a result of this, the results from studies using this database are generalizable to the UK population.[137, 139] It has been shown to be similar in organisational scope to CPRD[133, 140, 141] and very suitable for research in pharmaco-epidemiology[137, 138, 142]. At practice and dataset levels, its information has been shown to be comparable to other national data sources such as the Office for National Statistics (ONS), The Department of Health's READ codes for the Quality and Outcomes Framework (QOF) and the Census figures.[133, 134] The database is regularly updated thrice yearly with the addition of more clinical data and the inclusion of more practices.

2.3. Data Management:

THIN1401 was the version obtained for this thesis. This version contains updated data up to January 14th, 2014. The raw data-files were provided in a simplified flexible structure and organised by practice and by patients in the form of flat ASCII (American Standard Code for Information Interchange). Each practice data were split into four standard ASCII fixed width text files and three linked files. These include patient, medical, therapy and an additional health data (AHD) files. The linked files include postcode variable indicators (PVI), consult and staff files[131] (Figure 2.1). Also included were a series of dictionaries and look-up tables which allowed the coded information to be interpreted.

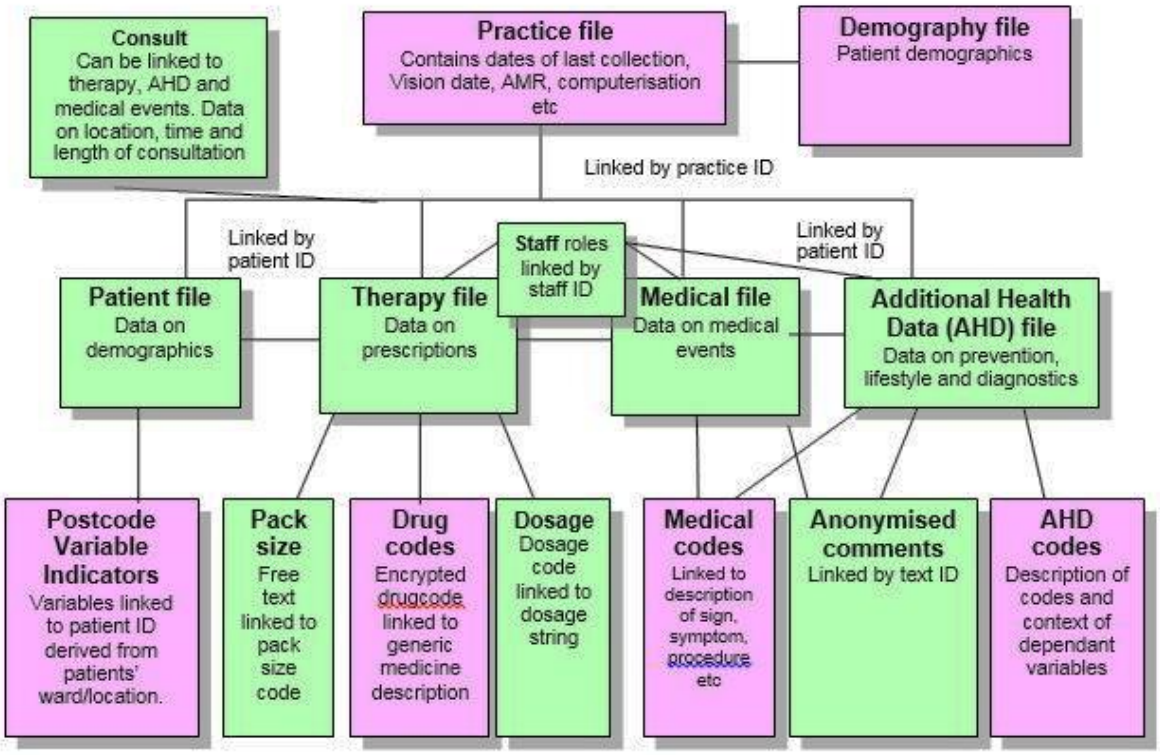


Figure 2.1. The structure of THIN Database[143]

Data management of the entire dataset was done under the supervision of Jil Mamza, a senior PhD candidate then in the research unit. This entailed using the Drug and BNF codes to extract information on all important drug prescriptions (for both diabetic and non-diabetic medications) from the dataset and store these in a separate data-file. Similarly, AHD codes were used to extract important covariates (as defined below) and their dates of recording. Separate data files were created for each covariate. The time-varying covariates as weight, height, HbA1c levels, and laboratory investigations were stratified yearly by the dates they were measured.

Finally, the READ codes for relevant medical diagnoses e.g. coronary heart disease (CHD), acute myocardial infarction (MI), cerebrovascular disease (stroke), peripheral arterial disease

(PAD), heart failure (HF), episodes of hypoglycaemia and mortality (see Appendix 1.1 to 1.6) were used to create separate data files for these important outcomes, including their respective dates of diagnoses.

Multiple Imputations

Missing data are a common feature in epidemiological studies which involve routinely collected data and also a huge source of bias which can undermine the validity of the findings and conclusions from such studies.[144-146] This is much more pronounced if the covariate(s) with the missing data is/are the exposure or outcome variable of interest, or a strong confounder. This later leads to biased results. The level of this bias is determined by the *missingness* (the degree or pattern of missing) of the covariate(s).[144, 145, 147] Subjects with missing data may differ systematically from those without with regards to the outcome of interest e.g. the elderly with T2DM may be more likely to visit the doctors and may have more recordings for BP, blood glucose levels and HbA1c levels than younger ones. Shortly after the THIN database commenced, Marston et al[145] reported that 22% and 38% of the data for smoking and height respectively between 2004 and 2008 were missing.[145] Nonetheless, this has greatly improved over the years. Since missing data are inevitable in routinely collected data, there is the need to devise an effect statistical method to eliminate or greatly minimise their impact.

Generally, there are three broad categories of *missingness*: missing at random (MAR); missing completely at random (MCAR); and missing not at random (MNAR).[147, 148] MAR was the pattern of *missingness* observed in this study. This occurs when the pattern of the missing data is dependent on already observed data.[147, 149] For instance, in a study on hypertension, data on BP are less likely to be recorded for the younger ones compared to the elderly. Once age is accounted for, the missingness will no longer dependent on their age. To deal with the issue of

missing data, a good number of methods are currently available, e.g. single value imputation, missing indicator method, complete-case analyses and Multiple Imputation (MI).[147, 148]

MI was used to deal with missing data in this study. This is because MI takes the improbability associated with missing data into consideration. In many statistical software models (e.g. Stata v.14 used for this study), it operates under the assumption that the data are MAR[150] and so can provide unbiased and valid estimates using the information from the dataset. It incorporates both the coefficient estimates of both the covariates with missing and non-missing data.[147] The use of MI has been on the rise since 2008 in many epidemiological studies.[151] Its techniques are centred on the assumption that any subject in a study sample can be replaced by another new randomly selected subject from the same population.[149] It does this by replacing the missing data in variables with values derived from various estimates of the probabilities of the distribution of these variables in the population. This gives rise to unbiased and valid estimates of study associations.[147, 149]

Multiple imputation by chained equation (MICE), also known as fully conditional specification (FCS) is a method of MI which starts with the replication of the incomplete dataset multiple times (usually ≥ 5 times) and replacing the missing data (e.g. HbA1c) in each replicate with plausible values derived from an imputation model. By so doing, it takes into consideration the probabilities within these values and between estimates across the "completed" datasets. This creates multiple versions of the complete dataset which are analysed using appropriate set-down models (for example, logistic or linear regression) on each "completed" dataset separately. Finally, a single overall MI estimate having a standard error is derived through the combination of these estimates which were gained from each "completed" dataset. The standard error for this overall estimate accounts for the variations between the estimates of the separate analyses of the "completed" datasets

2.4. Study Design (Cohort Study)

Except where indicated in the relevant chapter, retrospective cohort study design was mostly employed in the data analysis of the study. Traditionally, cohort studies are regarded as 'forward-looking' observational studies because they are planned and carried out over a period of time and can be used to establish a link or an association between risk factors and a health outcome in a group (cohort) of people who share similar characteristics e.g. They can be used to investigate aetiologies – an advantage it has over RCTs because the latter is not used for such due to ethical concerns. There are basically two types of cohort studies – prospective and retrospective cohort studies.

Prospective cohort studies portray the 'forward-looking' posture of cohort studies. It involves first, the identification of a risk factor in a cohort; and later, a follow up of those exposed to it or not, to see if they will develop the health outcome of interest. An example is shown in Figure 2.2 below. A population of metformin plus sulphonylurea users were exposed to either insulin or not (exposure). These two treatment groups were followed up (prospectively) for 5 years to see if they will develop any adverse CV event (outcome). Popular cohort studies include the Nurses' Health Study, Millennium Cohort Study and the 1970 British Cohort study.

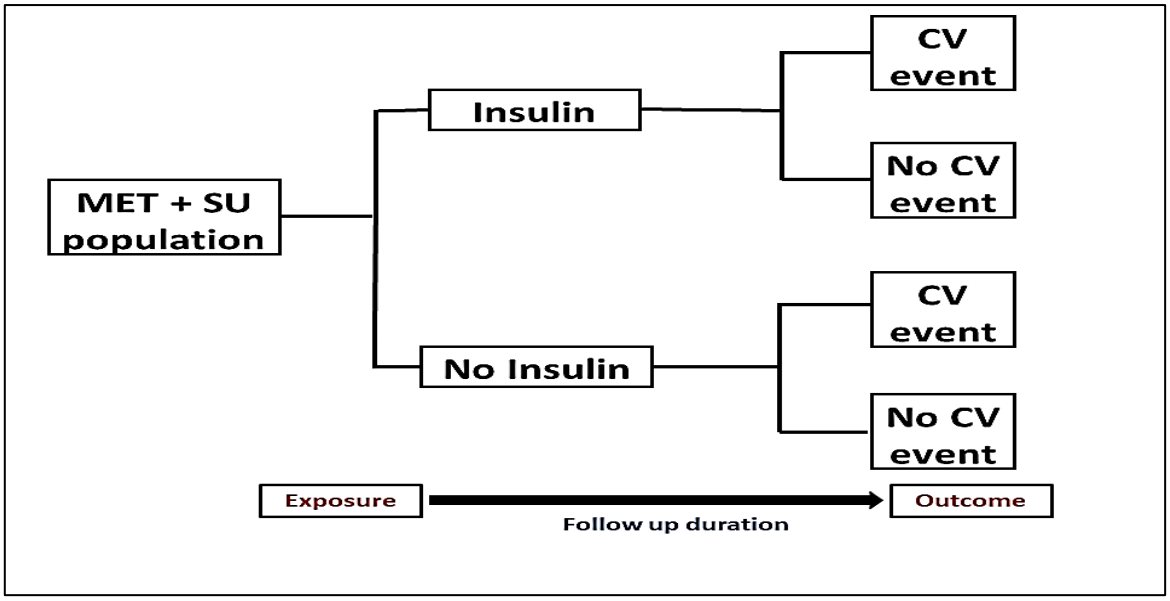


Figure 2.2. A schematic presentation of a prospective cohort study

Retrospective cohort studies are also known as historic or longitudinal cohort study. It primarily looks at already existing data which are usually stored in electronic databases. Although these data can be used to explore the association between an exposure and outcome, they were not initially collected just for the sole purpose of exploring that particular association between that exposure and the outcome. The beauty of retrospective cohort study is that they look back at events that had already taken place and been recorded in the register as if they are just occurring, and so reconstructs the experience as if it had been followed prospectively. The schematic diagram (Figure 2.3) below highlights its key features.

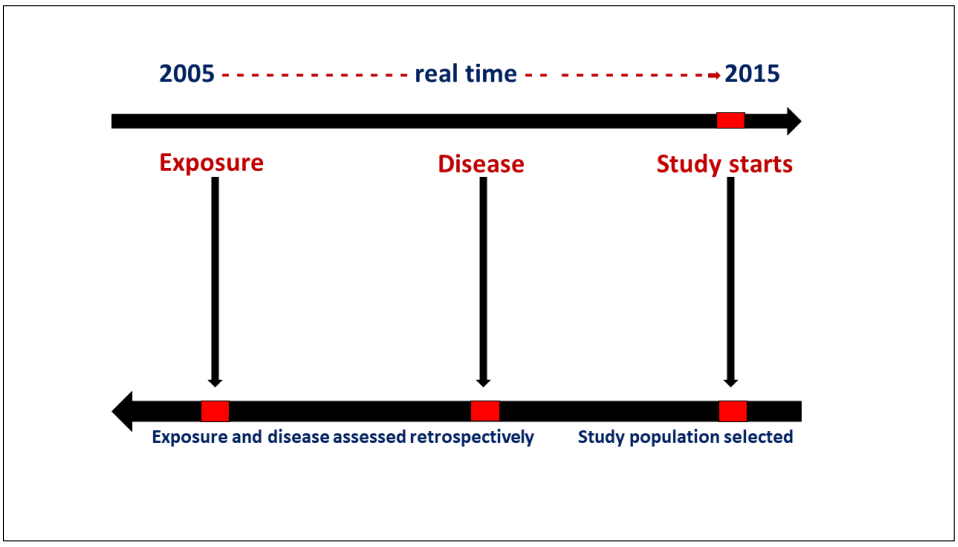


Figure 2.3. Schematic representation of retrospective cohort study

Generally, in this study, a cohort of insulin-users were followed prospectively in order to explore the CV and metabolic outcomes associated with insulin use by looking at different risk factors or baseline differences in the cohort. The advantage here is that, unlike in the conventional prospective cohort studies, both the exposure and outcomes of interest have occurred.[152]

2.5. Study Population

The study population comprises all adults (aged 18 and above) with T2DM on insulin therapy in the THIN database between September 2006 and January, 2014. Entrance into the study cohort was defined by the date of initiation of insulin therapy (index date). Similarly, diabetes duration was defined by the period between diagnosis of diabetes (diagnosis date) and index date while insulin duration is the period between index date and end date (end of follow-up period or death or loss to follow up (transfer out date) or occurrence of an outcome of interest as defined by the specific study).

The follow-up periods were specific for each study. Generally, this is defined as the period from the index date to either the occurrence of the study outcome(s), end of the study, discontinuation/substitution of the exposure of interest, or loss to follow up.

2.6. Definition of Study Variables

The following subsections provide an overview of variables considered in this thesis. The full details of these variables, where indicated, will be discussed in their relevant chapters.

2.6.1. Exposure

The study was exposure-defined – meaning that the entrance of any subject into the study cohort will be marked by initiation of the study's exposure. Since exposure differed for each study, this section is discussed in details in the relevant chapters.

2.6.2. Outcomes

Similarly, the outcomes of interest differed between the studies. These were further highlighted in their relevant sections.

2.6.3. Covariates

Based on evidence from existing literature and clinical significance, the covariates were selected a priori. At baseline, these were collected between 90 prior and 90 days after index date. These include demographic variables as age, sex, socioeconomic deprivation (measured by Townsend Deprivation Scores),[153, 154] smoking and alcohol status. Others include clinical measures as body weight (kg); body mass index (BMI, kg/m^2); and Systolic and Diastolic blood pressure (mmHg); and laboratory measures as baseline HbA1c,(mmol/mol, %), estimated

glomerular filtration rates (GFR, mls/min/1.73m^2); total cholesterol levels (TC, mmol/L); low-density lipoprotein (LDL, mmol/L); high-density lipoprotein (HDL, mmol/L); and triglycerides (mmol/L); and albumin-creatinine ratio (ACR, mg/mol). Finally, the use of other antidiabetic medications; and medications as statins, aspirin, and antihypertensive drugs were included alongside the presence of other comorbid conditions as coronary heart disease (CHD), acute myocardial infarction (MI), cerebrovascular disease (stroke), peripheral arterial disease (PAD), heart failure (HF) and episodes of hypoglycaemia.

Additionally, I obtained further follow-up data for time-varying covariates like body weight, BMI, and diastolic and systolic BP; HbA1c, ACR, TC, LDL, HDL and triglycerides; after 6 months, and yearly thereafter throughout the course of the study.

2.7. Potential Biases and Adjustments

Every research is aimed at estimating the measure of effect with a high degree of accuracy and precision. Using longitudinal electronic health records as THIN, this may not be possible due to certain inherent biases and confounders. Diabetes is a risk factor for CV diseases. Whilst the use of insulin in its management may negatively affect known CV risk factors, this interplay thus further confounds the positive effect of insulin on glycaemic control, thereby making insulin therapy to seem like a complication of diabetes itself[155]. So, this section highlights some of these potential biases and the methods employed to adjust for them.

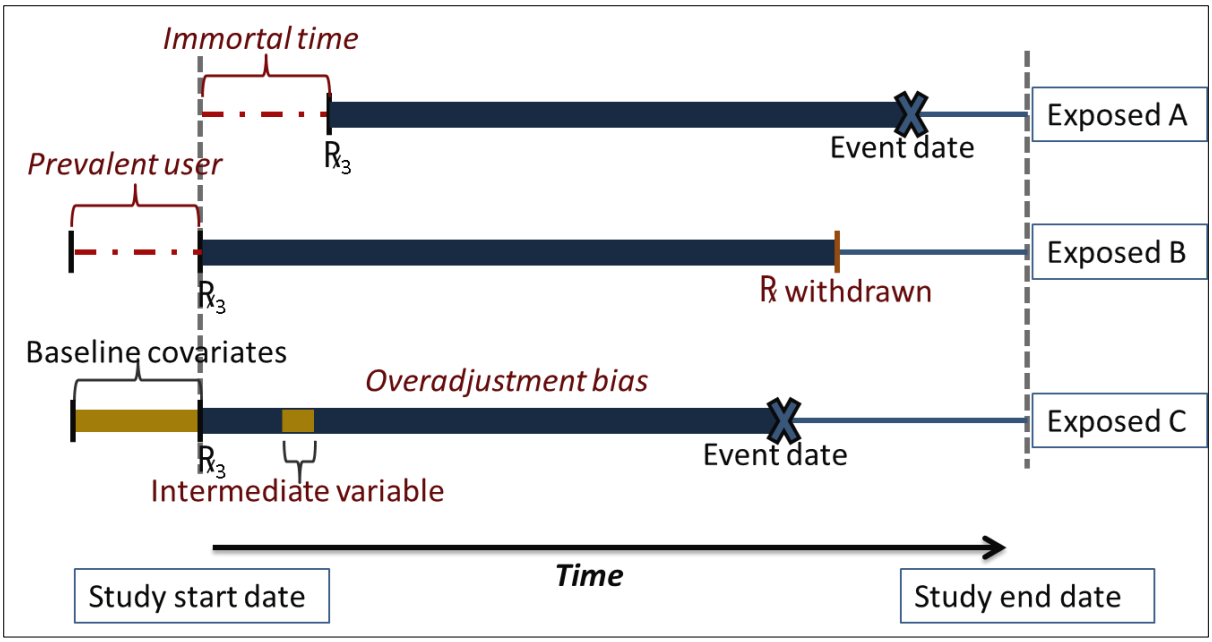


Figure 2.4. Potential Biases in the study

2.7.1. Some Biases and Adjustment strategies:

Immortal time bias is a form of bias which arises in routine database observational studies as a result of improper definition of the study exposure. It arises when the exposure or entry into the cohort is defined by a specific time (date) instead of the treatment of insulin (e.g. intensification of INS with a 2nd line drug). Due to this improper definition or misclassification, the outcome of interest may not occur during the follow-up period (immortal time).[129] To overcome bias due to immortal time (See Figure 2.1), an exposure-based definition, whereby subjects only entered the cohort at the point of contact with the exposure (e.g. intensification of INS with a 2nd-line therapy), as against a time-defined entry (the study start date) was adopted. Also, to minimise immortal time as a result

Secondly, **prevalent user bias** may arise following the presence of the outcome of interest before initiation into the study. For instance, the presence of MI before intensification of INS in study in which MI is assessed after the exposure. Prevalent user bias leads to overestimation

of the treatment effect, thereby pushing the hypothesis away the null.[155] To minimise this, an exposure-risk window of > 180 days was used throughout the study. This period is believed to be biologically plausible for the risk of the outcome (e.g. weight-change or glycaemic control) to be attributed to the exposure (e.g. insulin use). In reality, this was difficult to completely eliminate in the study because the complications of insulin therapy (e.g. hypoglycaemia) can manifest within a short period of time leading adverse CV outcomes and/or mortality. Similarly, as can be seen in Figure 2.1, this study runs a risk of both **unnecessary adjustment** (by trying to control the many covariates which do not directly affect the association between the study exposure and outcome) and **over-adjustment bias** (by attempting to control an intermediate variable on the causal path of the exposure to outcome.[156] Rather, in dealing with this, the covariates used for adjustment were defined and extracted at baseline in relation to *a priori* clinical evidence.

Thirdly, as T2D is a chronic condition, it is characterised by high rates of drug discontinuation, substitution, intensification or initiation due to reasons varying from poor glycaemic control, side effects and adverse effects on risk factors. This has the potential to lead to bias. As-treated (AT) analysis approach (instead of intention-to-treat (ITT) analysis) was used in this study whereby exposure to a drug terminated upon its discontinuation or substitution. At this point, the patients were censored. In this thesis, a drug was assumed discontinued when there were no records of its prescription found after 6 months of the last recorded prescription.

There remains the potential for **unmeasured confounding** which arose from the inability of this database to measure in details some important covariates[157] e.g. compliance and adherence to insulin regimens and other antidiabetic medications, the use of over the counter medications and other lifestyle factors. This led to residual confounding bias in this data. However, the data

were robust in terms of many measured sample size and study power (with 19,808 study participants) to minimise any effect this may have on the research validity.

The potential for **selection bias** is high in longitudinal databases because of lack of randomisation. This gives rise to study sample which is not representative of the population and limits the validity and generalizability of the study findings. Propensity score analyses were employed to address this in some chapters of this study.

2.7.2. Propensity Score (PS) Analyses:

One great advantage of RCTs over other study designs is randomisation – which removes the impact of confounding by baseline covariates on treatment assignment. As observational studies are being used more to estimate the effects of treatments on important clinical outcomes, often times, there are systematic differences in the way relevant baseline covariates in routine clinical data are distributed between the treatment groups. As a result of this, one cannot effectively compare the outcomes between these groups without the risk of selection bias which limits the validity of the outcome.[158-160]

The use of propensity score analytical methods has become increasingly popular in observational studies. It simply aims to mimic RCTs by reducing the effect of the confounding caused by those baseline differences, and compares the outcomes in the subjects in the treatment groups who share similar distribution of baseline covariates. It focuses on the association between prognostic variables and allocation of subjects to the treatment or control group and tries to "reconstruct a posteriori situation similar to random assignment"[158] using the baseline covariates which are associated with the treatment.[158] [159]

The effect of any treatment in survival analysis is measured by the difference between the two probable outcomes [i.e. $Y_i(1) - Y_i(0)$]. This implies that the average treatment effect (ATE) represents the mean difference in survival time as a result of the treatment of interest but the average effect of treatment on those subjects who eventually received the treatment is measured by the average treatment effect for the treated (ATT). [159, 160]

Propensity score (e_i) is the probability of receiving the active treatment ($Z = 1$ vs. $Z = 0$; where Z is treatment of interest; 1 is active treatment; and 0 is control or no-treatment) and it is conditional on the observed baseline covariates (**X**).[159-161]

$$\text{That is } e_i = \Pr(Z_i = 1 \mid \mathbf{X}_i).$$

It balances the distribution of measured baseline covariates to be the same in both the treated and untreated subjects so that outcomes can be effectively compared between them. It does this through 4 main methods:

i. Propensity score matching,
ii. Stratification on the propensity score,
iii. Inverse probability of treatment weighting (IPTW) using the propensity score, and
iv. Covariate adjustment using the propensity score.

These methods are robust, and allow one to estimate the marginal measures of treatment effect.[161] For this study, two methods were used – propensity score matching and IPTW. These will be briefly discussed below.

Although there is no conclusive evidence on the baseline covariate that can be included in the PS model, there is need to consider the specific peculiarities of the study, as well as the prevailing literature on the subject in choosing only the variables that are prognostic of the study outcome.[160, 162]

Propensity Score Matching (PSM): This involves more matching of the subjects who share similar propensity score to form pairs of treated vs untreated cohorts. The commonest method of matching is one-to-one matching,[159, 160] however, there are other ratios of matching.[163] First, a matched sample is formed, followed by the estimation of treatment effect through the comparison of the outcomes between treated vs untreated subjects within the matched sample.

This method has been validated and matched subjects have been shown to have similar value of propensity score and in the distribution of the observed baseline covariates.[159, 160] This removes any effect of confounding caused by the initial baseline differences. However, the PSM is modelled in such a way that ensures a minimal difference in global propensity score is maintained. The estimation of variance in the matched sample accounts for the lack of independence in outcomes induced by matching.[160, 163] The weighting and pairing of sample subjects leads to the construction of a sample of subjects whose only difference is the treatment. ATT can be estimated in a PS-matched cohort.

Briefly, another method of matching is the near-neighbour matching (greedy nearest neighbour matching). Here, a treated subject is selected and matched with an untreated subject whose propensity score is closest to it, so far as the differences between their propensity scores is less than a set maximum distance called the *caliper distance*. This method helps to overcome incomplete matching which in some cases may arise following PS matching.

In time-to-event outcomes analysis, Kaplan-Meier survival curves can be estimated for both the treated and untreated subjects using a PS matched sample. This enables one to directly compare the probability of survival between the different treatment groups. And because of the baseline similarity between the treatment groups, stratified log-rank test can be used to compare the equality of the survival curves instead of the log-rank test frequently used in other samples.[159, 164] Similarly, Cox proportional hazards model can be used to estimate the relative

change in the hazard of the outcome by regressing survival outcomes in treated vs untreated subjects.[164]

Inverse Probability of Treatment Weighting (IPTW): This method involves the use of PS-based weights to create a sample in which the distribution of the baseline covariates was not dependent of the treatment assignment. IPTW uses the marginal structural models which enables time-varying confounders to be properly accounted for during the estimation of the effect of time-varying exposures.[159, 160, 165] The possibility of having treated subjects with a very low PS or untreated ones with a high PS introduces instability in the weighting process. As a result of this, the use of stabilised weights has been advocated.[166] This is computed by multiplying the IPTW by the marginal probability of receiving the actual treatment of interest. This then allows the estimation of ATE.

In time-to-event outcome analyses, Xie and Lu[167] proposed an adjusted Kaplan–Meier estimate for the survival curves in the weighted sample and the use of a modified log-rank test to compare the equality of the survival curves. Similarly, regression models can be weighted by IPTW and used to estimate the causal effects of treatments. Robust variance estimation can be used to account for the sample weights. As with the PSM method, Cox proportional hazards model can be used to estimate the relative change in the hazards of the outcome. In this model, survival will be regressed on an indicator variable which represents treatment status.

2.8. Data Analyses:

2.8.1. Baseline Demographics

This study compared different outcomes among different drug-groups, baseline or metabolic groups. So, the baseline differences between the groups will be assessed using chi-square tests

and t-test for categorical and continuous variables respectively. Linear regression analysis will be used to estimate the differences where there are greater than 2 groups for continuous variables. Categorical variable values will be expressed as absolute numbers with proportions (%) while continuous variable values will be reports as mean and standard deviation (SD).

In matched analyses after PS matching, the standardised difference (d) was used to compare the baseline differences between the groups both for continuous and categorical variables. The standardised difference compares the mean differences (in unit) of the pooled SD and is used to compare the mean and proportion of baseline covariates in the PS-matched cohort.

PSM was the preferred choice over regression models in the adjusting for baseline variables in Chapters 6 and 8, which were studies involving different treatment groups. This is because a good advantage of PSM over the use of regression models is that while regression "controls for" the baseline characteristics in a linear manner, PSM eliminates the linearity assumption and focuses mainly on the particular exposure (observation) group of interest. Often times, observations outside this group may not be matched. For example, if a study involves elderly insulin users (aged 60 years and above), PSM will only match those aged 60 and above and ignore those not within this age limit. This can be both its strength and weakness – strength in that it creates a more concise measure of effect in this group; weakness in that its results cannot be generalised to those outside the matched population (e.g. those younger than 60). Also, in regression one can extrapolate using the linearity assumption unlike with PSM.

Another major advantage of PSM over regression is that it is non-parametric and so can obtain the best estimated probability of treatment assignment without being concerned with over-parameterizing this model. PSM can fit a very complicated propensity score model with interactions and higher order terms first. Unlike in the regression models, PSM is an efficient way to reduce many covariates into a single score which can then be used to adjust an effect of

interest for a set of variables. This gives it a wide statistical advantage because it saves degrees of freedom by only adjusting for a single propensity score instead of multiple covariates.

2.8.2. Meta-analysis

Chapter 3 is a meta-analysis of recent clinical trials which compared insulin therapy with any non-insulin GLT to obtain an average measure of effect for CV and metabolic outcomes. The detailed methodology has been presented in this chapter 3. Briefly, the primary outcome was the occurrence of CV events between the two treatment groups. The number of these events in each trial was extracted and pooled together using random effect method (which allows for the expression and adjustment of heterogeneity between the trials) to determine the odds of the risk of the outcomes – CV events, hypoglycaemia, adverse treatment events and proportion of patients attaining a set-target of HbA1c level – and the mean difference in terms of weight and HbA1c between the treatment groups. The pooled effect size for categorical variables were reported as odds ratio (OR) or risk ratio (RR) with 95% confidence interval; while the continuous variables were reported as standardized mean difference (SMD) with 95% confidence interval and p-values.[168] Sensitivity and subgroup analyses were conducted based on the classes of the non-insulin GLTs. The data were presented in tables, forest plots, Funnel plots, and risk of bias tables.

2.8.3. Cross-sectional Study

This provides a snap-shot of the relationship between an exposure and other covariates of interest in a population at any given point in time. In chapter 9 of this study, at the point of insulin initiation, a comparative cross-sectional study was carried between two populations – the UK insulin users population vs a local (Derbyshire) population of insulin users. Important

baseline covariates were compared using t-test (for continuous) and chi-square test for categorical covariates. These two populations were also compared based on their ability to achieve certain NHS treatment targets.

2.8.4. Linear Regression Analyses

Linear regression models the association between a continuous outcome (e.g. change in HbA1c level) and a continuous exposure (e.g. change in weight after one year of insulin initiation)[169] This can be shown with a scatterplot in which a predictive line can be fitted to predict the relationship between the exposure and outcome. It follows the equation of a straight line:[169]

Change in HbA1c = a + change in weight x b

a and **b** are the regression coefficients
a is the intercept - the value of HbA1c change when weight-change is zero
b is the slope - the increase in HbA1c for 1 unit increase in weight-change

This shows that for a given value of weight-change one year after insulin initiation, a corresponding expected change in HbA1c can be predicted. This model was applied in Chapter 4.

Linear regression analysis gives the t statistic, and the (Wald) P value for each regression coefficient. This tests the null hypothesis which assumes a no (zero) relationship between the exposure (weight-change) and the outcome (change in HbA1c). Linear regression assumes that a linear relationship exists between the outcome and exposure; and that the study outcome is normally distributed for each value of the exposure. It also assumes that the outcome is uniformly distributed and that each observation is independent.

So to test these assumptions in analysing the data, a scatterplot was fitted and examined to check if the association between the exposure and outcome (for example, change in weight (x) vs change in HbA1c (y)) was approximately linear. This was found to be true. Secondly, to check if the change in HbA1c (y) is normally distributed for each value of change in weight (x); the "post-estimation" commands in Stata were used to assess if there is normal distribution of the residuals. These were also noted to be true. Thirdly, I tested to see if the standard deviation of y is the same for each value of x by plotting the residuals against y and checking that the spread is constant across the range of values of x. This was also found to be true. Finally, I used a scatterplot to assess if each observation is independent (that is, one point per person) and this was found to be true..[169]

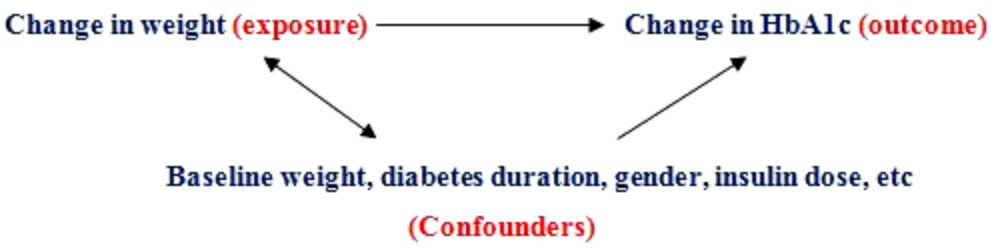


Figure 2.5: A schematic representation of an adjusted regression model.

As shown in Figure 2.5 above, multiple linear regression allows for the inclusion of confounding variable(s) into regression model in other to adjust for their effects. This process begins first by conducting a univariate analyses to establish the crude or unadjusted measure of the association between the exposure (change in weight) and the outcome (change in HbA1c). This is followed by the one-by-one inclusion of the potential confounders into the regression model, observing if the measure of effect changed (usually put at 10% change). The covariates which changed the effect by 10% are finally included into the final regression model. Though this method has been largely criticised by some statisticians who prefer the forced

entry method over it, there are however debates on its appropriateness with divergent opinions. This method was preferred and chosen for this study because it afforded me the opportunity to measure the actual confounding strength of each potential confounder, and allowed only the strong ones to be included in the final regression model. Also, it allowed for a test of interaction with certain effect modifiers. Figure 2.5 is a schematic representation of an adjusted model.

2.8.5. Logistic Regression Analyses

Unlike linear regression, logistic regression is used for the analysis of studies which have a binary outcome variable (e.g. proportion of people achieving a target HbA1c – yes or no). In cohort studies, it can be used when binary outcomes are collected at specific time points (proportion achieving a target HbA1c at 6, 12, 24, 36 months respectively) during the study follow-up duration. This is the method applied in the third aim of the study in Chapter 5.

Logistic regression produces estimates of odds ratios (OR) and 95% confidence interval like the traditional Mantel-Haenszel odds ratio. Its strength lies in its flexibility and ability to handle enormous confounding variables for adjustment; interaction terms; and the inclusion of continuous, binary or categorical exposure variables. Adjustment for potential confounders can also be done here as described in the logistic regression section above.

2.8.6. Cox Regression Analyses

In cohort studies, participants are followed up people for a specified duration of time to through time and find out who develops the outcome of interest or not. It measures the incidence of an

outcome, usually expressed as a rate. For example, the incidence of new CV event in a population with diabetes can be measured thus:

$$\text{Rate} = \frac{\text{Number of new CV events}}{\text{Total Person-time of diabetics at risk}}$$

This is presented as rates per 100 or 1,000 or 10,000 person-time. The person-time denotes the 'at risk' period – the sum total of the period each participant is at risk of the outcome.

In longitudinal data, information is collected on the length of time participants are followed up over time. One great advantage of Cox regression over linear, logistic or Poisson regression models is that it does not make the assumption that incidence rates are constant over the study period, or constant within some calendar-time periods or age bands. This is because the rates of an outcome change rapidly over time. For example, the rate of CV events following insulin use varies with the duration and dose of insulin used.

The Cox regression model is among a framework of analysis for time to event data known as survival analysis. So, Cox regression model is used to analyse data where the outcome being studied is the time till the occurrence of the event of interest because not all patients have an actual survival time (time to occurrence of an event) during the study period. The beauty of the Cox model is that it allows these censored patients to be included in the analysis. Secondly, it is robust, flexible, powerful, and able to cope with very complex survival data with multiple confounders, and handle many covariates and interactions.

The Cox proportional hazards model is used to compute hazard rates. It uses a conditional likelihood procedure to take account of censored observations. It is also used to derive hazard ratios in which the hazard rates in different exposure groups are compared. The Cox regression

model is based on the hazard rate at time (t) in the follow-up period: h(t). The hazard rate can change at any rate over time during the follow-up period, and does not need to be constant.

The following steps are involved in fitting a Cox regression model:

1. Survival analysis: This first step was developed to analyse the time to the occurrence of the outcome of interest, death, and loss to follow-up or the censoring date. However, the fall back here is that not all patients have an actual survival time (time to occurrence of an event) during the study period but all patients have a follow-up time.

2. Kaplan-Meier plots: This second step in building a Cox regression model. It allows for simple comparisons between the different study-groups using the log rank test which provides a direct way of comparing survival curves. All of the survival times, whether exact or censored, were used to compare treatment groups in the length of time after the start of the cohort until the end. It is based on the calculations of survival probabilities and median survival time throughout the study.

   The log rank test is then used to compare the probabilities of survival within the entire follow-up duration by computing the observed survival in the different treatment groups and comparing these with the expected events if all treatment groups had similar survival.
3. Fitting the Cox model first for unadjusted and for adjusted measures of effect.

Hazard ratio (HR) is the ratio of the hazard rate of the event in the people exposure to the treatment (e.g. INS + drug A) vs those not exposed (INS + drug B). Being a ratio, values > 1 indicate a higher hazard rate in the exposed group vs unexposed group. This implies that survival is lower. Conversely, values < 1 indicate a lower hazard rate and higher survival. Likelihood ratio tests (LRT) and Wald's tests can be calculated for Cox proportional hazards model to determine statistical significance while both categorical and continuous covariates

can be included in the Cox model during adjustment to obtain an adjusted hazard ration (aHR) with 95% confidence interval.

2.9. Subgroup and Sensitivity Analyses

In studies where these were done, the analyses were described in details in their respective chapters.

2.10. Statistical Software used:

Stata Software, V.14 [170] and Revmann were the statistical software packages which were used in this study's analyses. Most calculations, graphs and tables were designed in excel spreadsheets. Revmann was used for the meta-analysis and in designing the forest plots.

2.11. Limitations

One limitation of THIN database is that there are variable coding practices which lead to variations in the quality and scope of the data within its participating practices. Similarly, there are variations in the units of measurements, e.g. HbA1c is measured in mmol/mol in some practices vs percentage (%) in others leading to confusion where the lower range of normal in one, overlaps with the upper limits of the other. Another limitation is that some diagnoses of diabetes were found not linked to any confirmatory tests and where these were not further linked to any antidiabetic treatments, they were excluded from the study.

Also, some practices were unable to wholly systematically transfer their older paper-based records to the electronic forms. Furthermore, selective inclusion of only diagnoses considered important during this transition phase was noted. These have the potential of underestimating the incidence of incidence of certain diseases (especially the rare ones). Conversely, some events were overestimated due to double registration of patients following the inability to track these patients as they transferred from one participating practice to another.

In spite of these, THIN has been validated by several studies for several disease conditions and shown to be representative of the UK demographics and disease patterns. This study is adequately powered by the 19,808 participants in the dataset to provide a true treatment effect.

2.12. Ethical approval

It is mandatory in the UK that approval must be obtained from the Research Ethics Committee (REC) for all researches conducted using data obtained from the NHS. Consequently, all studies using the THIN database must go through the process of ethical application with the National Research Ethics Service (NRES) whose major duties are to review studies and clinical audit (data collection) projects which involve patients from several local areas. The Data Collection Scheme of THIN was approved by the South-East Multicentre Research Ethics Committee (SE-MREC), an arm of the NRES Committee.

For the studies involving this thesis, ethical approval was sought and obtained from the Scientific Review Committee (SRC) of THIN. The ethical agreement incorporates all studies done with this THIN dataset.

This document is attached in Appendix 1, section 1.8.

Chapter Three: Comparison of Cardiovascular and Metabolic Outcomes in people with Type 2 diabetes on Insulin versus Non-Insulin Glucose-Lowering Therapies (GLTs) – A Systematic Review and Meta-analysis of Clinical Trials.

3.1. Summary

Background and Aim

There is no conclusive evidence on the cardiovascular (CV) effects of insulin when used alone compared to other glucose-lowering therapy (GLTs). Clinical trials did not show any consensus pattern in outcomes. So, this study aimed to compare the CV and metabolic outcomes associated with insulin versus non-insulin GLTs.

Methods

RCTs which randomised patients aged >18 years with Type 2 Diabetes (T2D) to insulin vs non-insulin GLT. I used risk ratios (RR), risk difference (RD) and odds ratios (OR) with 95% confidence interval (95%CI) to analyse the treatment effects of dichotomous outcomes and mean differences (with 95% CI) for continuous outcomes.

Results

Eighteen (18) RCTs with 19,300 participants were selected. There was no significant difference in the risk of all-cause mortality and CV events between the groups (RR= 1.01; 95%CI: 0.96 - 1.06; p = 0.69). In 16 trials, insulin showed greater efficacy in glycaemic control (mean diff= -0.20%; 95%CI: -0.28 to -0.11 but the proportion achieving HbA1c level of either ≤7.0% or

7.4% (53 or 57mmol/mol) was similar in both (OR=1.55; 95%CI= 0.92 to 2.62). The non-insulin group had a significant reduction in weight (mean diff = -3.41; 95%CI: -4.50 to -2.32) and an increase in the proportion of adverse events (54.7% vs 45.3%, p= 0.044), but the insulin group showed a 90% (RR= 1.90; 95%CI: 1.44 to 2.51) increase in the risk of hypoglycaemia.

Conclusion

There was no difference in the risk of all-cause mortality and adverse CV events between insulin and non-insulin GLTs. Insulin was associated with superior reduction in HbA1c; least reduction in weight and higher risk of hypoglycaemia. Both showed similar proportion of patients achieving HbA1c target while the use of non-insulin GLTs was associated with a higher risk in reported adverse drug events.

3.2. Introduction

For many patients with T2D, treatment intensification using additional antihyperglycaemic agents is required in order to achieve optimal glycaemic control and prevent long-term vascular complications.[44, 171] A variety of antihyperglycaemic agents are available but questions regarding the long term safety and efficacy of some of these agents have been raised. In addition, recent focus by international regulatory agencies on the cardiovascular safety profile of commonly used antihyperglycaemic agents[105, 172] have led to debate about the most appropriate choice of therapy for treatment intensification.

Amidst this, exogenous insulin remains to be one of the most established glucose lowering therapies available[173-178] and its use in people with T2D has grown markedly over recent years. More recently however, the effectiveness and safety of insulin therapy has been a subject of

intense discussion.[104, 115, 179] Moreover, recent large epidemiological studies have reported adverse CV outcome and increase mortality with insulin compared with non-insulin therapy.[115, 180] While the possible mechanism behind the observed the association between insulin and adverse cardiovascular and metabolic outcomes and mortality remains unclear, it is hypothesized that these may include, but not limited to, hypoglycaemia and weight gain.

Although insulin therapy is associated with HbA1c lowering, weight gain and increased risk of hypoglycaemia, comparative analysis between insulin and non-insulin anti-diabetic therapy on these parameters are currently not available. A systematic review of RCT on the CV safety of insulin compared with non-insulin therapy has also not been reported. Thus, despite extensive experience of the use of insulin in routine clinical practice, I contend that the safety and efficacy of insulin has not been subjected to similar scrutiny in an adequately powered RCT setting, as is currently required for new antihyperglycaemic agents.[105]

I therefore aimed to compare the benefits and harms of Insulin versus non-insulin glucose GLT as reported in RCT involving people with T2D.

3.3. Methods

3.3.1. Search Strategy

I searched the following electronic databases from January, 2005 to December, 2014: The Cochrane Library, Ovid MEDLINE, EMBASE, and International Pharmaceutical Abstracts. I also scanned the reference lists of the included clinical trials for studies that met our inclusion criteria. The search terms used are in Figure 1 of Appendix 2.

3.3.2. Study selection

With my then PhD senior colleague (Jil Mamza), I independently searched and screened the titles of all studies to assess their relevance to this study in line with the inclusion criteria.

Inclusion Criteria: Clinical trials were included if they were …

i. Randomised.

ii. Involved only adults (18 years and above) with type 2 diabetes.

iii. Compared insulin with any non-insulin GLT irrespective of baseline GLT (so far as the only difference between both groups is insulin).

iv. Reported clinical outcomes as all-cause mortality, cardiovascular (CV) events (Myocardial infarction, stroke, heart failure, and CV mortality) and metabolic outcomes (e.g. glycaemic control, change in weight, and events of hypoglycaemia).

v. Had an intervention period of at least 24 weeks.[181, 182]

vi. Conducted within the past ten years (2005-2014). The last two decades have witnessed unprecedented advancement in diabetes care and management with the emergence of newer antidiabetic agents. So, the last decade was chosen to reflect current trends in diabetes care and provide recent evidence that will further guide the management of diabetes.

Exclusion Criteria

i. Unpublished and uncompleted trials

ii. Studies not published in English language.

Abstracts of the selected studies were then retrieved and reviewed thoroughly for inclusion in line with the inclusion criteria. The full text copies of the trials that met the inclusion criteria were then retrieved. Studies in persons with type 1 diabetes; without a clear protocol; with mixed age groups; no clear drug-combinations or short follow-up duration (<24 weeks) were

excluded. Where we differed with my colleague, the study supervisor's consideration was the final.

The finally selected studies were imported into Endnote referencing software[183] where duplicates from the different databases were removed. The flow chart graphically explains the pathway to the selection of studies (Figure 3.1).

3.3.3. Data Extraction and Risk of bias assessment

Again, independently with Jil Mamza, I extracted data from the 18 selected studies which met our inclusion criteria into a self-designed record form. These included basic study characteristics as number of participants, gender, patients' description, characteristics of the trials, follow-up and outcome measures.

Using the Cochrane Handbook for Systematic Reviews of Interventions tool,[184] we independently assessed the risk of bias and quality of each included trial according to the following domains: allocation sequence, allocation concealment, blinding (of participants, personnel and outcome assessors), incomplete outcome data, and selective outcome reporting and other sources of bias as funding of trials and drug quality. The trials were classified as low, high or unclear risk of bias.

Primary Outcomes

i. All-cause mortality and
ii. CV events (defined as CV mortality, non-fatal myocardial infarction (MI), non-fatal stroke and heart failure).

Secondary outcomes

i. Metabolic outcomes as glycaemic control (defined by the mean reduction in HbA1c and the proportion of patients attaining a target HbA1c level); and mean reduction in weight.

ii. Episodes of hypoglycaemia and

iii. The number of reported adverse drug events.

3.3.4. Statistical Analyses:

The extracted data were entered into Microsoft excel document and exported into The Review Manager Software version 5.3 which I used for all statistical analyses. For continuous outcomes (changes in HbA1c and weight), I computed the mean differences between both treatment groups. In doing this, I entered the actual mean differences from the analyses where these were provided in the trials and where not available, I computed the mean differences from the mean values recorded in the included trials.

Q-test and I^2 statistics were used to test for heterogeneity between the trials. A cut off of $I^2 \geq$ 50% was used to define heterogeneity. Where I^2 was $>$ 50%, the random model was used and where there is no significant heterogeneity, the fixed model was used.[184]

Risk Ratios (RR) or Odds Ratios (OR) with 95% confidence interval (95%CI) were used as the summary statistics for dichotomous variables (All-cause mortality; CV-outcomes; proportion of participants attaining the target HbA1c levels; risk of hypoglycaemia; and number of reported adverse events). These were derived from the number of events and the total number of participants in each treatment group. For continuous variables, weighted mean difference and 95% CI was used to summarise the data. Studies with missing data for any outcome were not included in the meta-analyses.

I performed subgroup analyses for the secondary outcomes of mean reduction in HbA1c and weight to assess if there are significant differences in the estimates according to the class of drugs in the non-insulin arm using a test of interaction. I also tested for interaction according to risk of bias. Finally, I used the funnel plot and Egger's test to detect the possibility of publication bias in the included trials in our meta-analysis.

All results were presented in tables, flow chart, forest plots, funnel plots, and bias tables.

The review protocol was registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/) with the registration number CRD42015024559. The subgroup analysis for weight and addition of a secondary outcome of reported adverse events were not captured in our original protocol.

3.4.Results:

3.4.1. Literature Search Results:

From the electronic searches, 2,445 papers were identified from the databases (Figure 3.1). Following the exclusion of duplicate reports and review of the titles, 2,172 were dropped. After abstraction, 28 citations were selected and their full papers retrieved. Further 10 studies were removed because two had no clearly defined intervention and comparator groups, one was published in Danish; another involved people with both type 1 and 2 diabetes while one was amongst cystic fibrosis patients; two were single arm and/or non-randomised; another had more than two comparator arms; one study compared different types of insulin versus altering insulin doses; another measured quality of life (QOL) as its outcome.

Though the ORIGIN trial was not very clear on the specific drugs in its standard care arm,[97] this large trial which explore CV risks was included in our meta-analysis based on the consistency of the use of Insulin Glargine in its insulin arm and to a large extent, the high probability of not including insulin in its standard care arm. Similarly, though DIGAMI-2 trial[185] had three arms, it was chosen because the insulin and non-insulin arms were clearly defined and outcomes compared between these two. Finally, 18 clinical trials[97, 181, 182, 185-199] were selected for meta-analysis (Figure 3.1).

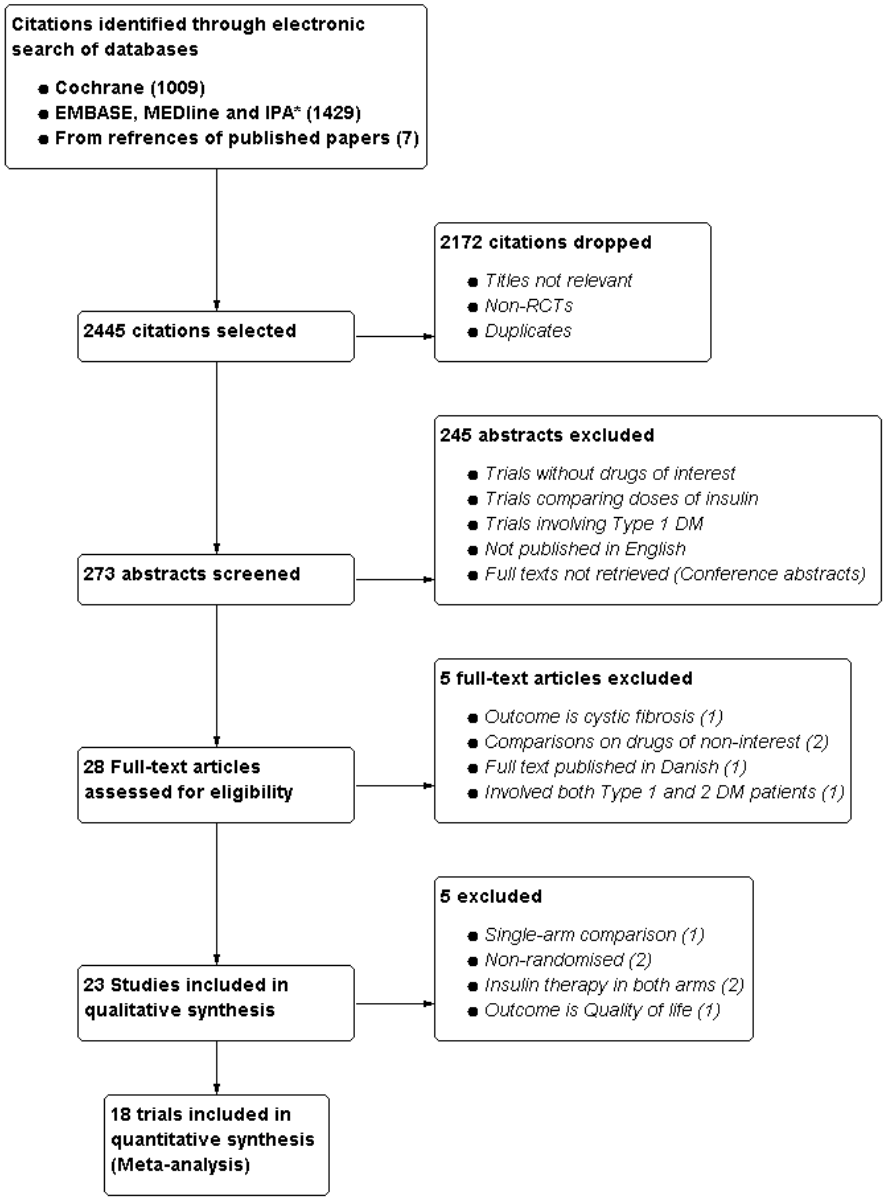


Figure 3.1: Flow Chart of Study Identification and selection

3.4.2. Baseline Characteristics:

A total of 19,300 participants were involved in the selected 18 RCTs in which 9476 were randomised to insulin and 9351 to non-insulin GLT. Table 3.1 below describes the baseline pre-trial characteristics of the trial participants. Majority (68.8%) of these trials compared insulin with GLP-1RA (mostly exenatide), other comparators were DPP-4 inhibitors (12.5%), thiazolidinediones (12.5%) and metformin (6.2%). Insulin glargine was used in 12 (68.8%) trials while Insulin NPH, lispro and degludec were used in one trial each. Eight trials compared Insulin glargine and Exenatide.[186, 187, 189-192, 195, 196] The trial duration ranged from 24 weeks to 6.2 years. The mean age range of participants was 53.6 to 61.2 years. Also, the mean baseline HbA1c range was 7.6 to 9.7%; BMI: 28.8 – 34.1kg/m^2; and diabetes duration: 4.5 to 11.5 years (Table 3.1).

In Table 3.2, the specific details of the trials- the treatment arms and a few outcome measures of interest- were highlighted

Table 3.1: Baseline Characteristics of Included Trials

Trial	No†	Sex¥ F(%)	Population	Trial drugs	Age (yrs)	Diabetes duration (yrs)	HbA1c (%)	Weight (Kg)	BMI (Kgm^{-2})	Trial duration
Aschner et al (2012)[181]	515	49	Insulin-naïve T2D patients taking only metformin with HbA1c≥7% and <11%	Insulin glargine vs Sitagliptin	53.6 (8.8)	4.5 (1.9-8.2)*	8.5(1.1)	83.8 (18.2)*	31.1(4.9)	24wks
Barnett et al (2006)[182]	427	47	T2D sulphonylurea (SU) failures with HbA1c 8-12%.	Insulin NPH vs Metformin	60.4 (35-79)*	9.2 (0.5-37.3)*	9.7 (1.1)	80.1 (50-136)*	28.8 (20-57)*	24wks
Barnett et al (2007)[186]	138	53	T2D aged ≥30yrs on Metformin (MET)± SU failures with HbA1c ≥7% and <11%, BMI>25 and <40kgm^{-2} and varying body weight	Insulin glargine vs Exenatide	54.9(0.8)	7.4(0.4)	9.0(0.1)	84.8(1.4)	31.1(0.4)	32wks
Bunck et al (2009)[187]	69	35	MET-treated T2D at a stable dose for 2 months and no other GLTs 3 months prior to screening.	Insulin glargine Vs Exenatide	58.4(1.4)	5.7(0.8)	7.6 ±0.1	92.4(2.4)	30.1 (0.6)	52wks
D'Alessio et al (2014)[188]	798	46	T2D >1yr duration; HbA1c ≥7.5 and ≤12%; BMI: 25-40kgm^{-2}; on MET (≥1g/day) ± SU or Glinides or DPP-4i > 3 months	Insulin glargine vs Liraglutide	57(9)	9(6)	9.0(1.1)	90.5 (16.7)	31.9(4.2)	24wks
Davies et al (2009)[190]	235	32	T2D with BMI>27kgm^{-2} and elevated cardiovascular risk, inadequately controlled on 2-3 oral GLTs.	Insulin glargine vs Exenatide	56.5(9.1)	8.7(4.5)	8.65(0.7)	99.5(18.3)	34.1(5.3)	26wks
Davies et al (2013)[189]	222	34	T2D adults not achieving adequate glycaemic control using MET or MET+SU	Insulin detemir vs Exenatide	58.5(10)	7.5(5.5)	8.36(0.9)	97.3(16.4)	33.7(4.7)	26wks
de Wit et al (2014)[199]	50	38	Insulin-users with T2D with weight gain ≥4% following ≤16months insulin therapy, HbA1c: ≥6.5 and <8%.	Insulin vs Liraglutide	58 (9)	8(6.1)	7.4(0.7)	100(19.3)	34 (7)	26wks
Diamant et al (2010)[192]	456	47		Insulin glargine vs	58(9.5)	7.9(6)	8.3(1.1)	90.9(17.5)	32(5)	26wks

			Adult T2D with suboptimum glycaemic control despite use of max tolerated dose of GLTs ≥ 3months	Exenatide						
Diamant et al (2012)[191]	467	NR	Adult T2D who failed to maintain adequate glycaemic control with MET alone or MET+SU	Insulin glargine vs Exenatide	NR[#]	NR	8.3	NR	NR	84wks
Diamant et al (2014)[193]	510	52	T2D patients treated with insulin glargine and MET±SU, HbA1c: 7-19% and BMI: 25.0kgm^{-2}	Insulin lispro vs Exenatide	59.5(9.5)	11.5 (8-17)*	8.3(1)	90.1(16.9)	32.5(4.7)	30wks
DIGAMI-2 (2011)[185]	1253	33	T2D patients with suspected acute myocardial infarction	Insulin (INS) vs INS +Non-INS GLTs vs Non-insulin GLTs	68.3(10.9)	8.14(8.4)	7.68(1.7)	NR	28.3(4.6)	2.1 years (with a median follow up of 4.1-8.1 years)
Dorkhan et al (2009)[194]	30	34	T2D patients with inadequate glycaemic control with MET+SU	Insulin glargine vs Pioglitazone	61.2(7.7)	10.3(6.8)	8.2(1.5)	NR	31.2(5.8)	26wks
Heine et al (2005)[195]	549	44	T2D patients with inadequate glycaemic control (HbA1c: 7-10%) with MET+SU	Insulin glargine vs Exenatide	58.9(9.2)	9.6(5.9)	8.3 (1.0)	87.9(17.4)	31.4(4.5)	26wks
Matyjaszek-Matuszek (2013)[196]	80	56	T2D adults (30-70yrs), stable on optimal doses of MET+SU ≥3months, and BMI:25-45kgm^2	Insulin glargine vs Exenatide	60(9.0)	8.4(5.14)	7.9(0.9)	85.7(16.7)	32.5(4.82)	26wks
ORIGIN (2012)[97]	12537	35	Outpatients with cardiovascular risk factors and T2D or IFG and IGT	Insulin glargine vs Standard Care	63.6(7.8) 63.5(7.9)	5.5(6.1) 5.3(5.9)	6.4 (5.8-7.2)*	83.3(16.8) 83.1(17.3)	29.8(5.2) 29.9(5.3)	6.2 years
Tsimikas et al (2013)[197]	458	41	Insulin-naïve T2D (>6mths), HbA1c: 7-11%, BMI≤40kgm^{-2}, treated with 1-2 non-insulin GLTs.	Insulin degludec vs Sitagliptin	56(10.8)	7.7(6.0)	8.9(1.0)	85(19.6)	30.4(5.2)	26wks
Rosenstock et al (2006)[198]	219	49	Insulin naïve, ≥18yrs T2D without CV risk factors, on MET and SU 3 months and above	Insulin glargine vs Rosiglitazone	55.6(11)	8.3(5.45)	8.8(1.0)	NR	34.(6.7)	24wks

Median and Interquartile range. [#]NR= Not Reported. [†]Population at the beginning of the trial. [¥]F= Females (Percentages approximated to the nearest whole number)
DIGAMI-2: Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction, ORIGIN: Outcome Reduction with an Initial Glargine Intervention

Table 3.2: Trial Interventions and Outcome measures

Trial	Design Type	Total[a]	Intervention groups	Baseline antidiabetics	Trial regime (dosage)		Outcome measures[b]
					Insulin	Comparator drug	
Aschner et al (2012)[181]	Randomised, Open-label, Parallel-arm, Controlled trial	515	Insulin glargine (250) Vs Sitagliptin (265)	Metformin	Subcutaneous dose of 0.2 unit/kg to attain fasting plasma glucose of 4.0-5.5mmol/L and increased or decreased by 2units respectively when below or above this range	Sitagliptin 100mg daily orally.	HbA1c Weight Hypoglycaemia at 6months
Barnett et al (2006)[182]	Randomised, open-label, parallel arm, Controlled trial Divided into two arms (HbA1c <9.5 and >9.5) before randomisation.	427	Insulin NPH(225) Vs Metformin(202)	Sulphonylurea	Inhalation (INH) in 1- and 3-mg dose blister packs	1g twice daily	Change in HbA1c
Barnett et al (2007)[186]	Randomised, Open-label, Crossover, Controlled trial	138	Insulin glargine (70) Vs Exenatide (68)	Metformin +/- Sulphonylurea	Once daily at bedtime targeting a fasting serum glucose level ≤5.6mmol/L for 16 weeks, then switch over to comparator after 16weeks	5µg BD for the first 4 weeks and 10µg thereafter. Then switch over to comparator after 16weeks	HbA1c, Weight FPG[1]
Bunck et al (2009)[187]	Randomised, Open-label, Parallel-arm, Controlled trial	69	Insulin glargine (33) Vs Exenatide (36)	Metformin	Initial dose of 10 IU to attain a glucose level of 4.5 and 5.5 mmol/L increased or decreased by 2 units when above or below this range respectively	Initiated dose of 5 µg BD for 4 weeks followed by 10 µg BD, titrated to a max dose of 20 µg.	B-cell function, HbA1c, Body weight
D'Alessio et al (2014)[188]	Randomised, open-label, Parallel-arm, Controlled trial with a 24-wk extension phase with crossover	798	Insulin glargine (489) Vs Liraglutide (489)	Metformin +/- Sulphonylurea	Adjusted (titrated)every 3 days to target a fasting plasma glucose of 4.0-5.5mmol/L	0.6mg once daily increased to 1.2mg and 1.8mg daily weekly according to response.	HbA1c Weight Hypoglycaemia

Davies et al (2009)[190]	Randomised, Open-label Parallel-arm, Controlled trial	235	Insulin glargine (117) Vs Exenatide (118)	Metformin, Sulphonylurea, Thiazolidinedione	Initial dose of 10IU/day and titrated weekly to target FPG level ≤5.6mmol/L	5µg BD for the first 4 weeks and 10 µg BD for the remainder of the study.	HbA1c Hypoglycaemia Weight
Davies et al (2013)[189]	Randomised, Open-label Parallel-arm, Controlled trial	222	Insulin detemir (105) Vs Exenatide (111)	Metformin +/- Sulphonylurea	Insulin determir once or twice daily, titrated to FPG level <5mmol/L	2mg subcutaneous once weekly	-Proportion of achieving HbA1c ≤7mmol/L and weight ≥1.0kg -HbA1c -Hypoglycaemia
de Wit et al (2014)[199]	Randomised, Open-label Parallel-arm, Controlled trial	50	Insulin (24) Vs Liraglutide (26)	Metformin +/- Sulphonylurea	Standard therapy (continuation and intensification of insulin therapy without Liraglutide)	1.8mg/day	HbA1c Body weight
Diamant et al (2010)[192]	Randomised Open-label Controlled non-inferiority trial	456	Insulin glargine (223) Vs Exenatide (233)	Metformin +/- Sulphonylurea And others	Once daily injection, starting does 10IU, target glucose range between 4.0-5.5 mmol/L	2mg once a week injection	HbA1c Weight gain
Diamant et al (2012)[191]	Randomised Open-label Parallel-arm, Controlled trial	467	Insulin glargine (234) Vs Exenatide (233)	Metformin +/- Sulphonylurea	Once daily (10IU/day	2mg once weekly	-Proportion of patients achieving HbA1c <7.0 -Change in HbA1c
Diamant et al (2014)[193]	Randomised Open-label Controlled non-inferiority trial	627	Insulin Lispro (312) Vs Exenatide (315)	Insulin glargine and metformin	Thrice daily meal time dose titrated to pre-meal glucose of 5.6-6mmol/L.	5µg BD for the first 4 weeks and 10µg thereafter.	HbA1c Weight
DIGAMI-2	Randomised Open-label	1253	Insulin (474) Vs	Not described			

(2011)[185]	Blinded evaluation trial (post hoc analysis)		INS + Non-INS GLT (473) Vs Non-INS GLT (304)		Short-acting insulin before meals and intermediate/long-acting insulin in the evening after 24-hr infusion of insulin and glucose.	Standard non-insulin GLTs given by a physician according to local routines after a 24-hr ins-glucose infusion.	Risk of all-cause mortality and CV events (including CV death)
Dorkhan et al (2009)[194]	Randomised Open-label Controlled trial (pilot study)	30	Insulin glargine (15) Vs Pioglitazone (15)	Metformin and Sulphonylurea	Insulin was up-titrated to achieve fasting plasma glucose <6mmol/l	Increased to 45mg/day after 16 weeks if HbA1c>6.2%	HbA1c, BMI
Heine et al (2005)[195]	Randomised Open-label Parallel-arm, Controlled trial	549	Insulin glargine (267) Vs Exenatide (282)	Metformin and Sulphonylurea	1 daily dose titrated to FPG level of less than 5.6mmol/L (<100mg/dl)	10 µg/day twice daily	HbA1c, Weight
Matyjaszek-Matuszek et al (2013)[196]	Randomised Open-label Parallel-arm, Controlled trial	80	Insulin glargine (40) Vs Exenatide (40)	Metformin and Sulphonylurea	10IU/day titrated with 2IU every 3 days (if needed) to achieve FPG <5.6mmol/L	5µg BD for 4 weeks, later increased to 10µg BD for the remaining trial period	HbA1c Body weight
ORIGIN (2012)[97]	Randomised Open-label Multi-centre trial	12,537	Insulin Glargine (6264) Vs Standard care (6273)	Glucose-lowering therapies(GLTs)	Insulin glargine	GLTs mainly metformin and sulphonylurea but never including Insulin glargine	CV events (including CV mortality) Weight
Philis-Tsimikas et al (2013)[197]	Randomised, open-label, parallel arm, Controlled trial	458	Insulin degludec (229) Vs Sitagliptin (229)	1-2 OADs (only among metformin, SU, Glinides or Pioglitazones)	10IU once daily titrated (if needed) to achieve FPG <5.0mmol/L	100mg orally once daily	HbA1c
Rosenstock et al (2006)[198]	Randomised, open-label, parallel arm, Controlled trial	219	Insulin glargine (105) Vs Rosiglitazone (112)	Metformin and Sulphonylurea	10units/day for 7 days with forced titrated to target FPG ≤5.5-6.7 mmol/L (≤100-120MG/dl)	4mg/day. Increased to 8mg/day any time after 6 weeks in FPG was >5.5mmol/l	HbA1c, Weight Hypoglycaemia

[a]Trial no: This includes only persons randomised to a treatment group
PG: Fasting Plasma Glucose;
[b]The list is not exhaustive. Only the outcome measures of interest were listed.

3.4.3. Bias Risk Assessment:

All the trials showed high risk of performance and detection bias. This is because all the trials were open-label with no blinding of participants and assessors except only one trial which reported blinding of assessors[192]. Conversely, the risk of selection bias was low for all trials except one pilot study[194] in which no random sequence was generated nor allocation concealed. The risk of attrition, reporting and academic biases were low in all the included trials (Figure 3.3)

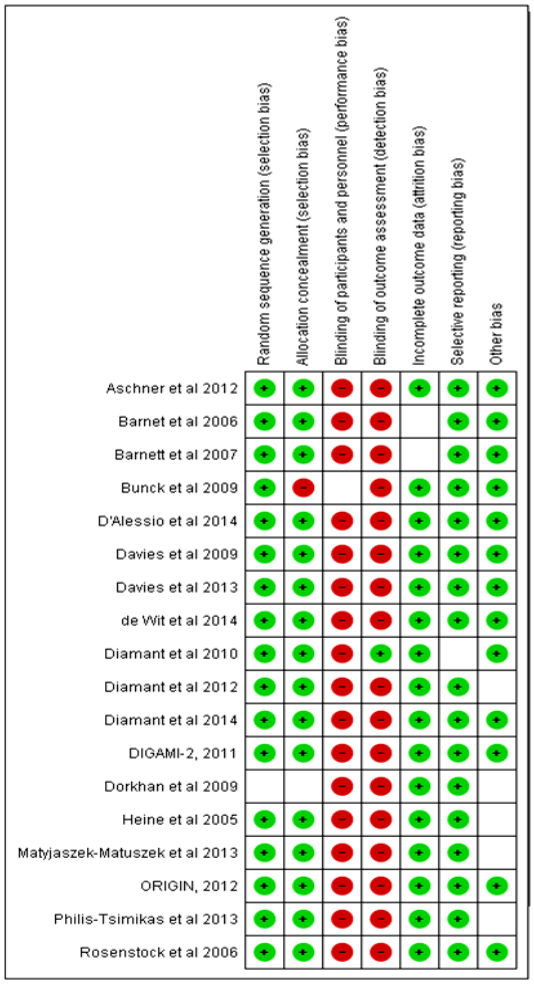


Figure 3.2: Risk of bias summary showing the judgements about each risk of bias item for each included study.

3.4.4. All-Cause Mortality and Cardiovascular (CV) Events:

The primary outcomes of all-cause mortality and CV events were only reported by two trials involving a total of 13,317 participants in which 6738 were randomised to insulin and 6579 to the non-insulin arm (Figure 3.3). I found no significant heterogeneity between the studies for any of these outcomes ($x^2 = 3.53$, $p = 0.47$, $I^2 = 0\%$). A total of 5,546 composite events were reported (2836 vs 2710). There was no significant difference in the risk of All-cause mortality and CV events between both treatment groups (RR= 1.01; 95%CI: 0.96 - 1.06; p = 0.69).

Risk of All-Cause Mortality: A total of 2,158 all-cause deaths occurred in the two included trials (1104 vs 1054). There was an equal risk of all-cause mortality between the two treatment arms (RR= 1.00; 95%CI: 0.93 - 1.08; p = 0.97) (Figure 3.3).

Risk of Cardiovascular Events: In Figure 3.3, the meta-analysis showed no significant difference in the risk of cardiovascular deaths in both treatment arms in the two trials which reported CV deaths (n= 1319; RR= 1.02; 95%CI: 0.92 - 1.13; p = 0.65). There was no heterogeneity among these studies (p= 0.69). A total of 735 events of non-fatal myocardial infarction were reported with a risk ratio of 1.07 (95%CI: 0.93 – 1.24; p = 0.32). Similarly, no significant difference was observed in the risk of non-fatal stroke (n = 663; RR= 1.04; 95%CI: 0.90 - 1.21; p = 0.56) and heart failure (n= 671; RR= 0.90; 95%CI: 0.77 - 1.04; p = 0.15).

I could not detect any evidence of publication bias in these trials in the meta-analysis for the risk of CV events. The funnel plot (Figure 3a, Appendix) and the Egger's test to detect any asymmetry in the funnel plot yielded no significant finding (p-value = 0.285).

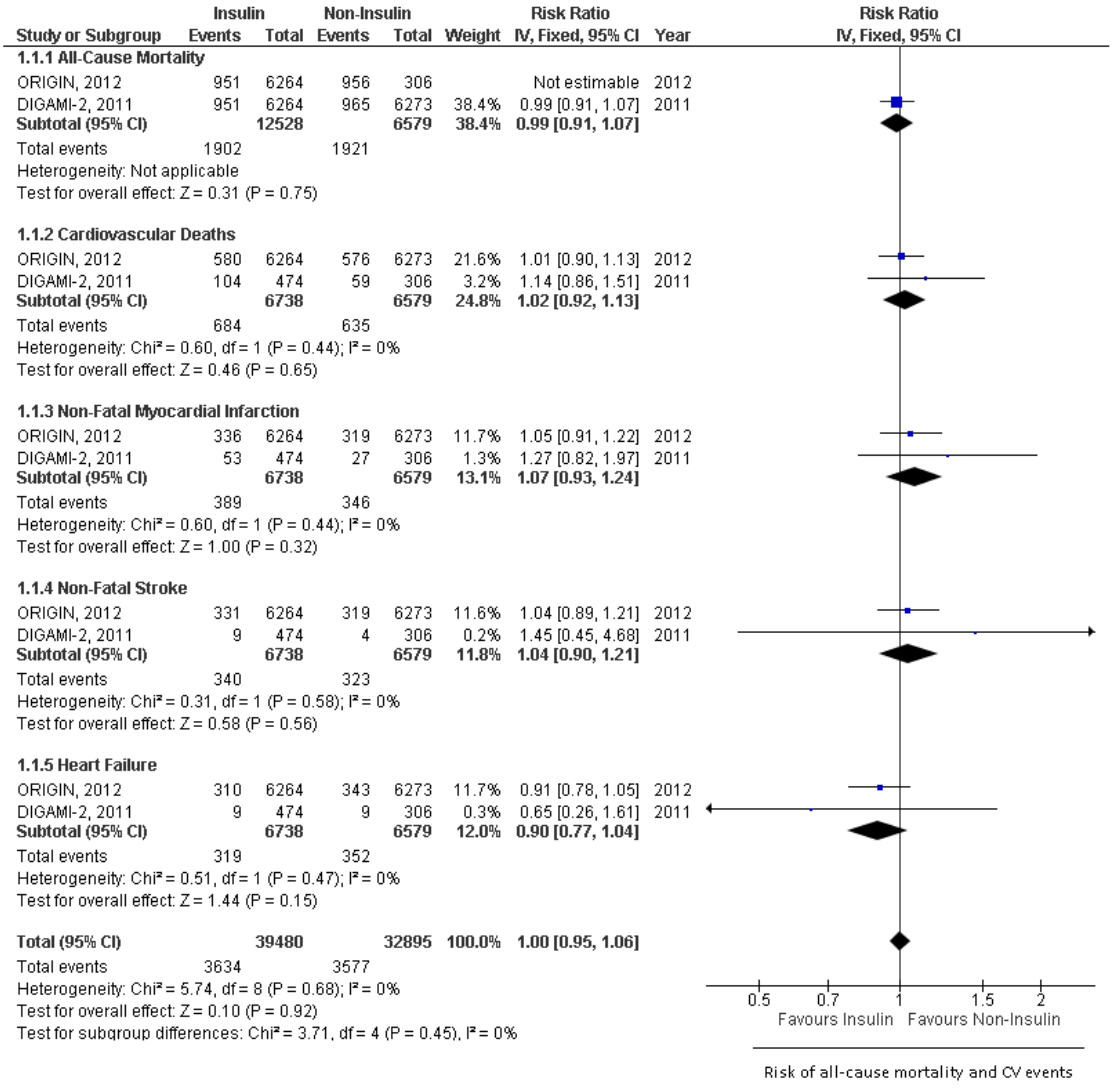


Figure 3.3: Forest Plot showing the risk of all-cause mortality and CV events between insulin and non-insulin treatment groups

3.4.5. Glycaemic Control

Mean Changes in HbA1c level: Only 16 of the 18 trials (N= 5201) reported mean changes in HbA1c in both treatment groups. Of these, three trials[187, 190, 198] reported only the mean changes in each arm. So, I computed the mean difference between both treatment groups, using the mean difference of each arm. Overall, insulin showed a statistically significant greater efficacy in glycaemic control compared to non-insulin GLTs (n=5201, mean difference= -0.20%;

95%CI: -0.28 to -0.11; heterogeneity I^2= 88%; p<0.00001) (Figure 3.4). Tests of interaction showed no significant difference between the trials based on the risk of bias (p= 0.61).

Figure 3.4 shows the comparison between insulin and different drug groups of the non-insulin arm. There was a significant heterogeneity between the subgroups. Tests of interactions showed significant subgroup differences according to the drug groups in the non-insulin arm (I^2 = 84.3%; p = 0.0003). With the GLP-1 analogues, 11 trials, involving 1,796 and 1,821 participants in the insulin and GLP-1RA arms respectively, showed that insulin was associated greater glycaemic efficacy (n=3,617 mean difference= -0.13; 95%CI: -0.21 to -0.05; heterogeneity I^2= 79%; p<0.001) compared to GLP-1 analogues. Only two trials with a total of 247 participants compared the Thiazolidinediones (127) with Insulin (120). The two trials showed no heterogeneity between them (p=0.57). Insulin showed greater glycaemic efficacy compared to the TZDs (n=247, mean difference= -0.17; 95%CI: -0.30 to -0.05; heterogeneity I^2= 0%; p<0.007). Two trials compared the DPP4 inhibitors with insulin. Compared to DPP4 inhibitors, insulin showed greater reduction in HbA1c (n=452, mean difference= -0.52; 95%CI: -0.67 to -0.36; heterogeneity I^2= 34%; p<0.00001). One trial compared biguanides (metformin) to insulin and showed the superiority of insulin in glycaemic control (n=214, mean difference= -0.22; 95%CI: -0.39 to -0.05; p = 0.01).

Proportion achieving a target HbA1c level: Ten trials with a total of 4,107 participants reported the proportion of patients achieving a target HbA1c level. In nine, the target was 7.0% (53mmol/mol) while one[190] had 7.4% (57mmol/mol) as its target. The included trials showed a significant heterogeneity (I^2 = 93%, p <0.00001) but showed no significant difference between insulin and non-insulin groups in achieving a glycaemic control level of ≤ 7.5% (n= 4107; OR= 1.55; 95%CI = 0.92 to 2.62; Heterogeneity I^2 =93%; p=0.10) (Figure 3.5).

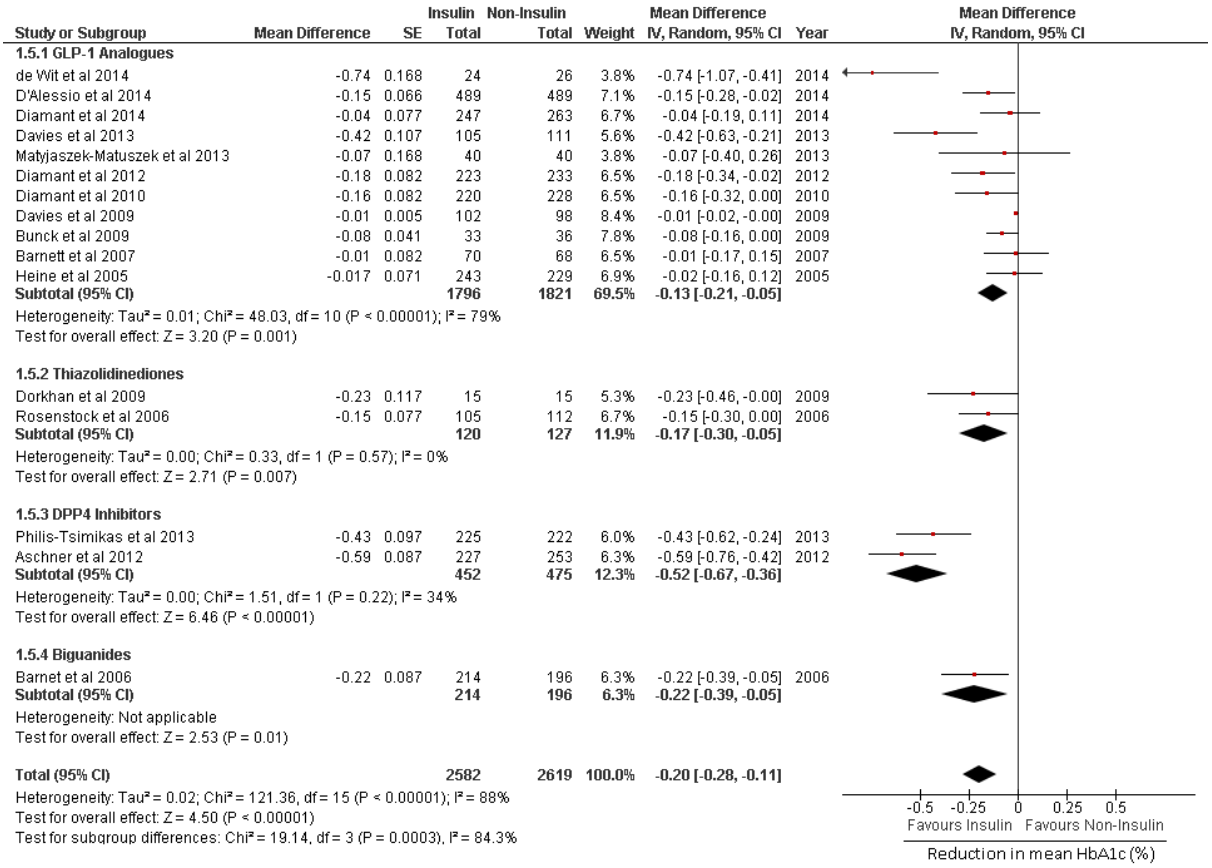


Figure 3.4: Forest plot for the mean change in HbA1c (%) between insulin and non-insulin treatment groups, stratified by the different drug classes of the non-insulin arm.

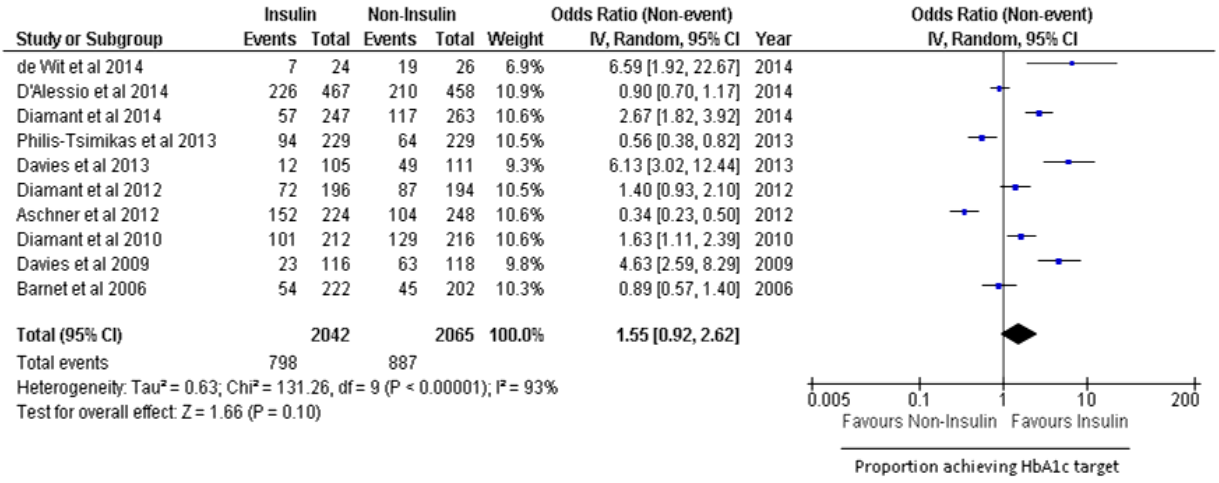


Figure 3.5: Forest plot for the proportion attaining target HbA1c between the treatment groups.

3.4.6. Changes in Weight:

A total of 16 trials with 17,795 participants reported mean changes in weight. One trial[194] reported mean change in BMI and was excluded in this meta-analysis. The non-insulin group had a significant reduction in weight from baseline to the endpoint than the insulin group (n= 17,795; mean diff = -3.41kg; 95%CI: -4.50 to -2.32; Heterogeneity I^2 = 100%; p < 0.0001).

There was a significant interaction between the subgroups of the non-insulin (p < 0.00001). A mean weight reduction of 4.23kg was observed in the GLP-1 analogues compared to insulin (n= 3704, mean diff = -4.23; 95%CI: -4.79 to -3.67; Heterogeneity I^2 = 90%; p < 0.00001). In the only trial involving the TZDs, insulin showed a mean reduction of 1.4kg in weight compared to rosiglitazone (n= 217; mean diff: -1.40; 95% CI: -1.29 to -1.51; p < 0.00001). On the contrary, the DPP4 inhibitors showed a significant reduction in weight (n=927; mean diff = -2.10; 95%CI: -3.31 to -0.89; Heterogeneity I^2 = 100%; p = 0.0007) compared to insulin; while the metformin group showed a mean weight reduction of 0.1kg compared to a mean weight gain of 3kg by the inhaled insulin- Exubera (n= 410; mean diff = -3.14; 95%CI -3.71 to -2.57; p < 0.00001). Finally, the standard care arm of the ORIGIN trial showed a mean weight reduction of 2.10kg compared to the insulin glargine arm (n= 12,537; mean diff: -2.10; 95%CI: -2.11 to -2.09; p < 0.00001 as shown in Figure 3.6.

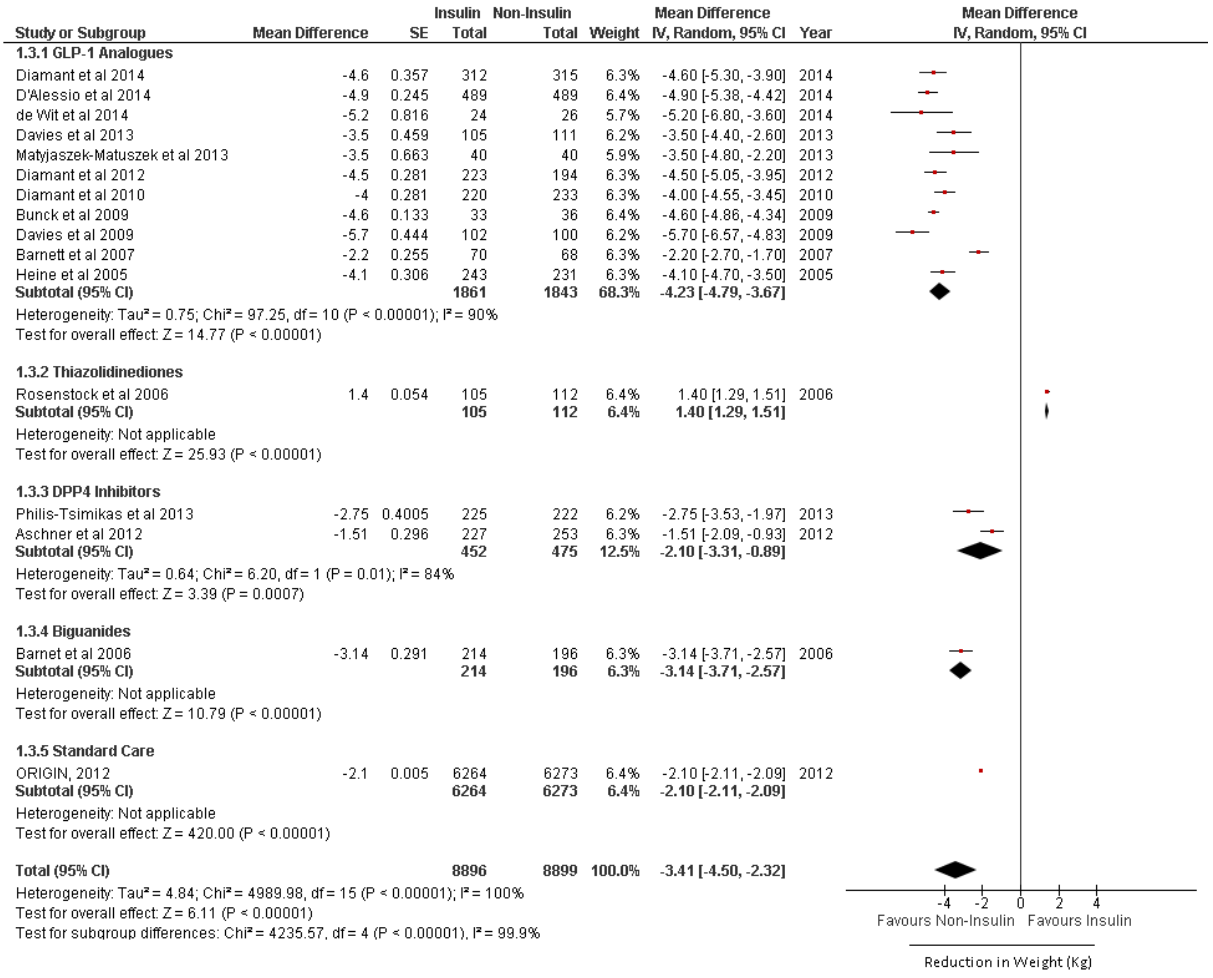


Figure 3.6: Forest plot for the mean change in weight (Kg) between insulin and non-insulin treatment groups, stratified by the different drug classes of the non-insulin arm

3.4.7. Episodes of Hypoglycaemia

The pattern of reporting hypoglycaemia differed among the trials and this made it difficult for the reports of five trials to be included in the meta-analysis. Most trials defined it as an event characterised by simple symptoms as sweating, palpitations, hunger pangs and lethargy irrespective of confirmatory blood glucose less than 4.0mmol/L. For this meta-analysis, I defined severe hypoglycaemia as that which may necessitate assistance from another person;

or associated with recovery after oral carbohydrate, glucagon or glucose administration; or with blood glucose less than 2.0mmol/L.

Figure 3.7 shows the proportion of adverse treatment effect represented by the events of hypoglycaemia as reported in 12 of the trials comprising 16,143 participants. There was almost a two-fold increased risk of hypoglycaemia in the participants on insulin therapy compared to those on non-insulin therapy (RR= 1.90; 95%CI: 1.44 to 2.51; Heterogeneity I^2 = 91%; p = 0.0001).

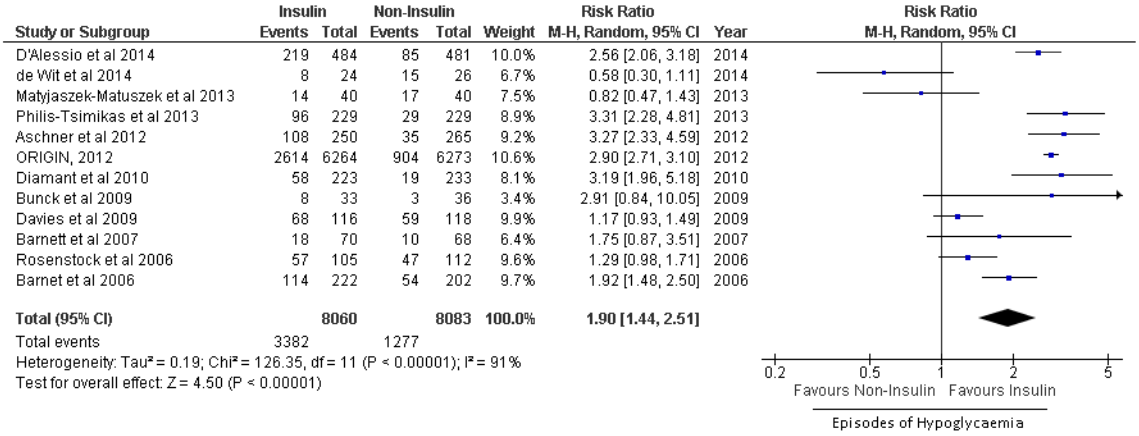


Figure 3.7: Forest plot showing the risk of hypoglycaemia in insulin vs non-insulin treatment groups

3.4.8. Reported Adverse Drug Events:

There were variations in the pattern, proportions, measures and number of adverse events reported in the different trials. These were either reported as the proportion of people with adverse drug-related events, and/or number of reported adverse events. One trial did not report any adverse event.[194] The overall proportion of reported adverse drug-related events was slightly higher in the non-insulin than in the insulin group (54.7% vs 45.3%, p= 0.044)

In the insulin group, the most reported adverse event was nasopharyngitis (21.08%) compared to nausea (42.71%) in the non-insulin group. Other common symptoms associated with insulin groups are headache (13.76%), diarrhoea (8.73%), influenza (6.0%), and cough (5.38%) while nasopharyngitis (17.93%), diarrhoea (16.69%), headache (14.72%), vomiting (12.9%) and gastrointestinal pain (7.87%) were most commonly reported in the non-insulin group (Table 3.3).

Table 3.3: Commonest reported adverse drug events in Insulin vs Non-insulin groups

Adverse Events	Number of Reported Events	
	Insulin, *n (%)*	Non-insulin, *n (%)*
Nasopharygitis	239 (21.08)	246 (17.93)
Influenza	68 (6.00)	68 (4.96)
Mss/Back Pain	51 (4.50)	62 (4.52)
Headache	156 (13.76)	202 (14.72)
Gastrointestinal pain	37 (3.26)	108 (7.87)
Dizziness	18 (1.59)	34 (2.48)
Arthralgia	32 (2.82)	38 (2.77)
Diarrhoea	99 (8.73)	229 (16.69)
Infections-Infestations	62 (5.47)	55 (4.01)
Hypertension/AMI	15 (1.32)	14 (1.02)
Vomiting	36 (3.17)	177 (12.90)
Nausea	60 (5.29)	586 (42.71)
Constipation	25 (2.20)	67 (4.88)
Dyspepsia	19 (1.68)	81 (5.90)
Cough	61 (5.38)	40 (2.92)
Reduced Appetite	12 (1.06)	79 (5.76)
CNS Symptoms	38 (3.35)	29 (2.11)
Injection site reactions	4 (0.35)	64 (4.66)
Total number of events	**1134 (100)**	**1372 (100)**

Only 12 trials with 2414 and 2363 participants in the non-insulin and insulin groups respectively reported the number of those with adverse drug-related events which I included in the meta-analysis (Figure 6). The non-insulin arm had 13 additional people per 100 with

adverse drug-related, compared to the insulin arm (Risk diff = 0.13; 95%CI = 0.05 – 0.21; Heterogeneity I^2 = 91%; p = 0.002). The fixed effect model showed no significant difference between both treatment groups (p= 0.236).

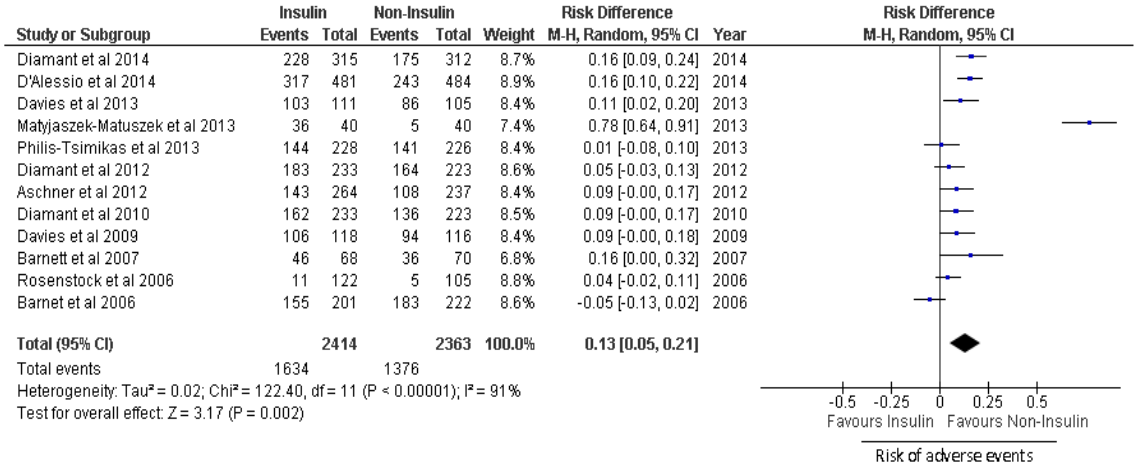


Figure 3.8: Forest plot for the risk of adverse events between the insulin vs non-insulin treatment groups

3.5. Discussion

This meta-analysis involving 18 trials with 19,300 participants compared CV and metabolic outcomes between insulin and non-insulin GLTs in adult patients with type 2 diabetes. Data for meta-analysis for CV outcomes were provided by only 2 trials involving 13,317 participants and showed no difference in the risk of all-cause mortality; cardiovascular deaths, non-fatal MI, non-fatal stroke, heart failure and a composite of these events in the insulin vs non-insulin treatment groups. Insulin showed superior efficacy in glycaemic control; while the non-insulin treatment arm consistently showed a reduction in weight. The risk of hypoglycaemia increased

almost 2-folds with insulin, while adverse events were slightly significantly higher in the non-insulin arm.

All the included trials lasted for more than 24 weeks. All trials had a low-risk of bias and this helped to mitigate the risk of overestimation of benefits and underestimation of risks associated with trials with high risk of bias.[200]

The DIGAMI-2 trial population was drawn from patients with clinically diagnosed diabetes, and established CV risk. I pooled and compared data from only two arms (insulin vs non-insulin GLTs) of the three-arm trial.[185] In the ORIGIN trial,[97] the population comprised both established cases of diabetes; people with impaired fasting plasma glucose and impaired glucose tolerance. Both trials involved patients who were at very high risk of cardiovascular event. Similarly, all the data were used in our analysis with the standard care arm (defined as any GLT apart from insulin glargine, based on the investigators' best judgement and prevailing local guidelines), used as the non-insulin arm of our analysis. Whilst this trial did not report any CV outcome specifically for people with established case of diabetes, I nonetheless used both in our meta-analysis. In addition, the ORIGIN trial's definition of CV deaths was that of exclusion. This implies that our finding should be interpreted with caution. The novel findings of the UKPDS study[34, 49] of the potential cardio-protective effect of insulin but this has not been consistent with other clinical trials and recent observational studies. So, the findings of this study seem to suggest that insulin may have similar cardiovascular effect, compared to other non-insulin GLTs (excluding mainly newer novel GLTs as GLP-1RA, SGLT2i,etc).

Insulin showed better glycaemic control than non-insulin therapy but there was no statistically significant difference between both treatment groups in the proportion of participants achieving the target HbA1c levels (≤ 7.0 or ≤7.4%) ((≤ 53 or ≤57mmol/mol). In a meta-analysis of 5 major trials comparing intensive and standard treatments, a reduction in HbA1c by 0.9% in the

intensive arm resulted in 17% reduction in non-fatal MI and 15% reduction in coronary heart disease but no effect on stroke [103]. The UKPDS study showed a 21% reduction in any diabetes-related endpoint [201] and a meta-analysis showed an 18% increased risk of any CVD per unit rise in HbA1c level [202]. A retrospective observational study using UK primary care database however have shown a U-shaped association between HbA1c level and mortality among insulin users,[37] implying that intensive glycaemic control in itself may also portend the same adverse event that it tries to avert.

In the present study, I also observed that insulin was associated with 2.65kg weight gain compared to the non-insulin group. Insulin-associated weight gain has been described in many studies and this weight gain can be excessive, affecting cardiovascular risk factors.[203-206] Fourteen of our included trials showed that insulin was associated with increase in weight compared to its comparators while in contrast, a single-arm 14-week trial of the PREDICTIVE study, using insulin determir, showed no weight gain in both types 1 and 2 diabetics[207]. This should be interpreted with caution due to the short trial duration, heterogeneity of the population studies and the different measures of outcomes among the participants. Weight gain has been shown to worsen all elements of CV risk profile—dyslipidaemia, hypertension, insulin-resistance and elevated fibrinogen—in a continuous graded fashion[208, 209]. In a vicious cycle, weight-gain associated insulin resistance increases the demand for exogenous insulin which in turn leads to insulin-associated weigh-gain which may further worsens cardiovascular risk and insulin resistance.

This study also showed that insulin is associated with 80% increased risk of hypoglycaemia than the non-insulin comparator group. This is consistent with those of major clinical trials as the ADVANCE, UKPDS, VADT and ACCORD which showed higher (19% up to 3-fold) risks of hypoglycaemia following intensive glycaemic control with insulin and other GLTs.[22, 55, 101,

[210, 211] Hypoglycaemia is a well-known side effect of antihyperglycaemic agents and is associated with sympathetic surge and release of catecholamines with resulting tachycardia, raised BP and other haemodynamic changes which increased risk of an atherosclerotic event.[212] This link is best explained by resultant increased myocardial activity, platelet-aggregation and activity, and haematocrit which can trigger cardiac and ischaemic events in diabetic (high-risk) patients.[93, 213-215] None of the included studies in this meta-analysis, however, compared between insulin vs sulfonylurea, the latter an important glucose lowering therapy which is known to be associated with an increased risk of hypoglycaemia.

I also reported that the risk of other severe and non-severe drug-related adverse events was greater in the non-insulin than insulin arms. This, however, had no significant effect on the rate of drop outs within the individual trials.

3.6. Strength and Limitation

This systematic review and meta-analysis derives its strength mostly from the use of only RCTs, the number of trials (totalling 18) and the large number of participants (19,300) involved (although, only two trials provided data on CV events), which provided enough statistical power to detect any true effect.

The major limitations of this study include (a) short trial duration (which may not have been adequate to fully explore the metabolic outcomes, especially changes in weight and HbA1c) associated with insulin use; (b) High heterogeneity among the included trials. This mirrored the study populations in all the included trials, and limits the applicability of the findings of this study; (c) The exclusion of those with a BMI >35 may limit generalising these results to the obese T2D patients, who even constitute a larger proportion of people on insulin therapy; (d) Most of the included trials were not designed to detect or assess CV events.

Another limitation of this study is inadequate blinding of participants and personnel, leading to the high risk of performance bias; and the non-blinding of assessors except in one trial[192] which led to a high risk of detection bias. As this limitation mirrors that of the included trials, these biases were mitigated by the fact that these outcomes (HbA1c and weight) were objectively assessed. Similarly, the non-standardised format of reporting the adverse events associated with the treatment groups could have led to either under- or over-reporting of events, as well as selective reporting. Other limitations include the variation in the study design between the studies; the broad classification of different classes of GLTs into only two groups despite the variations in their mechanisms of action and effect on known CV risk factors; and the fact that our analysis was limited only to published literature. Finally, most studies failed to adequately explore the impact of some CV risk factors that might predict adverse CV events in the treatment groups.

3.7. Conclusion

Based on the two included CV outcome trials, insulin showed similar risk of adverse CV outcomes with non-insulin GLTs but was associated with superior reduction in HbA1c (which was of limited clinical importance). Also, there was no difference in the proportion of patients achieving HbA1c target between both groups but observed that weight reduction was more in the non-insulin group. There was a 2-fold risk of hypoglycaemia with insulin but adverse events were more common in the non-insulin group. In view of CV outcomes, further studies with well-defined distinct treatment groups in a well-powered clinical trial are needed. This should be in line with the current requirement by international agencies that new antihyperglycaemic agents not only show glucose lowering ability, but also not associated with clinically meaningful increases in cardiovascular events.

Though these findings have implications for clinical practice, they should be interpreted with caution bearing in mind the inherent limitations which this study could not adjust or control. Therefore, individually-tailored holistic treatment strategy should be initiated, weighing the benefits of preventing microvascular complications and the risks of adverse cardiovascular and metabolic outcomes while incorporating lifestyle interventions.[12, 41, 216]

Chapter Four: Premixed vs Basal-bolus Insulin regimen in Type 2 Diabetes: Comparison of clinical outcomes from randomised controlled trials and real-world data.

4.1. Summary

Background and Aim

Evidence from randomised controlled trials (RCTs) does not always reflect what is obtained in routine clinical practice (real-world). The concordance between data derived from randomised controlled trials (RCT) and real-world estimates of HbA1c and weight change after 24 weeks of initiation of a basal-bolus was then compared with a premixed insulin regimen.

Methods

Data were pooled from 8 RCTs after a systematic review examining BB (n = 1893) or Premixed (n = 1517) regimens. Real-world data were extracted from the UK primary care dataset for basal-bolus (n = 7,483) or premix (n=10,744). T-tests were used to compute the mean differences between HbA1c and weight from baseline. Linear regression analyses were used to determine the predictors of this change.

Results

Both insulin regimens were associated with HbA1c reduction (-0.28% [real-world] and -1.4% [RCTs]) and weight gain (+0.27 kg [real-world]; +2.96kg [RCT]) but there were no significant differences between basal-bolus and premix. Discordances in the pattern of treatment response were, however, observed between real-world and RCT data for both insulin regimens. For any

given baseline HbA1c, the change (δ) HbA1c in RCT was greater than in real-world conditions and at any baseline weight above ~60kg, RCT population showed overall weight gain in contrast to slight weight loss in the real-world population. Lastly, for both populations, while greater baseline weight was associated with reduced response to treatment, the association was much steeper for the RCT compared with real-world population. Also, greater baseline weight was associated with more favourable effect on weight outcome following premixed and to a lesser extent with basal-bolus insulin regimen.

Conclusion

These results highlight discrepancies between real-world outcomes versus RCT results with respect to starting basal-bolus (which is lower in real-world) or premix insulin regimens in people with Type 2 Diabetes.

4.2. Introduction

Insulin therapy is essential for people with Type 2 diabetes (T2D), when diet and other glucose lowering therapy options have failed to achieve optimal HbA1c targets.[217] Intensification of insulin therapy has been shown to reduce the risks of long-term vascular complications.[218, 219] Although the basal-bolus and the premixed insulin are the two most widely used insulin regimens in T2D, there is no overall consensus regarding the most effective or optimal insulin regimen for people with diabetes mellitus.[44, 220] The basal-bolus regimen, which consists of multiple daily injections of rapid-acting insulin pre-prandially, in addition to a long-acting basal insulin, most closely mimics the pattern of insulin secretion,[221] but the flexibility of this regimen is, undermined by its complexity to count daily carbohydrate intake and adjust the

insulin dose accordingly[222-224] The premixed insulin regimen consists of a fixed ratio of rapid-acting insulin and intermediate insulin combined; thereby eliminating the need for people to mix or adjust the insulin themselves whilst also reducing the number of required daily injections. Although people may find it easier to adhere to the premixed regimen,[225] regular meal times and consistency in daily routine are sometimes necessary in order to gain maximum benefit and avoid the associated risk of hypoglycaemia.

Evidence from RCTs and meta-analyses have shown heterogeneous outcomes between basal-bolus and premixed insulin regimens.[226-228] As such, the choice of an optimal insulin regimen continues to be debated.[229] Although RCTs meet regulatory and scientific standards, they do not necessarily reflect what happens in real world. So, trial-derived estimates of clinical outcomes when used to underpin guidelines, may present a biased view of the relative outcomes of treatments when used in routine practice. Failing to account for this discrepancy may lead to suboptimal patient outcomes and wasted healthcare resources. I therefore aimed to evaluate the concordance between data derived from RCT and real-world estimates of HbA1c and weight reduction after 24 weeks of initiation of basal-bolus compared with a premixed insulin regimen and assess their interrelationship between clinical characteristics and relevant clinical profiles, as determinants of concordance.

4.3. Methods

Study Design and Data Sources

Data were extracted from two sources- observational data from the UK primary care via The Health Improvement Network (THIN) and RCTs in peoples with T2D.

The search strategy and terms used in the systematic selection of these trials have been fully described in a previous study by our research team.[230] However, I added an additional exclusion criterion in which trials lasting less than 6 months were excluded. These selected eight RCTs[226, 228, 231-236] were randomised, double-bind parallel or crossover designs in which basal-bolus insulin regimen was compared to premix.

In the observational population, I pooled data from the THIN database on all people with T2D who initiated insulin therapy (either basal-bolus or premix). THIN is the UK computerised anonymised longitudinal primary care records with details of over 10.5 million people derived from 532 general practices within the UK, shown to be demographically representative of the dynamics of the UK population.[137] Our research group has previously published diabetes-related outcomes in routine clinical practice using this database.[237, 238]

Exposures and Outcomes

In both populations, the main exposure was insulin regimen- basal-bolus vs premix. The premix (biphasic) regimen intervention was defined as two or more injections of any brand of premixed insulin per day while the basal-bolus regimen was defined as any basal injection with at least a single bolus injection per day. These were specified in details in the treatment protocols of the RCTs, while in the observational data, these prescriptions were identified by their appropriate READ codes in the THIN database. The main outcomes were mean differences in glycaemic control (measured by HbA1c) and weight between the two population groups measured at 6 months and above.

Covariates

For both populations (RCTs and Observational), data on baseline demographics and participants' characteristics were obtained. Also, baseline and 6-month measurements of

HbA1c and body weight were obtained. Other important clinical measures as comorbidity states, medication use and other biochemical variables were obtained in the observational study population.

Statistical Analyses

For both the RCTs and observational data, the difference between HbA1c at baseline and at 6 months (glycaemic control) was computed. Also, the difference in weight at baseline and 6 months will be computed. Generally, descriptive statistics was used to summarise the baseline variables in both population groups. Missing data among the baseline covariates in the real-world data were accounted for with multiple imputations using the chained equation model. Student t-test was used to determine the mean differences in HbA1c and weight between the insulin regimens at baseline and post 24 weeks. Linear regression analyses were conducted to identify the strongest predictors of glycaemic control and weigh change.

All analyses were conducted using Stata Software, version 14 with statistical significance put at a p-level ≤ 0.05.

4.4. Results

4.4.1. Baseline Characteristics

In all populations, there were 21,637 participants with 3,410 in the RCT and 18,227 in the real-world population. Among this, 9,376 received basal-bolus regimen, while 12,261 were on the premixed regimen.

In the observational (THIN) database population group, the overall mean age was 61.5 (SD13.8) years with the mean baseline HbA1c [72mmol/mol (8.7%) vs 72mmol/mol (8.7%)] and weight (90.7kg vs 92.1kg) in the premixed and basal-bolus groups respectively. Other

important baseline variables in this group are summarised in Table 4.1. Weight, age, diastolic BP and comorbidity status differed significantly between both regimens at baseline.

Table 4.1: Baseline Characteristics in real world (THIN Data) population

Baseline variable	Premix Insulin (n = 10,744)	Basal-bolus (n = 7,483)	Total (n = 18,227)	p-value for differences
Demographics				
Age (yrs), Mean (SD)	61.5 (12.7)	61.5 (14.9)	61.5 (13.8)	0.015
Gender, No. (%)				
Male	5717 (53.2)	3978 (53.2)	9,695 (53.2)	0.946
Female	5027 (46.8)	3505 (46.8)	8,532 (46.8)	
Townsend deprivation, No(%)				
Least deprived	2024 (19.8)	1563 (21.7)	3,587 (20.6)	
2nd quintile	1989 (19.4)	1508 (21.0)	3,497 (20.1)	
3rd quintile	2229 (21.8)	1501 (20.9)	3,730 (21.4)	<0.001
4th quintile	2258 (22.0)	1505 (20.9)	3,763 (21.6)	
Most deprived	1742 (17.0)	1117 (15.5)	2,859 (16.4)	
Clinical Covariates, Mean (SD)				
HbA1c (%)	8.7 (1.8)	8.7 (1.9)	8.6 (1.8)	0.903
BMI (kg/m2)	32.5 (6.8)	32.6 (6.9)	32.4 (6.9)	0.082
Weight (Kg)	90.7 (18.5)	92.1(19.1)	90.8 (18.7)	<0.0001
Height (m)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	<0.0001
SBP (mmHg)	136.4 (23.0)	136.2 (23.2)	136.4 (24.3)	0.122
DBP (mmHg)	76.5 (10.7)	75.6 (10.9)	75.9 (10.9)	<0.0001
TC (mmol/l)	4.5 (1.3)	4.5 (1.3)	4.5 (1.3)	0.370
HDL (mmol/l)	1.2 (0.5)	1.2 (0.5)	1.2 (0.4)	0.002
LDL (mmol/l)	2.4 (1.1)	2.4 (1.1)	2.4 (1.01)	0.084
Triglyceride (mmol/L)	2.1 (1.2)	2.0 (1.2)	2.0 (1.2)	0.188
Albumin (g/L)	4.0 (0.4)	4.1 (0.4)	4.0 (0.4)	0.012
eGFR (mls/min/1.73m^2)	62.3 (21.0)	63.8 (21.5)	62.8 (21.8)	<0.0001
ACR (mg/mol)	5.8 (8.4)	5.9 (8.6)	5.8 (8.5)	0.830
Diabetes duration (yrs)	3.9 (6.7)	4.8 (5.7)	4.3 (4.9)	<0.0001
Smoking status, No. (%)				
Non-smoker	5179 (48.2)	3682 (49.2)	8,809 (48.3)	
Current smoker	1498 (13.9)	1127 (15.1)	2,625 (14.4)	0.011
Ex-smoker	4067 (37.9)	2674 (35.7)	6,793 (37.3)	
Alcohol status, No. (%)				
Non-drinker	3667 (34.1)	2249 (30.1)	5,916 (32.5)	
Current drinker	5840 (54.4)	4403 (58.8)	10,243 (56.2)	<0.001
Ex-drinker	1237 (10.5)	831 (11.1)	2,068 (11.3)	
BMI Categories, No. (%)				
≤ 24.9kg/m^2	1451 (13.5)	1004 (13.4)	2,455 (13.5)	
25-29.9kg/m^2	2587 (24.1)	1756 (23.5)	4,343 (23.8)	0.588
≥ 30kg/m^2	6706 (62.4)	4723 (63.1)	11,429 (62.7)	
Other GLTs, No. (%)				
Metformin	9045 (84.2)	6548 (87.5)	15,593 (85.6)	<0.001
Sulphonylurea	8004 (74.5)	5790 (77.4)	13,794 (75.7)	<0.001
Thiazolidinedione	3009 (28.0)	2745 (36.7)	5,754 (31.6)	<0.001
GLP-1ar	1034 (9.6)	909 (1.2)	1943 (10.7)	<0.001
SGLT2	50 (0.5)	35 (0.5)	85 (0.5)	0.982
Glinides	422 (3.9)	368 (4.9)	790 (4.3)	0.001
DPP4i	1137 (10.6)	1432 (19.1)	2569 (14.1)	<0.001
Use of Medications, No. (%)				
Aspirin	10,647 (99.1)	7430 (99.3)	18,077 (99.2)	0.527
Antihypertensive	9684 (92.6)	6252 (88.6)	15,936 (91.0)	<0.001
LLT	9588 (91.7)	6388 (90.5)	15,976 (91.2)	0.005
Comorbidities, No. (%) [c]				
MI	472 (4.4)	227 (3.0)	699 (3.8)	<0.001
CHD	3665 (34.1)	1795 (24.0)	5,460 (30.0)	<0.001

PAD	1649 (15.4)	759 (10.1)	2,408 (13.2)	<0.001
Heart Failure	1689 (15.7)	768 (10.3)	2,457 (13.5)	<0.001
Hypoglycaemia	2256 (21.0)	929 (12.4)	3,185 (17.5)	<0.001
CVA	1766 (16.4)	972 (13.0)	2,738 (15.0)	<0.001

Abbreviations: MET (metformin); SU (sulphonylurea); GLP-1RA (Glucagon-like peptide 1 receptor analogues); INS (insulin); BMI (body mass index); SBP (systolic blood pressure); DBP (diastolic blood pressure); HbA1c (haemoglobin A1c); HDL (high-density lipoprotein); LDL (low-density lipoprotein); TC (total cholesterol); GFR (glomerular filtration rate); LLT (lipid lowering therapy); PAD (peripheral arterial disease); CHD (coronary heart disease); ACR (albumin creatinine ratio); SD (standard deviation)
Diabetes duration is time from first diagnosis of diabetes to date of commencement of insulin

In the population of the 8 RCTs [9, 10, 15 -20], the mean HbA1c and weight were [74mmol/mol (8.9%) vs 74mmol/mol (8.9%)] and (85.6kg vs 85.6kg) in the basal-bolus and premixed insulin regimens respectively. Other important baseline variables are summarised in Table 4.2 below.

Table 4.2: Summary of baseline characteristics of the Randomised Clinical Trials

Study	Baseline HbA1c mmol/mol[%]		HbA1c at ≥24wks mmol/mol[%]		Baseline Weight (kg)		Weight (kg) at ≥24wks		Age (yrs)		Diabetes duration (yrs)		Total number (N = 3410)	
	Basal	Premix	Basal	Premix	Basal	Premix	Basal	Premix	Basal	Premix	Basal	Premix	Basal	Premix
Bowering et al, 2012	75 [9]	74 [8.9]	56 [7.3]	54 [7.1]	72.8	73.8	75.7	76.6	56.7	56.3	10	10.6	214	212
Fritsche et al, 2010	70 [8.6]	69 [8.5]	56 [7.3]	61[7.7]	87	84.3	90.6	86.5	60.9	60.2	12.8	12.5	153	153
Hirao et al, 2008	90 [10.4]	88 [10.2]	62 [7.8]	60 [7.6]	62.5	62.1	NR*	NR	58.5	57.9	12.2	9.5	80	80
Jain et al, 2010	78 [9.3]	80 [9.5]	58 [7.5]	60 [7.6]	78.8	78.2	82	81.3	58.9	59.9	12	11.4	242	242
Levin et al, 2011	78 [9.3]	79 [9.4]	53 [7.0]	55 [7.2]	102.6	103.5	108.9	106.6	55.9	56.4	13.1	12.9	106	91
Liebl et al, 2009	69 [8.5]	68 [8.4]	53 [7.0]	55 [7.2]	NR	NR	NR	NR	61.7	60.3	9.4	8.9	541	178
Miser et al, 2010 (Arm A)	64 [8.0]	64 [8.0]	65 [8.1]	64 [8.0]	89.3	90.1	92.2	91.5	55.9	58.2	9.3	8.9	199	200
(Arm B)	64 [8.0]	64 [8.0]	66 [8.2]	66 [8.2]	91.9	93.6	94.2	92.8	55.4	54.5	9.6	10	171	174
Rosenstock et al, 2008	74 [8.9]	73 [8.8]	51[6.8]	53 [7.0]	99.8	99.1	104.3	103.1	55.4	54	11.2	10.9	187	187
Mean Total	**74 [8.9]**	**74 [8.9]**	**57 [7.4]**	**58 [7.5]**	**85.6**	**85.6**	**92.6**	**91.2**	**57.7**	**57.5**	**11.1**	**10.6**	**1893**	**1517**

NR = Not reported
N = total number of all trial participants in these trials
Diabetes duration is the duration of diabetes as at the commencement of the trial

4.4.2. Change in HbA1c

In the real-world (THIN) database, there was a significant reduction from the baseline HbA1c of 70mmol/mol (8.6%) to 67mmol/mol (8.3%) (mean diff = -0.28%; 95%CI: -0.30, – 0.27; p < 0.0001) after 6 months. Both the premixed (70mmol/mol (8.6%) vs 68mmol/mol (8.4%), mean diff: 0.25; 95%CI: -0.28, –0.23; p <0.0001) and basal-bolus (70mmol/mol (8.6%) vs 67mmol/mol (8.3%); mean diff: 0.33; 95%CI: -0.3, 0.3; p <0.0001) insulin regimens showed reductions at 6 months (Figure 4.1). However, glycaemic control was better in the basal-bolus (mean diff = -0.08%; 95%CI: -0.11, -0.04; p = 0.001).

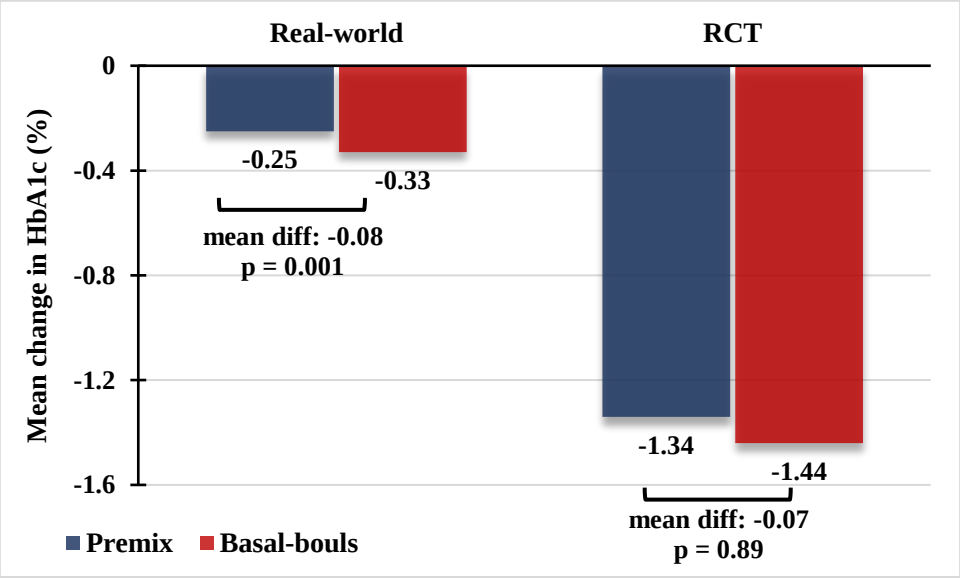


Figure 4.1: Mean changes in HbA1c (%) between premix and basal-bolus Insulin regimens in RCT vs Real-world data (Real-world data: adjusted for age, gender, diabetes duration, weight and SBP)

Similarly, the RCT population reported a significant improvement in glycaemic control, with a mean reduction in HbA1c of 1.4% (95% CI: –1.87, -0.92; p<0.0001) at 6 months from baseline. There was a significant reduction in HbA1c at 6 months 74mmol/mol (8.9%) vs 58mmol/mol (7.5%); mean diff: 1.34%; 95%CI: –2.09, -0.6; p = 0.003) in the premixed group; as was in the basal-bolus regimen 74mmol/mol (8.9%) vs 57mmol/mol (7.4%); mean diff: -

1.44%; 95%CI: –2.20, -0.69; p = 0.0023). No significant difference in glycaemic control was observed between the two insulin regimens after adjustment for age and baseline weight, (mean diff: -0.07%; 95%CI: -1.10, -1.25; p = 0.892) (Figure 4.1).

4.4.3. Change in Weight (Kg)

Overall, there was a significant increase in weight after 6 months in the THIN population (mean diff: 0.27; 95%CI: 0.18, 0.35; p < 0.0001). This represented an increase of 0.31kg (95%CI: 0.20, 0.42; p < 0.0001) in the premix arm vs 0.21kg (95%CI: 0.07, 0.34; p = 0.002) in the basal-bolus arm. Nonetheless, no significant difference in weight gain was recorded between these two (premixed vs basal-bolus) regimens at 6 months (mean diff: 0.11kg; 95%CI: -0.07, 0.28; p = 0.222).

Figure 4.2 shows that the RCT population recorded a significant increase in weight from 88.9kg at baseline to 91.9kg at 6 months (mean diff = 2.96kg; 95%CI: 2.05 – 3.88; p < 0.0001). In the premixed group, there was an increase in weight from 88.9kg to 91.2kg (mean diff: 2.26kg; 95%CI: 0.80, 3.71; p = 0.009) while the basal-bolus group had a greater increase of 88.8kg to 92.6kg (mean diff: 3.67; 95%CI: 2.43 – 4.92; p = 0.0004). In spite of these, there was no significant difference between the changes recorded between the insulin regimens - premixed (2.26kg) vs basal-bolus (3.67kg) at 6 months (mean diff: -1.41kg; 95%CI: -3.12, 0.29; p = 0.096).

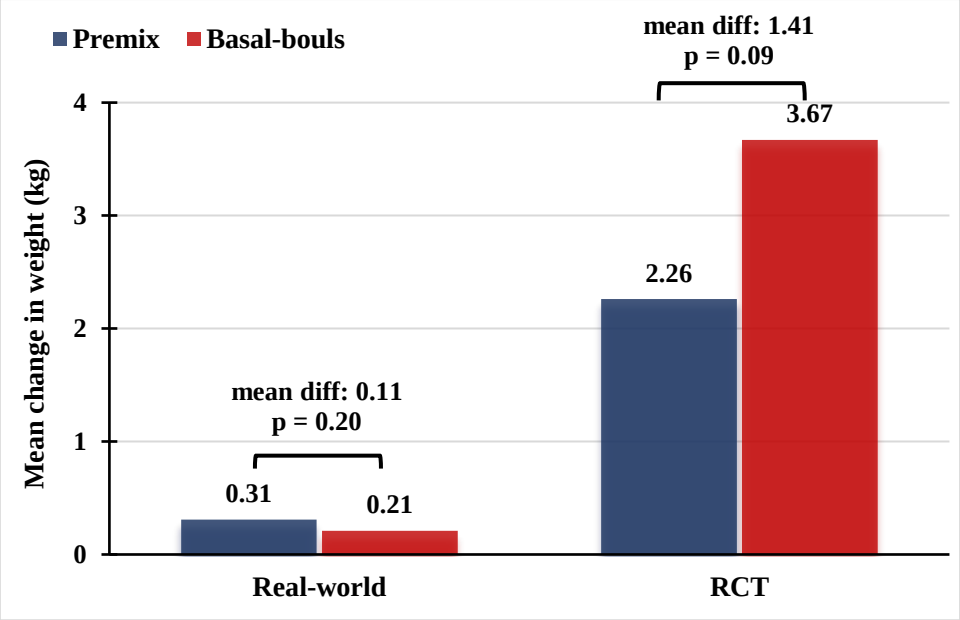


Figure 4.2: Mean changes in weight between premix and basal-bolus insulin regimens in RCT vs Real-world data. (Real-world data: adjusted for age, gender, diabetes duration, HbA1c and SBP)

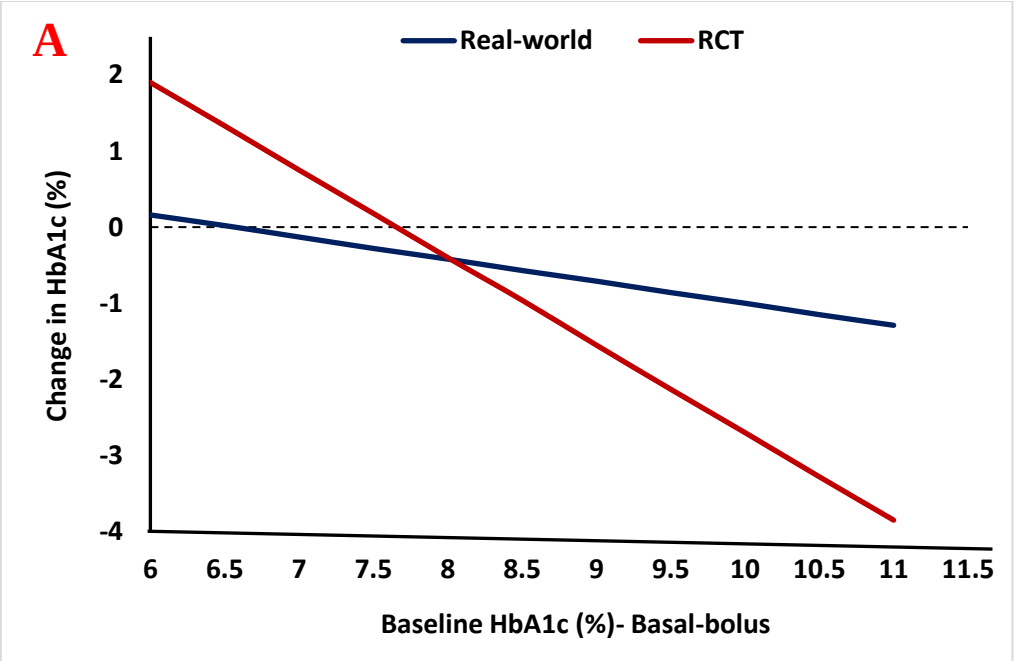
4.4.4. Predictors of response at baseline

In the THIN data population, there was a weak correlation between baseline HbA1c and response to treatment (δ HbA1c) because 20% of the variability in the change in HbA1c in this group was attributable to the HbA1c at baseline ($r^2 = 0.20$; slope = −0.30; 95% CI −0.31, −0.2; $p < 0.0001$). There was a very little correlation due to age (slope = −0.004; $p < 0.001$), gender (slope = −0.05; $p = 0.019$), and duration of diabetes (slope = −0.003; $p = 0.031$). In contrast, in the RCT population, there was a strong correlation between baseline HbA1c and δ HbA1c. 88% of this variability in δ HbA1c was attributable to the HbA1c at baseline ($r^2 = 0.88$; slope = −1.43; 95% CI −1.77, −1.08; $p < 0.0001$). There was a non-significant correlation with age (slope = 0.04; p=0.941) and weight (slope = −0.02; $p = 0.069$).

a. HbA1c reduction as a function of baseline HbA1c in premixed vs basal-bolus regimen

In Figures 4.3A and B, comparison is made between these two insulin regimens in real-world and RCT conditions. These showed similar patterns of response to treatment as a function of baseline HbA1c i.e. greater response to treatment with higher baseline HbA1c values but steeper in the RCT population for both regimens. At baseline HbA1c values of 64mmol/mol (8.0%) and 62mmol/mol (7.8%), both populations showed no change in HbA1c at 6 months, but below these, both populations reported an increase in HbA1c value at 6months, this being greater too in the RCT population. This same pattern was observed for basal-bolus.

Thus for any given baseline HbA1c for both insulin regimens, the δ HbA1c in RCT was greater than in real-world conditions. No interaction with study populations was observed (RCT vs THIN, coefficient = 0.003, p = 0.965).



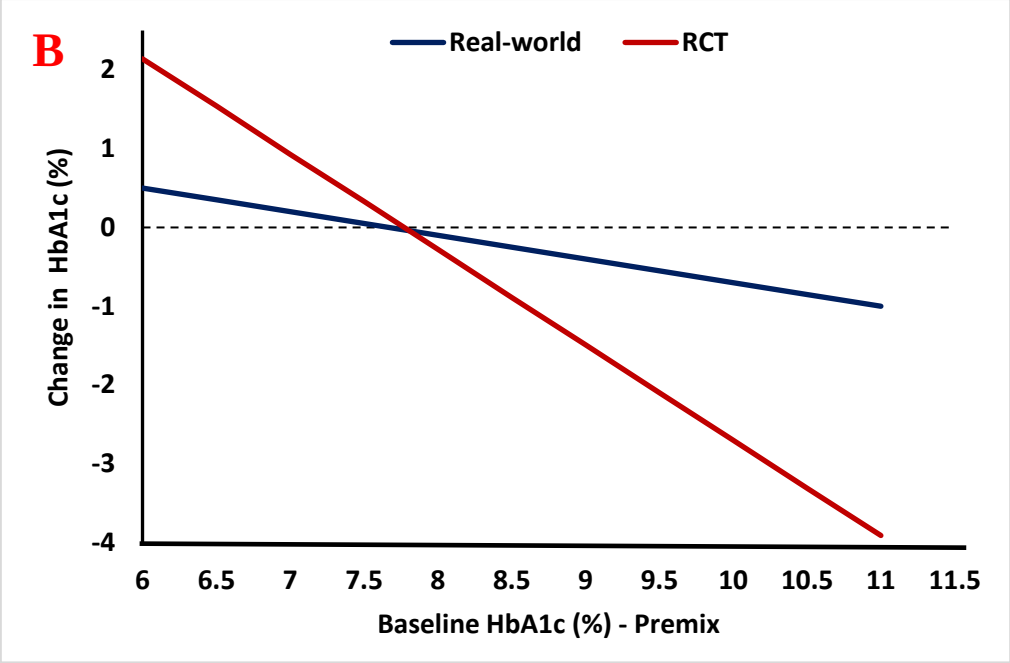


Figure 4.*3:* **A and B – Glycaemic Control: Basal-bolus vs Premix in RCT vs Real-World**

Figures 4.3 A and B show graphs depicting glycaemic control (measured by change in HbA1c) as a function of baseline HbA1c in type 2 diabetes population on insulin therapy after 24weeks and above. Comparison is made between the real world (THIN data) and the RCT populations in people on basal-bolus (A) and premix (B) insulin regimen. The interaction coefficient is, for (A) -0.30, $p<0.0001$; and (B) −1.43, $p<0.0001$.

b. Weight-Change as a function of Baseline Weight in premixed vs basal-bolus regimen

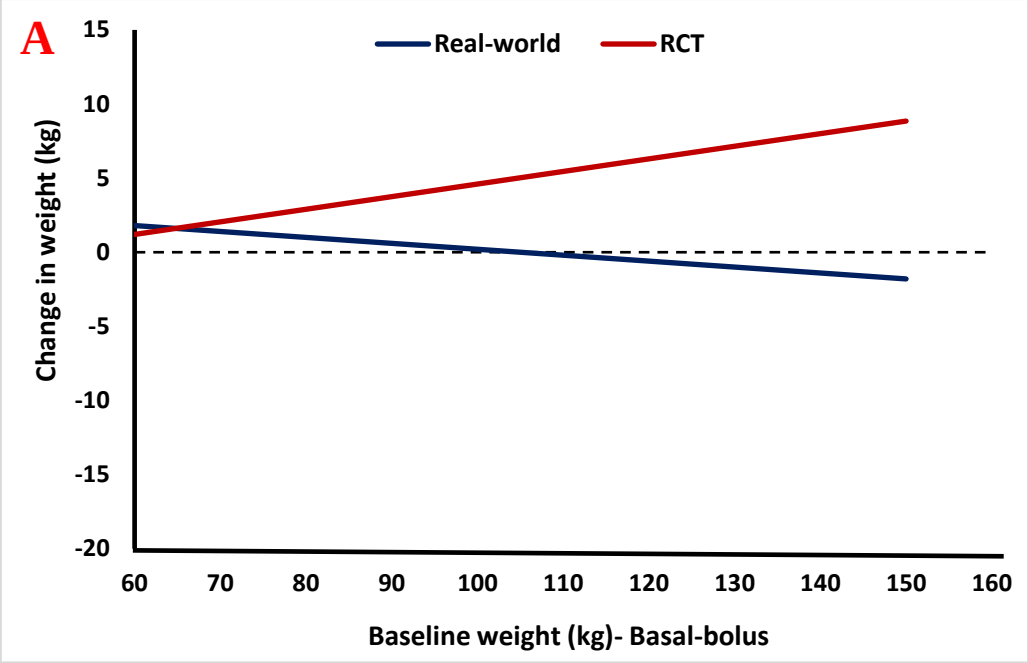
For changes in weight according to baseline weight, different response patterns were observed between different insulin regimens (Figures 4.4 A and B) in the RCT population. In the real-world population, there was a very weak correlation between baseline weight and weight after 6 months. 2% of the variability in weight change was attributable to the weight at baseline (r^2 = 0.02; slope = −0.049; 95% CI −0.05, −0.04; $p < 0.0001$). This was independent of gender, age, and duration of diabetes. In the RCT population, there was a slightly higher non-significant correlation between baseline weight and weight-change at 6 month as it shows that 49% the

variability in weight change was attributable to the weight at baseline (r^2 = 0.49; slope = 0.06; 95% CI −0.04, 0.15; p=0.204), independent of age (slope = 0.07; p = 0.74).

The premixed group showed a slight negative correlation in real-world (r^2=0.03; slope = −0.05; 95% CI −0.06, −0.04; p < 0.0001), i.e. those with a baseline weight of more than 100kg experienced weight reduction, while those below 100kg at baseline, experienced weight-gain at 6 months (Figure 4.4) but in the RCT population, this association was almost unity, i.e. no change in weight at 6 months irrespective of baseline weight.

For the basal-bolus treatment group, real world population showed a weak negative correlation (r^2 = 0.02; slope = −0.05; 95% CI −0.05, −0.04; p < 0.0001): slight weight reduction as baseline weight increases. Conversely, the RCT group showed a positive correlation (r^2 = 0.45; slope = 0.09; 95% CI −0.02, −0.19; p = 0.098), i.e. more weight-gain at 6 months as baseline weight increases.

Taken together, within the two populations, at any baseline weight above 60kg, while the RCT group showed a weight gain, the real-world group observed a slight reduction in weight.



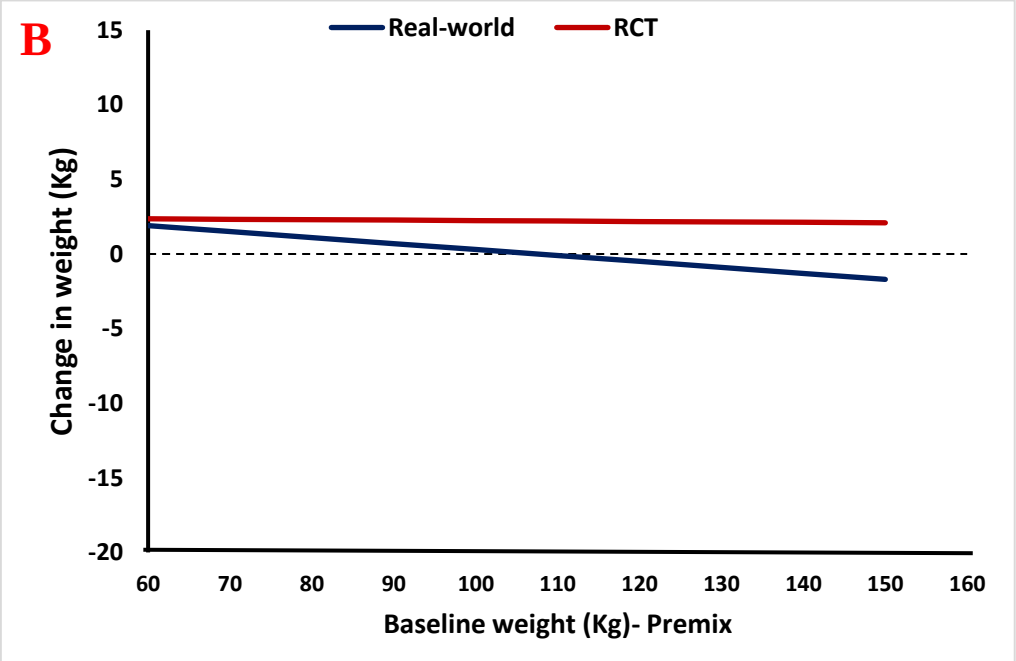


Figure 4.*4*: A and B - Weight-Change: Basal-bolus vs Premix in RCT vs Real-world

Figures 4.4 A and B show graphs depicting change in weight as a function of baseline weight (kg) in type 2 diabetes population on insulin therapy after 24weeks and above. Comparison is made between the real world (THIN data) and the RCT populations in people on premix (A) and basal-bolus (B) insulin regimen. The interaction coefficient is, for (A) −0.049, $p<0.0001$; and (B) 0.06, $p=0.204$).

c. HbA1c change as a function of Baseline Weight in premixed vs basal-bolus regimen

The change in HbA1c as a function of baseline weight for premixed and basal-bolus insulin regimens, showed that for both real world and RCT populations, greater baseline weight was associated with reduced response to treatment. However, the association was much steeper for the RCT compared with real world population. Furthermore, for the premixed population, for any baseline weight, response to treatment was greater in the RCT population compared with real world conditions up until weight of approximately 110kg, above which, response to treatment was greater for real world populations. Similarly, for the basal-bolus insulin regimen, for any baseline weight, response to treatment was greater in the RCT population compared with real world conditions up until weight of approximately 110kg, above which, response to treatment was greater for real world populations up until 140kg weight, above which, response to treatment was slightly greater for real world populations

4.5. Discussion

This analysis compared the relative HbA1c and weight outcomes of premixed insulin regimen or the basal-bolus insulin regimen in people with T2D in RCT vs in real-world conditions. Despite the significant difference in HbA1c found with basal-bolus in this study, its clinical significance is unclear and no difference in HbA1c and weight was noted between insulin regimens for both real-world and RCT populations at 6months. Discordance in the pattern of treatment response was however observed between the populations for both insulin regimens. While the present analysis confirms the expected relationship between baseline HbA1c and HbA1c reduction with either a premixed or a basal-bolus insulin regimen, the strength of this relationship was considerably more apparent in the RCT population compared with real world conditions. I observed a negative association between weight-change at 6months and baseline

weight among people receiving a premixed insulin regimen in both real-world and RCT populations, i.e. as baseline weight increases, the weights in these populations at 6 months slightly reduced, and more marked in the real-world populations. However, for people receiving a basal-bolus insulin regimen, discordance in response was observed between real world and RCT populations, i.e. a negative association (reduction in weight at 6months as baseline weight increases) in real-world but a positive association (increase in weight at 6months as baseline weight increases) in the RCT population. Lastly, for both premixed and basal-bolus insulin regimen, the expected relationship between baseline weight and response to insulin treatment was mainly apparent under RCT conditions.

The cause of the discrepancies in the HbA1c and weight response with premixed insulin or a basal-bolus insulin regimen in real world conditions compared with RCT is not clear. However, insulin regimen is associated with hypoglycaemia and weight gain,[227, 239, 240] with the latter often occurring only during the first months following insulin initiation; and an important difference between the premixed and the basal-bolus insulin regimen is that the latter can be more demanding due to increased frequency of insulin injections and dose adjustments. Thus, it is tempting to speculate that the any discrepancies between real world and RCT is borne out of fear of hypoglycaemia, especially in the basal-bolus insulin regimen,[227, 239] fear of weight gain,[240] reduced compliance with a basal-bolus insulin regimen or people's ambivalence to up-titrate insulin doses under real-world conditions due to lack of monitoring, patient education, or lack of rigid guidelines or protocols for participants to follow.[241] Fear of hypoglycaemia in real-world for example may explain the less apparent association between baseline HbA1c and response to treatment in real world conditions compared with RCT for both insulin regimens. Other likely possible explanations include the relatively younger age of the RCT population; and the higher rate of comorbidities and selection bias in the real-world population.

My observations that greater baseline weight was associated with more favourable effect on weight outcome following premixed and to a lesser extent with basal-bolus insulin regimen should provide important reassurance that in routine clinical practice, meaningful reduction in HbA1c can be achieved without significant detrimental effect on weight. This observation was supported by findings from two other studies.[242, 243] In one study involving 155,917 people who were recently initiated in insulin, Paul and colleagues reported that obese people gain significantly less weight with insulin and that progressive reduction in body weight gain was observed with progressive increases in baseline BMI above 30 kg/m^2 which may be due to the use of less intensive insulin therapy.[242] In another study, Balkau and colleagues reported significant inverse association of baseline BMI with weight gain in a cohort of 2,179 people with about nine years of median diabetes duration.[243] Interestingly, the converse relationship between baseline weight and weight change was observed in our RCT cohort who received a basal-bolus, but not the premixed insulin regimen. This implies an increase propensity to weight gain with basal-bolus insulin regimen compared with premixed insulin in an RCT setting, supported by our findings from a systematic review and meta-analysis comparing basal-bolus and the premixed insulin.[178, 244] In addition, the 4-T study reported that mean weight gain was higher in the prandial group than in either the biphasic group or the basal group.[178]

4.6. Limitations

This analysis is subject to some limitations inherent to observational studies, including potential confounders such as compliance, indication bias, effects on ethnicity and differences in insulin regimens or titration protocols used across different areas in the UK. I attempted to minimize this by restricting the analysis only to people who initiated a specific insulin regimen Importantly, I do not have robust information on hypoglycaemic events that may limit the

success of a given therapy, patient education programme, use and frequency of glucose self-monitoring, frequency of insulin dose adjustment, and rules for self-adjustment of insulin dose or adjustment by feeling which have been shown to be important confounders.[178, 223, 245]

With regards to the analysis of the RCT data, the previous meta-analysis of our research group in this area showed substantial heterogeneity was found in the meta-analysis on HbA1c change. This may be attributed to a number of confounding factors such as: poor study quality, small treatment groups, short study duration and different study designs. Lastly, I pooled trials and real-world data using regular and analogue insulin because previous meta-analysis suggests similar HbA1c outcomes between the two types.[241] Despite these limitations, it is important to note that the emphasis of this study is a pragmatic approach to decision making for initiation of insulin among people who require insulin soon after diagnosis of diabetes in 'real world' clinical practice based on variables that are available to clinicians and to compare this with outcomes derived from RCT.

4.7. Conclusion

In summary, this work showed that there is discordance in the pattern and magnitude of treatment response observed between real world and RCT populations between the two insulin regimens. The 'blunting' of the expected relationship between baseline HbA1c and the response to treatment with either a premixed or a basal-bolus insulin regimen in real world and the reverse association between weight change and baseline weight among people receiving the two insulin regimens between real world and RCT populations, emphasised the importance of people factors that would determine the potential success of one insulin regimen compared to another. Choice of insulin regimen should therefore be individualised according to peoples' personal, social and clinical characteristics.

Chapter Five: Metabolic Profile of Insulin users and association with Cardiovascular and Metabolic Outcomes

5.1. Overview

This chapter comprises 2 related studies which explored the metabolic profile of insulin users and their association with CV events and metabolic outcomes. Study One looked at the relationship between baseline obesity and glycaemic control and CV events; while Study Two examined the association between insulin-induced weight-change and CV mortality and the impact of this weight-change on glycaemic control after one year of insulin initiation.

In reporting Study Two, the introduction, methods and discussion sections will be discussed under the same heading while the result section was split into two parts – Objective 1 and 2 for clarity.

5.2. Study 1 – Effect of baseline obesity on metabolic outcomes and major adverse cardiovascular events following initiation of insulin therapy

5.2.1. Summary

Aim

Obesity is a known major risk factor for type 2 diabetes (T2D) and cardiovascular (CV) diseases. Little is known if obesity could have long term adverse metabolic and CV outcomes in insulin initiators.

Methods

A retrospective cohort study of 12,725 insulin initiators with T2D with data derived from the UK General Practices (The Health Improvement Network (THIN)) database. Multivariate repeated-measures linear and logistic regression analyses were used to estimate the 5-year metabolic outcomes of glycaemic control, and changes in weight and BMI while Cox proportional hazard models were fitted to estimate the 5-year risk of CV events and mortality between the baseline BMI categories: normal (1,665); overweight (3,022); obese class I (3,712); obese class II (2,637); and obese class III (1,689).

Results

The mean age was 58.6±13.8 years. There was a significant trend in reduction of the proportion of patients achieving the HbA1c targets across the BMI categories – reducing by 8% (aOR: 0.92; 95%CI: 0.89-0.95 p-value for trend <0.001) at 6 months; and 6% (aOR: 0.94; 95%CI: 0.91-0.97; p for trend = 0.0001) at 12 months. There was a total of 1,095 3-point composite events of all-cause mortality, non-fatal stroke and MI thus: normal (143), overweight (284),

obese class I (320), obese class II (201) and obese class III (147) with a 10% higher risk of MACE (aHR: 1.10; 95%CI: 0.90-1.35) in the overweight, 5% (aHR: 1.05; 95%CI: 0.86-1.29) in obese class I; 3% (aHR: 1.03; 95%CI: 0.83-1.29) in obese class II; and 30% (aHR: 1.30; 95%CI: 1.02-1.66) in the obese class III BMI categories.

Conclusion

Among patients with T2D started on insulin therapy, obesity at baseline does not influence glycaemic control beyond 24 months, but is associated with a decrease in weight and BMI compared to non-obese groups. However, morbidly obese patients initiating insulin have 30% increased risk of composite CV events after 5 years.

5.2.2. Introduction

The global burden of obesity is on a steep rise and in the UK, is estimated to affect 1 in every 4 adults. Nearly 1 out of 3 children between the ages of 2 to 15 years are obese and this tide is expected to rise in the next 2 decades, leaving UK with 26 million people at risk. Obesity is a known major risk factor for the development of type 2 diabetes (T2D)[246, 247] and adverse cardiovascular (CV) events including mortality.[248] Consequently, this group constitutes a significant proportion of people presenting with new onset diabetes or already living with T2D.

The therapeutic management of T2D aims at maintaining good glycaemic control in order to minimise cardiovascular and macrovascular complications. The NICE guideline emphasises the importance of individualised targeted treatment to achieve these goals.[41] In the obese population, balancing the appropriate choice of therapy with the unintended effects presents a dilemma. In spite of the controversies around the possible association of insulin therapy with adverse CV outcomes, insulin therapy is well known for its ability to maintain good glycaemic

control and association with weight gain.[249] In the United Kingdom Prospective Diabetes Study (UKPDS), patients in the intensive intervention cohort were observed to gain approximately 5 kg during the 10-year follow-up period, with most of this gain occurring in the first 12 months.[22] Our research team has also shown in routine clinical practice, the effectiveness of insulin therapy to lower HbA1c levels appears to be dependent on patients' baseline weight.[229, 250] I speculated that this could be due to insulin-induced weight gain resulting in an increase in the amount of insulin required to control hyperglycaemia[179, 251] at the expense of further weight gain, possible poor treatment compliance and increased insulin resistance.

Furthermore, despite the well-recognised correlation between obesity, exogenous hyperinsulinaemia and cardiovascular (CV) disease,[252] there is little direct evidence relating to the impact of baseline obesity mortality on outcomes following insulin initiation in routine clinical practice. However, there is indirect evidence that weight gain does adversely affect CV risk. The ACCORD study designed to investigate whether an aggressive therapeutic strategy to achieve tight glucose target (HbA1c <6.5%) would reduce CV events surprisingly resulted in an increased mortality in the intensively treated group. The mean BMI of patients in the study was 32.2 and weight gain by more than 10kg occurred in 27.8% of the intensively treated patients compared with 14.1% in the standard therapy.

While no causal relationship between obesity and adverse CV outcomes can be assumed, retrospective studies have shown that people with diabetes who actively lose weight improve not only their risk profile[253-255] but also survival rate.[254] Previous similar studies which focused on the association between obesity at insulin initiation were limited by either by their choice of patients (as in the UKPDS which used predominantly obese patients);[22] or study population size;[249] or the exclusion of younger patients with T2D, short follow up period, or failure to adjust for important risk factors associated with obesity.[256]

To our knowledge, no real-world study has explored the long-term effects of obesity at insulin initiation on metabolic and CV outcomes. So, I aimed therefore to investigate the association between obesity, metabolic outcomes (HbA1c and weight), CV events and mortality in patients with T2D who initiated insulin therapy.

5.2.3. Methods

5.2.3.1. Study Design and Data Source

This was a retrospective cohort study using data derived from the UK anonymised longitudinal electronic Primary Care data called The Health Improvement Network (THIN). This database has been described in Chapter 2.

5.2.3.2. Selection Criteria and Study Population

The patient cohort was selected from the database based on the following criteria at insulin initiation (index date):

1. Age ≥ 18 years
2. Records of diagnosis of T2DM (identified by their appropriate ICD-10 codes) made a minimum of 180 days before index date.
3. Continuous prescription of insulin beyond 180 days after index date

Patients with identifiable ICD-10 codes for type 1 diabetes, gestational or other forms of diabetes, or with no identifiable continuous insulin prescription in their records were excluded.

5.2.3.3. Study Exposure and Outcomes

The main exposure was the baseline BMI [computed by the formula: weight (kg) / (height (m) x height (m))]. This was assessed from 0 to 90 days before the index date. BMI was classified thus: normal (BMI ≤ 24.9kg/m^2), overweight (BMI: 25.0 - 29.9kg/m^2), obese/obese class I

(BMI: 30.0 – 34.9kg/m^2), clinically obese/obese class II (BMI: 35.0 – 39.9kg/m^2) and morbidly obese/obese class III (BMI: ≥40.0kg/m^2).

The primary outcomes were

1. Changes in HbA1c, weight and BMI from baseline to 6, 12, 24, 36, 48 and 60 months post index date; and
2. Proportion of patients achieving a target HbA1c of ≤ 7.5% at these time intervals.

All these were stratified by BMI at index date. Post-index date HbA1c, weight and BMI values were assessed at 6 months and later at yearly intervals till a maximum of 5 years after index date. Where more than one recording of a variable was noted within each time interval, the mean value was computed and recorded for that review date.

The secondary outcome was the risk of a three-point composite of Major Adverse Cardiovascular Events (MACE), comprising non-fatal myocardial infarction (MI), non-fatal stroke and all-cause mortality between the baseline BMI categories. In estimating this risk, patients were followed up from the point of insulin initiation (index date) and censored at the earliest of the following outcomes - discontinuation of insulin or occurrence of MACE or loss to follow-up or at the end of the end of the study at 5 years. The time (t) to any of these outcomes was determined for each patient, as well as the event of MACE (d) which occurred within this time interval and fitted in a Cox regression model.

5.2.3.4. Covariates

Significant a priori confounders which could impact on glycaemic control, change in weight and BMI, and the risk of MACE were extracted at baseline and adjustment was made for these in the multivariate linear and Cox regression models. These covariates have been described in Chapter 2.

5.2.3.5. Statistical Methods

A small proportion of patients had missing records for HbA1c, weight and height at different time intervals. These variables were uniformly distributed and missing at random. So, multiple imputations using the chained equation (MICE) model was used to account for these missing data and the imputed (complete) data were used for all analyses. The baseline characteristics of the study cohort was first summarised as mean (with standard deviation) and as absolute values (with proportions) stratified by BMI categories at baseline.

A univariate linear regression model was used to test the association between these baseline covariates and the study exposure and outcomes to adjust for any confounding effect they may have on the study outcomes. Covariates which were found to be significantly associated ($p < 0.05$) with the study exposure and outcomes were selected for inclusion in the multivariate model. So, for the primary outcomes of changes in HbA1c, weight and BMI, a multivariate repeated-measures linear regression model was fitted with their values at 6, 12, 24, 36, 48 and 60 months to estimate changes from index date. Pearson's Chi-square test was used to estimate the proportion achieving an HbA1c target of $\leq 7.5\%$ at each time interval.

To estimate the hazard of MACE, crude and adjusted Kaplan–Meier estimates of survival functions between the BMI categories were calculated and the log-rank test was used to compare the equality of the survival curves between them. From these survival functions, I computed the absolute reduction in the probability of the incidence of the all-cause mortality within a 5-year follow-up. Finally, a Cox proportional hazard model was fitted to estimate the marginal and adjusted hazard of MACE in all the BMI groups (treated groups), compared to the normal BMI group. Any violations in the proportional hazards assumptions were confirmed with Schoenfeld residuals tests.

5.2.3.6. Sensitivity and Subgroup analyses

To explore the impact the missing values may have on the overall outcome and assess the robustness of our imputation, all the analyses were repeated in the dataset with missing values and the study outcomes compared. Also, subgroup analyses were done for the individual components of MACE, as well as a composite of CV events (non-fatal MI or stroke).

In all the models, the point estimates were estimated with 95% confidence intervals (CI) at the conventional statistical significance level of < 0.05 while all analyses were conducted using Stata Software, version 14 (StataCorp. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP. 2015).

5.2.4. Results

5.2.4.1. Baseline Demographics

The study population comprised 12,725 patients with type 2 diabetes after the application of the inclusion and exclusion criteria on the initial 19,808 patients identified in the THIN dataset (Figure 5.1).

The least proportion (13%) of these patients was in the normal and obese class III BMI categories respectively while the greatest proportion (29%) was in the class I obese category. There were greater proportion of males in the normal BMI category but more females in the obese class III BMI category ($p < 0.0001$). Patients in the normal BMI category were older while those in the obese class III were younger. Conversely, baseline HbA1c and systolic blood pressure were highest and lowest in the obese class III and normal BMI categories respectively (Table 5.1).

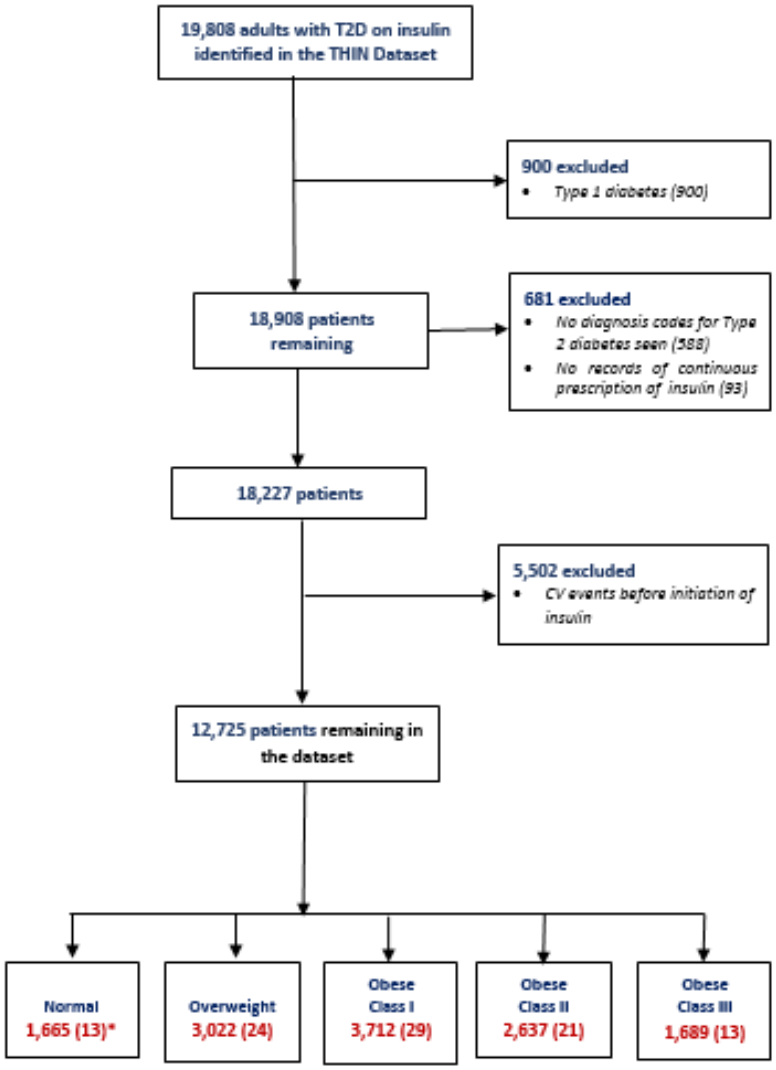


Figure 5.1: Selection of study participants (*proption of the total bracket in%)

Table 5.1: Baseline Characteristics of Study participants stratified by baseline BMI categories

	Normal (n=1665)	Overweight (n=3022)	Obese Class I (n=3712)	Obese Class II (n=2637)	Obese Class III (n=1689)	Total (n=12,725)
Demographics						
Age (yrs), Mean (SD)	60.2 (13.3)	59.8 (13.7)	58.7 (13.6)	57.9 (13.9)	56.0 (14.2)	58.6 (13.8)
Gender, No. (%)						
Male	1165 (70)	1799 (60)	1792 (48)	1058 (40)	531 (31)	6345 (50)
Female	500 (30)	1223 (40)	1920 (52)	1579 (60)	1158 (69)	6380 (50)
Townsend deprivation index, No. (%)						
Least deprived	372 (23)	653 (23)	710 (20)	503 (20)	316 (20)	2554 (20)
2nd quintile	336 (21)	612 (21)	716 (20)	505 (20)	302 (19)	2471 (19)
3rd quintile	358 (22)	598 (21)	804 (23)	559 (22)	358 (22)	2677 (21)
4th quintile	307 (19)	604 (21)	763 (21)	548 (22)	348 (22)	2570 (20)
Most deprived	229 (14)	412 (14)	574 (16)	419 (17)	284 (18)	1918 (15)
Age categories. No (%)						
18 to 39 years	141 (9)	261 (9)	405 (11)	332 (13)	258 (15)	1397 (11)
40 to 59 years	675 (41)	1199 (40)	1465 (40)	1042 (40)	753 (45)	5134 (41)
60 to 79 years	743 (45)	1377 (46)	1629 (44)	1149 (44)	616 (37)	5514 (43)
80 years and above	106 (6)	185 (6)	213 (6)	114 (4)	62 (4)	680 (5)
Clinical covariates, Mean (SD)						
HbA1c (%)	8.6 (1.9)	8.6 (1.8)	8.7 (1.8)	8.8 (1.9)	8.8 (1.8)	8.7 (1.8)
BMI (kg/m2)	21.8 (2.8)	27.7 (1.4)	32.5 (1.4)	37.2 (1.4)	44.1 (4.3)	32.7 (6.9)
Height (m)	1.7 (0.09)	1.7 (0.10)	1.7 (0.1)	1.7 (0.1)	1.6 (0.1)	1.7 (0.1)
Weight (Kg)	69.7 (12.2)	81.0 (11.6)	90.5 (12.1)	100.9 (13.1)	116.4 (16.3)	91.5 (18.8)
DBP (mmHg)	75.6 (11.1)	76.3 (10.9)	76.3 (10.6)	77.1 (11.0)	77.6 (10.7)	76.6 (10.9)
SBP (mmHg)	134.4 (23.3)	135.0 (22.9)	135.8 (23.0)	137.2 (22.8)	138.7 (23.4)	136.1 (23.1)
TC (mmol/l)	4.5 (1.4)	4.6 (1.3)	4.6 (1.3)	4.6 (1.3)	4.6 (1.3)	4.6 (1.3)
Triglyceride (mmol/L)	1.8 (1.2)	2.0 (1.2)	2.0 (1.2)	2.1 (1.2)	2.2 (1.2)	2.0 (1.2)
HDL (mmol/l)	2.4 (1.1)	2.4 (1.1)	2.4 (1.1)	2.4 (1.1)	2.4 (1.1)	2.4 (1.1)
LDL (mmol/l)	1.3 (0.5)	1.3 (0.4)	1.3 (0.4)	1.2 (0.5)	1.2 (0.4)	1.3 (0.5)
Albumin (g/L)	4.1 (0.4)	4.1 (0.4)	4.1 (0.4)	4.0 (0.4)	4.0 (0.4)	4.1 (0.4)
ACR (mg/mol)	4.7 (8.2)	5.6 (8.5)	5.6 (8.4)	5.9 (8.6)	6.0 (8.5)	5.6 (8.5)
eGFR (mls/min/1.73m^2)	66.4 (20.9)	65.2 (20.9)	65.1 (21.1)	64.6 (21.5)	64.3 (21.5)	65.1 (21.2)
Diabetes duration (yrs)	3.9 (5.0)	3.7 (5.0)	3.9 (5.0)	3.7 (4.6)	3.8 (4.6)	3.8 (4.9)
Lifestyle						
Smoking status, No. (%)						
Non-smoker	812 (49)	1536 (51)	2005 (54)	1403 (53)	930 (55)	6686 (52)

Ex-smoker	570 (34)	1050 (35)	1179 (32)	840 (32)	538 (32)	4177 (33)
Current smoker	283 (17)	436 (14)	528 (14)	394 (15)	221 (13)	1862 (15)
Alcohol status, No. (%)						
Non-drinker	453 (27)	880 (29)	1225 (33)	898 (34)	589 (35)	4045 (32)
Ex-drinker	194 (12)	362 (12)	409 (11)	310 (12)	178 (11)	1453 (11)
Current drinker	1018 (61)	1780 (59)	2078 (56)	1429 (54)	922 (55)	7227 (57)
GLTs, No. (%)						
Insulin						
Premix	978 (59)	1783 (59)	2206 (59)	1470 (56)	933 (55)	7370 (58)
Basal-bolus	687 (41)	1239 (41)	1506 (41)	1167 (44)	756 (45)	5355 (42)
Metformin	1308 (79)	2496 (83)	3164 (85)	2333 (88)	1530 (91)	10831 (85)
Sulphonylurea	1212 (73)	2186 (72)	2728 (73)	1952 (74)	1246 (74)	9324 (73)
Thiazolidinediones	491 (29)	891 (29)	1172 (32)	878 (33)	622 (37)	4054 (32)
GLP-1RA	159 (10)	281 (9)	431 (12)	371 (14)	289 (17)	1531 (12)
Gliptins	220 (13)	412 (14)	545 (15)	391 (15)	273 (16)	1841 (15)
SGLT-2i	6 (0)	19 (1)	16 (0)	18 (1)	12 (1)	71 (1)
Glinides	70 (4)	116 (4)	176 (5)	115 (4)	85 (5)	562 (4)
Use of Medications, No. (%)						
Aspirin	1572 (90)	2859 (92)	3519 (98)	2488 (96)	1584 (96)	12022 (94)
Antihypertensive	1337 (85)	2498 (87)	3114 (88)	2183 (88)	1406 (89)	10538 (83)
LLTs	1391 (88)	2566 (90)	3187 (91)	2238 (90)	1425 (90)	10807 (85)
Comorbidities, No. (%)[c]						
CHD	196 (12)	380 (13)	447 (12)	277 (11)	165 (10)	1465 (12)
PAD	116 (7)	212 (7)	263 (7)	143 (5)	89 (5)	2137 (17)
Heart Failure	90 (5)	167 (6)	205 (6)	141 (5)	110 (7)	713 (6)
Hypoglycaemia	286 (17)	500 (17)	670 (18)	445 (17)	236 (14)	2137 (17)

Abbreviations:
BMI (body mass index); SBP (systolic blood pressure); DBP (diastolic blood pressure); HbA1c (haemoglobin A1c); HDL (high-density lipoprotein); LDL (low-density lipoprotein); TC (total cholesterol); eGFR (estimated glomerular filtration rate); LLTs (lipid lowering therapies); PAD (peripheral arterial disease); CHD (coronary heart disease); ACR (albumin creatinine ratio); GLTs (Glucose-lowering therapies); AMI (Acute myocardial infarction); SD (standard deviation). Diabetes duration is the time from first diagnosis of diabetes to date of insulin initiation (index date)

5.2.4.2. Association between BMI at insulin initiation vs glycaemic control

A summary of the proportion of patients achieving the National Institute of Health and Care Excellence (NICE) target of ≤7.5% (58 mmol/mol) and the odds of attaining this target compared to the normal BMI category is shown in Table 5.2. Compared to the normal BMI group, the odds of achieving the target HbA1c significantly declined across all BMI levels at 6 and 12 months (Table 5.2). On the long term (beyond 24 months), there was no significant difference in the proportion achieving this target, neither was any significant trend observed on the reduction of the proportion of people achieving their target HbA1c.

Table 5.2: Proportions and odds of achieving the NICE target HbA1c of ≤7.5% (58 mmol/mol) by the BMI categories.

	6 months		12 months		24 months		36 months		48 months		60 months	
BMI categories at baseline	**Prop (%)**	**aOR* (95%CI)**	**Prop (%)**	**aOR* (95%CI)**	**Prop (%)**	**aOR* (95%CI)**	**Prop (%)**	**aOR* (95%CI)**	**Prop (%)**	**aOR* (95%CI)**	**Prop (%)**	**aOR* (95%CI)**
Normal	36.6	ref	37.0	ref	34.2	ref	34.1	ref	44.8	ref	45.6	ref
Overweight	32.8	0.86 (0.75-0.98)	33.1	0.85 (0.75-0.97)	31.0	0.87 (0.76-0.99)	32.2	0.95 (0.83-1.08)	44.9	0.99 (0.87-1.12)	44.4	0.95 (0.84-1.08)
Obese Class I	31.0	0.80 (0.71-0.91)	31.6	0.78 (0.70-0.91)	30.7	0.87 (0.77-0.99)	33.2	1.01 (0.88-1.15)	45.7	1.00 (0.89 -1.14)	45.9	0.98 (0.86-1.10)
Obese Class II	30.0	0.78 (0.68-0.90)	31.6	0.81 (0.70-0.93)	29.4	0.83 (0.72-0.95)	31.4	0.95 (0.83-1.10)	47.6	1.08 (0.95-1.23)	45.2	0.93 (0.82-1.06)
Obese Class III	27.8	0.69 (0.59-0.80)	30.0	0.73 (0.62-0.85)	30.9	0.91 (0.78-1.06)	32.5	1.03 (0.88-1.21)	47.1	1.07 (0.93-1.24)	46.4	0.99 (0.85-1.14)
	p < 0.0001**	LRT p-value*** 0.0001	p < 0.0001	LRT p-value 0.0011	p = 0.023	LRT p-value 0.2519	p = 0.377	LRT p-value 0.6366	p = 0.160	LRT p-value 0.4653	p = 0.942	LRT p-value 0.8255

Abbreviations: BMI (body mass index); Prop (Proportion in %);
**aOR = Adjusted Odds Ratio. Adjusted for age, duration of diabetes, gender, socioeconomic status (measured by Townsend Deprivation scores); smoking status, diastolic and systolic blood pressure and insulin-regimen*
*** p-value of the proportions at the follow-up timeline*
****LRT (Likelihood Ratio Test) p-value showing*
p-value for trend <0.0001 and 0.001 at 6 and 12 months respectively but not significant (>0.05) at 24, 36, 48 and 60 months

Figure 5.2 showed the mean change in HbA1c from baseline in all BMI categories. Overall, there was a significant reduction in HbA1c- the greatest reduction was seen in the normal BMI category from 6 to 24 months, but beyond this period, the morbidly obese category recorded the greatest reduction.

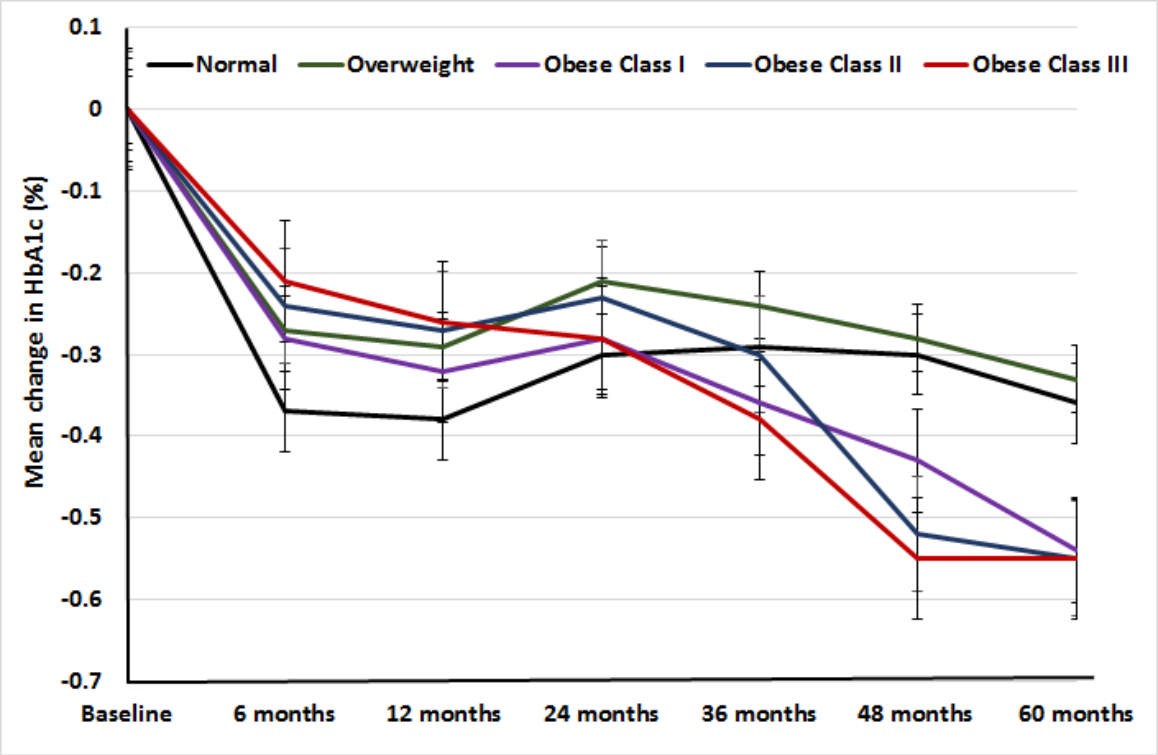


Figure 5.2: Mean Change (difference) in HbA1c (%) from baseline at 6 to 60 months by BMI categories *(all p-values <0.0001)*

With the normal BMI category as the reference group, the adjusted mean changes in HbA1c at 6 months were 0.10% (95%CI: -0.01, 0.21) in the overweight; 0.19% (95%CI: 0.08, 0.29) in the obese; 0.21% (95%CI: 0.10, 0.32) in the clinically obese and 0.29% (95%CI: 0.17, 0.42) more in the morbidly obese categories (LRT p-value <0.0001) (Table 5.3). At the end of follow up at 60 months, the morbidly obese group had the greatest reduction in HbA1c relative to the normal category (mean coeff: -0.02%, 95%CI: -0.20, 0.19)

Table 5.3: Mean follow-up HbA1c and mean coefficients of change in HbA1c compared to the normal BMI category

	6 months		12 months		24 months		36 months		48 months		60 months	
BMI categories at baseline	Mean HbA1c (%)	Coefff* (95%CI)	Mean HbA1c (%)	Coefff (95%CI)	Mean HbA1c (%)	Coefff (95%CI)	Mean HbA1c (%)	Coefff (95%CI)	Mean HbA1c (%)	Coefff (95%CI)	Mean HbA1c (%)	Coefff (95%CI)
Normal	8.20	ref	8.19	ref	8.27	ref	8.28	ref	8.27	ref	8.21	ref
Overweight	8.33	0.10 (-0.01, 0.21)	8.31	0.08 (-0.02, 0.19)	8.39	0.08 (-0.02, 0.19)	8.36	0.06 (-0.05, 0.17)	8.32	0.09 (-0.09, 0.26)	8.27	0.08 (-0.09, 0.25)
Obese Class I	8.44	0.19 (0.08, 0.29)	8.40	0.17 (0.06, 0.27)	8.43	0.11 (0.01, 0.21)	8.35	0.01 (-0.09, 0.12)	8.29	0.05 (-0.12, 0.22)	8.18	0.05 (-0.12, 0.21)
Obese Class II	8.48	0.21 (0.10, 0.32)	8.45	0.19 (0.08, 0.30)	8.49	0.14 (0.03, 0.24)	8.42	0.05 (-0.06, 0.16)	8.14	-0.05 (-0.24, 0.13)	8.17	0.06 (-0.11, 0.24)
Obese Class III	8.56	0.29 (0.17, 0.42)	8.50	0.25 (0.13, 0.38)	8.48	0.13 (0.01, 0.25)	8.38	0.01 (-0.11, 0.14)	8.20	0.0002 (-0.20, 0.20)	8.11	-0.002 (-0.20, 0.19)
		LRT p-value** <0.0001		LRT p-value 0.0002		LRT p-value 0.1362		LRT p-value 0.6939		LRT p-value 0.4038		LRT p-value 0.8304

Abbreviations: BMI (body mass index); Prop (Proportion in %);
**Mean coefficient **LRT (Likelihood Ratio Test) p-value showing*
p-value for trend <0.0001 and 0.001 at 6 and 12 months respectively but not significant (>0.05) at 24, 36, 48 and 60 months
Adjusted for age, duration of diabetes, gender, socioeconomic status (measured by Townsend Deprivation scores); smoking status, diastolic and systolic blood pressure, GLTs and insulin-regimen

5.2.4.3. Association between BMI at baseline and changes in weight and BMI

There was a consistent significant increase in weight and BMI in the normal and overweight categories throughout the study duration, while the other categories experienced a decrease ($p < 0.00001$ in all). Patients in the normal and overweight categories experienced weight gain from 71.8kg and 81.5kg respectively at 6 months, to 80.7kg and 85.3kg ($p < 0.0001$) at 60 months; but in the obese (classes I to III) categories, there was a significant reduction in weight from baseline at each study timeline (e.g. from 115.1kg at 6 months to 103.5kg at 60months ($p<0.0001$) in the morbidly obese category) as summarised in Table 5.4. Similarly, BMI increased from 23.3kg/m^2 and 28.3kg/m^2 at 6 months in the normal and overweight categories respectively to 28.2kg/m^2 and 30.5kg/m^2 respectively at 60months ($p<0.0001$) but other BMI categories had a significant decrease in BMI (Appendix 3.1).

The mean coefficient of change in weight compared to the normal BMI category showed greater reduction in weight and BMI across all the BMI categories, compared to the normal category at all study timelines (LRT p-values were <0.00001 in all). There was a significant trend ($p < 0.0001$) across the BMI categories. So, for each level of baseline BMI, there was a reduction in weight and BMI. For instance, our findings at 12 months show that for each level increase in BMI category, there was a reduction of 1.4kg (95%CI: -1.5, -1.3; $p < 0.0001$) in weight and 0.62kg/m^2 (95%CI: -0.67, -0.58; $p < 0.0001$) in BMI.

Table 5.4: Mean follow-up weight and mean coefficients of change in weight compared to the normal BMI category

	6 months		12 months		24 months		36 months		48 months		60 months	
BMI categories at baseline	Mean weight (kg)	Coefff* (95%CI)	Mean weight (kg)	Coefff* (95%CI)	Mean weight (kg)	Coefff* (95%CI)	Mean weight (kg)	Coefff* (95%CI)	Mean weight (kg)	Coefff* (95%CI)	Mean weight (kg)	Coefff* (95%CI)
Normal	71.8	ref	72.9	ref	75.6	ref	77.3	ref	78.9	ref	80.7	ref
Overweight	81.5	-1.31 (-1.67, -0.96)	82.1	-1.71 (-2.17, -1.25)	80.4	-3.22 (-3.89, -2.55)	83.9	-4.61 (-5.40, -3.82)	84.5	-5.59 (-6.45, -4.72)	85.3	-6.65 (-7.59, -5.72)
Obese Class I	90.4	-2.04 (-2.39, -1.70)	90.3	-3.16 (-3.61, -2.71)	83.4	-6.57 (-7.22, -5.91)	89.6	-8.92 (-9.69, -8.15)	89.0	-11.10 (-11.9, -10.3)	89.6	-12.57 (-13.5, -11.7)
Obese Class II	100.3	-2.60 (-2.98, -2.24)	99.8	-4.10 (-4.58, -3.62)	98.4	-8.62 (-9.32, -7.92)	97.6	-11.62 (-12.4, -10.8)	95.9	-14.8 (-15.7, -13.9)	95.7	-17.17 (-18.2, 16.2)
Obese Class III	115.1	-3.49 (-3.91, -3.08)	113.8	-5.95 (-6.49, -5.41)	110.8	-12.22 (-13.0, -11.5)	107.9	-17.09 (-18.0, -16.1)	104.4	-22.22 (-23.2, -21.2)	103.5	-25.35 (-26.4, -24.3)
		LRT p-value** <0.00001		LRT p-value 0.00001		LRT p-value <0.00001		LRT p-value <0.00001		LRT p-value <0.00001		LRT p-value <0.00001

Abbreviations: BMI (body mass index)
**Mean coefficient*
***LRT (Likelihood Ratio Test) p-value showing. p-value for trend <0.0001 for each follow up timeline*

Figures 5.3 A and B summarise the mean change in weight and BMI within the baseline BMI categories by the study timelines. The funnel-shape figures depict the different change patterns between the normal and overweight BMI categories vs the Obese (Classes II and III). The obese class I category maintained almost a plateau. At 60 months, the greatest reductions in weight and BMI were in the obese class III category (losing 12.91kg and 5.66kg/m^2 respectively from baseline) as against the normal category which recorded a gain of 11kg in weight and 6.32kg/m^2 in BMI from baseline.

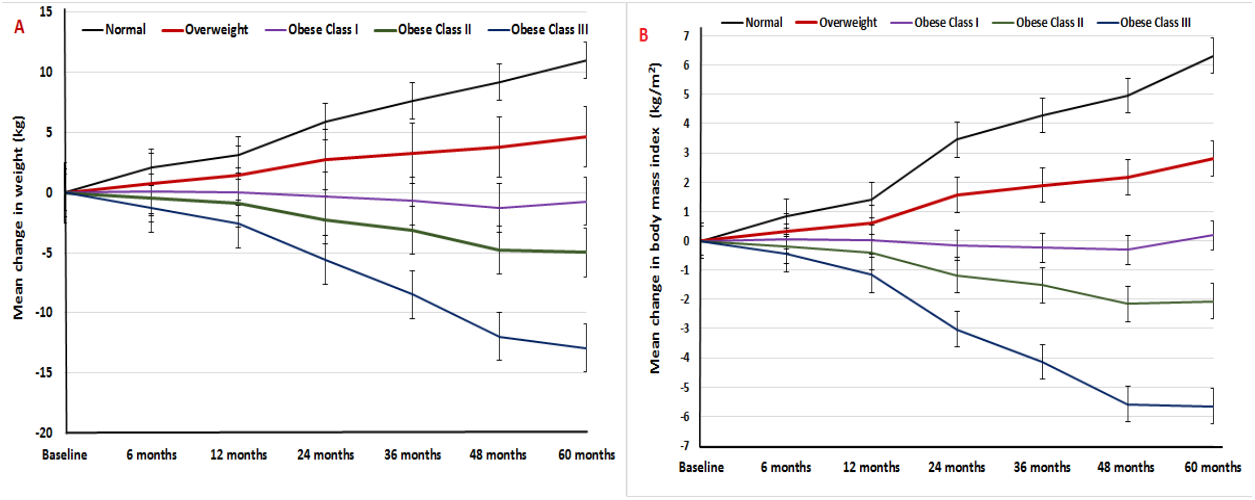


Figure 5.3: The mean difference in (A) weight (kg) and (B) BMI (kg/m^2) from baseline at 6 to 60 months by BMI categories (all p-values <0.0001)

5.2.4.4. Risk of Major Adverse Cardiovascular Event (MACE)

The mean follow-up duration was 4.38 years with a total follow-up of 49,516 person-years. There is no significant difference in survival between the baseline BMI categories at 5years (log-rank test p-value = 0.228). There were 1,095 composite events of MACE, with a crude event rate of 22.1 per 1,000 person-years (95%CI: 20.8, 23.5). Compared to the normal BMI category at insulin initiation, there were 10% [aHR: 1.10 (0.90 – 1.35)]; 5% [aHR: 1.05 (0.86

– 1.29)]; 3% [aHR: 1.03 (0.83 – 1.29)]; and 30% [aHR: 1.30 (1.02 – 1.66)] higher risks of MACE in the overweight, obese, clinically obese and morbidly obese categories respectively, after adjusting for age, gender, use of LLTs and antihypertensives, comorbidities of heart failure and coronary heart disease, albumin, GFR, lipid profile, and the use of GLP-1RA (Table 5.5).

5.2.4.5. Subgroup Analysis

In the adjusted model, compared to the normal BMI category on insulin initiation, the risk of all-cause mortality was 9% [aHR: 1.09 (0.81 – 1.45)]; 12% [aHR: 1.12 (0.84 – 1.49)]; 31% [aHR: 1.31 (0.96 – 1.77)]; and 75% [aHR: 1.75 (1.26 – 2.43)] higher in the overweight, obese, clinically obese and morbidly obese categories respectively; while the risks of a composite CV event were 25%, 21%, the same, and 34% respectively higher in the overweight, obese, clinically obese and morbidly obese BMI categories, compared to patients with normal BMI at baseline. This, and the risk of non-fatal stroke and MI are presented in Table 5.5.

Table 5.5: Events, rates and hazard ratios of composite MACE and subgroup of all-cause mortality, non-fatal MI and stroke by baseline BMI categories.

	Normal (n=1665)	Overweight (n=3022)	Obese Class I (n=3712)	Obese Class II (n=2637)	Obese Class III (n=1689)	Total (n=12,725)
Composite Outcome[a]						
No of events/person-years	143/6,508	284/11,694	320/14,542	201/10,275	147/6,495	1095/49,516
Composite event rates[b] (95%CI)	22.0 (18.6 – 25.9)	24.3 (21.6 – 27.3)	22.0 (19.7 – 24.6)	19.6 (17.0 – 22.5)	22.6 (19.3 – 26.6)	22.1 (20.8 – 23.5)
Adjusted HR[c] (95%CI)	ref	1.10 (0.90 – 1.35)	1.05 (0.86 – 1.29)	1.03 (0.83 – 1.29)	1.30 (1.02 – 1.66)*	-
Composite Cardiovascular event[d]						
No of events/person-years	70/6510	143/11,701	150/14,549	81/10,280	56/6,499	500/49,541
CV event rates[b] (95%CI)	10.8 (8.5 – 13.6)	12.2 (10.4 – 14.4)	10.3 (8.8 – 12.1)	7.9 (6.3 – 9.8)	8.6 (6.6 – 11.2)	10.1 (9.2 – 11.0)
Adjusted HR[c] (95%CI)	ref	1.25 (0.86 – 1.81)	1.21 (0.73 – 2.02)	0.99 (0.49 – 1.97)	1.34 (0.53 – 3.40)	-
All-cause mortality						
No of events/person-years	73/6,667	141/12,007	169/14,868	119/10,445	90/6,612	592/50,601
Mortality rates[b] (95%CI)	10.9 (8.7 – 13.8)	11.7 (10.0 – 13.8)	11.4 (9.8 – 13.2)	11.4 (9.5 – 13.6)	13.6 (11.1 – 16.7)	11.7 (10.8 – 12.7)
Adjusted HR[c] (95%CI)	ref	1.09 (0.81 – 1.45)	1.12 (0.84 – 1.49)	1.31 (0.96 – 1.77)	1.75 (1.26 – 2.43)*	-
Non-fatal Acute Myocardial Infarction (AMI)						
No of events/person-years	13/6,639	21/11,960	20/14,828	8/10,434	3/6,610	65/50,472
AMI event rates[b] (95%CI)	2.0 (1.1 – 3.4)	1.8 (1.1 – 2.7)	1.3 (0.9 – 2.1)	0.8 (0.4 – 1.5)	0.5 (0.1 – 1.4)	1.3 (1.0 – 1.6)
Adjusted HR[c] (95%CI)	ref	1.40 (0.51 – 3.84)	2.24 (0.53 – 9.48)	1.76 (0.23 – 13.3)	2.94 (0.19 – 46.0)	-
Non-fatal Stroke						
No of events/person-years	57/6,541	122/11,755	130/14,597	73/10,295	53/6,505	435/49,695
Stroke event rates[b] (95%CI)	8.7 (6.7 – 11.3)	10.4 (8.7 – 12.4)	8.9 (7.5 – 10.6)	7.1 (5.6 – 8.9)	8.1 (6.2 – 10.7)	8.8 (8.0 – 9.6)
Adjusted HR[c] (95%CI)	ref	1.25 (0.84 – 1.87)	1.13 (0.66 – 1.95)	0.92 (0.45 – 1.92)	1.17 (0.44 – 3.16)	-

[a] Composite outcome is a three-point MACE including all-cause mortality, non-fatal acute myocardial infarction (AMI) and non-fatal stroke.
[b] Rates at 1000 person-years. 95%CI – 95% confidence interval.
[c] aHR (Adjusted Hazard Ratio). Adjusted for age, gender, use of lipid-lowering therapies, use of antihypertensives, comorbidities of heart failure and coronary heart disease at baseline, albumin, glomerular filtration rate, lipid profile, and use of glucagon-like peptide receptor analogues (GLP-1RA) at baseline.
[d] Composite Cardiovascular event is a two-point event of non-fatal acute myocardial infarction (AMI) and non-fatal stroke.
** P-value <0.05*

5.2.5. Discussion

Several conclusions could be derived from this observational study obtained from a large longitudinal real world data. Firstly, HbA1c was reduced irrespective of baseline HbA1c with a marginal greater HbA1c reduction in the normal/overweight weight group in the first 2 years and obese group at 3 years of insulin treatment. Secondly, insulin induced significant weight gain among normal and overweight individuals but a paradoxical weight loss in the obese individual. Thirdly, the observed weight loss in the obese group especially stage III obesity, was consistent over 12, 24 and 36 months of insulin treatment; and lastly morbid obesity was associated with an increased risk of mortality at 5 years of follow up. This study provides reassurance of the efficacy of insulin treatment in patients with T2D, irrespective of their baseline BMI, but highlights the high mortality risk for the obese patients with T2D.

These findings are robust, and are supported by separate analyses to explore possible confounders and via sensitivity analysis. This is further supported by consistent findings in patients from the entire cohort. The level of HbA1c and CV risk profile (e.g. lipid, blood pressure) were clinically similar across all weight change categories. These findings were in concordance with a previous study using a US-based electronic medical record which reported a reduction in HbA1c was associated with progressively less weight gain as baseline BMI rose.[254] The inference from that study that the lesser weight gain seen in obese patients was due to the use of less intensive insulin therapy may also apply to this cohort, although interestingly, I observed greater HbA1c reduction and greater weight loss in the obese group, compared with the normal and overweight group at 36 months of insulin initiation. When adjusted for different confounders, I observed an overall greater HbA1c reduction in in the normal weight group and lesser weight in the overweight and obese group.

Although I observed the association between higher mortality rates with baseline obesity at insulin initiation, this study did not infer a causative role of insulin treatment in inducing the adverse mortality outcome in obese patients. Indeed, increased body weight among obese individuals per se is recognised to lead to worsening of cardiovascular risk factors[255] and in a prospective study of more than 17,000 middle-aged patients, obese patients with diabetes had a 3-fold greater risk of mortality compared to non-obese patients with diabetes, independent of their glucose lowering treatment.[55, 256] Whether insulin-induced weight gain is associated with adverse CV outcome remains unknown because robust large scale clinical trials such as UKPDS,[22] ADVANCE[210] and ACCORD[55] study did not stratify their CV outcomes by weight-loss or weight-gain, for any given level of glycaemic control. However, in a post hoc analysis of the ACCORD study, patients who were inadequately controlled at baseline and received intensive glucose lowering strategy but still had suboptimal glucose control (HbA1c >7%; >53 mmol/mol) experienced higher mortality rate.[94] This observation suggests patient-factors which are associated with persistently high HbA1c, despite intensive treatment, appear to be the most important determinant of increased mortality risks. To this end, an important confounder that needs to be considered in our observation is that insulin-induced weight gain suggests patients' compliance to insulin treatment intensification and thus a surrogate marker of compliance to holistic care and treatment.

Thus, the observation from this study that obese patients experienced relative weight loss and less HbA1c reduction (compared to the normal and overweight group) could potentially imply a less compliant or less aggressively managed patients. While compliance to insulin therapy may also be a factor in this observation, it might be conceivable that overweight patients were provided with more detailed advice regarding strategies to lose weight and/or a referral to dietitian, due to anticipated weight gain due to insulin, than individuals who are underweight or have normal weight. However, this observation only holds valid in the first 24 months of

treatment, because at 36 months of treatment, there appears to be a greater relative HbA1c reduction in the obese group, compared with normal or overweight. Nevertheless, I contend that that failure to achieve HbA1c reduction, despite optimal glucose-lowering treatment, in obese patients should trigger clinicians to intensify cardiovascular risk reduction strategies.

5.2.6. Limitations

These analyses were subject to some limitations that are inherent to observational studies. Firstly, as previously discussed, I could not ascertain treatment compliance. Also, some factors like lifestyle and dietary intervention may influence our findings. I was also not able to obtain the longitudinal insulin doses, an important predictor of insulin-induced weight gain. [240] Differences in the use of different glucose lowering therapy are large. This however reflects the current preference of glucose lowering therapy in UK primary care, i.e. a high preference for metformin and sulfonylurea, but less experience with novel therapies like DPP4 inhibitor, GLP-1RA and SGLT inhibitors. In addition, the long duration of diabetes may also account for differences in the use of GLT in this study. This may be, since the aim was to look at status of baseline weight per se on metabolic and CV outcomes, I would argue that this should not influence the robustness of our findings. Although I could not account for other potential residual confounders such, indications for intensification treatments, markers of β-cell deterioration, doses of lipid lowering or antihypertensive therapy and frequency of hypoglycaemia, I was able to account for differences in the observed covariates and used robust analytical techniques to control confounding that may bias the results of the estimated treatment effects. Finally, the THIN database, at the time of this dataset was obtained, had no records on ethnicity of the population. This could have implications for the Asian ethnic minorities in whom the above BMI classification does not strictly apply; whom also, at a lower BMI

(compared to the above), may have all the metabolic risks associated. These findings must be interpreted with great caution among this group.

5.2.7. Conclusion

In summary, I have shown that while insulin treatment is associated with weight gain in those with normal and overweight BMI, baseline weight confers only a marginal influence on its efficacy in achieving HbA1c target. Nevertheless, morbidly obese patients at the time of insulin initiation appear to be at high risk of mortality. While these findings should provide important reassurance among patients with T2DM who gained weight following insulin treatment in routine clinical practice, it also highlights the high mortality risk of obese people with T2D.

5.3. Study 2 – Association between insulin-induced weight change vs glycemic control, cardiovascular events and all-cause mortality.

5.3.1. Summary

Background

This study aims to explore the effect of insulin-induced weight (wt) gain on CV outcomes and mortality amongst patients with T2D following insulin initiation and to determine if any weight-gain has any effect on glycaemic control.

Methods

A retrospective cohort study was performed in adults with insulin-treated T2D derived from the UK Health Improvement Network (THIN) database. Based on the average weight change of 5kg one-year post-insulin initiation, patients were grouped into 5 categories (>5kg wt loss; 1.0-5.0kg wt loss; no wt change; 1.0-5.0kg wt gain; and >5.0kg wt gain) and followed-up for 5 yrs. Cox proportional hazard models and Kaplan-Meier estimators were fitted to estimate the hazards of a three-point composite of non-fatal myocardial infarction, stroke and all-cause mortality between the categories. While in a subgroup of this cohort, differences in weight and HbA1c from the baseline were determined at 6, 12, 24 and 36 months of insulin use and used to classify patients into weight-loss, weight-neutral and weight gain groups. Spearman's regression coefficient model was used to determine the relationship between weight-gain and glycaemic control at 6, 12, 24 and 36 months and the adjusted mean differences in HbA1c in these weight-change groups compared with the weight-neutral group.

Results

The median age was 62.8 (IQR: 52.3–71.8) years, HbA1c: 8.6% (IQR: 7.4–9.8) and mean BMI: 31.8(6.5) kg/m^2. The 5-year probability of survival differed significantly within the wt-change categories (log-rank test p-value = 0.0005). A total of 1963 composite events occurred. Compared to the weight-neutral group, the risk of composite events was 31% greater in the >5kg wt-loss group (aHR: 1.31; 95%CI: 1.02, 1.68), the same in the 1.0-5.0kg wt-gain category; but non-significantly increased by 15% and 13% in the 1.0-5.0kg wt-loss and >5.0kg wt-gain categories respectively. In the obese subgroup, this risk was 50% (aHR: 1.50, 95%CI: 1.08 – 2.08) more in the >5kg weight-loss group, compared to the weight-neutral group.

In the sub-cohort of 18,227 participants, 53.2% were males; mean age was 61.5±13.6 years; weight: 91.3±18.7 Kg; and HbA1c: 8.7±1.8 %. There was a weak negative correlation between weight and HbA1c as shown by HbA1c reductions of -0.011% at 6 months ($p < 0.0001$) and -0.0003% at 36 months ($p = 0.022$) for each unit increase in weight (kg). The weight-gain group had greater reductions in HbA1c compared to the weight-neutral group and this was greatest at 12 months (-0.121%, $p < 0.0001$) but the weight-loss group did not record any significant change in HbA1c.

Conclusion

Insulin-induced weight-gain was associated with significant reductions in HbA1c and did not translate to adverse CV outcomes and mortality in patients with T2D without any CVD at baseline. This provides reassurance and allays the fear of practitioners who experience clinical inertia in initiating insulin therapy due to concerns about weight-gain, glycaemic control, and cardiovascular safety.

5.3.2. Introduction

Insulin therapy commonly results in weight gain in people with T2DM.[242] In the United Kingdom Prospective Diabetes Study (UKPDS), patients in the intensive intervention cohort gained in excess of 5 kg during the 10-year follow-up period, with most of this gain occurring in the first 12 months.[22] In routine clinical practice, however, it has been previously shown that the effectiveness of insulin therapy to lower HbA1c levels however is variable and associated with patients' baseline weight.[229, 250] This is because insulin-induced weight gain results in an increase in the amount of insulin required to control hyperglycaemia,[179, 251] at the expense of further weight gain, possible poor treatment compliance and increased insulin resistance.

Despite the well-recognised correlation between weight gain and cardiovascular (CV) disease, there is little direct evidence relating to the impact of insulin-induced weight-gain on CV outcomes. However, there is compelling indirect evidence that weight-gain does adversely affect CV risk. In the Nurses' Health Study, weight gain of >2kg following a diagnosis of diabetes was associated with a 16% increased risk of CV heart disease.[257] The ACCORD study designed to investigate whether an aggressive therapeutic strategy to achieve tight glucose target (HbA1c <6.5%) would reduce CV events surprisingly resulted in an increased mortality in the intensively treated group.[55] The mean BMI of patients in the study was 32.2kg/m^2 and weight-gain by more than 10kg occurred in 27.8% of the intensively treated patients compared with 14.1% in the standard therapy. While a causal relationship between weight gain and adverse CV outcomes cannot be assumed, retrospective studies have shown that people with diabetes who actively lose weight improve not only their risk profile[253-255] but also survival rate. On the other hand, a study in a small population with type 1 diabetes reported that in spite of the weight-gain associated with insulin use, there was an improvement in HbA1c level,[258] similar to the UKPDS where people assigned to insulin reported the greatest weight gain over the shortest period despite improved glycaemic control.[22, 72] However, little is known of the

long-term association of weight-gain and glycaemic control in high-risk group of insulin users in routine clinical care. So, using evidence from real-world data, this study therefore aims to achieve two objectives: explore the association of insulin-induced weight gain and CV outcomes including all-cause mortality and the relationship between changes in weight post-insulin initiation and glycaemic control.

5.3.3. Methods

5.3.3.1. Study Design and Data Source

A retrospective cohort study was conducted with data obtained from the UK Primary Care via The Health Improvement Network (THIN) database. This database has been described in chapter 2.

5.3.3.2. Study Populations

All adult T2D insulin users were eligible for inclusion. Furthermore, these patients must have initiated insulin therapy between January 2007 and May 2014 irrespective of previous or concurrent use of other glucose-lowering therapies (GLTs). T2DM was identified based on the ICD-10 codes and patients with codes for both type 1 and type 2 diabetes, or those who discontinued insulin use within 6 months of initiation were excluded. People with history of CV diseases prior to insulin initiation were excluded from the study. Additionally, to minimise the prevalent user bias, patients with diagnoses of CV diseases (non-fatal MI and stroke) on insulin initiation or up to 180 days after were also excluded; while patients with type 1 diabetes were not eligible for inclusion in the study. For the second study objective, participants who had both weight and HbA1c recordings missing at baseline were excluded before imputation.

5.3.3.3. Exposure

For study objective 1, exposure was defined as change in weight, one-year post-insulin initiation. This was measured by the difference between the baseline weight (at insulin initiation) and the weight after one year, measured in kilogram. There was no consideration on the specific type or mode of administration of insulin. Change in weight was categorised into five groups based on the average weight change of 5kg within this period as reported by previous studies[22] thus: >5kg wt loss; 1.0-5.0kg wt loss; no wt change; 1.0-5.0kg wt gain; and >5.0kg wt gain. Participants were followed up for 5years to the earliest of the occurrence of any of the defined composite outcome, loss to follow-up (transfer out of practice), or discontinuation of insulin therapy, or at the end of the study.

For study objective 2, the exposure was defined as above and the cohort was grouped at 6, 12, 24 and 36-month timelines post-insulin initiation based on this into three broad categories: weight-loss, weight-neutral and weight-gain groups. This was to be able to effectively assess the relationship between weight-gain or otherwise and glycaemic control.

5.3.3.4. Outcome

In study objective 1, the study outcome was time to a three-point composite of all-cause mortality, non-fatal myocardial infarction (MI) and non-fatal stroke. These outcomes were identified and extracted with the appropriate READ CODES from the THIN database. For study objective 2, the main outcome was glycaemic control (measured by change in HbA1c (%) from baseline) at 6, 12, 24, 36 months' timelines.

5.3.3.5. Covariates

Baseline variables were selected *a priori* based on clinical significance. These were described in detail in chapter 2.

5.3.3.6. Statistical Analyses

For both study objectives, baseline variables were summarised within their respective categories of weight-change using mean values and standard deviation (SD) for continuous variables; and frequencies (%) for categorical variables. The differences between these baseline categories were analysed using Pearson's Chi square tests or linear regression and summarized in tables. Missing data among the exposure variable (weight) and other baseline covariates in the dataset were generally accounted for using multiple imputations with the chained equation (MICE) model.

In study objective 1, the primary analysis was time to a three-point composite outcome of non-fatal MI, non-fatal stroke and all-cause mortality. So, I obtained the crude and adjusted Kaplan–Meier estimates of survival functions for the 5 categories of weight-change with log-rank test comparing the equality of the survival curves between them. From these survival functions, the absolute reduction in the probability of an event occurring within a 5-year follow-up was determined. Later, I fitted a Cox proportional regression model to estimate the marginal hazard ratios and quantify the adjusted hazard of an event occurring in all the quintile groups compared to the third (no weight-change) group. Covariates which had changed the measure of effect by 10% in our univariate analysis were considered significant confounders and were included in, and adjusted for, in the final Cox model. Violations of the proportional hazards assumptions were confirmed through Schoenfeld residuals test.

For study objective 2, I first fitted a linear regression models at the 6, 12, 24, and 36th month timelines to evaluate the association between change in weight (expressed as a continuous variable) and change in HbA1c after adjusting for significant baseline covariates. Later, I fitted another linear regression model to compare the mean changes in HbA1c within the three weight-change categories after adjusting for baseline covariates. The mean differences (95% confidence interval) in HbA1c change (%) were compared to the weight-neutral category.

5.3.3.7. Subgroup/Sensitivity Analyses:

Additional sensitivity analyses were carried out to check the appropriateness of the 5 broad classifications adopted for study objective 1 by reclassifying the change in weight as quintiles of weight-change. Subgroup analyses were performed on patients with BMI > 30kg/m^2 to estimate the impact of weight changes on adverse composite outcomes in the obese population.

5.3.4. Objective 1 - Results

5.3.4.1. Cases and Total Follow up:

A total of 18,814 new insulin fulfilled our inclusion criteria. In Figure 5.4, a flow diagram illustrates how this cohort was derived. This population was distributed thus: >5kg wt loss (21.9%); 1.0-5.0kg wt loss (28.2%); no wt change (5.2%); 1.0-5.0kg wt gain (20.5%); and >5.0kg wt gain (24.3%). The mean follow-up duration was 3.7±2.9 years which represents a total follow-up period of 65,435.704 person-years.

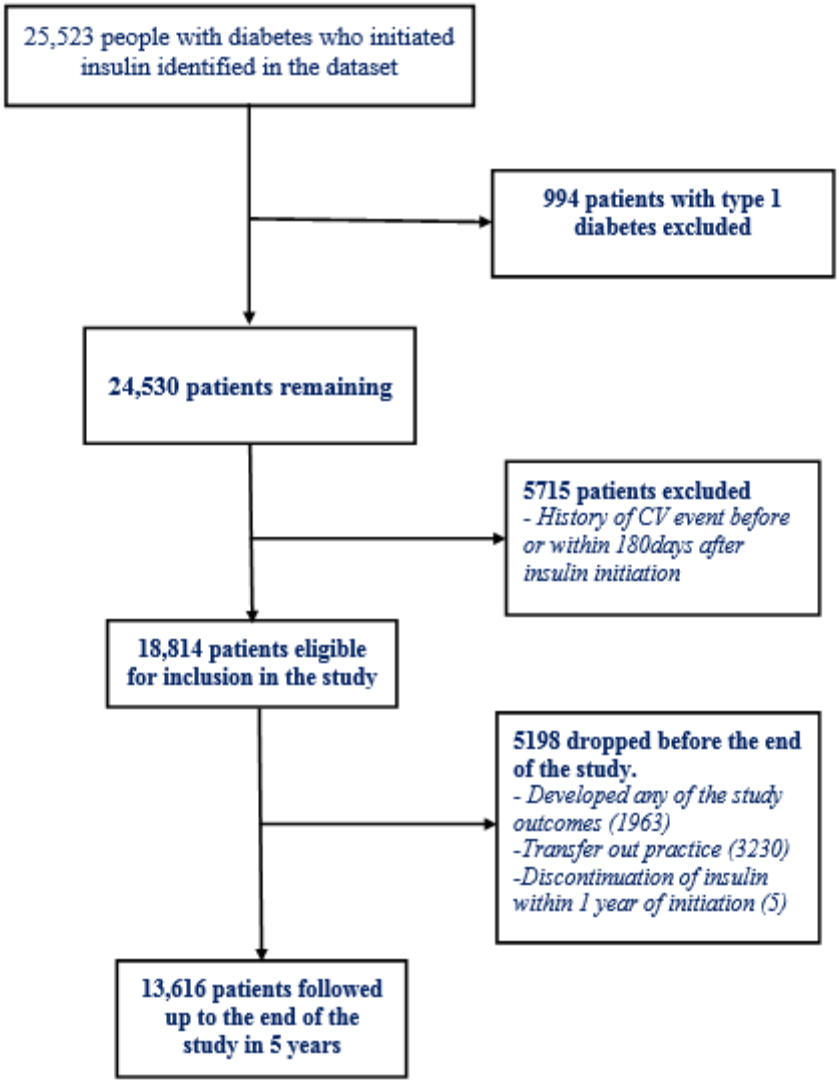


Figure 5.4: Selection of study cohort

5.3.4.2. Patients' Characteristics

The overall mean age was 61.5 (SD: 13.6) years with a mean HbA1c of 8.7% (SD: 1.8) and higher proportion (53.2%) of males. The 1.0 - 5.0kg group was younger, while the weight neutral group had lower HbA1c. The overall mean weight was 91.3kg but the group which lost more than 5kg had a greater weight of 96.6kg. Summarily, significant differences were observed between the categories in socio-economic status ($p = 0.05$), alcohol intake ($p = 0.048$) and use of lipid-lowering agents ($p=0.0001$). Table 5.6 summarises the baseline characteristics of the study cohort by the categories of change in weight one year after the initiation of insulin. The proportions of recorded data observed to be missing for weight were 15.8% and 36.5% at baseline and after one year were respectively. These were noted to be missing at random.

Table 5.6: Baseline characteristics of study cohort by categories of weight change

Weight Change	Lost > 5kg (n = 4116)	Lost 1.0 to 5.0kg (n = 5311)	No Change (n = 970)	Gained 1.0 to 5.0kg (n =3852)	Gained > 5.0kg (n = 4565)	Total (n = 18,814)
Demographics						
Age (yrs). Mean (SD)	61.8 (14.0)	61.3 (13.5)	61.8 (13.6)	60.8 (13.6)	62.1 (13.5)	61.5 (13.6)
Gender. No. (%)						
Male	2150 (52)	2807 (53)	503 (52)	2046 (53)	2508 (55)	10,014 (53.2)
Female	1966 (48)	2504 (47)	467 (48)	1806 (47)	2057 (45)	8800 (46.8)
Smoking Status. No (%)						
Non-smoker	2006 (49)	2607 (49)	464 (48)	1893 (49)	2208 (48)	9178 (48.8)
Ex-smoker	1497 (36)	1924 (36)	355 (37)	1402 (36)	1754 (38)	6,932 (36.8)
Current	613 (15)	780 (15)	151 (16)	557 (14)	603 (13)	2704 (14.4)
Alcohol Status. No (%)						
Never	1635 (40)	1960 (37)	338 (35)	1401 (36)	1725 (38)	1202 (6.4)
Ex-drinker	249 (6)	328 (6)	70 (7)	253 (7)	302 (7)	7059 (32.5)
Current	2232 (54)	3023 (57)	562 (58)	2198 (57)	2538 (56)	10,553 (56.1)
Deprivation. No (%)						
Least deprived	814 (21)	1042 (21)	204 (22)	732 (20)	888 (20)	3680 (19.7)
Second quintile	784 (20)	1016 (20)	187 (20)	751 (20)	863 (20)	3601 (19.1)
Third quintile	846 (22)	1088 (21)	193 (21)	740 (20)	963 (22)	3830 (20.4)
Fourth quintile	822 (21)	1116 (22)	202 (22)	818 (22)	937 (21)	3895 (20.7)
Most deprived	655 (17)	816 (16)	140 (15)	634 (17)	711 (16)	2956 (16.5)
Clinical Parameters. Mean (SD)						
HbA1c (%)	8.6 (1.8)	8.7 (1.8)	8.6 (1.8)	8.7 (1.8)	8.7 (1.9)	8.7 (1.8)
BMI (kg/m^2)	34.7 (6.8)	32.9 (6.6)	32.3 (6.4)	31.9 (6.7)	30.6 (6.8)	32.5 (6.9)
Diabetes duration (yrs)	4.5 (4.8)	4.1 (4.9)	4.3 (4.6)	4.1 (4.8)	4.6 (5.1)	4.3 (4.9)
Time on insulin (yrs)	4.1 (6.2)	3.8 (6.4)	4.3 (6.4)	3.7 (6.2)	4.0 (6.6)	3.9 (6.4)
Height (m)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Weight (kg)	96.6 (18.3)	92.1 (18.2)	90.3 (17.8)	89.8 (18.4)	87.0 (18.8)	91.3 (18.7)
DBP (mmHg)	76.2 (10.8)	75.8 (10.9)	75.9 (10.7)	75.8 (10.9)	76.1 (10.8)	76.0 (10.8)
SBP (mmHg)	138.7 (23.1)	136.6 (22.9)	135.7 (21.6)	135.7 (22.7)	134.5 (23.5)	136.3 (23.0)
Albumin (g/L)	4.0 (0.4)	4.1 (0.4)	4.1 (0.4)	4.1 (0.4)	4.1 (0.4)	4.0 (0.4)
ACR (mg/mol)	5.8 (8.5)	5.8 (8.6)	6.1 (8.4)	5.7 (8.4)	5.8 (8.4)	5.8 (8.5)
eGFR (mls/min/1.73m^2)	61.7 (21.3)	63.0 (21.2)	62.4 (21.4)	63.6 (20.8)	63.6 (21.3)	62.9 (21.2)
TC. (mmol/L)	4.6 (1.3)	4.5 (1.3)	4.5 (1.2)	4.5 (1.3)	4.5 (1.3)	4.5 (1.3)
Triglyceride (mmol/L)	2.1 (1.3)	2.1 (1.2)	2.0 (1.1)	2.0 (1.2)	2.1 (1.2)	2.0 (1.2)
LDL (mmol/L)	2.4 (1.1)	2.4 (1.1)	2.3 (1.0)	2.4 (1.1)	2.3 (1.1)	2.4 (1.1)

HDL (mmol/L)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.5)	1.2 (0.5)	1.2 (0.4)
BMI Categories						
Normal	319 (8)	580 (11)	128 (13)	569 (15)	948 (21)	2544 (13.5)
Overweight	717 (17)	1296 (24)	241 (25)	990 (26)	1233 (27)	4477 (23.8)
Obese	3080 (75)	3435 (65)	601 (62)	2293 (60)	2384 (52)	11,793 (62.7)
Use of Medications						
Aspirin	3940 (98)	5079 (97)	923 (99)	3710 (99)	4395 (98)	18047 (98)
LLT	3541 (90)	4621 (91)	840 (91)	3368 (91)	3972 (90)	16342 (90.5)
Antihypertensives	3565 (90)	4630 (91)	844 (91)	3370 (91)	4022 (91)	10830 (87.7)
Glucose Lowering Therapies						
Insulin - Premix	2389 (21)	3210 (29)	589 (5)	2348 (21)	2668 (24)	11204 (60)
- Basal-bolus	1727 (23)	2101 (27)	381 (5)	1504 (20)	1897 (25)	7610 (40)
Metformin	3523 (22)	4422 (28)	798 (5)	3278 (21)	3996 (25)	16017 (85)
Sulphonylurea	3203 (23)	3857 (27)	745 (5)	2899 (20)	3527 (25)	14235 (76)
Thiazolidinediones	1327 (23)	1548 (27)	276 (5)	1165 (20)	1505 (26)	5821 (31)
GLP-1RA	438 (22)	527 (27)	99 (5)	369 (19)	516 (26.5)	1949 (10)
Gliptins	589 (23)	698 (27)	125 (5)	546 (21)	618 (24)	2576 (14)
SGLT-2i	17 (20)	26 (31)	3 (4)	16 (19)	23 (27)	85 (0.6)
Glinides	133 (22)	171 (28)	25 (4)	130 (21)	149 (25)	805 (4)
Combination Therapies						
Dual	941 (21)	1458 (24)	236 (5)	938 (20)	1001 (25)	4574 (34)
Triple	1405 (22)	1736 (28)	351 (6)	1292 (21)	1492 (24)	6276 (34)
Quadriple	1750 (22)	2084 (26)	380 (5)	1610 (20)	2054 (26)	7964 (42)
Comorbidities						
Hypoglycaemia	725 (18)	902 (17)	177 (18)	686 (18)	790 (17)	3280 (17)
Heart Failure	568 (14)	712 (13)	138 (14)	518 (13)	663 (15)	2599 (13.9)
PAD	522 (13)	688 (13)	130 (13)	511 (13)	660 (14)	2511 (13.4)
Other CHD	1226 (30)	1615 (30)	276 (28)	1144 (30)	1420 (31)	5681 (30.2)

Diabetes duration is time from first diagnosis of diabetes to date of intensification with insulin (index date).
Comorbidities: other recorded medical disorders.
ACR, albumin creatinine ratio; BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, Haemoglobin A1c; HDL, high-density lipoprotein; INS, insulin; LDL, low-density lipoprotein; LLT, lipid-lowering therapy; PAD, peripheral arterial disease; SBP, systolic blood pressure; TC, total cholesterol.

5.3.4.3. Crude Event Rates:

Although the probability of survival was similar (99%) between the weight categories at one year, there was a general decrease at five years in all the weight-change categories. This ranged from 83% in the group who lost > 5kg, to 88% in the weight neutral group (log-rank test p-value =0.0005). Figure 5.5 shows a Kaplan-Meier plot of survival probability for the composite outcomes within the weight-change categories.

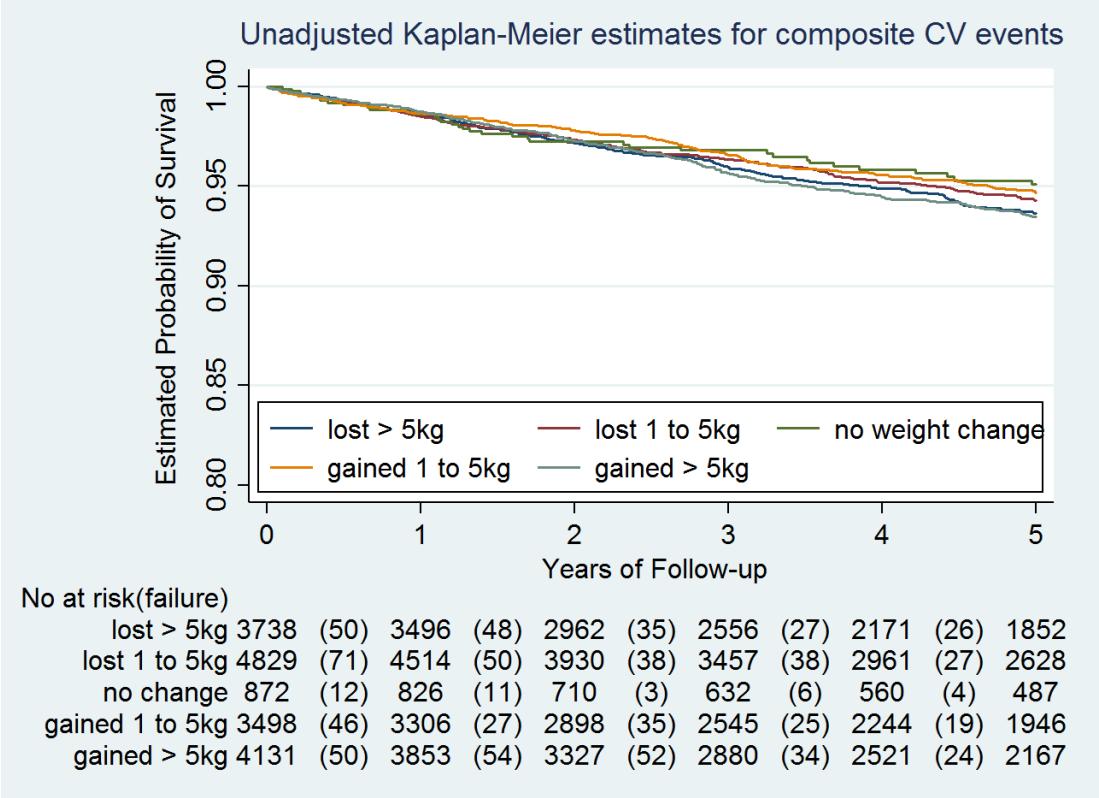


Figure 5.5: Kaplan-Meier Curve showing the probability of survival between the weight-change categories *(log-rank test p-value = 0.0005).*

Overall, there were 1,963 composite events of all-cause mortality, non-fatal stroke and non-fatal acute MI; with a crude incidence rate of 30 per 1,000 person-years (95%CI: 28.8 – 31.5). These were distributed thus within the weight change categories: Those with >5kg weight loss: 498 events (36 per 1000pyrs); 1 to 5kg weight loss: 544events (29 per 1000pyrs); no change in

weight: 87 events (26 per 1000pyrs); 1 to 5kg weight gain: 360events (26 per 1000pyrs); and >5kg weight gain: 474 events (30 per 1000pyrs). These events are summarised in Table 5.7.

5.3.4.4. Risk of Composite CV Outcomes:

The hazard of the three-point composite outcome of non-fatal AMI, non-fatal stroke and all-cause mortality was compared to the no weight change group (Table 5.7). The unadjusted hazard for the composite outcome was 41% higher (HR: 1.41, 95%CI: 1.23 – 1.77) in patients who lost greater than 5kg weight year post-insulin initiation compared to the weigh-neutral group. However, this risk was 15%, 3% and 19% non-significantly higher in the 1.0 – 5.0kg weight loss; 1.0 - 5.0kg weight gain and >5.0kg weigh-gain groups respectively in the unadjusted model.

Following adjustment for significant baseline variables as age, duration of diabetes, diastolic and systolic blood pressures, height, weight, albumin, glomerular filtration rate, gender, smoking status, alcohol status, lipid profile, socio-economic status (measured by Townsend deprivation scores), use of other glucose-lowering medications and antihypertensives; and other comorbidities (as heart failure and peripheral artery disease); the hazard slightly reduced to 31% (aHR: 1.31, 95%CI: 1.02 – 1.68) in patients who lost greater than 5kg compared to the weight-neutral group. Similarly, the hazard was non-significantly reduced to 13% (95%CI: 0.93 – 1.15) in those who gained > 5kg of weight but was the same (aHR: 1.15, 95%CI: 0.90 – 1.47) in those who lost 1 to 5kg and unity (aHR: 1.00, 95%CI: 0.78 – 1.30) in those who gained 1 to 5kg, compared to the weight-neutral group.

Table 5.7: Events, Incidence Rate and Hazards of Composite Outcome by Weight-Change Categories

Weight Change	Lost > 5kg (n = 4116)	Lost 1.0 to 5.0kg (n = 5311)	No Change (n = 970)	Gained 1.0 to 5.0kg (n =3852)	Gained > 5.0kg (n = 4565)	Total (n = 18,814)
Study Population						
Composite Outcome[a]	498	544	87	360	474	1963
Incidence rate (per 1000pyrs)	35.7	29.4	25.5	26.3	30.3	30.1
(95% CI)	(32.7 – 39.0)	(27.0 – 32.0)	(20.7 – 31.5)	(23.7 – 29.2)	(27.7 – 33.1)	(28.8 – 31.5)
Adjusted Hazard Ratio[b]	1.31	1.15	1 (ref)	1.00	1.13	-
(95% CI)	(1.02 – 1.68)	(0.90 – 1.47)	-	(0.78 – 1.30)	(0.93 – 1.15)	-
p-value	0.032	0.263	-	0.975	0.344	-
Obese subgroup (BMI ≥ 30kg/m^2)						
Composite Outcome[a]	362	335	49	209	246	1201
Incidence rate (per 1000pyrs)	34.5	27.7	23.3	25.5	29.8	29.2
(95% CI)	(31.2 – 38.3)	(24.9 – 30.9)	(17.6 – 30.8)	(22.2 – 29.1)	(26.3 – 33.8)	(26.3 – 33.8)
Adjusted Hazard Ratio[b]	1.50	1.27	1 (ref)	1.14	1.29	-
(95% CI)	(1.08 – 2.08)	(0.91– 1.76)	-	(0.81 – 1.60)	(0.92 – 1.81)	-
p-value	0.014	0.159	-	0.455	0.136	-

[a] *Composite outcome includes all-cause mortality, non-fatal acute myocardial infarction (AMI) and non-fatal stroke.*
[b] *Adjusted for age, diabetes duration diastolic and systolic blood pressure, height, weight, albumin, glomerular filtration rate, gender, smoking status, alcohol status, lipid profile, Townsend Deprivation score, number of glucose-lowering therapies, Lipid-lowering therapies, antihypertensives, heart failure and peripheral artery disease.*

The proportional hazards assumptions of the cox-regression analysis were tested by adding by comparing the cumulative hazard plots groups on the exposure group, including an interaction term of the predictor and log time and also by using Schoenfeld residuals test. No violations were observed as both were found to be non-significant and satisfied the proportional hazard assumption.

5.3.4.5. Sensitivity and Subgroup Analyses:

Obese subgroup: In the obese (BMI of 30kg/m^2 and above) population subgroup, 1,201 composite events occurred, giving a crude incidence rate of 29/1,000 person-years (95%CI: 28 - 31). The distribution of the events and their incidence rates by the weight change groups are shown in Table 5.7. Compared to the weight-neutral group, the adjusted risk of composite CV risk and all-cause mortality event was 50% (aHR: 1.50, 95%CI: 1.08 – 2.08) more in the obese population group who lost greater than 5kg at one-year post-insulin initiation compared to the weight-neutral group. Similarly, a non-significant increase of 27%, 14% and 29% in this risk was, however, reported in the 1 to 5kg weight-loss, 1 to 5kg weight-gain and >5kg weight-gain groups as shown in Table 5.7.

Risk of mortality, non-fatal MI and non-fatal stroke: The events, and hazards of the components of the three-point composite event are shown in Table 5.8. Patients who lost greater than 5 kg one-year post-insulin initiation showed increased risk of mortality of 27% (95%CI: 1.01 – 1.89, but no statistically significant difference in risk was found for non-fatal MI although it showed a 5-fold increased risk (aHR: 5.06, 95%CI:0.68 – 37.67). Also, the risk of non-fatal stroke was non-significantly increased by 15% (aHR: 1.15, 95%CI: 0.77 – 1.71) compared to the no weight-neutral category. Summarily, other weight categories in all the

composite components showed non-significant greater risks compared to the weight-neutral group as shown in Table 5.8 below.

Table 5.8: Events, Incidence Rate and Hazards of the Components of the Three-point Composite Outcome by Weight-Change Categories

Weight Change	Lost > 5kg	Lost 1.0 to 5.0kg	No Change	Gained 1.0 to 5.0kg	Gained > 5.0kg	Total
	(n = 4116)	(n = 5311)	(n = 970)	(n =3852)	(n = 4565)	(n = 18,814)
Mortality						
Total Events	312	320	51	208	260	1151
Incidence rate (per 1000)	19.9	15.3	13.2	13.5	14.6	15.6
(95% CI)	(17.8 – 22.2)	(13.7 – 17.1)	(10.0 – 17.4)	(11.8 – 15.5)	(12.9 – 16.5)	(14.8 – 16.6)
Adjusted Hazard Ratio[a]	1.37	1.14	1 (ref)	0.99	1.01	-
(95% CI)	(1.01 – 1.89)	(0.83 – 1.57)	-	(0.71 – 1.38)	(0.72 – 1.39)	-
p-value	0.051	0.421	-	0.947	0.986	-
Non-fatal Myocardial Infarction						
Total Events	25	25	2	28	36	116
Incidence rate (per 1000)	1.6	1.2	0.5	1.9	2.1	1.6
(95% CI)	(1.1 – 2.4)	(0.8 – 1.8)	(0.1 – 2.1)	(1.3 – 2.7)	(1.5 – 2.9)	(1.3 – 1.9)
Adjusted Hazard Ratio[a]	5.06	4.26	1 (ref)	5.42	7.71	-
(95% CI)	(0.68 – 37.67)	(0.58 – 31.57)	-	(0.73 – 40.33)	(1.06 – 56.34)	-
p-value	0.113	0.156	-	0.099	0.044	-
Non-fatal Stroke						
Total Events	161	199	34	124	178	696
Incidence rate (per 1000)	11.3	10.4	9.7	8.8	11.0	10.3
(95% CI)	(9.6 – 13.1)	(9.1 – 12.0)	(6.9 – 13.6)	(7.4 – 10.5)	(9.5 – 12.7)	(9.6 – 10.3)
Adjusted Hazard Ratio[a]	1.15	1.10	1 (ref)	0.95	1.12	-
(95% CI)	(0.77 – 1.71)	(0.74 – 1.63)	-	(0.63 – 1.43)	(0.75 – 1.65)	-
p-value	0.509	0.627	-	0.810	0.579	-

[a]*Adjusted for age, diabetes duration diastolic and systolic blood pressure, height, weight, albumin, glomerular filtration rate, gender, smoking status, alcohol status, lipid profile, Townsend Deprivation score, number of glucose-lowering therapies, Lipid-lowering therapies, antihypertensives, heart failure and peripheral artery disease.*

Sensitivity analyses comparing the hazards of the composite events between the weight-change categories ranked in quintiles, showed similar pattern in the risk of the three-point composite event. Similarly, I obtained similar results and trend in risk of the composite outcome and individual components of the 3-point composite outcome when I compared the incomplete and imputed datasets. This affirmed that the imputation robustly addressed the missing data.

5.3.5. Objective 2 - Results

5.3.5.1. Patients' Characteristics:

A total of 18,227 adults were left of the 18,814 selected for the study following the exclusion of 587 participants who did not have both weight and HbA1c values recorded at baseline. Their mean age was 61.5 (13.6) years while higher proportion (53.2%) were males. Table 5.9 summarises the distribution of the baseline characteristics of the study participants, categorised by the weight-change groups at 6 months after insulin initiation.

Table 5.9: Baseline characteristics of the participants grouped by weight-change categories at 6 months

	Weight loss (n=7,494)	Weight neutral (n=2,586)	Weight gain (n=8,147)	Total (18,227)
Demographics				
Age (yrs), Mean (SD)	61.7 (13.8)	61.1 (13.3)	61.5 (13.6)	61.5 (13.6)
Gender, No. (%)				
Male	3931 (52)	1359 (53)	4405 (54)	9695(53.2)
Female	3563 (48)	1227 (47)	3742 (46)	8532(46.8)
Townsend deprivation index, No. (%)				
Least deprived	1481 (21)	525 (21)	1581 (20)	3587(19.7)
2nd quintile	1433 (20)	500 (20)	1564 (20)	3497(19.2)
3rd quintile	1565 (22)	507 (21)	1658 (21)	3730 (20.5)
4th quintile	1542 (22)	528 (21)	1693 (22)	3763 (20.7)
Most deprived	1151 (16)	406 (16)	1302 (17)	2859 (15.7)
Clinical Parameters, Mean (SD)				
HbA1c (%)	8.6 (1.8)	8.7 (1.8)	8.7 (1.8)	8.7 (1.8)
BMI (kg/m2)	33.9 (6.7)	32.6 (6.8)	31.2 (6.8)	32.5 (6.9)
Weight (Kg)	94.6 (18.2)	91.2 (18.7)	88.3 (18.7)	91.3 (18.7)
Height (m)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
SBP (mmHg)	137.9 (23.4)	135.6 (21.2)	135.0 (23.1)	136.3 (23.0)
DBP (mmHg)	76.1 (10.9)	75.6 (10.7)	76.0 (10.8)	76.0 (10.8)
TC (mmol/l)	4.6 (1.3)	4.5 (1.2)	4.5 (1.3)	4.5 (1.3)
HDL (mmol/l)	1.2 (0.4)	1.2 (0.4)	1.2 (0.5)	1.2 (0.4)
LDL (mmol/l)	2.4 (1.1)	2.3 (1.1)	2.3 (1.1)	2.4 (1.1)
Triglyceride (mmol/L)	2.1 (1.2)	2.0 (1.2)	2.0 (1.2)	2.0 (1.2)
Albumin (g/L)	4.0 (0.4)	4.1 (0.4)	4.1 (0.4)	4.0 (0.4)
eGFR (mls/min/1.73m^2)	62.1 (21.4)	63.4 (21.0)	63.6 (21.1)	62.9 (21.2)
ACR (mg/mol)	5.8 (8.5)	6.0 (8.5)	5.8 (8.4)	5.8 (8.5)
Diabetes duration (yrs)	4.4 (4.8)	3.8 (4.7)	4.4 (4.9)	4.3 (4.9)
Smoking status, No. (%)				
Non-smoker	3644 (48)	1260 (48)	3957 (48)	8861 (48.6)
Current smoker	1106 (15)	393 (15)	1126 (14)	2625 (14.4)
Ex-smoker	2744 (37)	933 (36)	3064 (38)	6741 (37.0)
Alcohol status, No. (%)				

Non-drinker	2494 (33)	810 (31)	2612 (32)	5916 (32.5)
Current drinker	4162 (56)	1484 (57)	4597 (56)	10243 (56.2)
Ex-drinker	838 (11)	292 (12)	938 (12)	2068 (11.3)
BMI at baseline, No. (%)				
Normal	657 (9)	337 (13)	1461 (18)	2455 (13.5)
Overweight	1526 (20)	653 (25)	2164 (27)	4343 (23.8)
Obese	5311 (71)	1596 (62)	4522 (56)	11429 (62.7)
GLTs, No. (%)				
Dual Therapy	1168 (16)	437 (17)	1220 (15)	2825 (15.5)
Triple Therapy	2485 (33)	871 (34)	2677 (33)	6033 (33.1)
Quadruple Therapy and above	3841 (51)	1278 (49)	4250 (52)	9369 (51.4)
Use of Medications, No. (%)				
Aspirin	7193 (98)	2467 (96)	7847 (96)	17507 (96.1)
Antihypertensive	6537 (91)	2245 (91)	7154 (91)	15936 (87.4)
LLTs	6562 (91)	2250 (91)	7164 (91)	15976 (87.7)
Comorbidities, No. (%)[c]				
CHD	2252 (30)	759 (29)	2449 (30)	5460 (30.0)
AMI	286 (4)	99 (4)	314 (4)	699 (3.8)
PAD	959 (13)	331 (13)	1118 (14)	2408 (13.2)
Stroke	1124 (15)	379 (15)	1235 (15)	2738 (15)
Heart Failure	996 (13)	352 (14)	1109 (14)	2457 (13.5)
Hypoglycaemia	1284 (17)	464 (18)	1437 (18)	3185 (17.5)

Abbreviations:
BMI (body mass index); SBP (systolic blood pressure); DBP (diastolic blood pressure); HbA1c (haemoglobin A1c); HDL (high-density lipoprotein); LDL (low-density lipoprotein); TC (total cholesterol); eGFR (estimated glomerular filtration rate); LLTs (lipid lowering therapies); PAD (peripheral arterial disease); CHD (coronary heart disease); ACR (albumin creatinine ratio); GLTs (Glucose-lowering therapies); AMI (Acute myocardial infarction);
SD (standard deviation). Liver-associated diseases include liver cirrhosis, portal hypertension, liver failure and hepatocellular carcinoma.
Diabetes duration is the time from first diagnosis of diabetes to date of insulin initiation (index date)

5.3.5.2. Proportion undergoing weight change from baseline

Below, Figure 5.6 shows the proportions of the study participants undergoing weight change at the different timelines. The proportions of patients in the weight-neutral group were significantly lower at 36 months following insulin initiation, compared to 6 months (6.6% vs 19.6% $p < 0.0001$). Conversely, the proportions in both the weight-loss and weight-gain groups were significantly greater at 36 months compared to 6 months (38.3% vs 46.7%, $p = 0.002$ for weight-loss; and 42.1% vs 46.7%, $p = 0.004$ for weight-gain). However, in the weight-gain group, the greatest proportion achieving weight-gain was at 24 months, before it dipped thereafter.

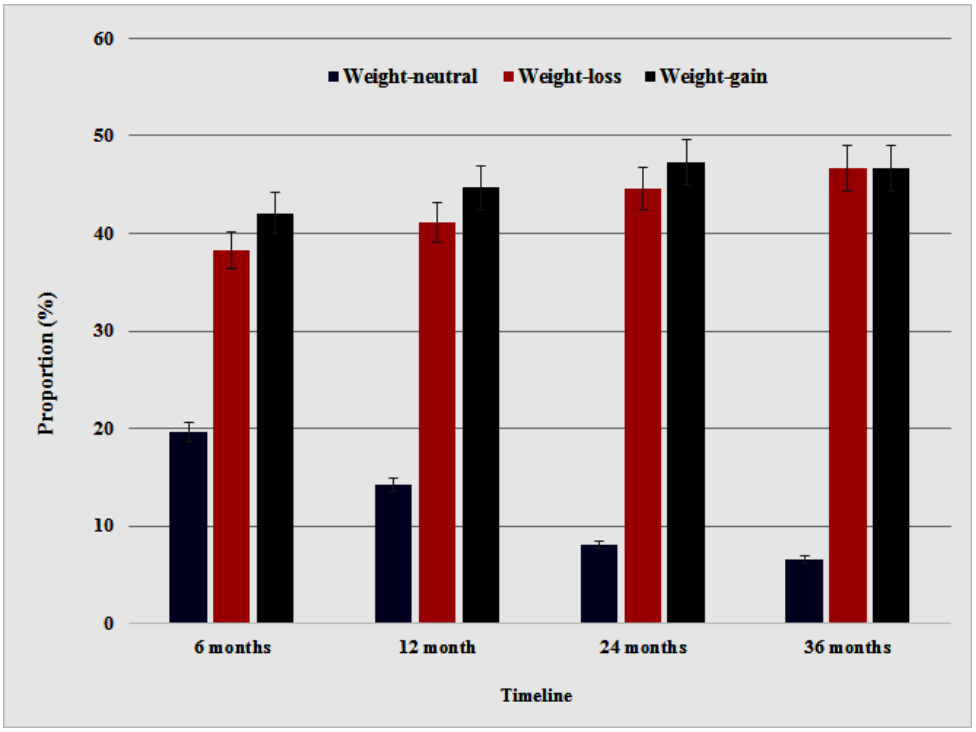


Figure 5.6: Proportion of the study participants undergoing weight change at the different timelines

Figure 5.7 below shows the yearly mean weight in the weight categories after 6 months. Whilst weight significantly increased in the weight-gain group from 91.7 ± 19.0 kg after 6 months to 92.9 ± 18.2 kg at 36 months ($p < 0.0001$); it reduced from 90.5 ± 18.4 kg to 88.4 ± 17.6 kg ($p < 0.0001$) in the weight-loss group; and almost formed a plateau (90.4 ± 18.9kg vs 89.9 ± 18.1kg, $p < 0.0001$) in the weight-neutral group

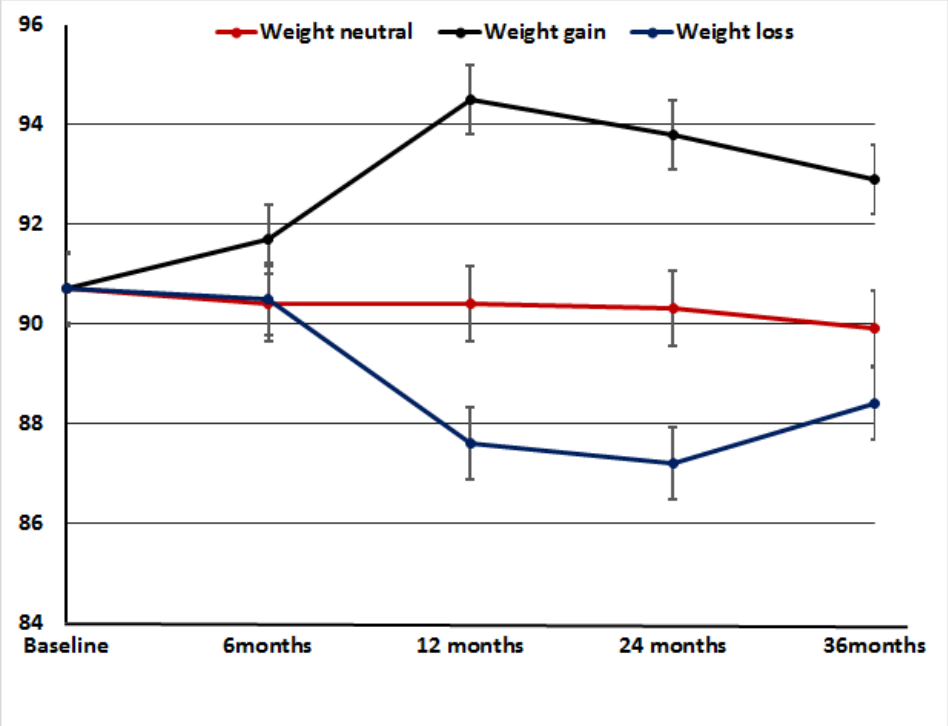


Figure 5.7: Yearly mean weight in the weight-change categories after 6 months of insulin initiation

5.3.5.3. Does insulin-induced weight gain affect glucose control?

Table 5.10 shows a weak negative relationship between change in weight and glycaemic control in the regression model where change in weight was fitted as a continuous variable. Therefore, each unit increase in weight was associated with a slight but significant reduction in HbA1c. Furthermore, this reduction was significantly lower with increasing time. So, for a kg of insulin-induced increase in weight, HbA1c significantly decreased by 0.011% (95% CI: -0.015, -0.008; $p < 0.0001$) at 6 months; 0.005% (95% CI: -0.008, -0.002; $p = 0.001$) at 12 months; 0.004% (95% CI: -0.006, -0.002; $p = 0.001$) at 24 months; and 0.003% (95% CI: -0.005, -0.0004; $p = 0.0022$) at 36 months after adjusting for age, blood pressure, height, eGFR, lipid profile and episodes of hypoglycaemia.

Similarly, Figure 5.8 is a pictorial representation of the association between change in weight and glycaemic control at the study timelines.

Table 5.10: Association between weight gain and glycaemic control

Timeline	△HbA1c (%)	95% CI	p-value
6 months	-0.011	-0.015, -0.008	< 0.0001
12 months	-0.005	-0.008, -0.002	0.001
24 months	-0.004	-0.006, -0.002	0.001
36 months	-0.003	-0.005, -0.0004	0.022

△HbA1c (%): mean change in HbA1c from baseline for each unit increase in weight after adjustment for age, systolic and diastolic blood pressure, height, total cholesterol, high-density lipoprotein, triglyceride and episodes of hypoglycaemia
95%CI: 95% confidence interval

This table shows the association between insulin-induced weight-gain and glycaemic control (measured by change in HbA1c) in the study population. It shows the change in HbA1c (%) per unit (1kg) increase in weight.

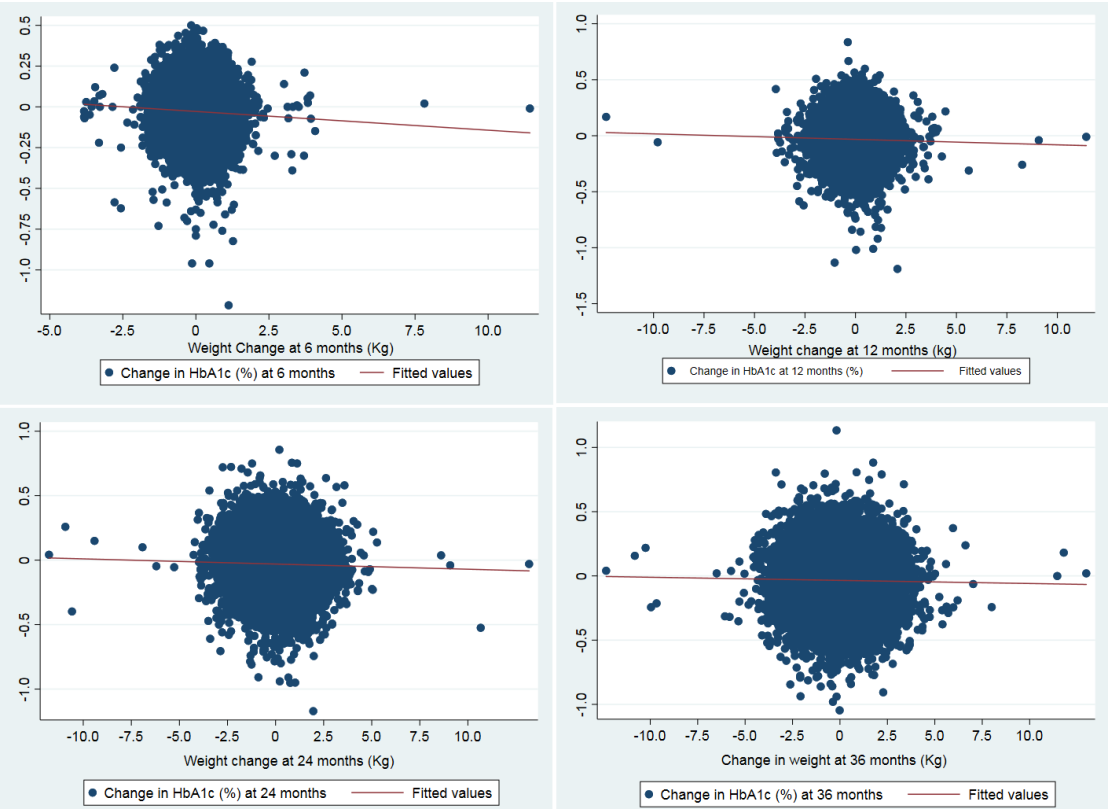


Figure 5.8: ***This figure illustrates the association between glycaemic control and change in weight at 6, 12, 24, 36 months of insulin initiation. Table 5.10 above shows the change in change in HbA1c for each unit increase in weight (kg).***

5.3.5.4. Relationship between weight and glycaemic control

Table 5.11 below shows the adjusted mean changes in HbA1c in the weight-loss and weight-gain categories, when compared to the weight-neutral group from 6 to 36 months. As can be seen, there was a non-significant increase in HbA1c value in the weight-loss group at 6 months (β = 0.012%, 95% CI: -0.038, 0.063; p = 0.631) and 36 months (β = 0.003%, 95% CI: -0.120, 0.126; p = 0.960). Conversely, compared to the weight-neutral group, there was a significant reduction in HbA1c in the weight-gain categories at 6 (β = -0.099%, 95% CI: -0.149, 0.049; p < 0.0001) and 12 months (β = -0.121%, 95% CI: -0.187, -0.054; p < 0.0001) only. Also, the weigh-gain category recorded the greatest reduction in HbA1c beyond 12 months (Table 5.11).

Table 5.11. Mean change in HbA1c and association with weight change

Weight-change categories	6 months	12 months	24 months	36 months
Weight-neutral	**Ref**	**Ref**	**Ref**	**Ref**
Weight-loss* (95% CI)	**0.012 (-0.038, 0.063)**	**-0.052 (-0.119, 0.015)**	**-0.002 (-0.103, 0.098)**	**0.003 (-0.120, 0.126)**
Weight-gain* (95% CI)	**0.099 (-0.149, -0.049)**	**-0.121 (-0.187, -0.054)**	**-0.084 (-0.184, 0.017)**	**-0.089 (-0.211, 0.034)**

95% CI (Confidence Interval); Ref (Reference)
**Mean beta-coefficient of change in HbA1c (%) in the weight-loss and weight-gain groups compared to the weight neutral group after adjustment for age, gender, systolic blood pressure, eGFR (glomerular filtration rate), total cholesterol, low-density lipoprotein and body mass index (BMI)*

5.3.6. Discussion

This observational study, derived from a large longitudinal real-world data provides reassurance that weight-gain associated with insulin treatment is not associated with adverse CV outcomes or poor glycaemic control. Conversely, patients who demonstrated significant weight loss with insulin treatment appear to have more adverse CV outcomes and worse glycaemic control compared to that observed in patients who maintained or increase their body weight. This observation persists when sub-analysed for patients who are obese (BMI 30kg/m^2) at baseline and when adjusted for various confounding factors.

These findings are further supported by consistency of the outcomes in patients from the entire cohort, and in the subgroup and sensitivity analyses. The level of HbA1c and CV risk profile (e.g. lipid, blood pressure) were clinically similar across all weight change categories. The impact of HbA1c change and weight change across different baseline weight categories as this study showed, is in concordance with a previous study using a US-based electronic medical record, which reported that a reduction in HbA1c was associated with progressively less weight gain as baseline BMI rose.[242] The inference from that study that the lesser weight gain seen in obese patients was due to the use of less intensive insulin therapy may also apply to this cohort.

As I argued earlier in section 5.2.5, it may seem logical that any increase in weight people in people with diabetes would increase CV events, there is in fact little direct evidence in support of this. Robust large scale clinical trials such as UKPDS, ADVANCE[210] and ACCORD[55] study did not stratify their CV outcomes by weight-loss or weight-gain, for any given level of glycaemic control. I opined further that though the ACCORD study reported excess mortality (and more weight gain) in the intensively treated group, a causal link cannot be inferred. This is further supported by the findings of a post hoc analysis of ACCORD in which patients who

were inadequately controlled at baseline and received intensive glucose lowering strategy but still had suboptimal glucose control (HbA1c >7% (>53 mmol/mol)) experienced higher mortality rate.[94] Thus, patient-factors associated with persistently high HbA1c, despite intensive treatment, appear to be the most important determinant of increased mortality risks. To this end, insulin-induced weight gain in our study was seen to be associated with a reduction in HbA1c, while those who lost weight were associated with a deterioration or unchanged HbA1c levels (Figure 5.8).

Three possible explanations could be inferred from this observation. Firstly, a rise in HbA1c levels may dilute any favourable impact of weight reduction and lead to an increase in CV events. In support of this, there is evidence that intensive control of blood glucose levels in patients with T2D reduces the long-term risk of adverse CV events.[103, 259] These benefits may take many years to become apparent but in view of the association between patients' HbA1c level, and risk of developing long-term vascular complications, current clinical guidelines recommend aggressive treatment escalations among patients with T2D to achieve low HbA1c targets.[41, 46, 260] Conversely, patients may however find the demands of intensive glycaemic control difficult to manage resulting in psychological stress, frustration and non-adherence especially if hypoglycaemia occurs.[261] A second, perhaps more likely explanation is the presence of other comorbidities (e.g. cancers, gastrointestinal disorders, other endocrine/metabolic disorders, etc.) which are associated with weight loss in the group who lost weight in excess of 5kg. These could have possibly driven the adverse outcomes seen in this group. Thirdly, insulin-induce weight gain could suggest patients' compliance to insulin treatment intensification and thus a surrogate marker of compliance to holistic care and treatment. Nevertheless, I contend that there is indirect evidence that failure to achieve HbA1c reduction, irrespective of the evidence for this, should be used as a trigger to intensify cardiovascular risk reduction strategies.

Our study findings are in keeping with the outcome of another real-world study in Australia which showed that insulin-induced weight-gain was not associated with adverse changes in cardiovascular risk factors after one year of insulin initiation.[262] Conversely, our data are in contrast to the findings in type 1 diabetes. In a sub-analysis of the DCCT study, Purnell et al. stratified data from the intensively treated DCCT cohort by quartiles of weight gain.[263] Comparing the first quartile (where BMI remained stable) with the fourth (where BMI increased by 7 kg/m^2), after a mean follow-up of 6.1 years, patients in the fourth quartile were associated with significant negative changes in all CV risk parameters. While a causal relationship between weight gain and adverse CV outcomes again cannot be assumed, other studies have reported that people with diabetes who actively lose weight improve not only their risk profile but also their longevity.[255, 264] These studies however did not focus on patients with T2D receiving insulin therapy. In this context, while weight-gain has to be viewed as an undesirable side effect of insulin therapy, may appear to be associated with adverse CV outcome in patients with type 1 diabetes.

5.3.7. Limitation

The analyses here were subject to a few limitations that are inherent in observational studies. Firstly, I cannot be certain that the patients were fully compliant with their medication. Also, some factors like lifestyle and dietary intervention and records of comorbidities as cancers and metabolic disorders (which were not so robustly included in our data) may influence our findings. I were also not able to obtain the longitudinal insulin doses, an important predictor of insulin-induced weight gain.[240, 243] [31,32] Since our aim was to look at status of weight-change due to insulin initiation per se on CV outcomes, I would argue that this should not influence the robustness of our findings. Although I could not account for potential residual confounders

such as compliance, indications for intensification treatments, markers of β-cell deterioration and frequency of hypoglycaemia, I were able to account for differences in the observed covariates and used robust analytical techniques to control confounding that may bias the results of the estimated treatment effects.

5.3.8. Conclusion

In conclusion, insulin-induced weight gain was neither associated with adverse CV outcomes as indirectly suggested in previous clinical trials, nor poor glycaemic control. These findings should provide important reassurance among patients with T2DM who gained weight following insulin treatment, and allay fears of physicians who develop inertia in initiation insulin therapy early in routine clinical practice.

Chapter Six: Cardiovascular Events, All-cause Mortality, and Metabolic Outcomes with Insulin Vs Glucagon-like Peptide Analogues (GLP-1RA)

6.1. Overview

This chapter comprises two related studies that explored the CV and metabolic outcomes associated with INS vs GLP-1RA (on a background of dual therapy - metformin and sulphonylurea) which I called Cohort 1; and insulin combination with GLP-1RA vs none (in a background of dual- or triple therapies) which I called Cohort 2. So, this chapter will be in two parts. The summary, introduction, method, and discussion sections will be combined for both studies, while the results sections will be presented separately under cohort 1 and 2.

6.2. Summary

Background

The cardiovascular (CV) benefits of the Glucagon like peptide-1 analogues (GLP1-RA), as well as its favourable effects on weight reduction and low risks of hypoglycaemia are known and when used in treatment intensification following metformin (MET) and sulphonylurea (SU) dual therapy failure; or in combination with insulin (INS) might be an attractive option to optimise glycaemic control, minimise CV risks and adverse metabolic outcomes.

Objectives

This chapter aimed to analysed time to cardiovascular events and mortality in two cohorts of patients with T2DM who received treatment intensification with (a) INS or a GLP-1RA following dual therapy failure with MET+SU; or (b) INS vs GLP-1RA after dual- or triple therapy failure.

Methods

A retrospective cohort study was conducted in patients who were newly treated with a GLP-1RA or INS following dual therapy (MET+SU) failure (Cohort 1) and in insulin users with an add-on treatment with GLP-1RA or not (Cohort 2) between 2006 and 2014. Data were sourced from The Health Improvement Network (THIN) database. The 5-year risk of a three-point composite of major cardiovascular outcome (MACE): all-cause mortality or non-fatal MI or stroke; and metabolic outcomes (glycaemic control and change in weight) were compared between these treatment groups in the propensity score-matched cohorts. Propensity score matching analysis and Cox proportional hazard models were employed.

Results

In cohort 1, the mean age was 52.8±14.1 years. Overall, the number of MACE was 231 vs 11 for patients who added insulin vs GLP-1RA respectively, (44.5 vs 7.7 per-1000-person-years adjusted Hazard Ratio (aHR): 0.27; 95%CI: 0.14-0.53; p<0.0001). INS was associated with significant increase in weight compared with GLP-1RA; (1.78 vs -3.93kg; p <0.0001) but HbA1c reduction was similar between both treatment groups; (-1.29 vs -0.98; p = 0.156). In a subgroup analysis of obese patients, (BMI>30kg/m2) there were 84 vs 11 composite outcomes

(38.6 vs 8.1 per 1000 person-years; aHR: 0.31; 95%CI: 0.16-0.61; p = 0.001) in the Insulin and GLP-1RA groups respectively.

In cohort 2, HbA1c reduction was similar between both groups (-0.42 vs -0.33%, p =0.089 at 12 months). Overall, three-point composite events of all-cause mortality and CV events (MACE) were 98 vs 55 for the insulin alone vs insulin+GLP-1RA groups respectively (14.7 vs 9.2 per 1000 person-years; adjusted Hazard Ratio (aHR): 0.64; 95%CI: 0.42-0.98; p=0.038). Corresponding composite non-fatal CV events were 33vs 28 (6.0 vs 5.6 per 1000 person-years; aHR: 0.76; 95%CI: 0.41- 1.42; p=0.393) while all-cause mortality events were 49 vs 13 (6.9 vs 2.0 per 1000 person-years; aHR: 0.35; 95%CI: 0.17- 0.73; p = 0.005)

Conclusion

Based on a large UK cohort in routine clinical practice, intensification of dual oral therapy by adding GLP-1RA or combining GLP-1RA with insulin therapy is associated with a reduction in risk of MACE outcome independent of body weight patients with Type 2 diabetes.

6.3. Introduction

The achievement of tight glucose control has been shown to reduce the risk of long term vascular complications in patients with type 2 diabetes (T2D).[103, 219] Following the initiation of antidiabetic medication with metformin (MET), about 40-60% of patients with T2D fail to achieve their glycaemic target, requiring intensification with a second-line agent, typically, with a sulphonylurea (SU).[265, 266] For many patients, failure to maintain optimal HbA1c level

despite up-titration to maximal doses of dual therapy (MET+SU) will necessitate the need for further intensification with a third-line agent.

Although a variety of treatment options are available following failure of MET+SU dual therapy, limited data are available on the cardiovascular (CV) safety and diabetes-related outcomes on the most appropriate third line antidiabetic therapy.[79, 267] For many patients with T2D, insulin treatment will be required to control hyperglycaemia and to reduce the risk of long-term vascular complications in patients with type 2 diabetes (T2D).[103, 259, 265, 266]. However, insulin therapy is known to induce ~4-9 kg weight gain in the first year of treatment.[206] Also, in the last 7 years, questions regarding the long term cardiovascular (CV) safety of insulin have been raised.[87, 105] These epidemiological studies however have mainly investigated the use of insulin as monotherapy or in combination with metformin.[115, 180, 216]

Conversely, the cardiovascular benefits of the Glucagon like peptide-1 analogues,[268, 269] a novel glucose lowering therapy with favourable effects on weight reduction and low risks of hypoglycaemia are an active area of clinical investigations (http://www.clinicaltrials.gov). GLP-1RA are hypothesized to have pleiotropic effects on the cardiovascular system based on evidence from experimental studies.[270] Preclinical studies have also already demonstrated the pleotropic effects of GLP-1RA on myocardium and vascular endothelium,[270, 271] and many clinical studies have reported improvement in surrogate markers of CV disease.[269] More recently, The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial showed that liraglutide, a GLP-1RA, is associated with significant reductions of CV events and death from CV causes.[272]

Thus, since insulin is known to be associated with weight gain and increased risk of hypoglycaemia, adding a GLP-1RA to MET+SU or the use of INS + GLP-1RA combination may be an attractive alternative to lower HbA1c in patients with T2D. No comparative 'real

world' outcome data of INS versus GLP-RA in patients with dual therapy failure or INS+GLP-1RA versus others, are however available. Further work is therefore needed to explore the CV safety of insulin compared or combined with GLP-1RA when used as a third line (injectable) therapy in patients with longer duration disease and higher CV risk.

The aims of the study therefore were to compare the real-world composite cardiovascular and mortality outcomes in UK clinical practice amongst patients with T2D following intensification of MET+SU dual-therapy with either insulin or a GLP-1RA or a combination of INS and GLP-1RA.

6.4. Methods

6.4.1. Study Design and Data Sources

This was a retrospective cohort study using the UK primary care database- The Health Improvement Network (THIN). THIN has been described fully in Chapter 2.

6.4.2. Study Population

This comprised patients with T2D aged 18 and above, whose MET+SU dual-therapy was intensified with either insulin or GLP-1RA (cohort 1) and those with insulin +/- GLP-1RA after dual- or triple therapy intensification (cohort 2), between January 2006 and May 2014. In cohort 1, participants were selected on treatment intensification with either insulin or GLP-1RA (index date). Patients who started insulin or GLP-1 analogue first before MET+SU commenced; or previously on other antidiabetic medication; or on more than dual therapy; or with any form of CV event before index date; or with type1 diabetes were excluded. In cohort 2, adult insulin users (on a background of dual or triple therapy) who went on to have their

insulin therapy intensified with either an add-on of GLP-1RA or not, independent of the use of other GLTs were selected. Those who started GLP-1RA before insulin were excluded. The other above exclusion criteria were applied.

6.4.3. Exposures and Outcomes

The exposures of interest for both studies were insulin (either ultra-short/short acting, premixed or long-acting) and GLP-1RA agonist analogues (exenatide, liraglutide or lixisenatide) with a follow up period of 5 years from index date. The study was exposure-based and from the index date, participants were followed up for a maximum of 5 years, and were censored at the earliest of the following: discontinuation or substitution of GLP-1RA or insulin; loss to follow-up (transfer out of practice); first occurrence of any of the study outcomes; or at the end of the study after 5 years. This implies that if no records of prescriptions of GLP-RA or insulin were found after one year in the electronic records, such medication was considered stopped and the patient censored at this point.

The primary outcomes were time to the risk of a three-point composite event of Major Adverse Cardiovascular Event (MACE) which comprises all-cause mortality, non-fatal MI and non-fatal stroke and all-cause mortality. In cohort 2, the time to the risk of two-point composite CV event (non-fatal myocardial infarction (MI) or non-fatal stroke) was estimated in a subgroup of patients from the main cohort, with no prior CV history. These outcomes and their dates of occurrence were identified and extracted using their appropriate Read Codes in the THIN database. The secondary outcomes were the mean changes in HbA1c (glycaemic control) and weight between both treatment groups from baseline at 6, 12, 24 and 36 months etc.

6.4.4. Covariates

Important time-varying clinical baseline covariates were extracted and included in the data. These were fitted in our regression models to adjust for their confounding effects on the study outcome. These have been described in Chapter 2.

6.4.5. Statistical Analyses

The data were summarised within the treatment groups in cohort 1 (MET+SU+INS vs MET+SU+GLP-1RA) and cohort 2 (INS+GLP-1RA vs INS+Non-GLP-1RA) using mean values and standard deviation (SD) for continuous variables; and frequencies (%) for categorical variables. I also estimated the propensity score (PS) for treatment with GLP-1RA using logistic regression as the conditional probability of being treated with GLP-1RA with the baseline covariates as age, gender, socioeconomic status, alcohol and smoking status, BMI, weight, height, systolic and diastolic blood pressure, HbA1c, lipid-profile, GFR, creatinine level, ACR, the use of other medications, comorbidity status and the duration of diabetes treatment. I matched both treatment groups (INS vs +GLP-1RA in cohort 1 and INS+GLP-1RA vs Non-GLP-1RA in cohort 2) based on their estimated treatment probabilities, with the average treatment effect on the treated (ATT) computed by 1:1 matching for each group at the nearest distance, measured by the estimated propensity score. The standardised differences between the treatment groups following adjustment with the PS and all the baseline variables were calculated using linear regression models with their p-values determined. A difference > 10% was considered significant. In the summary table as well, the distribution of the covariates between the treatment groups in the PS-matched group was also summarised.

Using the Kaplan-Meier survival estimate, the crude and adjusted 5-year estimates of survival functions for both treatment groups in both cohorts were obtained. The absolute reduction in

the probability of the incidence of the outcome within a 5-year follow-up from these survival functions was obtained. Also, the marginal hazard ratios to quantify the adjusted hazard of MACE and the incidence of mortality and CV events in the treated groups in each cohort respectively compared to the comparator group. Having considered PS a prognostic covariate, it was included in the final Cox proportional hazards regression model.

I tested for violations of the proportional hazard assumption of the Cox regression analyses by adding an interaction term of the predictor and log time and by analysing the Schoenfeld residuals. I did not observe any violations of the proportional hazard assumption because both were found to be non-significant. I used maximum likelihood estimation to explore if there is any possible interactions between the treatment groups and the baseline variables which were included in the propensity score but found no interactions with any of the covariates. Finally, I compared glycaemic efficacy (measured by change in HbA1c from baseline at different follow-up timelines) and in cohort 2, changes in weight between the two treatment groups using Student's t-test and linear regression while adjusting for significant baseline covariates.

Missing data among covariates were accounted for with multiple imputations using the chained equation (MICE) model. All analyses were conducted using Stata Software, version 13.[170]

Subgroup and Sensitivity Analyses

In cohort 1, I fitted Cox proportional hazard models to adjust for baseline and time-varying demographics, comorbidities, medications and metabolic indices for those with BMI of 30kg/m^2 and above and 40kg/m^2 in order to explore the impact of obesity in influencing the primary outcomes. In both cohorts, I compared the study outcomes between the full data and PS-matched population to compare the confounding effect of selection bias could have on the

full cohort. I also estimated the hazard of MACE, all-cause mortality and CV events in the subtypes of GLP-1RA identified in the dataset (liraglutide, exenatide and lixinatide), using the non-GLP-1RA group as the comparator.

Statistical significance was put at a p-level of 0.05 and to avoid the probability of type II error, the studies were powered to 0.9 with a minimum sample size of 400 in each arm was estimated to be adequate to detect a true difference of 0.1 between the two treatment groups at 5% significance level. In the regression models and all other analyses, the point estimates were computed, with 95% confidence intervals (CI), at the conventional statistical significance level of 0.05. I used multiple imputations using the chained equation (MICE) model to account for any missing data among covariates. All analyses were conducted using Stata Software, version 14[21].

Cohort 1

6.5. Cohort 1 - Results

6.5.1. Cases and Total Follow up

From the THIN database, I identified 2,003 eligible patients in the UK Primary care, whose MET+SU dual-therapy was intensified with the addition of either Insulin (1,584) or GLP-1RA (419). The flow diagram (Figure 1) shows how our cohort was derived. The median treatment duration was 8.33 (IQR: 6.63 to 8.34) years. The median follow-up was 3.74 years (IQR: 2.10–4.93) representing a total follow-up period of 6614.12 person-years.

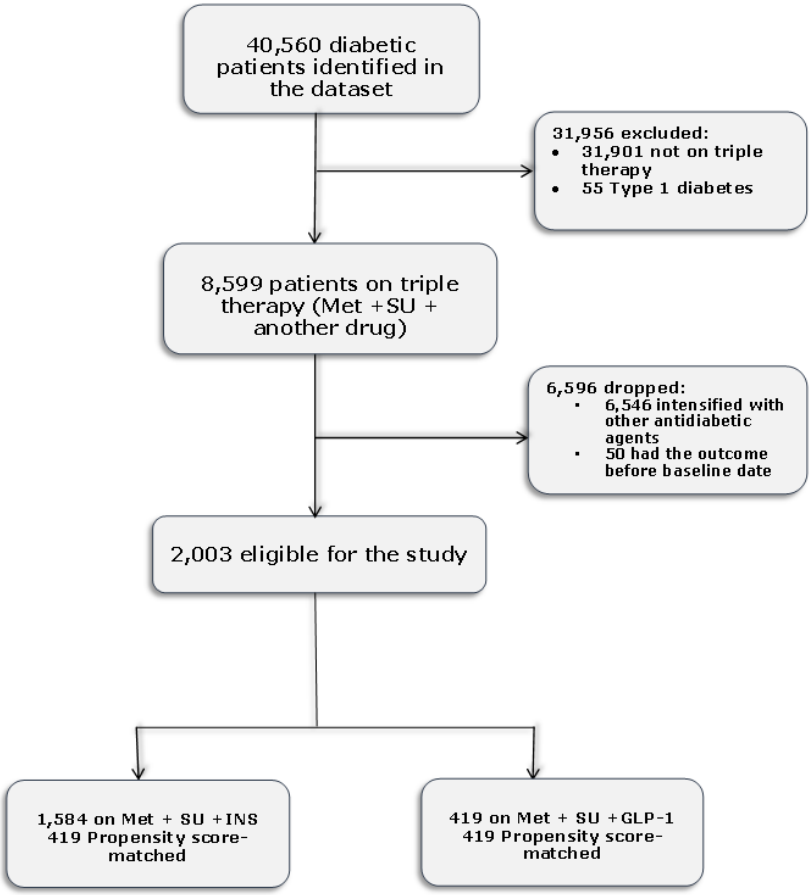


Figure 6.1: Selection of participants in Study cohort 1

6.5.2. Patients' Characteristics

In the full cohort, the overall median age was 53.0 (IQR: 43.0-63.0) years. 50.2% were females. The mean BMI and HbA1c level were 31.8 (7.9) kg/m^2 and 9.7(2.9)% respectively. One-on-one propensity score matching yielded 419 patients each in both treatment arms. The baseline characteristics in both treatment groups were compared between the full and matched cohort of patients with their standardised differences shown in Table 6.1 below.

Table 6.1: Baseline Characteristics (Cohort 1)

Baseline variable	Full Cohort			Propensity Matched Cohort		
	MET + SU			MET + SU		
	INS (n = 1584)	GLP-1RA (n = 419)	Std. diff [a]	INS (n = 419)	GLP-RA (n = 419)	Std. diff [b]
Demographics						
Age (yrs), Mean (SD)	53.8 (14.8)	49.6 (10.5)	- 0.33	49.0 (13.3)	49.6 (10.5)	0.05
Gender, No. (%)						
Male	770 (49.0)	227 (54.0)	0.12	193 (46.1)	227 (54.2)	0.16
Female	814 (51.0)	192 (46.0)	-0.12	226 (53.9)	192 (45.8)	-0.16
Townsend deprivation, No. (%)						
Least deprived	294 (18.6)	78 (18.6)	-0.01	86 (20.5)	78 (18.6)	-0.05
Less	300 (18.9)	84 (20.1)	-0.09	81 (19.3)	84 (20.1)	0.02
Average	333 (21.0)	75 (17.9)	-0.16	70 (16.7)	75 (17.9)	0.03
More	352 (22.2)	98 (23.4)	0.11	109 (26.0)	98 (23.4)	-0.06
Most deprived	305 (19.3)	84 (20.0)	0.17	73 (17.5)	84 (20.0)	0.07
Clinical Parameters, Mean (SD)						
HbA1c (%)	9.9 (2.9)	9.4 (2.0)	-0.13	9.4 (2.3)	9.4 (2.0)	-0.02
BMI (kg/m2)	29.8 (6.70)	39.6 (7.1)	1.28	39.7 (7.5)	39.6 (7.1)	-0.02
Weight (Kg)	84.6 (20.5)	115.4 (23.8)	1.31	114.4 (23.0)	115.4 (23.8)	0.04
SBP (mmHg)	132.6 (17.5)	136.1 (15.0)	0.37	136.8 (16.3)	136.1 (15.0)	-0.05
DBP (mmHg)	79.6 (10.5)	82.6 (10.1)	0.33	83.6 (11.2)	82.6 (10.1)	-0.10*
TC (mmol/l)	5.1 (1.6)	4.8 (1.5)	-0.03	5.0 (1.5)	4.8 (1.5)	-0.11*
HDL (mmol/l)	1.2 (0.4)	1.1 (0.3)	-0.34	1.0 (0.3)	1.1 (0.3)	0.07
LDL (mmol/l)	2.8 (1.1)	2.6 (1.1)	-0.08	2.7 (1.0)	2.6 (1.1)	-0.07
Triglyceride (mmol/L)	2.9 (5.8)	3.2 (4.0)	0.10	3.1 (3.0)	3.2 (4.0)	0.01
Albumin (g/L)	42.0 (4.3)	42.5 (3.7)	0.13	42.7 (3.9)	42.5 (3.7)	-0.06
eGFR (mls/min/1.73m2)	74.1 (19.0)	78.5 (16.2)	0.32	77.6 (16.9)	78.5 (16.2)	0.05
ACR (mg/mol)	4.8 (11.4)	4.0 (8.6)	0.01	4.2 (12.5)	4.0 (8.6)	-0.02
Diabetes duration (yrs)	2.6 (4.6)	2.7 (3.0)	0.19	2.9 (5.6)	2.7 (3.0)	-0.04
Smoking status, No. (%)						

Non-smoker	619 (39.0)	164 (39.2)	0.08	159 (38.0)	164 (39.2)	0.03
Current smoker	435 (27.5)	94 (22.4)	-0.16	86 (20.5)	94 (22.4)	0.05
Ex-smoker	530 (33.5)	161 (38.4)	0.07	174 (41.5)	161 (38.4)	-0.06
BMI Categories, No. (%)						
$\leq 30 kg/m^2$	918 (58.0)	19 (4.5)	-1.30	20 (4.8)	19 (4.5)	-0.01
$30\text{-}34.9 kg/m^2$	354 (22.3)	110 (26.3)	0.07	105 (25.0)	110 (25.3)	0.03
$\geq 35 kg/m^2$	312 (19.7)	290 (69.2)	1.06	294 (70.2)	290 (69.2)	-0.02
Use of Medications, No. (%)						
Aspirin	220 (13.9)	82 (19.6)	0.10	84 (10.1)	82 (19.6)	-0.01
Antihypertensive	587 (37.1)	212 (50.6)	0.23	201 (48.0)	212 (50.6)	0.05
LLT	608 (38.4)	240 (57.4)	0.28	227 (54.2)	240 (57.3)	0.06
Comorbidities, No. (%) [c]						
Other CHD	38 (2.4)	7 (1.6)	-0.05	3 (0.7)	7 (1.7)	0.09
PAD	29 (1.8)	7 (1.6)	-0.05	5 (1.2)	7 (1.7)	0.04
Heart Failure	31 (2.0)	4 (1.0)	0.03	1 (0.2)	4 (1.0)	0.09
Hypoglycaemia	124 (7.8)	13 (3.1)	-0.01	8 (1.9)	13 (3.1)	0.08

MET (metformin); SU (sulphonylurea); GLP-1RA (Glucagon-like peptide 1); INS (insulin); BMI (body mass index); SBP (systolic blood pressure); DBP (diastolic blood pressure); HbA1c (haemoglobin A1c); HDL (high-density lipoprotein); LDL (low-density lipoprotein); TC (total cholesterol); GFR (glomerular filtration rate); LLT (lipid lowering therapy); PAD (peripheral arterial disease); CHD (coronary heart disease); ACR (albumin creatinine ratio); SD (standard deviation)

Diabetes duration is time from first diagnosis of diabetes to date of intensification with 3rd line drug (index date)

[a] Standardized differences are the absolute difference in means or percentage divided by the standard deviation of the treated group

[b] Resulting standardized difference after 1:1 matching based on average treatment effect on treated (ATT) propensity score technique and robust variance estimation [c]Comorbidities: other recorded medical disorders

** In the matched cohort, only Diastolic BP and Total Cholesterol had statistically significant standardized difference at 0.01 level*

6.5.3. Crude Event Rates:

Survival analyses at 5 years were 95.8% vs 99.3% for insulin and GLP-1RA intensified therapies respectively (Figure 6.2). Overall, there were 242 composite events with a crude incidence rate of 36.9 per 1,000 person-years (95%CI: 32.3 – 41.5). There were 231 vs 11 composite events in the insulin vs GLP-1RA groups respectively, with unadjusted incidence MACE rates of 44.5 vs 7.7 per 1,000 person-yrs (Table 6.2). Among the obese population (BMI $\geq$ 30kg/m^2), there were 84 vs 11 composite MACE events, accounting for an unadjusted incidence rates of 38.6 vs 8.1 per 1,000 person-years in patients intensified with insulin vs GLP-1 respectively. Similarly, when stratified for morbid obesity (BMI $\geq$ 40kg/m^2), 30 vs 7 events (29.6 vs 7.1 per 1,000 person-years) occurred (Table 6.2).

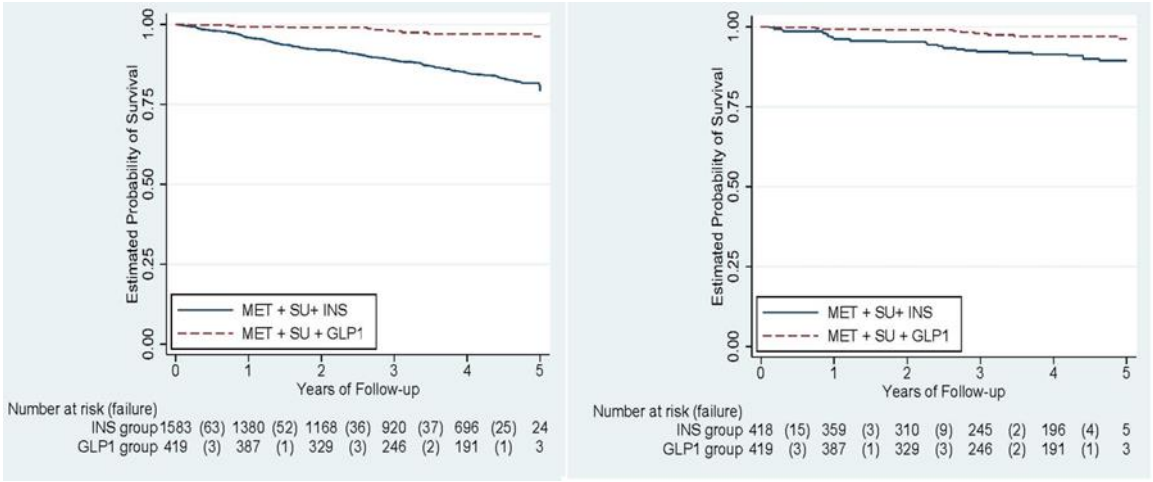


Figure 6.2: Kaplan Meier Survival analysis plot for full and matched cohort (log rank p-value <0.0001)

6.5.4. Risk of Composite Cardiovascular Outcomes and Mortality

Table 6.2 shows the comparison of number of composite cardiovascular events, crude incidence rate and hazard ratio between the treatment groups in the propensity score-matched cohort. In the unadjusted model, the risk of composite cardiovascular outcomes was 80% less

(HR: 0.20, 95%CI: 0.11-0.37) in patients whose dual therapies were intensified with GLP-1 analogue compared to insulin. Following adjustment for gender, there was a slight reduction to 73% (aHR: 0.27, 95%CI: 0.14–0.53). Similar patterns were shown when stratified for obesity (BMI ≥30 kg/m^2) and morbid obesity (BMI ≥40 kg/m^2) with the risks being lower in the GLP-1 group (aHR: 0.31, 95%CI: 0.16-0.61 and aHR: 0.31, 95%CI: 0.13-0.75 respectively).

Table 6.2: Comparison of Number of Events, Incidence Rate and Hazard Ratio between the treatment groups by the components of MACE

	MET + SU + INS (n = 419)	**MET + SU + GLP-1RA (n = 419)**
Follow-up period (years)	4.19	1.42
Sample population		
Composite outcome (No. of events) [a]	**231**	**11**
Incidence Rate (95% CI)[b]	**44.5 (39.1-50.6)**	**7.7 (4.5-14.0)**
Unadjusted hazard ratio (95% CI)	**1.0 [Reference]**	**0.20 (0.11-0.37)**
Adjusted hazard ratio (95% CI)[c]	**1.0 [Reference]**	**0.27 (0.58-0.97)**
Subgroup population		
BMI ≥ 30Kg/m^2		
Composite outcome (No. of events) [a]	**84**	**11**
Incidence Rate (95% CI)[b]	**38.6 (31.2-47.8)**	**8.1 (4.5–14.6)**
Unadjusted hazard ratio (95% CI)	**1.0 [Reference]**	**0.26 (0.14-0.49)**
Adjusted hazard ratio (95% CI)[c]	**1.0 [Reference]**	**0.31 (0.16-0.61)**
BMI ≥ 35Kg/m^2		
Composite outcome (No. of events) [a]	**30**	**7**
Incidence Rate (95% CI)[b]	**29.6 (20.7 - 42.4)**	**7.1 (3.4-14.8)**
Unadjusted hazard ratio (95% CI)	**1.0 [Reference]**	**0.32 (0.14-0.73)**
Adjusted hazard ratio (95% CI)[c]	**1.0 [Reference]**	**0.31 (0.13-0.75)**

Abbreviation: MET (metformin); SU (sulphonylurea); GLP-1 (Glucagon-like Peptide analogue); INS (insulin); BMI (body mass index)
[a] Composite outcome includes: non-fatal acute myocardial infarction (AMI), non-fatal stroke or all-cause death
[b] Rates are calculated per 1000 person-years
[c] Adjusted for gender

Table 6.3 shows the components of MACE- mortality, non-fatal MI and stroke. In the insulin vs GLP-1RA treatment groups, there were 151 vs 5; 38 vs 3; and 42 vs 3 events of mortality, MI and stroke respectively. Higher events of all the component outcomes were also reported in the insulin group than in the GLP-1RA groups for all the components.

Of all the individual components of MACE, adjusted hazard ratio was only significant for mortality. There was a 71% reduced risk of mortality (aHR: 0.21, 95%CI: 0.08-0.51), similar to that of the composite outcome. The risks of stroke and MI were also 61 and 55% less in the GLP-1RA group compared to insulin. However, this was not significant. This trend was also observed when stratified for obesity and morbid obesity (Table 6.3).

Table 6.3: Comparison of Number of Events, Incidence Rate and Hazard Ratio between the treatment groups by the components of MACE

	Mortality		Myocardial Infarction		Stroke	
Met + SU	**INS**	**GLP-1RA**	**INS**	**GLP-1RA**	**INS**	**GLP-1RA**
Sample population						
No. of events	151	5	38	3	42	3
Incidence Rate (95% CI)[a]	31.0 (26.6 – 36.2)	4.2 (1.9 – 9.4)	8.1 (6.0 – 11.0)	2.1 (0.7 – 6.5)	8.9 (6.6 – 11.8)	7.7 (0.7 – 6.5)
Unadjusted hazard ratio (95% CI)	1.0	0.21 (0.09 – 0.52)*	1.0	0.45 (0.12 – 1.67)	1.0	0.39 (0.11 – 1.43)
Adjusted hazard ratio (95% CI)[b]	1.0	0.21 (0.08 – 0.51)*	1.0	0.45 (0.12 – 1.69)	1.0	0.39 (0.10 – 1.44)
Subgroup population						
BMI ≥ 30kg/m^2						
Composite outcome (No. of events)	55	5	17	3	16	3
Incidence Rate (95% CI)[a]	25.3 (19.4 – 32.9)	4.4 (2.0 – 9.8)	7.8 (4.9 – 12.6)	2.2 (0.71 – 6.85)	7.4 (4.5 – 12.0)	2.2 (0.70 – 6.80)
Unadjusted hazard ratio (95% CI)	1.0	0.24 (0.10 – 0.59)*	1.0	0.56 (0.15 – 2.11)	1.0	0.45 (0.12 – 1.70)
Adjusted hazard ratio (95% CI)[b]	1.0	0.24 (0.10 – 0.59)*	1.0	0.57 (0.15 – 2.14)	1.0	0.45 (0.12 - 1.72)
BMI ≥ 40kg/m^2						
Composite outcome (No. of events)	23	5	4	1	5	2
Incidence Rate (95% CI)[a]	22.7 (15.1 – 34.2)	5.0 (2.1 – 12.1)	4.0 (1.5 – 10.5)	1.0 (0.2 – 7.2)	4.9 (2.1 – 11.9)	2.0 (0.50 - 8.10)
Unadjusted hazard ratio (95% CI)	1.0	0.34 (0.12 – 0.94)*	1.0	0.36 (0.04 – 3.65)	1.0	0.50 (0.09 – 2.89)
Adjusted hazard ratio (95% CI)[b]	1.0	0.33 (0.12 – 0.92)*	1.0	0.33 (0.03 – 3.29)	1.0	0.48 (0.8 – 2.8)

Abbreviation: MET (metformin); SU (sulphonylurea); GLP-1RA (Glucagon-like Peptide analogue); INS (insulin); BMI (body mass index)
[a] Incidence rates are calculated per 1,000 person-years
[b] Adjusted for gender; * P-values <0.05

6.5.5. Changes in HbA1c and Weight

In figures 6.3 and 6.4, the trend in changes in HbA1c and weight per year in both treatment groups within the 5-year follow up period is highlighted. There was no statistically significant change in the mean HbA1c levels in both treatment group although reduction in HbA1c was seen more in the insulin group throughout the follow up period (-1.27 vs -1.0%, p=0.117). Conversely, the insulin group recorded more weight gain than the observed weight loss in the GLP-1RA group (1.19 vs -3.35kg, p<0.0001) during the study period.

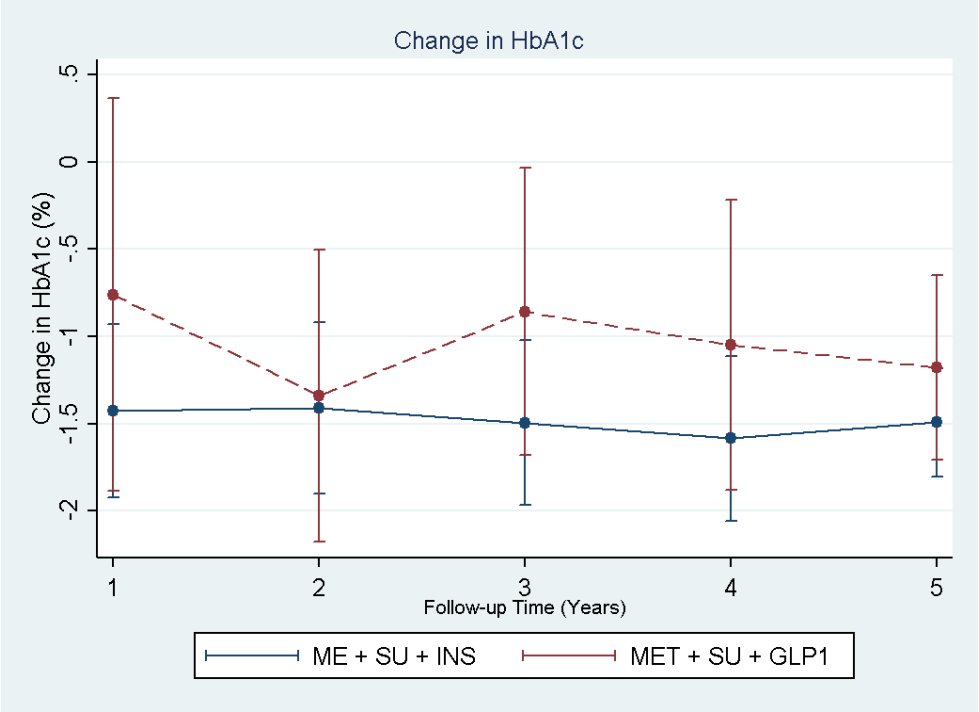


Figure 6.3: Mean Changes in HbA1c

Trend in mean changes in HbA1c level (%) between the treatment groups (Met+SU+INS vs Met+SU+GLP-1RA). There was no significant change in both group treatment groups throughout the study period (p > 0.05).

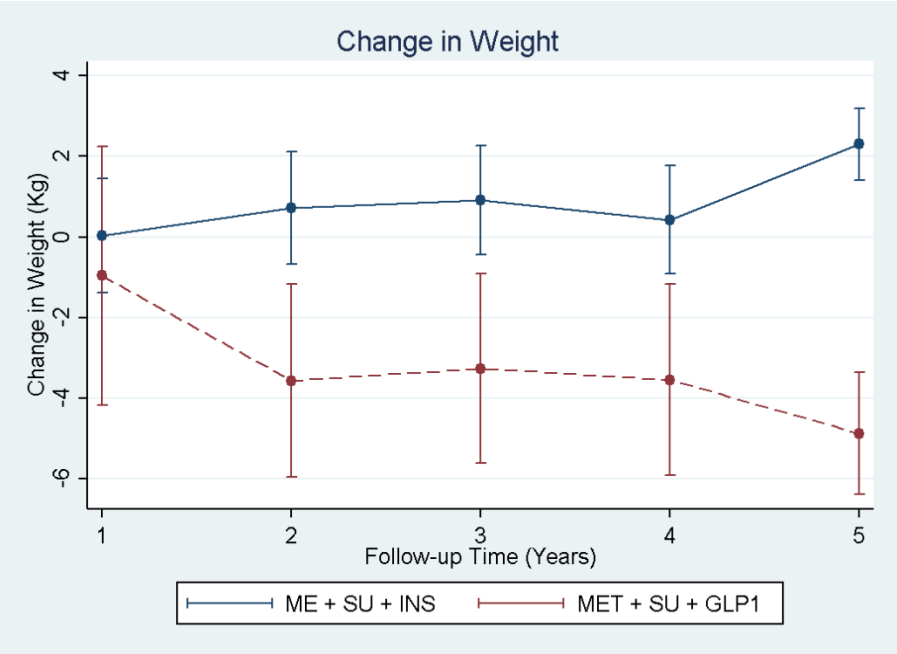


Figure 6.4: Mean changes in weight (kg)

Trend in mean changes in weight (kg) between the treatment-groups (Met+SU+INS vs Met+SU+GLP-1RA). For all the years of the follow-up duration, the p-values < 0.05

Sensitivity analyses which compared the changes in weight and HbA1c between both treatment groups in the complete and missing data reported similar trend in both groups; showing that the imputation robustly addressed the missing data.

Cohort 2

6.6. Cohort 2 – Results

6.6.1. Cases and Total Follow up:

A total of 18,227 adults with insulin treated T2D whose standard care with insulin was intensified with either GLP-RA (1,943) or not (16,284) were selected from the THIN database.

Furthermore, as shown in Figure 6.5, after propensity-score-matching in both cohorts, the total population was reduced to 3,586 (N= 1793 in each arm) in the main cohort.

The mean follow-up duration was 3.2 (SD: 3.07) years), representing a total follow-up period of 12,681.9 person-years.

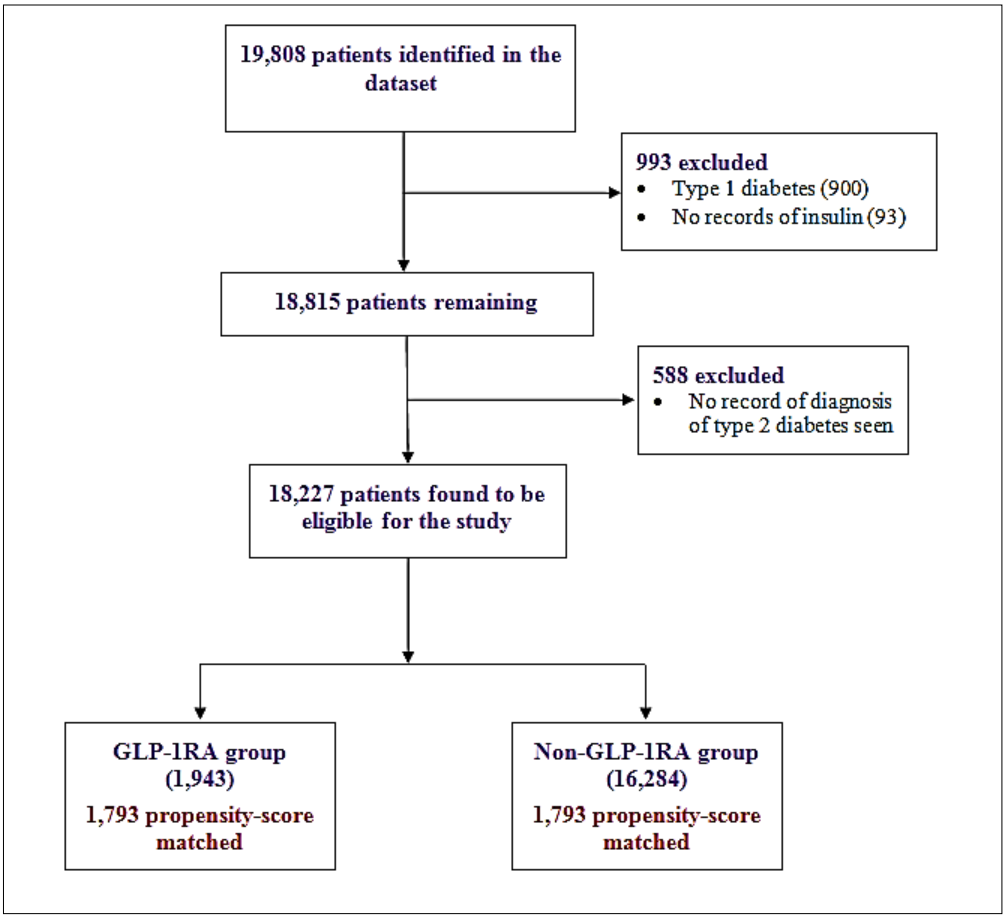


Figure 6.5: Selection of participants in study Cohort 2

6.6.2. Patients' Characteristics

Table 6.4 is a summary of the distribution of the baseline characteristics of the study participants between the treatment groups in the full and matched cohorts respectively. The overall mean age was 62.7 (13.8) years. A slightly higher proportion (53.2%) was composed

of males while the mean baseline HbA1c level was 8.6 (1.8) %. Furthermore, the overall baseline weight and BMI were 90.8 (18.7) kg and 32.4(6.9) kg/m^2 respectively.

Significant differences in the distribution of the baseline variables between the treatment groups in the full cohort were observed. These were in baseline HbA1c, BMI, weight, diabetes duration, current alcohol-intake, among others which were higher in the GLP-1RA group, while age and SBP were significantly higher in the non-GLP-1RA group. Following one-on-one propensity score matching, 1,793 patients were matched to each other in both treatment groups and no differences in baseline variables were noted. Table 1 shows the distribution of the baseline variables between both treatment groups with these baselines compared between the full and matched cohort of patients, with their standardised differences shown.

Table 6.4: Baseline characteristics in the full and propensity-matched cohorts

Baseline variables	Cohort					
	Full			Propensity Matched		
	INS + Others (n = 16,284)	INS+GLP-1RA (n = 1,943)	Std diff	INS + Others (n = 1,793)	INS+GLP-1RA (n = 1,793)	Std diff
Demographics						
Age (yrs), Mean (SD)	62.4 (13.6)	54.6 (11.7)	0.048	54.9 (12.9)	54.9 (11.5)	0.007
Gender, No. (%)						
Male	8683 (53.0)	1012 (52.0)	0.015	990 (55.0)	937 (52.0)	0.010
Female	7601 (47.0)	931 (48.0)	-0.015	803 (45.0)	856 (48.0)	-0.010
Townsend dep, No. (%)						
Least deprived	3219 (20.1)	368 (20.0)	0.054	373 (21.0)	349 (19.0)	0.035
2nd quintile	3139 (20.0)	358 (19.1)	0.035	342 (19.0)	343 (19.0)	0.020
3rd quintile	3302 (21.9)	428 (22.9)	-0.020	427 (24.0)	406 (23.0)	-0.023
4th quintile	3353 (22.0)	410 (22.0)	-0.026	375 (21.0)	392 (22.0)	-0.010
Most deprived	2543 (16.0)	316 (16.0)	-0.046	276 (15.0)	303 (17.0)	-0.023
Clinical Variables, Mean (SD)						
HbA1c (%)	8.6 (1.8)	8.9 (1.9)	-0.014	8.9 (1.8)	8.9 (1.9)	-0.007
BMI (kg/m2)	32.3 (6.8)	33.9 (7.3)	0.016	33.5 (7.1)	33.8 (7.3)	-0.008
Weight (Kg)	90.6 (18.5)	96.6 (19.8)	0.069	96.1 (19.6)	96.5 (19.7)	-0.018
Height (m)	1.7 (0.1)	1.7 (0.1)	0.069	1.7 (0.1)	1.7 (0.1)	-0.013
SBP (mmHg)	136.5 (23.1)	135.0 (22.9)	0.004	134.7 (22.6)	134.9 (23.0)	-0.012
DBP (mmHg)	75.8 (10.9)	77.5 (10.4)	0.084	77.9 (11.1)	77.5 (10.5)	-0.002
TC (mmol/l)	4.5 (1.3)	4.6 (1.2)	0.009	4.6 (1.3)	4.6 (1.2)	0.001
HDL (mmol/l)	1.2 (0.4)	1.2 (0.4)	-0.061	1.2 (0.4)	1.2 (0.4)	0.021
LDL (mmol/l)	2.4 (1.1)	2.4 (1.1)	0.027	2.4 (1.1)	2.4 (1.1)	0.009
Triglyceride (mmol/L)	2.0 (1.2)	2.1 (1.2)	0.019	2.1 (1.2)	2.1 (1.2)	-0.023
Albumin (g/L)	4.0 (0.4)	4.1 (0.4)	0.004	4.1 (0.5)	4.1 (0.4)	0.003
eGFR (mls/min/1.73m^2)	62.2 (21.3)	68.2 (20.0)	0.056	66.8 (21.6)	68.0 (19.8)	0.003
ACR (mg/mol)	5.8 (8.5)	5.7 (8.3)	0.014	6.0 (8.4)	5.7 (8.4)	-0.009
Diabetes duration (yrs)	4.2 (4.9)	4.9 (4.5)	0.262	4.9 (4.8)	5.0 (4.5)	0.013
Smoking status, No. (%)						
Non-smoker	7916 (49.0)	945 (49.0)	-0.034	849 (47.0)	865 (48.0)	-0.021
Current smoker	2358 (14.0)	267 (14.0)	0.009	267 (15.0)	242 (13.0)	0.002
Ex-smoker	6010 (37.0)	731 (38.0)	0.035	677 (38.0)	686 (38.0)	0.027

Alcohol status, No. (%)						
Non-drinker	6183 (38.0)	623 (32.1)	-0.030	569 (32.0)	568 (32.0)	-0.051
Current drinker	9061 (56.0)	1182 (61.2)	-0.092	1117 (62.0)	1096 (61.0)	0.054
Ex-drinker	1040 (6.0)	138 (6.7)	0.097	107 (6.0)	129 (7.0)	-0.019
BMI Categories, No. (%)						
$\leq 24.9 kg/m^2$	2248 (14.0)	207 (11.0)	0.004	193 (11.0)	191 (11.0)	-0.006
$25\text{-}29.9 kg/m^2$	3975 (24.0)	368 (19.0)	-0.006	373 (21.0)	342 (19.0)	0.004
$\geq 30 kg/m^2$	10061 (62.0)	1368 (70.0)	0.003	1227 (68.0)	1260 (70.0)	0.001
Other GLTs, No. (%)						
Metformin	13670 (84.2)	1923 (99.0)	0.058	1738 (97.2)	1773 (99.1)	-0.038
Sulphonylurea	12191 (75.1)	1603 (83.4)	0.041	1472 (82.0)	1485 (83.0)	0.081
Thiazolidinedione	4646 (29.3)	1108 (57.6)	0.180	699 (39.0)	1030 (57.0)	0.062
SGLT2	39 (0.5)	46 (2.1)	0.001	5 (0.3)	42 (2.0)	-0.002
Glinides	657 (4.9)	133 (7.9)	0.050	103 (6.0)	125 (7.0)	0.032
DPP4	1900 (12.1)	669 (34.2)	0.256	292 (16.0)	620 (35.4)	0.187*
Use of Medications, No. (%)						
Aspirin	14596 (90.1)	1911 (99.8)	-0.007	1723 (99.6)	1723 (99.6)	-0.008
Antihypertensive	14223 (91)	1713 (90)	-0.030	1608 (90.0)	1608 (90.0)	-0.036
LLT	14156 (91.7)	1820 (95.5)	-0.059	1717 (96.0)	1708 (95.0)	0.015
Comorbidities, No. (%) [c]						
CHD	5062 (31.0)	398 (20.0)	-0.213*	361 (20.0)	367 (20.0)	-0.147
PAD	2259 (14.1)	149 (8.2)	-0.148*	144 (8.0)	133 (7.0)	-0.105*
Heart Failure	2324 (14.8)	133 (7.5)	-0.151*	110 (6.0)	120 (7.0)	0.001
Hypoglycaemia	2995 (18.2)	190 (10.1)	-0.239*	156 (9.0)	169 (9.0)	-0.036

GLP-1RA (Glucagon-like peptide 1 receptor agonist); INS (insulin); SGLT2 (Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors); DPP4 (Dipeptidyl peptidase-4 (DPP-4) inhibitors); BMI (body mass index); SBP (systolic blood pressure); DBP (diastolic blood pressure); HbA1c (haemoglobin A1c); HDL (high-density lipoprotein); LDL (low-density lipoprotein); TC (total cholesterol); GFR (glomerular filtration rate); LLT (lipid lowering therapy); PAD (peripheral arterial disease); CHD (coronary heart disease); ACR (albumin creatinine ratio); SD (standard deviation)

Diabetes duration is time from first diagnosis of diabetes to date of intensification with insulin (index date)

[a] *Standardized differences are the absolute difference in means or percentage divided by the standard deviation of the treated group*

[b] *Resulting standardized difference after 1:1 matching based on average treatment effect on treated (ATT) propensity score technique and robust variance estimation*

** In the matched cohort, only DPP4 and PAD had statistically significant standardized difference at 0.10 level*

6.6.3. Crude Event Rates:

Composite Outcome (MACE): The probability of survival for a three-point composite MACE was similar (99%) in both treatment groups after one year, but was significantly reduced at 5 years to 96% and 93% in the GLP-1RA and non-GLP-1RA groups respectively (log-rank test p-value = 0.0055) (Figure 6.6). The unadjusted crude incidence rate was 12.1 per 1,000 person-years (9.1 vs 14.7) signifying a total of 153 events (55 vs 98) in the GLP-1RA vs non-GLP-1RA groups respectively (Table 6.5).

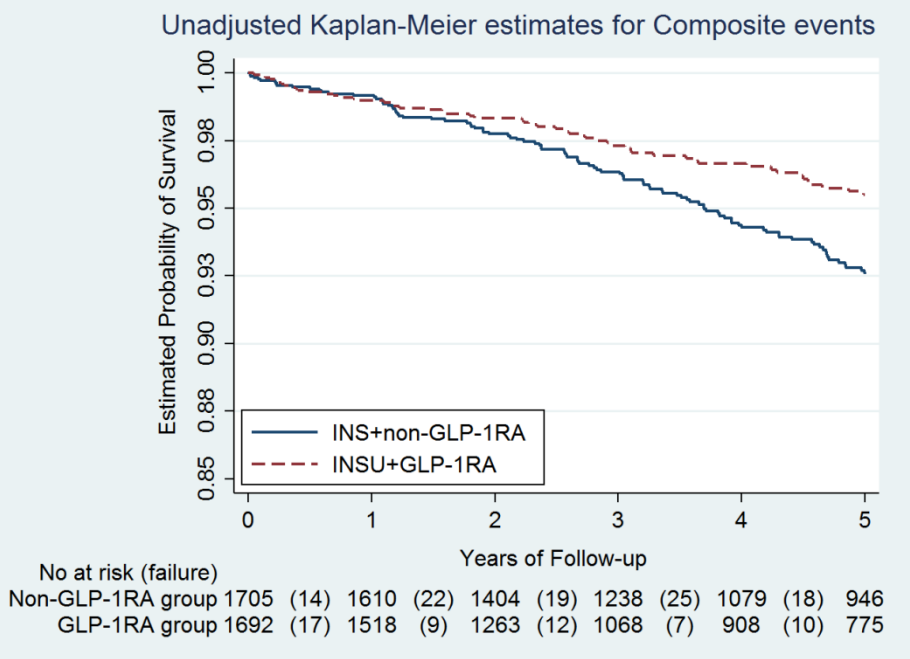


Figure 6.6: Kaplan-Meier curves showing the 5-year probability of survival for three-point composite of all-cause mortality, non-fatal MI and stroke (MACE) between INS +/- GLP1-RA treatment groups (log-rank test p-value = 0.0055).

Mortality: Also in the main cohort as shown in Figure 6.7, the probability of survival was 100% in both treatment groups after one year, but at the end of the 5-year follow-up period, this was significantly reduced to 98% and 96% in the GLP-1RA and non-GLP-1RA groups respectively (log-rank test p-value = 0.0001) (Figure 6.7). There was a total of 62 (13 vs 49)

morality events with a crude incidence rate of 4.6 (2.0 vs 6.9) per 1,000 person-years in the GLP-1RA vs non-GLP-1RA groups respectively. There are summarised in Table 6.5.

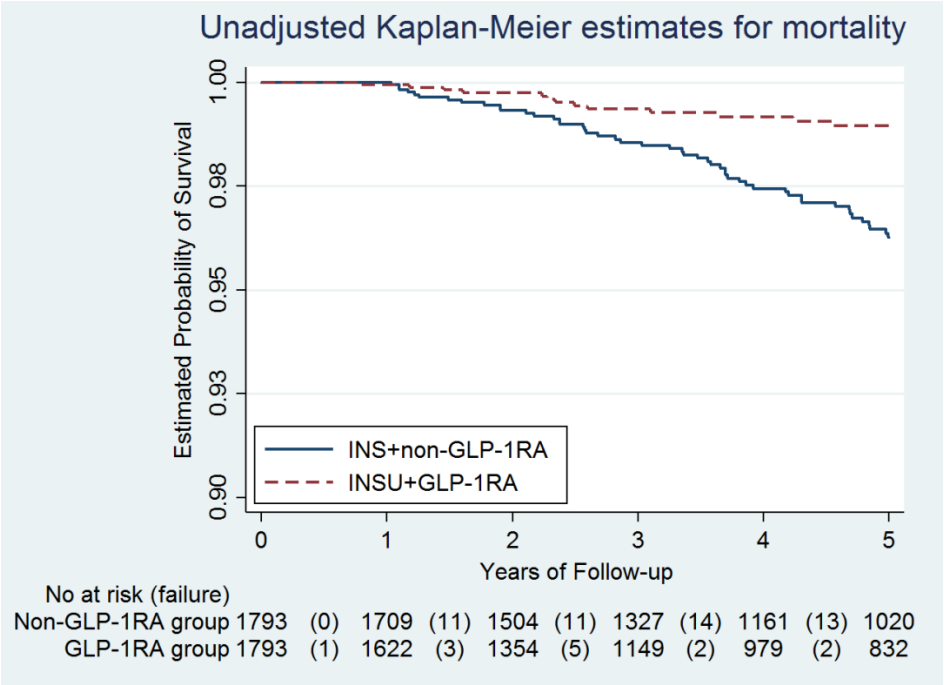


Figure 6.7: Kaplan-Meier curves showing the 5-year probability of survival for all-cause mortality between INS +/- GLP1-RA treatment groups (log-rank test p-value = 0.0001).

Cardiovascular Events: Among the 2,820 matched participants in the subgroup with no prior history of CV events (Figure 6.8), the probability of survival for the two-point cardiovascular event of non-fatal MI and stroke fell from 99.5% and 99.3% after one year in the GLP-1RA vs non-GLP-1RA groups respectively to 97% in both groups at 5 years (log-rank test p-value = 0.7880). Additionally, there was a total 61 CV events, with an unadjusted crude incidence rate of 5.8 per 1,000 person-years with 28 and 33 events in the GLP-1RA vs Non-GLP-1RA groups respectively (crude incidence rates: 5.6 vs 6.0 per 1,000 person-years).

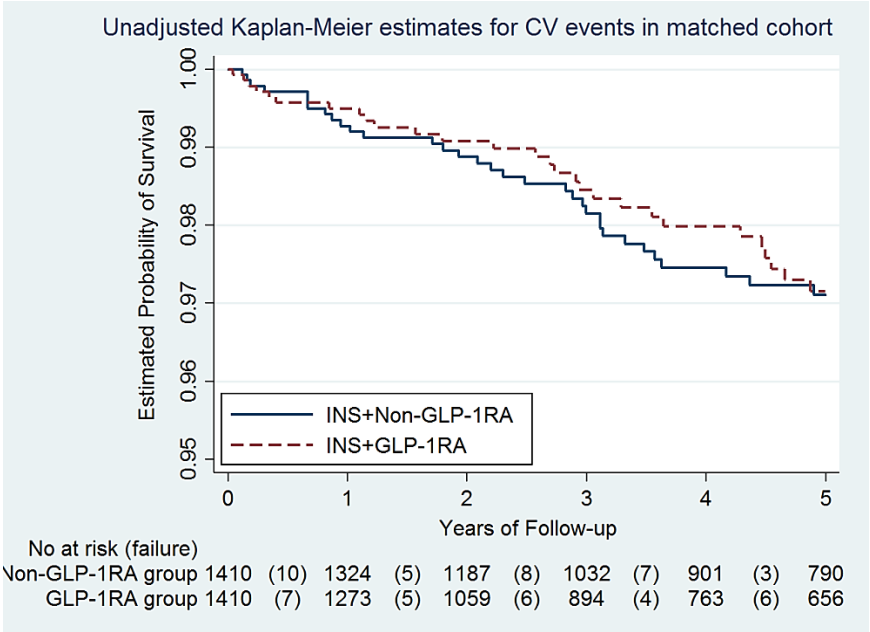


Figure 6.8: Kaplan-Meier curves showing the 5-year probability of survival for Two-point composite of CV events (non-fatal MI and stroke) between INS +/- GLP1-RA treatment groups. Log-rank test p-value = 0.829.

Finally, in the subgroup analysis for non-fatal MI, there were 7 events (3 vs 4 events in the GLP-1RA vs non-GLP-1RA groups respectively (crude incidence rates: 0.6 vs 0.7 per 1,000 person-years), while similarly, a total of 25 vs 29 non-fatal stroke events was reported, signifying an unadjusted crude incidence rate of 5.0 vs 5.2 per 1,000 person-years (Table 6.5).

6.6.4. Risk of MACE, All-cause mortality, and Composite Cardiovascular Outcomes

The summary of the hazard of MACE, all-cause mortality and CV events between the treatment groups is presented in Table 6.5. The unadjusted risk of MACE was 37% less (HR: 0.63, 95%CI: 0.45 – 0.86) in the GLP-1RA treatment group compared to the non-GLP-1RA group. Following adjustment for age, duration of diabetes and insulin use, gender, socioeconomic stats, alcohol use, eGFR, lipid profile, and events of hypoglycaemia, this slightly reduced to

36% (aHR: 0.64, 95%CI: 0.42 – 0.98). Similarly, the risk of all-cause mortality was 65% less (HR: 0.35, 95%CI: 0.17 – 0.73) in the GLP-1RA group, following adjustment.

The risk of composite cardiovascular outcomes was 24% less (aHR: 0.76, 95%CI: 0.41 – 1.42) in patients whose insulin therapy was intensified with GLP-1RA compared to non-GLP-1RA. Specifically, the risk of MI was 38% lower (aHR: 0.62, 95%CI: 0.06 – 6.53); while the risk of non-fatal stroke was 7% less (aHR: 0.93; 95%CI: 0.54 – 1.61) in the GLP-1RA group compared to the non-GLP-1RA group after adjustment for significant confounders (Table 6.5).

Table 6.5: Events, Crude Incidence Rates and Hazard Ratios of MACE, all-cause mortality and cardiovascular events in the two treatment groups

	INS + Non-GLP-1RA	INS + GLP-1RA	Total
Population	1,793	1,793	3,586
Composite Outcomes*			
No. of events	98	55	153
Crude Incidence Rate (95% CI)[a]	14.7 (12.0 – 17.9)	9.2 (7.0 – 11.9)	12.1 (10.3 – 14.1)
Unadjusted Hazard Ratio (95% CI)	1.0 [Ref]	0.63 (0.45 – 0.86)	-
Adjusted Hazard Ratio (95% CI)[b]	1.0 [Ref]	0.64 (0.42 – 0.98)	-
All-cause Mortality			
No. of events	49	13	62
Crude Mortality Rate (95% CI)	6.9 (5.2 – 9.1)	2.0 (1.2 – 3.5)	4.6 (3.6 – 5.9)
Unadjusted Hazard Ratio (95% CI)	1.0 [Ref]	0.30 (0.16 – 0.56)	-
Adjusted Hazard Ratio (95% CI)	1.0 [Ref]	0.35 (0.17 - 0.73)	-
Population**	1,410	1,410	2,820
Composite Cardiovascular events***			
No. of events/population	33	28	61
Crude Incidence Rate (95% CI)	6.0 (4.2 – 8.4)	5.6 (3.8 – 8.0)	5.8 (4.5 – 7.4)
Unadjusted Hazard Ratio (95% CI)	1.0 [Ref]	0.93 (0.56 – 1.54)	-
Adjusted Hazard Ratio (95% CI)	1.0 [Ref]	0.76 (0.41 – 1.42)	-
Acute Myocardial infarction (MI)			
No. of events/population	4	3	7
Crude Incidence Rate (95% CI)	0.7 (0.3 – 1.9)	0.6 (0.2 - 1.8)	0.7 (0.3 – 1.4)
Unadjusted Hazard Ratio (95% CI)	1.0 [Ref]	0.87 (0.19 – 3.88)	-
Adjusted Hazard Ratio (95% CI)	1.0 [Ref]	0.62 (0.06 – 6.53)	-
Non-fatal Stroke			
No. of events/population	29	25	54
Crude Incidence Rate (95% CI)[a]	5.2 (3.6 – 7.5)	5.0 (3.4 – 7.3)	5.1 (3.9 – 6.7)
Unadjusted Hazard Ratio (95% CI)	1.0 [Ref]	0.94 (0.55 – 1.61)	-
Adjusted Hazard Ratio (95% CI)	1.0 [Ref]	0.93 (0.54 – 1.61)	-

Abbreviation: GLP-1RA (Glucagon-like Peptide analogue receptor); INS (insulin); CI (Confidence Interval)

** MACE includes a composite of all-cause mortality, non-fatal acute myocardial infarction (AMI) and non-fatal stroke*

*** This population excludes patients with prior history of CV events (as defined below) at insulin initiation*

**** Composite cardiovascular events include non-fatal AMI and non-fatal stroke*

[a] *Crude incidence rates are calculated per 1,000 person-years*

[b] *Adjusted for age, duration of diabetes, duration of insulin use, gender, Townsend deprivation score, alcohol, albumin, Lipid profile, medication (Lipid-lowering therapy, antihypertensives), eGFR (glomerular filtration rate), events of hypoglycaemia, and number of glucose-lowering therapies.*

6.6.5. Glycaemic Control (Change in HbA1c) and Change in Weight.

Both treatment groups showed a significant reduction in HbA1c throughout the study period, but there was no significant difference between the groups at any of the study timelines (-0.32% vs -0.39%, p = 0.0076 at 6 months; and -0.34% vs -0.41%, p = 0.334 at 36 months) (Figure 6.9).

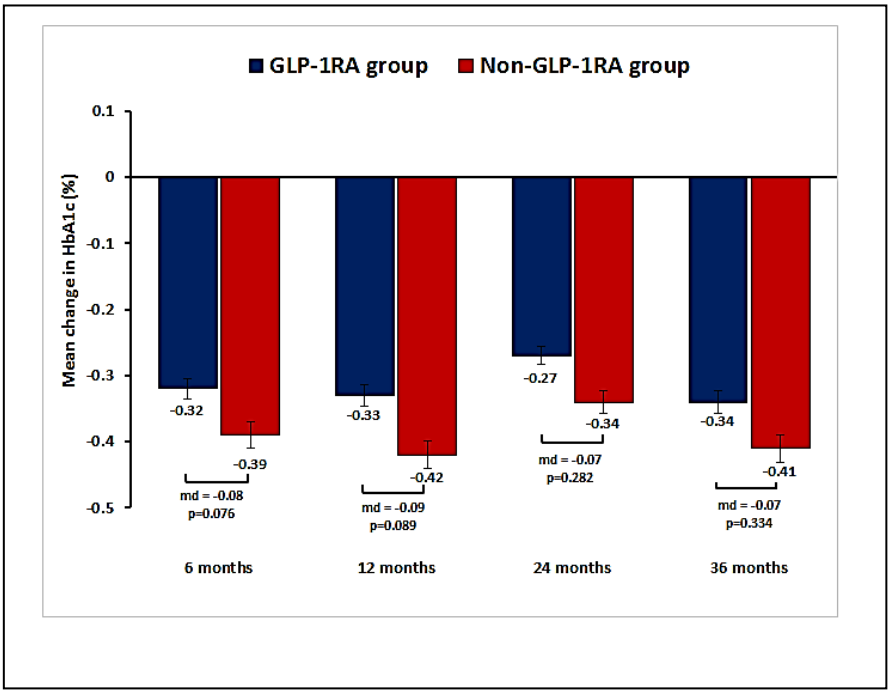


Figure 6.9: Comparison of glycaemic efficacy (measured by change in HbA1c) in INS+GLP-1RA vs INS+non-GLP1-RA treatment groups along the study timeline *(md = mean difference, p = p-value)*

Conversely, there were significant increases in weight in both treatment groups in the first 6 months, and further to 12 months in the non-GLP-1RA group. From 12 and 24 months, there were significant reductions in weight in both groups (Figure 3). No significant differences in changes in weight were observed between the groups in the first 24 months. However, at 36 months, adjuvant use of a GLP-1RA was associated with a significantly greater weight

reduction compared with non GLP-1RA group (-0.99kg vs -0.85kg, mean diff = -0.92, 95%CI: -1.02, 0.75; p = 0.768) (Figure 6.10).

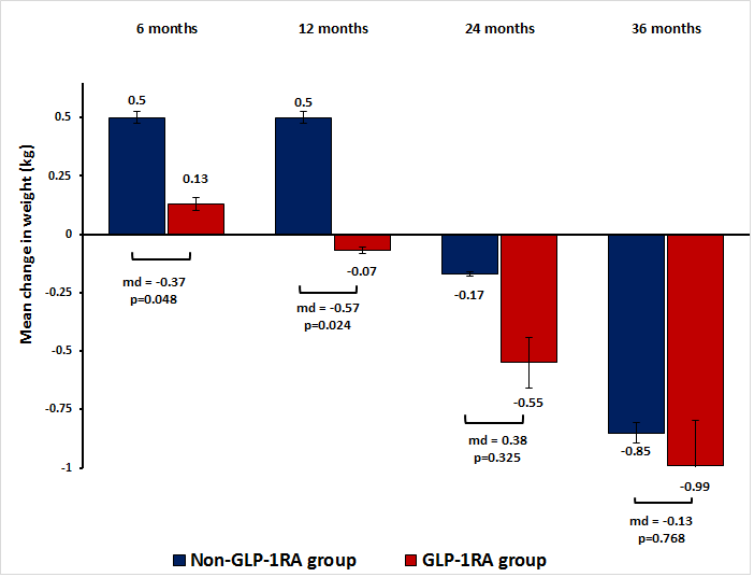


Figure 6.10: Comparison of changes in weight in INS+GLP-1RA vs INS+non-GLP1-RA treatment groups throughout the study duration *(md = mean difference, p = p-value)*

6.6.6. Subgroup and Sensitivity analyses:

Table 6.6 shows the risk of composite MACE, all-cause mortality and CV events in the different GLP-1RA subtypes – liraglutide, exenatide and lixinatide. Compared to the insulin users who had no GLP-1RA add-on, the risk of MACE was 47% (aHR: 0.53; 95%CI: 0.32 – 0.89) and 19% (aHR: 0.81; 95%CI: 0.50 – 1.31) less in liraglutide and exenatide respectively, while no event was recorded for lixinatide. Similarly, all-cause mortality was 83% (aHR: 0.17; 95%CI: 0.06 – 0.47) and 51% less (aHR: 0.49; 95%CI: 0.24 – 0.99) with no event for lixinatide. No difference was observed between the drug subtypes on CV events.

Sensitivity analyses to compare the risks of the study outcomes in the full and matched cohorts showed no difference in the magnitudes of the effect sizes. Also, I compared the differences in

change in HbA1c between treatment groups, using both complete and missing data and reported similar trend in both groups. This affirmed that the imputation robustly addressed the missing data.

Table 6.6: Subgroup analysis for events, crude incidence rates and hazard ratios of MACE, all-cause mortality and cardiovascular events in the GLP-1RA subtypes

	None	Exenatide	Liraglutide	Lixinatide	Total
Population	**1,793**	**751**	**1008**	**34**	**3,586**
Composite Outcomes (MACE)*					
No. of events/person-time	**98/6674**	**30/2552**	**25/3340**	**0/116**	**153/12682**
Crude Incidence Rate (95% CI)[a]	**14.7 (12.0 – 17.9)**	**11.8 (8.2 – 16.8)**	**7.5 (5.1 – 11.1)**	**-**	**12.1 (10.3 – 14.1)**
Adjusted Hazard Ratio (95% CI)[b]	**1.0 [Ref]**	**0.81 (0.50 – 1.31)**	**0.53 (0.32 – 0.89)**	**-**	**-**
All-cause Mortality					
No. of events/person-time	**49 / 7125**	**9/2757**	**4/3561**	**0/118**	**62/13561**
Crude Mortality Rate (95% CI)	**6.9 (5.2 – 9.1)**	**3.3 (1.70 – 6.3)**	**1.1 (0.42 – 3.0)**	**-**	**4.6 (3.6 – 5.9)**
Adjusted Hazard Ratio (95% CI)	**1.0 [Ref]**	**0.49 (0.24 – 0.99)**	**0.17 (0.06 – 0.47)**	**-**	**-**
Population**	**1,410**	**576**	**806**	**28**	**2,820**
Composite Cardiovascular events***					
No. of events/population	**33/5541**	**16/2093**	**12/2840**	**0/107**	**61**
Crude Incidence Rate (95% CI)	**5.5 (4.2 – 8.4)**	**7.6 (4.7 – 12.5)**	**4.2 (2.4 – 7.4)**	**-**	**5.8 (4.5 – 7.4)**
Adjusted Hazard Ratio (95% CI)	**1.0 [Ref]**	**0.75 (0.36 – 1.56)**	**0.48 (0.22 – 1.04)**	**-**	**-**
Acute Myocardial infarction (MI)					
No. of events/population	**4/5612**	**1/2127**	**2/2863**	**0/108**	**7**
Crude Incidence Rate (95% CI)	**0.7 (0.3 – 1.9)**	**0.5 (0.1 – 3.3)**	**0.7 (0.2 - 2.8)**	**-**	**0.7 (0.3 – 1.4)**
Adjusted Hazard Ratio (95% CI)	**1.0 [Ref]**	**0.44 (0.05 – 4.01)**	**0.71 (0.13 – 3.91)**	**-**	**-**
Non-fatal Stroke					
No. of events/population	**29/5550**	**15/2094**	**10/2841**	**0/107**	**54**
Crude Incidence Rate (95% CI)[a]	**5.2 (3.6 – 7.5)**	**7.2 (4.3 – 11.9)**	**3.5 (1.9 – 6.5)**	**-**	**5.1 (3.9 – 6.7)**
Adjusted Hazard Ratio (95% CI)	**1.0 [Ref]**	**1.33 (0.72 – 2.49)**	**0.64 (0.31 – 1.32)**	**-**	**-**

** MACE includes a composite of all-cause mortality, non-fatal acute myocardial infarction (AMI) and non-fatal stroke*

*** This population excludes patients with prior history of CV events (as defined below) at insulin initiation*

**** Composite cardiovascular events include non-fatal AMI and non-fatal stroke*

[a] *Crude incidence rates are calculated per 1,000 person-years*

[b] *Adjusted for age, duration of diabetes, duration of insulin use, gender, Townsend deprivation score, alcohol, albumin, Lipid profile, medication (Lipid-lowering therapy, antihypertensives), eGFR (glomerular filtration rate), events of hypoglycaemia, and number of glucose-lowering therapies.*

6.7. Discussion

This study showed that, among patients who are taking MET+SU, intensification of glucose lowering therapy with GLP-1RA in routine clinical practice was associated with a significant 73% risk reduction in the risk of adverse composite CV events and mortality compared with intensification with insulin therapy. Also, in among overweight patients with insulin-treated T2D in routine clinical practice, adding a GLP-1RA was associated with a significant 36% risk reduction in a three-point composite of all-cause mortality, non-fatal MI and stroke; a 65% reduction in all-cause mortality and a non-significant 24% reduction in CV events, compared with no adjunctive GLP-1RA treatment. HbA1c reduction was similar between the two groups but significant difference in weight response was observed between the two groups, i.e. weight gain with insulin and significant weight reduction with GLP-1RA, as well as a significant reduction in weight with the use of GLP-1RA with insulin compared with none.

Many trials comparing GLP-1RA with insulin or other comparators including placebo have reported conflicting findings with those with placebo comparators showing CV benefits. Two recent meta-analyses however reported cardiovascular benefits of GLP-1RA.[268, 269] A similar recent observational study in a large cohort of 39,225 T2D patients reported a similar reduced risk of heart failure, MI and stroke in three treatment groups comparing exenatide- and exenatide + insulin to insulin only (61/56%, 50/38% and 52/63% respectively).[273] This collaborates with other reports showing the novel pleiotropic cardio-protective effects of GLP-1RA have also been described.[274] Additionally, the observation of reduced composite of CV events and all-cause mortality of adding a GLP-1RA to insulin therapy, independent of HbA1c reduction supports novel pleiotropic cardio-protective effects of GLP-1 agonist, which have been previously described.[270, 271] A further possible explanation for the observed reduction in the composite events with GLP-1RA could be due to the reduced risks of hypoglycaemia as

well as the beneficial effects of GLP-1RA in inducing weight loss – both via the addition of a GLP-1RA and concurrent reductions in insulin doses.[275] Both hypoglycaemia[276] and weight gain,[257] which are commonly associated with insulin therapy, are known risk factors for adverse CV events and mortality.

While further exploring the possible effect of obesity in the first study cohort, it demonstrated a greater reduction of cardiovascular events with GLP-1RA compared with insulin therapy in the subgroup of obese (BMI $\geq$30kgm^{-2}) and morbidly obese (BMI $\geq$40kgm^{-2}) patients with T2D.

The CV safety of insulin is a controversial issue. Despite methodological adjustments, it is hard to exclude in observational studies all the potential bias. In the ORIGIN study, a randomized clinical trial with insulin glargine in a high CV risk population, insulin therapy was not associated with higher CV events. On the other hand, although preclinical studies and some meta-analysis suggest that GLP-1RA could have a protective CV effect, the ELIXA study (the first published CV randomized clinical trial with a GLP-1RA analogue) showed that lixisenatide had a neutral CV effect compared with other antidiabetic therapies but the recently released landmark LEADER trial showed significant CV benefits with liraglutide.[272]

Our study showed comparable reductions in HbA1c levels in the patients on either GLP-1 or Insulin. Clinical trials[186, 187] involving Exenatide and Liraglutide[188] have reported similar HbA1c reduction compared with insulin. Similarly, among patients on MET+SU, a recent randomized clinical trial reported similar HbA1c reduction between the GLP-1RA, Taspoglutide and insulin glargine.[277] Evidence from RCT have shown that the complementary mechanism of actions of GLP-1RA and insulin therapy offers a unique advantage to patients with T2D, and is associated with significant reduction in HbA1c (mean ~0.8%), fasting and postprandial glucose, lower risk of hypoglycaemia, prevention of weight gain and concurrent

reduction of insulin doses.[278-280] It is conceivable that the weight reduction from GLP-1RA may be partly responsible for an increased effect of exogenous insulin delivered by insulin injections in study participants. However, the discrepancies in the HbA1c reduction observed in RCT following the addition of GLP-1RA to insulin therapy, compared with our neutral effect on HbA1c levels from real world practice may reflect 'real life' patients fear of hypoglycaemia and weight gain, as well as the complexities of insulin dose reduction when adding a GLP-1RA to ongoing insulin therapy. Of note, most RCT have employed a treat to target design, where insulin doses were optimized by investigators simultaneous to adding a GLP-1RA.

Insulin therapy has been known to be associated with weight gain and this was consistent throughout the study period in contrast to GLP-1RA which showed consistent decline in weight. The observed increase in body weight following insulin therapy is in conformity with previous studies.[206, 266, 281] In contrast to evidence from RCT, where weight loss of between 0-4-1.8kg was observed in the first 24-30 weeks of adding a GLP-1RA to insulin therapy (in cohort 2), significant weight loss was only observed after 12 months of adding a GLP-1RA in routine clinical practice. At 24 months of follow up however, I observed a significant weight loss of -0.55kg with adjuvant GLP-1RA compared with -0.17kg without a GLP-1RA.The delay in weight response in this observational study may reflect in a delay in down-titration of insulin doses in routine clinical practice due to the lack of regular follow up or a rigid treat-to-target treatment protocol. Of note, the baseline weight of our cohort is comparable to that from RCT. The observed increase in body weight with insulin therapy (without adjuvant GLP-1RA) however is in conformity with previous studies.[278-280] Although the baseline BMI in our matched first study cohort was close to the morbid obesity range, our findings can be generalised to all people with T2D because sub-analyses in the obese and morbidly obese subgroups showed very similar findings.

The main strength of our study derives from the inclusion of a large cohort of T2DM patients receiving insulin therapy in a real-world population which is largely representative of the UK population. This implies that our findings will be generalizable to various population that share similar demographics. The large cohort of patients studied here provides adequate statistical power and also contains information on other time-varying covariates to adjust for possible confounding. I adjusted for a large set of factors that could have differed at the baseline through propensity score matching. This is crucial since the decision to add a GLP-1RA in routine clinical practice is often based on the fact that patients are overweight as per UK NICE guidelines,[257] also confirmed by these two related studies in Tables 6.1 and 6.4 (where baseline weight in the full cohort (before matching) was significantly greater in the GLP-1RA group). Nevertheless, some residual confounding in our study could persists due to our inability to measure and adjust for the dosage of the insulin therapy as well as the reliability of diabetes duration due to the ongoing issue of identifying incident versus prevalent diabetes. A potential source bias was the inconsistency in the measurement of HbA1c levels according to guidelines (3-6 monthly). Due to this, many patients had no recordings for weight and HbA1c beyond the baseline. Nonetheless, the multiple imputation of the missing data robustly addressed this as can be seen form the results of the sensitivity analysis (Appendix 4.1). Also, the classification of exposure into two broad drug groups could have possibly masked the effects of individual drugs and could have driven our study away or closer to the null hypothesis. Finally, the low outcomes recorded in the subgroup analysis could be a reflection of poor recording or coding of these outcomes in the dataset.

6.8. Conclusion

In summary, the evidence from this large cohort study, tracking outcomes in routine clinical practice suggests that intensification of dual oral therapy by adding insulin is associated with a higher risk of CV events, compared to adding a GLP-1RA therapy following dual therapy failure but the addition of GLP-1RA as an adjunct to insulin therapy in overweight patients with T2D is associated with a significant reduction in a composite of all-cause mortality and CV events (MACE) and all-cause mortality, compared with not adding a GLP-1RA therapy. The mechanism for these cardio-protective effects remained speculative but further study in a randomised clinical trial setting is required to confirm this observation.

Chapter Seven: Relationship between HbA1c and All-cause Mortality in Elderly Patients

7.1. Summary

Background

The aim was to study the relationship between HbA1c and cardiovascular morbidity and all-cause mortality among elderly insulin-treated patients with type 2 diabetes after adjustment for multiple confounders.

Methods

Data for 8,192 adults with type 2 diabetes (>65yrs) whose treatment was intensified by starting insulin treatment were sourced from the Health Improvement Network (THIN) database. Cox proportional hazard models and Kaplan-Meier estimators were fitted to derive the hazards of all-cause mortality by HbA1c decile after 5-yrs of follow-up. A sub-cohort of patients with no prior history of CV disease was generated (n=4,589) to also determine the hazard ratio of major CV events (incidence of non-fatal myocardial infarction and stroke, hospitalization for heart failure and unstable angina, and acute coronary syndrome).

Results

I observed a U-shaped relationship between all-cause mortality and HbA1c, with the lowest risk seen in the HbA1c interquartile range (IQR) of 7.4-7.7%. The highest mortality risks were significantly associated with the lowest (5.8%) and highest (10.7%) HbA1c deciles. Among patients with no prior history of cardiovascular disease there was no significant association between HbA1c and cardiovascular events.

Conclusions

Both low and high HbA1c were associated with increased all-cause mortality, but no increase in cardiovascular events, among elderly patients with insulin-treated type 2 diabetes. This cohort study supports the need for individualisation of care and suggests optimal outcomes with HbA1c levels around 7.5%.

7.2. Introduction

More than 25% of all patients with type 2 diabetes are aged over 65 years,[282] and the risk-benefit balance for anti-hyperglycaemic therapies can vary considerably in older compared with younger age groups. The UK Prospective Diabetes Study (UKPDS) excluded patients >65 yrs[22] and more recent outcome trials in T2DM, e.g. ACCORD,[92] ADVANCE[95] and VADT,[96] have failed to provide a clear consensus on the optimal HbA1c target for elderly patients, especially those who are started on insulin therapy.

Outcomes modelling suggests that the cardiovascular and mortality benefits of lowering HbA1c can take 2 or more decades to manifest.[283] Thus, when treatments have limited or delayed benefits, the risk-benefit balance changes with increasing age. This is particularly so with the use of insulin treatment in older patients in whom the benefits of HbA1c lowering may be offset by the increased risks of hypoglycaemia, frailty, cardiovascular disease, cognitive impairment and falls.[284] Indeed, large epidemiological studies have observed a dose-response relationship between increasing insulin exposure (duration) and all-cause mortality[109, 285, 286]

International guidelines emphasise the importance of individualising HbA1c targets and recommend a less stringent approach in older patients with longer duration diabetes.[41, 43, 46]

Nevertheless, failing to adequately treat hyperglycaemia in elderly patients may increase the risk of acute metabolic events[287] and potentially the risks of morbidity and mortality.[103] Given the ongoing uncertainty, I sought to evaluate the relationship between all-cause mortality and HbA1c among a large UK cohort of older patients with insulin-treated T2D under routine care.

7.3. Methods

7.3.1. Study Design and Data Sources

I conducted a retrospective cohort study using data obtained from UK Primary Care practices via the THIN database which has been fully described in Chapter 2.

7.3.2. Study Population

This comprised elderly insulin users with a diagnosis of T2D who were aged 65 years and above. They must have initiated insulin therapy between January 2007 and 2014, irrespective of their history of intake of other antidiabetic drug combinations. They must have been on insulin therapy for at least 180 days before being eligible for inclusion in the study. Patients with type 1 diabetes were excluded. For study cohort 1, patients with a history of cardiovascular diseases were included, while in the subgroup analysis for cardiovascular risks (study cohort 2) patients with prior cardiovascular events before insulin initiation were excluded.

7.3.3. Exposures and Outcomes

Our main exposure was insulin initiation (index date). Insulin therapy here could be ultra-short/short acting, premixed or long-acting, and was independent of any other co-administered glucose-lowering therapy. The study was exposure-based starting from index date and

participants were censored following the development of the earliest of our defined primary outcomes; change of Insulin; loss to follow-up (transfer out of practice) or at the end of the study after 5 years.

The outcome measure was the risk of composite MACE (major adverse cardiac events, which includes non-fatal myocardial infarction; non-fatal stroke; hospitalization for heart failure, and unstable angina; acute coronary syndrome; and all-cause mortality). For study cohort 1, the time to the risk of all-cause mortality was the primary outcome while a composite of non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure and unstable angina, and acute coronary syndrome (cardiovascular events) and cardiovascular mortality were the primary outcomes for cohort 2. These outcomes were as identified by their appropriate READ codes in the THIN database and must have occurred at least 180 days after the baseline or index date (initiation of insulin).

7.3.4. Covariates

Baseline covariates were extracted within 90 days before and after the initiation of insulin according to previous literature. These baseline covariates have been discussed in section 2.6.3 (Chapter 2).

7.3.5. Procedure

Glycaemic control was measured by post-index mean HbA1c. This was calculated as the mean of all recorded post-insulin HbA1c values from the index date to the censorship of participants at the occurrence of any of the outcomes, loss to follow-up, discontinuation of insulin or end of the study period at 5 years. The mean of all post-index HbA1c values for each patient within this period was computed and used to rank the study population into deciles. The hazard of the

primary outcomes was explored in each decile and compared to the 4th decile (HbA1c range: 7.4-7.7%). In order to account for individual variations in HbA1c over the study period and to avoid violating the survival analysis assumptions, I conducted sensitivity analyses in which post-insulin $Hb_{A1c}$was calculated in two ways before inclusion in our Cox model. First, I calculated it as a yearly mean value (the average of the mean yearly HbA1c recorded for years), having used multiple imputations (using the chain equation) to account for missing data; and secondly, as a cumulative yearly mean (cumulative total and average of last HbA1c recordings for each year).

7.3.6. Statistical Analyses

The primary analyses were all-cause mortality in the full cohort; and a composite outcome of non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure, and unstable angina; acute coronary syndrome in a sub-cohort of patients with no prior history of cardiovascular events. The mean, frequency distribution and differences between the measured baseline covariates between deciles were calculated and summarized. Baseline differences amongst the cohort were assessed using student t-test and Pearson's Chi-squared test.

Crude and adjusted Kaplan–Meier estimates of survival functions were obtained for the decile groups. I used the log-rank test to compare the equality of the survival curves between the deciles. From these survival functions, the absolute reduction in the probability of an event occurring within a 5-year follow-up was calculated.

I fitted a Cox proportional hazard model to estimate the marginal hazard ratios, to enable us to quantify the adjusted hazard of an event occurring in all the decile groups compared to the fourth decile (HbA1c range: 7.4-7.7%). In this model, all the covariates which showed significant association with both the exposure and outcome in our univariate analyses and

changed the effect size by ≥10% were included alongside a priori confounders. Proportional hazards assumptions were confirmed through Schoenfeld residuals test. Point estimates with 95% confidence intervals (CI) at the conventional statistical significance level of 0.05 were used in the regression models.

7.3.7. Subgroup/Sensitivity Analyses

Test of interaction was conducted to determine any association between the common combination therapies with insulin in the main cohort and the outcomes and based on this, a subgroup analysis on all-cause mortality in patients on insulin monotherapy; dual therapy with insulin + metformin (INS+MET) and those on insulin + sulphonylurea (INS+SU). With the methods described above, the hazards of the outcomes between the deciles in these groups were also compared.

7.4. Results

7.4.1. Cases and Total Follow up

For cohort 1, I identified 8,192 eligible elderly patients in the THIN database on insulin therapy. Of these, 4,589 had no prior history of CV events (Cohort 2) at the index date (insulin initiation). Figure 7.1 outlines the selection process for these study cohorts. The median follow-up period for the cohorts was 3.6 years (IQR: 2.3–4.9), representing a total follow-up period of 46,189 person-years.

7.4.2. Patient Characteristics

At baseline, the overall median age was 73.0 yrs (IQR: 68.9 - 78.2); median HbA1c:8.1% (IQR: 7.0 – 9.2); 48.1% were female; while the mean BMI was 31.9±6.5 kg/m^2 and the average duration of insulin treatment was 5.2±6.8 years. Table 7.1 summarises the baseline characteristics of our study cohort by each decile group. Significant differences between the decile groups were observed in socio-economic status (p = 0.05), history of alcohol intake (p = 0.048) and use of lipid-lowering agents (p = 0.0001).

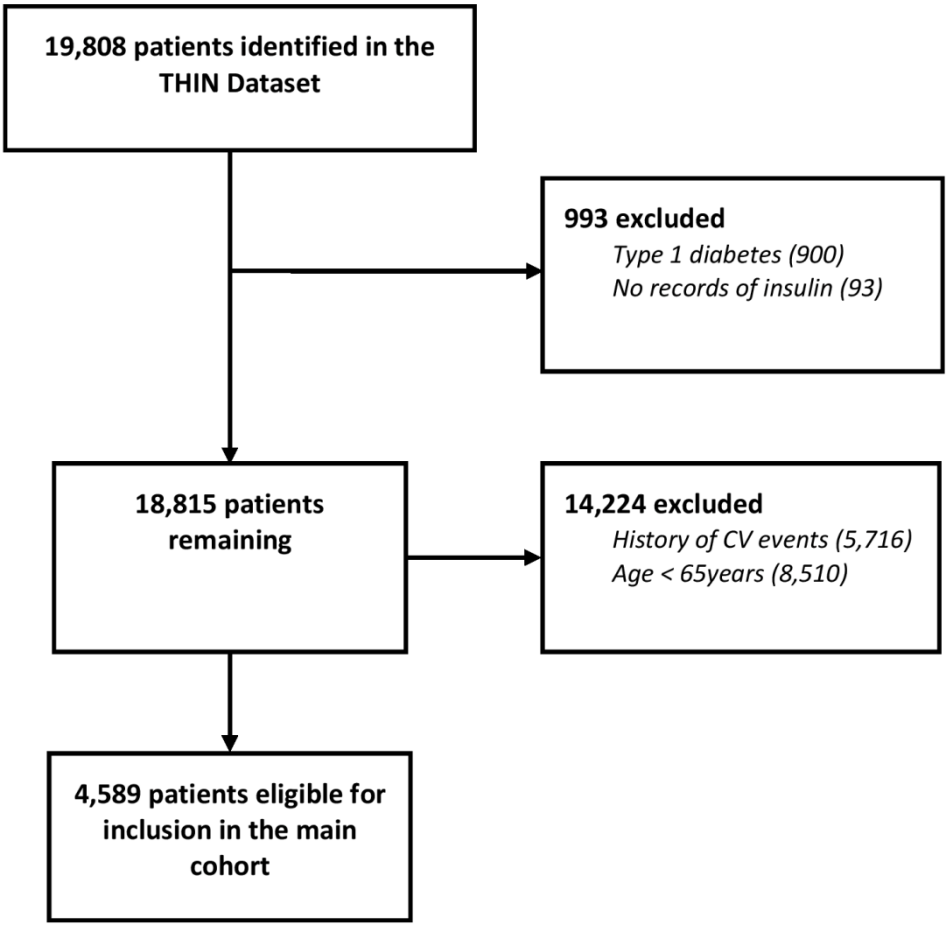


Figure 7.1: Flow diagram of selection of study participants

Table 7.1: Baseline Characteristics of Study Cohort

HbA1c deciles (N)	**1 (n=459)**	**2 (n=460)**	**3 (n=458)**	**4 (n=459)**	**5 (n=459)**	**6 (n=459)**	**7 (n=459)**	**8 (n=459)**	**9 (n=459)**	**10 (n=458)**	**Total (n=4589)**
Mean HbA1c (%) (95%CI)	**5.7 (0.6) (3.95-6.40)**	**6.7 (0.2) (6.41-6.95)**	**7.1 (0.1) (6.96-7.35)**	**7.5 (0.10) (7.36-7.69)**	**7.8 (0.10) (7.70-8.02)**	**8.2 (0.1) (8.03-8.38)**	**8.5 (0.1) (8.39-8.76)**	**9.0 (0.1) (8.77-9.25)**	**9.5 (0.2) (9.26-9.88)**	**10.6 (0.7) (9.89-16.03)**	**8.1 (1.4) (3.95-16.03)**
Demographics											
Age (yrs). Mean (SD)	75.0 (6.7)	74.1 (6.4)	74.0 (6.3)	74.1 (6.3)	74.0 (6.5)	74.1 (6.5)	73.6 (6.1)	73.9 (6.2)	73.2 (6.2)	72.9 (5.8)	73.9 (6.3)
Gender. No. (%)											
Male	442 (54)	439 (54)	409 (50)	420 (51)	432 (53)	429 (52)	415 (51)	419 (51)	409 (50)	417 (51)	4231 (51.7)
Female	378 (46)	380 (46)	410 (50)	399 (49)	387 (47)	391 (48)	404 (49)	400 (49)	410 (50)	402 (49)	3961 (48.3)
Smoking Status. No (%)											
Ex-smoker	375 (46)	354 (43)	352 (43)	303 (37)	324 (40)	367 (45)	348 (42)	354 (43)	344 (42)	347 (42)	3468 (42.8)
Non-smoker	403 (49)	388 (47)	404 (49)	447 (54)	431 (52)	386 (46)	414 (50)	399 (49)	396 (47)	414 (50)	4082 (49.4)
Current	42 (5)	77 (9)	63 (8)	69 (8)	64 (8)	67 (8)	57 (7)	66 (8)	79 (10)	58 (7)	642 (7.8)
Alcohol Status. No (%)											
Ex-drinker	55 (7)	60 (7)	42 (5)	50 (6)	40 (5)	43 (5)	56 (7)	55 (7)	47 (6)	46 (6)	494 (6.0)
Never	287 (35)	269 (33)	284 (35)	315 (38)	275 (34)	255 (31)	282 (34)	285 (35)	285 (35)	326 (40)	3356 (41.0)
Current	429 (52)	441 (54)	439 (54)	405 (49)	452 (55)	467 (57)	437 (53)	441 (54)	436 (53)	395 (48)	4863 (53.0)
Deprivation. No (%)											
Least deprived	178 (23)	159 (21)	188 (24)	178 (23)	203 (26)	178 (23)	162 (21)	184 (23)	166 (21)	152 (20)	1748 (22.4)
Second quintile	169 (21)	163 (21)	162 (21)	179 (23)	189 (24)	160 (20)	162 (21)	159 (20)	158 (20)	168 (22)	1669 (21.4)
Third quintile	164 (21)	158 (21)	169 (22)	166 (21)	175 (22)	167 (21)	163 (21)	180 (23)	166 (21)	172 (22)	1680(21.5)
Fourth quintile	166 (21)	173 (23)	149 (19)	165 (21)	126 (16)	172 (22)	174 (22)	162 (20)	159 (21)	174 (23)	1620 (20.8)
Most deprived	114 (14)	110 (14)	112 (14)	98 (12)	87 (11)	105 (13)	126 (16)	106 (13)	126 (16)	104 (14)	1088(13.9)
Clinical Parameters. Mean (SD)											
HbA1c (%)	6.6 (1.5)	7.4 (1.4)	7.7 (1.4)	7.9 (1.3)	8.4 (1.4)	8.6 (1.3)	8.8 (1.4)	9.1 (1.4)	9.7 (1.4)	10.5 (1.6)	8.5 (1.8)
BMI (kg/m^2)	31.2 (6.9)	31.5 (6.7)	32.0 (6.3)	31.7 (6.8)	31.9 (6.4)	31.7 (6.6)	31.6 (6.8)	32.7 (6.6)	32.5 (6.7)	32.4 (6.5)	31.9 (6.6)
Diabetes duration (yrs)*	6.2 (5.2)	5.7 (4.9)	5.7 (4.7)	5.9 (4.9)	5.8 (5.3)	5.7 (5.1)	6.0 (5.1)	5.8 (5.0)	5.5 (4.8)	5.4 (4.9)	5.8 (5.0)
Time on insulin (yrs)	5.4 (6.2)	4.9 (6.2)	5.4 (6.7)	5.4 (6.8)	5.4 (6.8)	4.9 (6.6)	5.4 (7.0)	4.9 (6.9)	5.2 (7.7)	5.1 (6.7)	5.2 (6.8)
Height (m)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Weight (kg)	87.8 (18.7)	88.2 (17.9)	88.5 (17.8)	87.5 (17.8)	87.7 (17.3)	87.9 (18.5)	87.4 (17.9)	89.7 (17.7)	88.5 (17.5)	88.1 (16.9)	88.1 (17.8)
Time on insulin (yrs)	4.9 (6.2)	4.7 (6.4)	4.6 (6.7)	5.1 (7.0)	5.0 (6.9)	4.7 (6.4)	4.6 (6.9)	4.6 (7.1)	5.0 (8.6)	4.5 (6.7)	4.8 (6.9)
DBP (mmHg)	73.2 (10.9)	73.4 (10.4)	73.6 (10.6)	74.6 (10.8)	74.6 (11.0)	74.0 (10.8)	74.7 (10.8)	73.9 (10.5)	74.2 (10.6)	75.1 (10.7)	74.1 (10.7)
SBP (mmHg)	139.1 (24.7)	138.9 (23.1)	139.1 (23.4)	139.2 (22.0)	140.8 (22.6)	137.9 (22.5)	139.3 (22.7)	138.0 (22.1)	138.3 (22.6)	136.6 (23.6)	138.7 (22.9)
Albumin (g/L)	4.0 (0.5)	4.0 (0.4)	4.0 (0.4)	4.0 (0.4)	4.0 (0.4)	4.0 (0.4)	4.0 (0.4)	4.0 (0.4)	3.9 (0.4)	3.9 (0.4)	4.0 (0.4)

ACR (mg/mol)	5.4 (8.6)	6.7 (9.2)	6.2 (9.3)	6.4 (8.5)	6.4 (8.4)	6.4 (8.5)	6.5 (8.3)	6.3 (8.2)	6.7 (8.5)	6.9 (8.4)	6.4 (8.6)
eGFR (mls/min/1,73m²)	51.7 (19.1)	55.3 (19.5)	52.9 (19.6)	54.7 (20.3)	54.8 (20.0)	52.8 (19.8)	56.7 (19.2)	54.8 (18.1)	55.2 (19.6)	57.0 (19.7)	54.6 (19.6)
TC. (mmol/L)	4.2 (1.3)	4.3 (1.2)	4.3 (1.3)	4.4 (1.2)	4.3 (1.5)	4.4 (1.2)	4.4 (1.3)	4.5 (1.3)	4.4 (1.2)	4.5 (1.3)	4.4 (1.3)
Triglyceride (mmol/L)	1.8 (1.2)	1.9 (1.2)	1.9 (1.1)	2.0 (1.1)	2.0 (1.3)	2.0 (1.2)	2.0 (1.1)	2.1 (1.2)	2.1 (1.2)	2.1 (1.3)	2.0 (1.2)
LDL (mmol/L)	2.1 (1.1)	2.2 (1.0)	2.2 (1.1)	2.3 (1.0)	2.2 (1.2)	2.2 (1.0)	2.2 (1.1)	2.3 (1.1)	2.2 (1.0)	2.3 (1.1)	2.2 (1.1)
HDL (mmol/L)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.5)	1.2 (0.4)	1.2 (0.5)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)
BMI Categories. N (%)											
Normal	155 (19)	137 (17)	115 (14)	124 (15)	109 (13)	117 (14)	124 (15)	94 (11)	106 (13)	105 (13)	1186 (14.5)
Overweight	204 (25)	199 (24)	201 (25)	219 (27)	219 (27)	217 (26)	212 (26)	198 (24)	192 (23)	198 (24)	2059 (25.1)
Obese	461 (56)	483 (59)	503 (61)	476 (58)	491 (60)	486 (59)	483 (59)	527 (64)	521 (64)	516 (63)	4947 (60.4)
Use of Medications. N (%)											
Aspirin	805 (100)	812 (100)	814 (100)	806 (100)	806 (100)	811 (100)	807 (100)	807 (100)	805 (100)	806 (100)	8079 (99.9)
LLT	674 (84)	717 (88)	727 (89)	727 (90)	719 (89)	733 (90)	726 (90)	704 (87)	730 (91)	727 (90)	7184 (88.9)
Antihypertensive	765 (95)	787 (97)	783 (96)	763 (95)	775 (96)	778 (96)	776 (96)	776 (96)	771 (96)	771 (96)	7745 (95.8)
Comorbidities. N (%)											
Hypoglycaemia	166 (20)	176 (21)	175 (21)	160 (20)	174 (21)	160 (20)	168 (21)	187 (23)	181 (22)	190 (23)	1737 (21.2)
Heart Failure	186 (23)	175 (21)	186 (23)	180 (22)	169 (21)	171 (21)	174 (21)	189 (23)	176 (21)	181 (22)	1787 (21.8)
PAD	172 (21)	164 (20)	152 (19)	142 (17)	132 (16)	138 (17)	147 (18)	137 (17)	138 (17)	145 (18)	1467 (17.9)
Other CHD	312 (38)	313 (38)	339 (41)	326 (40)	318 (39)	315 (38)	305 (37)	332 (41)	329 (40)	320 (39)	3209 (39.2)

**Diabetes duration is time from first diagnosis of diabetes to date of intensification with insulin (index date).*
Comorbidities: other recorded medical disorders.
ACR, albumin creatinine ratio; BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; INS, insulin; LDL, low-density lipoprotein; LLT, lipid-lowering therapy; PAD, peripheral arterial disease; SBP, systolic blood pressure; TC, total cholesterol.

7.4.3. Crude Event Rates

The 1- and 5-year probability of survival differed significantly between the decile groups at 1 year (99 – 100%) and 5 years (73 – 84%) respectively (log-rank test p-value < 0.00001). Overall, there were 2,417 all-cause mortality events with a crude incidence rate of 52 per 1,000 person-years (95%CI: 50.28 – 91.14). The highest number of mortality events (280) was reported for the 1st HbA1c post-insulin decile (HbA1c=5.8%) group; followed by 261 events in the 10th decile group (HbA1c=10.7%) while the 4th decile (HbA1c=7.5%) had the least number of events of 209. The greatest and least crude mortality incidence rates of 68.2 and 67.8/1000 person-years respectively were seen in the 1st and 10th decile groups respectively. Table 7.2 summarises the number of mortalities, crude mortality rates and the hazard of mortality within the HbA1c decile groups.

For the second cohort, there were 2,069 composite cardiovascular events with a crude incidence rate of 125events/1000 person-years (95%CI: 120 - 130). The least number of cardiovascular events of 182 was recorded in the 6th decile group while the 2nd decile had the highest recorded number. Conversely, the incidence of cardiovascular events was also greatest in the 2nd decile group, followed by the 1st and the 8th. For cardiovascular mortality in this cohort, the 2nd (HbA1c = 6.7%) and 9th (HbA1c = 9.5%) decile groups recorded the highest (87) and least (51) number of deaths respectively; while the highest crude mortality rate in insulin users with no prior history of cardiovascular event was in patients with very tight glycaemic control (post-insulin HbA1c of 5.8% - 1st decile group) (Table 7.2).

Table 7.2: Events, Rates and Hazards of Mortality and CV events in elderly T2DM on Insulin Therapy

HbA1c deciles (Total)	**1 (n=820)**	**2 (n=819)**	**3 (n=819)**	**4 (n=819)**	**5 (n=819)**	**6 (n=820)**	**7 (n=819)**	**8 (n=819)**	**9 (n=819)**	**10 (n=819)**	**Total (n=8192)**
Mean post-index HbA1c (%)	**5.79**	**6.71**	**7.15**	**7.51**	**7.85**	**8.2**	**8.56**	**9**	**9.53**	**10.67**	**8.1**
Range	**3.95-6.40**	**6.41-6.95**	**6.96-7.35**	**7.36-7.69**	**7.70-8.02**	**8.03-8.38**	**8.39-8.76**	**8.77-9.25**	**9.26-9.88**	**9.89-16.03**	**3.95-16.03**
All-cause Mortality in the entire study population											
Number of events	280	243	235	209	217	236	232	251	253	261	2417
*IR (per 1,000 person-yrs)	68.2	55.6	54.1	41.1	48.3	51.0	49.7	56.3	60.5	67.8	52.3
(95%CI)	(60.7-76.7)	(49.1-63.1)	(47.9-61.2)	(38.0-56.0)	(42.4-55.0)	(45.0-57.7)	(39.1-51.2)	(50.0-63.5)	(54.5-67.4)	(59.9-53.3)	(50.3-54.5)
Adjusted Hazard Ratio	1.36	1.22	1.17	ref	1.01	1.13	1.12	1.21	1.24	1.31	-
(95% CI)	(1.10-1.62)	(0.98-1.46)	(0.94-1.44)	-	(0.82-1.21)	(0.92-1.35)	(0.90-1.24)	(0.98-1.44)	(0.99-1.49)	(1.06-1.56)	-
Cardiovascular events (non-fatal acute MI, stroke, hospitalization for heart failure and unstable angina; acute coronary syndrome) in patients with no prior cardiovascular event at index date											
HbA1c deciles (Total)	**1 (n=459)**	**2 (n=460)**	**3 (n=458)**	**4 (n=459)**	**5 (n=459)**	**6 (n=459)**	**7 (n=459)**	**8 (n=459)**	**9 (n=459)**	**10 (n=458)**	**Total (n=4589)**
Number of events	215	217	205	193	211	182	211	218	210	207	2069
*IR (per 1,000 person-yrs)	130.0	133.7	121.8	114.3	128.2	106.6	131.1	132.8	125.0	114.0	125.3
(95%CI)	(113.7-148.5)	(117.1-152.8)	(106.2-139.7)	(99.2-131.6)	(112.0-146.7)	(92.1-123.2)	(114.5-150)	(116.3-151.7)	(109.2-143.1)	(114.0-149.7)	(120.0-130.8)
Adjusted Hazard Ratio	1.21	1.22	1.19	ref	1.34	1.04	1.18	1.27	1.10	1.24	-
(95% CI)	(0.96-1.54)	(0.97-1.55)	(0.94-1.51)	-	(1.06-1.69)	(0.82-1.31)	(0.93-1.49)	(1.01-1.59)	(0.87-1.39)	(0.98-1.56)	-
Cardiovascular mortality in those with no prior cardiovascular event at index date											
HbA1c deciles (Total)	**1 (n=459)**	**2 (n=460)**	**3 (n=458)**	**4 (n=459)**	**5 (n=459)**	**6 (n=459)**	**7 (n=459)**	**8 (n=459)**	**9 (n=459)**	**10 (n=458)**	**Total (n=4589)**
Number of events	86	87	64	69	68	53	66	79	51	58	681
*IR (per 1,000 person-yrs)	35.7	33.2	22.3	24.7	24.7	18.4	22.7	28.7	17.3	20.7	24.5
(95%CI)	(28.9-44.1)	(26.9-41.0)	(17.5-28.5)	(19.5-31.2)	(19.4-31.3)	(14.0-24.0)	(17.8-28.9)	(23.1-35.8)	(13.1-22.7)	(16.0-26.8)	(22.8-26.5)
Adjusted Hazard Ratio	1.49	1.26	1.01	Ref	1.08	0.76	1.17	1.22	0.75	0.90	-
(95% CI)	1.00-2.22	0.85-1.89	0.66-1.53	-	0.72-1.61	0.49-1.16	0.77-1.77	0.82-1.81	0.48-1.16	0.59-1.38	-

**IR= Incidence Rate.*
Adjusted for age, gender, smoking status, history of alcohol intake, socio-economic status, body mass index (BMI), diabetes duration, duration of insulin therapy, estimated glomerular filtration rate (eGFR), albumin-creatinine ration (ACR) and total cholesterol (TC)

7.4.3. Risk of All-cause Mortality and Composite Cardiovascular Outcomes

Table 7.2 summarises the composite events, incidence rates and hazards of mortality in the first study cohort and composite cardiovascular outcome. The hazards of these events were compared to the 4th post-insulin HbA1c decile of 7.5% (range 7.4-7.7%).

There was a variation in mortality with an increase in the hazard of mortality from decile HbA1c of 7.5% (IQR: 7.4 - 7.7%), the reference decile (Figure 7.2A). Higher mortality hazards were significantly associated with the lowest (5.8%) and highest (10.7%) post-insulin HbA1c deciles. In the adjusted model, compared to the reference HbA1c decile group of 7.5%, there was a 36% increase in the hazard of death in the lowest decile (HbA1c of 5.8%) with tight glycaemic control (HR: 1.36, 95%CI: 1.10 – 1.62), while an increase of 31% (HR: 1.31, 95%CI: 1.06 – 1.56) in the hazard of death was reported in the poor glycaemic control group (highest HbA1c decile of 10.7%). Other decile groups also showed increased mortality but these were not significant. In Figure 7.2, this association is represented in a U-shaped curve for Cohort 1.

In the subpopulation group with no prior history of cardiovascular events on insulin initiation, a slightly similar but non-consistent pattern emerged for both the cardiovascular events and cardiovascular mortality. In the adjusted cox model, the risk increased further away from the comparator HbA1c group of 7.5% but this was not in a consistent pattern (Figure 7.2B). Also, there was no significant association between post-insulin HbA1c and the hazard of cardiovascular events except in the 5th and 8th deciles groups. Conversely, for cardiovascular mortality, there was a 49% significant increase (HR: 1.49%, 95%CI: 1.0 – 2.22) in the risk of death in the lowest HbA1c decile group compared to 7.5%. In addition, higher HbA1c targets (9.5% and 10.7%) were shown to be associated with 25% (HR: 0.75, 95%CI: 0.48 – 1.16) and

10% (HR: 0.90, 95%CI: 0.59 – 1.38) reduced risk of CV deaths, respectively. However, this was not significant (Table 7.2).

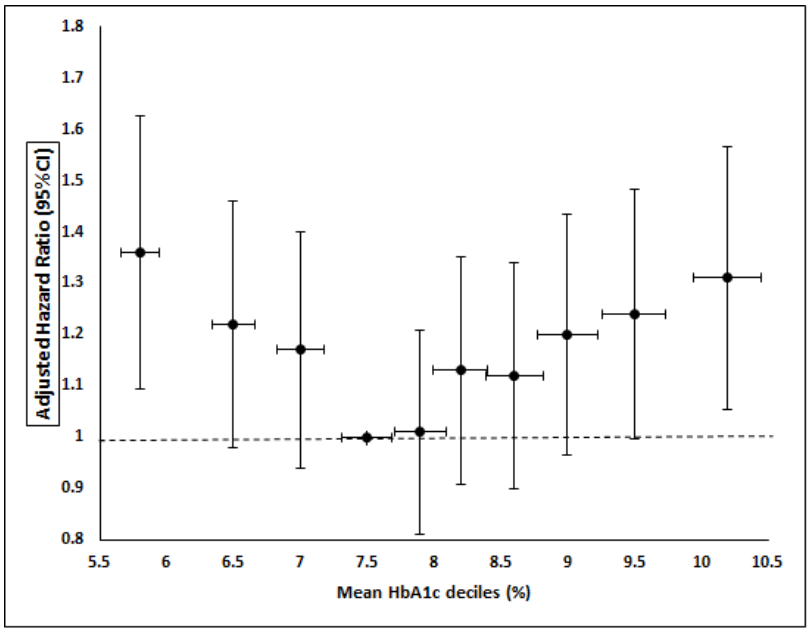


Figure 7.2A: Adjusted hazard ratios for mortality in the full cohort by HbA1c deciles (Cohort 1). The vertical bars show 95% CI while the horizontal bars show HbA1c range.

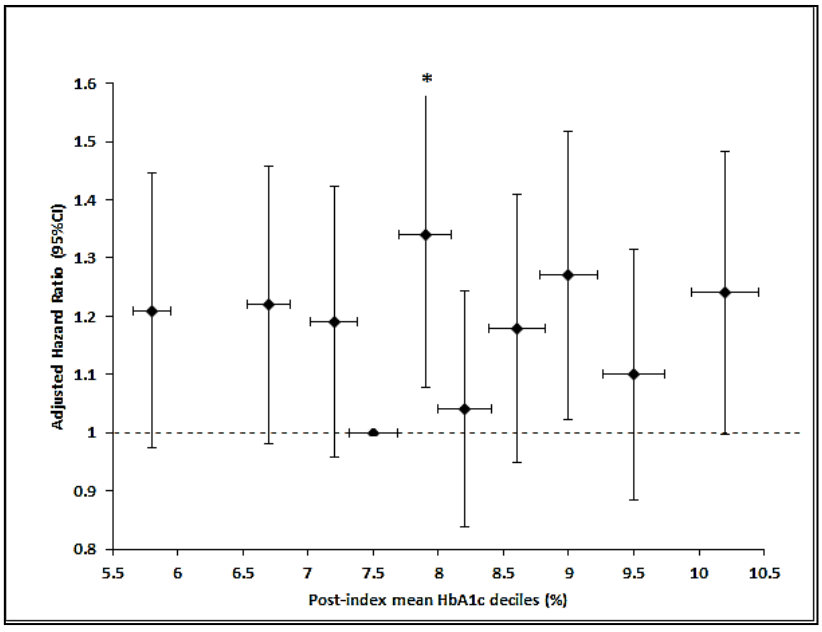


Figure 7.2B. Adjusted hazard ratios for CV events in the full cohort by HbA1c deciles (Cohort 1). The vertical bars show 95% CI while the horizontal bars show HbA1c range. * Shows truncation of range at the upper range limit.

I tested for violations of the proportional hazards assumptions using Schoenfeld residuals test, in which I examined the null hypothesis that the hazard ratio is constant over time and I found no evidence (p=0.342) to reject this assumption of proportional hazards for the decile groups.

7.4.4. Sensitivity and Subgroup Analyses

Table 7.3 highlights the predictors for progression to all-cause mortality in the full cohort (Cohort 1) and in the subgroups of the population which include insulin (INS) monotherapy; Insulin and Metformin (INS+MET) and sulphonylurea (INS+SU) dual-therapy subgroups. Within this elderly insulin treated cohort of T2D, not surprisingly, age and smoking status appear to be significant independent demographic predictors of mortality. With regards to clinical parameters, body mass index, kidney function and total cholesterol levels were independent predictors of mortality for the entire cohort. However, only BMI persists as an independent predictor of mortality across all subgroups of insulin treatment (monotherapy, INS+MET and INS+SU). Interestingly, disease duration was an independent predictor of mortality only in the 'Insulin only' treatment subgroup.

Table 7.3: Cox proportional hazard models for progression to mortality in all elderly insulin users and by treatment regimen

	Full cohort			Insulin only			Ins + Met			Ins + SU		
	Hazard Ratio (95%CI)		p-value	Hazard Ratio (95%CI)		p-value	Hazard Ratio (95%CI)		p-value	Hazard Ratio (95%CI)		p-value
Demographics												
Age	1.1	(1.09-1.11)	<0.0001	1.06	(1.03-1.08)	<0.0001	1.08	(1.04-1.14)	<0.0001	1.05	(1.02-1.08)	0.001
Gender (male vs female)	0.70	(0.61-0.80)	<0.0001	1.27	(0.82-1.95)	0.280	0.65	(0.38-1.09)	0.102	0.95	(0.51-1.79)	0.880
Smoking Status.												
Non-smoker	1	-	-	1	-	-	1	-	-	1	-	-
Ex-smoker	1.15	(1.03-1.27)	0.009	0.96	(0.68-1.37)	0.829	1.20	(0.80-1.81)	0.384	0.96	(0.68-1.37)	0.829
Current	1.79	(1.50-2.13)	<0.0001	2.03	(1.15-3.57)	0.014	1.43	(0.64-3.00)	0.102	2.03	(1.15-3.57)	0.014
Alcohol Status.												
Never	1	-	-	1	-	-	1	-	-	1	-	-
Ex-drinker	0.78	(0.63-0.96)	0.021	1.74	(0.74-4.11)	0.207	1.00	(0.50-1.97)	0.995	0.26	(0.09-0.76)	0.013
Current	0.75	(0.61-0.93)	0.008	1.34	(0.88-2.23)	0.157	0.98	(0.51-4.31)	0.964	0.37	(0.19-0.74)	0.005
Deprivation.												
Least deprived	1	-	-	1	-	-	1	-	-	1	-	-
Second quintile	0.99	(0.86-1.15)	0.917	0.77	(0.48-1.23)	0.280	1.63	(0.97-2.76)	0.066	2.09	(1.14-3.84)	0.018
Third quintile	1.08	(0.93-1.24)	0.328	0.82	(0.52-1.27)	0.368	1.16	(0.62-2.21)	0.638	0.76	(0.41-1.40)	0.378
Fourth quintile	1.27	(1.10-1.46)	0.001	0.66	(0.99-1.11)	0.118	1.13	(0.67-1.90)	0.642	1.51	(0.82-2.77)	0.183
Most deprived	1.08	(0.92-1.27)	0.334	0.52	(0.30-0.92)	0.025	1.01	(0.53-1.93)	0.982	1.32	(0.63-2.81)	0.456
Clinical Parameters												
BMI (kg/m^2)	1.36	(1.22-1.42)	0.012	1.27	(1.08-1.49)	0.001	1.22	(1.04-1.56)	0.004	1.31	(1.01-1.65)	0.036
Diabetes duration (yrs)	1.00	(0.99-1.01)	0.186	1.02	(1.01-1.04)	0.004	1.05	(0.97-1.01)	0.348	0.99	(0.94-1.05)	0.804
DBP (mmHg)	1.00	(0.99-1.01)	0.774	1.01	(0.99-1.02)	0.608	1.02	(1.00-1.04)	0.040	0.99	(0.97-1.01)	0.482
SBP (mmHg)	1.00	(0.99-1.00)	0.139	0.99	(0.99-1.00)	0.653	0.99	(0.98-1.00)	0.250	1.00	(0.99-1.01)	0.689
ACR (mg/mol)	1.00	(0.99-1.00)	0.980	1.01	(0.98-1.02)	0.876	1.00	(0.98-1.02)	0.833	0.99	(0.97-1.02)	0.777
eGFR (mls/min/1.73m^2)	0.99	(0.99-0.99)	<0.001	1.00	(0.99-1.00)	0.245	0.99	(0.98-1.00)	0.239	1.01	(0.99-1.01)	0.884
TC. (mmol/L)	1.70	(1.42-2.01)	<0.001	0.67	(0.40-1.11)	0.120	0.68	(0.33-1.40)	0.291	0.63	(0.31-1.28)	0.204
BMI Categories												
Normal	1	-	-	1	-	-	1	-	-	1	-	-
Overweight	1.06	(0.90-1.26)	0.482	0.86	(0.50-1.45)	0.564	1.22	(0.66-2.26)	0.523	0.92	(0.45-1.87)	0.822
Obese	1.05	(0.85-1.29)	0.678	0.64	(0.33-1.24)	0.185	1.31	(0.56-3.09)	0.533	1.86	(0.70-4.97)	0.211
Post-Insulin mean HbA1c decile												

D1 (mp 5.8%)	1.36	(1.10-1.62)	0.075	1.25	(0.62-2.54)	0.534	0.92	(0.41-2.07)	0.839	0.61	(0.26-1.43)	0.258
D2 (mp 6.7%)	1.22	(0.98-1.46)	0.151	1.20	(0.58-2.50)	0.624	0.73	(0.33-1.65)	0.452	1.13	(0.50-2.54)	0.776
D3 (mp 7.1%)	1.17	(0.94-1.44)	0.178	2.12	(1.05-4.28)	0.035	1.40	(0.66-2.99)	0.382	0.54	(0.24-1.24)	0.145
D4 (mp 7.5%)	ref	-	-	ref	-	-	ref	-	-	ref	-	-
D5 (mp 7.9%)	1.01	(0.82-1.21)	0.058	1.44	(0.69-3.00)	0.326	0.92	(0.41-2.10)	0.861	0.41	(0.15-1.17)	0.097
D6 (mp 8.2%)	1.13	(0.92-1.35)	0.977	1.12	(0.58-2.19)	0.722	1.35	(0.63-2.92)	0.444	0.44	(0.20-0.98)	0.045
D7 (mp 8.7%)	1.12	(0.90-1.24)	0.135	1.33	(0.63-2.78)	0.452	0.81	(0.37-1.75)	0.585	0.34	(0.13-0.89)	0.028
D8 (mp 9.0%)	1.21	(0.98-1.44)	0.013	1.89	(0.96-3.72)	0.067	0.56	(0.24-1.31)	0.181	1.09	(0.48-2.49)	0.836
D9 (mp 9.5%)	1.24	(0.99-1.49)	0.962	1.38	(0.68-2.80)	0.368	0.63	(0.27-1.51)	0.301	0.78	(0.31-2.00)	0.613
D10 (mp 10.8%)	1.31	(1.06-1.56)	0.315	1.67	(0.82-3.44)	0.161	1.42	(0.66-3.06)	0.373	0.38	(0.15-0.99)	0.047

Diabetes duration is time from first diagnosis of diabetes to date of intensification with insulin (index date). mp, median point. ACR, albumin creatinine ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; INS, insulin; Met, metformin; SU, sulphonylurea; DBP, diastolic blood pressure; SBP, systolic blood pressure; TC, total cholesterol.

Sensitivity analysis for the hazard of composite events as a time-fixed or time-dependent covariate, in three models in which the mean post-insulin HbA1c was fitted differently in the Cox regression model (as mean of all values, cumulative mean and yearly mean) in the final model is shown in Figure 7.3. Compared to the reference 4th decile (HbA1c of 7.5%), the adjusted hazard of mortality showed slight variations when HbA1c was fitted as cumulative mean but the overall U-shaped association between hazard ratio and mean HbA1c decile persists.

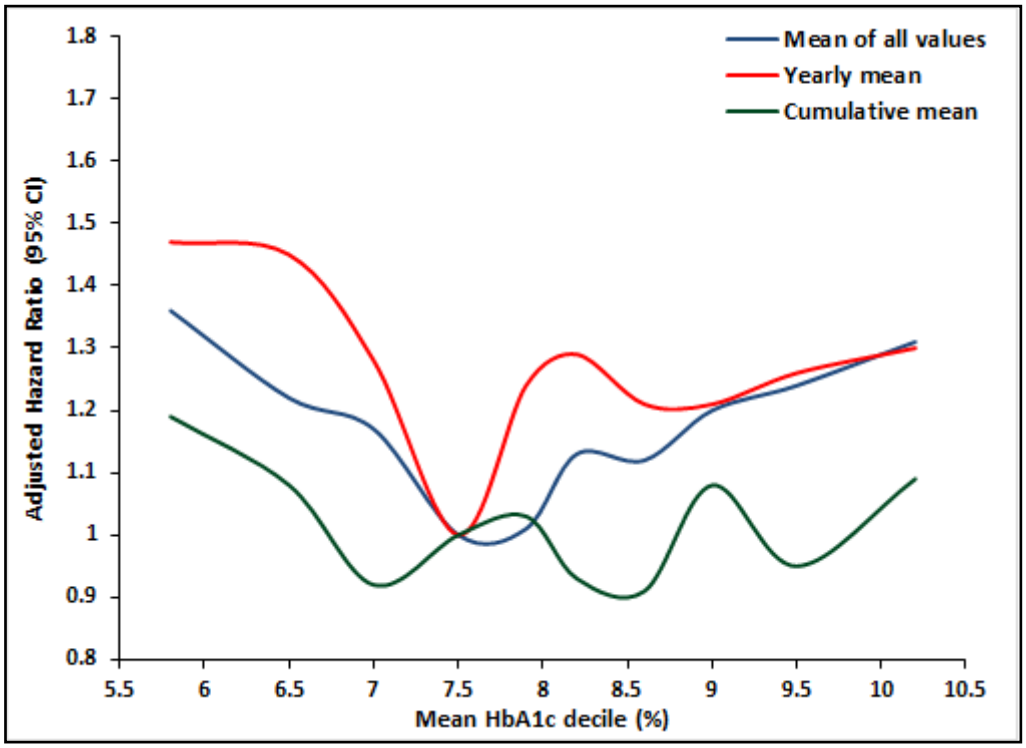


Figure 7.3: Adjusted Hazard Ratios for mortality based on the different models of HbA1c deciles - Mean of all values (blue), Cumulative (updated) mean (green) and yearly mean (red).

7.5. Discussion

I have shown that for older patients (aged >65 years) with Insulin-treated type 2 diabetes, following adjustment for various confounders, very high and very low levels of HbA1c were associated with higher risks of adverse outcomes, with the optimal level of HbA1c ranging between 7.4-7.7%. The highest mortality risks were observed at the lowest (5.8%) and highest (>10.7%) levels of HbA1c. Interestingly, however, this U-shaped association between HbA1c and mortality was not observed in the subgroup of patients with no previous history of a CV event at baseline.

Evidence derived from randomised controlled trials has shown that intensive control of blood glucose levels in patients with type 2 diabetes reduces the risk of long-term vascular complications leading to blindness, kidney failure, lower limb amputation and adverse cardiovascular events.[22, 103, 259] Previous observational studies, however, have provided conflicting evidence regarding the association between achieved HbA1c levels and mortality among patients with type 2 diabetes in routine care. Studies using earlier datasets have reported a more linear relationship[288, 289] whereas more recent studies have reported a U-shaped association between HbA1c and mortality[37, 290, 291] Of note, in a study by Currie et al,[37] a U-shaped association was observed among insulin users, but this was not apparent among non-insulin treated patients. The discrepancies between older and more recent studies are likely to be attributable to the more aggressive glycaemic targets being adopted in response to recent national and international guidelines, as well as the greater use of combination therapies which include insulin.

A post-hoc analysis of the ACCORD trial has revealed a discordant HbA1c-mortality relationship between the control arm and the intensively treated arm,[94] indicating that aggressive use of glucose-lowering treatments might influence the HbA1c-mortality relationship. In a more recent sub-analysis of the ACCORD trial, regardless of intervention

arm, the subgroup of older patients experienced higher annualized rates of severe hypoglycaemia. Thus, the recommendation for individualization of HbA1c targets for older people needs to be based on a variety of considerations including levels of frailty, presence of multiple comorbidities and the complexities and safety of polypharmacy. Yet, despite the well-recognised associations between intensive glucose control and the increased risk of hypoglycaemia, and the links between hypoglycaemia and enhanced sympathomimetic (adrenergic) drive,[292] cardiac arrhythmias[293] and mortality,[294] there is limited data on defining the optimal HbA1c-target (or target range) in elderly patients with insulin treated T2D.

This analysis therefore advances current knowledge in several ways: (1) it assessed the association between HbA1c and mortality specific to older patients with Insulin-treated type 2 diabetes; (2) it utilised a large electronic record of individual patient-data among a cohort receiving routine care in UK General Practice; (3) I derived an optimal HbA1c range for this patient cohort associated with reduction in the risk of mortality, (4) a range of values was observed following adjustment for important confounders and time varying co-variates, as well as appropriate management of missing data using multiple imputation techniques; and (5) I have identified independent predictors of mortality.

These findings in elderly insulin treated patients with type 2 diabetes are consistent with recent observational studies in general patients with type 2 diabetes which reported a strong U-shaped HbA1c –mortality association. However, rather than aiming to achieve an optimal HbA1c target to below a certain value, the data suggest the need to control HbA1c to a certain range (7.4-7.7%) in order to maximally reduce mortality. Of note, while age, smoking status, BMI, renal function and cholesterol were independent predictors of mortality, it is interesting that the impact of diabetes duration as an independent predictor of mortality was eliminated for patients who were co-prescribed metformin therapy, which might indirectly signify a cardiovascular benefit of metformin in this patient group.

Unlike mortality, I did not observe a U-shape association between cardiovascular events and HbA1c in this group of patients, but rather a similar cardiovascular risk across all HbA1c levels. This implies that this older patient cohort are generically at higher risk of cardiovascular events, irrespective of HbA1c levels, and that other non- cardiovascular factors may influence mortality outcomes at high or low levels of HbA1c. Older patients at low levels of HbA1c may have poor glycogen reserve due to poor nutritional status and are generally more frail,[295] whereas those with higher HbA1c may have a higher risk of dehydration, infection, electrolyte abnormalities and metabolic complications,[296] all of which may contribute to an elevated mortality risk, independent of cardiovascular events. A discrepancy between mortality and cardiovascular outcomes was also observed in the ACCORD study where, despite an increase in mortality with intensive glucose control, the number of patients achieving the primary outcome of a composite of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes was lower in the intensive compared with the standard therapy groups, although this finding was not statistically significant.[92]

7.6. Limitations

These analyses were subject to some limitations inherent to observational studies, such as coding errors, unlisted comorbidities or missing data, although the use of multiple imputations[297] would have provided some protection against the latter. In addition, our exposure data relates to prescriptions so I cannot be certain that the patients were completely compliant with their medication. However, should there be any over-estimation of exposure to the medications in our analysis, such a misclassification would be non-differential and only bias results towards unity. Other factors apart from HbA1c may also influence the decision to intensify treatment by starting insulin. These may include tolerability, safety, cost and a

patient's preference, but this analysis was unable to evaluate how these factors might have influenced the findings. Although I could not account for potential residual confounders such as indications for intensification of treatment or differences in doses, I was able to account for differences in the observed covariates and I used robust analytical techniques to control confounding that may bias the results of the estimated treatment effects. Nonetheless, the issue of unmeasured confounding does persist, e.g. the relationship between severity of risk factors and clinical outcomes or differences in the time varying relationship for each risk factor with individual outcomes. Lastly, differences in the time window for HbA1c collection, largely necessitated by yearly Quality and Outcome Framework (QOF) recording by GP practices, may introduce bias for survival analysis. I therefore conducted sensitivity analyses using three different methods for HbA1c data analysis and found the findings to be similar.

Recent local and international guidelines have emphasised the importance of individualised HbA1c targets to consider patient factors such as age, body mass index, comorbidities or duration of diabetes. This is particularly relevant when determining the safety profile of insulin treatment in elderly patients.

7.7. Conclusion

This data support a strong U-shaped association between HbA1c and mortality with minimum safe and high HbA1c values identified to reduce the risks of mortality in this high risk group of patients in routine care. The observational data presented here therefore provide important guidance to the management of the rapidly growing number of older patients with type 2 diabetes who require insulin therapy to manage their hyperglycaemia and symptoms.

Chapter Eight: Effects of Background Statin Therapy on Glycaemic Response and Cardiovascular Events

8.1. Summary

Aim

Statins may increase the risk of new-onset diabetes and adversely affect glycaemic control, but their effects on the glycaemic response and mortality outcomes following commencement of insulin therapy in patients with Type 2 Diabetes (T2D) are unclear.

Methods

A retrospective cohort study was conducted in 12,725 insulin initiators with T2D using The Health Improvement Network (THIN) UK database. Changes in HbA1c at 6, 12, 24 and 36 months, and the 5-year risk of mortality and (3-point) major adverse cardiovascular events (MACE), were compared between prior users (n=10,682) and non-users (n=2,043) of statin therapy who were newly commenced on insulin treatment. Cox proportional hazard models were used to estimate the hazard ratios of the different outcomes.

Results

Mean age of the cohort was 58.7±14.0 years (51% male) and mean baseline HbA1c was 8.7±1.8%. A greater initial reduction in HbA1c was observed following insulin initiation in the non-users of statins compared with the users, which was significant in the short term (-0.34% vs -0.26% at 6 months; mean diff = -0.09%, p=0.004) but not in the long term: -0.31% vs -0.35% at 3 yrs (mean diff = 0.05%, p=0.344). CV events (3-point MACE) were 878 vs 217

in statin users vs non-users (20.7 vs 30.9 per 1000 person-yrs; adjusted Hazard Ratio (aHR) 1.36 (95%CI: 1.15-1.62; p<0.0001). In a subgroup analysis of individual statins, HbA1c was higher throughout the study duration with all statins relative to non-users of statin therapy (p < 0.05). The aHRs for 3-point MACE for atorvastatin, simvastatin, rosuvastatin and pravastatin were 0.82 (95%CI: 0.68–0.98), 0.67 (0.55–0.82), 0.56 (0.39-0.81) and 0.78 (0.60-1.01), respectively.

Conclusion

Following initiation of insulin therapy in patients with T2D in routine care, concurrent use of a statin was associated with less good (clinically non-relevant) glycaemic control in the short-term but a much lower risk of major adverse CV events.

8.2. Introduction

Evidence from randomized controlled trials shows that statin therapy reduces the risk of fatal and nonfatal cardiovascular (CV) events in patients with T2D[298-300] Thus, clinical guidelines advocate their routine use in all patients with diabetes aged 40-75 years, and in younger patients with high CV risk.[301, 302]

Various studies have shown that statins may also have modest adverse effects on glucose and insulin metabolism, e.g. increasing the risk of new-onset diabetes, especially in higher doses and with the more potent statins,[41, 65, 303-305] but the relationship between statin use and glycaemic control in patients with established T2D is much less clear. Previous studies have reported an increase in HbA1c[306, 307] while others have reported either no effect or a reduction in glucose levels.[308, 309] A meta-analysis of 9 randomized controlled trials (RCTs) involving 9,696 participants reported that glycaemic control was adversely affected among those patients

randomized to a statin compared with placebo, and that statin treatment also increased HbA1c in those patients with established T2D.[310] None of these studies, however, has specifically focused on T2D patients who are commencing insulin therapy, nor have they excluded the possibility of bias due to differential attrition rates and/or differential adjustment of other glucose-lowering therapies (GLTs) between the statin and control groups.[23]

More information is certainly needed about the associations between statin use, glycaemic control and CV risk specifically in the insulin-treated T2D population, because these patients tend to have more complications, higher absolute CV risk and a longer duration of diabetes. Commencing insulin can also affect lipid levels and overall CV risk.[124] Thus, in routine practice some of the well-recognised clinical inertia may be due to uncertainty about the optimal timing and the overall risk-benefit balance of insulin initiation in these patients. For example, it was reported that primary prevention with statins was initiated in less than half of diabetic patients after a first MI, despite the presence of one or more markers of very high cardiovascular risk in nearly all.[311] Therefore, the aim of this large cohort study was to investigate the effects of background statin use on glycaemic control and CV outcomes following commencement of insulin therapy in patients with T2D in a routine primary care setting.

8.3. Methods

8.3.1. Study Design:

This was a retrospective cohort study using a UK primary care database. This has been described fully in Chapter 2.

8.3.2. The Health Improvement Network (THIN) Database

THIN is a large UK electronic Primary Care database with longitudinal records obtained from approximately 587 General Practices. This has been described in Chapter 2.

8.3.3. Study Participants

I obtained data on 12,725 people in the THIN database who had a diagnosis of T2D, were >18 years of age and who initiated insulin therapy between December 2006 and May 2014. Patients with type 1 or gestational diabetes, or other forms of diabetes, and those with no continuous regular prescriptions for insulin in their records were excluded. For analysis of our secondary objective, I excluded patients with a history of CV disease before or 180 days after initiating insulin.

8.3.4. Follow-up and Endpoints

I followed-up all insulin-initiators from the point they commenced statin treatment and compared them with those who did not commence statins until the first incident of any of the secondary outcomes: 3-point Major Adverse Cardiovascular Events (MACE: all-cause mortality or non-fatal myocardial infarction or stroke); loss to follow-up; discontinuation of insulin and/or statin therapy; or at the end of the 5-year follow-up period. Similarly, their baseline HbA1c, body weight and blood pressure were measured at baseline and at different time points after starting insulin (6, 12, 24 and 36 months).

The primary endpoints were glycaemic control (measured by change in HbA1c), changes in body weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline to 6, 12, 24 and 36 months after commencement of insulin treatment. These differences were computed and compared between the two treatment groups (statin users versus non-users). The secondary endpoint was the time to the risk of a 3-point MACE.

8.3.5. Baseline and endpoint characteristics

To adjust for the confounding effects some differences in baseline characteristics may have on the study outcomes, I extracted data on important clinical covariates. These included demographic variables such as age, gender, socioeconomic status, alcohol and smoking status; important clinical measures such as body weight, height, SBP and DBP; biochemical parameters, e.g. baseline HbA1c, serum creatinine, lipid-profile, use of other medications including other glucose-lowering therapies (GLTs); as well as comorbidity status, duration of diabetes treatment, and duration of insulin use. These were included in our univariate analysis models from which the significant covariates (those which had a significant association with both the exposure and outcomes) were added to the final Cox and linear regression models.

8.3.6. Statistical Analysis

I computed summary data for the mean, standard deviations and proportions of the baseline characteristics and used Pearson's chi-square test and t-test to determine the differences between the treatment groups at baseline.

For the missing values in HbA1c, weight, SBP and DBP at baseline and all the study time points, I observed that a small proportion of values for these covariates were completely missing at random. These missing values were then computed using multiple imputations using the chained equation (MICE) model. Thereafter, linear regression models were used to compute the mean differences between baseline HbA1c, weight, SBP and DBP and the 6, 12, 24 and 36-month measurements respectively while adjusting for significant baseline covariates.

For the secondary endpoints of MACE, I used a Cox proportional hazard model to estimate the marginal and adjusted hazard ratios (HRs) with 95% confidence intervals, comparing the outcomes in the statin treated group to the non-user group. Furthermore, the crude and adjusted Kaplan–Meier estimates of survival functions between the two treatment groups were computed and the log-rank test was used to compare the equality of the survival curves between them. The absolute reduction in the probability of the incidence of MACE within the 5-year follow-up was computed from these survival functions.

Finally, I tested for any violation of the proportional hazard assumption of the Cox regression model, first by adding an interaction term of the predictor; secondly by log-minus-log survival curves; and thirdly by Schoenfeld residuals tests.

Subgroup Analysis: I also performed a subgroup analysis to explore the individual statins (atorvastatin, simvastatin, rosuvastatin and pravastatin) identified in the database. The primary and secondary endpoints were determined in these individual statin groups compared to the non-statin user group.

In all the analyses, I computed the point estimates with 95% confidence intervals (CI) at the conventional statistical significance level of 0.05. All analyses were conducted using Stata Software, version 14.

8.4. Results

8.4.1. Patient Characteristics, Cases and Total Follow up

A total of 12,725 new insulin users with T2D (mean age 58.6±14 yrs) were selected (Figure 8.1). Among these 83.9% were statin users. Mean follow up was 3.9±1.5 yrs, which represents

a total follow-up of 49,516 person-years. Table 8.1 shows the baseline characteristics of the treatment groups. Non-users of statins were significantly younger, more likely to be female and had a significantly shorter duration of diabetes and insulin use. Baseline HbA1c, body weight and DBP were similar in the two groups (Table 1). SBP was higher in the statin users.

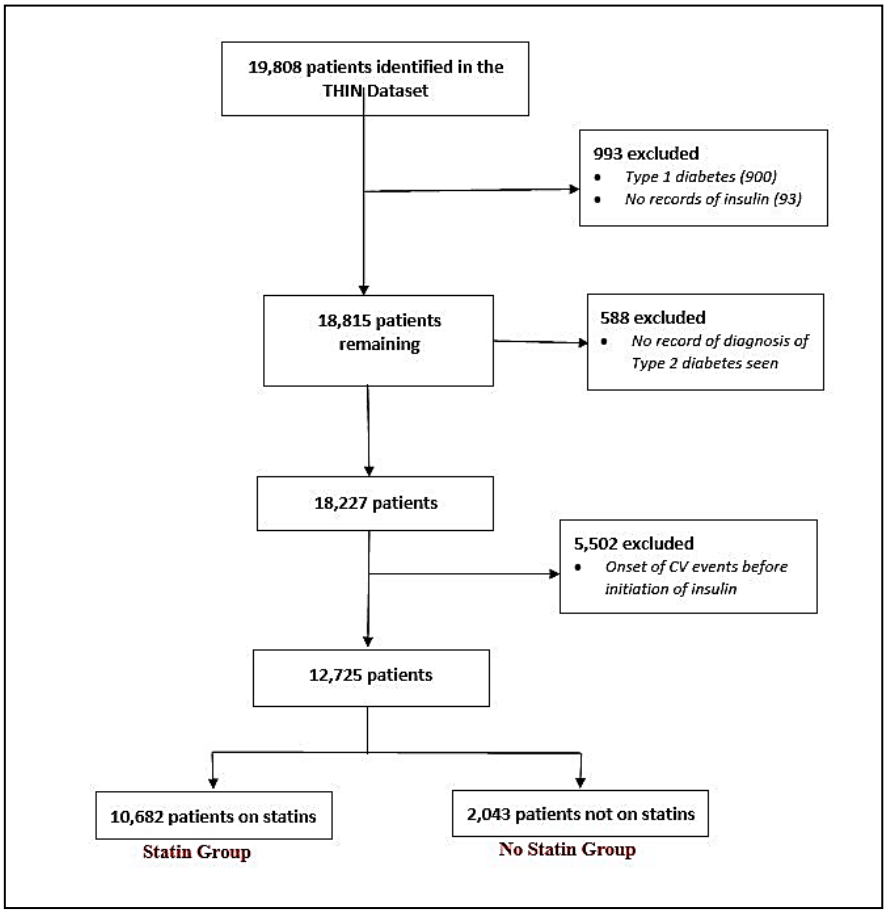


Figure 8.1: Selection of study participants

8.4.2. Primary Endpoints: Metabolic Outcomes

(i). Association between prior statin use and glycaemic response: Glycaemic response was defined by the changes from baseline in HbA1c at 6, 12, 24 and 36 months after initiating insulin therapy. Figures 8.2A and 8.2B show the mean reductions in HbA1c and the mean HbA1c levels, respectively, at each of these time points. Both treatment groups (statin users and non-users) showed a significant reduction in HbA1c throughout the duration of the study (Figure 8.2B) but insulin therapy resulted in a greater reduction in HbA1c among non-users of

statins (Figure 8.2A). This was significant at 6 months with mean reductions of -0.26% vs -0.34% (mean diff: 0.09%; 95%CI: 0.03 – 0.15; p = 0.004) in the statin user vs non-user groups respectively, but not at 36 months (corresponding mean reductions of -0.31% vs -0.35%; mean diff: 0.05%; 95%CI: -0.04 – 0.14; p = 0.172); though this does not appear to be clinically relevant.

Table 8.1: Baseline characteristics of study participants

	Statin use (n = 10,682)	None (n = 2,043)	Total (n = 12,725)	p-value
Demographics				
Age (yrs). Mean (SD)	59.4 (12.7)	54.3 (18.2)	58.6 (13.8)	< 0.001
Gender. No. (%)				
Female	5258 (49)	1122 (55)	6380 (50)	< 0.001
Smoking Status. No (%)				
Non-smoker	5549 (52)	1137 (56)	6686 (52)	
Ex-smoker	3634 (34)	543 (27)	4177 (33)	< 0.001
Current	1499 (14)	363 (18)	1862 (15)	
Alcohol Status. No (%)				
Never	3431 (32)	614 (30)	4045 (32)	
Ex-drinker	1133 (11)	320 (16)	1453 (11)	< 0.001
Current	6118 (57)	1109 (54)	7227 (57)	
Deprivation. No (%)				
Least deprived	2151 (21)	403 (21)	2554 (20)	
Second quintile	2089 (20)	382 (20)	2471 (19)	
Third quintile	2255 (22)	422 (22)	2677 (21)	0.631
Fourth quintile	2171 (21)	399 (21)	2570 (20)	
Most deprived	1591 (16)	327 (17)	1918 (15)	
Clinical Parameters. Mean (SD)				
HbA1c (%)	8.7 (1.8)	8.7 (2.0)	8.7 (1.8)	0.556
BMI (kg/m^2)	32.7 (6.9)	32.8 (7.2)	32.7 (6.9)	0.252
Diabetes duration* (yrs)	4.0 (4.9)	2.5 (4.3)	3.8 (4.9)	< 0.001
Time on insulin (yrs)	3.7 (6.3)	2.3 (6.0)	3.5 (6.3)	<0.001
Height (m)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	0.860
Weight (kg)	91.4 (18.8)	91.9 (19.1)	91.5 (18.8)	0.268
DBP (mmHg)	76.5 (10.8)	76.9 (11.1)	76.6 (10.9)	0.129
SBP (mmHg)	136.4 (23.0)	134.6 (23.4)	136.1 (23.1)	0.002
Albumin (g/L)	4.1 (0.4)	4.0 (0.4)	4.1 (0.4)	0.002
ACR (mg/mol)	5.7 (8.4)	5.2 (8.5)	5.6 (8.5)	0.014
eGFR (mls/min/1.73m^2)	64.6 (21.0)	68.0 (22.0)	65.1 (21.2)	< 0.001
TC. (mmol/L)	4.6 (1.3)	4.7 (1.4)	4.6 (1.3)	< 0.001
Triglyceride (mmol/L)	2.0 (1.2)	2.0 (1.2)	2.0 (1.2)	0.072
LDL (mmol/L)	2.4 (1.1)	2.5 (1.1)	2.4 (1.1)	< 0.001
HDL (mmol/L)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	0.225
BMI Categories, No. (%)				
Normal	1371 (13)	294 (14)	1665 (13)	
Overweight	2533 (24)	489 (24)	3022 (24)	0.131
Obese	6778 (63)	1260 (62)	8038 (63)	
Use of Medications, No. (%)				
Aspirin	10481 (95)	1541 (94)	12022 (94)	0.723
Antihypertensives	9321 (87)	1217 (91)	10538 (83)	< 0.001
GLTs No (%)**				
Dual Therapy	2334 (22)	904 (44)	3238 (28)	
Triple Therapy	3400 (33)	609 (30)	4009 (33)	< 0.001
More than Triple Therapy	4948 (45)	669 (26)	5478 (39)	
Comorbidities, No. (%)				
Hypoglycaemia	1824 (17)	313 (15)	2137 (17)	0.052
Heart Failure	641 (6)	72 (4)	713 (6)	< 0.001
PAD	756 (7)	67 (3)	823 (7)	< 0.001
CHD	1390 (13)	75 (4)	1465 (12)	< 0.001

BMI (body mass index); SBP (systolic blood pressure); DBP (diastolic blood pressure); HbA1c (haemoglobin A1c); HDL (high-density lipoprotein); LDL (low-density lipoprotein); TC (total cholesterol); GFR (glomerular filtration rate); LLT (lipid lowering therapy); PAD (peripheral arterial disease); CHD (coronary heart disease); ACR (albumin creatinine ratio); SD (standard deviation).

**Diabetes duration is time from first diagnosis of diabetes to date of insulin initiation*

***GLTs (Glucose Lowering Therapies) denote the number of GLTs ever recorded for patients within the study duration and not the current regimen*

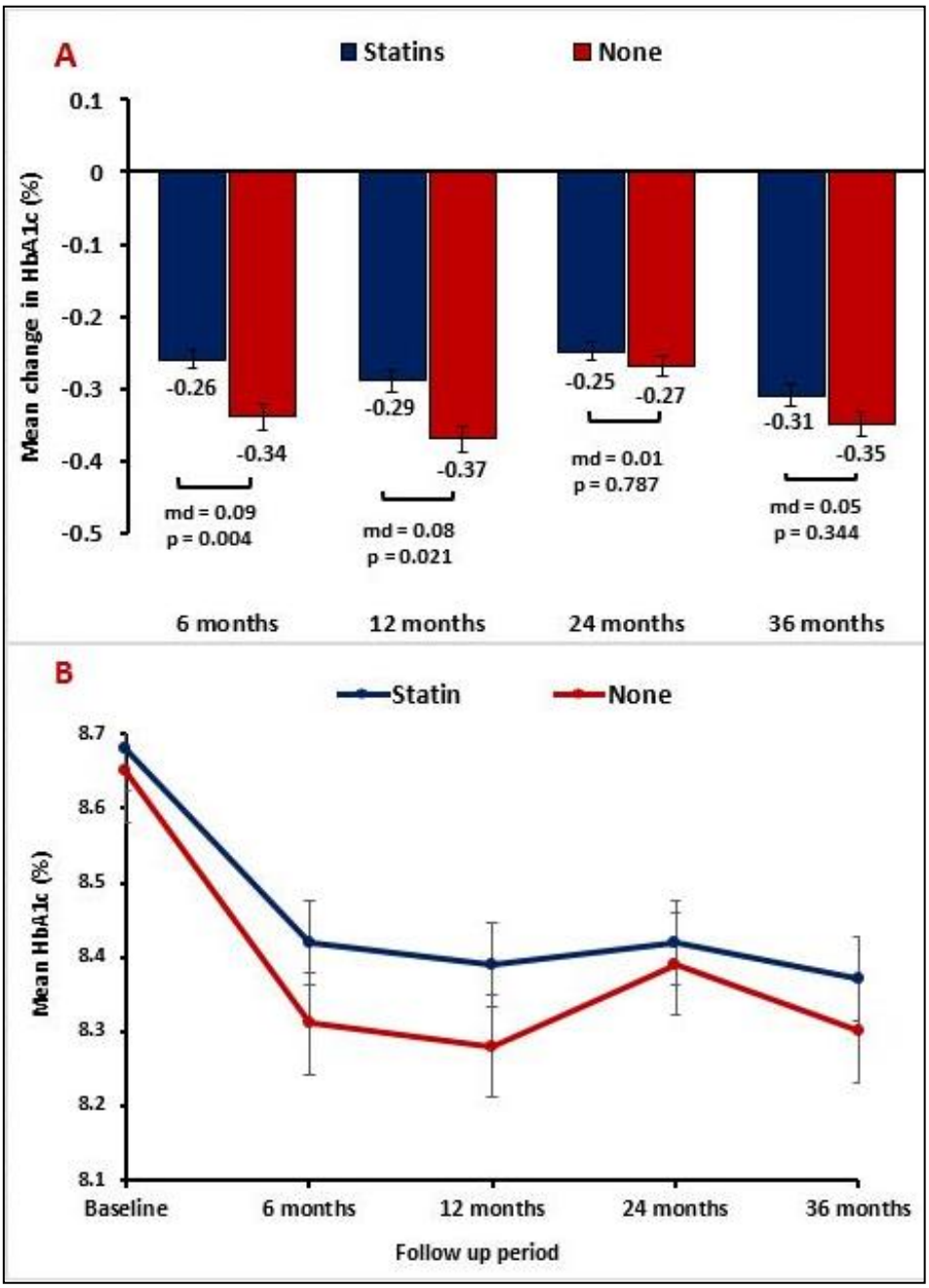


Figure 8.2: Mean differences in changes in HbA1c levels between the treatment groups (A) and the mean HbA1c levels in both treatment groups (B) (p <0.05 from baseline for the study duration).

(ii). Relationship between statin use and other clinical measurements: There were increases in body weight following insulin initiation but no significant differences between the 2 groups from 6-24 months (Figure 8.3). At 36 months, however, statin users showed a small reduction in weight of 0.18kg (p = 0.031) versus an increase of 0.26kg (p = 0.405) in the non-statin group (mean diff = -0.54kg, 95%CI: -0.35 – 0.88; p =0.099).

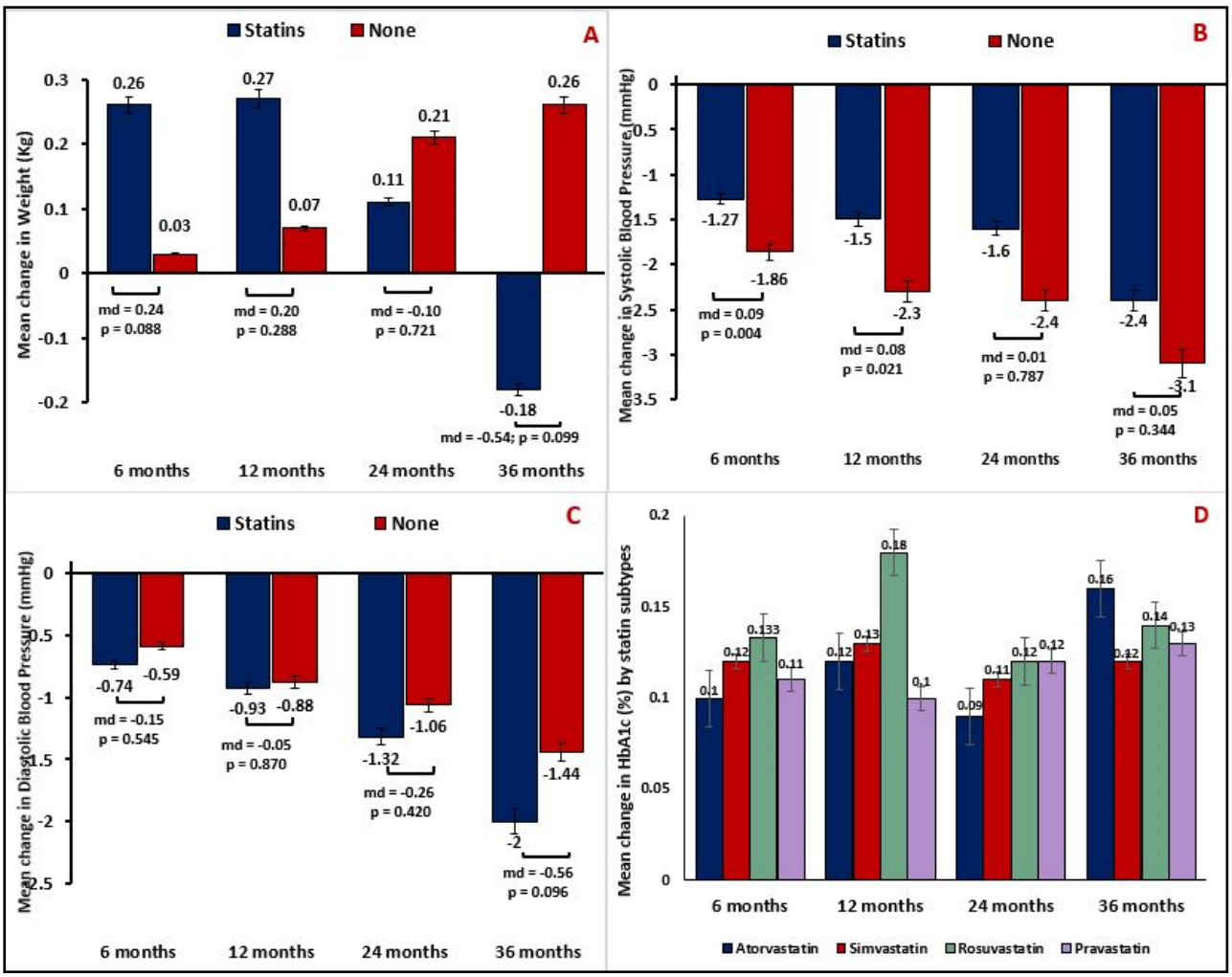


Figure 8.3: Mean change and differences in weight (A), Systolic Blood Pressure (B) and Diastolic Blood Pressure (C) between the two treatment groups. Mean changes in HbA1c in the different types of statins, compared to non-statin users (D). P value for all is < 0.05

SBP decreased in both treatment groups throughout the study, but more so in non-users of statins (Figure 8.3) with a significant difference at 6 months (-1.27 vs -1.86 mmHg; p = 0.004) and 12 months (-1.5 vs -2.3mmHg; p = 0.021). These differences were not maintained at 24

months (-1.6 vs -2.4mmHg; p = 0.787) and 36 months (-2.4 vs -3.1mmHg; p = 0.344). There was also a significant reduction in DBP in both treatment groups. Throughout the study, DBP was non-significantly lower among statin users compared to non-users. For example, the respective changes in DBP ranged from 0.74 vs 0.59mmHg at 6 months to 2.0 vs 1.44mmHg at 36 months (Figure 8.3).

8.4.3. Secondary Endpoints: Risk of Major Adverse Cardiovascular Events

(i). Crude Event Rates: The probability of survival for the 3-point composite outcome of all-cause mortality, non-fatal MI and stroke was significantly different between the both groups at 1-year (98.8% vs 99.2%) and 5-years (89.9% vs 84.7%) of follow-up (log-rank test p-value < 0.0001) (Figure 8.4A). A total of 1,095 (878 vs 217) composite events were reported with a crude event rate of 22.1 (20.7 vs 30.9) per 1,000 person-years (95%CI: 20.8 – 23.5) (Table 1). Table 2 shows a summary of the events for each of the individual MACE components with the absolute event rates.

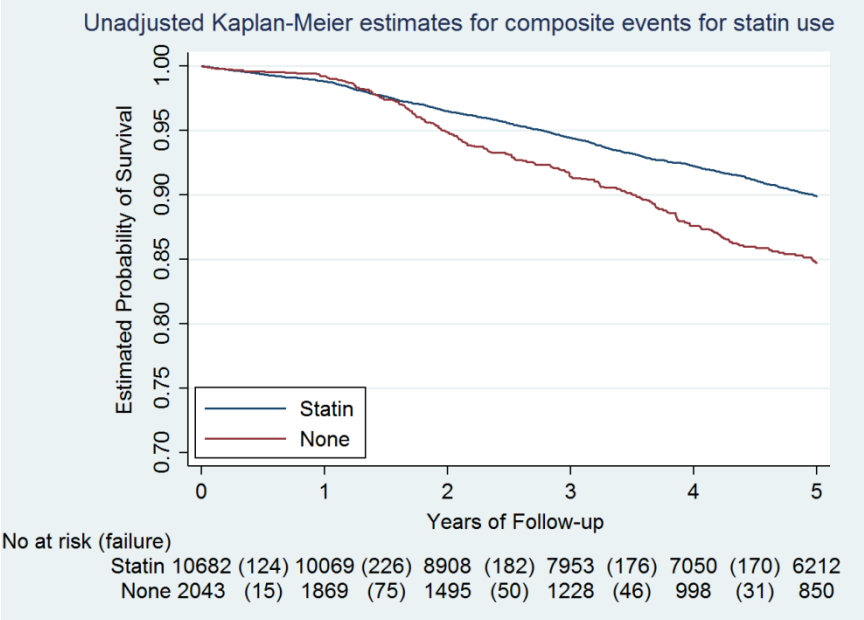


Figure 8.4: Kaplan-Meier curves showing the 5-year probability of survival for the 3-point composite MACE between the Statin vs No-Statin groups (Log-rank test p-value < 0.0001)

(ii). Risk of 3-point Composite of MACE: The risk of a MACE in the unadjusted model was 53% (aHR: 1.53; 95%CI: 1.32 - 1.77) higher among non-users compared to statin users. This was reduced slightly to 36% (HR: 1.36; 95%CI: 1.15 – 1.62) when I adjusted for age, gender, duration of insulin use, albumin, glomerular filtration rate, lipid profile, and coronary heart disease history. A similarly higher risk (89%) was observed for all-cause mortality (aHR: 1.89; 95%CI: 1.51 – 2.37) among non-users of statins compared to statin users, but an opposite trend was observed for non-fatal MI and stroke: non-users of statins had a 12% lower risk of MI (aHR: 0.88, 95%CI: 0.35 – 2.23) and a 45% lower risk of stroke (HR: 0.55; 95%CI: 0.38 – 0.81) (Table 8.2).

Table 8.2: Events, Crude Incidence Rates and Hazard Ratios of Events in the Two Treatment groups

	Statin use	None
	(N = 10,682)	*(N = 2,043)*
Composite Outcome[a]		
No of events/person-years	878/42,484	217/7,032
Absolute rates[b] (95%CI)	20.7 (19.3 – 22.1)	30.9 (27.0 – 35.3)
HR[c] (95%CI)	1 (reference)	1.53 (1.32 – 1.77)
aHR[d] (95%CI)	1 (reference)	1.36 (1.15 – 1.62)
All-Cause Mortality		
No of events/person-years	*415/43,503*	*177/7,098*
Absolute rates (95%CI)	*9.5 (8.7 – 10.5)*	*24.9 (21.5 – 28.9)*
HR (95%CI)	*1 (reference)*	*2.61 (2.19 – 3.12)*
aHR (95%CI)	*1 (reference)*	*1.89 (1.51 – 2.37)*
Acute Myocardial Infarction (AMI)		
No of events/person-years	*60/43,377*	*5/7,094*
Absolute rates (95%CI)	*1.4 (1.1 – 1.8)*	*0.7 (0.3 – 1.7)*
HR (95%CI)	*1 (reference)*	*0.50 (0.20 – 1.25)*
aHR (95%CI)	*1 (reference)*	*0.88 (0.35 – 2.23)*
Non-fatal Stroke		
No of events/person-years	*401/42,643*	*34/7,051*
Absolute rates (95%CI)	*9.4 (8.5 – 10.4)*	*4.8 (3.4 – 6.7)*
HR (95%CI)	*1 (reference)*	*0.51 (0.36 – 0.72)*
aHR (95%CI)	*1 (reference)*	*0.55 (0.38 – 0.81)*

[a] Composite outcome is a three-point MACE including all-cause mortality, non-fatal acute myocardial infarction (AMI) and non-fatal stroke.
[b] Absolute Rate at 1000 person-years
[c] HR (Unadjusted Hazard Ratio)
[d] aHR (Adjusted Hazard Ratio). Adjusted for age, gender, duration of insulin use, albumin, glomerular filtration rate, lipid profile, and coronary heart disease.

8.4.4. Subgroup and Sensitivity Analyses

Compared to non-users of statins, all of the individual statins showed higher HbA1c levels throughout the study (Figure 8.3). The number of events for the 3-point composite of MACE was 398, 342, 41 and 461 among patients on atorvastatin, simvastatin, rosuvastatin and pravastatin respectively. The 5-year probability of survival differed significantly between the various statins (Log-rank test p-value < 0.0001). Below, Table 8.3 shows a summary of these events, event rates and hazard ratios for the 3-point MACE composite and the individual components. When compared to non-statin users, the risk of the composite MACE was 18% lower (aHR: 0.82; 9%CI: 0.68 – 0.98) among atorvastatin users, 33% lower (aHR: 0.67; 9%CI: 0.55 – 0.82) among simvastatin users, 44% lower (aHR: 0.56; 9%CI: 0.39 – 0.81) among rosuvastatin users and 22% lower (aHR: 0.78; 9%CI: 0.60 – 1.01) among pravastatin users.

Finally, to test the adequacy of our multiple imputation approach in addressing the impact of some missing data in our dataset, I conducted a sensitivity analysis wherein the primary endpoints in the imputed dataset were compared with the dataset with missing values and found to be similar, thereby affirming the robustness of the imputation method employed. The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on exposure; no violations were observed.

Table 8.3: Events, Crude Incidence Rates and Hazard Ratios of Events by Statin types

	None (N = 2,043)	Atorvastatin (N = 4,415)	Simvastatin (N = 4,462)	Rosuvastatin (N = 713)	Pravastatin (N = 1,092)
Composite Outcome[a]					
No of events/person-years	217/7,032	398/16,840	342/18,287	41/2,894	97/4,461
Absolute rates[b] (95%CI)	30.9 (27.0 – 35.3)	23.6 (21.4 – 26.1)	18.7 (16.8 – 20.8)	14.2 (10.4 – 19.2)	21.7 (17.8 – 26.5)
HR[c] (95%CI)	1(Reference)	0.75 (0.64 – 0.89)	0.59 (0.50 – 0.70)	0.45 (0.32 – 0.62)	0.68 (0.54 – 0.87)
aHR[d] (95%CI)	1 (Reference)	0.82 (0.68 – 0.98)	0.67 (0.55 – 0.82)	0.56 (0.39 – 0.81)	0.78 (0.60 – 1.01)
All-Cause Mortality					
No of events/person-years	177/7,098	203/17,229	162/18,710	17/2,947	33/4,616
Absolute rates (95%CI)	24.9 (21.5 – 28.9)	11.8 (10.3 – 13.5)	8.7 (7.4 – 10.1)	5.8 (3.6 – 9.3)	7.1 (5.1 – 10.1)
HR (95%CI)	1(Reference)	0.45 (0.37 – 0.55)	0.32 (0.26 – 0.40)	0.22 (0.13 – 0.36)	0.27 (0.19 – 0.39)
aHR (95%CI)	1 (Reference)	0.61 (0.48 – 0.78)	0.49 (0.38 – 0.64)	0.39 (0.22 – 0.67)	0.39 (0.26 – 0.60)
Acute Myocardial Infarction (AMI)					
No of events/person-years	5/7,094	26/17,168	21/18,670	2/2,948	11/4,590
Absolute rates (95%CI)	0.7 (0.3 – 1.7)	1.5 (1.0 – 2.2)	1.1 (0.7 – 1.7)	0.7 (0.2 – 2.7)	2.4 (1.3 – 4.3)
HR (95%CI)	1(Reference)	2.17 (0.83 – 5.65)	1.62 (0.61 – 4.30)	0.98 (0.19 – 5.03)	3.45 (1.20 – 9.94)
aHR (95%CI)	1 (Reference)	1.42 (0.53 – 3.78)	0.88 (0.32 – 2.40)	0.63 (0.12 – 3.33)	1.61 (0.54 – 3.78)
Non-fatal Stroke					
No of events/person-years	34/7,051	168/16,919	158/18,337	22/2,896	53/4,489
Absolute rates (95%CI)	4.8 (3.4 – 6.7)	9.9 (8.5 – 11.6)	8.6 (7.4 – 10.1)	7.6 (5.0 – 11.5)	11.8 (9.0 – 15.5)
HR (95%CI)	1(Reference)	2.07 (1.43 – 2.99)	1.80 (1.24 – 2.61)	1.59 (0.93 – 2.72)	2.47 (1.61 – 3.80)
aHR (95%CI)	1 (Reference)	1.82 (1.22 – 2.72)	1.67 (1.11 – 2.51)	1.64 (0.91 – 2.94)	2.42 (1.52 – 3.84)

[a] *Composite outcome is a three-point MACE including all-cause mortality, non-fatal acute myocardial infarction (AMI) and non-fatal stroke.*
[b] *Absolute Rate at 1000 person-years*
[c] *HR (Unadjusted Hazard Ratio)*
[d] *aHR (Adjusted Hazard Ratio). Adjusted for age, gender, duration of insulin use, albumin, glomerular filtration rate, lipid profile, and coronary heart disease.*

8.5. Discussion

Although statins are well recognised to confer cardio-protective benefits,[298-300] there is increasing evidence of a link between statin use and new-onset diabetes.[65, 303, 304, 312] The cardiovascular benefits usually outweigh the risk of developing insulin resistance.[313] More recently, systematic reviews of randomised trials and observational studies have shown a modest adverse effect of statin therapy on glycaemic control (specifically HbA1c).[306-309] In a meta-analysis of 9 randomised trials involving 9,696 participants with a mean follow-up of 3.6 years, the average HbA1c of those randomised to statin treatment was 0.12% (95% CI 0.04, 0.20) higher compared with those randomised to placebo.[310] There was also some heterogeneity of effect among the different statins.[310] However, this small effect on HbA1c may be an underestimate of the true effect of statins on glycaemic control in everyday practice because of the selective nature of patients included in RCTs, who are likely to be more compliant and motivated, and there may be bias in the data due to an unbalanced need to adjust GLTs between the statin and control groups. Thus, caution is needed in the extrapolation of RCT-derived estimates of clinical outcomes when formulating guidelines for routine clinical practice. For example, in a large observational cohort study the differences in HbA1c between statin users and non-users was much greater than that previously reported from RCTs.[314]

Clinical Implication

Previous observational studies and RCTs have not reported the effects of concomitant statin use on HbA1c or CV outcomes among those patients who are often at highest risk with established T2D and who are newly started on insulin therapy.[314, 315] This is an important and growing sub-population as primary care clinicians are challenged to up-titrate medication, seek better control of diabetes symptoms and HbA1c, and to judge the overall risks and benefits, the alternatives and the optimal timing of commencement of insulin therapy. Given that insulin-

initiated patients with T2D are likely to be more complex, have longer disease duration and a much higher risk of CV disease, the present study provides important new information about the effects of background statin therapy on metabolic and CV outcomes in the first 5 years after starting insulin.

Several conclusions can be derived from this large cohort study. Firstly, despite significant reductions in HbA1c in both groups following commencement of insulin therapy, non-users of statins achieved better (but non-clinically relevant) HbA1c lowering compared with statin users. There were no differences in insulin-induced weight gain between the two groups but systolic BP was also lower in the non-statin users. It is notable in the present study that patients receiving statins were older, and had longer duration of diabetes and insulin treatment compared to non-users. However, the lower HbA1c reduction among statin users persisted even after adjusting for multiple confounders.

Secondly, compared with non-users, all of the individual statins were associated with worse HbA1c outcomes. This contrasts with previous RCTs which have suggested differential adverse effects on glycaemic control among the different statins.[307-310] However, in a real-world cohort study of insulin-treated patients, any differential effect of different statins on glycaemic control may have been offset by differences in insulin dose adjustment.

Despite achieving less of a reduction in HbA1c, statin users had a significantly higher probability of survival for the 3-point composite MACE outcome (all-cause mortality, non-fatal MI and stroke) but this finding was not replicated when considering the individual risks of non-fatal MI or stroke. In this regard, it is worth noting that from RCTs the reduction in CV events is linearly related to LDL-cholesterol (LDL-C) reduction, especially in the first year of treatment, but observational studies comparing different statins in routine clinical practice have

reported inconsistent outcomes depending upon the endpoints examined and the methods used.[316-318] Thus, discordance between RCT and observational data on statins is not unusual, but in this study the overall 'real life effect' of statins on MACE and all-cause mortality reduction seems to be consistent with the established evidence from statin trials. However, in a similar real clinical setting, unlike our in our study, moderate-intensity statin treatment was found to be ineffective in cardiovascular primary prevention for patients with diabetic nephropathy.[319] This can be explained by the differences between these two populations, nonetheless, it provides a good insight as the mean eGFR of our population was 66mls/min/1.73m^2.

Possible underlying mechanisms

Several mechanisms have been proposed to explain how statins may worsen dysglycaemia: (1) impaired pancreatic β-cell secretion of insulin due to direct and indirect effects on calcium channels; (2) reduced insulin-mediated glucose uptake, especially in skeletal muscle, due to impaired expression and/or translocation of GLUT4 transporters from the cytosol to the plasma membrane; and (3) exacerbation of insulin resistance in muscle, liver and adipose tissues via multiple effects on insulin signal transduction, e.g. depletion of coenzyme Q10, inhibition of phosphorylation events downstream of the insulin receptor and inhibition of adipocyte differentiation.[320] In addition, statins have varying degrees of lipophilicity. The lipophilic statins diffuse passively through the hepatocellular membrane to inhibit HMG-CoA reductase in the liver but they can also diffuse passively and easily into extrahepatic tissues whereas the hydrophilic statins require carrier-mediated transport to enter cells. This may explain some of the observations of a higher incidence of new-onset diabetes with the lipophilic statins, e.g. simvastatin and atorvastatin, via effects on peripheral insulin sensitivity.[321] Similarly, a 6-year follow up study of the METSIM cohort showed that statin treatment increases the risk of type

2 diabetes by 46%, attributable to decreases in insulin sensitivity and insulin secretion,[322] while simvastatin may induce insulin resistance through a novel fatty acid mediated cholesterol independent mechanism.[323]

8.6. Strength and Limitations

Our analyses are subject to a number of limitations including allocation bias and residual confounders. This includes possible differences in compliance, indications for intensification of treatments, markers of β-cell deterioration, frequency of hypoglycaemia and some lifestyle and dietary factors which could influence our findings. Although I could not exclude the possibility of residual confounders, I were able to account for differences in the observed covariates and used robust analytical techniques to control for any confounding factors that may bias the results of the estimated treatment effects.

Our data were derived from a large UK database and therefore cannot be generalised to other ethnic groups. I was also unable to obtain longitudinal data on insulin doses, which are important in assessing insulin-induced weight gain,[243] which in turn could potentially influence glycaemic and CV outcomes.

On the other hand, a real strength of this study is the relatively large number of patients, the availability of, and adjustment for, a large number of known confounders, and the routine systematic nature of data collection in THIN which reflects real world practice and outcomes. I have also focused this study on an important patient population, which has not been previously studied.

8.7. Conclusion:

In summary, in a large cohort of T2D patients who are newly started on insulin therapy, and who reflect a real-world population in routine clinical practice, I have confirmed the major benefits of statin use in reducing CV risk and mortality. I have also quantified, for the first time, the modest adverse effects of background statin use on the HbA1c outcomes following insulin initiation. In this high-risk population, the benefits of statins on CV outcomes outweigh the small adverse metabolic effects on glycaemic control.

Chapter Nine: Comparison of the demographics, insulin use and clinical outcomes of insulin users with Type 2 diabetes in the Erewash (Integrated) Diabetes Service with the UK population

9.1. Summary

Background

Insulin treated patients with Type 2 Diabetes require specialist multidisciplinary input to achieve treatment targets. I compared the demographics; achievement of combined NICE targets for HbA1c (<7.5%), blood pressure (<140/80) and total cholesterol (<4mmol/L); and insulin use between patients from a local Integrated Diabetes Service with a representative UK population

Methods

Cross-sectional evaluation of individual patient data from six randomly selected primary Care practices in Erewash Integrated Diabetes service were compared with The Health Improvement Network (THIN), UK primary care database.

Results

Baseline age (61.5years vs 65.8 years; p <0.0001 and duration of insulin (4.3 vs 6.3 years, P<0.0001) use was lower in the THIN population. Mean HbA1c was similar between the two cohorts but weight, blood pressure, total and LDL cholesterol were significantly lower in the

Erewash population compared with THIN. The combined achievement of HbA1c, total cholesterol and blood pressure was 17.5% in the Erewash cohort compared with 9.6% in the UK THIN cohort ($p<0.0001$). There was a higher proportion of insulin users on basal-bolus than premix in the Erewash cohort (89.3% vs 10.7%) compared with THIN (59.0% vs 41.1%). Proportion of patients who received concurrent oral glucose lowering therapies in the Erewash integrated service was lower, except for SGLT2-inhibitor, (2.5% in the Erewash vs 0.5% in the THIN; $p<0.0001$).

Conclusion

This model of integrated diabetes service appears to confer better clinical outcomes compared with the UK population. Further studies are required to investigate impact of this service model on health economic, patients' pathway and patient experience.

9.2. Introduction

In view of the significant vascular benefits of tight glucose control in patients with type 2 diabetes (T2DM),[22] consensus guidelines have recommended aggressive treatment escalations, including the earlier use of insulin therapy in patients with T2DM to achieve optimal Hb_{Alc} target,[324] an important Quality and Outcomes Framework (QOF) target for general practitioners.[325] The management of insulin treatment however is complex. Local preferences of healthcare providers and guidelines of Clinical Commissioning Groups (CCGs) play an important role in determining patients' care package which includes advice on lifestyle modification, compliance, choice of insulin therapies and regimens, as well as education on self-titration of insulin dose.

Due to the rising cost and prevalence of diabetes,[326] the responsibility for providing care for most patients with diabetes has fallen to primary care. However, in many areas, the infrastructure to deliver an effective care is inadequate due to a variety of factors, including the lack of coordination between primary and secondary care. The Erewash Diabetes Service (EDS) in Derbyshire provides a novel set up of diabetes care which integrates delivery of its services across both primary and secondary care derived from experiences from two Southern Derbyshire Integrated service models - First Diabetes and Intercare Health[327] and built on a strong consensus among policy-makers and patient groups on the importance of improving integrated care in the NHS.[328, 329] This service model brings primary and secondary care together in a clinical, financial, and legal not-for-profit company, using programme budgeting, shared electronic clinical records and integrated clinical governance to deliver clinical care to patients throughout their clinical journey and has received local and national recognition.[330-332] Clinical demographic data and clinical outcome among insulin treated patients with T2DM within this model however is not available.

Therefore, this study was aimed at identifying individual information of insulin users with T2DM, who received medical care in Erewash, with a view of characterising their demographic profile, insulin regimen, and cross sectional clinical outcomes parameters (as HbA1c, weight and lipid profile), compared with the UK national data, with a view of identifying local differences for audit and improved clinical practice in our area.

9.3. Methods

9.3.1. Study Population and Design

Based on the latest National Cardiovascular Intelligence Network figures, the 2015 prevalence of diabetes in the Erewash region is 8.4%, which is higher than the national prevalence of 6.55%. According to the *2015 Director of Public Health Annual Report for Derbyshire*, 68.8% of adults in Derbyshire are classed as overweight or obese. This is higher than the East Midlands regional figures at 66.7% and the national figures for England at 64.7%.

A comparative cross-sectional study was conducted among people with T2D on insulin therapy, using local data obtained of patient population from 6 randomly selected Primary Care practices in Erewash, Derbyshire CCGs. This was compared with a cross-section of the UK national UK Primary Care data via The Health Improvement Network (THIN) database which has been described in Chapter 2. I selected only patients with insulin-treated T2D as this is the most challenging group of patients with T2D, many of which require specialist multidisciplinary input and would best highlight the clinical effectiveness of a given model of a specialised diabetes service.

Six Primary Care centres were randomly from the 12 centres in the Erewash CCGs. Data from the centres were extracted via PRIMIS audit tool.[333] In both this and the THIN dataset population groups, I obtained data on all adult T2D insulin users, aged 18 and above, who initiated insulin therapy between January 2007 and 2014 in spite of previous or concurrent use of other glucose-lowering therapies (GLTs). Where similar patient identifiers were discovered in both populations, such patients were excluded.

9.3.2. Exposure and Outcome

The main exposure was the use of insulin while the outcome was to compare demographic and clinical parameters among insulin-users, between the local Erewash Integrated service data and the UK national (THIN data).

9.3.3. Covariates

Baseline demographic parameters as age, sex; clinical measures as body weight, body mass index (BMI) and blood pressure (systolic and diastolic); biochemical parameters as baseline HbA1c, creatinine level, total cholesterol levels, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides; as well as diabetes profile as the duration of diabetes, duration of insulin use; insulin regimen and the duration of treatment of diabetes were extracted and compared between these population groups.

9.3.4. Statistical Analyses:

Descriptive statistical analysis was done to obtain the mean and frequency distribution of the baseline demographics in both population groups. Pearson's Chi-squared tests and independent student t-test were used to summarise and compare the categorical and continuous baseline variables respectively between the population groups.

9.4. Results

9.4.1. Patients Characteristics:

There was a total of 18,533 insulin-users of which 18,227 were derived from the UK national data, and 326 from the Erewash data. The mean age was 61.6±13.6 years, while a little above half of the population (53.2%) were males. The mean HbA1c level was 8.7±1.8% (72 ±

20mmol/mol); weight: 91.2±18.7kg; with a greater proportion (62.5%) obese. Also, in both populations, Metformin (84.9%) was the commonest glucose lowering therapy (GLT) in use, followed by sulphonylurea (74.6%); thiazolidinedione (31.1%) and DPP4i (Dipeptidyl peptidase-4 inhibitor) (13.9%); while the least used GLT is Sodium-glucose Cotransporter-2 inhibitors (SGLT2) (0.5%). Finally, the premix insulin regimen was the commonest regimen in use. Table 9.1 provides a summary of the baseline characteristics of the study population.

Table 9.1: Baseline Characteristics by population Groups and differences between them

Baseline variable	Population: THIN cohort (N = 18,227)	Erewash Integrated Service (N = 326)	Total (N = 18,533)	Differences* (95% CI)	p-value
Demographics					
Age (yrs), Mean (SD)	61.5 (13.6)	65.8 (12.7)	61.6 (13.6)	-4.6 (-6.1, -3.1)	<0.0001
Gender, No. (%)					
Male	9695 (53.2)	176 (54.0)	9871 (53.2)	χ^2 = 0.0818	0.775
Female	8532 (46.8)	150 (46.0)	8682 (46.8)		
Clinical Parameters, Mean (SD)					
HbA1c (%)	8.7 (1.8)	8.5 (1.8)	8.7 (1.8)	0.4 (-0.16, 0.25)	0.6551
(mmol/mol)	72 (20)	69 (20)	72 (20)	-	-
BMI (kg/m2)	32.5 (6.9)	30.3 (6.9)	32.5 (6.9)	1.63 (0.88, 2.39)	<0.0001
Weight (Kg)	91.3 (18.7)	86.1 (20.4)	91.2 (18.7)	4.54 (1.67, 7.42)	0.0019
SBP (mmHg)	136.3 (23.0)	132.2 (14.2)	136.3 (23.0)	3.30 (0.64, 5.96)	0.015
DBP (mmHg)	76.0 (10.8)	72.5 (9.2)	76.0 (10.8)	3.21 (2.02, 0.41)	<0.0001
TC (mmol/l)	4.5 (1.3)	4.1 (1.1)	4.5 (1.3)	0.34 (0.20, 0.49)	<0.0001
HDL (mmol/l)	1.2 (0.4)	1.3 (0.4)	1.2 (0.4)	-0.03 (-0.08, -0.02)	<0.0001
LDL (mmol/l)	2.4 (1.1)	2.1 (0.9)	2.4 (1.1)	0.36 (0.23, 0.48)	<0.0001
Triglyceride (mmol/L)	2.0 (1.2)	1.7 (0.8)	2.0 (1.2)	-0.001 (-0.14, 0.13)	0.9859
eGFR (mls/min/1.73m^2)	62.3 (21.0)	63.8 (21.5)	63.1 (21.3)	-1.35 (-3.73, -1.04)	0.013
Diabetes duration (yrs)	3.9 (6.4)	8.7 (8.0)	6.3 (6.2)	-3.08 (-3.81, -2.35)	<0.0001
Insulin Duration (yrs)	4.3 (4.9)	6.3 (5.1)	4.3 (4.9)	-2.61 (-3.1, -2.1)	<0.0001
BMI No. (%)					
≤ 24.9kg/m^2	2455 (13.5)	56 (13.4)	2511 (13.5)		
25-29.9kg/m^2	4343 (23.8)	103 (31.6)	4446 (24.0)	χ^2 = 18.07	<0.0001
≥ 30kg/m^2	11429 (62.7)	167 (51.2)	11596 (62.5)		
Other GLTs, No. (%)					
Metformin	15593 (85.6)	163 (50.0)	15756 (84.9)	χ^2 = 316.13	<0.0001
Sulphonylurea	13794 (75.7)	47 (14.4)	13841 (74.6)	χ^2 = 634.39	<0.0001
Thiazolidinedione	5754 (31.6)	9 (2.8)	5763 (31.1)	χ^2 = 124.12	<0.0001
GLP-1ar	1943 (10.7)	13 (4.0)	1956 (10.5)	χ^2 = 15.12	<0.0001
SGLT2	85 (0.5)	8 (2.5)	31 (0.5)	χ^2 = 25.37	<0.0001
Glinides	790 (4.3)	1 (0.3)	791 (4.3)	χ^2 = 12.72	<0.0001
DPP4i	2569 (14.1)	11 (3.4)	2580 (13.9)	χ^2 = 30.74	<0.0001
Insulin Regimen					
Basal-bolus	10744 (59.0)	291 (89.3)	7518 (40.5)	χ^2 = 122.15	<0.0001
Premix	7483 (41.1)	35 (10.7)	11035 (59.5)		

**Differences- This is a measure of the differences in the variables between the two populations (mean difference in continuous variables with 95% confidence interval; and chi-square test in categorical variables).*

SD (standard deviation); Diabetes duration is time from first diagnosis of diabetes to date of initiating insulin; Duration of insulin is the time between initiation of insulin and date of commencing study

MET (metformin); SU (sulphonylurea); GLP-1ar (Glucagon-like peptide 1); INS (insulin); SGLT2 (Sodium-glucose Cotransporter-2 inhibitors); Glinides (Meglitinides); DPP4i (Dipeptidyl peptidase-4 inhibitors)

BMI (body mass index); SBP (systolic blood pressure); DBP (diastolic blood pressure); HbA1c (haemoglobin A1c); HDL (high-density lipoprotein); LDL (low-density lipoprotein); TC (total cholesterol); eGFR (estimated glomerular filtration rate)

9.4.2. Insulin-users with T2DM: Integrated Diabetes Service vs THIN cohort

i. Demographic Characteristics:

An independent t-test and chi-square test was run on both population samples to determine differences in the demographics of insulin-users with T2DM in both population groups (Table 9.1). The baseline age was 4.6years significantly lower in the UK general population (61.5years vs 65.8 years; p <0.0001). There were similarities in gender distribution between both population groups (Males: 53.2% vs 54.0%, χ^2 = 0.0818; p = 0.775).

ii. Clinical Parameters:

I explored the differences in important clinical parameters which predict treatment outcomes in the management of T2D. It was observed that HbA1c was similar in both populations (8.7% vs 8.5%; mean diff: 0.46; [95%CI: -0.16, 0.25]; p =0.6551), but the duration of insulin use (6.3years vs 4.3years; mean diff; 2.61; [95%CI: 2.10, 3.10], p <0.0001) was significantly higher in the Erewash Integrated Service compared to the THIN cohort.

Some clinical measures were significantly lower in the Erewash integrated service population group compared to the THIN cohort – such as weight (p = 0.0019); BMI (p < 0.0001); systolic BP (p=0.0015); diastolic BP (p< 0.0001); total cholesterol (p< 0.0001); low-density lipoprotein (p<0.0001) and the proportion of the obese sub-population group (51.2% vs 62.7%; p<0.0001). Conversely, high-density lipoprotein (p<0.0001); and glomerular filtration rate (p=0.013) were significantly higher in the local population, while triglycerides (p=0.9859) was similar in both.

iii. Use of Insulin and other GLTs:

Although in both populations, there was a higher proportion of insulin-users on basal-bolus than premix (UK: 59.0% vs 41.1% and Integrated service: 89.3% vs 10.7%; p <0.0001), the

use of basal bolus was found to be very high (approximately 9:1) compared to premix in the Erewash local data (Table 9.1).

Similarly, there were significant differences in the proportion of users of other GLTs between the two population groups, and in all GLTs of interest, I found a lesser proportion of users in the local data of Erewash integrated service, compared to the national except for SGLT2 inhibitors: 2.5% of the local integrated service population, compared to 0.5% in the THIN cohort ($p<0.0001$). Also, the proportion of metformin users was highest in both populations (85.6% vs 50.0%) compared to other GLTs, followed by sulphonylureas (75.7% vs 14.4%); while glinides were the least used GLT in the local population (0.3%), against SGLT2i (0.5%) in the national data.

iv. Achievement of NICE targets.

No significant difference was noted in the percentage of patients achieving NICE HbA1c target of 7.5% between the two population cohorts. However significantly higher number of patients within the Erewash cohort achieved NICE targets for total cholesterol, systolic and diastolic blood pressure, compared with the UK THIN cohort. Thus, for the achievement of combined HbA1c, total cholesterol and blood pressure, 17.5% in the Erewash cohort achieved the combined target compared with 9.6% in the UK THIN cohort ($p<0.0001$). (Table 9.2)

Table 9.2: The proportion of patients achieving the NICE targets of HbA1c ≤7.5% (59 mmol/mol); Blood Pressure <140/80 mmHg and Cholesterol: 4 mmol/l.

	THIN cohort	Erewash Integrated Service	Chi-square	p-value
HbA1c				
< 7.5%	4,195 (27.0)	91 (28.0)	0.1463	0.702
≥ 7.5%	13,312 (73.0)	235 (72.0)		
Total Cholesterol				
< 5.0mmol/L	12,025 (66.0)	258 (79.1)	24.82	<0.0001
≥ 5.0mmol/L	6,202 (34.0)	68 (20.9)		
Diastolic BP				
≤ 80mmHg	12,069 (66.2)	267 (81.9)	35.37	<0.0001
> 80mmHg	6,158 (33.8)	59 (18.1)		
Systolic BP				
≤ 140mmHg	10,651 (58.4)	247 (78.8)	36.69	<0.0001
> 140mmHg	7,576 (41.6)	79 (24.2)		
NICE Target*	1,750 (9.6)	57 (17.5)	22.64	<0.0001

NICE target: Proportion of patients achieving the NICE targets of HbA1c ≤7.5% (59 mmol/mol); Blood Pressure <140/80 mmHg and Total Cholesterol: 4 mmol/l.

9.5. Discussion

This observational study reports the demographic, metabolic and cardiovascular risk parameters, use of insulin therapy/ regimens and choices of concurrent oral glucose lowering therapies among patients with T2D undergoing routine care at a local Integrated Diabetes service compared with a representative UK cohort. While simple conclusions cannot be made from this cross-sectional data analysis, some discussion and speculation can be derived.

Firstly, the mean percentage of patients achieving the three NICE treatment targets of HbA1c <58mmol/mol, blood pressure of <140/80mmHg and total cholesterol <4mmol/L was significantly higher in the Erewash integrated service cohort compared with the UK (THIN)

population. The mean HbA1c level and the % patients achieving HbA1c target of <7.5% within the Integrated care cohort was however comparable to the UK cohort. This was despite significantly longer duration of diabetes and of insulin therapy in the integrated care cohort. This is relevant because increased diabetes duration is known to be associated with progressive decline of HbA1c level,[22] continual decline of C-peptide level[334, 335] and reduced responsiveness to intensive insulin therapy,[334] which is partly augmented by increased age.[336] The latter is also relevant because our cohort is significantly older than the UK cohort. Importantly, cardiovascular risk profile such as systolic BP, diastolic BP, total cholesterol and low-density lipoprotein levels were significantly lower in the integrated care cohort compared to the UK population. The reason for this is not known but I would speculate that the implementation of cardiovascular risk reduction strategies among patients who receive their routine care in an integrated service is likely to be more robust than that in the general population. Unfortunately, the extracted data did not provide us with information regarding the use antihypertensive drugs, statins and aspirin therapy in both patient cohorts. This study supports observation from a previous trial which randomised intermediate care clinics for diabetes versus usual care and reported greater achievement of achievement of all three of the NICE targets[337] in the intermediate care cohort with collaboration and joint working between primary and secondary care services.

Secondly, in the integrated service compared with the THIN cohort, I observed a significantly greater use of a basal-bolus insulin regimen compared with the premixed insulin regimen. These two insulin regimens are the two most widely used insulin regimens but there remains no overall consensus regarding the most effective or optimal insulin regimen for patients with diabetes mellitus.[220] The basal-bolus regimen, which consists of multiple daily injections of rapid-acting insulin pre-prandially in addition to a long-acting basal insulin, most closely mimics the pattern of insulin secretion in individuals without diabetes.[221] The flexibility of this

regimen is, however, undermined by its complexity in the need to count daily carbohydrate intake and adjust the insulin dose accordingly, as well as the lifestyle restrictions implicated by the high number of injections.[224] The premixed insulin regimen accounts for the majority of insulin prescriptions worldwide and consists of a fixed ratio of rapid-acting insulin and intermediate insulin combined; thereby eliminating the need for patients to mix the insulin themselves, while also reducing the number of required daily injections.

I would speculate that the much higher preference for a basal-bolus insulin regimen relative to a premixed regimen within an integrated service compared to the THIN cohort reflects the greater patient access to clinicians and diabetes educators, required for the more complex basal-bolus regimen, accorded by an integrated diabetes service.

Similarly, this may also influence the much lower use of concurrent oral GLT in the integrated cohort, except for the SGLT2 inhibitor, a novel therapy for T2DM associated with weight loss. The latter may explain the lower mean weight in the integrated service population, compared to the THIN cohort, despite the higher background prevalence of overweight and obesity in the Erewash region compared with the THIN cohort.

In a previous Cochrane systematic review on interventions to improve the management of diabetes mellitus in primary care and community settings,[338] 41 studies were included which involved more than 200 practices and 48 000 patients. The majority of these studies involved interventions which focused on: 'up-skilling' of primary care (non-specialist clinicians) via postgraduate education; patient-tracking systems or other systems for regular follow up; provision of patient education and/or a link research nurse to liaise with patients and clinicians; the impact of nurses in replacing physicians; and the effectiveness of a pharmaceutical care model in delivering advice on glucose-lowering therapy. No studies were identified that dealt with trial or audit outcome of an integrated service as defined by the 'Best practice for

commissioning diabetes services'6 and the joint position statement from the Primary Care Diabetes Society, the Association of British Clinical Diabetologists, Diabetes UK, and the Royal College of Nursing[329]

9.6. Limitations

Due to the cross-sectional nature of this study, I was not able to investigate the health economic outcome, patient pathway and the patient experience of the integrated service – three of the most important non-clinical determinants of the success of an integrated service. A further prospective randomised trial is required to address the research gap.

9.7. Conclusion

This model of integrated diabetes service appears to confer better clinical outcomes compared with the UK population. This attests to the gains of this model in terms of better treatment outcomes for patients – a feat other for centres in the United Kingdom to adopt in the management of T2DM. However, further studies are required to investigate impact of this service model on health economic, patients' pathway and patient experience.

Chapter Ten: Conclusions and Recommendation

There is a strong evidence on the glycaemic efficacy of insulin, as well as the long-term micro- and macrovascular benefits of optimal glucose control.[52, 149] This, I think, puts insulin at the epicentre of the management of diabetes. In view of the rising use of, and safety concerns about, insulin in the management of T2DM, this thesis focused entirely on insulin users in 'real-word' condition (routine clinical practice), drawing evidence from a representative UK population. It is well known that insulin users represent a high-risk group of people with T2DM – being older, with longer duration of diabetes, and having had failure of other GLTs to achieve optimal glucose control, more disease severity, and the presence of other comorbidities.

This research was grounded on the fact that insulin cannot seem to do so good, yet so bad in terms of certain important clinical outcome; and so sets out to explore the real-world cardiovascular and metabolic outcomes associated with the use of exogenous insulin, with a primary focus on its clear benefit or otherwise in high risk group of people with T2DM. Particular attention was paid on insulin use in terms of age and metabolic profile of its users, interactions with medications that modify glucose control and CV risk factors (e.g. statins), insulin's effect on CV risk factors as weight, and obesity, appropriate glycaemic targets and goals, and combination of insulin use with newer novel GLTs (like GLP-1 receptor analogues).

This concluding chapter therefore highlights the main findings of the studies conducted in this thesis and how these met the set aim and objectives outlined in section 1.5. It also emphasises the clinical importance and application of these findings to ensure the best treatment outcomes for people with T2D, and recommends grey areas for future studies.

10.1. Summary of Evidence and Recommendations

In Chapter 3, I brought together in one piece, recent evidences from 18 recently conducted clinical trials which compared clinical outcomes as CV events, glycaemic control, episodes of hypoglycaemia, effect on weight and adverse drug reactions between insulin and non-insulin GLTs (objective 2). Majority (68.8%) of these trials involved insulin glargine in its active arm, while GLP-1RA was used most (68.8%) of all the drugs in the comparator arms. Reassuringly, it showed that there was no difference in the risk of all-cause mortality and CV events between insulin and non-insulin GLTs despite insulin showing almost a 2-fold higher risk of hypoglycaemia. Similarly, there was no difference in the proportion of users achieving their HbA1c targets although insulin showed superiority in glycaemic control. Finally, the use of non-insulin GLTs was found to be associated with significant weight loss of up to 3.5kg. This evidence from a meta-analysis of recent trials, which have now been published provides reassurance on the safety of insulin use regardless of its well-known effects on CV risk factors as weight gain and hypoglycaemia – which are the main drivers of the clinical inertia shown by physicians and people with T2D in starting insulin.[339-342]

While the finding from chapter 3 was indeed reassuring, the next consideration was whether evidence from clinical trials truly translates to what is obtained in real-life practice. As evidence from clinical trials guides management of diabetes, one often wonders if this leads to the same clinical outcomes in routine care. One questions the validity of these outcomes and how much different they could be from findings from real-world data. To this end, my focus was on insulin regimens in type 2 diabetes.

The two most widely prescribed insulin regimen is the basal-bolus or premixed regimens. The benefit of one regimen over the other in terms of improved clinical outcomes has been explored in clinical trials, including a previous study from our research group, but whether this translates

to similar benefits in routine clinical care is unknown. So, in line with objective 2, Chapter 4 sets out to identify the gaps between clinical outcomes derived from RCTs and real-world. In spite of the highest level evidence ascribed to data derived from RCTs, they do not necessarily mirror what obtains in real-world. I observed, in real-world condition, there was a lesser reduction in HbA1c than in RCTs for both premix and basal-bolus but there was greater weight gain in the RCT population than in real-world. Additionally, a weak correlation existed between baseline HbA1c and glycaemic response in real-world population as against a stronger correlation seen in RCTs. For both real-world and RCT populations, greater baseline weight was associated with better glycaemic control (reduced HbA1c) but response was greater in the RCT population. This further reinforces the need for cautious interpretation and application of findings from clinical trials in routine clinical practice.[124] This I believe is particularly relevant to insulin therapy where the adverse effect on weight gain and hypoglycaemia risks may affect compliance to treatment in real world practice.

In continuation, I went further to explore how the metabolic profiles of insulin users may affect important clinical outcomes. In Chapter 5, I showed that baseline obesity did not affect glycaemic control both in the short- and in the long term. At 5 years, the morbidly obese group of insulin users had the greatest reduction in HbA1c, compared to patients with normal BMI. Similarly, the proportion of people achieving the NICE target HbA1c level of $\leq$ 7.5% (58mmol/mol) increased with time, independent of their baseline BMI while the obese group had reduction in both weight and BMI in contrast to the normal and overweight BMI groups who experienced an increase. Finally, a 30% increased risk of a 3-point composite of non-fatal MI, stroke and all-cause mortality was reported only in the morbidly obese group after a 5-year follow-up period.

Furthermore, since weight gain is associated with adverse risk for cardiovascular disease, objective 3 focused on the association of insulin-induced weight-gain on CV outcomes and mortality and to see if this weight-gain has any effect on glycaemic control in real world practice. This data showed that weight-gain following insulin initiation was not significantly associated with increased risk of adverse CV events and mortality. On the contrary, this risk was increased by 31% in those who lost >5kg weight, compared to the weight-neutral group independent of baseline BMI. The mechanism for this is unclear, but I have made some speculations and discussed some limitation to the study analysis, including effects of residual confounders.

On the association between weight-gain and glycaemic control, a weak negative correlation was shown. So, for a unit increase in weight (in kg), HbA1c reduced by 0.11%, 0.005%, 0.004% and 0.003% at 6, 12, 24, and 36 months respectively. Additionally, when compared to the weigh-neutral group, those who gained weight had a significant greater reductions in HbA1c all through the study follow up duration.

These studies provide some reassurances among patients with T2DM who gained weight following insulin treatment, and allay fears of physicians who develop inertia in initiation insulin therapy early in routine clinical practice. However, must be interpreted with caution as the possible use of higher doses of insulin in the obese group should have driven the observed associations discovered.

Given the potential adverse effect of insulin on weight and the previously reported association between insulin therapy and adverse cardiovascular outcomes, in Chapter 6, the clinical benefits of combining insulin therapy with newer, novel glucose lowering therapies like GLP-1RA, which have been shown to have favourable effects on the weight and hypoglycaemia (known CV risk factors)[268, 269] were investigated (Objective 4). Following failure to maintain

optimal HbA1c level despite up-titration to maximal doses of dual- or triple therapy, there is the need for intensification but the dilemma remains that there are many treatment options but limited evidence on the appropriate choice. The use of insulin and GLP-1RA is becoming popular in routine clinical care and may seem to confer CV benefits when combined together. In view of the concerns about the CV safety of insulin therapy,[79, 267] it was hypothesised that insulin's effect on weight gain and risk of hypoglycaemia can be neutralised when used in combination with GLP-1RA.

After a follow-up period of 5-years, the risk of adverse CV events (of non-fatal stroke and MI) and all-cause mortality was first compared in a cohort of propensity-score matched individuals, who intensified their MET+SU dual therapy with either insulin or GLP1-1RA; and in another population of insulin users who went on the add a GLP-1RA or none in routine clinical care. It was shown in the first cohort that the use of GLP-1RA instead of insulin after dual therapy failure was associated with a 73% reduction in the risk of non-fatal CV events and all-cause mortality; while when used in combination with insulin (in the second cohort) was associated a 36% reduction in risk. In both cohorts, these glycaemic control were similar, while weight remained higher in the insulin groups. Also, the risks of adverse CV events were greater in the obese subgroups. These findings provide reassurance on the possible benefits of combining GLP-1RA with insulin irrespective of body. Although the mechanism for the cardio-protective effects of GLP-1RAs remains speculative further study in a randomised clinical trial setting is required to confirm this observation. This finding has now been published.

Elderly people with T2DM on insulin therapy represent a very special class of people due to their advanced age, longer duration of diabetes, more disease (diabetes) severity, and presence of other comorbidities. I hypothesised here, that as a result of the high prevalence of comorbidities and frailty in older people, tight glucose control may have deleterious effect on

them just as poor glucose control, drawing from evidences of a U- or J-shaped relationship between glucose control targets and the risk of adverse events, including mortality shown by recent studies using routine clinical data.

So, in a cohort of 8,192 insulin users, Cox proportional hazard models and Kaplan-Meier estimators were fitted to derive the hazards of all-cause mortality by HbA1c decile after 5-yrs of follow-up. A U-shaped relationship was observed between all-cause mortality and HbA1c, with the lowest risk of mortality seen in the HbA1c interquartile range (IQR) of 7.4-7.7%. Conversely, no significant association was observed with cardiovascular events.

This study supports a strong U-shaped association between HbA1c and mortality with minimum safe and high HbA1c values identified to reduce the risks of mortality in this high risk group of patients in routine care. The observational data presented here therefore provide important guidance to the management of the rapidly growing number of older patients with type 2 diabetes who require insulin therapy to manage their hyperglycaemia and other symptoms, and emphasises the need for study for individualisation of care and treatment targets in line with international guidelines.

Chapter 8 examines the association between concurrent use of other medications which may modify CV risk factors (objective 6) among insulin users. Statins were used as a case-study because evidence from randomized controlled trials shows though they reduce the risk of fatal and nonfatal cardiovascular (CV) events in patients with T2D, they may also have modest adverse effects on glucose and insulin metabolism, e.g. increasing the risk of new-onset diabetes, especially in higher doses and with the more potent statins. I was able to show this in an earlier published systematic review.[65]

In a cohort of 12,725 insulin initiators, logistic regression was used to compute the mean changes in HbA1c between statin and non-users and in different statin subtypes; while the risk

of adverse CV events and all-cause mortality was compared between statin vs non-statin users. It was shown that within the first year, non-statin users experienced a greater reduction in HbA1c compared to users but the risk of composite adverse CV event was 36% higher in this group with an almost 2-fold greater risk of all-cause mortality in non-statin users compared to users. It is however encouraging to observe that this pattern persisted for all types of statins used in this study. As people with T2DM often use other medications due to the long-term complications of diabetes, it can be seen from this large cohort of T2D patients who newly started on insulin therapy, and who reflect a real-world population in routine clinical practice, the major benefits of statin use in reducing CV risk and mortality; and for the first time, quantified the modest adverse effects of background statin use on the HbA1c outcomes. It is clear that, in this high-risk population, the benefits of statins on CV outcomes outweigh the small adverse metabolic effects on glycaemic control.

Finally, objective 7 was met in Chapter 9 which compared the patients within Erewash Integrated Diabetes Service in my locality (Derby) with a representative UK population (THIN) of T2D in terms of demographics; achievement of combined NICE targets and patterns of insulin use. In a comparative cross-sectional survey, the local area (Erewash) insulin users were older, had longer diabetes duration before the commencement of insulin, and had lower weight, blood pressure, and total and LDL cholesterol than the THIN population. HbA1c was similar between them. In spite of the high proportion of the obese in Erewash compared to UK, a greater proportion of insulin users attained the combined NICE targets of HbA1c (<7.5%), blood pressure (<140/80) and total cholesterol (<4mmol/L). Also, a greater proportion of insulin users in the Erewash was on the basal-bolus regime, instead of premix in the Erewash cohort while the reverse was the case in THIN.

With the rising cost and prevalence of diabetes and the lean NHS budget, there has been a shift in the responsibility for providing care for most patients to primary care – which in most cases, lacks manpower and the needed expertise deliver an effective care. The Erewash Diabetes Service (EDS) in Derbyshire provides a novel set up of diabetes care which integrates delivery of diabetes services across both primary and secondary care to deliver well-coordinated holistic care to patients. So findings of this study/audit show the clear benefit of such care plan and portrays what the entire country stands to gain if this approach is adopted by all NHS Trusts.

10.2. Application of Findings to Clinical Practice

Since undertaking an RCT in a high-risk population of people with T2DM as insulin users may pose some ethical and costs concerns, this study provides a credible 'real-world' evidence that can guide clinical practice and management guidelines. With the large sample population studied and the diverse distribution of the study population, the findings of this study have the potential to inform and transform clinical practice as it relates to the diabetes care globally.

I believe my thesis has provided a better understanding of the benefits of the combination of insulin with newer GLTs to provide a therapeutic synergy that minimises the adverse treatment effects associated with the use of only a single therapy, as reflected by the number of studies which have now been published or in press in various peer reviewed journals This can be fed into the algorithm on the management of T2DM.

Furthermore, it has allayed the fear of physicians in prescribing insulin especially among those who are obese and for the fear of hypoglycaemia. It has been shown here that although insulin is associated with weight gain, and higher risk of hypoglycaemia, this did not translate to adverse CV events. Rather, insulin-induced weight gain was weakly, but significantly

associated with better glycaemic control. Additionally, the concurrent use of medications which worsen glycaemic control but modify CV risk factors has proved to be beneficial. These provide water-tight evidence that can guide NICE treatment guidelines in T2DM.

Finally, the gains of the Erewash Integrated Diabetes Care model, specific to Insulin treated patients with T2DM have been highlighted here. This care model can be replicated to deliver diabetes care across the UK and so minimise cost, optimise the scarce healthcare manpower, and deliver the best clinical and psychological outcomes for patients.

10.3. Areas for Future Research

Follow up epidemiological studies and *post-hoc* analyses of cardiovascular outcome trials have shown that the beneficial CV outcomes or otherwise of treatment effects can be felt mostly after a long term period. This was observed in the long-term follow up studies on the UKPDS, DIGAMI-1, ACCORD and VADT where most trials showed a long-term benefit.[99] In light of this, a longitudinal database as THIN, which is constantly being updated, offers a good platform to explore the real-world long term outcomes of the insulin treatment. So, longer follow up studies of at least ten years will be needed in future in order to fully explore the risks and benefits of insulin use.

Secondly, there is need to link the THIN database to other wider specialised health-care databases which hold data for some clinical outcomes like mortality and work-related issues e.g. Office of the National Statistics (ONS); hospital admission records e.g. Hospital Episode Statistics (HES) database and surgical procedures e.g. Office of Population, Censuses and Surveys' classification of surgical operations and procedures (OPCS). It is believed that such

a linkage will give a robust data to explore many more outcomes associated with insulin use, as well as minimise the effects of residual confounders.

Thirdly, future studies in this area may incorporate information on insulin dosages and titrations, cost, and quality of life measures. These very important factors will provide useful clues underpinning the risk or benefits associated with insulin use.

Finally, as stated above, the incorporation of data on surgical procedures like bariatric surgery, which is carried on patients with diabetes will be of great benefit in providing alternative real-world evidence in the management of T2DM.

10.4. Conclusion

With the application of good statistical methods which address the inherent limitations of routine observational data, observational study using primary care database can provide a credible evidence that mimic RCTs'. This also has an additional advantage of providing a 'real-world' picture which mimics the outcomes obtained in routine clinical care. Also, since conducting an RCT in a high-risk population as insulin users may pose some ethical concerns and is very expensive, this study then provides a credible evidence that can guide clinical practice and management guidelines.

Firstly, this research was borne of the desire to provide real-world evidence of the benefit and risk of insulin among a population of insulin users and to explore the dynamics of this group which could underpin these outcomes. The result of the meta-analysis of the clinical trials provides an assurance about the CV safety of insulin – in the midst of growing concerns from conflicting outcomes from different trials. Given that ORIGIN trial, being the first to report CV outcomes in a trial that had an insulin-only arm direct comparison, showed similar

outcomes with standard care; post hoc analyses and epidemiological follow-up studies on previous trials equally showed some benefits. This thesis has tried to bring all these evidences together.

Secondly, in view of failure to achieve optimal glucose control with first or second line medications, coupled with the fear of insulin initiation and/or insulin induced weight gain or hypoglycaemia risks, this thesis has demonstrated that insulin-GLP-1RA combination therapy is a good therapeutic option. The use of this combination (e.g. IDegLira and LixiLan – fixed dose combinations of GLP-1RA and long acting insulin) has been on the increase in routine clinical practice but its CV and metabolic benefits are yet to be explored. Now, this thesis is the first to demonstrate its benefits in real world practice, as it relates to composite CV outcomes of non-fatal stroke, non-fatal MI and all-cause mortality.

Finally, this research has shown the need to take a cautious approach to treatment targets in elderly insulin users. This is given the fact that this special group represents a high risk class of T2DM in whom treatment must be highly individualised and not based on HbA1c monitoring alone. Furthermore, for another high-risk group who are obese also have higher chances of having their treatment intensified with insulin, or their insulin doses up-titrated, this thesis has also demonstrated that the glycaemic benefits of insulin use, and assuaged the fears that insulin-induced weight gain may be associated with adverse CV outcomes. Nonetheless, it only demonstrated excess mortality in only morbidly obese patients. In conclusion, this thesis also demonstrated that the concurrent use of medications which modify CV risk factors (e.g. statins) is beneficial in insulin users.

References

1. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2010; **33**(Supplement 1): S62-S9.

2. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2008; **31**(Supplement 1): S55-S60.

3. World Health Organisation, International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia Report of a WHO/IDF Consultation. Geneva, Switzerland: WHO, 2006.

4. International Diabetes Federation. IDF Diabetes Atlas. online version of IDF Diabetes Atlas: www.idf.org/diabetesatlas; 2013.

5. Haines L, Wan KC, Lynn R, Barrett TG, Shield JPH. Rising Incidence of Type 2 Diabetes in Children in the U.K. *Diabetes Care* 2007; **30**(5): 1097-101.

6. Diabetes UK. State of the Nation: Challenges for 2015 and Beyond (England). London: Diabetes UK; 2015.

7. Diabetes UK. Diabetes: Facts and Stats. 3 ed: Diabetes UK; 2014.

8. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: pathogenesis and treatment. *The Lancet* 2008; **371**(9631): 2153-6.

9. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *The Lancet* 2005; **365**(9467): 1333-46.

10. Keller, Keller U. From Obesity to Diabetes. *International Journal for Vitamin and Nutrition Research* 2006; **76**(4): 172-7.

11. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001; **414**(6865): 782-7.

12. Hu FB. Globalization of Diabetes: The role of diet, lifestyle, and genes. *Diabetes Care* 2011; **34**(6): 1249-57.

13. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Research and Clinical Practice* 2010; **87**(1): 4-14.

14. World Health Organisation (WHO). Country and Regional Data on Diabetes. (Online). http://www.who.int/diabetes/facts/world_figures/en/ (Accessed 22nd January, 2015).

15. Diabetes expenditure, burden of disease and management in 5 EU countries. London: LSE Health, London School of Economics, 2012.

16. Diabetes UK. State of the Nation England. London: Diabetes UK; 2014.

17. Kerr M. Inpatient Care for People with Diabetes: The Economic Case for Change. NHS, 2011.

18. Diabetes UK. The Cost of Diabetes: Report. UK: Diabetes UK, 2014.

19. International Diabetes Federation. Global Guideline for Type 2 Diabetes. 2012.

20. The Emerging Risk Factors C. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *The Lancet*; **375**(9733): 2215-22.

21. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* 2001; **44 Suppl 2**: S14-21.

22. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The Lancet* 1998; **352**(9131): 837-53.

23. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; **364**(9435): 685-96.

24. The Emerging Risk Factors C. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *The Lancet* 2010; **375**(9733): 2215-22.

25. Jeerakathil T, Johnson JA, Simpson SH ea. Short-term risk for stroke is doubled in persons with newly treated Type 2 diabetes compared with persons without diabetes: a population based cohort study. *Stroke* 2007; **38**(6): 1739-43.

26. Gilg J, Pruthi R, Fogarty D. UK Renal Replacement Therapy Incidence in 2013: National and Centre-specific Analyses. UK, 2014.

27. Rao A, Casula A, Castledine C. UK Renal Registry 17th Annual Report: Chapter 2 UK Renal Replacement Therapy Prevalence in 2013: National and Centre-specific Analyses. *Nephron* 2015; **129(suppl 1)**(Suppl. 1): 40-65.

28. Wu SC, Driver VR, Wrobel JS, Armstrong DG. Foot ulcers in the diabetic patient, prevention and treatment. *Vascular Health and Risk Management* 2007; **3**(1): 65-76.

29. Boulton AJ. Guidelines for diagnosis and outpatient management of diabetic peripheral neuropathy. European Association for the Study of Diabetes, Neurodiab. *Diabetes & metabolism* 1998; **24 Suppl 3**: 55-65.

30. Boulton AJM. Management of Diabetic Peripheral Neuropathy. *Clinical Diabetes* 2005; **23**(1): 9-15.

31. Daneman D. Type 1 diabetes. *The Lancet* 2006; **367**(9513): 847-58.

32. Health and Social Care Information Centre. National Diabetes Audit 2011/12: Report 2: Complications and Mortality, 2013.

33. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* 1999; **22**(2): 233-40.

34. The United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. *BMJ (Clinical research ed)* 1995; **310**(6972): 83-8.

35. Borg R, Kuenen JC, Carstensen B, et al. HbA(1c) and mean blood glucose show stronger associations with cardiovascular disease risk factors than do postprandial glycaemia or glucose variability in persons with diabetes: the A1C-Derived Average Glucose (ADAG) study. *Diabetologia* 2011; **54**(1): 69-72.

36. Eeg-Olofsson K, Cederholm J, Nilsson PM, et al. New aspects of HbA1c as a risk factor for cardiovascular diseases in type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR). *Journal of Internal Medicine* 2010; **268**(5): 471-82.

37. Currie CJ, Peters JR, Tynan A, et al. Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. *The Lancet* 2010; **375**(9713): 481-9.

38. The International Expert Committee. International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes. *Diabetes Care* 2009; **32**(7): 1327-34.

39. The International Expert Committee. Report of The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997; **20**: 1183-97.

40. Bonora E, Tuomilehto J. The Pros and Cons of Diagnosing Diabetes With A1C. *Diabetes Care* 2011; **34**(Supplement 2): S184-S90.

41. The National Institute for Health and Care Excellence (NICE). Type 2 diabetes: the management of type 2 diabetes. NICE clinical guideline 87. 2009. https://www.nice.org.uk/guidance/cg87/chapter/1-Guidance (accessed 10 April 2015).

42. American Diabetes Association. Standards of Medical Care in Diabetes-2017 Abridged for Primary Care Providers. *Clin Diabetes* 2017; **35**(1): 5-26.

43. American Diabetes Association.. Standards of Medical Care in Diabetes–2006. *Diabetes Care* 2006; **29**(suppl 1): s4-s42.

44. Nathan DM, Buse JB, Davidson MB, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; **32**(1): 193-203.

45. Turner RC, Cull CA, Frighi V, Holman RR, for the UKPDSG. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: Progressive requirement for multiple therapies (ukpds 49). *Jama* 1999; **281**(21): 2005-12.

46. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach: Position Statement of the American Diabetes Association

(ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012; **35**(6): 1364-79.

47. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P. Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline From the American College of Physicians. *Annals of Internal Medicine* 2012; **156**(3): 218-31.

48. Esposito K, Bellastella G, Giugliano D. WHen metformin fails in type 2 diabetes mellitus. *Archives of internal medicine* 2011; **171**(4): 365-9.

49. The United Kingdom Prospective Diabetes Study (UKPDS) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ (Clinical research ed)* 1998; **317**(7160): 703-13.

50. Cederholm J, Zethelius B, Nilsson PM, Eeg-Olofsson K, Eliasson B, Gudbjörnsdottir S. Effect of tight control of HbA1c and blood pressure on cardiovascular diseases in type 2 diabetes: An observational study from the Swedish National Diabetes Register (NDR). *Diabetes Research and Clinical Practice* 2009; **86**(1): 74-81.

51. Grundy SM, Pasternak R, Greenland P, Smith S, Jr., Fuster V. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation* 1999; **100**(13): 1481-92.

52. Alvarez CA, Lingvay I, Vuylsteke V, Koffarnus RL, McGuire DK. Cardiovascular Risk in Diabetes Mellitus: Complication of the Disease or of Antihyperglycemic Medications. *Clinical pharmacology and therapeutics* 2015; **98**(2): 145-61.

53. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: A systematic review and meta-analysis. *Jama* 2015; **313**(6): 603-15.

54. The SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *New England Journal of Medicine* 2015; **373**(22): 2103-16.

55. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of Intensive Glucose Lowering in Type 2 Diabetes. *New England Journal of Medicine* 2008; **358**(24): 2545-59.

56. Charbonnel B, Dormandy J, Erdmann E, Massi-Benedetti M, Skene A. The prospective pioglitazone clinical trial in macrovascular events (PROactive): can pioglitazone reduce cardiovascular events in diabetes? Study design and baseline characteristics of 5238 patients. *Diabetes Care* 2004; **27**(7): 1647-53.

57. Erdmann E, Spanheimer R, Charbonnel B. Pioglitazone and the risk of cardiovascular events in patients with Type 2 diabetes receiving concomitant treatment with nitrates, renin-angiotensin system blockers, or insulin: results from the PROactive study (PROactive 20). *J Diabetes* 2010; **2**(3): 212-20.

58. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 2009; **373**(9681): 2125-35.

59. Wang B, Zhong J, Lin H, et al. Blood pressure-lowering effects of GLP-1 receptor agonists exenatide and liraglutide: a meta-analysis of clinical trials. *Diabetes, obesity & metabolism* 2013; **15**(8): 737-49.

60. Mohammad K, Hong Z, Jessica R, et al. Effect of GLP-1 Mimetics on Blood Pressure and Relationship to Weight Loss and Glycemia Lowering: Results of a Systematic Meta-Analysis and Meta-Regression. *American journal of hypertension* 2014; **27**: 130-9.

61. Abdul-Ghani MA, Norton L, DeFronzo RA. Role of Sodium-Glucose Cotransporter 2 (SGLT 2) Inhibitors in the Treatment of Type 2 Diabetes. *Endocrine Reviews* 2011; **32**(4): 515-31.

62. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* 2013; **159**(4): 262-74.

63. Mistry GC, Maes AL, Lasseter KC, et al. Effect of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on blood pressure in nondiabetic patients with mild to moderate hypertension. *Journal of clinical pharmacology* 2008; **48**(5): 592-8.

64. Koren S, Shemesh-Bar L, Tirosh A, et al. The effect of sitagliptin versus glibenclamide on arterial stiffness, blood pressure, lipids, and inflammation in type 2 diabetes mellitus patients. *Diabetes technology & therapeutics* 2012; **14**(7): 561-7.

65. Anyanwagu U, Idris I, Donnelly R. Drug-induced diabetes mellitus: Evidence for statins and other drugs affecting glucose metabolism. *Clinical Pharmacology & Therapeutics* 2015: n/a-n/a.

66. Cholesterol Treatment Trialists C. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *The Lancet*; **376**(9753): 1670-81.

67. Monami M, Vitale V, Ambrosio ML, et al. Effects on Lipid Profile of Dipeptidyl Peptidase 4 Inhibitors, Pioglitazone, Acarbose, and Sulfonylureas: Meta-analysis of Placebo-Controlled Trials. *Advances in Therapy* 2012; **29**(9): 736-46.

68. Buse JB, Drucker DJ, Taylor KL, et al. DURATION-1 exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. *Diabetes Care* 2010; **33**.

69. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* 2009; **374**(9683): 39-47.

70. Nauck MA, Del Prato S, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. *Diabetes Care* 2011; **34**(9): 2015-22.

71. Rosenstock J, Forst T, Aronson R, et al. Once-daily lixisenatide added on to consistently titrated insulin glargine plus oral agents in type 2 diabetes: the GetGoal-Duo 1 study. 2012. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70888828 (accessed (Rosenstock) Dallas Diabetes and Endocrine Center at Medical City, Dallas, United States 55).

72. The United Kingdom Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *The Lancet* 1998; **352**(9131): 854-65.

73. Diabetes Prevention Program Research Group. Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin. *New England Journal of Medicine* 2002; **346**(6): 393-403.

74. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch CL. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. *The Cochrane database of systematic reviews* 2008; (2): CD006739.

75. The United Kingdom Prospective Diabetes Study 24: A 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. United Kingdom Prospective Diabetes Study Group. *Ann Intern Med* 1998; **128**(3): 165-75.

76. McGuire DK, Inzucchi SE. New Drugs for the Treatment of Diabetes Mellitus. *Circulation* 2008; **117**(3): 440.

77. Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *BMJ (Clinical research ed)* 2012; **344**.

78. Potts JE, Gray LJ, Brady EM, Khunti K, Davies MJ, Bodicoat DH. The Effect of Glucagon-Like Peptide 1 Receptor Agonists on Weight Loss in Type 2 Diabetes: A Systematic Review and Mixed Treatment Comparison Meta-Analysis. *PLoS ONE* 2015; **10**(6): e0126769.

79. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015; **38**(1): 140-9.

80. British Medical Association Royal Pharmaceutical Society. British National Formulary. London: BMJ Group and Pharmaceutical Press; 2015.

81. Chao EC. SGLT-2 Inhibitors: A New Mechanism for Glycemic Control. *Clinical Diabetes* 2014; **32**(1): 4-11.

82. Haas B, Eckstein N, Pfeifer V, Mayer P, Hass MDS. Efficacy, safety and regulatory status of SGLT2 inhibitors: focus on canagliflozin. *Nutrition & Diabetes* 2014; **4**: e143.

83. Triggle CR, Ding H. Cardiovascular impact of drugs used in the treatment of diabetes. *Therapeutic Advances in Chronic Disease* 2014; **5**(6): 245-68.

84. Mannucci E, Dicembrini I, Lauria A, Pozzilli P. Is Glucose Control Important for Prevention of Cardiovascular Disease in Diabetes? *Diabetes Care* 2013; **36**(Supplement 2): S259-S63.

85. Roumie CL, Greevy RA, Grijalva CG, Hung AM, Griffin MR, et al. Association Between Intensification of Metformin Treatment With Insulin vs Sulfonylureas and Cardiovascular Events and All-Cause Mortality Among Patients With Diabetes. 2014311).

86. Holden SE, Jenkins-Jones S, Morgan CL, Schernthaner G, Currie CJ. Glucose-lowering with exogenous insulin monotherapy in type 2 diabetes: dose association with all-cause mortality, cardiovascular events and cancer. *Diabetes, obesity & metabolism* 2015; **17**(4): 350-62.

87. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; **356**(24): 2457-71.

88. The Food and Drug Administration (FDA). Guidance for industry diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. In: U.S. Department of Health and Human Services Food and Drug Administration CfDEaRC, editor. New Hampsire; 2008.

89. Malmberg K, Rydén L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): Effects on mortality at 1 year. *Journal of the American College of Cardiology* 1995; **26**(1): 57-65.

90. Malmberg K, Ryden L, Wedel H, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *European heart journal* 2005; **26**(7): 650-61.

91. Ritsinger V, Malmberg K, Martensson A, Ryden L, Wedel H, Norhammar A. Intensified insulin-based glycaemic control after myocardial infarction: mortality during 20 year follow-up of the randomised Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI 1) trial. *The lancet Diabetes & endocrinology* 2014; **2**(8): 627-33.

92. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**(24): 2545-59.

93. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study; 2010.

94. Riddle MC, Ambrosius WT, Brillon DJ, et al. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. *Diabetes Care* 2010; **33**(5): 983-90.

95. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358**(24): 2560-72.

96. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; **360**(2): 129-39.

97. The ORIGIN Trial Investigators. Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia. *New England Journal of Medicine* 2012; **367**(4): 319-28.

98. Marso SP, McGuire DK, Zinman B, et al. Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes. *New England Journal of Medicine* 2017;**377**:723-732August 24, 2017DOI: 10.1056/NEJMoa1615692l.

99. Fisher M. Is diabetes still a state of premature cardiovascular death? *Practical Diabetes* 2016; **33**(8): 261 -96.

100. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009; **52**(11): 2288-98.

101. Guillausseau PJ, Virally M, Kevorkian JP, et al. Intensive blood suger control in type 2 diabetes: Results of recent interventional trials (ADVANCE, VA Diabetes Trial and ACCORD). 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2009105495 (accessed (Guillausseau, Virally, Kevorkian, Meas, Laloi-Michelin, Ambonville, Bitu) Service de Medecine B, Universire Paris-VII, Hopital Lariboisiere, 2, rue Ambroise-Pare, 75010 Paris, France 21).

102. Dailey G, Wang E. A Review of Cardiovascular Outcomes in the Treatment of People with Type 2 Diabetes. *Diabetes Therapy* 2014; **5**(2): 385-402.

103. Ray KK, Seshasai SRK, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *The Lancet* 2009; **373**(9677): 1765-72.

104. Rensing KL, Reuwer AQ, Arsenault BJ, et al. Reducing cardiovascular disease risk in patients with type 2 diabetes and concomitant macrovascular disease: can insulin be too much of a good thing? *Diabetes, obesity & metabolism* 2011; **13**(12): 1073-87.

105. Holman RR, Sourij H, Califf RM. Cardiovascular outcome trials of glucose-lowering drugs or strategies in type 2 diabetes. *Lancet* 2014; **383**(9933): 2008-17.

106. Reaven PD, Moritz TE, Schwenke DC, et al. Intensive glucose-lowering therapy reduces cardiovascular disease events in veterans affairs diabetes trial participants with lower calcified coronary atherosclerosis. *Diabetes* 2009; **58**(11): 2642-8.

107. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The Incidence of Congestive Heart Failure in Type 2 Diabetes. *An update* 2004; **27**(8): 1879-84.

108. Nichols GA, Koro CE, Gullion CM, Ephross SA, Brown JB. The incidence of congestive heart failure associated with antidiabetic therapies. *Diabetes/Metabolism Research and Reviews* 2005; **21**(1): 51-7.

109. Gamble JM, Simpson SH, Eurich DT, Majumdar SR, Johnson JA. Insulin use and increased risk of mortality in type 2 diabetes: a cohort study. *Diabetes, Obesity and Metabolism* 2010; **12**(1): 47-53.

110. Hall GC, McMahon AD, Carroll D, Home PD. Macrovascular and microvascular outcomes after beginning of insulin versus additional oral glucose-lowering therapy in people with type 2 diabetes: an observational study. *Pharmacoepidemiology and Drug Safety* 2012; **21**(3): 305-13.

111. Jil M, Rajnikant M, Richard D, Iskandar I. The effects of dual-therapy intensification with insulin or dipeptidylpeptidase-4 inhibitor on cardiovascular events and all-cause mortality in patients with type 2 diabetes: A retrospective cohort study. *Diab Vasc Dis Res* 2017; **14**(4): 295-303.

112. Vallarino C, Perez A, Fusco G, et al. Comparing Pioglitazone to Insulin with Respect to Cancer, Cardiovascular and Bone Fracture Endpoints, Using Propensity Score Weights. *Clinical Drug Investigation* 2013; **33**(9): 621-31.

113. Paul SK, Klein K, Maggs D, Best JH. The association of the treatment with glucagon-like peptide-1 receptor agonist exenatide or insulin with cardiovascular outcomes in patients with type 2 diabetes: a retrospective observational study. *Cardiovascular Diabetology* 2015; **14**(1): 10.

114. Margolis DJ, Hoffstad O, Strom BL. Association between serious ischemic cardiac outcomes and medications used to treat diabetes. *Pharmacoepidemiol Drug Saf* 2008; **17**(8): 753-9.

115. Currie CJ, Poole CD, Evans M, Peters JR, Morgan CL. Mortality and other important diabetes-related outcomes with insulin vs other antihyperglycemic therapies in type 2 diabetes. *J Clin Endocrinol Metab* 2013; **98**(2): 668-77.

116. Nijjar APK, Wang H, Quan H, Khan NA. Antihyperglycemic Therapy and Cardiovascular Outcomes After Acute Myocardial Infarction in Elderly Patients with Diabetes. *Canadian Journal of Diabetes*; **38**(6): 396-400.

117. Holden SE, Jenkins-Jones S, Currie CJ. Association between Insulin Monotherapy versus Insulin plus Metformin and the Risk of All-Cause Mortality and Other Serious Outcomes: A Retrospective Cohort Study. *PLoS One* 2016; **11**(5): e0153594.

118. Nystrom T, Bodegard J, Nathanson D, Thuresson M, Norhammar A, Eriksson JW. Novel oral glucose-lowering drugs are associated with lower risk of all-cause mortality, cardiovascular events and severe hypoglycaemia compared with insulin in patients with type 2 diabetes. *Diabetes, obesity & metabolism* 2017.

119. Holden SE, Jenkins-Jones S, Morgan CL, Schernthaner G, Currie CJ. Glucose-lowering with exogenous insulin monotherapy in type 2 diabetes: dose association with all-cause mortality, cardiovascular events, and incident cancer. *Diabetes, obesity & metabolism* 2014.

120. Gamble J-M, Chibrikov E, Twells LK, et al. Association of insulin dosage with mortality or major adverse cardiovascular events: a retrospective cohort study. *The Lancet Diabetes & Endocrinology* 2017; **5**(1): 43-52.

121. Abrahamson MJ, Peters A. Intensification of insulin therapy in patients with type 2 diabetes mellitus: An algorithm for basal-bolus therapy. *Annals of Medicine* 2012; **44**(8): 836-46.

122. Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical Inertia in People With Type 2 Diabetes: A retrospective cohort study of more than 80,000 people. *Diabetes Care* 2013; **36**(11): 3411-7.

123. Mata-cases M, Franch-Nadal J, Real J, et al. Therapeutic Inertia in Patients Treated With Two or More Antidiabetics in Primary Care: Factors Predicting Intensification of Treatment. *Diabetes, Obesity and Metabolism* 2017: n/a-n/a.

124. Mannucci E, Ferrannini E. Cardiovasular safety of insulin: Between real-world data and reality. *Diabetes, obesity & metabolism* 2017.

125. Stürmer T, Funk MJ, Poole C, Brookhart MA. Nonexperimental Comparative Effectiveness Research Using Linked Healthcare Databases. *Epidemiology (Cambridge, Mass)* 2011; **22**(3): 298-301.

126. Ray WA. Improving automated database studies. *Epidemiology (Cambridge, Mass)* 2011; **22**(3): 302-4.

127. Bobo WV, Cooper WO, Stein CM, et al. Positive predictive value of a case definition for diabetes mellitus using automated administrative health data in children and youth exposed to antipsychotic drugs or control medications: a Tennessee Medicaid study. *BMC Medical Research Methodology* 2012; **12**: 128-.

128. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes; 2010.

129. Suissa S. Immortal time bias in pharmaco-epidemiology. *American journal of epidemiology* 2008; **167**(4): 492-9.

130. de Lusignan S, van Weel C. The use of routinely collected computer data for research in primary care: opportunities and challenges. *Fam Pract* 2006; **23**(2): 253-63.

131. IMS Health. Epidemiology and Pharmacology Information Core. Available from: http://www.epic-uk.org/about-us/about-us.shtml. online (accessed July 7, 2017).

132. Clinical Practice Research Datalink (CPRD). Welcome to The Clinical Practice Research Datalink. Available from: http://www.cprd.com/intro.asp. online (accessed July 7, 2017).

133. Gelfand J, Margolis D, Dattani H. The UK General Practice Research Database. . 3rd ed. Chichester: Wiley; 2005.

134. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. *J Am Acad Dermatol* 2006; **55**(5): 829-35.

135. The Health Improvement Network (THIN). About us - The Health Improvement Network (THIN). available at http://www.inps.co.uk/vision/thin/about-us 2017 (accessed June 5, 2017).

136. NHS. READ codes. online. Available at https://digital.nhs.uk/article/1104/Read-Codes (accessed July 7, 2017).

137. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Informatics in Primary Care* 2011; **19**(4): 251-5.

138. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiology and Drug Safety* 2007; **16**(4): 393-401.

139. Zhou X, Murugesan S, Bhullar H, et al. An Evaluation of the THIN Database in the OMOP Common Data Model for Active Drug Safety Surveillance. *Drug Saf* 2013; **36**(2): 119-34.

140. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf* 2007; **16**(4): 393-401.

141. Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. *BMJ : British Medical Journal* 1991; **302**(6779): 766-8.

142. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA* 2006; **296**(14): 1735-41.

143. Cegedim Strategic Data (CSD) Medical Research UK.. THIN Data Guide for Researchers. Revised 2014. 2014. p. 3.

144. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009; **338**.

145. Marston L, Carpenter JR, Walters KR, Morris RW, Nazareth I, Petersen I. Issues in multiple imputation of missing data for large general practice clinical databases. *Pharmacoepidemiol Drug Saf* 2010; **19**(6): 618-26.

146. Karahalios A, Baglietto L, Carlin JB, English DR, Simpson JA. A review of the reporting and handling of missing data in cohort studies with repeated assessment of exposure measures. *BMC Med Res Methodol* 2012; **12**.

147. Pedersen AB, Mikkelsen EM, Cronin-Fenton D, et al. Missing data and multiple imputation in clinical epidemiological research. *Clinical Epidemiology* 2017; **9**: 157-66.

148. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009; **338**.

149. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol* 2006; **59**(10): 1087-91.

150. Schafer JL, Graham JW. Missing data: our view of the state of the art. *Psychol Methods* 2002; **7**(2): 147-77.

151. Hayati Rezvan P, Lee KJ, Simpson JA. The rise of multiple imputation: a review of the reporting and implementation of the method in medical research. *BMC Medical Research Methodology* 2015; **15**(1): 30.

152. Sedgwick P. Retrospective cohort studies: advantages and disadvantages. *BMJ : British Medical Journal* 2014; **348**.

153. Townsend P. Deprivation. *Journal of Social Policy* 2009; **16**(2): 125-46.

154. Adams J, Ryan V, White M. How accurate are Townsend Deprivation Scores as predictors of self-reported health? A comparison with individual level data. *Journal of Public Health* 2005; **27**(1): 101-6.

155. Patorno E, Patrick AR, Garry EM, et al. Observational studies of the association between glucose-lowering medications and cardiovascular outcomes: addressing methodological limitations. *Diabetologia* 2014; **57**(11): 2237-50.

156. Schisterman EF, Cole SR, Platt RW. Overadjustment Bias and Unnecessary Adjustment in Epidemiologic Studies. *Epidemiology (Cambridge, Mass)* 2009; **20**(4): 488-95.

157. Fewell Z, Davey Smith G, Sterne JAC. The Impact of Residual and Unmeasured Confounding in Epidemiologic Studies: A Simulation Study. *American Journal of Epidemiology* 2007; **166**(6): 646-55.

158. Gayat E, Resche-Rigon M, Mary J-Y, Porcher R. Propensity score applied to survival data analysis through proportional hazards models: a Monte Carlo study. *Pharmaceutical Statistics* 2012; **11**(3): 222-9.

159. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Statistics in Medicine* 2014; **33**(7): 1242-58.

160. Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. *Stat Med* 2007; **26**(4): 734-53.

161. Rosenbaum PR. Propensity Score. Wiley StatsRef: Statistics Reference Online: John Wiley & Sons, Ltd; 2014.

162. Dehejia RH, Wahba S. Propensity Score-Matching Methods for Nonexperimental Causal Studies. *The Review of Economics and Statistics* 2002; **84**(1): 151-61.

163. Ming K, Rosenbaum PR. Substantial gains in bias reduction from matching with a variable number of controls. *Biometrics* 2000; **56**(1): 118-24.

164. Lu B. Propensity Score Matching with Time-Dependent Covariates. *Biometrics* 2005; **61**(3): 721-8.

165. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000; **11**(5): 550-60.

166. Cole SR, Hernan MA. Adjusted survival curves with inverse probability weights. *Comput Methods Programs Biomed* 2004; **75**(1): 45-9.

167. Xie J, Liu C. Adjusted Kaplan-Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. *Stat Med* 2005; **24**(20): 3089-110.

168. Haidich AB. Meta-analysis in medical research. *Hippokratia* 2010; **14**(Suppl 1): 29-37.

169. Epidemiology and Public Health (EPH) Division. Multiple Linear Regression. In: University of Nottingham Lecture Notes. Nottingham: Epidemiology and Public Health Division; 2014.

170. StataCorp. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP. 2014.

171. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006; **355**(23): 2427-43.

172. Center for Drug Evaluation and Research (CDER) Food and Drug Administration (FDA). Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. In: Services US Department of Health and Human Services. Silver Spring, MD; 2008.

173. Keen H, Glynne A, Pickup J, al e. Human insulin produced by recombinant DNA technology: safety and hypoglycaemic potency in healthy men. *Lancet* 1980; **2**: 398-401.

174. Malmberg K, Ryden L, Wedel H, al. E. "FASTTRACK intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortlaity and morbidity". *European heart journal* 2005; **26**(7): 650-61.

175. Cahn A, Miccoli R, Dardano A, Del Prato S. New forms of insulin and insulin therapies for the treatment of type 2 diabetes. *The Lancet Diabetes & Endocrinology* 2015; **3**(8): 638-52.

176. Bliss M. The History of Insulin. *Diabetes Care* 1993; **16**(Supplement 3): 4-7.

177. Pontiroli A, Miele L, Morabito A. Metabolic control and risk of hypoglycaemia during the first year of intensive insulin treatment in type 2 diabetes: systematic review and meta-analysis. . *Diabetes Obes Metab* 2012; **14**: 433-46.

178. Holman RR, Farmer AJ, Davies MJ, et al. Three-Year Efficacy of Complex Insulin Regimens in Type 2 Diabetes. *New England Journal of Medicine* 2009; **361**(18): 1736-47.

179. Van Avendonk MJP, Rutten GEHM. Insulin therapy in type 2 diabetes: what is the evidence? *Diabetes, Obesity and Metabolism* 2009; **11**(5): 415-32.

180. Roumie CL, Greevy RA, Grijalva CG, et al. ASsociation between intensification of metformin treatment with insulin vs sulfonylureas and cardiovascular events and all-cause mortality among patients with diabetes. *Jama* 2014; **311**(22): 2288-96.

181. Aschner P, Chan J, Owens DR, et al. Insulin glargine versus sitagliptin in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): a multicentre, randomised open-label trial. *The Lancet* 2012; **379**(9833): 2262-9.

182. Barnett AH, Dreyer M, Lange P, Serdarevic-Pehar M, Exubera Phase IIISG. An open, randomized, parallel-group study to compare the efficacy and safety profile of inhaled human insulin (Exubera) with metformin as adjunctive therapy in patients with type 2 diabetes poorly controlled on a sulfonylurea. 200629).

183. Endnote Referencing Software. Available at www.myendnoteweb.com

184. Higgins J, Green Se. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011.

185. Mellbin LG, Malmberg K, Norhammar A, Wedel H, Ryden L. Prognostic implications of glucose-lowering treatment in patients with acute myocardial infarction and diabetes: experiences from

an extended follow-up of the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 Study. *Diabetologia* 2011; **54**(6): 1308-17.

186. Barnett AH, Burger J, Johns D, et al. Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: a multinational, randomized, open-label, two-period, crossover noninferiority trial. *Clinical therapeutics* 2007; **29**(11): 2333-48.

187. Bunck MC, Diamant M, Corner A, et al. One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. *Diabetes Care* 2009; **32**(5): 762-8.

188. D'Alessio D, Haring HU, Charbonnel B, et al. Comparison of insulin glargine and liraglutide added to oral agents in patients with poorly controlled type 2 diabetes. *Diabetes, Obesity & Metabolism* 2015; **17**(2): 170-8.

189. Davies M, Heller S, Sreenan S, et al. Once-weekly exenatide versus once- or twice-daily insulin detemir: randomized, open-label, clinical trial of efficacy and safety in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylureas. *Diabetes Care* 2013; **36**(5): 1368-76.

190. Davies MJ, Donnelly R, Barnett AH, Jones S, Nicolay C, Kilcoyne A. Exenatide compared with long-acting insulin to achieve glycaemic control with minimal weight gain in patients with type 2 diabetes: results of the Helping Evaluate Exenatide in patients with diabetes compared with Long-Acting insulin (HEELA) study. *Diabetes, Obesity & Metabolism* 2009; **11**(12): 1153-62.

191. Diamant M, Van Gaal L, Stranks S, et al. Safety and Efficacy of Once-Weekly Exenatide Compared With Insulin Glargine Titrated to Target in Patients With Type 2 Diabetes Over 84 Weeks. *Diabetes Care* 2012; **35**(4): 683-9.

192. Diamant M, Van Gaal L, Stranks S, et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. *Lancet* 2010; **375**(9733): 2234-43.

193. Diamant M, Diamant M, Nauck MA, Shaginian R, et al. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. *Diabetes Care* 2014; **37**(10): 2763-73.

194. Dorkhan M, Dencker M, Stagmo M, Groop L. Effect of pioglitazone versus insulin glargine on cardiac size, function, and measures of fluid retention in patients with type 2 diabetes. *Cardiovascular Diabetology* 2009; **8**: 15.

195. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 2005; **143**(8): 559-69.

196. Matyjaszek-Matuszek B, B, Lenart-Lipinska M, Rogalska D, Nowakowski A. Exenatide twice daily versus insulin glargine for the treatment of type 2 diabetes in Poland - subgroup data from a randomised multinational trial GWAA. *Endokrynologia Polska* 2013; **64**(5): 375-82

197. Philis-Tsimikas A, Del Prato S, Satman I, et al. Effect of insulin degludec versus sitagliptin in patients with type 2 diabetes uncontrolled on oral antidiabetic agents. *Diabetes, Obesity & Metabolism* 2013; **15**(8): 760-6.

198. Rosenstock J, Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. *Diabetes Care* 2006; **29**(3): 554-9.

199. de Wit HM, Vervoort GM, Jansen HJ, de Grauw WJ, de Galan BE, Tack CJ. Liraglutide reverses pronounced insulin-associated weight gain, improves glycaemic control and decreases insulin dose in patients with type 2 diabetes: a 26 week, randomised clinical trial (ELEGANT). *Diabetologia* 2014; **57**(9): 1812-9.

200. Moher D, Pham B, Jones A, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998; **352**(9128): 609-13.

201. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ (Clinical research ed)* 2000; **321**(7258): 405-12.

202. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-Analysis: Glycosylated Hemoglobin and Cardiovascular Disease in Diabetes Mellitus. *Annals of Internal Medicine* 2004; **141**(6): 421-31.

203. Niswender K, Pi-Sunyer X, Buse J, et al. Weight change with liraglutide and comparator therapies: an analysis of seven phase 3 trials from the liraglutide diabetes development programme. *Diabetes, Obesity & Metabolism* 2013; **15**(1): 42-54.

204. Shaefer CF, Reid TS, Dailey G, et al. Weight change in patients with type 2 diabetes starting basal insulin therapy: correlates and impact on outcomes. *Postgraduate Medicine* 2014; **126**(6): 93-105..

205. Venables MC, Jeukendrup AE. Physical inactivity and obesity: links with insulin resistance and type 2 diabetes mellitus. *Diabetes/metabolism research and reviews* 2009; **25 Suppl 1**: S18-23.

206. Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes – causes, effects and coping strategies. *Diabetes, Obesity and Metabolism* 2007; **9**(6): 799-812.

207. Dornhorst A, Luddeke HJ, Sreenan S, et al. Safety and efficacy of insulin detemir in clinical practice: 14-week follow-up data from type 1 and type 2 diabetes patients in the PREDICTIVE European cohort. *International Journal of Clinical Practice* 2007; **61**(3): 523-8

208. Wilson P, McGee D, Kannel W. Obesity, very low density lipoproteins, and glucose intolerance over fourteen years: the Framingham Study. *Am J Epidemiol* 1981; **114**: 697-704.

209. Kannel WB, D'Agostino RB, Cobb JL. Effect of weight on cardiovascular disease. *The American Journal of Clinical Nutrition* 1996; **63**(3): 419S-22S.

210. The ADVANCE Collaborative Group.Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine* 2008; **358**(24): 2560-72.

211. Koska J, Saremi A, Bahn G, Yamashita S, Reaven PD. The effect of intensive glucose lowering on lipoprotein particle profiles and inflammatory markers in the Veterans Affairs Diabetes Trial (VADT). *Diabetes Care* 2013; **36**(8): 2408-14.

212. Yakubovich N, Gerstein HC. Serious Cardiovascular Outcomes in Diabetes: The Role of Hypoglycemia. *Circulation* 2011; **123**(3): 342-8.

213. Svensson A-M, McGuire DK, Abrahamsson P, Dellborg M. Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. *European heart journal* 2005; **26**(13): 1255-61.

214. Frier BM, Schernthaner G, Heller SR. Hypoglycemia and Cardiovascular Risks. *Diabetes Care* 2011; **34**(Supplement 2): S132-S7.

215. McCrimmon RJ, Frier BM. Hypoglycaemia, the most feared complication of insulin therapy. *Diabete & metabolisme* 1994; **20**(6): 503-12.

216. Colayco DC, Niu F, McCombs JS, Cheetham TC. A1C and Cardiovascular Outcomes in Type 2 Diabetes: A nested case-control study. *Diabetes Care* 2011; **34**(1): 77-83.

217. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: Scientific review. *Jama* 2003; **289**(17): 2254-64.

218. The Diabetes Control and Complications Trial Research Group. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *New England Journal of Medicine* 1993; **329**(14): 977-86.

219. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359**(15): 1577-89.

220. Garber AJ. Methods to enhance delivery of prandial insulin and basal-prandial insulin. *Diabetes, Obesity and Metabolism* 2013; **15**(s1): 11-7.

221. Hamaty M. Insulin treatment for type 2 diabetes: when to start, which to use. *Cleveland Clinic Journal of Medicine* 2011; **78**(5): 332-42.

222. Beluchin E, Baz L, Muller Nea. Frequency of self-adjustment of insulin dose and metabolic control in Type 2 diabetes -is there an association? . *Diabetic Medicine* 2013; **30**(3): e91-4.

223. Kramer G, Kuniss N, Jorgens V, et al. Prospective analysis of principles and frequency of self-adjustment of insulin dose in people with diabetes type 1 before and after participation in a diabetes treatment and teaching programme. *Diabetes Res Clin Pract* 2016; **119**: 65-70.

224. Peyrot M, Rubin RR, Kruger DF, Travis LB. Correlates of insulin injection omission. *Diabetes Care* 2010; **33**(2): 240-5.

225. Turner HE, Matthews DR. The use of fixed-mixture insulins in clinical practice. *European Journal of Clinical Pharmacology* 2000; **56**(1): 19-25.

226. Bowering K, Reed VA, Felicio JS, Landry J, Ji L, Oliveira J. A study comparing insulin lispro mix 25 with glargine plus lispro therapy in patients with Type 2 diabetes who have inadequate glycaemic control on oral anti-hyperglycaemic medication: results of the PARADIGM study. *Diabetic medicine : a journal of the British Diabetic Association* 2012; **29**(9): e263-72.

227. Kramer G, Kuniss N, Kloos C, et al. Metabolic control and hypoglycaemia in people with type 2 diabetes on conventional or intensified insulin therapy: a 22 year retrospective single centre survey. *Diabetes/metabolism research and reviews* 2016; **32**(6): 652-8.

228. Fritsche A, Larbig M, Owens D, Häring HU, on behalf of the Gsg. Comparison between a basal-bolus and a premixed insulin regimen in individuals with type 2 diabetes–results of the GINGER study. *Diabetes, Obesity and Metabolism* 2010; **12**(2): 115-23.

229. Idris I, Pillai A, Fernando DJ, Thomson G, Tate H. Responders to insulin therapy at 18 months in adults with newly diagnosed diabetes: which insulin regimen? *Diabetic Medicine* 2013; **30**(3): e95-e100.

230. Wang C, Mamza J, Idris I. Biphasic vs basal bolus insulin regimen in Type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetic medicine : a journal of the British Diabetic Association* 2015; **32**(5): 585-94.

231. Hirao K, Arai K, Yamauchi M, Takagi H, Kobayashi M. Six-month multicentric, open-label, randomized trial of twice-daily injections of biphasic insulin aspart 30 versus multiple daily injections of insulin aspart in Japanese type 2 diabetic patients (JDDM 11). *Diabetes Research and Clinical Practice* 2008; **79**(1): 171-6.

232. Jain SM, Mao X, Escalante-Pulido M, Vorokhobina N, Lopez I, Ilag LL. Prandial–basal insulin regimens plus oral antihyperglycaemic agents to improve mealtime glycaemia: initiate and progressively advance insulin therapy in type 2 diabetes. *Diabetes, Obesity and Metabolism* 2010; **12**(11): 967-75.

233. Levin PA, Zhang Q, Mersey JH, et al. Glycemic Control With Insulin Glargine Plus Insulin Glulisine Versus Premixed Insulin Analogues in Real-World Practices: A Cost-Effectiveness Study With a Randomized Pragmatic Trial Design. *Clinical therapeutics* 2011; **33**(7): 841-50.

234. Liebl A, Prager R, Binz K, et al. Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER Study: a randomized controlled trial. *Diabetes, Obesity and Metabolism* 2009; **11**(1): 45-52.

235. Miser WF, Arakaki R, Jiang H, Scism-Bacon J, Anderson PW, Fahrbach JL. Randomized, open-label, parallel-group evaluations of basal-bolus therapy versus insulin lispro premixed therapy in patients with type 2 diabetes mellitus failing to achieve control with starter insulin treatment and continuing oral antihyperglycemic drugs: a noninferiority intensification substudy of the DURABLE trial. *Clinical Therapeutics* 2010; **32**(5): 896-908.

236. Rosenstock J, Ahmann AJ, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing Insulin Therapy in Type 2 Diabetes Previously Treated With Glargine Plus Oral Agents. *Diabetes Care* 2007; **31**(1): 20.

237. Anyanwagu U, Mamza J, Mehta R, Donnelly R, Idris I. Cardiovascular events and all-cause mortality with insulin versus glucagon-like peptide-1 analogue in type 2 diabetes. *Heart* 2016.

238. Mamza J, Mehta R, Donnelly R, Idris I. Comparative Efficacy of Adding Sitagliptin to Metformin, Sulfonylurea or Dual Therapy: A Propensity Score-Weighted Cohort Study. *Diabetes Therapy* 2015; **6**(2): 213-26.

239. Polonsky WH, Thompson S, Wei W, et al. Greater fear of hypoglycaemia with premixed insulin than with basal-bolus insulin glargine and glulisine: patient-reported outcomes from a 60-week randomised study. *Diabetes, obesity & metabolism* 2014; **16**(11): 1121-7.

240. Pontiroli AE, Miele L, Morabito A. Increase of body weight during the first year of intensive insulin treatment in type 2 diabetes: systematic review and meta-analysis. *Diabetes, obesity & metabolism* 2011; **13**(11): 1008-19.

241. Concert CM, Burke RE, Eusebio AM, Slavin EA, Shortridge-Baggett LM. The Effectiveness of Motivational Interviewing on Glycemic Control for Adults with Type 2 Diabetes Mellitus (DM2): A Systematic Review. *JBI library of systematic reviews* 2012; **10**(42 Suppl): 1-17.

242. Paul SK, Shaw J, Montvida O, Klein K. Weight gain in insulin treated patients by BMI categories at treatment initiation: New evidence from real-world data in patients with type 2 diabetes. *Diabetes, Obesity and Metabolism* 2016;18(12):1244-1252

243. Balkau B, Home PD, Vincent M, Marre M, Freemantle N. Factors associated with weight gain in people with type 2 diabetes starting on insulin. *Diabetes Care* 2014; **37**(8): 2108-13.

244. Siebenhofer A, Plank J, Berghold A, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. *The Cochrane database of systematic reviews* 2006; (2): CD003287.

245. Müller N, Lehmann T, Gerste B, et al. Increase in the incidence of severe hypoglycaemia in people with Type 2 diabetes in spite of new drugs: analysis based on health insurance data from Germany. *Diabetic Medicine* 2017: n/a-n/a.

246. Freemantle N, Holmes J, Hockey A, Kumar S. How strong is the association between abdominal obesity and the incidence of type 2 diabetes? *International journal of clinical practice* 2008; **62**(9): 1391-6.

247. Garber AJ. Obesity and type 2 diabetes: which patients are at risk? *Diabetes, obesity & metabolism* 2012; **14**(5): 399-408.

248. Kim SH, Després J-P, Koh KK. Obesity and cardiovascular disease: friend or foe? *European heart journal* 2016; **37**(48): 3560-8.

249. Biesenbach G, Raml A, Alsaraji N. Weight gain and insulin requirement in type 2 diabetic patients during the first year after initiating insulin therapy dependent on baseline BMI. *Diabetes, obesity & metabolism* 2006; **8**(6): 669-73.

250. Owen V, Seetho I, Idris I. Predictors of responders to insulin therapy at 1 year among adults with type 2 diabetes. *Diabetes, Obesity & Metabolism* 2010; **12**(10): 865-70.

251. Ryysy L, Häkkinen AM, Goto T, et al. Hepatic fat content and insulin action on free fatty acids and glucose metabolism rather than insulin absorption are associated with insulin requirements during insulin therapy in type 2 diabetic patients. *Diabetes* 2000; **49**(5): 749-58.

252. Currie CJ, Johnson JA. The safety profile of exogenous insulin in people with type 2 diabetes: justification for concern. *Diabetes, Obesity and Metabolism* 2012; **14**(1): 1-4.

253. Anderson JW, Kendall CW, Jenkins DJ. Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. *Journal of the American College of Nutrition* 2003; **22**(5): 331-9.

254. Khan MA, St. Peter JV, Breen GA, Hartley GG, Vessey JT. Diabetes Disease Stage Predicts Weight Loss Outcomes with Long-Term Appetite Suppressants. *Obesity Research* 2000; **8**(1): 43-8.

255. Lean ME, Powrie JK, Anderson AS, Garthwaite PH. Obesity, weight loss and prognosis in type 2 diabetes. *Diabetic medicine : a journal of the British Diabetic Association* 1990; **7**(3): 228-33.

256. Watson L, Wilson BP, Alsop J, Kumar S. Weight and glycaemic control in type 2 diabetes: what is the outcome of insulin initiation? *Diabetes, obesity & metabolism* 2011; **13**(9): 823-31.

257. Cho E, Manson JE, Stampfer MJ, et al. A Prospective Study of Obesity and Risk of Coronary Heart Disease Among Diabetic Women. *Diabetes Care* 2002; **25**(7): 1142-8.

258. Wing RR, Klein R, Moss SE. Weight gain associated with improved glycemic control in population-based sample of subjects with type I diabetes. *Diabetes Care* 1990; **13**(11): 1106-9.

259. Holman R, Paul S, Bethel M, Matthews D, Neil H. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359**: 1577 - 89.

260. Association AD. Standards of Medical Care in Diabetes—2012. *Diabetes Care* 2011; **35**(Supplement 1): S11.

261. Montori VM, Fernandez-Balsells M. Glycemic control in type 2 diabetes: time for an evidence-based about-face? *Ann Intern Med* 2009; **150**(11): 803-8.

262. Yadgar-Yalda R, Colman PG, Fourlanos S, Wentworth JM. Factors associated with insulin-induced weight gain in an Australian type 2 diabetes outpatient clinic. *Internal Medicine Journal* 2016; **46**(7): 834-9.

263. Purnell JQ, Zinman B, Brunzell JD. The Effect of Excess Weight Gain With Intensive Diabetes Mellitus Treatment on Cardiovascular Disease Risk Factors and Atherosclerosis in Type 1 Diabetes Mellitus: Results From the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) Study. *Circulation* 2013; **127**(2): 180-7.

264. Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T. Intentional weight loss and mortality among overweight individuals with diabetes. *Diabetes Care* 2000; **23**(10): 1499-504.

265. Diabetes Prevention Program Research G. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *The Lancet* 2009; **374**(9702): 1677-86.

266. Dixon L, Weiden P, Delahanty J, et al. Prevalence and correlates of diabetes in national schizophrenia samples. *Schizophrenia bulletin* 2000; **26**(4): 903-12.

267. American Diabetes Association (ADA). Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003; **26 Suppl 1**: S5-20.

268. Best JH, Hoogwerf BJ, Herman WH, et al. Risk of Cardiovascular Disease Events in Patients With Type 2 Diabetes Prescribed the Glucagon-Like Peptide 1 (GLP-1) Receptor Agonist Exenatide Twice Daily or Other Glucose-Lowering Therapies: A retrospective analysis of the LifeLink database. *Diabetes Care* 2011; **34**(1): 90-5.

269. Monami M, Cremasco F, Lamanna C, et al. Glucagon-Like Peptide-1 Receptor Agonists and Cardiovascular Events: A Meta-Analysis of Randomized Clinical Trials. *Experimental Diabetes Research* 2011; **2011**: 10.

270. Okerson T, Chilton R. The cardiovascular effecst of GLP-1 receptor agonists. *Cardiovascular Therapeutics* 2012; **30**: e146-e55.

271. Ussher JR, Drucker DJ. Cardiovascular actions of incretin-based therapies. *Circ Res* 2014; **114**(11): 1788-803.

272. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine* 2016; **375**(4): 311-22.

273. Paul SK, Klein K, Maggs D, Best JH. The association of the treatment with glucagon-like peptide-1 receptor agonist exenatide or insulin with cardiovascular outcomes in patients with type 2 diabetes: a retrospective observational study. *Cardiovascular diabetology* 2015; **14**(1): 1-9.

274. Avogaro A, Vigili de Kreutzenberg S, Fadini GP. Cardiovascular actions of GLP-1 and incretin-based pharmacotherapy. *Curr Diab Rep* 2014; **14**(5): 483.

275. Waldrop G, Zhong J, Peters M, Rajagopalan S. Incretin-Based Therapy for Diabetes: What a Cardiologist Needs to Know. *J Am Coll Cardiol* 2016; **67**(12): 1488-96.

276. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. *BMJ (Clinical research ed)* 2013; **347**: f4533.

277. Nauck M, Horton E, Andjelkovic M, et al. Taspoglutide, a once-weekly glucagon-like peptide1 analogue, vs. insulin glargine titrated to target in patients with Type2 diabetes: An open-label randomized trial. 2013; **30**((Nauck) Diabeteszentrum Bad Lauterberg, Bad Lauterberg im Harz, Germany): 109-13.

278. Lind M, Hirsch IB, Tuomilehto J, et al. Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial). *BMJ (Clinical research ed)* 2015; **351**: h5364.

279. Ahrén B. Insulin plus incretin: A glucose-lowering strategy for type 2-diabetes. *World Journal of Diabetes* 2014; **5**(1): 40-51.

280. Mathieu C, Rodbard HW, Cariou B, et al. A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON). *Diabetes, obesity & metabolism* 2014; **16**(7): 636-44.

281. Aas AM, Öhrvik J, Malmberg K, Rydén L, Birkeland KI, the DI. Insulin-induced weight gain and cardiovascular events in patients with type 2 diabetes. A report from the DIGAMI 2 study. *Diabetes, Obesity and Metabolism* 2009; **11**(4): 323-9.

282. Prevention CfDCa. National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States. Atlanta, Georgia, : U.S. Department of Health and Human Services, Center for Disease Control and Prevention, 2011.

283. Vijan S, Hofer TP, Hayward RA. Estimated benefits of glycemic control in microvascular complications in type 2 diabetes. *Ann Intern Med* 1997; **127**(9): 788-95.

284. Selvin E, Coresh J, Brancati FL. The burden and treatment of diabetes in elderly individuals in the u.s. *Diabetes Care* 2006; **29**(11): 2415-9.

285. Dosluoglu HH, Lall P, Nader ND, Harris LM, Dryjski ML. Insulin use is associated with poor limb salvage and survival in diabetic patients with chronic limb ischemia. *Journal of Vascular Surgery* 2010; **51**(5): 1178-89.

286. Pyorala M, Miettinen H, Laakso M, Pyorala K. Plasma insulin and all-cause, cardiovascular, and noncardiovascular mortality: the 22-year follow-up results of the Helsinki Policemen Study. *Diabetes Care* 2000; **23**(8): 1097-102.

287. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. *Diabetes Care* 2012; **35**(12): 2650-64.

288. Blaum CS, Volpato S, Cappola AR, et al. Diabetes, hyperglycaemia and mortality in disabled older women: The Women's Health and Ageing Study I. *Diabetic medicine : a journal of the British Diabetic Association* 2005; **22**(5): 543-50.

289. Nelson KM, Boyko EJ, Koepsell T. All-cause mortality risk among a national sample of individuals with diabetes. *Diabetes Care* 2010; **33**(11): 2360-4.

290. Huang ES, Liu JY, Moffet HH, John PM, Karter AJ. Glycemic control, complications, and death in older diabetic patients: the diabetes and aging study. *Diabetes Care* 2011; **34**(6): 1329-36.

291. Kontopantelis E, Springate DA, Reeves D, et al. Glucose, blood pressure and cholesterol levels and their relationships to clinical outcomes in type 2 diabetes: a retrospective cohort study. *Diabetologia* 2015; **58**(3): 505-18.

292. Bruderer SG, Bodmer M, Jick SS, Bader G, Schlienger RG, Meier CR. Incidence of and risk factors for severe hypoglycaemia in treated type 2 diabetes mellitus patients in the UK--a nested case-control analysis. *Diabetes, Obesity & Metabolism* 2014; **16**(9): 801-11.

293. Davies JS, Hinds NP, Millward EM, McDowell I, Scanlon MF. Hypokalaemia during insulin-induced hypoglycaemia in hypopituitary adults with and without growth hormone deficiency. *Clinical endocrinology* 1998; **49**(2): 217-20.

294. Khunti K, Davies M, Majeed A, Thorsted BL, Wolden ML, Paul SK. Hypoglycemia and risk of cardiovascular disease and all-cause mortality in insulin-treated people with type 1 and type 2 diabetes: a cohort study. *Diabetes Care* 2015; **38**(2): 316-22.

295. Kim TN, Park MS, Yang SJ, et al. Prevalence and determinant factors of sarcopenia in patients with type 2 diabetes: the Korean Sarcopenic Obesity Study (KSOS). *Diabetes Care* 2010; **33**(7): 1497-9.

296. Sinclair A, Morley JE. How to Manage Diabetes Mellitus in Older Persons in the 21st Century: Applying These Principles to Long Term Diabetes Care. *Journal of the American Medical Directors Association*; **14**(11): 777-80.

297. Groenwold RHH, Donders ART, Roes KCB, Harrell JFE, Moons KGM. Dealing With Missing Outcome Data in Randomized Trials and Observational Studies. *American journal of epidemiology* 2012; **175**(3): 210-7.

298. Kearney PM, Blackwell L, Collins R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008; **371**(9607): 117-25.

299. Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012; **380**(9841): 581-90.

300. Fulcher J, O'Connell R, Voysey M, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015; **385**(9976): 1397-405.

301. Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; **375**(9733): 2215-22.

302. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. *Circulation* 2013.

303. Sattar N, Preiss D, Murray H, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010; **375**: 735-42.

304. Preiss D, Kondapally S, Welsh P, et al. Risk of Incident DiabetesWith Intensive-Dose Compared WithModerate-Dose Statin Therapy: A Meta-analysis. *Jama* 2011; **305**(24): 2556-64.

305. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study. *BMJ (Clinical research ed)* 2013; **346**: f2610.

306. Takano T, Yamakawa T, Takahashi M, Kimura M, Okamura A. Influences of statins on glucose tolerance in patients with type 2 diabetes mellitus. *J Atheroscler Thromb* 2006; **13**(2): 95-100.

307. Simsek S, Schalkwijk CG, Wolffenbuttel BH. Effects of rosuvastatin and atorvastatin on glycaemic control in Type 2 diabetes---the CORALL study. *Diabetic Medicine : A Journal of the British Diabetic Association* 2012; **29**(5): 628-31.

308. Liu P-Y, Lin L-Y, Lin H-J, et al. Pitavastatin and Atorvastatin Double-Blind Randomized ComPArative Study among HiGh-Risk Patients, Including ThOse with Type 2 Diabetes Mellitus, in Taiwan (PAPAGO-T Study). *PLOS ONE* 2013; **8**(10): e76298.

309. Chapman MJ, Orsoni A, Robillard P, Hounslow N, Sponseller CA, Giral P. Effect of high-dose pitavastatin on glucose homeostasis in patients at elevated risk of new-onset diabetes: insights from the CAPITAIN and PREVAIL-US studies. *Curr Med Res Opin* 2014; **30**(5): 775-84.

310. Erqou S, Lee CC, Adler AI. Statins and glycaemic control in individuals with diabetes: a systematic review and meta-analysis. *Diabetologia* 2014; **57**(12): 2444-52.

311. Mortensen MB, Kulenovic I, Falk E. Statin use and cardiovascular risk factors in diabetic patients developing a first myocardial infarction. *Cardiovascular Diabetology* 2016; **15**(1): 81.

312. Sattar NA, Ginsberg H, Ray K, et al. The use of statins in people at risk of developing diabetes mellitus: Evidence and guidance for clinical practice. *Atherosclerosis Supplements* 2014; **15**(1): 1-15.

313. Muscogiuri G, Sarno G, Gastaldelli A, et al. The good and bad effects of statins on insulin sensitivity and secretion. *Endocrine research* 2014; **39**(4): 137-43.

314. Bardini G, Giannini S, Rotella CM, Pala L, Cresci B, Mannucci E. Lower and higher-potency statins on glycemic control in type 2 diabetes: A retrospective cohort study. *Diabetes Res Clin Pract* 2016; **120**: 104-10.

315. Liew SM, Lee PY, Hanafi NS, et al. Statins use is associated with poorer glycaemic control in a cohort of hypertensive patients with diabetes and without diabetes. *Diabetology & Metabolic Syndrome* 2014; **6**.

316. Heintjes EM, Penning-van Beest FJ, Johansson S, Stalenhoef AF, Herings RM. Comparison of incidences of cardiovascular events among new users of different statins: a retrospective observational cohort study. *Curr Med Res Opin* 2009; **25**(11): 2621-9.

317. Dieleman JP, van Wyk JT, van Wijk MA, et al. Differences between statins on clinical endpoints: a population-based cohort study. *Curr Med Res Opin* 2005; **21**(9): 1461-8.

318. Foody JM, Joyce AT, Rudolph AE, Liu LZ, Benner JS. Cardiovascular outcomes among patients newly initiating atorvastatin or simvastatin therapy: a large database analysis of managed care plans in the United States. *Clinical therapeutics* 2008; **30**(1): 195-205.

319. Sasso FC, Lascar N, Ascione A, et al. Moderate-intensity statin therapy seems ineffective in primary cardiovascular prevention in patients with type 2 diabetes complicated by nephropathy. A multicenter prospective 8 years follow up study. *Cardiovascular Diabetology* 2016; **15**: 147.

320. Brault M, Ray J, Gomez YH, Mantzoros CS, Daskalopoulou SS. Statin treatment and new-onset diabetes: A review of proposed mechanisms. *Metabolism-Clinical and Experimental* 2014; **63**(6): 735-45.

321. Baker WL, Talati R, White CM, Coleman CI. Differing effect of statins on insulin sensitivity in non-diabetics: A systematic review and meta-analysis. *Diabetes Research and Clinical Practice* 2010; **87**(1): 98-107.

322. Cederberg H, Stancakova A, Yaluri N, Modi S, Kuusisto J, Laakso M. Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort. *Diabetologia* 2015; **58**(5): 1109-17.

323. Kain V, Kapadia B, Misra P, Saxena U. Simvastatin may induce insulin resistance through a novel fatty acid mediated cholesterol independent mechanism. 2015; **5**: 13823.

324. Nathan D, Buse J, Davidson M, Heine R, Holman R, Sherwin R. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2006; **29**: 1963 - 72.

325. British Medical Association (BMA). Quality and outcomes framework guidance for GMS contract 2009/10. London: British Medical Association (BMA) NHS Employers, 2009.

326. Hex N, Bartlett C, Wright D, Taylor M, Varley D. Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. *Diabetic medicine : a journal of the British Diabetic Association* 2012; **29**(7): 855-62.

327. Rea R, al. e. Integrated diabetes care in Derby: a new NHS organizations for new challenges. *Practical Diabetes* 2011; **28**: 312.

328. Diabetes UK. Best practice for commissioning diabetes services - An integrated care framework. http://www.diabetes.org.uk/Documents/Position%20statements/best-practice-commissioning-diabetes-services-integrated-framework-0313.pdf (accessed March 21, 2017).

329. Society PCD, Diabetologist AoBC, the DUa, Nursing Rco. Integrated care in the reforming NHS – ensuring access to high quality care for all people with diabetes- a joint position statement from the Primary Care diabetes society, Association of British Clinical Diabetologist, Diabetes UK and the Royal college of Nursing. December 2007. 2007.

330. Guardian T. Derby leads the way on integrated care in the NHS. 2011. http://www.theguardian.com/society/2011/jul/13/nhs-diabetes-care-hospital-derby (accessed March 21, 2017).

331. Quality in Care: Diabetes. Available at http://connect.qualityincare.org/diabetes/cross-organisational_partnership_of_the_year/case_studies. (accessed March 21, 2017).

332. Hospital DT. http://www.derbyhospitals.nhs.uk/about/latest-news/latest-news-archive/news-archive-2011 (Accessed March 21, 2017).

333. PRIMIS. Available at: http://www.nottingham.ac.uk/primis/tools-audits/tools-audits/diabetes-care.aspx (accessed March 21, 2017)

334. Duckworth WC, Abraira C, Moritz TE, et al. The duration of diabetes affects the response to intensive glucose control in type 2 subjects: the VA Diabetes Trial. *J Diabetes Complications* 2011; **25**(6): 355-61.

335. Zangeneh F, Arora PS, Dyck PJ, et al. Effects of duration of type 2 diabetes mellitus on insulin secretion. *Endocrine Practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists* 2006; **12**(4): 388-93.

336. Hao W, Gitelman S, DiMeglio LA, Boulware D, Greenbaum CJ. Fall in C-Peptide During First 4 Years From Diagnosis of Type 1 Diabetes: Variable Relation to Age, HbA1c and Insulin Dose. *Diabetes Care* 2016; DOI: 10.2337/dc16-0360.

337. Wilson A, O'Hare JP, Hardy A, et al. Evaluation of the Clinical and Cost Effectiveness of Intermediate Care Clinics for Diabetes (ICCD): A Multicentre Cluster Randomised Controlled Trial. *PLOS ONE* 2014; **9**(4): e93964.

338. Renders CM, Valk GD, Griffin S, Wagner EH, Eijk JT, Assendelft WJ. Interventions to improve the management of diabetes mellitus in primary care, outpatient and community settings. *The Cochrane database of systematic reviews* 2001; (1): CD001481.

339. Mata-Cases M, Franch-Nadal J, Real J, et al. Therapeutic inertia in patients treated with two or more antidiabetics in primary care: Factors predicting intensification of treatment. *Diabetes, Obesity and Metabolism*: n/a-n/a.

340. Tanaka N, Kurose T, Seino Y. Therapeutic inertia or individualization? Delay in clinical management of type 2 diabetes mellitus. *Current Medical Research and Opinion* 2016; **32**(9): 1477-8.

341. Khunti K, Millar-Jones D. Clinical inertia to insulin initiation and intensification in the UK: A focused literature review. *Primary Care Diabetes* 2017; **11**(1): 3-12.

342. Raccah D, Haak TJ, Huet D, et al. Comparison of stepwise addition of prandial insulin to a basal-bolus regimen when basal insulin is insufficient for glycaemic control in type 2 diabetes: results of the OSIRIS study. Diabetes & Metabolism 2012; **38**(6): 507-14.

Appendices

Appendix 1 (Chapter 2 – Methods: Definition of READ codes).

1.1. Acute Myocardial Infarction (AMI)

Description	Code
Acute ST segment elevation myocardial infarction	G30X000
Acute anterolateral infarction	G300.00
Acute anteroseptal infarction	G301100
Acute coronary syndrome	G311500
Acute inferolateral infarction	G302.00
Acute myocardial infarction	G30..00
Acute myocardial infarction NOS	G30z.00
Acute non-ST segment elevation myocardial infarction	G307100
Attack - heart	G30..11
Coronary thrombosis	G30..12
Heart attack	G30..14
Inferior myocardial infarction NOS	G308.00
MI - acute myocardial infarction	G30..15
Other specified anterior myocardial infarction	G301.00
Posterior myocardial infarction NOS	G304.00
Silent myocardial infarction	G30..17
Subsequent myocardial infarction	G35..00

1.2. Coronary Heart Diseases (CHD)

Description	Code
Acute coronary insufficiency	G31y000
Acute inferoposterior infarction	G303.00
Angina at rest	G311200
Angina on effort	G33z300
Angina pectoris	G33..00
Angina pectoris NOS	G33zz00
Anterior myocardial infarction NOS	G301z00
Arteriosclerotic heart disease	G3...11
Asymptomatic coronary heart disease	G34z000
Atherosclerotic cardiovascular disease	G342.00
Atherosclerotic heart disease	G3...12
Chronic myocardial ischaemia	G34y100
Coronary artery disease	G340.12
Coronary artery spasm	G332.00
Coronary atherosclerosis	G340.00
Crescendo angina	G311.11
Double coronary vessel disease	G340100
Dressler's syndrome	G310.11
IHD - Ischaemic heart disease	G3...13
Ischaemic cardiomyopathy	G343.00
Ischaemic chest pain	G33z400
Ischaemic heart disease	G3...00
Ischaemic heart disease NOS	G3z..00
Lateral myocardial infarction NOS	G305.00
Mural thrombosis	G30A.00
New onset angina	G33z600
Old myocardial infarction	G32..00
Other acute and subacute ischaemic heart disease	G31..00
Other chronic ischaemic heart disease	G34..00
Other specified ischaemic heart disease	G3y..00
Prinzmetal's angina	G331.00
Single coronary vessel disease	G340000
Stable angina	G33z700
Triple vessel disease of the heart	G340.11
Unstable angina	G311.13
Worsening angina	G311400

1.3. Cerebrovascular Accident (Stroke)

Description	Code
Amaurosis fugax	F423600
Brain stem stroke syndrome	G663.00
CVA - Cerebrovascular accident unspecified	G66..13
CVA - cerebral artery occlusion	G64..11
CVA - cerebrovascular accid due to intracerebral haemorrhage	G61..11
CVA unspecified	G66..11
Carotid artery occlusion	G631.00
Carotid artery stenosis	G634.00
Cerebellar haemorrhage	G613.00
Cerebellar infarction	G64z.12
Cerebral aneurysm, nonruptured	G673.00
Cerebral arterial occlusion	G64..00
Cerebral embolism	G641.00
Cerebral infarct due to thrombosis of precerebral arteries	G63y000
Cerebral infarction NOS	G64z.00
Cerebral infarction due to embolism of cerebral arteries	G641000
Cerebral infarction due to embolism of precerebral arteries	G63y100
Cerebral infarction due to thrombosis of cerebral arteries	G640000
Cerebral thrombosis	G640.00
Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs	G6X..00
Cerebrovascular disease	G6...00
Cerebrovascular disease NOS	G6z..00
Chronic cerebral ischaemia	G671100
Drop attack	G65..11
Extradural haemorrhage - nontraumatic	G620.00
Hypertensive encephalopathy	G672.00
Infarction - cerebral	G64..12
Infarction - precerebral	G63..11
Infarction of basal ganglia	G64z400
Intracerebral haemorrhage	G61..00
Intracerebral haemorrhage NOS	G61z.00
Intracerebral haemorrhage, intraventricular	G617.00
Left sided CVA	G667.00
Left sided cerebral infarction	G64z200
Middle cerebral artery syndrome	G660.00
Other transient cerebral ischaemia	G65y.00
Pontine haemorrhage	G614.00
Posterior cerebral artery syndrome	G662.00
Pure motor lacunar syndrome	G665.00
Right sided CVA	G668.00
Right sided cerebral infarction	G64z300
Stenosis, carotid artery	G631.11
Stroke and cerebrovascular accident unspecified	G66..00

Description	Code
Stroke due to cerebral arterial occlusion	G64..13
Stroke due to intracerebral haemorrhage	G61..12
Stroke unspecified	G66..12
Subclavian steal syndrome	G652.00
Subdural haematoma - nontraumatic	G622.00
Subdural haemorrhage - nontraumatic	G621.00
Subdural haemorrhage NOS	G623.00
Transient cerebral ischaemia	G65..00
Transient cerebral ischaemia NOS	G65z.00
Transient global amnesia	G655.00
Transient ischaemic attack	G65..12
Vertebrobasilar insufficiency	G656.00

1.4. Heart Failure

Description	Code
Acute congestive heart failure	G580000
Acute heart failure	G582.00
Acute left ventricular failure	G581000
Biventricular failure	G580.14
Cardiac failure	G58..11
Cardiac failure NOS	G58z.12
Chronic congestive heart failure	G580100
Congestive cardiac failure	G580.11
Congestive heart failure	G580.00
Decompensated cardiac failure	G580200
H/O: aortic aneurysm	14AE.00
H/O: heart failure	14A6.00
Heart failure	G58..00
Heart failure NOS	G58z.00
Heart failure confirmed	1O1..00
Impaired left ventricular function	G581.13
Left ventricular diastolic dysfunction	G5yyA00
Left ventricular failure	G581.00
Left ventricular systolic dysfunction	G5yy900
New York Heart Association classification - class I	662f.00
New York Heart Association classification - class II	662g.00
New York Heart Association classification - class III	662h.00
New York Heart Association classification - class IV	662i.00
Pulmonary oedema - acute	G581.12
Right heart failure	G580.12
Right ventricular failure	G580.13

1.5. Hypoglycaemia

Description	Code
Drug-induced hypoglycaemia without coma	C11y100
Frequency of GP or paramedic treated hypoglycaemia	66A7100
Frequency of hospital treated hypoglycaemia	66A7000
Hypoglycaemia unspecified	C112.00
Hypoglycaemia unspecified NOS	C112z00
Hypoglycaemic attack requiring 3rd party assistance	66Ad.00
Hypoglycaemic coma	C110.00
Hypoglycaemic coma NOS	C110z00
Insulin dependent diabetes mellitus with hypoglycaemic coma	C108E00
Loss of hypoglycaemic warning	66AJ200
Other hypoglycaemia	C116.00
Post-prandial hypoglycaemia	C116000
Reactive hypoglycaemia NOS	C112000
Type 1 diabetes mellitus with hypoglycaemic coma	C10EE00
Type 2 diabetes mellitus with hypoglycaemic coma	C10FD00
[X]Other hypoglycaemia	Cyu3000

1.6. Peripheral Arterial Disease (PAD)

Description	Code
AAA - Abdominal aortic aneurysm without mention of rupture	G714.11
Abdominal aortic aneurysm without mention of rupture	G714.00
Aortic aneurysm	G71..00
Aortic aneurysm repair	7A14.11
Aortic atherosclerosis	G700.00
Arterial embolism and thrombosis	G74..00
Arterial leg ulcer	M271300
Axillo-unifemoral PTFE bypass graft	7A10300
Bypass femoral artery by fem/pop art anast c vein graft NEC	7A48200
Cardiac failure therapy	8B29.00
Chronic peripheral venous hypertension	G8y3.00
Claudication	G73z011
Diabetic peripheral angiopathy	G73y000
Dissecting aortic aneurysm	G710.00
Embolism and thrombosis of the axillary artery	G74y700
Embolism and thrombosis of the femoral artery	G742400
Embolism and thrombosis of the iliac artery unspecified	G74y300
Embolism and thrombosis of the subclavian artery	G74y500
Extremity artery atheroma	G702.00
Femoro-femoral prosthetic cross over graft	7A48E00
Gangrene of finger	G732200
Gangrene of foot	G732100

Description	Code
Gangrene of toe	G732000
Intermittent claudication	G73z000
Ischaemia of legs	G73..12
Ischaemic leg ulcer	M271.12
Ischaemic ulcer diabetic foot	M271000
Mixed venous and arterial leg ulcer	M271400
Other bypass of common femoral artery	7A48.12
Other bypass of femoral artery	7A48.14
Other bypass of femoral artery or popliteal artery	7A48.00
Other bypass of femoral artery or popliteal artery NOS	7A48z00
Other bypass of femoral artery or popliteal artery OS	7A48y00
Other bypass of superficial femoral artery	7A48.16
Other emergency bypass of femoral artery	7A47.16
Other emergency bypass of popliteal artery	7A47.14
Other peripheral vascular disease	G73..00
Other specified peripheral vascular disease NOS	G73yz00
Percutaneous transluminal balloon angioplasty of aorta	7A1A000
Peripheral gangrene	G732.00
Peripheral ischaemia	G73..13
Peripheral ischaemic vascular disease	G73..11
Peripheral vascular disease NOS	G73z.00
Peripheral vascular disease monitoring	662U.00
Raynaud's disease	G730000
Raynaud's phenomenon	G730100
Raynaud's syndrome	G730.00
Ruptured abdominal aortic aneurysm	G713.11
Ruptured aortic aneurysm NOS	G715.00
Saddle embolus	G740.14
Thoracic aortic aneurysm which has ruptured	G711.00
Thoracic aortic aneurysm without mention of rupture	G712.00
Thrombosis - arterial	G74..12

1.7. Mortality

Description	Code
Death grant	13Q4.00
h/o: perinatal death	15A8.11
death	22J..12
o/e - dead - unattended death	22J3.00
o/e - dead - sudden death	22J4.00
o/e - dead - suspicious death	22J6.00
death - cause unknown	22J8.00
perioperative death	22J9.00
postoperative death	22JA.00
o/e - death rattle	2329.00
o/e - respiratory death	236..12
imminent expected death	2JL..00
preoperative anaesthetic death	7L1M000
death in hospital	8HG..11
fp22-death	9234.00
death administration	94...00
death certificate form med a	941..00
certificate - death	941..11
death cert. med a due	9411.00
death cert. med a signed	9412.00
death cert. med a nos	941Z.00
hospital death discharge notif	945..00
death notif. from hospital	9451.00
await hosp death disch letter	9452.00
receiv hosp death disch letter	9453.00
ask for hosp death disch lett.	9454.00
hospital death disch. nos	945Z.00
death notif.- non.hosp source	946..00
cause of death clarif. sd17/18	947..00
sd17 - cause of death clarif	947..11
sd18 - cause of death clarif	947..12
sd17/18 received-death clarif.	9471.00
sd17/18 cause of death nos	947Z.00
place of death	949..14
unexpected death-coroner told	94A..00
cause of death	94B..00
condition fatal-cause of death	94B..11
hospital notified of death	94D..00
date of death	94E..00
unexpected death	94F..00
verification of expected death	94G..00
death administration nos	94Z..00
sudden cardiac death, so described	G575100
death obst cse occur more 42 day less than one yr aft deliv	L39A.00
death from sequelae of direct obstetric causes	L39B.00
obstetric death of unspecified cause	L39X.00

[x]obstetric death of unspecified cause	Lyu7500
[d]instantaneous death	R211.00
[d]death less than 24 hours from onset of illness	R212.00
[d]death, not instantaneous cause unknown	R212000
[d]death less than 24 hours from onset of illness nos	R212z00
[d]unattended death	R213.00
[d]found after death, unknown cause of death	R213000
[d]unattended death nos	R213z00
[d]sudden death, cause unknown nos	R21z.00
[x]other sudden death, cause unknown	RyuC100
[x]other ill-defined and unspecified causes of death	RyuC200
[v]issue of death certificate	ZV68011

1.8. Ethical Approval

NHS
National Research Ethics Service
South East Research Ethics Committee
South East Coast Strategic Health Authority
Preston Hall
Aylesford
Kent
ME20 7NJ

Telephone: 01622 713097
Facsimile: 01622 885966

06 March 2008

Mrs Alison Bourke
Managing Director
EPIC
Regeneration House
York Way
London
N1 0UZ

Dear Mrs Bourke

Full title of study: **The Health Improvement network (Data Collection Scheme)**
REC reference number: **07/H1102/103**

Thank you for your letter of 13 February 2008, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair and named members who were present at the meeting.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

In point (a) of our letter dated 18 October 2007, we said that the Committee would draw up a set of conditions. These are as follows:

The Committee need assurance that the details will either be incorporated into, presumably, the contract they have between them, or some other acknowledgement that the researchers will comply with the requirements. If sent by letter, a signed copy of the letter would be sufficient. If sent by email, a definite reply, printed out and kept, would be needed or something like that. The same applies to researchers outside the UK (as per your point 5 bullet point 3).

Ethical review of research sites

The Committee has designated this study as exempt from site-specific assessment (SSA. There is no requirement for [other] Local Research Ethics Committees to be informed or for site-specific assessment to be carried out at each site.

This Research Ethics Committee is an advisory committee to South East Coast Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application		19 September 2007
Investigator CV		
Protocol		
Advertisement	Poster content for GP surgeries	
Response to Request for Further Information		13 February 2008
SRC ← Protocol review checklist	1	01 February 2008
Letter to Inps		31 January 2008
Practice visit checklist	1	01 February 2008
Suggested wording for practice patient leaflet	2	01 February 2008
Practice poster	2	01 February 2008
Research agreement for supply of THIN data subsets		
sub licence agreement		
Data audit procedures		
SRC ← Scientific review of research		

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from http://www.rdforum.nhs.uk/rdform.htm.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

Here you will find links to the following

a) Providing feedback. You are invited to give your view of the service that you have received from the National Research Ethics Service on the application procedure. If you wish to make your views known please use the feedback form available on the website.

b) Progress Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
c) Safety Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
d) Amendments. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
e) End of Study/Project. Please refer to the attached Standard conditions of approval by Research Ethics Committees.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nationalres.org.uk .

07/H1102/103	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

pp **Dr L. Alan Ruben**
Chair

Email: nicki.watts@nhs.net

Enclosures: *Standard approval conditions*

Copy to:

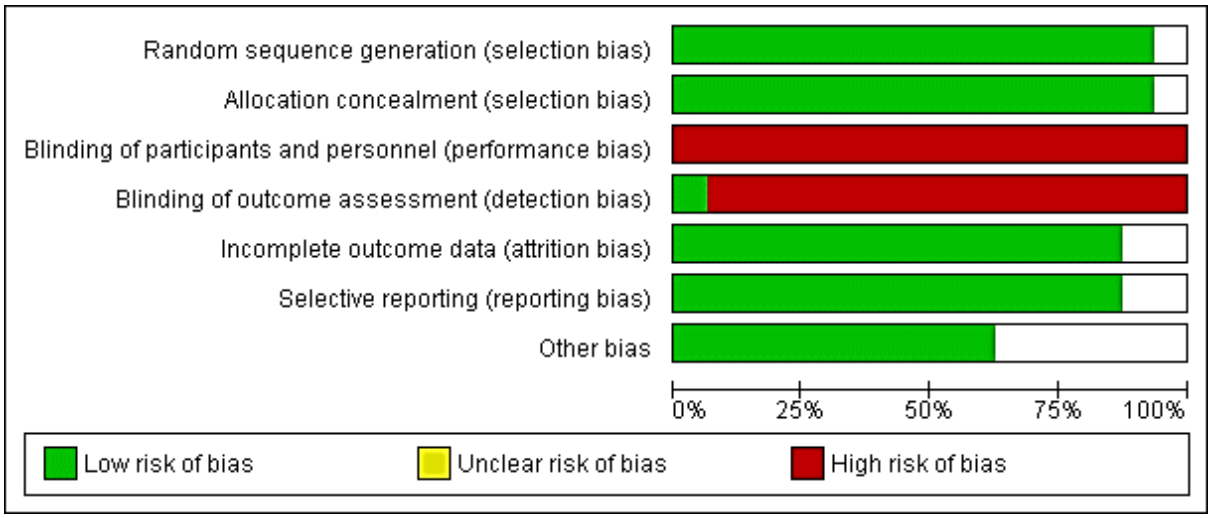
Appendix 2 (Chapter 3 – Systematic Review and Meta-analysis)

2.1. Search Terms

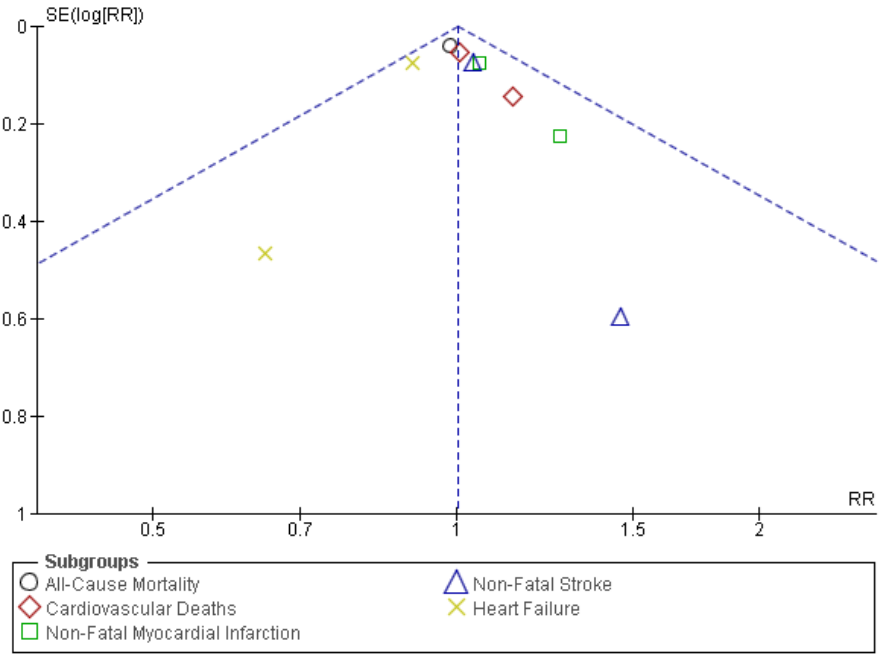
These databases were electronically search using the using keywords, mesh headlines and terms as

“Diabetes Mellitus, Type 2/complications"[Mesh] OR "Diabetes Mellitus, Type 2/drug therapy"[Mesh] AND "Diabetes Mellitus, Type 2/epidemiology"[Mesh] OR "Diabetes Mellitus, Type 2/mortality"[Mesh] OR "Diabetes Mellitus, Type 2/prevention and control"[Mesh] OR "Diabetes Mellitus, Type 2/therapy"[Mesh] AND "insulin regime" OR "insulin schedule" OR insulin tim* OR "insulin itinerary" OR insulin us* OR insulin dose OR "insulin administration" OR insulin quantit* OR "insulin shot" OR "insulin measure" AND “cardiovascular disease" OR "heart disease" OR macrovascular OR cardio* OR "myocardial infarction" OR MI OR stroke OR cerebrovascular OR cerebro* OR "major adverse cardiovascular event" OR "major adverse coronary event" OR MACE OR "all-cause mortality" AND “Randomized Controlled Trials”.

2.2. Risk of Bias Graph



2.3. Funnel plot showing the risk of publication bias (Egger's test)



This funnel plot shows Egger's test of the risk of publication bias in the trials. As you can see, the outcomes (shown by the different shapes) are spread within all parts of the funnel showing that the risk of publication bias was low. If only significant results were published by the trials, part of the funnel would have been sparse or empty and the outcomes would appear to have mean relative risk closer to 1.0

Appendix 3 (Chapter 5 – Metabolic Profile and CV/Metabolic Outcomes)

3.1. Mean follow-up BMI and mean coefficients of change in BMI compared to the normal BMI category

	6 months		12 months		24 months		36 months		48 months		60 months	
BMI categories at baseline	Mean BMI (kg/m^2)	Coefff* (95%CI)	Mean BMI (kg/m^2)	Coefff* (95%CI)	Mean BMI (kg/m^2)	Coefff* (95%CI)	Mean BMI (kg/m^2)	Coefff* (95%CI)	Mean BMI (kg/m^2)	Coefff* (95%CI)	Mean BMI (kg/m^2)	Coefff* (95%CI)
Normal	22.7	ref	23.3	ref	25.3	ref	26.2	ref	26.8	ref	28.2	ref
Overweight	28.0	-0.52 (-0.65, -0.39)	28.3	-0.77 (-0.96, -0.59)	29.2	-1.93 (-2.28, -1.59)	29.6	-2.52 (-2.90, -2.14)	29.9	-2.95 (-3.35, -2.56)	30.5	-3.72 (-4.12, -3.31)
Obese Class I	32.6	-0.78 (-0.90, -0.65)	32.5	-1.38 (-1.56, -1.21)	32.4	-3.83 (-4.17, -3.50)	32.3	-4.88 (-5.25, -4.51)	32.2	-5.65 (-6.04, -5.27)	32.7	-6.59 (-6.99, -6.20)
Obese Class II	37.0	-1.03 (-1.17, -0.90)	36.8	-1.84 (-2.03, -1.65)	36.0	-4.94 (-5.30, -4.59)	35.7	-6.33 (-6.72, -5.93)	35.1	-7.66 (-8.07, -7.25)	35.2	-9.11 (-9.53, 8.69)
Obese Class III	43.7	-1.33 (-1.48, -1.18)	43.0	-2.64 (-2.85, -2.43)	41.1	-6.92 (-7.32, -6.52)	40.0	-9.03 (-9.47, -8.58)	38.5	-11.18 (-11.6, -10.7)	38.4	-12.89 (-13.4, -12.42)
		LRT p-value** <0.00001		LRT p-value 0.00001		LRT p-value <0.00001		LRT p-value <0.00001		LRT p-value <0.00001		LRT p-value <0.00001

*Abbreviations: BMI (body mass index) *Mean coefficient of change ion BMI compared to the normal BMI category **LRT (Likelihood Ratio Test) p-value showing the mean changes in BMI according to baseline BMI categories p-value for trend <0.0001 for each follow up timeline*

Appendix 4 (Chapter 6 – Insulin vs GLP-1RA)

4.1. Mean change in HbA1c

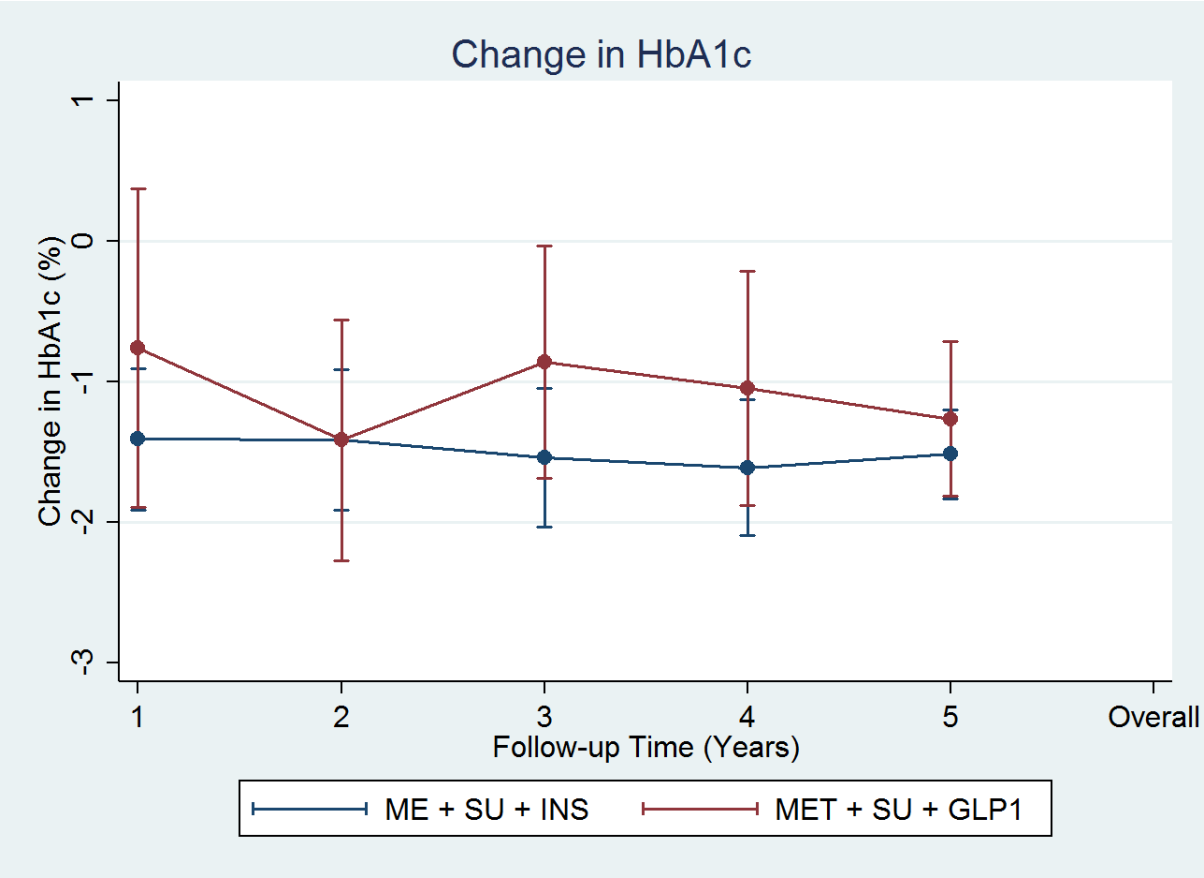


Figure 4.1. Mean Changes in HbA1c (p-value > 0.005 all through the study timeline)

This figure shows the trend in mean changes in HbA1c level (%) between Met+SU+INS vs Met+SU+GLP-1RA treatment groups in the incomplete dataset before multiple imputation. This sensitivity analysis was conducted to check the robustness of the multiple imputation done in the dataset.

When compared to Figure 6.3 (in the main text), one can see the robustness of the imputation as both graphs showed same pattern, measures of effects and significance