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# Incidence of Venous Thromboembolism Following Colorectal Surgery

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## Acknowledgements

This thesis is dedicated to Farah, my fiancée and now wife, and Anne and Geoff, my parents, who have always shown me unwavering love and support as well as believing in and pushing me to reach my full potential.

I would like to acknowledge and wholeheartedly thank my supervisors Mr David Humes and Dr Colin Crooks, without whose expert guidance I would not have been able to complete this work and who have helped develop me as an academic.

I would like to thank Mr Alfred Adiamah who convinced me to strive for a career in academia and undertake this PhD.

## Impact of the Coronavirus 2019 (COVID-19) Pandemic on this thesis

Between 01/04/2020 and 05/08/2020 I was re-deployed from my research role to work full time as a General Surgery Senior House Officer within Nottingham University Hospitals National Health Service (NHS) Trust which significantly impacted on my research time. This comprised working a significant number of on call shifts during the day- and night-time. Due to my clinical duties my research time became significantly limited to my off days from clinical work. I worked from home whenever I could, however there were numerous difficulties using statistical software packages whilst using a small laptop that slowed my progress, with my research work essentially put on hold.

During the Coronavirus 2019 (COVID-19) Pandemic both my partner's maternal grandparents, who helped raise her as a child, suddenly died during the international lockdown. Due to the regulations at the time she was unable to return home, see her grandparents' bodies or attend their funerals. This led to an extremely stressful period with a lasting depressive/bereavement episode in which I had to care for my partner.

The global consequences of the COVID-19 pandemic has meant it has taken longer for specific institutions to reply regarding permissions, ethics approvals and access to data for me to continue my research work. Specifically, awaiting confirmation for the acceptance of research proposal amendments to access data from the Medicines and

Healthcare products Regulatory Agency and National Institute for Health Research that were crucial to my thesis.

I have where possible attended all mandatory translational skills courses and events required of a thesis virtually or passed/completed replacement online learning modules. This is despite not being able to attend mandatory Doctorate courses within my first year of study as I transferred from a Masters by Research (MRes) course only at the end of my first year of study. During the lockdown periods I had discussions with my supervisors about how best to proceed and what I could to maximise my time.

## Abstract

Colectomy is the second most common major abdominal operation globally with colorectal cancer (CRC) being the most common indication. Venous thromboembolism (VTE), comprising deep vein thrombosis and pulmonary embolism, is a potentially fatal yet preventable postoperative complication of which colectomy has one of the highest risks of any abdominal operation. However, perioperative care over the last two decades has changed with an increase in minimally invasive surgery and focus on VTE prevention. This has led to the introduction of international guidance advocating pharmacological VTE prophylaxis for a minimum of inpatient stay or 7-days following benign colectomy that extends to 4-weeks for those with CRC. Therefore, the aim of this thesis was to quantify changes in incidence rates of VTE following colectomy in relation to international changes in perioperative care and so help guide future improvements in VTE prevention.

The first study in this thesis (Chapter 2) is a systematic review and meta-analysis on the incidence and variation of VTE following CRC resection. Following guidelines on meta-analysis reporting, Medline and Embase databases were searched from database inception to August 2019 including 3 other registered medical databases. Only patients aged ≥ 18 years-olds post CRC resection were included and selected studies comprised randomised controlled trials and population-based database/registry cohorts. Of 6,441 studies 18 were available for meta-analysis reporting on 539,390 patients. Pooled 30- and 90-day

incidence rates of VTE following resection were 195 (95% CI 148–256, $I^2$ 99.1%) and 91 (95% CI 56–146, $I^2$ 99.2%) per 1,000 person-years respectively. When separated by United Nations Geoscheme Areas differences in the incidence of postoperative VTE were observed with 30- and 90-days pooled rates per 1,000 person-years of 284 (95% CI 238–339) and 121 (95% CI 82–179) in the Americas and 71 (95% CI 60–84) and 57 (95% CI 47–69) in Europe.

Chapters 3 and 4 are national cohort studies of colectomy patients between 2000 and 2019 using using linked primary (Clinical Practice Research Datalink) and secondary (Hospital Episode Statistics) care data.

Chapter 3 examines the changes in VTE rates over time from 2000 to 2019 following colorectal resection by admission type, surgical indication and operative technique. Reporting absolute incidence rates (IR) and adjusted incidence rate ratios (aIRR) using Poisson regression for the per year change in VTE risk within 30-days following colectomy. Of 183,791 colectomy patients, 1,337 (0.73%) developed 30-day postoperative VTE. Overall, VTE rates reduced over the 20-year study period following elective (relative risk reduction 31.25%, 95% CI 5.69%–49.88%) but not emergency surgery. Similarly, yearly changes in VTE risk reduced following minimally invasive resections (elective benign: aIRR 0.93, 95% CI 0.90–0.97, elective malignant: aIRR 0.94, 95%CI 0.91–0.98 and emergency benign: aIRR 0.96, 95% CI 0.92–1.00), but not following open resections. There was a per year VTE risk

increase following open emergency malignant resections (aIRR 1.02, 95% CI 1.00–1.04).

Chapter 4 examines in detail the duration and magnitude of post-discharge VTE during the period 2010 to 2019. Stratified by admission type and surgical indication, IRs per 1,000 person-years and aIRRs for post-discharge VTE were calculated for the first 4-weeks following resection and post-discharge VTE IRs for each postoperative week to 12-weeks post-op. Of 104,744 patients, 663 (0.63%) developed post-discharge VTE within 12-weeks after colectomy. Post-discharge VTE IRs for the first 4-weeks post-operation were low following elective resections (benign (20.66, 95% CI 13.73–31.08) and malignant (28.95, 95% CI 23.09–36.31)) and higher following emergency resections (benign (47.31, 95% CI 34.43–65.02) and malignant (107.18, 95% CI 78.62–146.12)). Compared to elective malignant resections, there was no difference in post-discharge VTE risk within the first 4-weeks following elective benign colectomy (aIRR 0.92, 95% CI 0.56–1.50). However, post-discharge VTE risks within 4-weeks following emergency resections were significantly greater for benign (aIRR 1.89, 95% CI 1.22–2.93) and malignant (aIRR 3.13, 95% CI 2.06–4.76) indications compared to elective malignant colectomy.

The final study (Chapter 5) in this thesis comprises two service evaluations examining the compliance of extended or 7-day postoperative VTE prophylaxis prescription on discharge following CRC resection, pre and post an educational intervention for junior doctors, and abdominal surgery respectively at a tertiary care centre within

England. Following CRC resection, of 80 pre- and 41 post-intervention patients eligible for inclusion there was an 11.43% absolute increase in VTE prophylaxis prescription compliance from 81.25% to 92.68% yet this was not significant (P = 0.0944). Overall, VTE risk assessment did not have a significant impact on extended VTE prophylaxis prescription at discharge. However, patients were significantly less likely to receive extended VTE prophylaxis prescription on discharge if extended VTE prophylaxis instruction was not accurately recorded in the postoperative note (Risk difference -26.75%, 95% CI -44.03%–-9.48%, P = 0.0269). Of 97 eligible benign abdominal surgery patients for 7-days postoperative VTE prophylaxis, none were prescribed appropriate continuing VTE prophylaxis at discharge or specifically had 7-days postoperative VTE prophylaxis recorded in the postoperative plan.

This thesis provides new evidence regarding the incidence of VTE following colectomy and how this has changed with advancements in perioperative care within Colorectal surgery over the last 20 years. It highlights the incidence of VTE following CRC resection is high and remains so more than 1-month after surgery with clear disparities between global regions. It demonstrates VTE risk has reduced following minimally invasive surgery in the elective setting, but this reduction is not temporally related to international guidance with further efforts needed to implement advances in surgical care within emergency and/or open surgery to reduce VTE risk. In terms of post-discharge VTE, it shows rates are low in line with current VTE guidance following elective colectomies. However, emergency benign resections that

currently do not receive extended VTE prophylaxis have an approximately 2-fold greater post-discharge VTE compared to elective malignant resections, suggesting emergency benign colectomy patients, particularly those undergoing inflammatory bowel disease resection, may benefit from extended VTE prophylaxis. Emergency malignant colectomies have the greatest risk of post-discharge VTE despite receiving extended VTE prophylaxis, indicating further perioperative measures are needed to reduce the post-discharge VTE risk in this group. It shows that current compliance with extended VTE prophylaxis prescription at discharge for CRC resectional patients is high yet requires further improvements to reach national targets. Although this is not the case for the minimum 7-days postoperative VTE prophylaxis following benign abdominal operations. This suggests further educational initiatives and performance markers, such as the measurement of detailed documentation of VTE prophylaxis duration within postoperative records, are needed to improve appropriate post-discharge VTE prophylaxis prescription following malignant and benign operations.

## Presentations arising from doctoral studies

- Risk of Postoperative Venous Thromboembolism After Surgery for Colorectal Malignancy: A Systematic Review and Meta-analysis
    1. European Society of Surgical Oncology (ESSO) [Virtual], Prague, Czech Republic, October 23 to 24, 2020. (Poster presentation)[1]
    2. Sue Watson Postgraduate Oral Presentation Prize Event [Virtual], Nottingham, United Kingdom, March 24, 2021. (Oral presentation)
    3. East Midlands Chapter of the Association of Surgeons of Great Britain and Ireland (ASGBI) Journal Club [Virtual], Nottingham, United Kingdom, August 25, 2021. (Oral presentation)

- Time Trends in the Incidence Rates of Venous Thromboembolism Following Colorectal Resection
    1. European Society of Coloproctology (ESCP) 2021 Virtual 16th Scientific and Annual Conference [Virtual], September 22 to 24, 2021. (Poster presentation)[2]
    2. Tripartite Colorectal Meeting (TCM) 2022 [Virtual], Auckland, New Zealand, February 21 to 24, 2022. (Poster presentation)[3]

- The Duration and Magnitude of Post-Discharge Venous Thromboembolism Following Colectomy
    1. Tripartite Colorectal Meeting (TCM) 2022 [Virtual], Auckland, New Zealand, February 21 to 24, 2022. (Poster presentation)[4]

- Improving extended venous thromboembolism prophylaxis prescription compliance at discharge for colorectal cancer resection patients
    1. Association of Surgeons of Great Britain and Ireland (ASGBI) Congress [Virtual], London, United Kingdom, May 4 to 8, 2021. (Poster presentation)[5]

## Publications arising from doctoral studies

- Lewis-Lloyd CA, Pettitt EM, Adiamah A, Crooks CJ, Humes DJ. Risk of Postoperative Venous Thromboembolism After Surgery for Colorectal Malignancy: A Systematic Review and Meta-analysis. *Dis Colon Rectum*. 2021 Apr 1;64(4):484-496. DOI: 10.1097/DCR.0000000000001946.[6]

- Lewis-Lloyd CA, Crooks CJ, West J, Peacock O, Humes DJ. Time Trends in the Incidence Rates of Venous Thromboembolism Following Colorectal Resection by Indication and Operative Technique. *Colorectal Dis*. 2022 Nov;24(11):1405-1415. DOI: 10.1111/codi.16233.[7]

- Lewis-Lloyd CA, Humes DJ, West J, Peacock O, Crooks CJ. The Duration and Magnitude of Post-Discharge Venous Thromboembolism Following Colectomy. *Ann Surg*. 2022 Sep 1;276(3):e177-e184. DOI: 10.1097/SLA.0000000000005563.[8]

## Glossary of Terms

List of glossary terms in the text not explained within table or figure legends:

ACCP, American College of Chest Physicians

ACPGBI, Association of Coloproctology of Great Britain and Ireland

ACS-NSQIP, American College of Surgeons National Surgical Quality Improvement Program

aIRR, Adjusted incidence rate ratio

BNF, British National Formulary

CD, Crohn's disease

COVID-19, Coronavirus 2019

CPRD, Clinical Practice Research Datalink

CQUIN, Commissioning for Quality and Innovation

CRC, Colorectal cancer

CT, Computed tomography

CTPA, Computed tomography pulmonary angiography

DVT, Deep vein thrombosis

ENDORSE, Epidemiological International Day for the Evaluation of Patients at risk of Venous Thromboembolism in the Acute Hospital Care Setting

ERAS, Enhanced recovery after surgery

eVTE, Electronic VTE risk assessment

HES, Hospital Episode Statistics

HPB, Hepatopancreaticobiliary

ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision

IBD, Inflammatory bowel disease

IQR, Interquartile range

IR, Absolute incidence rate

ISAC, Independent Scientific Advisory Committee

LDUH, Low dose unfractionated heparin

LMWH, Low molecular weight heparin

MOOSE, Meta-analyses Of Observational Studies in Epidemiology

NBOCA, National Bowel Cancer Audit

NELA, National Emergency Laparotomy Audit

NHS, National Health Service

NICE, National Institute of Health and Care Excellence

ONS, Office for National Statistics

OPCS-4, Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures version 4

OR, unadjusted odds ratio

PE, Pulmonary embolism

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QALY, Quality-adjusted life-year

RCT, Randomised Controlled Trial

SCOAP, Washington State Surgical Care and Outcomes Assessment Program

STROBE, Strengthening the Reporting of Observational Studies in Epidemiology

UK, United Kingdom

UN, United Nations

US/USA, United States of America

VTE, Venous thromboembolism

WHO, World Health Organisation

$\chi 2$, Chi squared

95% CI, 95% confidence interval

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# Chapter 1: Introduction

## Section 1.1 Background

### 1.1.1 Colorectal resection and cancer

Colorectal resection or colectomy refers to the total or partial surgical removal of the large intestines consisting of the caecum to ascending, transverse, descending and sigmoid colon and rectum. This may be for benign disease processes including diverticulitis or inflammatory bowel disease (IBD), consisting predominately of Crohn's (CD) and Ulcerative colitis (UC), or malignancies such as colorectal cancer (CRC). Over the last few decades there have been advances in operative techniques within Colorectal surgery including the adoption of minimally invasive resection such as laparoscopic colectomy and more recently robotic resections.[9-13] Colorectal resection is the second most common inpatient and major abdominal operation globally forming a substantial proportion of abdominal resectional surgery.[14,15] In the United States of America (US) alone, 2.5% of all surgical procedures are colectomies with approximately 320,000 performed each year.[16,17] Within Colorectal surgery, CRC can be treated definitively with surgical resection and forms a significant proportion of oncological surgical resections globally. CRC is the second most common cause of mortality from malignant disease in the world and responsible for around 21,700 deaths per year in the United Kingdom (UK).[18,19] Approximately 155,000 and 52,000 new diagnoses of CRC are made each year in the US and UK respectively, with around 30,000 CRC surgeries performed annually in

England and Wales, of which 18,000 are major resections. Figures that have increased over the last 10 years.[18,20,21]

### 1.1.2 Venous thromboembolism and colectomy

Venous thromboembolism (VTE) is a common vascular disease, comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), that has a significant effect on patient morbidity and mortality.[22] VTE is a potentially avoidable yet costly and possibly fatal major postoperative complication of which colorectal resections have some of the highest rates of postoperative VTE of all abdominal operations.[23,24] This increased VTE risk in Colorectal surgery is believed to be associated with open or emergency surgery, pelvic dissection and positioning during surgery, steroid use, metastatic disease, increasing age, obesity and co-morbidities, postoperative complications such as surgical site infection and Caucasian ethnicity.[25-27] Despite advances in healthcare and better diagnostic tools, large cohort studies have shown the incidence rates of VTE have continued to increase, suggesting further improvements and strategies in VTE prevention are needed.[28] Approximately 600,000 to 900,000 cases of VTE occur in the US per year with a current annual estimated cost ranging between $10 billion and $27.3 billion in the US and £640 million in the UK which is rising with the number of patients developing VTE expected to double in the US alone within 30 years.[29-33]

The main intervention in the prevention of VTE following surgery is in the form of VTE prophylaxis. This predominantly comes in either mechanical; graduated compression stockings or intermittent pneumatic compression, or pharmacological; low molecular weight heparin (LMWH), low dose unfractionated heparin (LDUH) or fondaparinux, forms.[34,35] The effectiveness of mechanical VTE prophylaxis following general surgical procedures has been extensively researched with systematic reviews demonstrating a reduction in VTE risk.[36,37] The ENOXACAN study initially showed that both LMWH and LDUH are equally safe and effective at preventing postoperative VTE following elective abdominal or pelvic cancer surgery.[38] Since then several studies, specifically involving patients undergoing colectomy have examined the type and effect of pharmacological VTE prophylaxis on postoperative VTE risk.[39-44] The Cochrane systematic review of this subject in Colorectal surgery found both mechanical and pharmacological VTE prophylaxis significantly reduced the risk of VTE compared to no treatment or placebo, found no inferiority between LMWH and LDUH and that a combination of mechanical and pharmacological prophylaxis was more effective than either treatment modality alone.[23,45] However, the review did not distinguish studies between benign and malignant cohorts, provide an overall rate of VTE and included studies only between 1974 and 2001 with no patients recruited operated on within the 21st Century.

VTE is considered so important that in 2010 it was made a Commissioning for Quality and Innovation (CQUIN) target within the UK

and is a performance measure also in the US and Australia with a focus on appropriate prophylaxis and risk assessment.[46,47] Both the American College of Chest Physicians (ACCP) in 2008[22] and National Institute of Health and Care Excellence (NICE) in 2010[48] have published landmark guidance on the management and prevention of postoperative VTE, updated in 2012 and 2018 respectively, and adopted internationally.[34,49,50] This was in response to high quality studies and several Cochrane systematic reviews investigating the effects of postoperative VTE prophylaxis.[23,45,51-53] The risk assessment stratification model for developing postoperative VTE used within these guidelines was formed from an amalgamation of two previously validated scoring systems, the Caprini and Rogers scores.[54,55] These scores range from low/very low to high risk of postoperative VTE and correspond to a level of VTE prophylaxis recommended from early ambulation, to mechanical or pharmacological up to combined prophylaxis inpatient regimens.[50] The guidance strongly recommends use of combined mechanical, in the form of anti-embolism graduated compression stockings or intermittent pneumatic compression, and pharmacological VTE prophylaxis, either as LDUH, LMWH or fondaparinux sodium, for all at risk abdominal surgical patients.[23,45] Specifically, pharmacological VTE prophylaxis should be continued for at least 7-days post gastrointestinal resection and extended for 28-days post-surgery for malignant, including CRC, resections.[34] The NICE guidance specifically recommended research be undertaken using routinely collected health care data to further understand the risk of

VTE in and around the time of surgery which this thesis aims to undertake.

### 1.1.3 Colorectal cancer, surgery and venous thromboembolism

It has long been established that cancer increases the risk of VTE substantially with almost 20% of out of hospital VTE events occurring in this population and a VTE event associated with a cancer diagnosis indicates advanced neoplasia and poor prognosis.[56,57] VTE is not only the commonest preventable cause of 30-day mortality in abdominal and pelvic resections in cancer patients,[58-60] but those with malignancy have at least a doubled risk of DVT and more than tripled risk of fatal PE compared to patients undergoing the same operations for benign indications.[19,22,23,61,62]

There has been extensive research into the relationship between VTE and CRC. Patients are at high risk of developing VTE after the diagnosis of CRC whilst undergoing treatment, especially in the first 6-months or those receiving palliative chemotherapy, and this risk increases with disease severity and the number of patient medical co-morbidities.[63-65] Irrespective of surgery, CRC is itself an independent risk factor for VTE.[60,66,67] From a review looking at the incidence of VTE around Colorectal surgery the estimated incidence of VTE in patients with colorectal malignancy has been reported to range between 2.75%-8.9% and post Colorectal surgery 1.15%-2.47%.[68] However, the authors did not stratify data by surgical indication or follow-up length

with repetition of studies utilising the same database. There is even contemporary research, investigating the pathogenesis of cancer related VTE, suggesting CRC patients based on their genetics could potentially be selected as high or low-risk for VTE.[69]

Furthermore, research into the incidence and timing of symptomatic VTE post CRC surgery is of significant interest with a substantial proportion of surgical colorectal patients developing VTE post-discharge with studies quoting between a fifth and half their population who develop a VTE occurring in this period.[27,70-73]

However, the growing number of publications focusing on the incidence of postoperative VTE in patients with CRC report conflicting results, likely attributable to the difference in characteristics of the study populations used and the length of time frame follow-up period in which VTE events were measured. A few studies, not exclusively concerning CRC surgery, have suggested patients undergoing cancer surgery have an overall reduced risk of VTE compared to patients not undergoing surgery or who are currently receiving chemotherapy. This may be reflected by the cohort of patients not undergoing surgery potentially having more advanced pathology and co-morbidities preventing surgery as a treatment option that are themselves independent risk factors for the development of VTE.[74-76] Two studies specifically reporting on the incidence of VTE and CRC are evidence of this, both finding a decrease in the risk of VTE postoperatively compared to the comparison group.[64,65] These two population-based studies used comparison cohorts of patients not undergoing surgery

with advanced metastatic disease and or comorbidity and did not report on incidence by admission type. The effect of advancement in disease stage on risk of postoperative VTE is another question entirely with studies focusing on high risk groups receiving chemotherapy or patients with stage III and IV CRCs.[77,78] In contrast, there are studies that have shown abdominal and cancer surgery to increase the risk of VTE following an operation with one study suggesting women undergoing gastrointestinal cancer surgery having an increased relative risk compared to those not having surgery with the greatest risk within 6-weeks after surgery.[79,80] Unfortunately, the study does not stratify by indication (benign/malignant) or timing (elective/emergency) of surgery. The incidence of VTE after Colorectal surgery also varies depending on resection site with some studies[43,81,82] reporting higher incidence rates in colon as compared to rectal surgery and vice versa.[83]

Another factor that may affect the disparity in incidence of VTE post CRC surgery is the length of follow-up of the sample population used in each study. Studies utilising the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) and National Inpatient Sample databases, or those modelled upon their design, are limited in the period of patient follow up and outcomes, 30-days and inpatient hospitalisation respectively. For example, Davenport et al. report that post colorectal resection for malignancy the overall rate of VTE is 2.0% (446 of 21,943) and decreases steadily from day 9 until 1-month after surgery with the majority of post-discharge VTE events occurring within 2 weeks from the discharge date.[84] However, studies

that have followed populations for longer have found the incidence of VTE after surgery remains high past the inpatient and 30-day postoperative period that the aforementioned databases only cover. In a study that looked at 90-day thromboembolic complications after Colorectal surgery using the Washington State Surgical Care and Outcomes Assessment Program (SCOAP) the incidence of postoperative VTE was 2.6% (103 of 3,917) for tumour stages between T1 and T4.[85] While another SCOAP paper reporting 90-day outcomes showed that 20% of post colorectal resection VTE events occurred after 30 days from the operation.[86] Walker et al. investigated variation in VTE risk and CRC stage and found the cumulative incidence of postoperative VTE continued to increase up to 180-days, with 52 of the 79 (65.8%) VTE events occurring in the 28-180 day period.[87] Studies have even found the incidence of VTE post CRC surgery remained high up to one year post procedure. Humes et al. used UK Hospital Episode Statistics (HES) and linked Clinical Practice Research Datalink (CPRD) data to show the rate of VTE following both malignant colorectal resections remained high between the first month and 1-month to 1-year following surgery. 28.56 from 61.83 and 54.42 from 120.98 per 1,000 person-years for elective and emergency cases respectively.[21] This high rate mirrored Alcalay et al. who reported a postoperative CRC VTE incidence of 40 per 1,000 person-years at 6-months follow-up. Additionally, these rates are similar to a recent study also using HES data that reported a cumulative VTE incidence of 2.6% (492 of 19,046) at 1-year (26.17 per 1,000 person-years) after CRC surgery where the

postoperative VTE incidence remained significantly high until 6-months after discharge.[65,88] Interestingly, a contemporary prospective study reporting on postoperative VTE in abdomino-pelvic oncology surgery went as far as stating the greatest incidence rate of VTE is from 1- to 3-months and 1- to 6-months and not the first 30 days after surgery, however confounders such as initiation of chemotherapy were considered as potential causes for the findings.[89]

There have been many systematic reviews and meta-analysis investigating the importance of postoperative VTE and different regimens of prophylaxis. A recent Cochrane review encompassing previous analyses[52,90] reported on extended VTE prophylaxis in abdominal and pelvic surgery (not specifically Colorectal or cancer surgery) and found strong evidence to suggest it reduced symptomatic DVTs without affecting bleeding complications.[51] Two very recent reviews published in 2019 have reported on the incidence of VTE after abdomino-pelvic oncology surgery. Both include large population database studies, however the comparison of so many different disciplines of cancer surgery combined with the openness of the research question reduces the specificity of their findings for oncological Colorectal surgery. More targeted questions regarding a specific type of cancer surgery would be a more suitable review choice to reduce the effect of study heterogeneity on a meta-analysis's validity. A recent meta-analysis has reported on the incidence of post rectal surgery VTE comparing numerous variables. The authors comment on the incidence of VTE after rectal cancer surgery and compare this to

benign disease, however they amalgamate different study designs including single centre retrospective case series with randomised controlled trials (RCT). This unfortunately affects the epidemiological strength of the analysis and overall interpretation of the results.[91] The incidence rate of VTE in patients diagnosed with CRC has been reported however attempts to define the incidence after CRC surgery from a systematic review have been minimal.[63]

### 1.1.4 Symptomatic and asymptomatic venous thromboembolism

In the literature there is a wide range in the incidence of postoperative VTE and this may be attributed to study methodology and significant differences in reporting symptomatic vs. asymptomatic VTE events. In one systematic review of 3 influential RCTs exploring the difference in VTE occurrence depending on the use of extended prophylaxis in abdominal surgery there were only 5 symptomatic events (0.63%, all in control groups) compared to 73 asymptomatic (9.2%, 73 of 793).[53] Such a low incidence may in part be attributed to the intervention arm receiving extended VTE prophylaxis however, as patients were assessed for VTE using venography, a number of patients diagnosed with an asymptomatic VTE might have gone on to develop symptoms yet were found prior to symptom onset. The Canadian Colorectal DVT Prophylaxis Trial comparing different forms of chemoprophylaxis after Colorectal surgery (35% of which were for cancer) similarly found a low incidence of symptomatic VTE (0.53%, 5 of 936) compared to asymptomatic events (8.9%, 83 of 936).[43] Patients were however only

investigated for a short time period whilst as an inpatient with venography performed on day 10 post-operation. In comparison prospectively collected data from ACS-NSQIP retrospective cohort studies report the 30-day incidence of VTE after CRC surgery to be roughly 2%.[92,93] This rate is consistent to that reported by a recent systematic review looking at VTE rates post abdominal and pelvic cancer surgery in their meta-analysis of retrospective studies (2.2%). In this review the authors show that not only is the incidence of VTE higher (9.6%) in prospective RCTs that mainly screened for asymptomatic VTE via venography, but the pooled incidence of symptomatic VTEs from prospective studies (1.3%) was close to that found from the larger retrospect cohort studies.[94] This suggests that large cohort databases are more predictive of the incidence of symptomatic VTE events and more meaningful in terms of defining clinical outcomes compared with predominantly asymptomatic VTE incidence reported by RCTs whose clinical significance is unclear. Similarly, an RCT reporting on the differences in VTE outcomes after CRC surgery depending on chemoprophylaxis used found the incidence of overall symptomatic VTE to be 0.79% and asymptomatic DVT 13.58% at day 12 post-operation with the symptomatic VTE rate increasing to 1.34% at 60 days after surgery (10 of 1271, 129 of 950 and 17 of 1271 respectively).[41]

Laparoscopy also appears to play a part in the disparity between symptomatic and asymptomatic VTE. A paper, on reviewing 4 studies, quoted the ultrasonographically identified DVT rate to be between 0

and 50% for laparoscopic CRC surgery.[95] Kimura et al. found an incidence of 18.3% postoperative VTE one week after surgery in Japanese patients undergoing laparoscopic gastrointestinal (half Colorectal) surgery with no symptomatic events [96]. This is consistent with Tokuhara et al. and Nakagawa et al. who investigated VTE post laparoscopic CRC surgery in Japanese populations reporting an asymptomatic DVT incidence of 2.5% at day 7 and 12.1% at day 28 respectively with both studies not detecting a single symptomatic VTE.[97,98] One observational study in a Chinese population showed that after laparoscopic resection of rectosigmoid cancer the incidence of asymptomatic calf vein DVT was relatively high (38%). The majority resolved without anticoagulation and there were no cases of symptomatic VTE, however the population size was small with patients pre-operatively screened for DVT who incidentally were found to have a VTE excluded. These patients may have been representative of those who could have developed a symptomatic VTE postoperatively who pre-operatively would have been considered low risk for developing VTE and so their exclusion brings in selection bias that could have accounted for the lack of symptomatic events recorded.[99] Such a low incidence of symptomatic VTE has led some authors to conclude the use of extended VTE prophylaxis in CRC surgical patients is not necessary, as its use appears to only significantly affect the incidence of asymptomatic VTE in the RCTs used as evidence for its use.[39,95,100-103] This and the lack of feasibility in powering a prospective study, has steered authors to suggest focusing on high risk subgroups of

interest.[104] However, this review failed to consult large cohort database results that have shown the maintained high rate of postoperative VTE after CRC surgery at least 1-month after discharge, and as most of the RCTs only followed-up patients for less than two weeks meaning symptomatic VTE detection may have been missed and those asymptomatic VTEs that were detected and treated may have progressed and developed to become symptomatic. Also, recent RCT data suggest patients with asymptomatic VTE have significantly higher all-cause mortality compared to those without VTE and in cancer patients morbidity and mortality outcomes are equivalent in those who develop either form of VTE with prolonged anticoagulant use found to reduce symptomatic VTE recurrence, highlighting prevention of any type of VTE is beneficial.[105-108]

### 1.1.5 Benign colorectal resectional surgery and venous thromboembolism

As well as in cancer surgery, colorectal resection has one of the highest reported rates of postoperative VTE among benign conditions.[109] IBD has an estimated UK prevalence of 261,000 persons of which between 25%-35% of UC and 70%-90% of CD patients will require a resection within their lifetime, highlighting colectomy for non-malignant disease forms a substantial proportion of elective and predominantly emergency Colorectal surgery.[110,111] The risk of VTE is especially high in IBD patients, with IBD itself a well-known independent risk factor for VTE particularly during acute disease exacerbations and postoperatively in

both inpatient and post-discharge periods.[70,75,112-115] The risk is even more elevated in those undergoing surgery for IBD with reports of comparable or greater VTE rates between those undergoing IBD and CRC surgery.[88,92,116,117] Of interest, data has shown patients with IBD that develop VTE have a significant increased risk of cancer, suggesting VTE may act as a marker of occult cancer in IBD patients. Furthermore, IBD patients having CRC resections have a higher postoperative VTE risk compared to those without IBD undergoing CRC surgery.[118,119] Within IBD, the risk of postoperative VTE differs between condition subtype, with the majority of studies suggesting increased risk in UC resections compared to those for CD, with high rates of VTE post-discharge.[67,120-125] By operative technique, minimally invasive colectomy for IBD appears to lower the risk of VTE compared to laparotomy.[26,83] Overall, recent systematic review data suggests the incidence of postoperative VTE following IBD colectomy ranges between 0.6%-8.9%[116] with 30-day large population data ranging between 2.1%-2.5%[67,120,121,125] with two outlying studies reporting VTE rates of 1.2%[126] and 6.6%.[92]

Contemporary population-based data suggests approximately 12,500 (40%) colectomies performed each year in England are for benign conditions.[20,127] Presently, there is growing interest surrounding the risk of postoperative VTE following benign colectomies and how this relates to current perioperative care strategies and guidance for malignant resections. Particularly as the prevalence of IBD and diverticulitis is increasing and the majority of emergency colectomies in England (65%)

are performed for benign indications, suggesting their risk of VTE is likely high.[128,129] Despite clear guidance on cancer resections, there is paucity of indication specific guidance relating to benign abdominal procedures and unlike CRC, there are no annual nationally audited reports on outcomes following colectomy for benign indications.[20] Opinion within the literature is varied. A number of studies have suggested the risk of VTE after benign, particularly laparoscopic, colectomy is so low that extended prophylaxis is not warranted[130] and the risks of VTE are 2- to 3-fold greater in patients having malignant compared to benign colectomy.[22,26,131] However, recent research into stratified postoperative VTE rates, specifically in IBD patients, suggests the contrary. There is evolving evidence that patients undergoing IBD colorectal resection and emergency benign colectomy have either the same or if not greater risk of developing postoperative VTE compared with those having malignant resections and this extends well into the post-discharge period.[21,85,116,120,125,132] This has led some authors to conclude there is a precedent for patients with benign conditions whose risk of VTE after colectomy mirrors that of malignant resections should equally receive extended VTE thromboprophylaxis.[88,120,133,134]

There is a growing trend in the uptake of prescribing extended VTE prophylaxis for IBD patients,[135] with recent international guidelines recommending its prescription for specific high risk patients supported by the European Crohn's and Colitis Organisation (ECCO), European Society of Coloproctology (ESCP) and American Society of Colon and Rectal Surgeons (ASCRS) clinical practice guidelines.[30,136,137] However,

these recommendations are weak and of low quality as so far no RCT exists that has assessed whether extended VTE prophylaxis is effective in reducing postoperative VTE in benign colorectal or IBD resectional patients.[30] Further to this, there are reports that current standard LMWH VTE prophylaxis prescription is sub-prophylactic in IBD compared to CRC surgical patients with a view to increasing current dosage regimens.[138] Despite the introduction of guidance surrounding extended VTE prophylaxis in IBD surgery, its cost-effectiveness remains debatable. Several contemporary studies report conflicting results, Trepanier et al. showed using a microsimulation model from ACS-NSQIP data that extended VTE prophylaxis for CRC and IBD colectomy patients, despite more expensive than standard management, was cost-effective with more quality-adjusted life-years (QALYs).[139] However, Leeds et al. concluded extended VTE prophylaxis for CD resectional patients was only cost-effective when the post-discharge VTE cumulative risk was ≥4.9%, yet they do not define their postoperative follow-up time.[140] Lee et al. report a compromise, suggesting extended VTE prophylaxis for IBD colectomy patients results in higher QALYs yet is only cost-effective for selected patients on a case-by-case basis.[141] Recent data suggest risk factors for postoperative VTE following IBD surgery are emergency admission, open resection, anaemia, poor nutrition/functional status, obesity, steroid use and increasing operative duration and age among others, although there is discrepancy among some risk factors.[67,70,121,123] With

patient-specific selection, those deemed at highest risk of postoperative VTE may benefit from extended VTE prophylaxis.

### 1.1.6 Minimally invasive colectomy and enhanced postoperative recovery and venous thromboembolism

With advances in surgical techniques and practice, minimally invasive colectomy, including both laparoscopic and robotic resections, has led to a major change in perioperative care since its inception in 1991 to the present day.[10-13,20] Current VTE risk assessment guidelines have been published by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and are built upon the 2012 ACCP guidance.[142] Ongoing debate surrounds the impact of laparoscopic surgery in the prevention of VTE and with this the importance of standard or extended postoperative VTE prophylaxis. The use of a laparoscopic approach within some general surgical procedures appears to lower the risk of VTE and in some cases negate the need for postoperative VTE prophylaxis, yet this is not recommended following colorectal resection.[142-146] Although with improving perioperative care there is an emerging argument for the selective use of extended VTE prophylaxis for patients undergoing minimally invasive colectomy.[104,130,147] However, an RCT specifically examining the effectiveness of extended vs standard VTE prophylaxis in patients undergoing laparoscopic CRC resection found extended VTE prophylaxis to significantly reduce VTE risk without increasing the risk of bleeding.[95]

Evidence within the literature suggests protracted operating times observed in laparoscopic surgery and the induction of iatrogenic pneumoperitoneum prolongs the activation of the coagulation system and increases venous stasis, heightening the risk of postoperative VTE compared with open surgery.[148-152] However, numerous population-based data overall suggest minimally invasive compared to open colectomy significantly halves the risk of VTE for both benign and malignant disease.[68] Reports from US and UK studies suggest the risk of VTE is doubled following open compared to laparoscopic colectomy and tripled in the emergency setting.[26,71,88,153,154] Buchberg et al., reported on 149,304 inpatients and found a significant reduction in overall VTE risk (1.44% vs. 0.83%) and in diverticulitis (0.88% vs. 0.47%) patients undergoing laparoscopic colectomy compared with those undergoing laparotomy.[83] Although, some contemporary international population-based studies report no difference in the risk of VTE between minimally invasive and open colectomy.[70,120,155] Alhassan et al. found in their study patients undergoing laparoscopic colorectal resection were significantly less likely to develop an inpatient VTE however were at increased risk of post-discharge VTE compared to those undergoing open resections.[92] Yet, all these studies do not stratify their data by admission type. Reasons for these differences may lie in the inherent selection biases potentially present within these cohort studies. There is evidence to suggest patients selected for laparoscopic surgery are likely to be younger and less co-morbid and therefore at reduced risk of postoperative VTE with a higher proportion

of minimally invasive surgery performed at high-volume/teaching centres, that have a presumed superior level of care.[156-159]

One brief review that only included data on RCTs between 2000-2009 reported on the incidence of CRC post-operation DVTs and found no statistically significant difference in the incidence of DVT between patients undergoing open or laparoscopic surgery.[160] This is similar to a previous meta-analysis of 3,058 patients comparing the same factors that also found no difference in the incidence of VTE or DVT post CRC surgery despite their combined odds ratio favouring laparoscopic surgery.[161] However, neither study reported the overall incidence of VTE after CRC surgery and/or as a rate in per person-years, included large prospective cohort databases within their study or separated papers based on rectal or colonic surgery. Cui et al. discerned from their study that larger RCTs are required in order to try and assess the difference between open and laparoscopic CRC postoperative VTE however powering such a study would be very difficult.[161]

Of intrigue is the effect of robotic operative techniques on VTE risks following colorectal resection. Robotic colectomy has become increasingly utilised over the last decade with mixed reports regarding improvements in postoperative complications, including VTE, compared to open or laparoscopic surgery. A population-based cohort study of Medicare beneficiaries found the risk of postoperative medical complications, including VTE, was significantly reduced in patients undergoing elective robotic colectomy compared to those undergoing laparotomy, yet found no difference in complications between robotic

and laparoscopy techniques.[9] This is mirrored by a meta-analysis of patients undergoing rectal surgery that despite favouring a reduction in postoperative VTE following robotic resection found no difference between the minimally invasive procedures.[91] It is clear there is a need to investigate VTE risk following robotic colectomy to reliably quantify any differences observed between minimally invasive techniques. Although, this would necessitate a database with significant numbers of robotic resections in order to provide definitive answers.[162]

Within the advances of perioperative care, coupled with minimally invasive surgery is the global increase in utilisation of enhanced recovery after surgery (ERAS) protocols.[136] European guidelines, initially published in 2005 and 2009, encompass elective colon and rectal surgery and have since spread internationally with ERAS Societies and guidelines in every continent.[163-165] The benefits of ERAS are apparent with the introduction of emergency Colorectal ERAS pathways.[166] Particularly the use of ERAS programmes within elective Colorectal surgery have shown reductions in perioperative complications and hospital length of stay whilst improving patient mobility.[167] This increased mobility and reduced hospital stay may have substantially reduced the VTE risk observed in elective Colorectal ERAS patients.[34,147] However, there is minimal published literature on the effect ERAS has on VTE risk post colectomy.[168]

### 1.1.7 Compliance with venous thromboembolism prophylaxis guidance

Despite evidence-based consensus guidelines in place since the mid-2000s, it appears not until 2010 that the use of extended prophylaxis for major abdominal and pelvic oncology surgery was more actively followed. The Epidemiological International Day for the Evaluation of Patients at risk of Venous Thromboembolism in the Acute Hospital Care Setting (ENDORSE) multinational cross-sectional survey that involved 32 countries worldwide in 2008 aimed to determine the proportion of at-risk patients for VTE who received appropriate prophylaxis. The study reported that between 2006-2007 among 19,842 (10% Colorectal) surgical patients, 17,084 of which were undergoing major including cancer surgery, classed as at risk for VTE, only 58.5% (62.3% major surgery) received thromboprophylaxis in line with the 2004 ACCP evidence-based guidelines[169,170] In addition to this there was a lower proportion of patients undergoing emergency surgery receiving adequate chemoprophylaxis (57.9%) as compared to those having elective operations (66.3%) despite evidence showing that this subgroup of surgical patients has the highest incidence of postoperative VTE.[21,153,169] Furthermore, there has been consistent reporting of compliance rates in prescribing in-hospital prophylaxis as low as 40-70%.[171] Specifically in Colorectal surgery, a UK national questionnaire survey in 2012 involving members of the Association of Coloproctology of Great Britain and Ireland (ACPGBI) on thromboprophylaxis after Colorectal surgery demonstrated a high degree of concordance with the

guidelines available at the time with over 95% of responders using a combination of mechanical and chemical prophylaxis. The authors state there was only a 27.4% uptake of national guidance with regards to postoperative extended VTE prophylaxis up to 4-6 weeks.[19] This is mirrored by a similar survey conducted in Australia involving members of the Colorectal Surgical Society of Australia and New Zealand where the majority of surgeons (98%) advocated inpatient pharmacological VTE prophylaxis, yet 45% did not routinely use post-discharge extended VTE prophylaxis.[172] However neither questionnaire clarified whether the participants were responding to questions specifically regarding CRC surgery for which extended prophylaxis guidelines applied, or non-malignant surgery for which they did not. In the US Merkow et al. reported that of Medicare beneficiaries studied between 2008-2009 undergoing CRC surgery only 1.5% received post-discharge VTE prophylaxis.[173] More recently, a single centre study found that initially 0% of CRC patients undergoing surgery were receiving extended prophylaxis as per guidelines and still only 31% of CRC patients post-surgery were receiving appropriate prophylaxis after surgeons received an educational intervention programme.[174] This is concerning considering delays or interruptions in postoperative pharmacological VTE prophylaxis prescription has been shown to increase the risk of VTE by 2- to 3-fold.[175] However, improvement is possible as shown by a small quality improvement report from a UK institution in 2012 who after auditing their CRC extended VTE prophylaxis post discharge rates and initially finding only 44% of

patients were receiving effective prophylaxis improved this to 100% after a 3rd audit cycle.[176] Interestingly a recent multi-institutional study in 2019 involving 36 hospitals evaluating the adherence to postoperative VTE chemoprophylaxis found that still up to 18% of patients undergoing colectomies were not receiving prophylaxis as per guidelines. However, patient refusal of or compliance with the chemoprophylaxis regimens was highlighted as a main reason for non-adherence.[177] This raises the questions that even if in-hospital and on discharge VTE prophylaxis is prescribed effectively for cancer surgery patients, what proportion of patients are taking chemoprophylaxis appropriately in line with guidance after discharge and does this influence post-discharge VTE rates in CRC surgery patients. However, postoperative VTE prophylaxis compliance may change with the use of direct oral anticoagulants as alternatives to subcutaneous prophylaxis preparations with new research demonstrating their effectiveness compared to LMWH in VTE prevention.[178-180]

### 1.1.8 Unanswered questions

So far, several systematic reviews and meta-analyses have superficially examined the risk of VTE following abdominal and or pelvic cancer surgery. Yet no specific meta-analysis exists regarding the postoperative incidence rate of VTE following CRC resection and how this varies globally.

Despite advancements in perioperative care, including minimally invasive surgery, enhanced recovery and increased awareness of VTE, no study has assessed if these internal changes have affected the risk of VTE over time and whether these improvements have contributed to postoperative VTE prevention.

Numerous cohort studies have examined the stratified risk of VTE following colorectal resection. However, no study has specifically reported the stratified weekly rates of post-discharge VTE following colectomy and what the differences in duration and magnitude of VTE risk means in terms of future VTE prevention.

Although there is growing literature from the US, only a few small audits have assessed the contemporary compliance of extended VTE prophylaxis following CRC resection within the UK in relation to NICE guidance. However, no study has examined the relationship of non-compliance with respect to the uptake of other VTE risk prevention methods such as VTE risk assessments or examined the compliance of the updated 7-days VTE prophylaxis guidance on patients undergoing benign surgery.

## Section 1.2 Aims and chapter outlines of thesis

1. Chapter 2: “Risk of Postoperative Venous Thromboembolism after Surgery for Colorectal Malignancy”. This systematic review and meta-analysis aims to characterise the rate of postoperative VTE in patients undergoing surgery for colorectal malignancy and highlight its variability globally.
2. Chapter 3: “Time Trends in the Incidence Rates of Venous Thromboembolism Following Colorectal Resection by Indication and Operative Technique”. This cohort study aims to quantify variations in VTE rates over the last 20 years in relation to international changes in perioperative care following colorectal resection.
3. Chapter 4: “The Duration and Magnitude of Post-Discharge Venous Thromboembolism Following Colectomy”. This cohort study aims to describe stratified weekly post-discharge VTE rates following colectomy in reference to previously defined post colectomy VTE rates used to justify extended VTE prophylaxis.
4. Chapter 5: “Compliance with Venous Thromboembolism Prophylaxis Guidance at Discharge Following Colorectal Cancer and Benign Abdominal Surgery”. This study aimed to assess contemporary compliance to national postoperative VTE prophylaxis guidance by examining VTE prophylaxis prescription on discharge for CRC and abdominal, including Colorectal, surgery patients at a UK tertiary centre.

# Chapter 2: Risk of Postoperative Venous Thromboembolism after Surgery for Colorectal Malignancy: A Systematic Review and Meta-Analysis

## Section 2.1 Introduction

CRC is the second highest cause of mortality from malignant disease in the world with a case incidence of more than 1.9 million per year.[18] Surgical resection provides potentially curative management, but has one of the highest risks of postoperative VTE events of all abdominal operations.[23,24] VTE, encompassing DVT and PE, albeit an infrequent event is a costly and potentially avoidable complication after surgery for CRC that can be fatal.[58-60] A recent narrative review estimated the incidence risk of VTE in patients with colorectal malignancy to be between 2.75%–8.9% and post Colorectal surgery 1.15%–2.47%.[68] The authors' review did not stratify data by surgical indication or follow-up length and included multiple repetition of databases. Understanding these stratified risks is critical for VTE prophylaxis guidelines, as the risk of VTE might be finely balanced by the bleeding risk of postoperative VTE thromboprophylaxis use.

Current guidance is based on heterogenous studies of patients with abdominal and pelvic malignancies undergoing surgery. Their referenced studies quote a 1% incidence of symptomatic VTE at 30-days for patients without extended prophylaxis.[52] The updated Cochrane systematic review of this subject reported a similar 30-day symptomatic VTE rate of 117 per 1,000 person-years, compared to the

3-month major and minor bleeding rate of 113 per 1,000 person-years, with a major bleed rate of 45 per 1,000 person-years.[51] In the last decade there have been continual changes in the perioperative management of patients with CRC; with the increased adoption of minimally invasive surgery and ERAS protocols which may reduce the perioperative risk of VTE. Although a recent review of laparoscopic vs. open CRC surgery found no difference in postoperative VTE risk between surgical techniques. However, this review focused on studies pre-dating current guidelines, merged data on studies where one or other DVT or PE outcome was not reported, thus inaccurately representing the risk of VTE within each included study, and did not review population-based data.[161] The uptake of these changes and application of this guidance is known to vary globally.[169,181] Given these changes in surgical practice internationally it is important to quantify the contemporary risk of VTE in patients with CRC undergoing surgery to ensure the potential benefit of this treatment is maintained when set against the risk of bleeding.

### 2.1.1 Aim

The aim of this systematic review and meta-analysis is to characterise the rate of postoperative VTE in patients undergoing surgery for colorectal malignancy and highlight its variability globally.

## Section 2.2 Methods

### 2.2.1 Data sources, searches and selection criteria

The review was registered with Prospero before data extraction, ID: CRD42019148828 (see Appendix 1 for PROSPERO registration), and conducted in accordance with the MOOSE (Meta-analyses Of Observational Studies in Epidemiology) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statements for reporting systematic reviews and meta-analyses[182,183] (see Appendices 2-3, MOOSE and PRISMA checklists). A systematic search was performed using the OVID platform to search the Medline and Embase electronic databases from 1946 and 1974 to mid-August 2019 respectively as well as the Cochrane Library, US National Library of Medicine ClinicalTrials.gov and International Clinical Trials Registry Platform databases. Grey literature was sought via Google Scholar, including studies with relevant titles, in conjunction with the use of hand searching. No language limitation or geographical exclusion criteria was applied to the search. RCT hedge filters, available at the time of searching, were adapted from the Scottish Intercollegiate Guidelines Network to remove unwanted literature e.g. case reports (see Appendix 4, for full OVID database search strategies).

Titles, abstracts and full texts were screened in progression for relevance by two blinded reviewers. A third reviewer was involved at each iteration to resolve any discordance.

Studies were included if their sample population met the following criteria: Adult participants, aged greater than or equal to 18-years, with a primary diagnosis of either colon or rectal cancer who had undergone definitive surgery specifically relating to the removal of their CRC.

Studies were excluded if their sample population met any of the following criteria: Patient cohort specifically aged less than 18-years, patients who have had Colorectal surgery for benign disease only, patients who had undergone completely endoscopic procedures or CRC surgery without cancer resection. Studies were also excluded if VTE event data did not include DVT and PE outcomes.

To derive absolute rates of VTE and duration of risk, studies in representative population-based samples were selected that provided the number of VTE events and duration of follow-up to allow absolute rates to be calculated. Selected study designs were RCTs and large population-based database/registry cohort studies, nationwide and/or regional. Single centre cohort studies were excluded to limit selection bias.

### 2.2.2 Data extraction and management

Data were extracted from included studies using a standardised proforma. This included the; author, publication year, study country, study database, postoperative follow-up period, study time frame, cancer type, population number, number of symptomatic VTE events (asymptomatic where unavailable), VTE definition, VTE incidence risks

and rates and where available operative technique (open/laparoscopic) and admission status (elective/emergency). Studies were grouped by epidemiological design, postoperative follow-up duration, cancer type, operative technique and United Nations (UN) Geoscheme Area.[184] If the absolute number of VTE events was not given, the sum of the DVT and PE outcomes was used as the numerator instead. If studies using the same databases had overlapping time frames, this was acknowledged within the meta-analysis with the inclusion of only the study with the largest population for that study's time frame to reduce duplication bias. Within all studies, population number and VTE event frequency was calculated from all available data and in RCTs from each trial arm where possible. Assessment of bias was conducted using a modified Newcastle-Ottawa scale for the population database cohort studies and the Cochrane risk of bias tool for the RCTs (see Figures 2.1 and 2.2, and Appendices 5-6 for risk of bias). Total years of follow-up and incidence of VTE for each study were analysed by calculating mean follow-up duration for all participants.

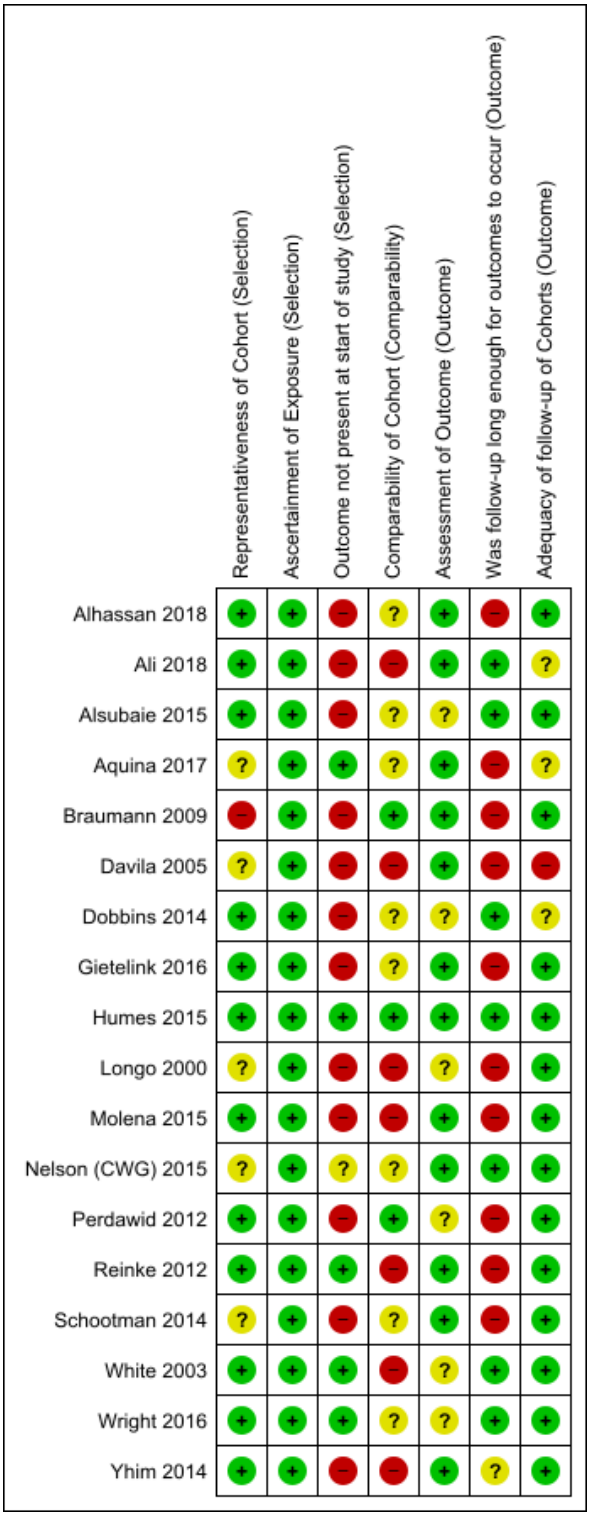



**Figure 2.1: Modified Newcastle-Ottawa cohort studies scale risk of bias summary of resectional colorectal cancer studies included within the quantitative synthesis**

Review author's judgements using a traffic light system about each risk of bias item for each included study within the quantitative synthesis. Red indicating high risk, amber indicating unclear risk and green indicating low risk.

Representativeness of Cohort: Studies with validated databases using routinely collected data that did not exclude patients based on surgical or demographic factors were considered low risk. Risk increased based on cumulative exclusion of patients from the general population of resectional colorectal cancer patients.

Ascertainment of Exposure: Risk assigned based on validity of patients within the database accurately coded as undergoing resectional colorectal cancer surgery.

Outcome not present at start of study: Studies clearly defining patients with a diagnosis of venous thromboembolism prior to index surgical resection were considered low risk. Studies that did not specify if an event had occurred prior to index surgery were classed as high risk. Studies were considered unclear risk if they alluded to but were unclear about measuring and excluding cases where the outcome occurred prior to surgery.

Comparability of Cohort: Studies allowing stratification of resectional colorectal cancer patients by admission type were considered low risk. Studies that did not allow stratification by admission type, but stratification of another key variable e.g. surgical indication were

classed as unclear risk with studies not allowing any stratification classed as high risk.

Assessment of Outcome: Risk assigned based on validity of patients within the database accurately coded as being diagnosed with a venous thromboembolism. Risk increased if studies did not clearly describe how an outcome was defined.

Was follow-up long enough for outcomes to occur: Studies that followed patients for only 1-month were considered high risk. Studies were classed as low risk if the cohort was followed for at least 3-months with studies classed as unclear risk if the follow-up period was between 1- and 3-months.

Adequacy of follow-up of Cohorts: Studies with > 90% of patients remaining in the cohort for the entire study follow-up period were considered low risk. Studies were considered to have an unclear risk if the percentage loss to follow-up was not well defined or < 90% but > 70%. Studies were considered high risk if the percentage loss to follow-up was < 70%.

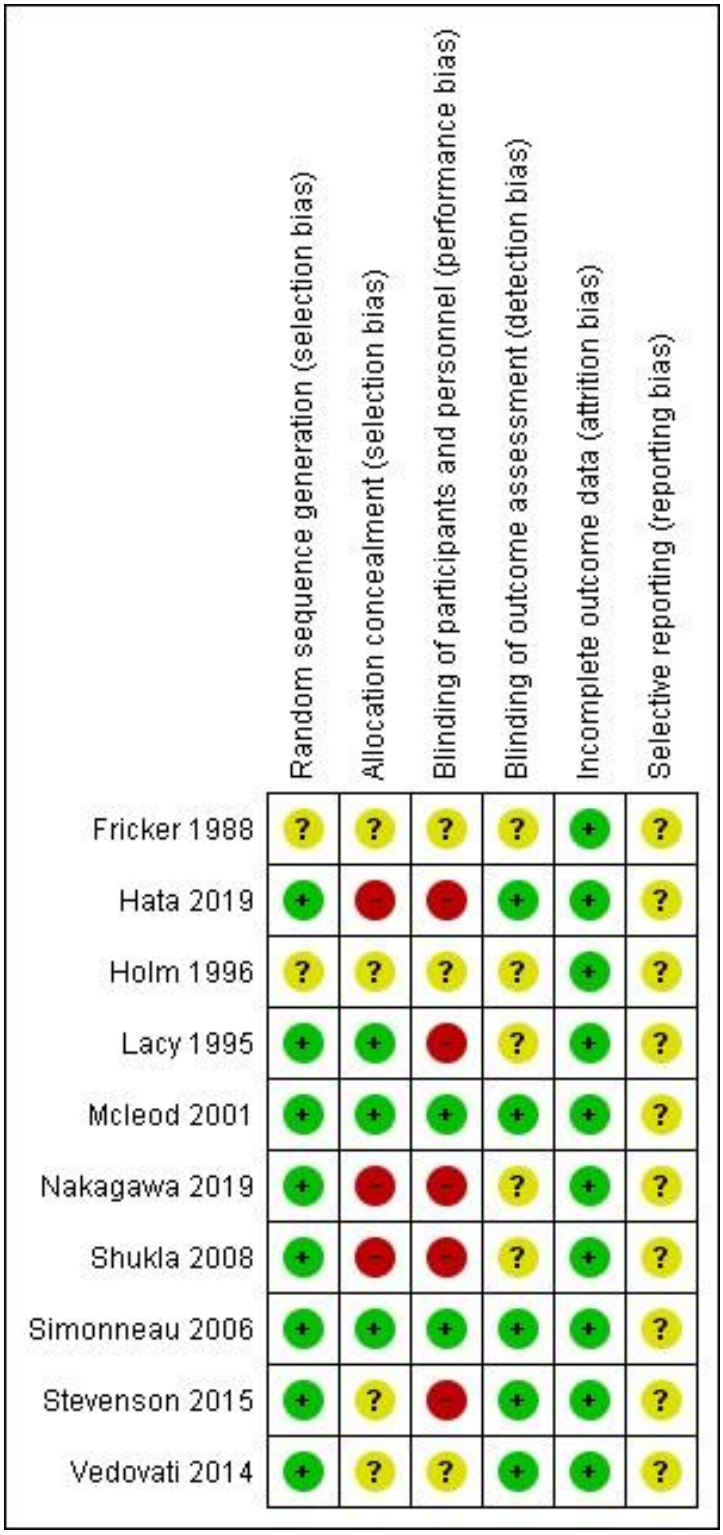



**Figure 2.2: Cochrane randomised controlled trials risk of bias summary of resectional colorectal cancer studies included within the quantitative synthesis**

Review author's judgements using a traffic light system about each risk of bias item for each included study within the quantitative synthesis. Red indicating high risk, amber indicating unclear risk and green indicating low risk.

Random sequence generation: Studies were considered low risk if randomisation was described clearly. Studies where randomisation was mentioned but not described clearly were classed as unclear risk with no description of randomisation considered high risk.

Allocation concealment: Studies were considered low risk if allocation concealment was described clearly. Studies where allocation concealment was mentioned but not described clearly were classed as unclear risk with no description of allocation concealment considered high risk.

Blinding of participants and personnel: Studies were considered low risk if there was a clear description of both participant and personnel blinding (double blinding). Studies where blinding description was unclear were classed as unclear risk and those without blinding considered high risk (open label).

Blinding of outcome assessment: Studies were considered low risk if assessors were clearly described as blinded to the outcome. Studies where assessor blinding was not clearly described were considered unclear risk with no assessor blinding to the outcome classed as high risk.

Incomplete outcome data: Studies with minimal attrition at the end of the trial follow-up period, > 90% of patients remaining, were considered low risk. Studies were considered to have an unclear risk if the percentage attrition was < 90% but > 70%. Studies were considered high risk if the percentage attrition was not described or < 70%.

Selective reporting: Studies were considered low risk if there was a clear description that no selective reporting occurred. Studies where it was unclear if selective reporting had occurred were classed as unclear risk with studies clearly mentioning selective reporting deemed high risk.

### 2.2.3 Statistical analysis

Primary outcomes were 30 and 90-days incidence rates of VTE per 1,000 person-years following CRC surgery presented with their 95% confidence interval (95% CI). Meta-analysis of VTE incidence was performed using Stata Version 16.0. Studies were pooled assuming a random-effects model (DerSimonian and Laird) with the inverse-variance method used to estimate heterogeneity. For each study within the meta-analysis, the natural logarithm of the incidence rate was calculated as well as the standard error ($1/\sqrt{(\text{VTE events})}$) to allow for the calculation of within-study variance. Between-study variance ($\tau^2$) was calculated as the difference between the total observed variance and the within-study variance. This method within a random-effects model allows studies with more VTE events to be weighted more heavily than those with fewer events, because it uses the inverse of the variance of the effect estimate and inverse of the between-study variance ($1/(\text{Standard Error})^{\wedge 2}+\tau^2$) as the weight allocated to each study.[185] Heterogeneity was assessed using the $I^2$ statistic.

## Section 2.3 Results

### 2.3.1 Overview of included studies

In total 6,441 studies were retrieved from the five electronic databases, grey literature and hand searching. After hedge filter exclusion 4,842 articles remained with a following 354 duplicates excluded, leaving 4,488 records to be screened on their titles alone. Successively, 697 abstracts were appraised, and 185 full publications retrieved for critical evaluation. 52 publications met the inclusion criteria with 28 subsequently used within the quantitative analysis. 18 large database/registry cohorts and 10 RCTs reporting on 539,390 and 3,882 patients respectively, stratified on meta-analysis (Figure 2.3, PRISMA flow diagram). Details and characteristics of studies within the quantitative analysis and qualitative synthesis are included in Table 2.1 and Appendix 7 respectively.

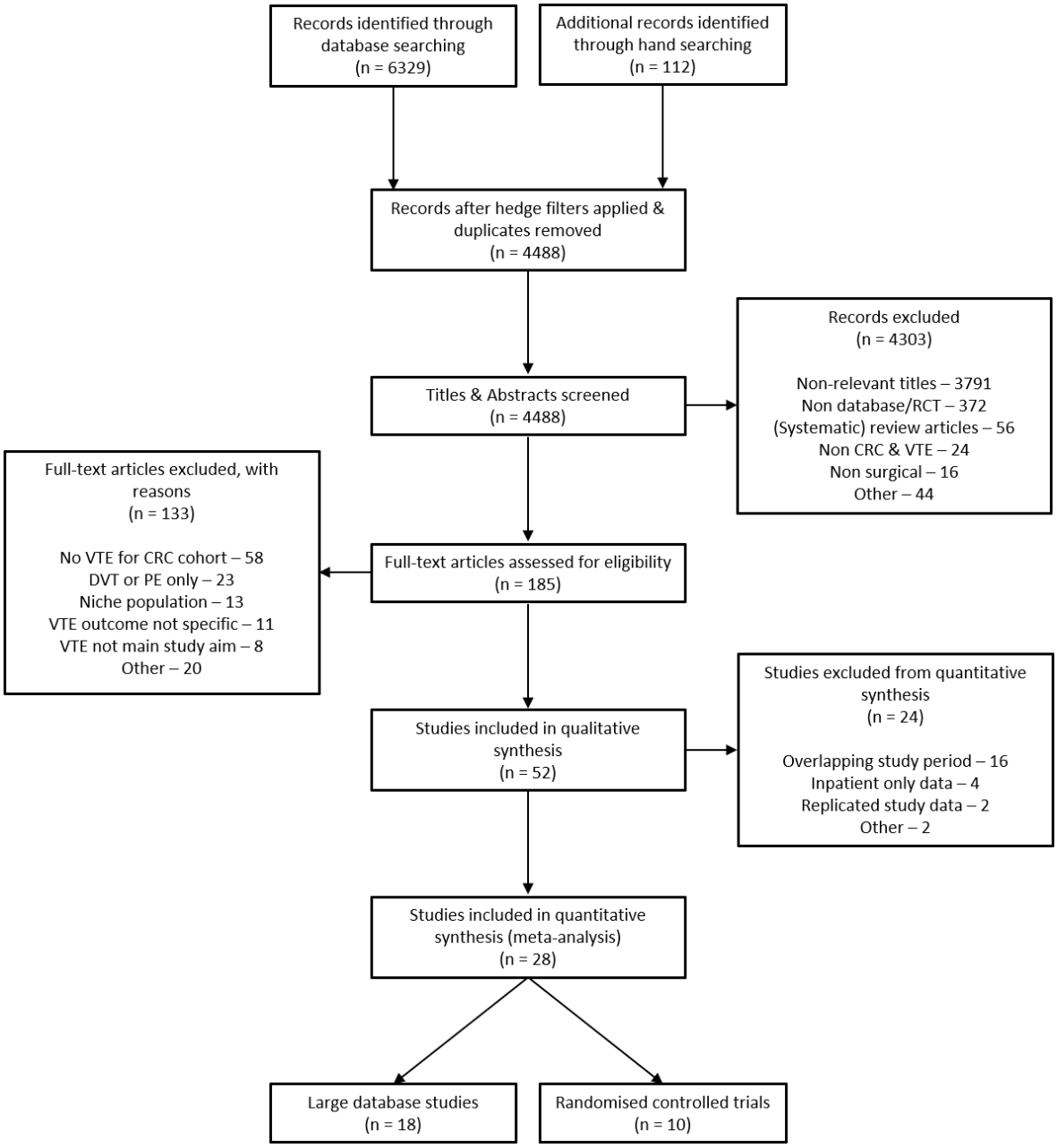



**Figure 2.3: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Flow Diagram of resectional colorectal cancer studies**

Abbreviations: CRC, Colorectal cancer; DVT, Deep vein thrombosis; PE, Pulmonary embolism; RCT, Randomised controlled trial; VTE; Venous thromboembolism.

| Author | Year | Country | Database | Follow-up | Study time frame | Cancer | VTE type | No. | No. of VTE events | | Incidence risk | | VTE rate per 1,000 person-years | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | 1-Month | 3-Months | 1-Month | 3-Months | 1-Month | 95% CI | 3-Months | 95% CI |
| Alhassan[92] | 2018 | USA | ACS-NSQIP | 30-days | 2012-2016 | CR | VTE, PE, DVT | 101822 | 1948 | - | 1.91% | - | 235 | 225-246 | - | - |
| Ali[120] | 2018 | USA | Explorys | 7, 30 & 90-days | 1999-2017 | CR | VTE | 32020 | 929 | 1377 | 2.90% | 4.30% | 358 | 336-382 | 178 | 169-188 |
| Alsubaie[186] | 2015 | CAN | MCR | 90-days | 2004-2009 | C & R | VTE | 3090 | - | 113 | - | 3.66% | - | - | 151 | 126-182 |
| Aquina[187] | 2017 | USA | NYSCR & SPARCS | 30-days | 2004-2011 | C | VTE | 25537 | 589 | - | 2.31% | - | 284 | 262-308 | - | - |
| Braumann[188,ad] | 2009 | DEU | FTCII | 30-days | 2005-2007 | C | VTE | 748 | 2 | - | 0.27% | - | 33 | 8-130 | - | - |
| Davila[189] | 2005 | USA | VA SQIP | 30-days | 1987-2000 | CR | VTE | 12607 | 243 | - | 1.93% | - | 237 | 209-269 | - | - |
| Dobbins[190,c] | 2014 | AUS | NSW CCR | 90-days | 2000-2008 | C & R | PE & DVT | 27947 | - | 441 | - | 1.58% | - | - | 65 | 59-71 |
| Gietelink[155,c] | 2016 | NLD | DSCA & NCR | 30-days | 2010-2013 | CR | VTE | 35566 | 228 | - | 0.64% | - | 78 | 69-89 | - | - |
| Humes[21,b] | 2015 | GBR | HES &CPRD | 1 and 3-months | 2001-2011 | CR | VTE | 8309 | 49 | 111 | 0.59% | 1.34% | 74 | 56-97 | 57 | 47-69 |
| Longo[191] | 2000 | USA | VA SQIP | 30-days | 1991-1995 | C | PE & DVT | 5853 | 55 | - | 0.94% | - | 115 | 88-150 | - | - |
| Molena[192] | 2015 | USA | ACS-NSQIP | 30-days | 2005-2012 | C | VTE | 38898 | 665 | - | 1.71% | - | 210 | 194-226 | - | - |
| Nelson CWG[85] | 2015 | USA | SCOAP | 90-days | 2006-2011 | CR | VTE | 6216 | - | 128 | - | 2.06% | - | - | 84 | 71-100 |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Perdawid[193,a] | 2012 | DNK | DCCG NCCR | 30-days | 2001-2008 | C | VTE | 9149 | 44 | - | 0.48% | - | 59 | 44-79 | - | - |
| Reinke[194] | 2012 | USA | ACS-NSQIP | 30-days | 2005-2010 | C & R | VTE | 44396 | 902 | - | 2.03% | - | 250 | 234-267 | - | - |
| Schootman[195] | 2014 | USA | SEER & Medicare | 30-days | 2000-2005 | CR | VTE | 35946 | 1071 | - | 2.98% | - | 368 | 347-391 | - | - |
| White[73] | 2003 | USA | CA PDDS | 91-days | 1992-1996 | C & R | VTE | 36746 | - | 610 | - | 1.66% | - | - | 67 | 62-73 |
| Wright[154,c] | 2016 | USA | MarketScan IBM | 3-months | 2009-2013 | C | VTE | 40579 | - | 1671 | - | 4.12% | - | - | 171 | 163-179 |
| Yhim[196] | 2014 | KOR | NHI HIRA | 5-weeks | 2007-2011 | CR | VTE, PE, DVT | 73961 | 1236 | - | 1.67% | - | 176 | 166-186 | - | - |

**Table 2.1: Description of resectional colorectal cancer cohort database/registry studies included within the quantitative synthesis**

Abbreviations: CWG, Colorectal Writing Group; USA, United States of America; CAN, Canada; DEU, Germany; AUS, Australia; NLD, Netherlands; GBR, United Kingdom; DNK, Denmark; KOR, Republic of Korea; ACS-NSQIP, American College of Surgeons – National Surgical Quality Improvement Program; MCR, Manitoba Cancer Registry; NYSCR SPARCS, New York State Cancer Registry & Statewide Planning and Research Cooperative System; FTCII, Fast-track Colon II; VA SQIP, Veterans Affairs Surgical Quality Improvement Program; NSW CCR, NEW South Wales Central Cancer Registry; DSCA & NCR, Dutch Surgical Colorectal

Audit & Netherlands Cancer Registry; HES & CPRD, Hospital Episode Statistics & Clinical Practice Research Datalink; SCOAP, Surgical Care and Outcomes Assessment Program; DCCG NCCR, Danish Colorectal Cancer Group National Colorectal Cancer Database; SEER & Medicare, Surveillance, Epidemiology, and End Results Program & Medicare; CA PDDS, California Patient Discharge Data Set; NHI HIRA, National Health Insurance Health Insurance Review and Assessment Service; CR, Colorectal; C & R, Colon and Rectal; C, Colon; VTE, Venous Thromboembolism; DVT, Deep Vein Thrombosis; PE, Pulmonary Embolism.

[a] Elective only; [b] Elective and Emergency subgroup; [c] Minimally Invasive Surgery vs. Open subgroup; [d] Open surgery only.

### 2.3.2 Description of database and registry cohort studies

11 database studies were from the US[73,85,92,120,154,187,189,191,192,194,195] and 1 each from Canada,[186] the UK,[21] Denmark,[193] the Netherlands,[155] Germany,[188] South Korea[196] and Australia.[190] 12 studies defined their cohort as undergoing CRC surgery,[21,85,92,120,155,189,195,196] 4 of which divided their population into colon and rectal cancer cohorts,[73,186,190,194] 6 studies reported on colon cancer populations solely.[154,187,188,191-193] Sample size studied varied greatly, ranging from 748 to 101,822 spanning years 1987–2017. The majority of studies did not stratify data by operative status or technique. Postoperative follow-up varied between 1 and/or 3-months. Due to the population-based/registry study design all reported VTE events were assumed symptomatic. For study specific demographic proportions see Table 2.2.

### 2.3.3 Description of randomised controlled trials

Of the RCTs 2 each were from France[41,197] and Japan[97,198] with 1 each from Canada,[43] Spain,[199] Italy,[95] Sweden,[200] India[201] and Australia.[202] 6 studies defined their cohort as undergoing CRC surgery[41,43,95,97,198,201] with a further 2 each solely reporting on either colon[197,199] or rectal cancer[200,202] populations. 6 studies defined their cohort as elective operations only.[41,43,95,198,200,202] 5 studies reported a laparoscopic cohort within their analysis,[199,202] 3 of which solely reported on laparoscopic procedures.[95,97,198] Postoperative follow-up for reporting of morbidity ranged from 6-days to 5-years. Studies varied in their reporting of VTE

outcome using combinations of symptomatic and non-symptomatic events within their analyses leading to variation in VTE incident risk, 0–15.38%. This heterogeneity in postoperative follow-up length and VTE outcome definition was the reason RCTs were deemed unsuitable to be included within the meta-analysis. Details and characteristics of the RCTs are included in Table 2.3.

| Author | Year | Country | Database | Study time frame | Cancer | Proportion CRC within study | Emergency surgery | Laparoscopic surgery | Age (Years) | Obesity (≥30Kg/m$^2$) | Tumour stages |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Alhassan[16] | 2018 | USA | ACS-NSQIP | 2012-2016 | CR | 39.1% | 29.8% (CR surgery) | 48.4% (CR surgery) | mean 61.6-65.5 (SD 15.4) | 15.9% (CR surgery) | N/A |
| Ali[17] | 2018 | USA | Explorys | 1999-2017 | CR | 100% | N/A | 23.0% | 69.0% (≥60) | 43.0% | N/A |
| Alsubaie[27] | 2015 | CAN | MCR | 2004-2009 | C & R | 46.7% | N/A | 8.1% (Abdominal/pelvic cancer surgery) | mean 65.5 (SD 12.7) | N/A | T1 - T4 |
| Aquina[18] | 2017 | USA | NYSCR & SPARCS | 2004-2011 | C | 100% | N/A | 26.4% | 68.0% (>65) - 44.0% (>75) | 6.5% | T1 - T4 |
| Braumann[31,ad] | 2009 | DEU | FTCII | 2005-2007 | C | 100% | 0% | 0% | mean 70.4 (range 26.2-95.7) | N/A | N/A |
| Davila[24] | 2005 | USA | VA SQIP | 1987-2000 | CR | 100% | N/A | N/A | 83.0% (≥61) - 6.4% (≥81) | N/A | T1 - T4 |
| Dobbins[33,c] | 2014 | AUS | NSW CCR | 2000-2008 | C & R | 100% | 11.6% | 8.3% | mean 66.4-69.7 | N/A | T1 - T4 |
| Gietelink[30,c] | 2016 | NLD | DSCA & NCR | 2010-2013 | CR | 100% | 14.5% | 47.0% | 37.8% (>70) | N/A | T1 - T4 |
| Humes[28,b] | 2015 | GBR | HES &CPRD | 2001-2011 | CR | 67.1% | 21.1% | 12.5% (CR surgery) | 58.5% (≥70) median 72 (IQR 64-79) | 20.1% (CR surgery) | T1 - T4 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Longo[26] | 2000 | USA | VA SQIP | 1991-1995 | C | 100% | 15.0% | N/A | median 68 (range 19-100) | N/A | N/A |
| Molena[20] | 2015 | USA | ACS-NSQIP | 2005-2012 | C | 52.3% | 1.7% (All cancer surgery types) | N/A | 40.1% (≥70) - 14.6% (≥80) | 29.1% (All cancer surgery types) | N/A |
| Nelson CWG[21] | 2015 | USA | SCOAP | 2006-2011 | CR | 38.6% | 22.7% (CR surgery) | 30.9% (CR surgery) | mean 61.4 (SD 15.7) | 30.1% (CR surgery) | T1 - T4 |
| Perdawid[29,a] | 2012 | DNK | DCCG NCCR | 2001-2008 | C | 100% | 0% | 18.7% | median 72 (range 24-98) | N/A | T1 - T4 |
| Reinke[23] | 2012 | USA | ACS-NSQIP | 2005-2010 | C & R | 100% | N/A | N/A | median 62-69 (IQR 53-79) | median BMI 26.7-27Kg/$m^2$ (IQR23-31) | N/A |
| Schootman[22] | 2014 | USA | SEER & Medicare | 2000-2005 | CR | 100% | 22.2% | N/A | 100% (≥66) - 64.4% (≥75) | N/A | T1 - T3 |
| White[25] | 2003 | USA | CA PDDS | 1992-1996 | C & R | 100% | N/A | N/A | N/A | N/A | N/A |
| Wright[19,c] | 2016 | USA | MarketScan IBM | 2009-2013 | C | 100% | N/A | 26.9% | 35.2% (≥65) | N/A | N/A |
| Yhim[32] | 2014 | KOR | NHI HIRA | 2007-2011 | CR | 100% | N/A | N/A | N/A | N/A | N/A |

**Table 2.2: Characteristics of resectional colorectal cancer database/registry cohort studies included in the quantitative synthesis by admission status, surgical technique, demographics and tumour stage**

Abbreviations: CWG, Colorectal Writing Group; USA, United States of America; CAN, Canada; DEU, Germany; AUS, Australia; NLD, Netherlands; GBR, United Kingdom; DNK, Denmark; KOR, Republic of Korea; ACS-NSQIP, American College of Surgeons – National Surgical Quality Improvement Program; MCR, Manitoba Cancer Registry; NYSCR SPARCS, New York State Cancer Registry & Statewide Planning and Research Cooperative System; FTCII, Fast-track Colon II; VA SQIP, Veterans Affairs Surgical Quality Improvement Program; NSW CCR, NEW South Wales Central Cancer Registry; DSCA & NCR, Dutch Surgical Colorectal Audit & Netherlands Cancer Registry; HES & CPRD, Hospital Episode Statistics & Clinical Practice Research Datalink; SCOAP, Surgical Care and Outcomes Assessment Program; DCCG NCCR, Danish Colorectal Cancer Group National Colorectal Cancer Database; SEER & Medicare, Surveillance, Epidemiology, and End Results Program & Medicare; CA PDDS, California Patient Discharge Data Set; NHI HIRA, National Health Insurance Health Insurance Review and Assessment Service; CR, Colorectal; C & R, Colon and Rectal; C, Colon; CRC, Colorectal cancer; SD, Standard deviation; IQR, Interquartile range; BMI, Body mass index.

[a] Elective only; [b] Elective and Emergency subgroup; [c] Minimally Invasive Surgery vs. Open subgroup; [d] Open surgery only.

| Author | Year | Country | Follow-up | Study time frame | Cancer | VTE type | No. | Overall No. of VTE events | Incidence risk[a] | Person-years | VTE rate per 1,000 person-years[a] | 95% CI | Trial Question |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fricker[35] | 1988 | FRA | 4-weeks | Not specified | C | VTE, PE, DVT | 6 | 0 | 0.00% | 0.46 | 0 | N/A | LDH vs. LMWH as VTE prophylaxis following abdominal cancer surgery |
| Hata[36,bd] | 2019 | JPN | 16-days | 2011-2015 | CR | VTE, PE, DVT | 290 | 12[e] | 4.14%[e] | 12.45 | 964[e] | 547-1697 | IPC vs. IPC + anticoagulant therapy as VTE prophylaxis in Japanese patients following laparoscopic CRC surgery |
| Holm Stockholm I & II Trials[41,b] | 1996 | SWE | 5-years | 1980-87 & 1987-93 | R | VTE | 1027 | 49 | 4.77% | 5012.50 | 10 | 7-13 | Long-term morbidity and mortality rectal adenocarcinoma resection receiving adjuvant radiotherapy and/or surgery alone |
| Lacy[39,c] | 1995 | ESP | up to 1-year | 1993-1994 | C | VTE, PE, DVT | 51 | 0 | 0.00% | 51.00 | 0 | N/A | Short term outcomes following laparoscopic vs. open colectomy for colon cancer |
| McLeod[38,b] | 2001 | CAN | 9-days | Not specified | CR | VTE | 324 | 50[e] | 15.38%[e] | 7.37 | 6758[e] | 5119-8920 | Subcutaneous heparin vs. LMWH VTE prophylaxis following CR surgery |
| Nakagawa YCOG 1404[37,d] | 2019 | JPN | 7 and 28-days | 2015-2017 | CR | VTE, PE, DVT | 116 | 0 | 0.00% | 8.90 | 0 | N/A | IPC vs. IPC + anticoagulant therapy as VTE prophylaxis following laparoscopic CRC surgery |
| Shukla[42] | 2008 | IND | 6-days | 2002-2004 | CR | VTE, PE, DVT | 99 | 0 | 0.00% | 1.63 | 0 | N/A | LMWH vs. no prophylaxis following as VTE prophylaxis following CRC surgery |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Simonneau[34,b] | 2006 | FRA | 12 and 60-days | 1994-1999 | CR | VTE, PE, DVT | 1271 | 17 | 1.34% | 207.53 | 82 | 51-132 | LMWHs, nadroparin vs. enoxaparin, as VTE prophylaxis following CRC surgery |
| Stevenson ALaCaRT[43,bc] | 2015 | AUS | 30-days | 2010-2014 | R | VTE | 473 | 1 | 0.21% | 38.84 | 26 | 4-183 | Pathological outcomes following laparoscopic-assisted vs. open rectal cancer resection |
| Vedovati PROLAPS[40,bd] | 2014 | ITA | 28-days and 3-months | 2010-2012 | CR | VTE, PE, DVT | 225 | 3 | 1.33% | 55.11 | 54 | 18-169 | 1-week vs. 4-week VTE prophylaxis following laparoscopic CRC surgery |

**Table 2.3: Description of resectional colorectal cancer randomised controlled trials included within the quantitative synthesis**

Abbreviations: ALaCaRT, Australasian Laparoscopic Cancer of the Rectum; FRA, France; JPN, Japan; SWE, Sweden; ESP, Spain; CAN, Canada; IND, India; AUS, Australia; ITA, Italy; C, Colon; CR, Colorectal; R, Rectal; VTE, Venous Thromboembolism; DVT, Deep Vein Thrombosis; PE, Pulmonary Embolism; LDH, Low Dose Heparin; LMWH, Low Molecular Weight Heparin; IPC, Intermittent Pneumatic Compression.

[a] Values given are for the longest time period of follow-up stated. [b] Elective only; [c] Minimally Invasive Surgery vs. Open subgroup; [d] Laparoscopic surgery only. [e] Includes asymptomatic venous thromboembolism events.

### 2.3.4 Meta-analysis

*2.3.4.1 Frequency and overall pooled incidence of VTE in CRC surgery*

The aggregated frequency of VTE events following CRC resection at 1-month was 1.92% (6606/344627). Overall pooled incidence rate of VTE at 1-month in CRC patients undergoing surgery was 195 per 1,000 person-years (95% CI 148–256) ($I^2$ value 99.1%), see Figure 2.4.

Within the 3-months CRC resection cohort the aggregated VTE event frequency was 2.43% (2780/114328). Overall pooled incidence rate of VTE at 3-months in CRC patients undergoing surgery was 91 per 1,000 person-years (95% CI 56–146) ($I^2$ value 99.2%), see Figure 2.5.

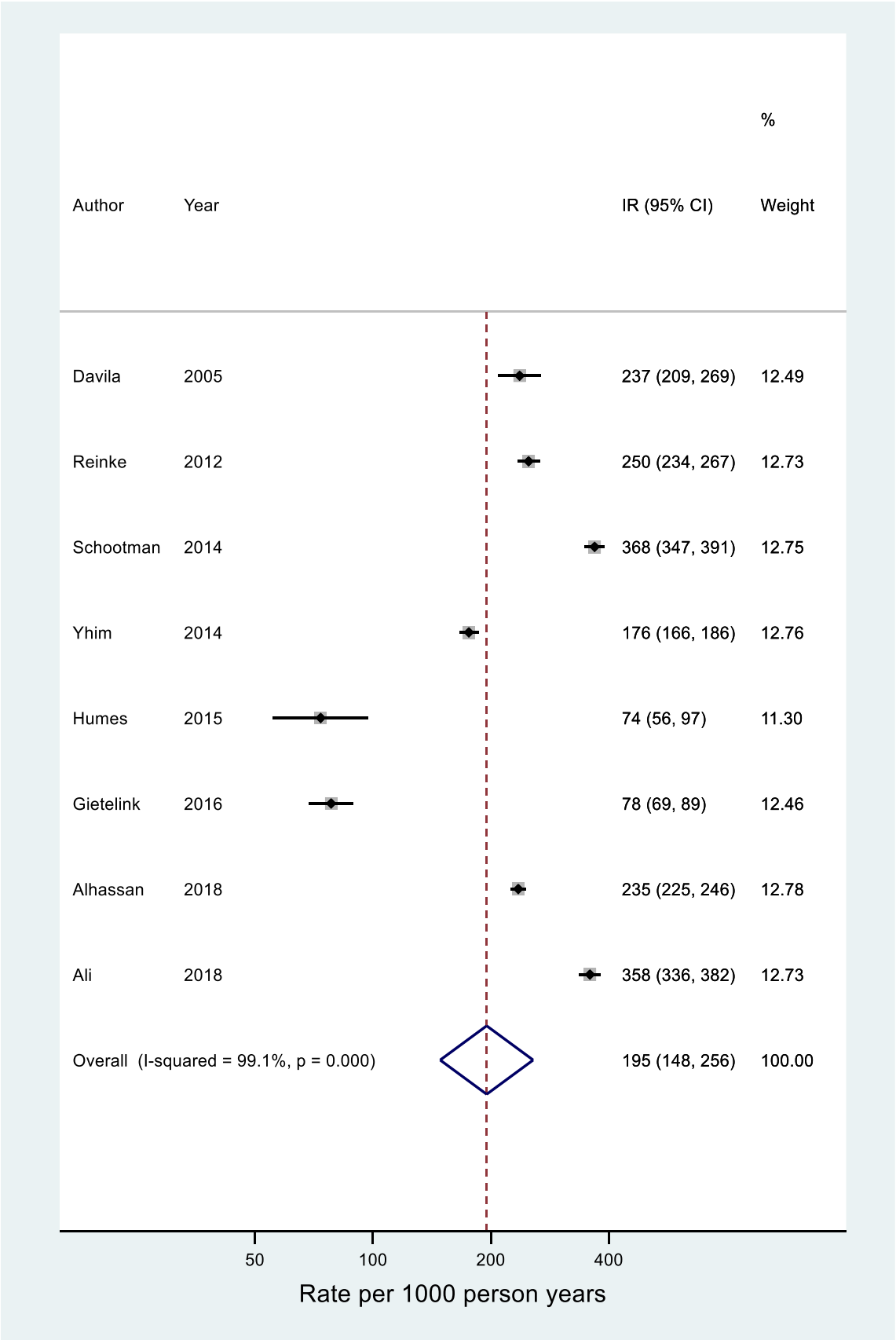



**Figure 2.4: 1-Month venous thromboembolism rates per 1,000 person-years of postoperative colorectal cancer patients**

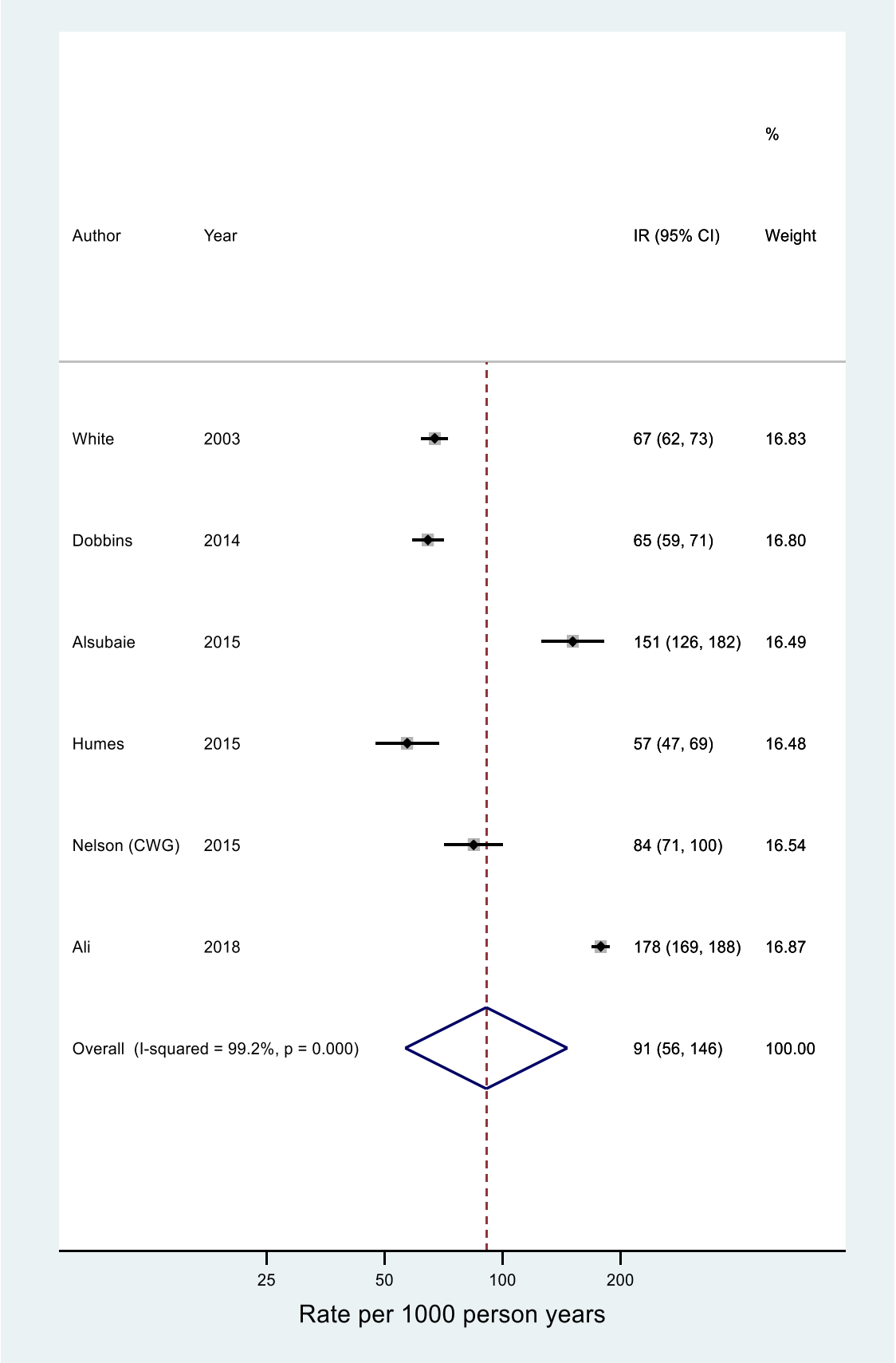



**Figure 2.5: 3-Months venous thromboembolism rates per 1,000 person-years of postoperative colorectal cancer patients**

*2.3.4.2 Frequency and overall pooled incidence of VTE in CRC surgery by UN Geoscheme Areas*

Within the 1-month cohort there were 11 studies of which 3 reported solely on colon cancer patients.[187,188,193] There were 6 studies in Northern America,[92,120,187,189,194,195] 4 in Northern and Western Europe[21,155,188,193] and 1 in Eastern Asia[196] with aggregated VTE event frequencies of 2.25% (5682/252328), 0.60% (323/53772) and 1.67% (1236/73961) respectively. Overall pooled incidence rate per 1,000 person-years of VTE at 1-month post CRC resection was 284 (95% CI 238–339) ($I^2$ value 97.7%) for the Americas, 71 (95% CI 60–84) ($I^2$ value 32.3%) for Europe and 176 (95% CI 166–186) for Asia (Overall $I^2$ value 98.9%), Figure 2.6.

Within the 3-months cohort there were 7 studies of which only 1 reported solely on colon cancer patients.[154] There were 5 studies in Northern America[73,85,120,154,186] and 1 each in Northern Europe[21] and Australia & New Zealand[190] with aggregated VTE event frequencies of 3.29% (3899/118651), 1.34% (111/8309) and 1.58% (441/27947) respectively. Overall pooled incidence rate per 1,000 person-years of VTE at 3-months post CRC resection was 121 (95% CI 82–179) ($I^2$ value 99.2%) for the Americas, 57 (95% CI 47–69) for Europe and 65 (95% CI 59–71) for Oceania (Overall $I^2$ value 99.3%), Figure 2.7.

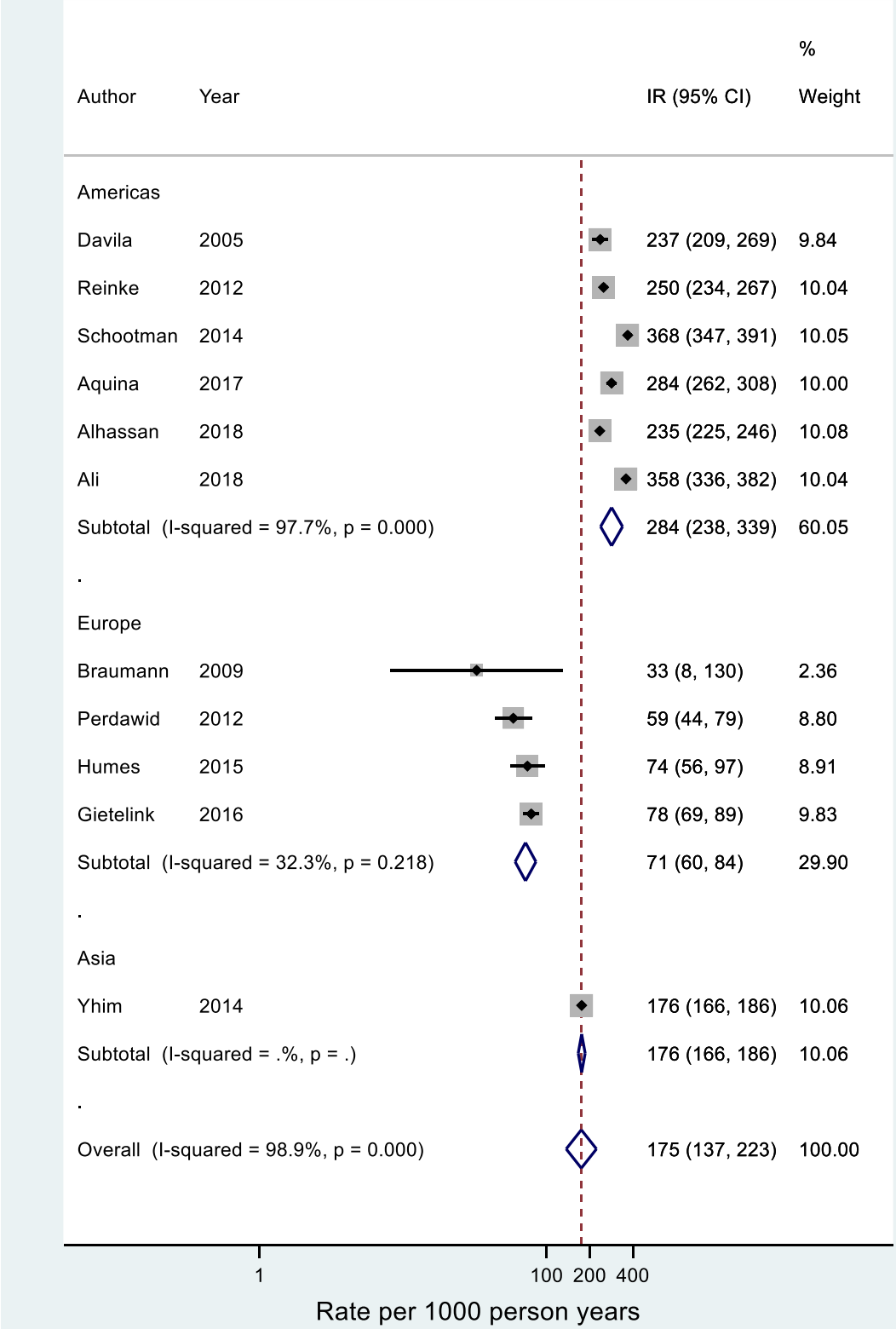



**Figure 2.6: 1-Month venous thromboembolism rates per 1,000 person-years of postoperative colorectal and colon cancer patients by United Nations Geoscheme Areas**

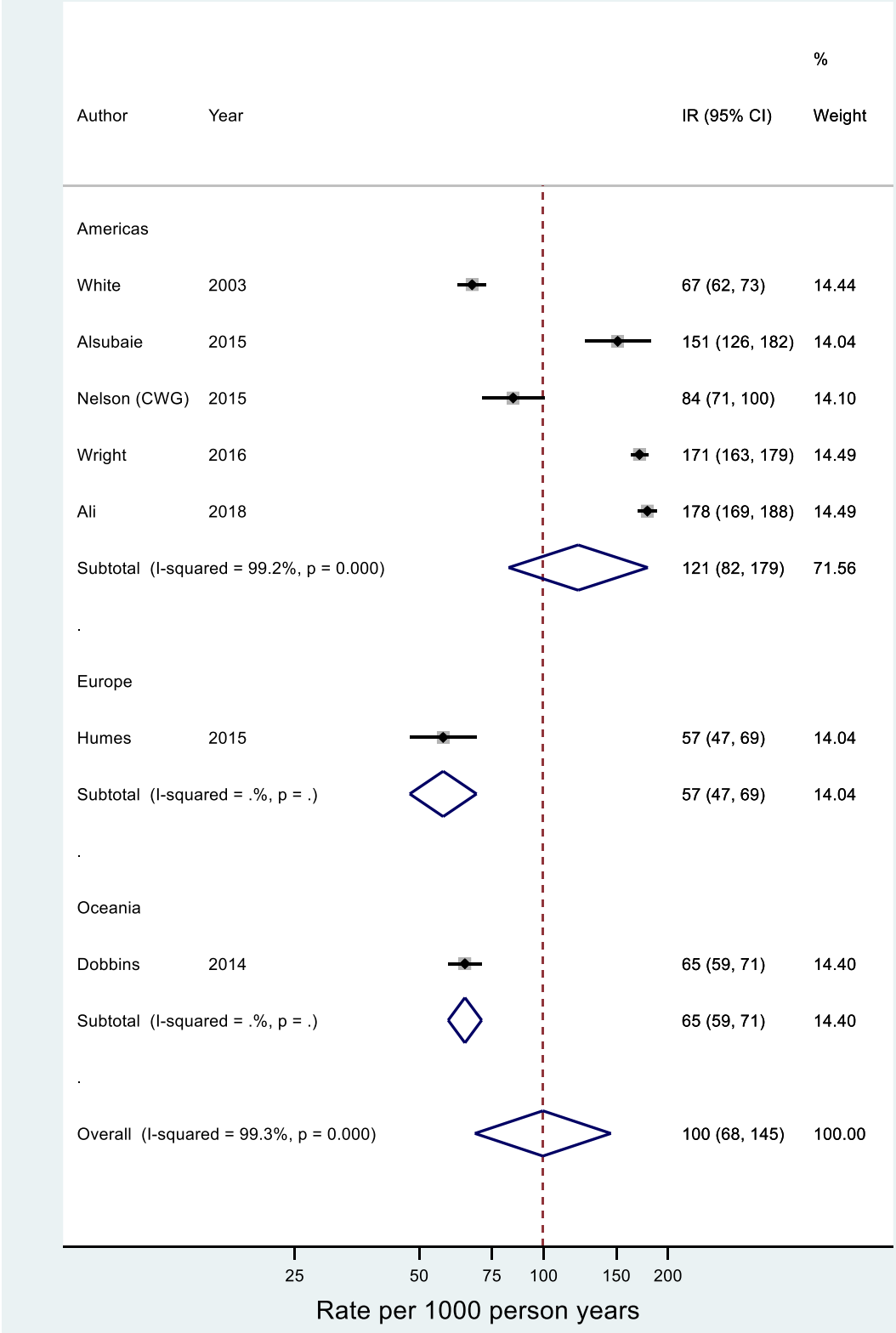



**Figure 2.7: 3-Months venous thromboembolism rates per 1,000 person-years of postoperative colorectal and colon cancer patients by United Nations Geoscheme Areas**

*2.3.4.3 Frequency and overall pooled incidence of VTE in colon and rectal cancer surgery*

Within the 1-month cohort there were 5 colon[187,188,191-193] and 1 rectal cancer[194] studies both with aggregated VTE event frequencies of 1.69% (1355/80185 and 275/16275) respectively. Overall pooled incidence rate per 1,000 person-years of VTE at 1-month after surgical resection was 132 (95% CI 87–200) ($I^2$ value 97.3%) for colon cancer and 207 (95% CI 184–233) for rectal cancer (Overall $I^2$ value 96.6%), see Figure 2.8.

Within the 3-months cohort there were 4 colon[73,154,186,190] and 3 rectal[73,186,190] cancer studies with aggregated VTE event frequencies of 2.77% (2566/92640) and 1.71% (269/15722) respectively. Overall pooled incidence rate per 1,000 person-years of VTE at 3-months after surgical resection was 102 (95% CI 56–184) ($I^2$ value 99.4%) for colon cancer and 86 (95% CI 52–143) ($I^2$ value 93.8%) for rectal cancer (Overall $I^2$ value 99.0%), see Figure 2.9.

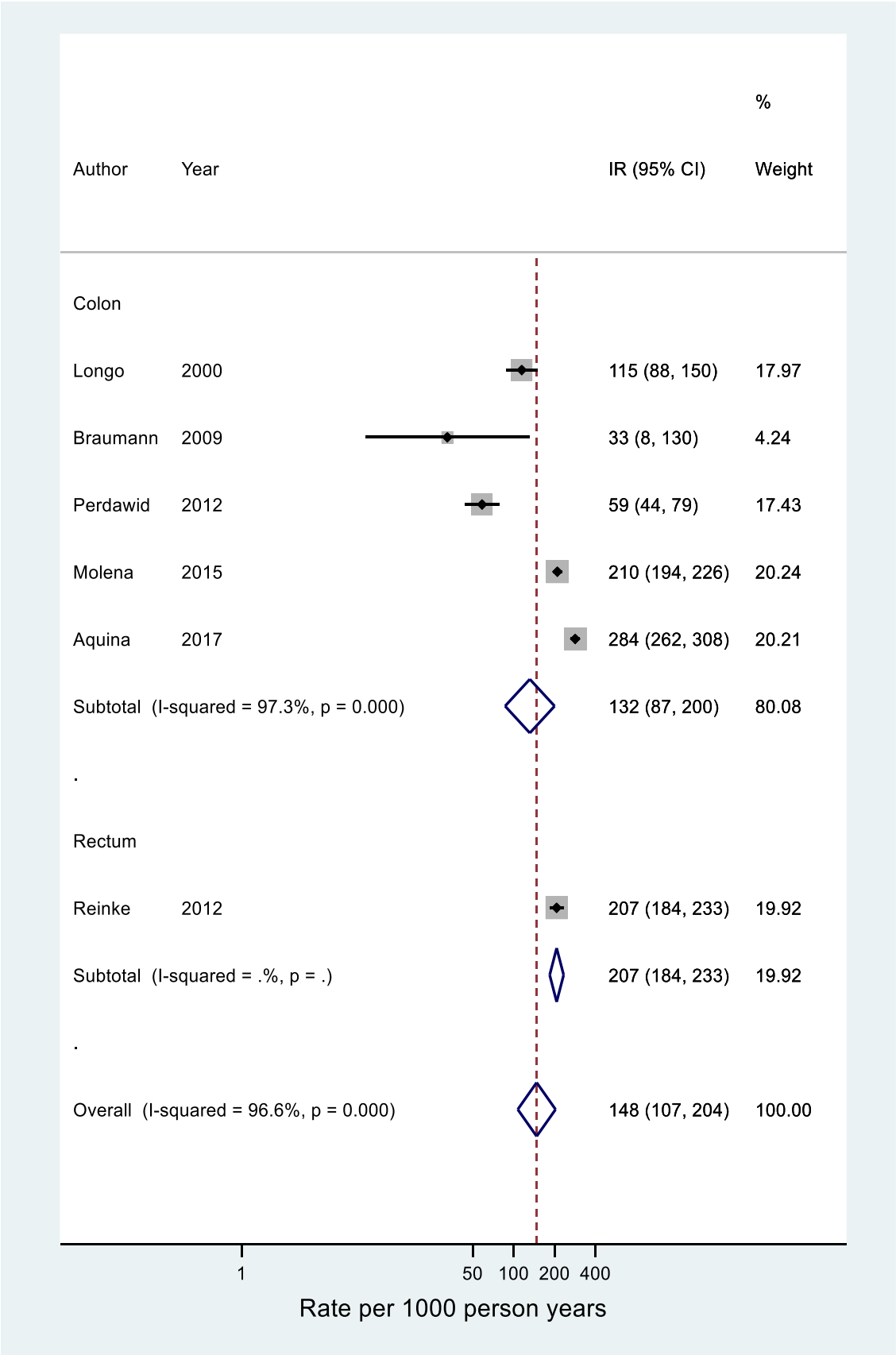



**Figure 2.8: 1-Month venous thromboembolism rates per 1,000 person-years of postoperative colon vs. rectal cancer patients**

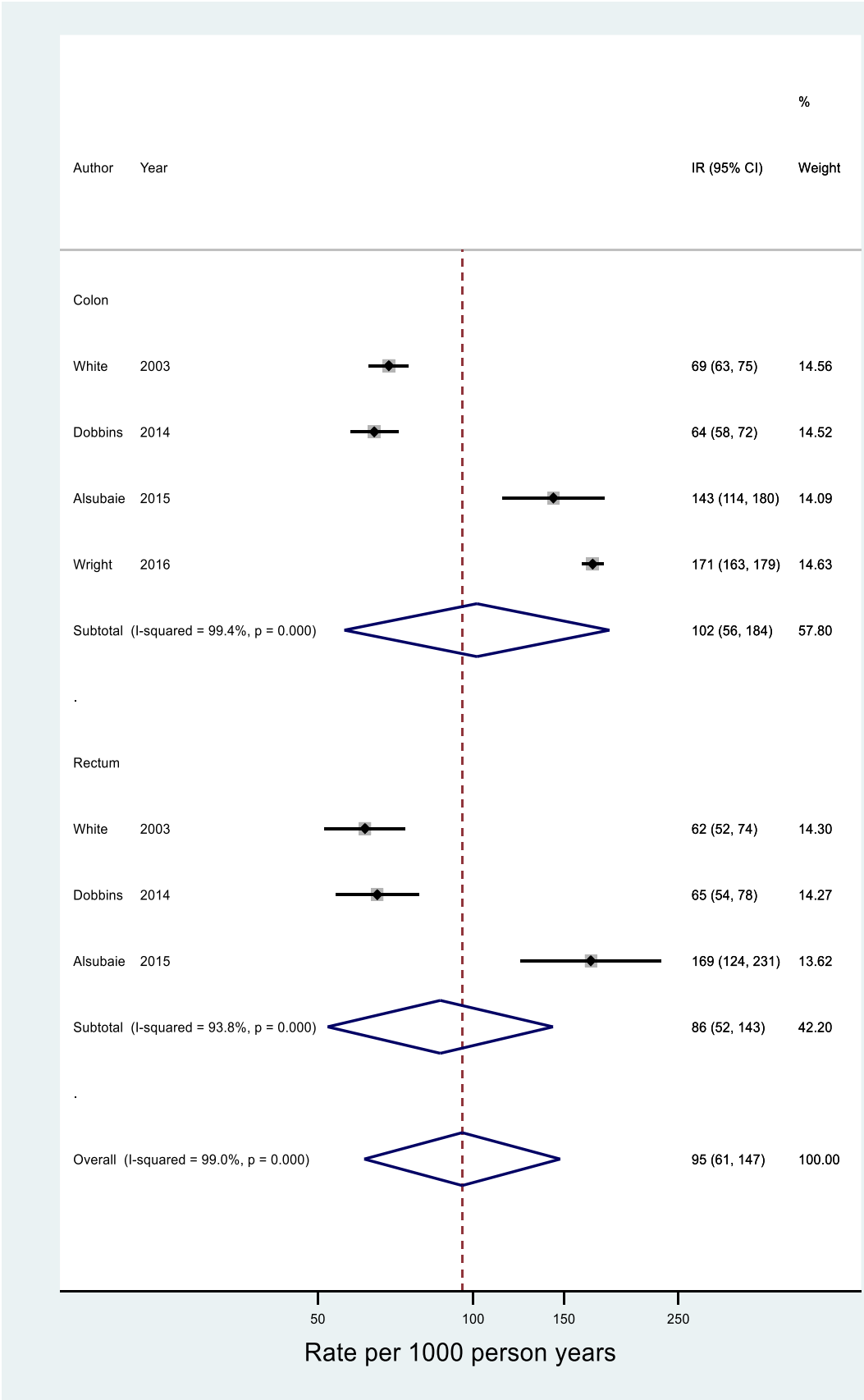



**Figure 2.9: 3-Months venous thromboembolism rates per 1,000 person-years of postoperative colon vs. rectal cancer patients**

*2.3.4.4 Frequency and overall pooled incidence of VTE in open and laparoscopic CRC surgery*

Data were available in 2 studies, both assessing outcomes at 3-months, for the comparison between open and laparoscopic surgical techniques.[154,190] 1 study reporting a CRC cohort the other solely colon cancer. Aggregated VTE event frequencies for open and laparoscopic surgery were 3.19% (1764/55276) and 2.63% (348/13250) and overall pooled incidence rates per 1,000 person-years of VTE were 111 (95% CI 39–316) ($I^2$ value 99.7%) and 82 (95% CI 38–177) ($I^2$ value 94.2%) respectively (Overall $I^2$ value 99.2%), see Figure 2.10.

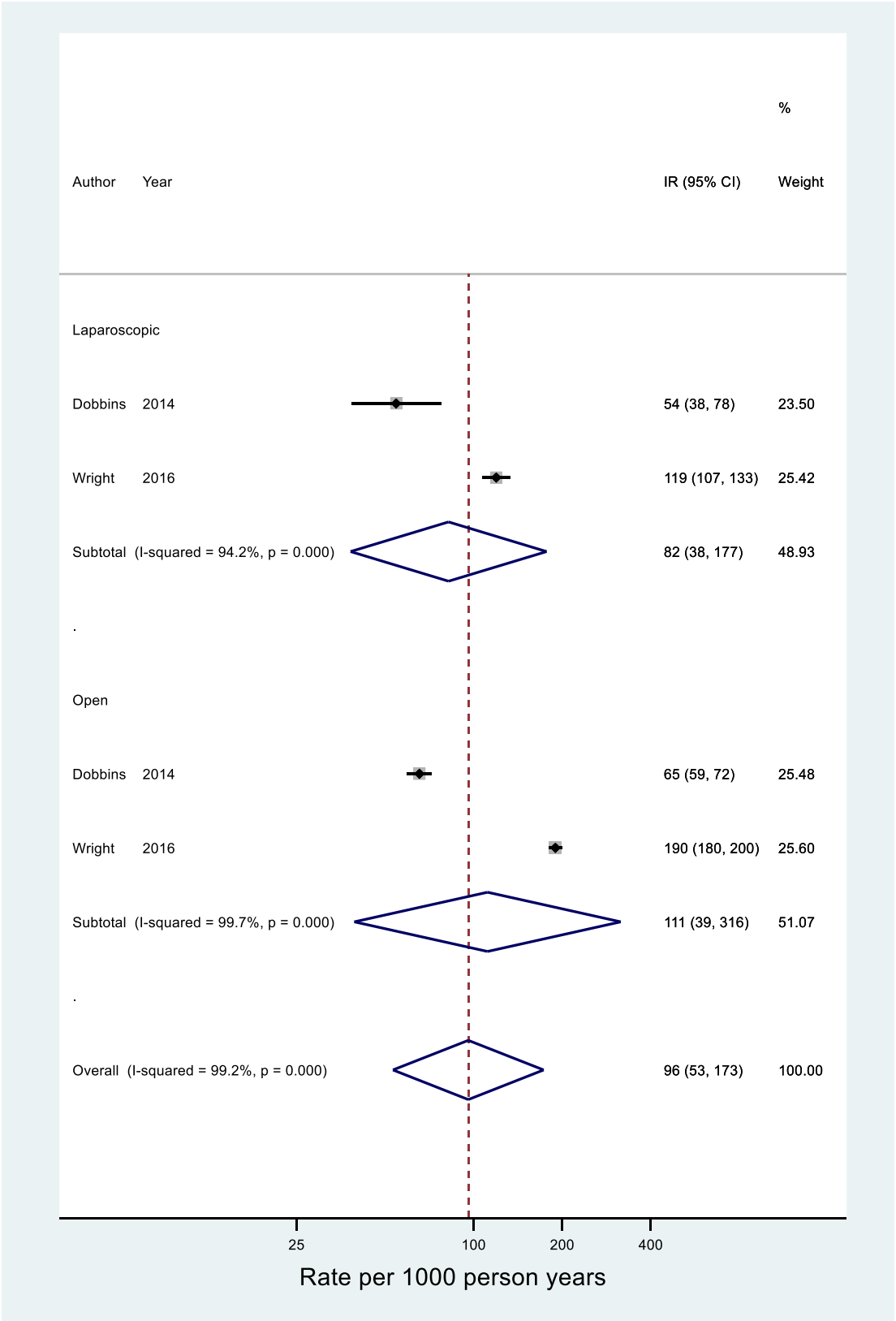



**Figure 2.10: 3-Months venous thromboembolism rates per 1,000 person-years of postoperative colorectal and colon cancer patients by laparoscopic vs. open operative technique**

### 2.3.5 Chapter summary

This systematic review and meta-analysis found from 18 pooled national or regional population-based cohort studies, that the incidence of VTE following CRC surgery is high at 1-month post resection (195 per 1,000 person-years (95% CI 148–256)). This postoperative VTE rate is greater than the pooled rate extrapolated from studies included in the updated Cochrane review of patients only receiving in-hospital VTE prophylaxis post predominantly abdominal or pelvic cancer surgery (117 per 1,000 person-years at 30-days following surgery (0.95%)).[51] This suggests the maintained benefit of extended VTE prophylaxis post CRC surgery at least to 1-month post resection. Despite a reduction in the incidence rate of VTE at 3-months post CRC resection (91 per 1,000 person-years (95% CI 56–146)), the postoperative VTE rate is still greater than those previously reported following benign general surgery.[203-205] Interestingly the postoperative VTE rates from the UN Geoscheme area of the Americas for both 30-days (284 per 1,000 person-years (95% CI 238–339)) and 90-days (121 per 1,000 person-years (95% CI 82–179)) were greater than those of Europe, Asia and Oceania. These global regional variations may be due to differences in clinical practice factors, such as surveillance protocols, and demographics seen between populations. Therefore, when determining recommendations and guidance on postoperative VTE prevention, VTE incidence rates should be assessed at regional levels.

This chapter has established postoperative VTE rates following CRC resection are high and that rates should be interpreted on a regional basis. Yet, Colorectal surgery and perioperative care has changed over the last 20 years with improvements such as the uptake of minimally invasive surgery comprising laparoscopic and more recently robotic resections. As well as international attention on postoperative VTE with clinical guidelines including the use of extended VTE prophylaxis for cancer resections and mandatory national VTE risk assessment. Plus, the incorporation of VTE within the World Health Organisation's (WHO) Surgical Safety Checklist and development of Colorectal specific ERAS protocols. These changes will likely have altered VTE risk following colectomy, however, no literature has assessed the trends in VTE risk in relation to these changes over time within a UK population. Therefore, the assessment of which perioperative advancements have benefited patients and which subgroups are of interest for future focus on VTE prevention is needed if we are to continue to improve patient safety and postoperative outcomes. This forms the objective of the next chapter.

# Chapter 3 Time Trends in the Incidence Rates of Venous Thromboembolism Following Colorectal Resection by Indication and Operative Technique

## Section 3.1 Introduction

Colorectal resection, the second most common major abdominal operation in the developed world, forms a substantial proportion of resectional abdominal surgery.[15] In the US alone, approximately 320,000 colectomies are performed annually.[17] VTE is a potentially preventable, sometimes fatal complication following colectomy occurring in 1.92% of patients within 30 days following CRC resection.[6]

Within the last two decades colorectal surgical care has changed. Globally VTE became a significant postoperative complication with multiple high-quality studies devoted to investigating methods of reducing its risk following colorectal resection.[23,52,95,100] In response, the ACCP in 2008[22] and NICE in 2010[48] published landmark guidance on VTE prevention following abdominal and pelvic surgery that has been adopted internationally.[206-210] This guidance advocated the use of inpatient combined pharmacological and mechanical VTE prophylaxis following gastrointestinal operations for benign disease and specifically extended postoperative pharmacological prophylaxis following cancer resections for 28 days.[34,50] VTE is considered so important, it forms part of the WHO Surgical Safety Checklist and is a performance measure in the US, UK and Australia with emphasis on timely risk assessment and appropriate prophylaxis prescription.[47,211] Furthermore, the impact of

incidental VTE is becoming apparent, with evidence suggesting similar rates of morbidity and mortality as those with symptomatic VTE in cancer patients and the reduction of asymptomatic VTE observed in laparoscopic CRC surgery with extended VTE prophylaxis use.[95,106]

In addition to VTE guidance, minimally invasive resection has been increasingly adopted for benign and malignant colorectal disease in developed and developing nations globally.[10-12,20,212-216] Minimally invasive surgery is coupled with the increased global utilisation of elective ERAS programs that have reduced perioperative complications and hospital length of stay.[163,167] Current literature debates the effect minimally invasive surgery has on VTE risk.[91,120,161,217] Reports state prolonged operating times and iatrogenic pneumoperitoneum increase venous stasis yet population-based evidence from literature review suggests minimally invasive compared to open colectomy reduces VTE risk.[68,151,152] However, none of these studies report VTE risk by operative technique stratified by admission type, examine incidence rates or account for time within their analyses.

Focus on VTE prevention, changes in operative techniques and ERAS will have likely altered VTE risk following colectomy, yet this has not been established.

### 3.1.1 Aim

The aim of this cohort study is to quantify variations in VTE rates over the last 20 years in relation to international changes in perioperative care following colorectal resection.

## Section 3.2 Methods

The study was approved by the Independent Scientific Advisory Committee (ISAC) approval board (Protocol 19_180RA3, see Appendix 8) and complies with Equator reporting guidelines for cohort studies (see STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist Appendix 9).

### 3.2.1 Data sources

This study utilised three validated and linked healthcare databases that have previously been described.[203,205,218] The CPRD, comprising GOLD and Aurum databases, contains primary care prescription and diagnostic data for approximately 60 million patients of the UK general population, with 16 million actively contributing data.[219] HES since 1989 has compiled detailed records for each episode of admitted patient care delivered in England, either by the NHS or commissioned by the NHS within the independent sector.[220] HES patient records are coded using a combination of the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes for discharge diagnoses and the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures version 4 (OPCS-4) codes for detailing procedures relating to an admission. These data have been shown to be demographically equivalent to data from the UK population having been compared to Office for National Statistics (ONS) data.[221,222]

### 3.2.2 Cohort

The cohort of patients undergoing colorectal resection between the years 2000 and 2019 were identified using OPCS-4 codes (Appendix 10) from HES data that was linked to CPRD GOLD and Aurum general practitioner practices. Within the CPRD databases, data quality can be assessed using two sets of metrics, acceptability and the up to standard date. Data is only considered acceptable if specific quality measures are met including valid age, gender, accuracy of recorded patient events and registration status. The up to standard date focuses on the accuracy of data continuity recorded by individual primary care practices for patients and is the latest date at which these practices met the minimum quality criteria outlined by the CPRD.[223] Therefore, patients were only included within the validated cohort if data collection time periods for both primary and secondary care databases coincided, and their data classed as up to research standard and acceptable.[224]

Patients undergoing colon or rectal resections were included in the analysis. Completely endoscopic operations and those confined to the anal canal were excluded, including patients aged < 18 years-old at date of operation. Patients identified as having a VTE event prior to resection were also excluded due to their inherently increased risk of VTE.[225] Previous VTE was defined using the same definition of VTE for the entire study. Patient follow-up included VTEs on the day of surgery, and lasted until earliest date of VTE event, death, change to a non-participating general practice or for 30 days after surgery.

### 3.2.3 Exposures

Calendar year was the main exposure of interest, defined as a continuous variable and as a binary variable pre and post 2010 (the year NICE guidance [CG92] from England, advocating extended VTE prophylaxis in CRC resections was published). Other exposures were selected from previous literature as follows:[21,84] Surgical indication was defined as malignant or benign. A malignant indication was defined within the CPRD and HES data using relevant ICD-10 codes for CRC (C18–C20, excluding C18·1 Appendix, malignant neoplasm). A benign indication was defined using ICD-10 discharge codes, including IBD, diverticular disease and other (Appendix 10). Admission type was defined as elective or emergency based on the admission classification recorded for the surgical procedure in HES data. Age was categorised into < 60, 60–69, 70–79, and ≥ 80 years. Sex was defined from HES data as either male or female. Co-morbidity was classified using the Charlson index prior to surgical admission and determined from CPRD and HES data, categories used were 0, 1, and ≥ 2.[226] The categorised scores reflect the original Charlson score and not the number of co-morbidities. Each patient's score was individually calculated from data prior to admission, with VTE outcomes not included within peripheral vascular disease as well as potential exposures of interest including age and presence of CRC. Ethnicity was determined from HES and categorised as white, other or unknown. Operative technique was classified into open, minimally invasive or those converted from minimally invasive to open surgery. Minimally invasive technique was

defined as laparoscopic or robotic surgery using OPCS-4 codes (Y50.8, Y57.1 and Y75.2) and (Y75.3) respectively. Hospital length of stay was defined from HES as the difference between colectomy admission episode start and end dates.

National NICE guidance from England on postoperative VTE prevention, published in 2010, stated that those undergoing abdominal surgery at risk of VTE should receive combined mechanical and chemical VTE prophylaxis during admission and those undergoing cancer surgery should receive extended 28-days of postoperative VTE chemoprophylaxis.[34] Therefore, within a population-based cohort from a nationally organised health service, all patients prior to the year 2010 were considered to have had inpatient VTE prophylaxis. However, from the year 2010 onwards those undergoing benign resections were deemed to have received inpatient but not extended or post-discharge VTE prophylaxis while those undergoing malignant resections were deemed to have received inpatient and a total of 28-days extended VTE prophylaxis and where applicable, prophylaxis into the post-discharge period.

### 3.2.4 Outcomes

The primary outcome was a VTE, either a PE or peripheral DVT, event diagnosis defined from medical and ICD-10 codes in the linked CPRD and HES datasets 30-days post resection. VTE events were only considered valid if supported by either a prescription for any

anticoagulant medication from the British National Formulary (BNF) licenced to treat a VTE in the UK or other evidence of treatment within an anticoagulation clinic (for example a medical code) between 15 days before and 90 days after VTE diagnosis, or a date of death within 30 days of the event. This time frame was used to allow for anticoagulant prescribing in the community to follow on from anticoagulation clinic or inpatient prescribing for a VTE event. Furthermore, VTE as an underlying cause of death was included as evidence of VTE diagnosis. 30-day postoperative follow-up was selected because this is the period of time required for the intervention of extended VTE prophylaxis and is a standard follow-up end point in other national population-based cohort studies allowing ease of comparison.[6] Only the first confirmed VTE episode was incorporated within the analysis. This definition using primary care data has been formally validated and published, specifically validating a VTE diagnosis against individual patient records with a positive predictive value of 84%[227] and used in previously published work conducted within The University of Nottingham for colectomy.[21]

### 3.2.5 Statistical analysis

Cohort demographics were presented as proportions and stratified by admission type and surgical indication. 30-day post colectomy incidence risks, presented as percentages, and absolute VTE incidence rates (IR) per 1,000 person-years were calculated for each year of the

study period and stratified *a priori* by admission type and surgical indication.[21,34,50]

Poisson regression was used to calculate adjusted incidence rate ratios (aIRR) for linear trend in year-on-year VTE risk, adjusted for all other exposures within the analyses and where relevant the relative change in VTE risk as a percentage over the 20-year study period. Effect modification, significance set at $P < 0.1$ using a generalised likelihood ratio test, was assessed within the multivariable model to test for any interactions between linear trend by year of colectomy and admission type, surgical indication, and operative technique.

In addition, a sensitivity analysis examining whether there was an interaction between the linear trend in VTE rates by year and pre and post 2010, the year NICE guidance on extended VTE prophylaxis use post malignant colectomy was published, was conducted.

All data management and analyses were performed using Stata SE® version 16.1 (StataCorp LLC, College Station, Texas, USA), see Appendix 11 for Chapter Stata Do file.

## Section 3.3 Results

### 3.3.1 Cohort demographics

Overall, 183,791 patients in the validated cohort underwent colorectal resection and 1,337 (0.73%) developed VTE within 30 days after surgery with an absolute IR of 90.67 (95% CI 85.94–95.66) per 1,000 person-years. Most patients were of white ethnicity (91.19%) and 93,598 (50.93%) were male, see Table 3.1.

There was an increase in minimally invasive surgery over time. Between 2000 and 2019 the yearly proportion of colectomies performed minimally invasively increased from 0.59% to 73.31% in the elective setting and from 0.36% to 26.17% in the emergency setting (both $P < 0.0001$, Chi-squared ($\chi 2$) test for trend), see Figure 3.1 & Figure 3.2. Overall hospital length of stay decreased over the study period from 12 (Interquartile range (IQR) 9–18) to 6 (IQR 4–11) days ($P < 0.0001$, Kruskal-Wallis test), see Figure 3.3.

| | No. = 183,791 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Emergency (No. = 62,183) | | | | Elective (No. = 121,608) | | | |
| | Benign (No. = 41,095) | | Malignant (No. = 21,088) | | Benign (No. = 36,183) | | Malignant (No. = 85,425) | |
| | No. | (%) | No. | (%) | No. | (%) | No. | (%) |
| **Age (Years)** | | | | | | | | |
| **< 60** | 19,319 | **(47.01)** | 4,537 | **(21.51)** | 19,439 | **(53.72)** | 17,951 | **(21.01)** |
| **60 - 69** | 7,448 | **(18.12)** | 4,542 | **(21.54)** | 7,736 | **(21.38)** | 23,413 | **(27.41)** |
| **70 - 79** | 8,383 | **(20.40)** | 6,266 | **(29.71)** | 6,598 | **(18.24)** | 27,936 | **(32.70)** |
| **≥ 80** | 5,945 | **(14.47)** | 5,743 | **(27.23)** | 2,410 | **(6.66)** | 16,125 | **(18.88)** |
| **Sex** | | | | | | | | |
| **Male** | 18,859 | **(45.89)** | 10,481 | **(49.70)** | 15,493 | **(42.82)** | 48,765 | **(57.09)** |
| **Female** | 22,236 | **(54.11)** | 10,607 | **(50.30)** | 20,690 | **(57.18)** | 36,660 | **(42.91)** |
| **Charlson Score** | | | | | | | | |
| **0** | 17,547 | **(42.70)** | 6,380 | **(30.25)** | 15,422 | **(42.62)** | 6,678 | **(7.82)** |
| **1** | 3,389 | **(8.25)** | 2,777 | **(13.17)** | 3,435 | **(9.49)** | 7,367 | **(8.62)** |
| **≥ 2** | 20,159 | **(49.05)** | 11,931 | **(56.58)** | 17,326 | **(47.88)** | 71,380 | **(83.56)** |
| **Ethnicity** | | | | | | | | |
| **White** | 37,018 | **(90.08)** | 18,883 | **(89.54)** | 33,190 | **(91.73)** | 78,511 | **(91.91)** |
| **Other** | 2,452 | **(5.97)** | 955 | **(4.53)** | 2,166 | **(5.99)** | 3,982 | **(4.66)** |
| **Unknown** | 1,625 | **(3.95)** | 1,250 | **(5.93)** | 827 | **(2.29)** | 2,932 | **(3.43)** |
| **Operative Technique** | | | | | | | | |
| **Open** | 36,098 | **(87.84)** | 19,239 | **(91.23)** | 23,583 | **(65.18)** | 50,028 | **(58.56)** |
| **Minimally Invasive converted to Open** | 1,927 | **(4.69)** | 535 | **(2.54)** | 2,042 | **(5.64)** | 5,053 | **(5.92)** |
| **Minimally Invasive** | 3,070 | **(7.47)** | 1,314 | **(6.23)** | 10,558 | **(29.18)** | 30,344 | **(35.52)** |
| **VTE at 30-days** | | | | | | | | |
| **Yes** | 380 | **(0.92)** | 295 | **(1.40)** | 169 | **(0.47)** | 493 | **(0.58)** |
| **No** | 40,715 | **(99.08)** | 20,793 | **(98.60)** | 36,014 | **(99.53)** | 84,932 | **(99.42)** |

**Table 3.1: Demographics of English colectomy cohort from 2000–2019, by admission type and indication for surgery**

VTE, Venous thromboembolism.

Minimally Invasive Surgery consists of procedure completed either by a laparoscopic or robotic technique.

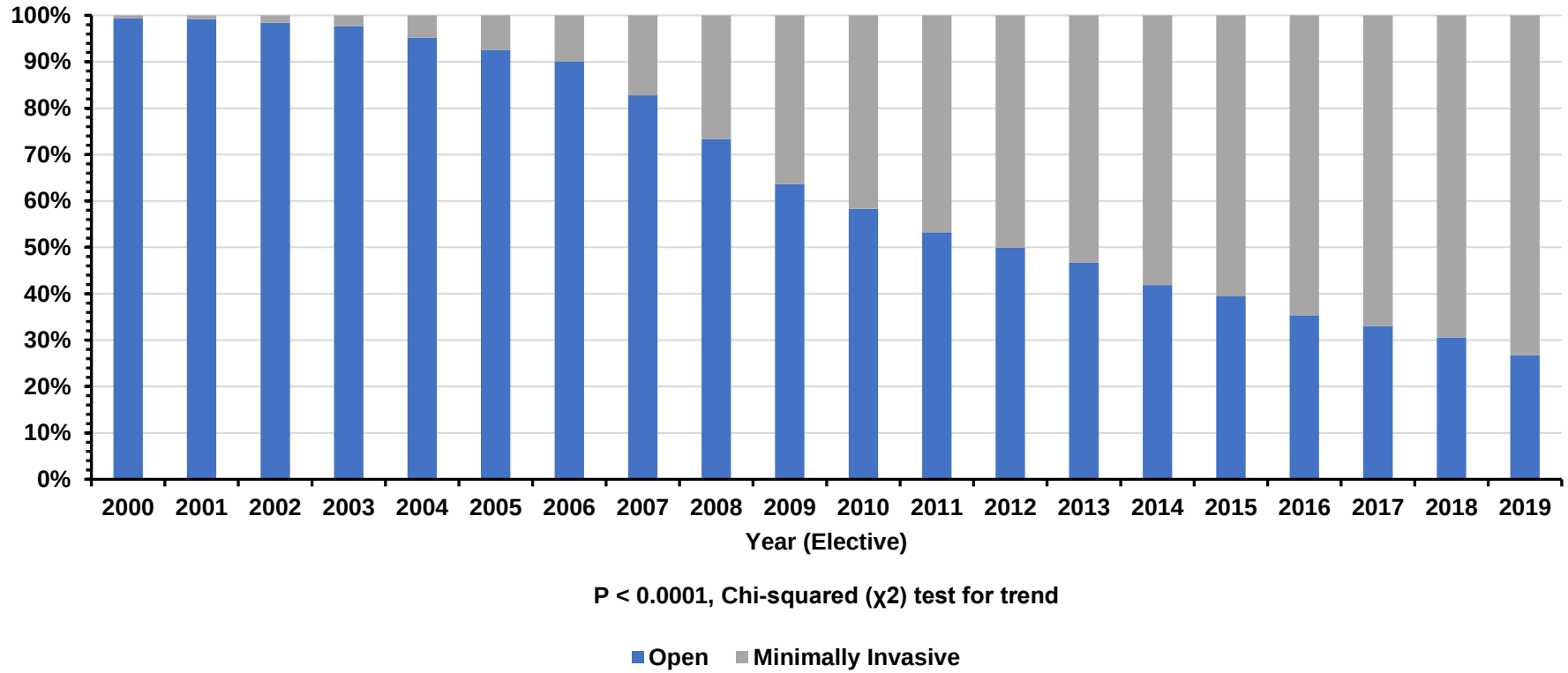



**Figure 3.1: Proportion of elective colectomies by operative technique over time from 2000–2019 in England:**

Minimally Invasive Surgery consists of procedures started either by a laparoscopic or robotic technique.

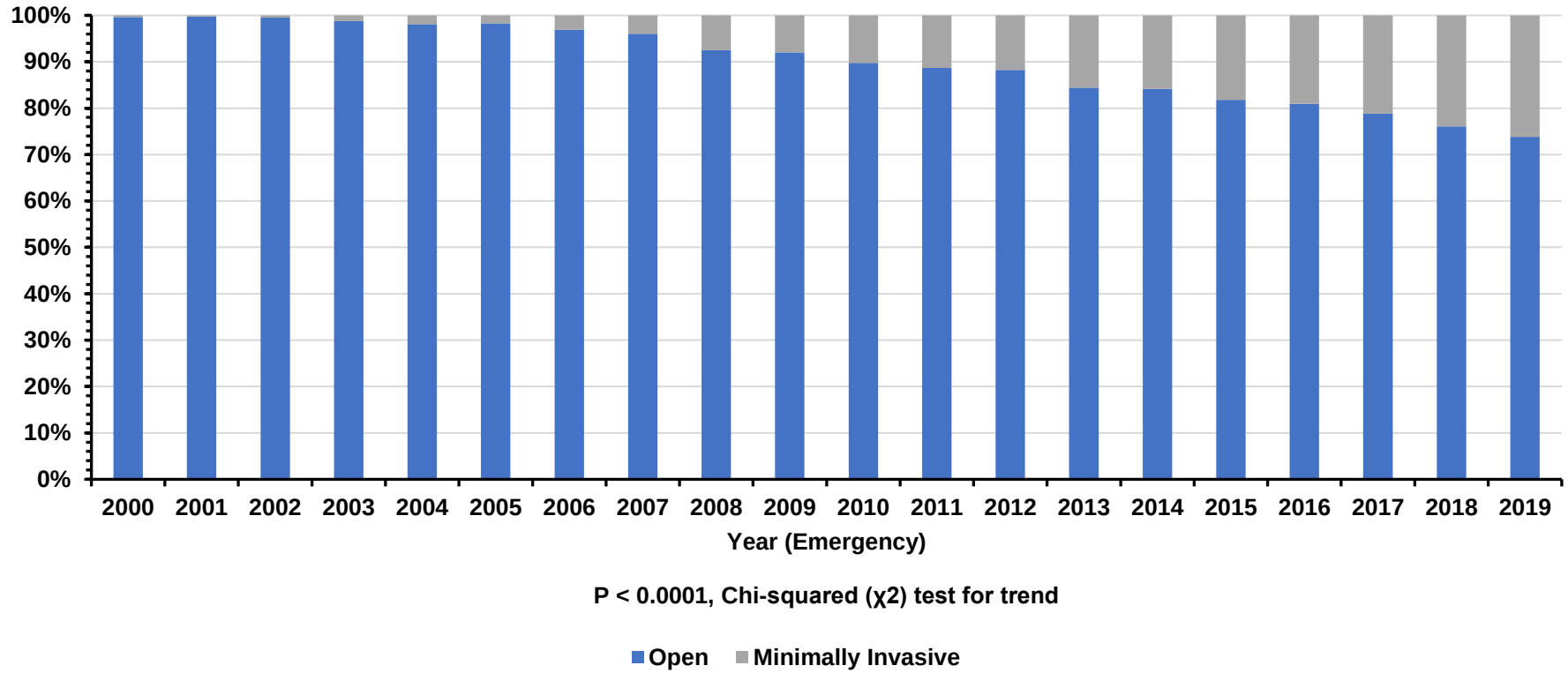



**Figure 3.2: Proportion of emergency colectomies by operative technique over time from 2000–2019 in England:**

Minimally Invasive Surgery consists of procedures started either by a laparoscopic or robotic technique.

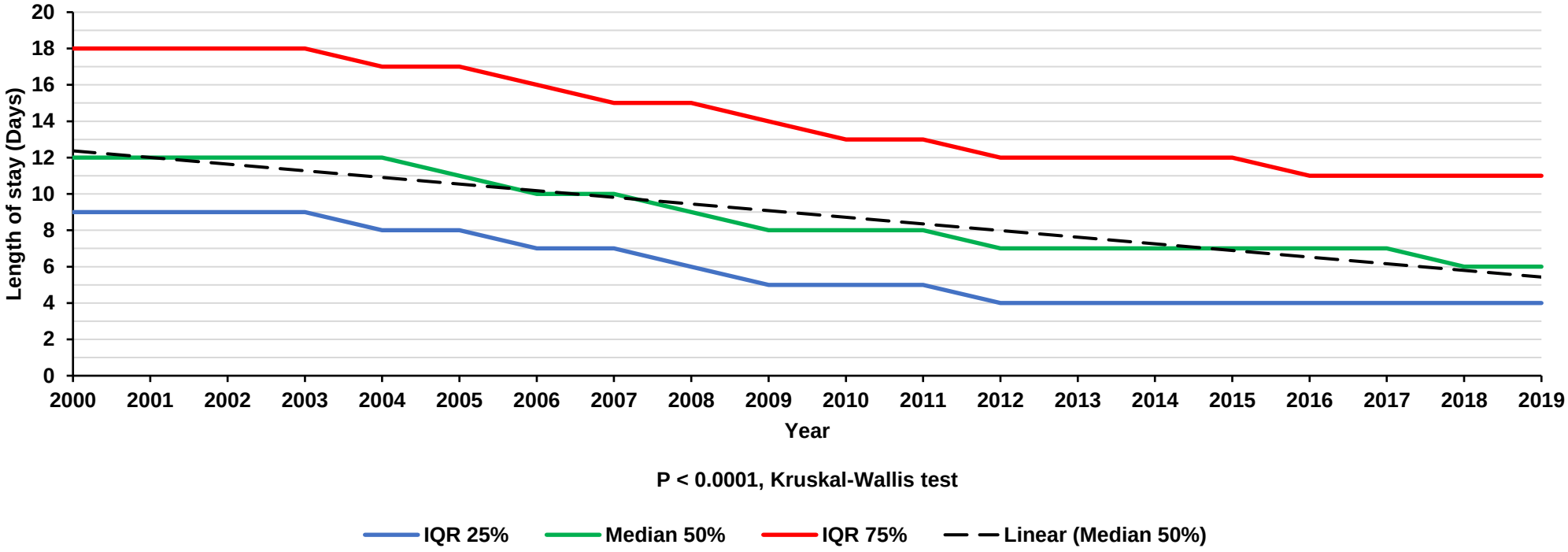



**Figure 3.3: 3-year rolling averaged overall hospital length of stay following colectomy in England from 2000 to 2019**

IQR, Inter quartile range.

Years 2005 (Colonic)[165] and 2009 (Rectal)[164] Enhanced Recovery After Surgery (ERAS) programmes introduced.

### 3.3.2 Venous thromboembolism following colorectal resection over time

*3.3.2.1 30-day rates and risks of VTE per year by admission type*

Patients undergoing elective colorectal resections had a 30-day VTE IR of 66.34 (95% CI 61.47–71.59) per 1,000 person years (0.54%) and overall significant relative VTE risk reduction of 31.25% (95% CI 5.69%–49.88%) over the 2000–2019 study period (year-on-year VTE risk change: aIRR 0.98, 95% CI 0.97-1.00, see Table 3.2), with yearly reductions in VTE rates observed prior to 2010, see Figure 3.4. However, no statistically significant relative VTE risk change was detected in those undergoing emergency resections over the 20-year study period (relative VTE risk increase: 22.38%, 95% CI -7.39%–61.73%, year-on-year VTE risk change: aIRR 1.01, 95% CI 1.00–1.02), with a 30-day VTE IR of 141.60 (95%CI 131.31–152.70) per 1,000 person years (1.09%), see Figure 3.5 & Table 3.3.

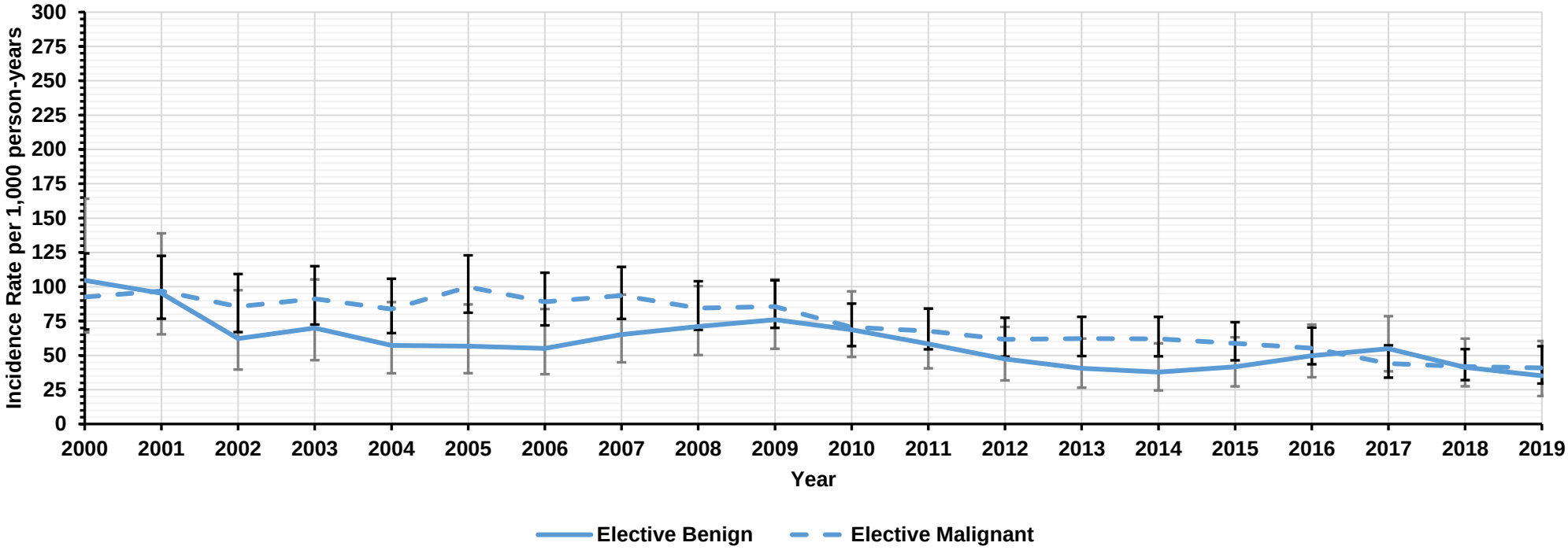



**Figure 3.4: 3-year rolling averaged 30-day venous thromboembolism rates per 1,000 person-years following elective colectomy in England from 2000–2019 stratified by surgical indication**

Error bars indicate 95% confidence intervals.

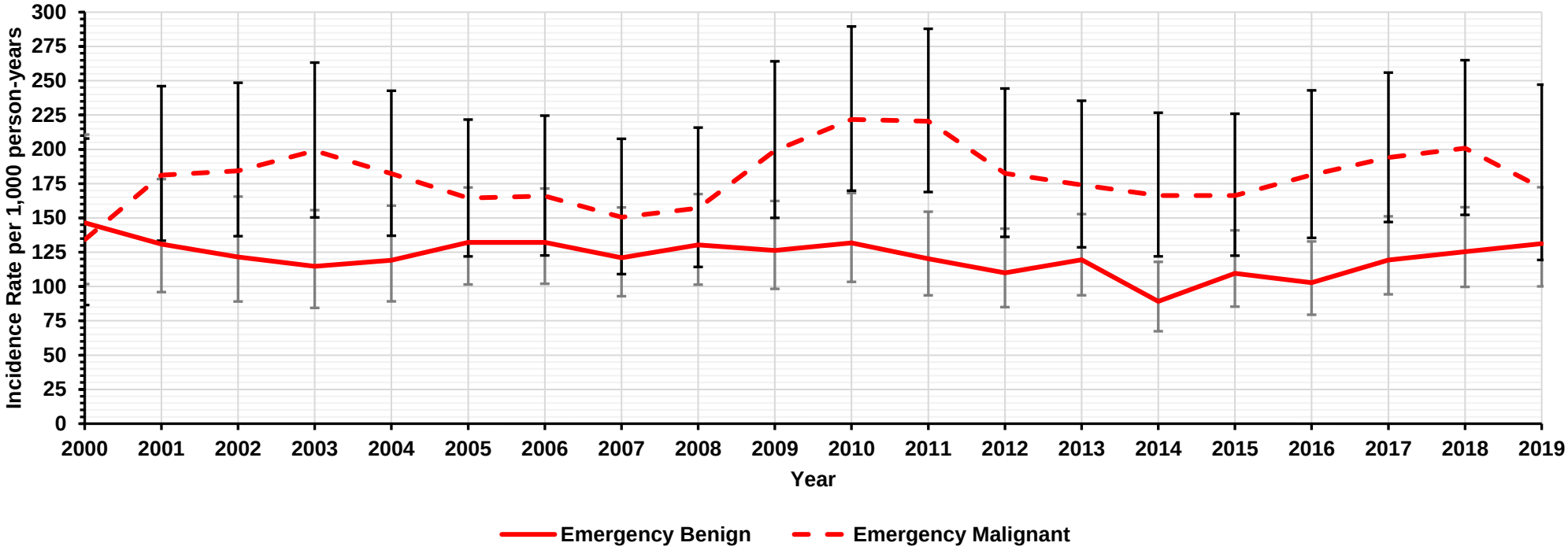



**Figure 3.5: 3-year rolling averaged 30-day venous thromboembolism rates per 1,000 person-years following emergency colectomy in England from 2000–2019 stratified by surgical indication**

Error bars indicate 95% confidence intervals.

| Elective (No. = 121,608) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Event No. | Person-years | Rate per 1,000 person-years | | | Unadjusted Incidence Rate Ratio | | Adjusted Incidence Rate Ratio[a] | |
| | | | | (95% CI) | | | (95% CI) | | (95% CI) |
| **Surgical Indication** | | | | | | | | | |
| **Benign** | 169 | 2.97 | **56.81** | (48.86 | 66.06) | **1.00** | (Reference) | **1.00** | (Reference) |
| **Malignant** | 493 | 7.00 | **70.38** | (64.44 | 76.88) | **1.24** | (1.04 1.48) | **0.96** | (0.79 1.16) |
| **Age (Years)** | | | | | | | | | |
| **< 60** | 122 | 3.10 | **39.34** | (32.94 | 46.98) | **1.00** | (Reference) | **1.00** | (Reference) |
| **60 - 69** | 170 | 2.57 | **66.22** | (56.98 | 76.96 | **1.68** | (1.33 2.12) | **1.57** | (1.23 1.99) |
| **70 - 79** | 255 | 2.82 | **90.52** | (80.07 | 102.34) | **2.30** | (1.85 2.86) | **2.09** | (1.67 2.63) |
| **≥ 80** | 115 | 1.49 | **76.98** | (64.12 | 92.41) | **1.96** | (1.52 2.52) | **1.78** | (1.36 2.32) |
| **Sex** | | | | | | | | | |
| **Male** | 375 | 5.25 | **71.37** | (64.50 | 78.98) | **1.00** | (Reference) | **1.00** | (Reference) |
| **Female** | 287 | 4.73 | **60.74** | (54.10 | 68.19) | **0.85** | (0.73 0.99) | **0.86** | (0.74 1.01) |
| **Charlson Score** | | | | | | | | | |
| **0** | 88 | 1.82 | **48.22** | (39.13 | 59.43) | **1.00** | (Reference) | **1.00** | (Reference) |
| **1** | 62 | 0.89 | **69.88** | (54.48 | 89.63) | **1.45** | (1.05 2.01) | **1.21** | (0.86 1.69) |
| **≥ 2** | 512 | 7.27 | **70.45** | (64.61 | 76.83) | **1.46** | (1.17 1.83) | **1.27** | (0.99 1.62) |
| **Ethnicity** | | | | | | | | | |
| **White** | 612 | 9.17 | **66.73** | (61.65 | 72.23) | **1.00** | (Reference) | **1.00** | (Reference) |
| **Other** | 19 | 0.51 | **37.50** | (23.92 | 58.80) | **0.56** | (0.36 0.89) | **0.70** | (0.44 1.10) |
| **Unknown** | 31 | 0.30 | **102.95** | (72.40 | 146.38) | **1.54** | (1.08 2.21) | **1.40** | (0.97 2.01) |
| **Operative Technique** | | | | | | | | | |
| **Open** | 498 | 6.01 | **82.80** | (75.84 | 90.40) | **1.00** | (Reference) | **1.00** | (Reference) |
| **Minimally Invasive converted to Open** | 33 | 0.58 | **56.69** | (40.30 | 79.74) | **0.68** | (0.48 0.97) | **0.75** | (0.52 1.08) |
| **Minimally Invasive** | 131 | 3.38 | **38.73** | (32.63 | 45.96) | **0.47** | (0.39 0.57) | **0.53** | (0.43 0.66) |
| **Year (2000 - 2019)** | | | | | | | | | |
| **Per Year Change** | - | - | **-** | - | - | **0.96** | (0.94 0.97) | **0.98** | (0.97 1.00) |

**Table 3.2: Absolute rates and incidence rate ratios of venous thromboembolism 30-days after elective resectional Colorectal surgery in England from 2000–2019**

Minimally Invasive Surgery consists of procedure completed either by a laparoscopic or robotic technique.

[a]Adjusted for surgical indication, age, sex, Charlson score, ethnicity, operative technique and year.

| Emergency (No. = 62,183) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Event No. | Person-years | Rate per 1,000 person-years | | | Unadjusted Incidence Rate Ratio | | Adjusted Incidence Rate Ratio[a] | |
| | | | | (95% CI) | | | (95% CI) | | (95% CI) |
| **Surgical Indication** | | | | | | | | | |
| **Benign** | 380 | 3.14 | **121.20** | (109.61 | 134.02) | **1.00** | (Reference) | **1.00** | (Reference) |
| **Malignant** | 295 | 1.63 | **180.80** | (161.30 | 202.66) | **1.49** | (1.28 1.74) | **1.24** | (1.05 1.45) |
| **Age (Years)** | | | | | | | | | |
| **< 60** | 157 | 1.94 | **81.08** | (69.34 | 94.80) | **1.00** | (Reference) | **1.00** | (Reference) |
| **60 - 69** | 148 | 0.93 | **159.33** | (135.62 | 187.18) | **1.97** | (1.57 2.46) | **1.73** | (1.38 2.18) |
| **70 - 79** | 201 | 1.09 | **184.65** | (160.81 | 212.02) | **2.28** | (1.85 2.81) | **1.94** | (1.56 2.42) |
| **≥ 80** | 169 | 0.81 | **207.86** | (178.77 | 241.68) | **2.56** | (2.06 3.19) | **2.12** | (1.68 2.69) |
| **Sex** | | | | | | | | | |
| **Male** | 301 | 2.27 | **132.78** | (118.59 | 148.66) | **1.00** | (Reference) | **1.00** | (Reference) |
| **Female** | 374 | 2.50 | **149.60** | (135.18 | 165.56) | **1.13** | (0.97 1.31) | **1.09** | (0.93 1.26) |
| **Charlson Score** | | | | | | | | | |
| **0** | 209 | 1.89 | **110.30** | (96.31 | 126.31) | **1.00** | (Reference) | **1.00** | (Reference) |
| **1** | 74 | 0.48 | **154.82** | (123.27 | 194.43) | **1.40** | (1.08 1.83) | **1.12** | (0.86 1.47) |
| **≥ 2** | 392 | 2.39 | **163.74** | (148.31 | 180.78) | **1.48** | (1.26 1.76) | **1.17** | (0.98 1.39) |
| **Ethnicity** | | | | | | | | | |
| **White** | 616 | 4.30 | **143.21** | (132.34 | 154.98) | **1.00** | (Reference) | **1.00** | (Reference) |
| **Other** | 21 | 0.27 | **77.34** | (50.42 | 118.61) | **0.54** | (0.35 0.83) | **0.67** | (0.43 1.04) |
| **Unknown** | 38 | 0.19 | **195.85** | (142.51 | 269.16) | **1.37** | (0.99 1.90) | **1.32** | (0.94 1.83) |
| **Operative Technique** | | | | | | | | | |
| **Open** | 631 | 4.21 | **149.88** | (138.63 | 162.04) | **1.00** | (Reference) | **1.00** | (Reference) |
| **Minimally Invasive converted to Open** | 16 | 0.20 | **80.40** | (49.26 | 131.24) | **0.54** | (0.33 0.88) | **0.63** | (0.38 1.04) |
| **Minimally Invasive** | 28 | 0.36 | **78.25** | (54.03 | 113.34) | **0.52** | (0.36 0.76) | **0.58** | (0.40 0.86) |
| **Year (2000 - 2019)** | | | | | | | | | |
| **Per Year Change** | - | - | **-** | - | - | **1.00** | (0.98 1.01) | **1.01** | (1.00 1.02) |

**Table 3.3: Absolute rates and incidence rate ratios of venous thromboembolism 30-days after emergency resectional Colorectal surgery in England from 2000–2019**

Minimally Invasive Surgery consists of procedure completed either by a laparoscopic or robotic technique.

[a]Adjusted for surgical indication, age, sex, Charlson score, ethnicity, operative technique and year.

*3.3.2.2 30-day VTE risks per year by operative technique*

Minimally invasive compared to open surgery reduced VTE risk by approximately 50% following both elective and emergency colorectal resections (aIRR 0.53, 95% CI 0.43–0.66 and aIRR 0.58, 95% CI 0.40–0.86 respectively). There were also significant interactions between the linear trend in VTE risk and both admission type, P = 0.0055, and operative technique, P = 0.0084. Therefore, for the remaining results the linear trend in VTE risks were further stratified by operative technique as in Table 3.4. For the final multivariable analysis, procedures that began using a minimally invasive approach were classed as minimally invasive surgery due to the overall small numbers and reduced statistical power within the minimally invasive converted to open subgroup.

| Per Year Change (2000 - 2019) | Incidence Risk (%) | Adjusted Incidence Rate Ratio[a] | | | Percentage (%) change of Adjusted Model | | | P-value[b] |
|---|---|---|---|---|---|---|---|---|
| | | | (95%CI) | | % | (95%CI) | | |
| **Elective Benign** | | | | | | | | |
| **Open** | 0.57 | **0.98** | (0.96 | 1.00) | **-2.03** | (-4.21 | 0.19) | 0.073 |
| **Minimally Invasive** | 0.27 | **0.93** | (0.90 | 0.97) | **-6.78** | (-10.26 | -3.15) | <0.001 |
| **Elective Malignant** | | | | | | | | |
| **Open** | 0.73 | **0.99** | (0.98 | 1.01) | **-0.81** | (-2.48 | 0.88) | 0.344 |
| **Minimally Invasive** | 0.37 | **0.94** | (0.91 | 0.98) | **-5.62** | (-8.84 | -2.27) | 0.001 |
| **Emergency Benign** | | | | | | | | |
| **Open** | 0.99 | **1.01** | (0.99 | 1.02) | **0.64** | (-0.99 | 2.29) | 0.446 |
| **Minimally Invasive** | 0.48 | **0.96** | (0.92 | 1.00) | **-4.24** | (-7.88 | -0.45) | 0.029 |
| **Emergency Malignant** | | | | | | | | |
| **Open** | 1.43 | **1.02** | (1.00 | 1.04) | **1.89** | (0.05 | 3.77) | 0.044 |
| **Minimally Invasive** | 1.08 | **0.97** | (0.93 | 1.01) | **-3.04** | (-6.78 | 0.84) | 0.123 |

**Table 3.4: Multivariable analysis of 30-day venous thromboembolism risk per year change following colectomy in England between 2000–2019 by admission type, surgical indication and operative technique**

Minimally Invasive Surgery consists of procedures started either by a laparoscopic or robotic technique.

[a]Adjusted for admission type, surgical indication, age, sex, Charlson score, ethnicity, operative technique and year.

[b]P-value for adjusted model.

*3.3.2.2.1 Elective colectomy*

Following elective benign and malignant minimally invasive colorectal resections a 6.78% and 5.62% year-on-year reduction in VTE risk were observed (aIRR 0.93, 95% CI 0.90–0.97 and aIRR 0.94, 95% CI 0.91–0.98 respectively) with 30-day VTE IR per 1,000 person-years of 32.57 (95% CI 23.27–45.58) (0.27%) and IR 44.51 (95% CI 37.48–52.86) (0.37%) respectively. Following elective benign or malignant open resections no significant year-on-year VTE risk reductions were observed (aIRR 0.98, 95% CI 0.96–1.00 and aIRR 0.99, 95% CI 0.98–1.01 respectively) with 30-day VTE IR per 1,000 person-years of 69.92 (95% CI 59.07–82.77) (0.57%) and IR 88.88 (95% CI 80.19–98.51) (0.73%) respectively.

*3.3.2.2.2 Emergency colectomy*

In the emergency setting, patients undergoing minimally invasive benign colorectal resections had a significant year-on-year reduction in VTE risk of 4.24% (aIRR 0.96, 95% CI 0.92–1.00) with a 30-day VTE IR of 58.89 (95% CI 39.47–87.86) per 1,000 person-years (0.48%). No significant year-on-year reduction in VTE risk was observed in emergency malignant minimally invasive resections (aIRR 0.97, 95% CI 0.93–1.01) with a 30-day VTE IR of 133.98 (95% CI 86.44–207.66) per 1,000 person-years (1.08%). In patients undergoing emergency open Colorectal surgery, those undergoing cancer resection had a significant 1.89% year-on-year increase in VTE risk (aIRR 1.02, 95% CI 1.00–1.04) with a 30-day VTE IR of 185.52 (95% CI 164.84–208.79) per 1,000 person-years (1.43%). In benign emergency open resections, no

significant year-on-year increase in VTE risk was seen (aIRR 1.01, 95% CI 0.99–1.02) with a 30-day VTE IR of 130.51 (95% CI 117.63–144.80) per 1,000 person-years (0.99%).

*3.3.2.3 Postoperative VTE rates pre and post 2010*

Within the final model, no significant effect modification, P = 0.9305, was found between year-on-year VTE trend post colorectal resection and pre/post the year 2010, the year NICE guidance on extended VTE prophylaxis use was published, with no overall significant step change in VTE risk between pre and post 2010 observed (aIRR 0.96, 95% CI 0.78–1.19). No change in effect modification or step change in VTE risk was observed using 1- or 2-year washout periods post the introduction of NICE guidelines. This was despite the overall reduction in VTE rates seen in elective colorectal resections that began prior to the year 2010, see Figure 3.4.

### 3.3.3 Chapter summary

This national population-based cohort study of colectomy patients from England has shown over the last 20 years there has been an overall significant relative risk reduction of 31.25% of 30-day VTE following elective colectomies. Whereas no significant change in VTE risk was observed in patients undergoing emergency colectomy. This reduction in VTE risk appears multifactorial and in part attributable to the uptake of minimally invasive colectomy techniques that increased over the study period as well as approximately halving the VTE risk in both

elective and emergency resections. Similarly, the implementation and uptake of Colorectal ERAS protocols, with an observed reduction in hospital length of stay over the study period, has likely contributed to the decrease in VTE risk. As well as the increase in awareness surrounding VTE prevention and following of national guidance in relation to extended VTE prophylaxis. Although the introduction of national guidance did not solely lead to a significant annual reduction in postoperative VTE risk. The greatest annual reductions in VTE risk and absolute incidence risk of VTE were observed in elective minimally invasive colectomies (Benign (aIRR 0.93, 95% CI 0.90–0.97) and Malignant (aIRR 0.94, 95% CI 0.91–0.98)). While open or emergency operations trended to have no change in annual VTE risk. Specifically, emergency malignant open resections were found to have a significant increase in annual VTE risk over the study period (aIRR 1.02, 95% CI 1.00–1.04).

The findings in this chapter highlight future focus in VTE prevention needs to be directed at patients undergoing emergency and or open colectomy. This might be achieved by increasing the uptake of emergency minimally invasive colectomy as well as establishing emergency specific ERAS protocols within Colorectal surgery. In those undergoing benign resections the use of extended VTE prophylaxis might also be beneficial yet is not currently advocated by UK national guidance. However, no contemporary data exists on the magnitude and duration of post colectomy VTE risk, specifically into the post-discharge period, within a UK population. This could help compare and determine

whether current national perioperative VTE prophylaxis regimens adequately reduce VTE incidence rates. Particularly in relation to subgroups of interest that are now considered high risk for postoperative VTE, such as those undergoing emergency benign colectomy that might now require extended VTE prophylaxis. This forms the objective of the next chapter.

# Chapter 4 The Duration and Magnitude of Post-Discharge Venous Thromboembolism Following Colectomy

## Section 4.1 Introduction

Colectomy is the second most common major inpatient abdominal operation globally, comprising 2.5% of all surgical procedures performed in the US each year.[14,16] However, colorectal resections have one of the highest abdominal postoperative risks of VTE, an avoidable and potentially fatal major postoperative complication.[23,24] This risk is especially elevated post emergency and CRC surgery with over a third of VTEs occurring post-discharge.[6,21,71]

To prevent postoperative VTE, international guidance strongly recommends combined mechanical and pharmacological VTE prophylaxis as an inpatient, or if discharged within the first week a minimum 7-days postoperative pharmacological VTE prophylaxis is required following benign colectomies, and for 4-weeks post CRC resection.[34,50] However, evidence used for these recommendations is of moderate to low quality, predominantly analysed open elective operations only and no studies have examined weekly VTE rates following colectomy.[51,52] Furthermore, changes in operative management might have altered post colectomy VTE risk, for example the uptake of minimally invasive surgery,[7,83,228] and additional groups, that some now consider are at higher risk of postoperative VTE, such as those undergoing emergency benign or IBD resections, might now warrant extended VTE prophylaxis.[21,30,116,120,135,137]

Therefore, contemporary stratified VTE rates following colorectal resection are needed to accurately define the duration and magnitude of postoperative VTE risk within this population to aid guidance on VTE prophylaxis length.

### 4.1.1 Aim

The aim of this cohort study is to describe detailed stratified post-discharge VTE rates in different discharge time risk periods following colectomy to inform extended VTE prophylaxis guidelines.

## Section 4.2 Methods

The study was approved by the ISAC approval board (Protocol 19_180RA3, see Appendix 8) and complies with Equator reporting guidelines for cohort studies (see STROBE checklist Appendix 12).

### 4.2.1 Data sources

This study utilised three validated and linked healthcare databases previously described.[203,205,218] The CPRD, comprising GOLD and Aurum databases, contains primary care prescription and diagnostic data for approximately 60 million patients of the UK general population, with 16 million actively contributing data.[219] Since 1989 HES has compiled detailed records for each episode of admitted patient care delivered in England, either by the NHS or commissioned by the NHS within the independent sector.[220] HES patient records are coded using a combination of the ICD-10 codes for discharge diagnoses and OPCS-4 codes for detailing procedures relating to an admission. These data have been shown to be demographically equivalent to data from the UK population having been compared to ONS data.[221,222]

### 4.2.2 Cohort

The cohort of patients undergoing colectomy between the years 2010 and 2019 were identified using OPCS-4 codes (Appendix 10) from HES data that was linked to CPRD GOLD and Aurum general practitioner practices. Within the CPRD databases, data quality can be assessed

using two sets of metrics, acceptability and the up to standard date. Data is only considered acceptable if specific quality measures are met including valid age, gender, accuracy of recorded patient events and registration status. The up to standard date focuses on the accuracy of data continuity recorded by individual primary care practices for patients and is the latest date at which these practices met the minimum quality criteria outlined by the CPRD.[223] Therefore, patients were only included within the validated cohort if data collection time periods for both primary and secondary care databases coincided, and their data classed as up to research standard and acceptable.[224] The time frame was selected on the basis that by 2010 NICE postoperative VTE guidance in England had been published and was in effect.[19,48]

Patients undergoing colon or rectal resections were included in the analysis. Completely endoscopic operations, those confined to the anal canal, and patients aged < 18 years-old were excluded. Patients identified as having a VTE event prior to colectomy were also excluded due to their inherently increased risk of VTE.[225] Person-time and post-discharge follow-up started the day after the date of hospital discharge. All follow-up lasted until earliest date of VTE event, death, change to a non-participating general practice or 12-weeks from the date of operation, see Figure 4.1. 12-weeks postoperative follow-up was chosen from previous literature.[80]

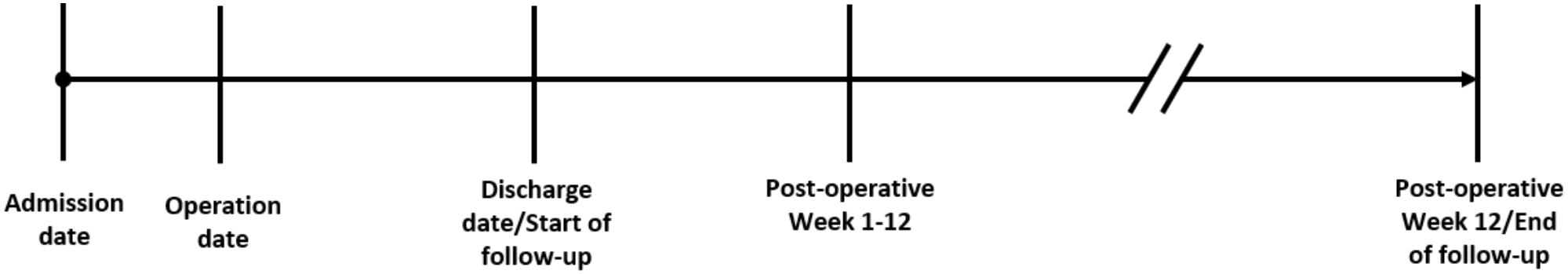



**Figure 4.1: Summary and example timeline of English 2010–2019 colectomy cohort patient follow-up period examining postoperative post-discharge venous thromboembolism**

VTE, Venous thromboembolism.

- Person-time and post-discharge follow-up started the day after the discharge date and ended 12 weeks post the operation date. VTE events occurring in this period were classed as postoperative post-discharge VTEs.

### 4.2.3 Exposures

Admission type, surgical indication and operative technique were the main exposures of interest and selected from previous literature.[21,84] Admission type was defined as elective or emergency based on the admission classification recorded for the surgical procedure in HES data. Surgical indication was defined as benign or malignant. A benign indication was defined using ICD-10 discharge codes, including IBD, diverticular disease and other (Appendix 10). A malignant indication was defined within the CPRD and HES data using relevant ICD-10 codes for CRC (C18–C20, excluding C18·1 Appendix, malignant neoplasm). Metastatic disease within malignant indications was defined within the CPRD and HES data using relevant ICD-10 codes for secondary malignant neoplasms related to CRC (C78.0, C78.6–8, C79.3 and C79.5) that were first coded for during the index colectomy admission. Operative technique was classified into open and minimally invasive surgery. Minimally invasive technique was defined as laparoscopic or robotic surgery using OPCS-4 codes (Y50.8, Y57.1 and Y75.2) and (Y75.3) respectively. Procedures that began using a minimally invasive approach were classed as minimally invasive surgery. Age at time of operation was categorised into < 60, 60–69, 70–79, and ≥ 80 years and as a binary variable, ≤ 60 and > 60 years. Co-morbidity was classified using the Charlson index prior to surgical admission and determined from CPRD and HES data and categorised into 0, 1, and ≥ 2 as well the binary variable 0 or ≥ 1.[226] The categorised scores reflect the original Charlson score and not the number of co-

morbidities. Each patient's score was individually calculated from data prior to admission, with VTE outcomes not included within peripheral vascular disease as well as potential exposures of interest including age and presence of CRC. The binary variables were based on the NICE VTE risk assessment tool score groupings.[34] Sex was defined from HES data as either male or female. Ethnicity was determined from HES and categorised as white, other or unknown. Postoperative hospital length of stay was defined from HES as the time from colectomy operation to discharge date and classed as a binary variable, ≤ 7 or > 7 days post-operation.

National NICE guidance from England on postoperative VTE prevention during the cohort time frame stated that those undergoing abdominal surgery at risk of VTE should receive combined mechanical and chemical VTE prophylaxis during admission and those undergoing cancer surgery should receive extended 28-days of postoperative VTE chemoprophylaxis.[34] Therefore, within a population-based cohort from a nationally organised health service, those undergoing benign resections were deemed to have received inpatient but not extended or post-discharge VTE prophylaxis while those undergoing malignant resections were deemed to have received inpatient and a total of 28-days extended VTE prophylaxis and where applicable, prophylaxis into the post-discharge period.

### 4.2.4 Outcomes

The primary outcome was a postoperative post-discharge VTE, either a PE or peripheral DVT, event diagnosis defined from medical and ICD-10 codes in the linked CPRD and HES datasets. Post-discharge VTE was defined as a VTE event occurring after the HES colectomy discharge date. VTE events were only considered valid if supported by either a prescription for any anticoagulant medication from the BNF licenced to treat a VTE in the UK or other evidence of treatment within an anticoagulation clinic (for example a medical code) between 15 days before and 90 days after VTE diagnosis, or a date of death within 30 days of the event. This time frame was used to allow for anticoagulant prescribing in the community to follow on from anticoagulation clinic or inpatient prescribing for a VTE event. Furthermore, VTE as an underlying cause of death was included as evidence of VTE diagnosis. Only the first confirmed VTE episode was incorporated within the analysis with further follow up time censored. This definition using primary care data has been formally validated and published, specifically validating a VTE diagnosis against individual patient records with a positive predictive value of 84%[227] and used in previously published work conducted within The University of Nottingham for colectomy.[21]

### 4.2.5 Statistical analysis

Cohort demographics were presented as proportions and stratified by admission type and operative technique. Absolute IRs of VTE were calculated per 1,000 person-years with 95% CI.

Post-discharge VTE rates for each week from the date of operation up to 12-weeks following colectomy were calculated and stratified *a priori* by admission type and surgical indication then operative technique.[21,34,50] However, it was anticipated numbers undergoing emergency minimally invasive colectomies would be small preventing stratification by operative technique.[20,229]

Post-discharge VTE rates and aIRRs for linear trend, adjusted for age, sex, co-morbidity and operative technique, were calculated for the first 4-weeks following colectomy and stratified *a priori* by admission type and surgical indication.[21,34,50]

Post-discharge VTE rates and aIRR for linear trend stratified by operative technique were also calculated for the first 4-weeks following colectomy, adjusted for age, sex, co-morbidity, admission type and surgical indication.

To assess the impact of IBD resections on overall benign colectomy post-discharge VTE risk. A sensitivity analysis of post-discharge VTE rates for each week from the date of operation up to 12-weeks following benign colectomy were calculated and further stratified into 'benign other' and IBD surgical indications. This included an analysis of the multivariable model for the first 4-weeks following colectomy with

benign surgical indications stratified into ‘benign other’ and IBD conditions.

A further sensitivity analysis was conducted on those undergoing malignant resections to examine the effect of metastatic disease on post-discharge VTE rates using a Poisson regression model for the first 4-weeks following colectomy adjusted for admission type age, sex, co-morbidity and operative technique.

Additionally, where numbers were sufficient, post-discharge VTE rates were assessed by other VTE risk factors; age, ≤ 60 or > 60 years-old, co-morbidity, Charlson score 0 or ≥ 1, and postoperative length of stay, ≤ 7 or > 7 days, stratified by admission type for each week following the date of surgery up to postoperative week 12.[21,71] Post-discharge VTE rates and aIRRs for linear trend, stratified by each of these three binary variables, were also calculated for the first 4-weeks following colectomy and adjusted in turn for age, sex, co-morbidity, operative technique, admission type and surgical indication.

All data management and analyses were performed using Stata SE® version 16.1 (StataCorp LLC, College Station, Texas, USA), see Appendix 13 for Chapter Stata Do file.

## Section 4.3 Results

### 4.3.1 Cohort demographics

Of 104,744 patients undergoing colectomy included in the cohort, 663 (0.63%) developed a post-discharge VTE within 12 weeks following resection. Over half of elective colectomies were performed using a minimally invasive approach (58.88%) with an increase in proportion over the study period from 41.77% in 2010 to 73.36% by 2019. The overall conversion from minimally invasive to open colectomy was 7.99%, and 8.75% for elective and 6.40% for emergency resections respectively. Elective patients were older (≥60 years-old 67.16%), underwent malignant resections (69.89%) and had ≥1 significant co-morbidity (83.95%). Most emergency colectomies were performed using an open approach (82.49%) with an increase in minimally invasive surgery over the study period from 10.20% in 2010 to 26.16% by 2019 and underwent resections for benign disease (69.28%). Over half of emergency patients had ≥1 significant co-morbidity (63.29%). Median postoperative length of stay following colectomy was 7 days (IQR 5–11) for elective benign, 7 days (IQR 5–10) for elective malignant, 11 days (IQR 7–20) for emergency benign and 11 days (IQR 7–19) for emergency malignant resections. Overall, 49.32% of patients were in hospital for ≤ 7 days post-operation, see Table 4.1.

| | No. = 104,744 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Emergency (No. = 34,083) | | | | Elective (No. = 70,661) | | | |
| | Open (No. = 28,115) | | Minimally invasive (No. = 5,968) | | Open (No. = 29,059) | | Minimally invasive (No. = 41,602) | |
| | No. | (%) | No. | (%) | No. | (%) | No. | (%) |
| **Surgical Indication** | | | | | | | | |
| **Benign** | 19,205 | **(68.31)** | 4,406 | **(73.83)** | 10,629 | **(36.58)** | 10,646 | **(25.59)** |
| **Malignant** | 8,910 | **(31.69)** | 1,562 | **(26.17)** | 18,430 | **(63.42)** | 30,956 | **(74.41)** |
| **Age (Years)** | | | | | | | | |
| **< 60** | 10,867 | **(38.65)** | 3,623 | **(60.71)** | 9,782 | **(33.66)** | 13,421 | **(32.26)** |
| **60 - 69** | 5,711 | **(20.31)** | 849 | **(14.23)** | 7,326 | **(25.21)** | 10,864 | **(26.11)** |
| **70 - 79** | 6,516 | **(23.18)** | 859 | **(14.39)** | 7,721 | **(26.57)** | 11,456 | **(27.54)** |
| **≥ 80** | 5,021 | **(17.86)** | 637 | **(10.67)** | 4,230 | **(14.56)** | 5,861 | **(14.09)** |
| **Sex** | | | | | | | | |
| **Male** | 13,477 | **(47.94)** | 2,861 | **(47.94)** | 14,827 | **(51.02)** | 22,546 | **(54.19)** |
| **Female** | 14,638 | **(52.06)** | 3,107 | **(52.06)** | 14,232 | **(48.98)** | 19,056 | **(45.81)** |
| **Charlson Score** | | | | | | | | |
| **0** | 9,796 | **(34.84)** | 2,716 | **(45.51)** | 4,625 | **(15.92)** | 6,714 | **(16.14)** |
| **1** | 2,562 | **(9.11)** | 477 | **(7.99)** | 2,057 | **(7.08)** | 2,966 | **(7.13)** |
| **≥ 2** | 15,757 | **(56.04)** | 2,775 | **(46.50)** | 22,377 | **(77.01)** | 31,922 | **(76.73)** |
| **Ethnicity** | | | | | | | | |
| **White** | 25,771 | **(91.66)** | 5,252 | **(88.00)** | 26,871 | **(92.47)** | 37,925 | **(91.16)** |
| **Other** | 1,756 | **(6.25)** | 558 | **(9.35)** | 1,725 | **(5.94)** | 2,656 | **(6.38)** |
| **Unknown** | 588 | **(2.09)** | 158 | **(2.65)** | 463 | **(1.59)** | 1,021 | **(2.45)** |
| **Post-Op Length of Stay (days)** | | | | | | | | |
| **≤ 7** | 7,427 | **(26.42)** | 2,724 | **(45.64)** | 13,257 | **(45.62)** | 28,252 | **(67.91)** |
| **> 7** | 20,688 | **(73.58)** | 3,244 | **(54.36)** | 15,802 | **(54.38)** | 13,350 | **(32.09)** |

**Table 4.1: Demographics of English colectomy cohort between 2010–2019, by admission type and operative technique**

VTE, Venous thromboembolism.

Minimally Invasive Surgery consists of procedure completed either by a laparoscopic or robotic technique.

### 4.3.2 Post-discharge venous thromboembolism rates by admission type and surgical indication

#### *4.3.2.1 Weekly post-discharge VTE rates*

All weekly post-discharge VTE rates were analysed by admission type and surgical indication. However, only elective malignant procedures had sufficient numbers to allow stratification by operative technique.

##### *4.3.2.1.1 Elective colectomy*

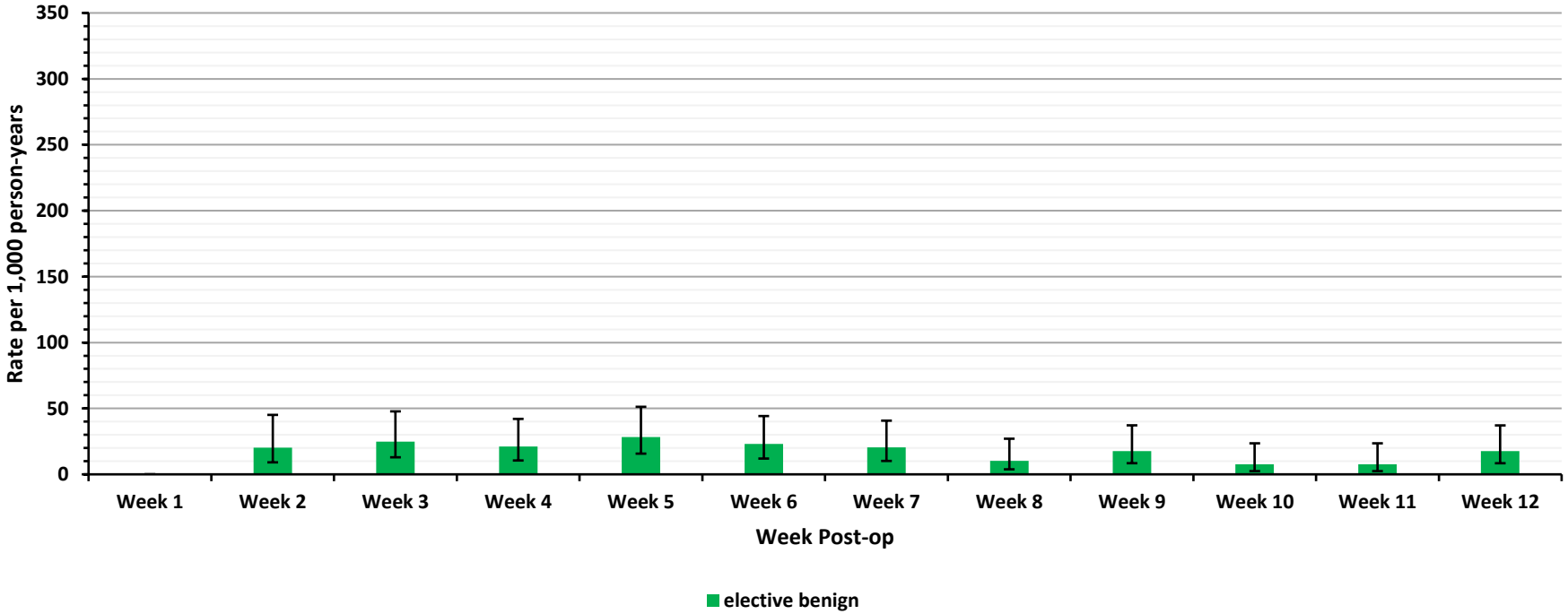
Following elective benign surgery, all post-discharge VTE rates were less than 30 per 1,000 person-years with no VTE events occurring in discharged patients in the first postoperative week, see Figure 4.2 (A). Following elective malignant colectomies, all post-discharge VTE rates were less than 50 per 1,000 person-years, see Figure 4.2 (B). However, on stratification by operative technique, following elective malignant open resections post-discharge VTE rates were greater than 50 per 1,000 person-years in postoperative weeks 1, 3 and 5, see Figure 4.3. All post-discharge VTE rates following elective malignant minimally invasive colectomy were less than 50 per 1,000 person-years with no VTE events in discharged patients in the first postoperative week.

##### *4.3.2.1.2 Emergency colectomy*

All emergency rates were stratified by surgical indication. However, most emergency colectomies for benign (81.34%) and malignant (85.08%) disease were open resections meaning there were too few minimally invasive emergency colectomies to allow further stratification by operative technique, see Table 4.1. Following emergency benign colectomies, the highest rate of VTE in discharged patients was in the

first week following resection (IR 77.36 per 1,000 person-years, 95% CI 19.35–309.34). Then from the second week after the operation post-discharge VTE rates were less than 50 per 1,000 person-years except in postoperative weeks 4, 5 and 8, see Figure 4.2 (C).

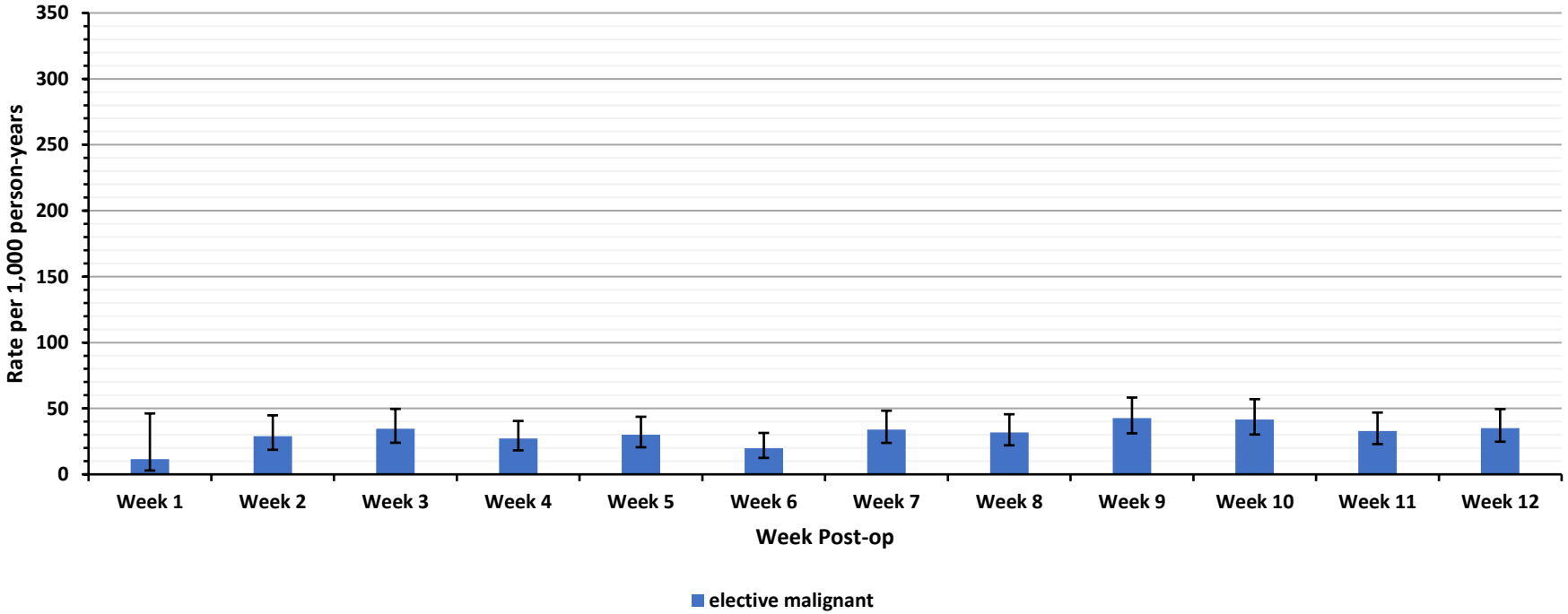
Following emergency malignant resections, VTE rates in discharged patients were greater than 100 per 1,000 person-years from the second to fourth postoperative week, with a further rise in postoperative week eight (IR 129.79 per 1,000 person-years, 95% CI 85.46–197.11). No VTE events occurred in discharged patients in the first postoperative week, although person-time was negligible, see Figure 4.2 (D).




**(A)**

**Figure 4.2: Post-discharge venous thromboembolism rates per 1,000 person-years by postoperative week following colectomy in England between 2010–2019 stratified by admission type and surgical indication:** (A) Elective benign

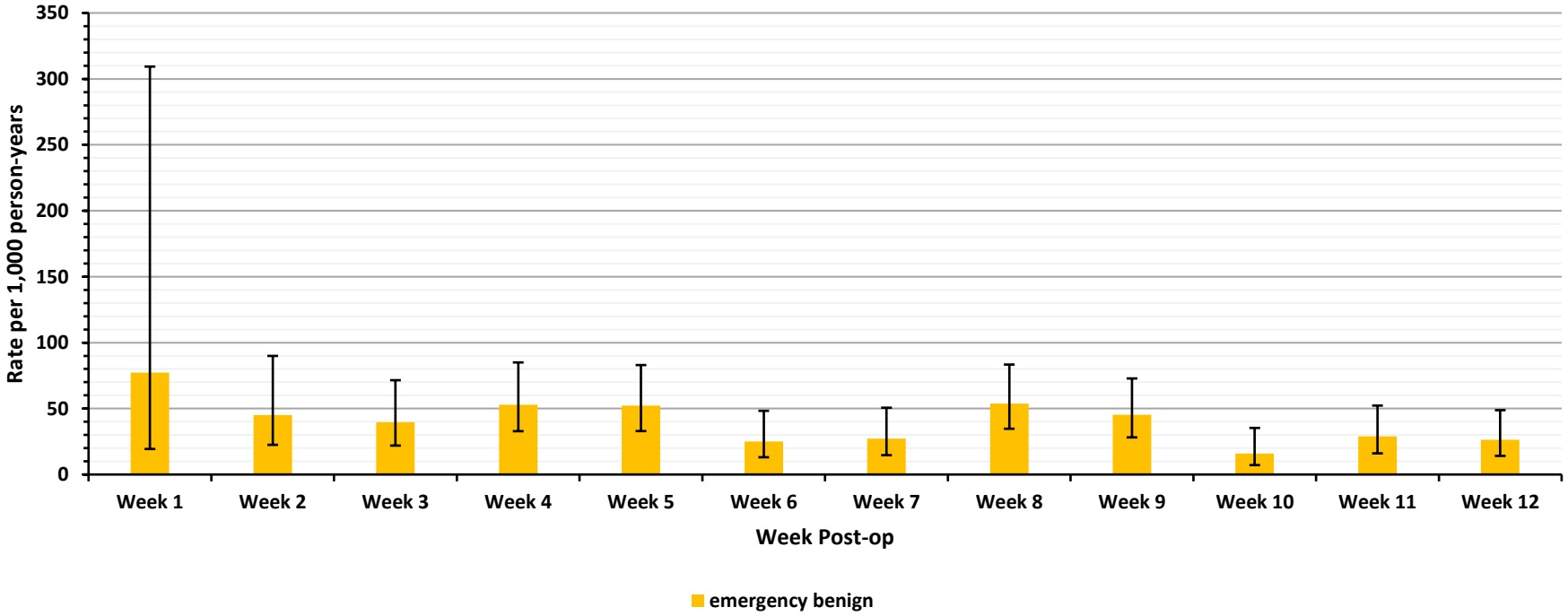
Error bars indicate 95% confidence intervals.




**(B)**

**Figure 4.2: Post-discharge venous thromboembolism rates per 1,000 person-years by postoperative week following colectomy in England between 2010–2019 stratified by admission type and surgical indication:** (B) Elective malignant

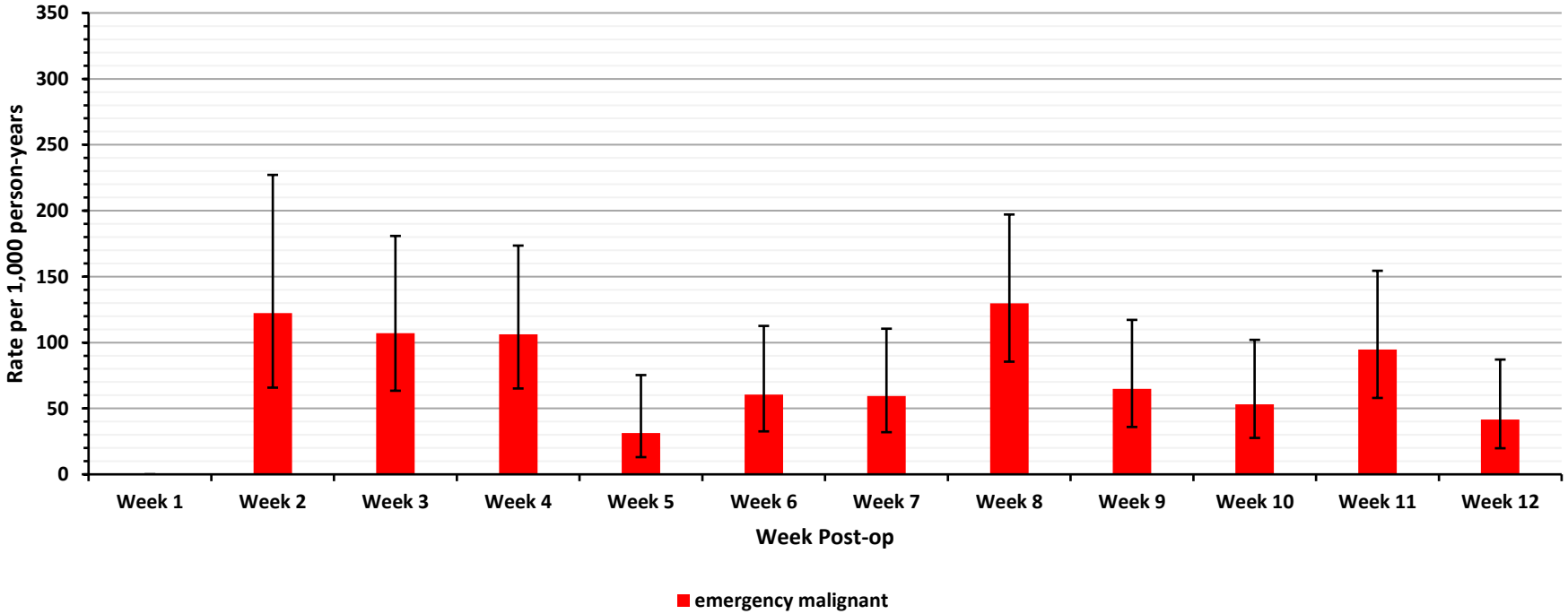
Error bars indicate 95% confidence intervals.




**(C)**

**Figure 4.2: Post-discharge venous thromboembolism rates per 1,000 person-years by postoperative week following colectomy in England between 2010–2019 stratified by admission type and surgical indication:** (C) Emergency benign

Error bars indicate 95% confidence intervals.




**(D)**

**Figure 4.2: Post-discharge venous thromboembolism rates per 1,000 person-years by postoperative week following colectomy in England between 2010–2019 stratified by admission type and surgical indication:** (D) Emergency malignant

Error bars indicate 95% confidence intervals.

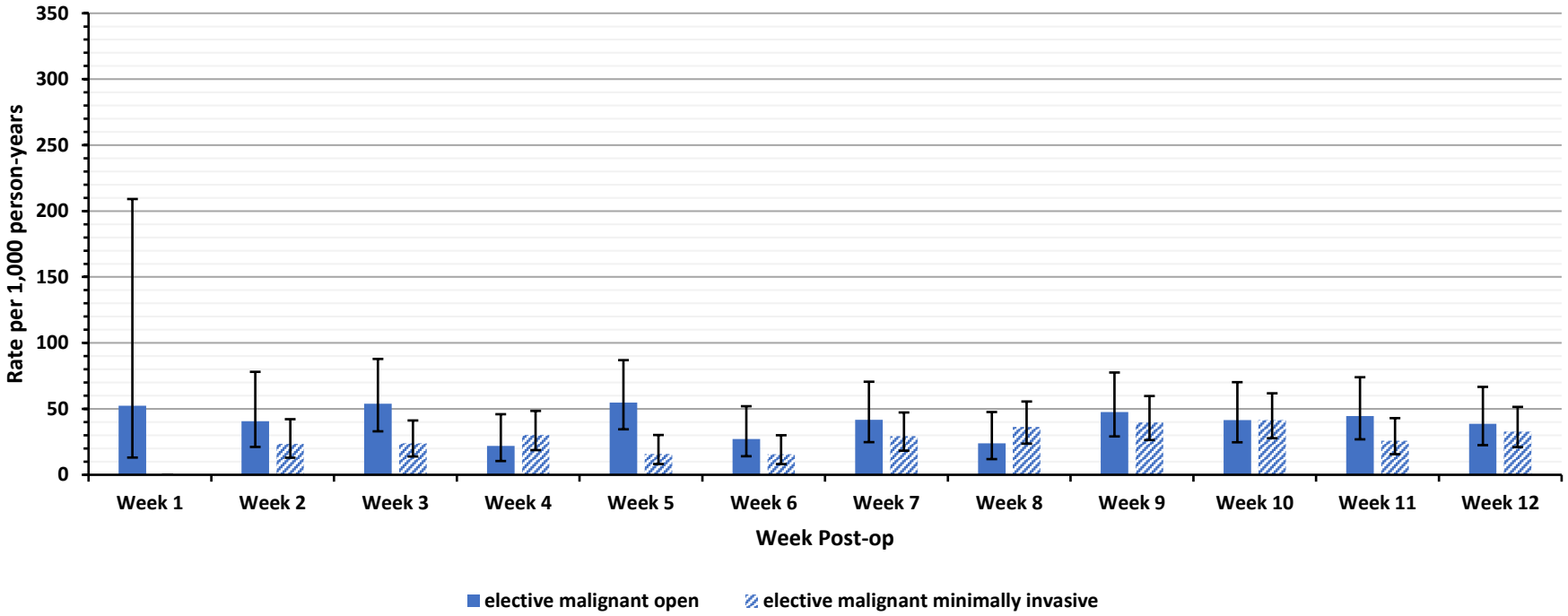



**Figure 4.3: Post-discharge venous thromboembolism rates per 1,000 person-years by postoperative week following elective malignant colectomy in England between 2010–2019 stratified by operative technique**

Minimally Invasive Surgery consists of laparoscopic or robotic procedures. Error bars indicate 95% confidence intervals.

*4.3.2.2 4-weeks postoperative post-discharge VTE rates*

Crude VTE rates for the first 4-weeks following colectomy were low for elective resections following both benign IR 20.66 per 1,000 person-years (95% CI 13.73–31.08) and malignant indications IR 28.95 per 1,000 person-years (95% CI 23.09–36.31). In contrast, the emergency resection 4-weeks post-discharge VTE rates were higher for both benign IR 47.31 per 1,000 person-years (95% CI 34.43–65.02) and malignant indications IR 107.18 per 1,000 person-years (95% CI 78.62–146.12). These differences remained significant after adjusting for age, sex, co-morbidity and operative technique, with a 2- to 3-fold increased risk for emergency benign and malignant resections compared to elective malignant resections (aIRR 1.89, 95% CI 1.22–2.93 and aIRR 3.13, 95%CI 2.06–4.76 respectively). Elective benign resections did not have an increased risk compared to malignant resections (aIRR 0.92, 95% CI 0.56–1.50), see Table 4.2.

By operative technique, the crude VTE rate for the first 4-weeks following minimally invasive colectomy was low, IR 22.03 per 1,000 person-years (95% CI 16.99–28.55), compared to open colectomy, IR 51.91 per 1,000 person-years (95% CI 43.38–62.13). After adjusting for age, sex, co-morbidity, admission type and surgical indication this difference remained significant with an approximately 50% reduction in post-discharge VTE risk in minimally invasive compared to open colectomies (aIRR 0.54, 95% CI 0.38–0.77).

| | Event No. | Person-years | Rate per 1,000 person-years | | | Unadjusted Incidence Rate Ratio | | | Adjusted Incidence Rate Ratio[a] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Elective Malignant** | 75 | 2.59 | **28.95** | 23.09 | 36.31 | **1.00** | (Reference) | | **1.00** | (Reference) | |
| **Elective Benign** | 23 | 1.11 | **20.66** | 13.73 | 31.08 | **0.71** | 0.45 | 1.14 | **0.92** | 0.56 | 1.50 |
| **Emergency Benign** | 38 | 0.80 | **47.31** | 34.43 | 65.02 | **1.63** | 1.11 | 2.41 | **1.89** | 1.22 | 2.94 |
| **Emergency Malignant** | 40 | 0.37 | **107.18** | 78.62 | 146.12 | **3.70** | 2.52 | 5.43 | **3.13** | 2.06 | 4.76 |

**Table 4.2: 4-Weekly rates per 1,000 person-years and incidence rate ratios of postoperative post-discharge venous thromboembolism following colectomy in England between 2010–2019 by admission type and surgical indication**

[a]Adjusted for age, sex, Charlson score and operative technique.

*4.3.2.3 Benign colectomy and IBD*

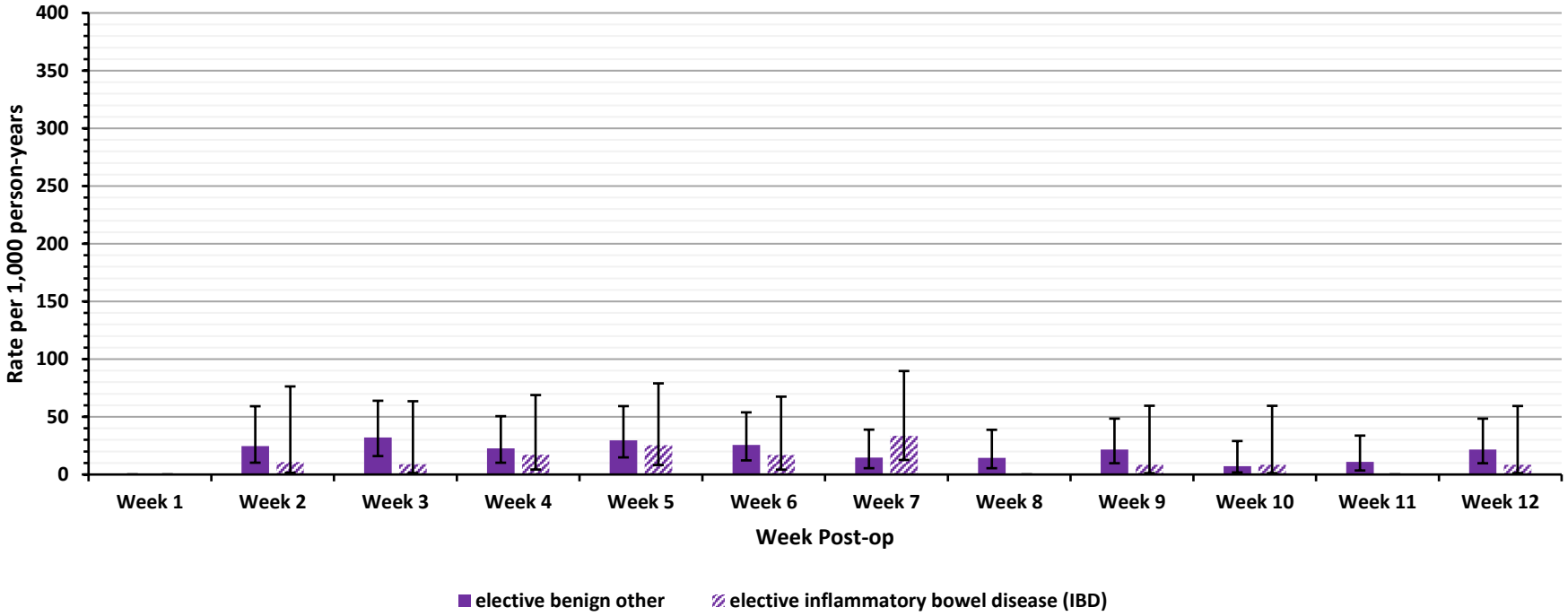
On stratification of benign surgical indication into ‘benign other’ and IBD, following elective surgery all post-discharge VTE rates were less than 35 per 1,000 person-years with no VTE events occurring in discharged patients in the first postoperative week, see Figure 4.4 (A). However, following emergency surgery, ’benign other’ procedures post-discharge VTE rates were all less than or equal to 50 per 1,000 person-years. While those undergoing emergency IBD resections, where the highest rate of VTE in discharged patients was in the first week following resection (IR 134.95 per 1,000 person-years, 95% CI 19.01–958.00), post-discharge VTE rates were greater than 50 per 1,000 person-years until postoperative week 10, except in weeks 2, 6 and 7 post-op, see Figure 4.4 (B).

On stratification of benign disease, the 4-weeks post colectomy post-discharge crude VTE rate following elective IBD resections, IR 11.71 per 1,000 person-years (95% CI 4.39–31.19), was lower than in those undergoing elective ‘benign other’ resections, IR 24.62 per 1,000 person-years (95% CI 15.70–38.60). However, after multivariable adjustment there was no significant difference in post-discharge VTE risk between elective IBD and ‘benign other’ colectomies (aIRR 0.84, 95% CI 0.28–2.50). In contrast, the 4-weeks post colectomy post-discharge crude VTE rate following emergency IBD resections, IR 62.49 per 1,000 person-years (95% CI 37.01–105.52), was higher than in those undergoing emergency ‘benign other’ resections, IR 41.44 per 1,000 person-years (95% CI 27.78–61.83). After multivariable

adjustment, there was a greater than 2.5-fold increased risk of post-discharge VTE in emergency IBD compared to ‘benign other’ colectomies (aIRR 2.54, 95% CI 1.29–5.02).

#### *4.3.2.4 Malignant colectomy and metastatic disease*

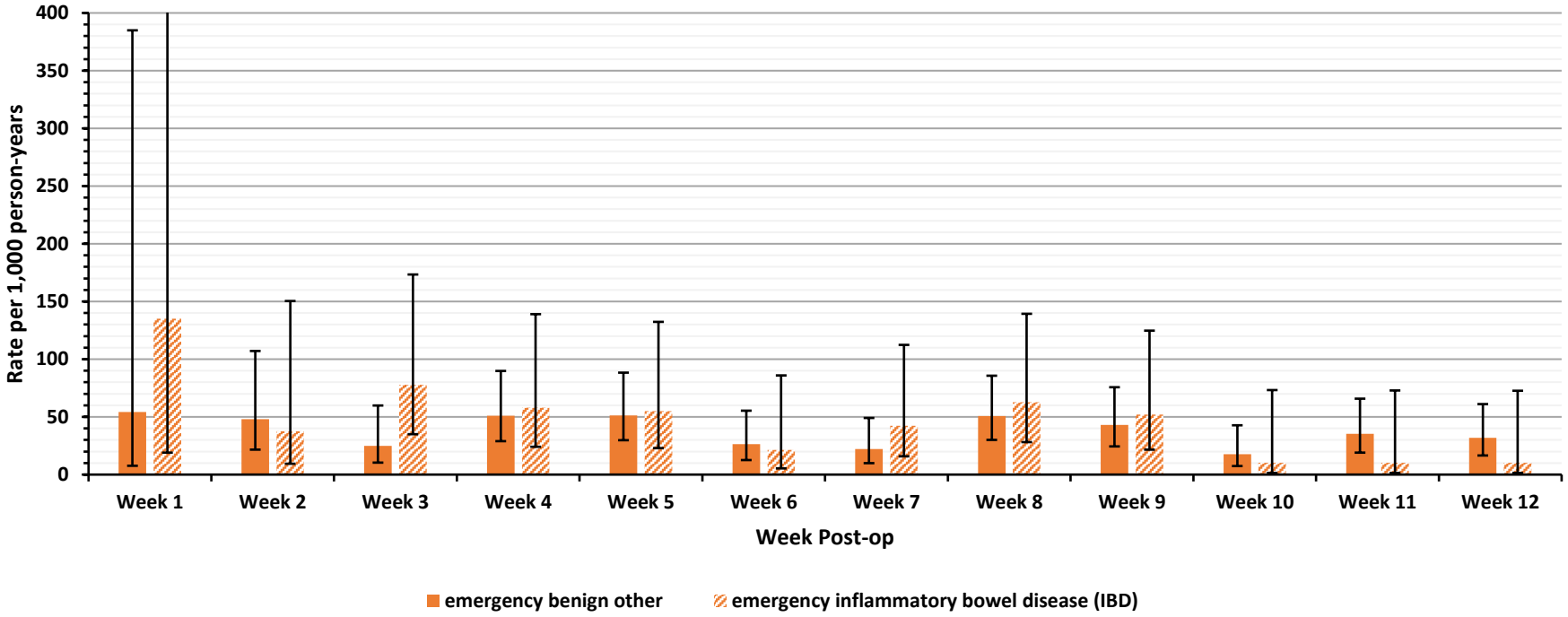
Overall 6.32% of CRC resections were in patients with metastatic disease, with 5.55% in elective and 7.93% in emergency operations. The crude VTE rate for the first 4-weeks following metastatic malignant colectomy, IR 63.42 per 1,000 person-years (95%CI 37.56–107.08), was greater than those without metastasis, IR 36.83 per 1,000 person-years (95%CI 30.30–44.75). However, after adjusting for admission type age, sex, co-morbidity and operative technique, there was no increased risk of post-discharge VTE in those undergoing metastatic compared to non-metastatic malignant colectomy (aIRR 1.18, 95%CI 0.66–2.10).




**(A)**

**Figure 4.4: Post-discharge venous thromboembolism rates per 1,000 person-years by postoperative week following colectomy in England between 2010–2019 stratified by benign surgical indication:** (A) Elective

Error bars indicate 95% confidence intervals.




**(B)**

**Figure 4.4: Post-discharge venous thromboembolism rates per 1,000 person-years by postoperative week following colectomy in England between 2010–2019 stratified by benign surgical indication:** (B) Emergency

Error bars indicate 95% confidence intervals. (Week 1 emergency IBD rate: 134.95 per 1,000 person-years, 95% CI 19.01-958.00)

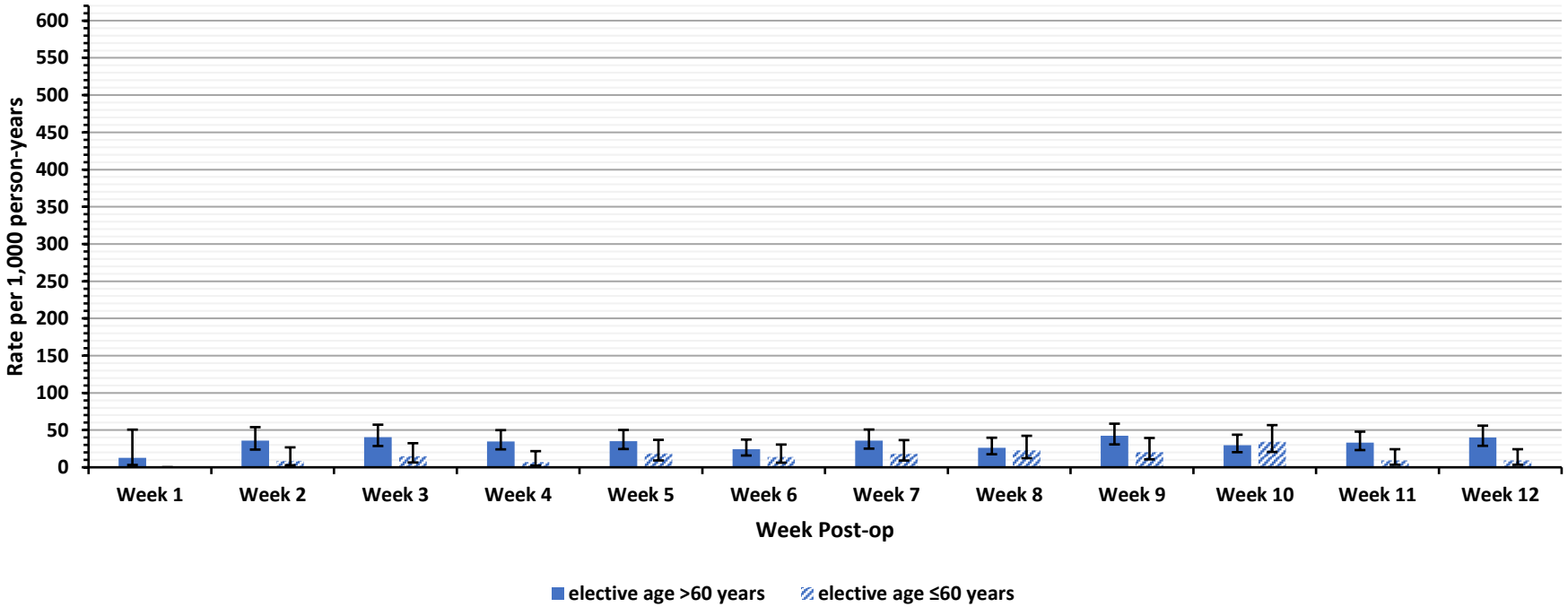
### 4.3.3 Weekly post-discharge venous thromboembolism rates by age, co-morbidity and postoperative length of stay

Further stratifying post-discharge VTE rates by admission type then age or co-morbidity did not change the patterns to post-discharge VTE rates described above, see Figures 4.5 (A-B) and 4.6 (A-B).

By age, the crude VTE rate for the first 4-weeks following colectomy in > 60-year-olds was high, IR 47.33 per 1,000 person-years (95% CI 40.13–55.82), compared to ≤ 60-years-olds, IR 18.41 per 1,000 person-years (95% CI 13.22–25.65). After adjusting for sex, co-morbidity, operative technique, admission type and surgical indication this difference remained significant with a greater than 2.5-fold increased VTE risk in > 60 compared to ≤ 60-years-olds following colectomy (aIRR 2.59, 95% CI 1.74–3.83). By co-morbidity, the crude VTE rate for the first 4-weeks following colectomy in patients with a Charlson score of ≥ 1 was high, IR 38.65 per 1,000 person-years (95% CI 32.82–45.50), compared to those with a Charlson score of 0, IR 27.73 per 1,000 person-years (95% CI 19.61–39.22). After adjusting for age, sex, operative technique, admission type and surgical indication there was no significant difference in VTE risk by co-morbidity post colectomy (aIRR 1.33, 95% CI 0.88–2.01).

Stratifying elective patients by their postoperative length of stay showed higher rates following a > 7-day admission than in admissions shorter than or equal to a week, see Figure 4.7 (A-B). The highest VTE rate in discharged patients after an elective admission lasting > 7 days, was in the second week following colectomy (IR 69.73, 95% CI 41.30–117.74

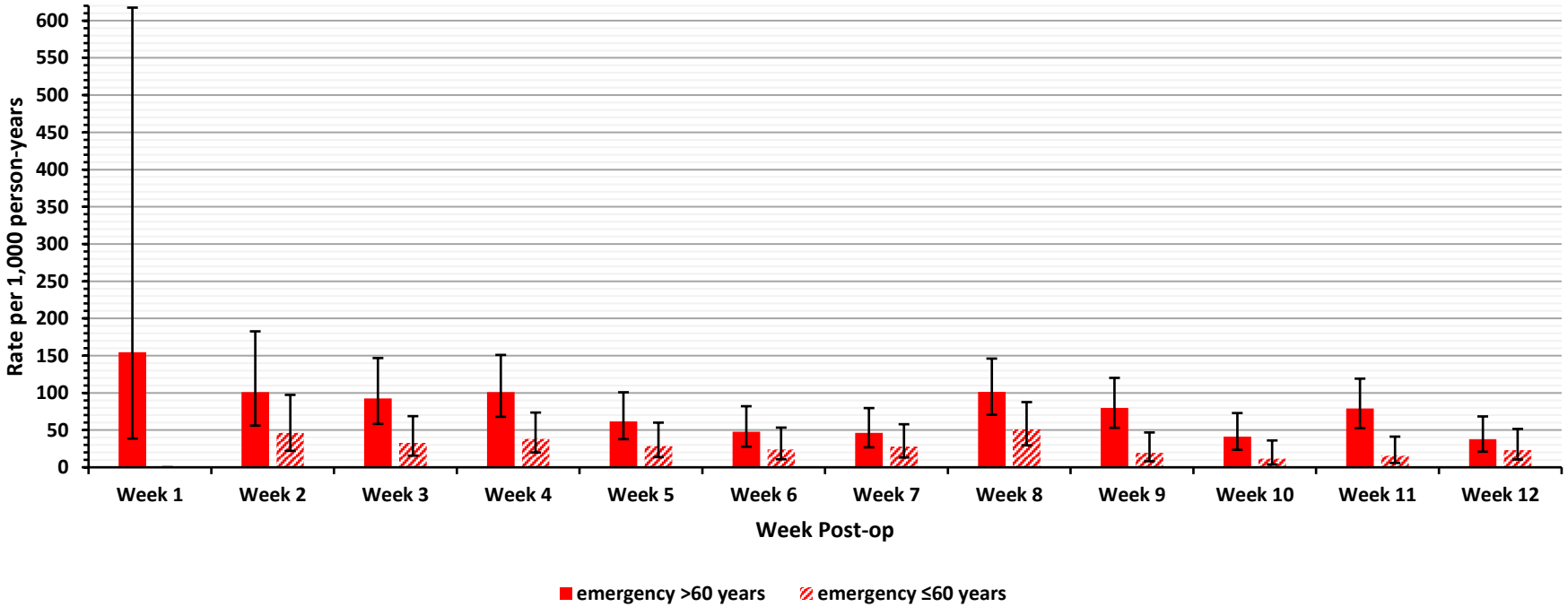
per 1,000 person-years). Following emergency resections, post-discharge VTE rates followed similar patterns previously reported irrespective of postoperative length of stay. By postoperative length of stay, the crude VTE rate for the first 4-weeks following colectomy in patients staying > 7 days was high, IR 62.26 per 1,000 person-years (95% CI 51.65–75.06), compared to those staying ≤ 7 days, IR 21.20 per 1,000 person-years (95% CI 16.65–26.98). After adjusting for age, sex, co-morbidity, operative technique, admission type and surgical indication this difference remained significant with a greater than 2-fold increased post-discharge VTE risk in colectomy patients admitted for > 7 compared to ≤ 7 days (aIRR 2.12, 95% CI 1.53–2.94).




**(A)**

**Figure 4.5: Post-discharge venous thromboembolism rates per 1,000 person-years by postoperative week following colectomy in England between 2010–2019 stratified by admission type and age:** (A) Elective

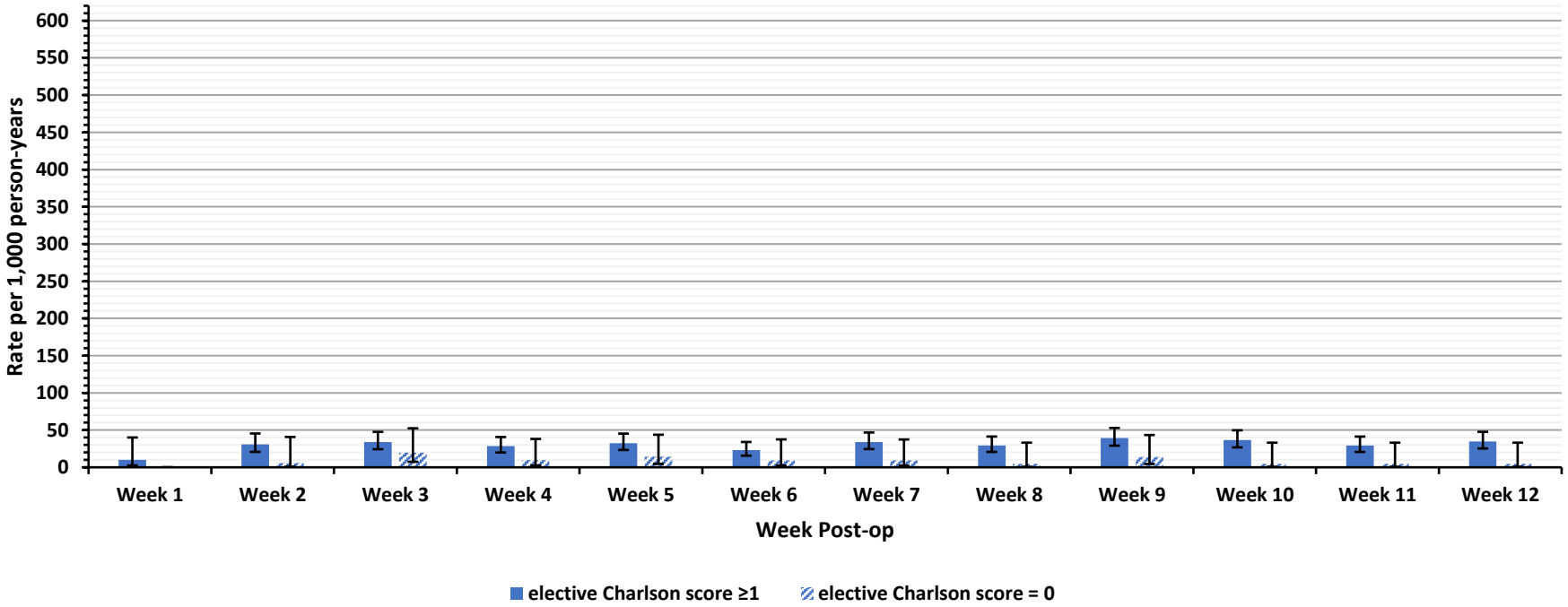
Error bars indicate 95% confidence intervals.




**(B)**

**Figure 4.5: Post-discharge venous thromboembolism rates per 1,000 person-years by postoperative week following colectomy in England between 2010–2019 stratified by admission type and age:** (B) Emergency

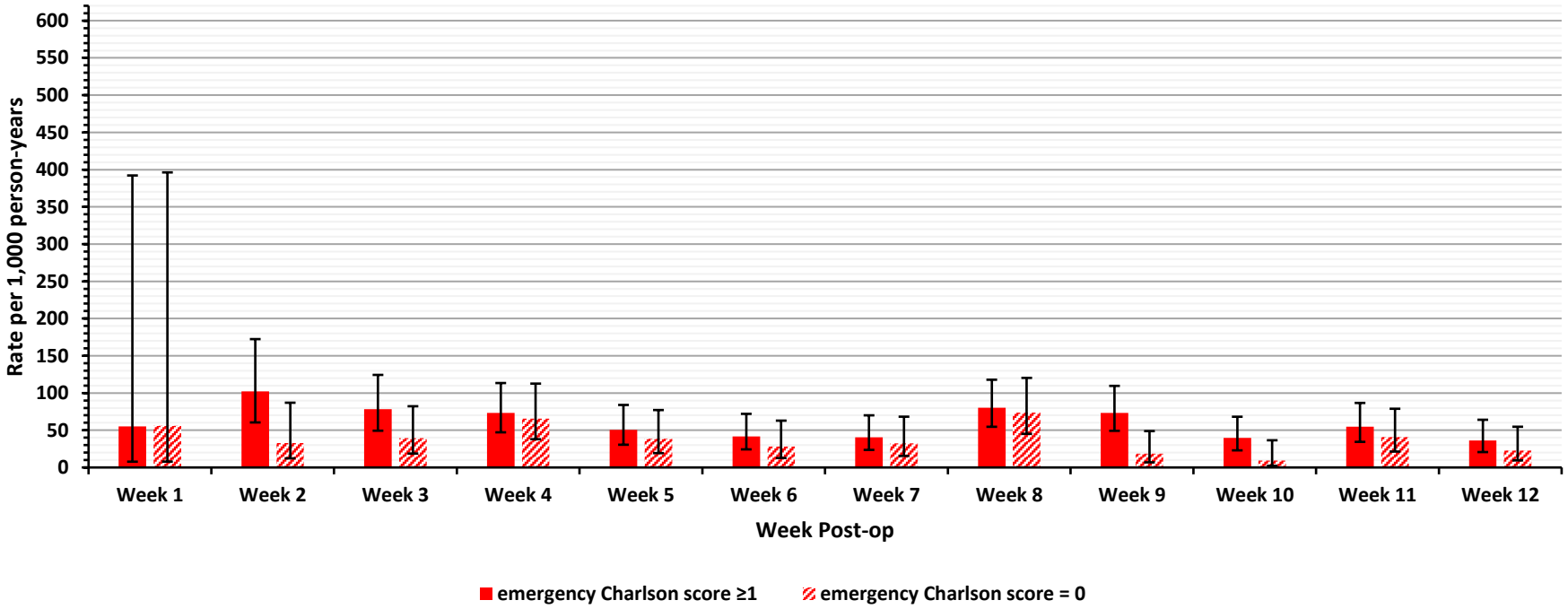
Error bars indicate 95% confidence intervals.




**(A)**

**Figure 4.6: Post-discharge venous thromboembolism rates per 1,000 person-years by postoperative week following colectomy in England between 2010–2019 stratified by admission type and co-morbidity:** (A) Elective

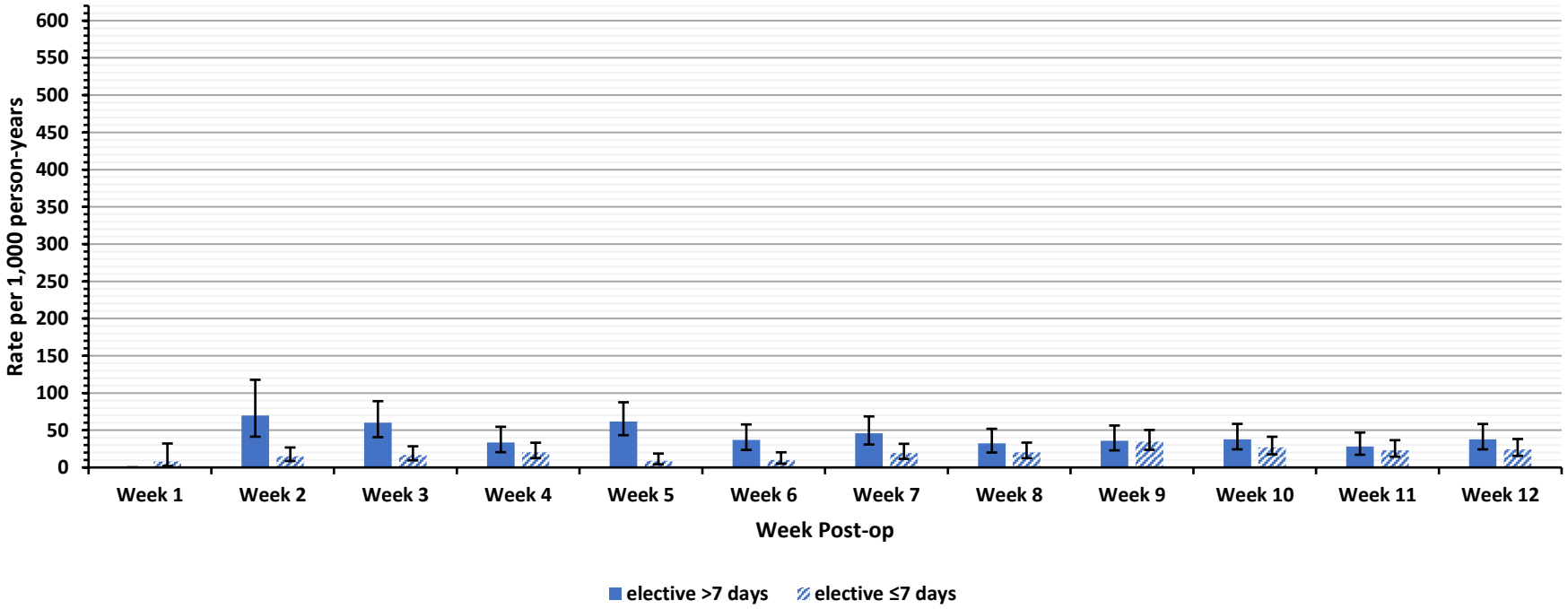
Error bars indicate 95% confidence intervals.




**(B)**

**Figure 4.6: Post-discharge venous thromboembolism rates per 1,000 person-years by postoperative week following colectomy in England between 2010–2019 stratified by admission type and co-morbidity:** (B) Emergency

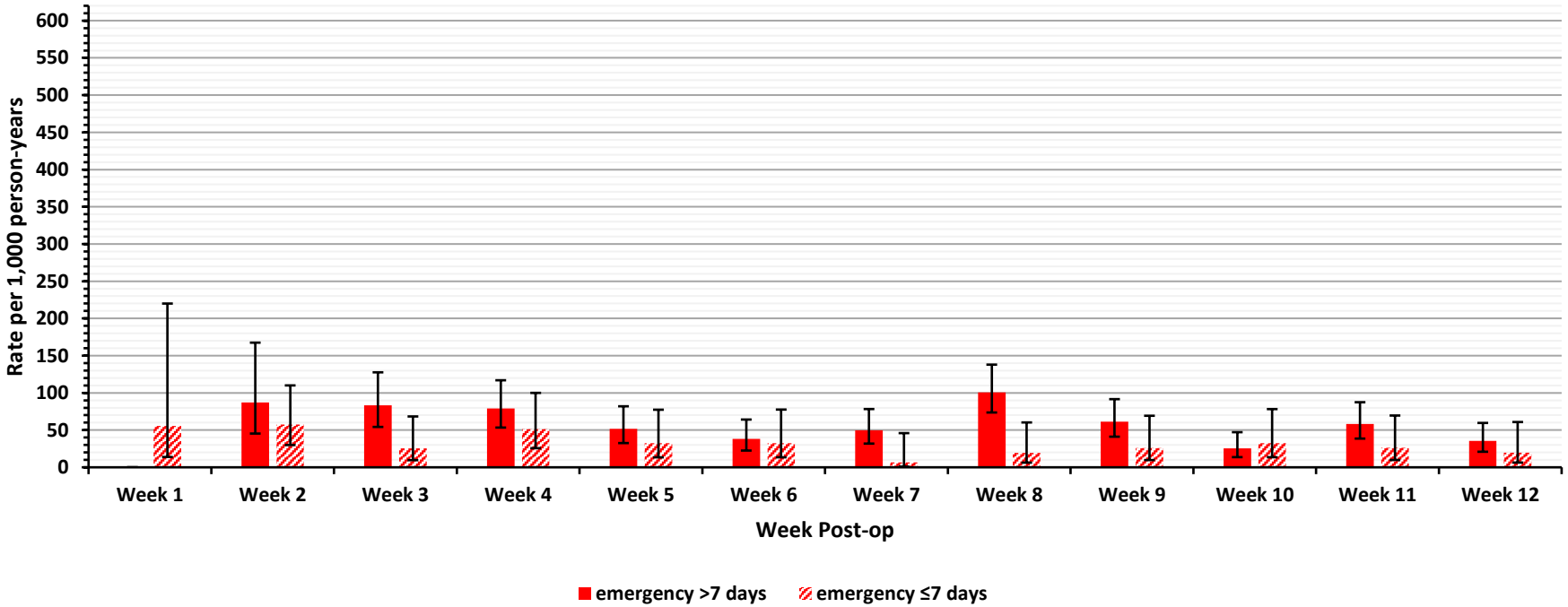
Error bars indicate 95% confidence intervals.




**(A)**

**Figure 4.7: Post-discharge venous thromboembolism rates per 1,000 person-years by postoperative week following colectomy in England between 2010–2019 stratified by admission type and postoperative length of stay:** (A) Elective

Error bars indicate 95% confidence intervals.




**(B)**

**Figure 4.7: Post-discharge venous thromboembolism rates per 1,000 person-years by postoperative week following colectomy in England between 2010–2019 stratified by admission type and postoperative length of stay:** (B) Emergency

Error bars indicate 95% confidence intervals.

### 4.3.4 Chapter summary

This national population-based cohort study of colectomy patients in England has shown absolute rates of post-discharge VTE following elective benign or malignant colectomy are similar and relatively low within the first 4-weeks post resection. This suggests current VTE prophylaxis guidance in these groups of patients is appropriate. Interestingly, those undergoing emergency benign resections had approximately 2-fold greater risk of post-discharge VTE compared to elective cancer resections at 4-weeks post-op (aIRR 1.89, 95% CI 1.22–2.93). However, emergency benign colectomies currently do not routinely receive extended VTE prophylaxis while elective malignant resections do. This indicates patients discharged after emergency benign resections might benefit from a period of extended VTE prophylaxis. Particularly, those undergoing emergency IBD colectomy may benefit as their risk of post-discharge postoperative VTE at 4-weeks following resection is more than 2.5-fold greater than patients undergoing emergency ‘benign other’ colectomies (aIRR 2.54, 95% CI 1.29–5.02). The greatest risk at 4-weeks post colectomy of post-discharge postoperative VTE was in emergency malignant resections (aIRR 3.13, 95%CI 2.06–4.76) compared to elective CRC surgery.

This chapter highlights the need to reconsider the focus of VTE prevention. Specifically, which subgroups of colectomy patients currently need further implementations in perioperative care to reduce post-discharge VTE. The findings consider that those undergoing emergency resections for benign and IBD indications may benefit most

from implementing an outpatient VTE preventative strategy such as extended VTE prophylaxis which they currently do not receive. While those undergoing emergency malignant resection might benefit from further intervention. However, to change and implement effective guidance on postoperative VTE prophylaxis it is crucial to know the current state of compliance to different national postoperative VTE prophylaxis regimens. Although, hospital prescribing at patient level is not currently available within NHS Digital This forms the objective of the next chapter.

# Chapter 5 Compliance with Venous Thromboembolism Prophylaxis Guidance at Discharge Following Colorectal Cancer and Benign Abdominal Surgery

## Section 5.1 Introduction

CRC resection forms a large proportion of major oncological surgery globally with recent data suggesting approximately 18,000 to 20,000 major CRC colectomies are performed in England each year.[20] VTE, is a potentially fatal postoperative complication occurring in 0.8% to 1.8% of patients within 30-days following elective and emergency general surgical procedures.[153] Within general surgery, colorectal resections have some of the highest rates of postoperative VTE of all abdominal operations[23,24] with contemporary meta-analysis reporting the VTE risk following malignant colectomy as 1.92% and 2.43% at 1- and 3-months following surgery.[6]

To address VTE within the UK it was made a CQUIN target in 2010/2011 and included in the Operating Framework for England to ensure 90% of adult admissions within English Trusts were risk assessed for VTE.[46] In the same year NICE published guidelines on postoperative VTE prevention that were subsequently updated in 2018.[34,48] Recognised internationally, this advocated all patients should be risk assessed for VTE on admission and receive postoperative pharmacological VTE prophylaxis for a minimum 7-days for gastrointestinal operations and extended to 28-days following abdominal/pelvic cancer surgery.[22] However despite this, VTE remains

one of the commonest causes of preventable 30-day mortality following major abdominal/pelvic cancer surgery.[58-60] Clinician and patient compliance with extended VTE prophylaxis following CRC surgery is variable, with recent data from the US and internationally suggesting mixed to poor compliance primarily following colectomy.[85,135,140,154,172-174,177,230-233]

No contemporary UK study has assessed extended VTE prophylaxis prescription compliance for postoperative CRC patients despite small single centre audit or evaluated VTE risk assessment and postoperative documentation in relation to prophylaxis compliance.[176,234-236] Only one survey published in 2012 has examined UK clinician compliance of national guidelines in relation to post Colorectal surgery VTE prophylaxis.[19] However, this study was conducted over a decade ago, did not specify surgical indication in relation to VTE regimen use and consulted only ACPGBI members. Furthermore, no study has examined the compliance to national guidance of the minimum 7-days postoperative VTE prophylaxis following benign abdominal and therefore Colorectal operations.

### 5.1.1 Aim

The aim of this audit is to assess contemporary compliance to national postoperative VTE prophylaxis guidance by examining VTE prophylaxis prescription on discharge for CRC and abdominal, including Colorectal, surgery patients at a UK NHS Trust tertiary centre.

## Section 5.2 Methods

This audit analysed two sperate prospective cohort service evaluations approved by the NHS Trust's clinical governance board:

1) Improving extended VTE prophylaxis prescription compliance at discharge for CRC resection patients (19-562Q). A double cycle audit measuring extended VTE prophylaxis compliance against NICE guidance NG89 1.14.4.[34]

2) Improving 7-days VTE prophylaxis compliance at discharge for patients undergoing abdominal surgery (20-685C). A single cycle audit measuring a minimum 7-days VTE prophylaxis against NICE guidance NG89 1.14.3.[34]

### 5.2.1 Colorectal cancer extended venous thromboembolism prophylaxis (19-562Q)

*5.2.1.1 Design*

Data on CRC resectional patients at the tertiary care institution were collected in 2 stages, pre and post an educational intervention for junior doctors during their surgical induction at the start of December 2019 (04/12/2019). This included a dedicated lecture on extended VTE prophylaxis prescription for CRC resectional patients within the Trust and placement of posters in key areas highlighting the importance of extended VTE prophylaxis on discharge, See Figure 5.1. All CRC patients discharged between August and November 2019 served as the pre-intervention and those discharged between December 2019 and

February 2020 as the post-intervention cohorts. Time periods chosen reflected periods junior doctors rotated between departments within the country's healthcare system and so provided more comparable data sets. Patients were included if they were ≥ 18 years-old and had undergone CRC resection within the Trust. Patients were excluded if they underwent presumed benign resection, were discharged >28 days post-operation, were on or had contraindications to long-term anticoagulation (e.g. Warfarin) prior to admission or were on end of life care or died in-hospital.

*5.2.1.2 Exposures*

Data were collected using the Trust's prospectively maintained internal electronic patient records database. ICD-10 codes for discharge diagnoses were used to identify patients undergoing potential CRC resections (C18.0-9, C7A.02, C19, C20, D12.0-8, D3A.02, C48.0-9). Age in years, length of stay in days, admission type, classed as elective or emergency, and readmission were predefined from the hospital episode recorded within the Trust's database. Hospital discharge date was used to define the calendar month of discharge.

*5.2.1.3 Outcomes*

The main outcome was the overall proportion of CRC patients discharged with extended/28-days postoperative VTE prophylaxis pre- and post-intervention. Secondary outcomes were the proportion of valid electronic VTE risk assessments (eVTE) and extended VTE prophylaxis instruction within the operation note postoperative plan in relation to

appropriately prescribed VTE prophylaxis at discharge. All targets set at 95% compliance.

Data on extended VTE prophylaxis prescription compliance were assessed by analysing patient discharge summaries relating to colectomy admission. Discharge prescriptions containing an appropriate VTE prophylaxis anticoagulant, as defined by NICE guidance (e.g. LMWH), covering for at least 28-days post-operation were considered compliant. Data on eVTE risk assessments are captured within the Trust's electronic database and considered valid only if completed within 24 hours from admission. eVTE risk assessments were selected as an outcome based on their recognition as a nationally annually audited outcome and CQUINN target. The importance of eVTE risk assessments within Colorectal surgery is it is not only mandatory in English Trusts but used to establish bleeding risk does not outweigh thrombosis risk.[46] All CRC resectional patients meet criteria for extended VTE prophylaxis prescription, as per NICE VTE risk assessment guidance, unless there is a contraindication based on bleeding risk.[34] Therefore, appropriate eVTE assessment without VTE prophylaxis contraindication would indicate a need for extended VTE prophylaxis prescription on discharge. Operation note extended VTE prophylaxis instruction was assessed by analysing postoperative plans in operation notes. Extended VTE prophylaxis instruction was only considered appropriately documented if the duration of VTE prophylaxis stated contained the word "extended" or referenced the "28-days" time frame required in relation to "VTE" prophylaxis.

# Dear Doctors,



- **Has the patient whose TTO you are writing had cancer surgery?**
- **Have you considered prescribing extended VTE prophylaxis?**

**Trust & NICE guidelines suggest:**

"all patients having major abdominal/pelvic **CANCER surgery** should receive at least **28-days VTE prophylaxis** postoperatively."




Please remember to prescribe extended VTE prophylaxis if needed.

**Thank you, remember it may save someone's life.**

An audit within the Colorectal Department is currently underway looking at how well we manage to prescribe extended VTE prophylaxis to our colorectal cancer patients, let's do a great job!

**Figure 5.1: Educational poster from service evaluation 19-562Q highlighting the importance of extended venous thromboembolism prophylaxis for colorectal cancer resectional patients on discharge**

### 5.2.2 7-day abdominal venous thromboembolism prophylaxis (20-685C)

#### *5.2.2.1 Design*

Data were collected on abdominal surgery patients at the tertiary care institution who were operated on over a 4-week period in 2020 (04/11/2020–02/12/2020). Patients were included if they were ≥ 18 years-old and had undergone a general surgical operation at the Trust's acute admissions site. Patients were excluded if they underwent presumed cancerous resection, were discharged > 7 days post-operation, were on or had contraindications to long-term anticoagulation (e.g. Direct oral anticoagulants) prior to admission or were on end of life care or died in-hospital.

#### *5.2.2.2 Exposures*

Data were collected using the Trust's prospectively maintained internal electronic patient records database. General surgical patients undergoing an operation were identified from the Trust's theatre management system. Age in years, length of stay in days, sex, classed as male or female, surgical subspecialty, classed as Emergency General/Other, Colorectal or Hepatopancreaticobiliary (HPB) surgery, and operative technique, classed as open or laparoscopic, were predefined from the hospital episode recorded within the Trust's database.

#### *5.2.2.3 Outcomes*

The main outcome was the proportion of abdominal surgical patients discharged with VTE prophylaxis for a minimum total of 7-days post-

operation. The secondary outcome was the proportion of patients with 7-days VTE prophylaxis post-operation instruction recorded within the postoperative plan.

Data on VTE prophylaxis prescription compliance was assessed by analysing patient discharge summaries relating to colectomy admission. Discharge prescriptions containing an appropriate VTE prophylaxis anticoagulant, as defined by NICE guidance (e.g. LMWH), covering for at least 7-days post-operation were considered compliant. Operation note 7-day post-operation VTE prophylaxis instruction was assessed by analysing postoperative plans in operation notes. 7-day VTE prophylaxis instruction was only considered documented appropriately if the duration of VTE prophylaxis referenced the “7-days” time frame required in relation to “VTE” prophylaxis. All targets set at 95% compliance.

### 5.2.3 Statistical analysis

Descriptive statistics were used to report cohort demographics. Categorical variables were presented as frequencies and proportions with risk difference, attributable risk fraction and unadjusted odds ratios (OR) and their 95% CI used to describe the measures of effect where appropriate. Data normality was assessed by visualising histograms with non-parametric data presented as medians and IQRs. Statistical significance, P-value < 0.05, was determined where appropriate by using the $\chi 2$, Fisher’s Exact, Mann-Whitney U and Likelihood ratio

tests. All data management and analyses were performed using Stata SE® version 17.0 (StataCorp LLC, College Station, Texas, USA), See Appendix 14 for Chapter Stat Do file

## Section 5.3 Results

### 5.3.1 Colorectal cancer extended venous thromboembolism prophylaxis (19-562Q)

#### *5.3.1.1 Cohort demographics*

Of 151 CRC resection patients, 104 were included within the pre-intervention and 47 in the post-intervention groups. 30 (19.87%) patients in total were excluded from the audit, see Figure 5.2. 11 were prescribed long-term anticoagulation prior to surgery (7 pre- and 4 post-intervention), 7 were an inpatient for > 28 days (all pre-intervention), 5 either died or were started on end-of-life care in hospital (4 pre- and 1 post-intervention) and 7 were other exclusionary causes (6 pre- and 1 post-intervention). Ultimately leaving a cohort of 121 CRC patients with 80 in the pre- and 41 in the post-intervention groups. Within the final cohort, all patients' risk of thrombosis outweighed their risk of bleeding on independent assessment of their pre-operative VTE risk. The median age of surgical CRC patients was 66 (IQR 59–73) years with a median length of hospital stay 6 (IQR 4–11) days and most were admitted in the elective setting (No. = 108, 89.26%), see Table 5.1.

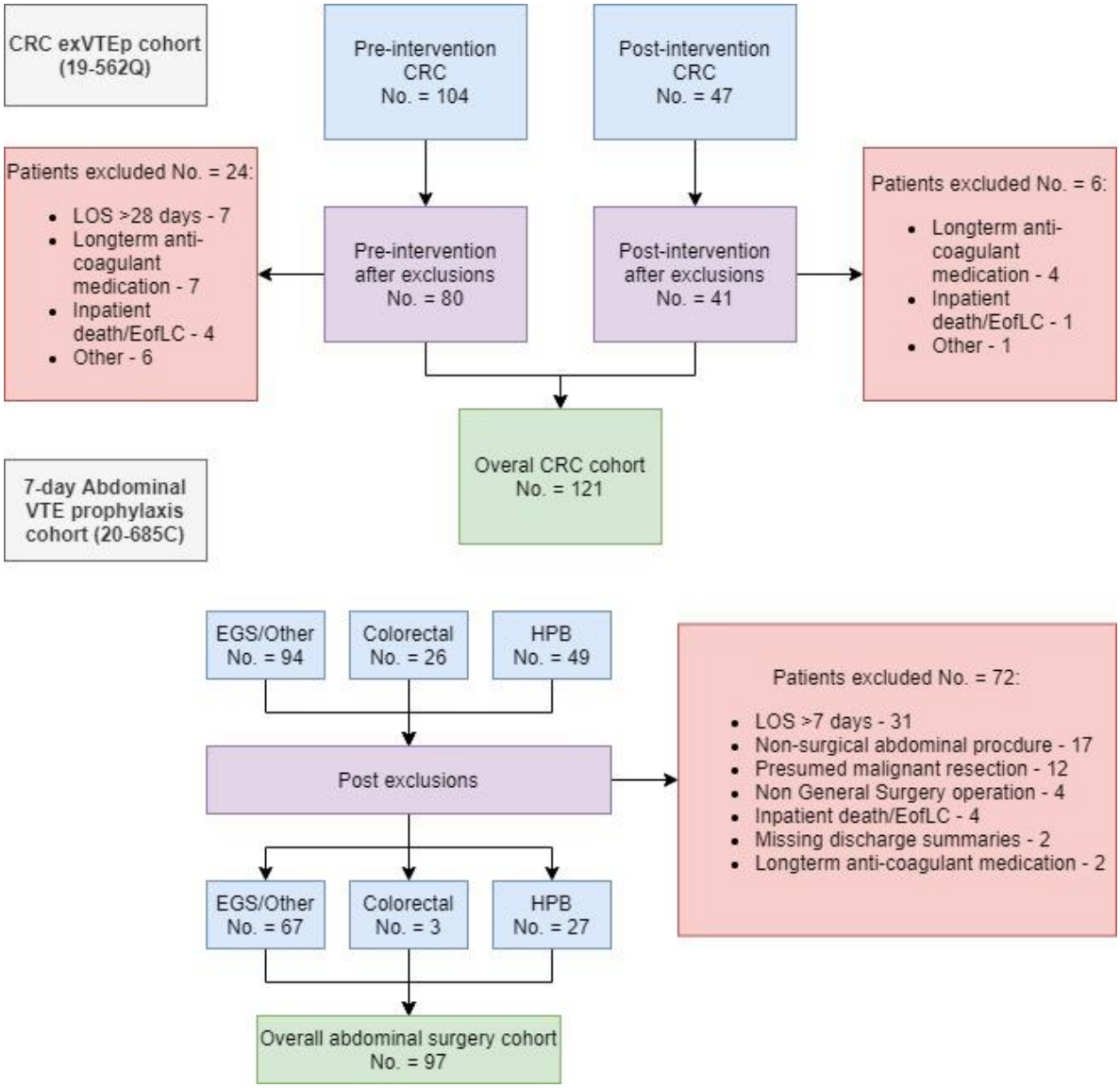



**Figure 5.2: Flow diagram of cohort construction for both colorectal cancer extended (19-562Q) and 7-day abdominal venous thromboembolism prophylaxis (20-685C) cohorts**

CRC, Colorectal cancer; exVTEp. Extended venous thromboembolism prophylaxis; LOS, Length of stay; EofLC, End of life care; VTE Venous thromboembolism; EGS, Emergency General surgery; HPB, Hepatopancreaticobiliary surgery.

| | Pre-intervention (No. = 80) | | Post-intervention (No. = 41) | | P-value[b] |
|---|---|---|---|---|---|
| | No. | (%) | No. | (%) | |
| **Age (Years) (Median (IQR))** | 67 (59 - 73) | | 66 (59 - 72) | | 0.6122[c] |
| **Length of Stay (Days) (Median (IQR))** | 7.5 (5 - 11) | | 5 (3 - 8) | | 0.0076[c] |
| **Admission type** | | | | | |
| **Elective** | 70 | (87.50) | 38 | (92.68) | 0.5393[d] |
| **Emergency** | 10 | (12.50) | 3 | (7.32) | |
| **Readmission** | | | | | |
| **Yes** | 47 | (58.75) | 32 | (78.05) | 0.0348 |
| **No** | 33 | (41.25) | 9 | (21.95) | |
| **Extended VTE prophylaxis on discharge** | | | | | |
| **Yes** | 65 | (81.25) | 38 | (92.68) | 0.0944 |
| **No** | 15 | (18.75) | 3 | (7.32) | |
| **Extended VTE prophylaxis within operation note** | | | | | |
| **Yes** | 26 | (32.50) | 15 | (36.59) | 0.6532 |
| **No** | 54 | (67.50) | 26 | (63.41) | |
| **Electronic VTE risk assessment valid[a]** | | | | | |
| **Yes** | 72 | (69.23) | 34 | (72.34) | 0.6989 |
| **No** | 32 | (30.77) | 13 | (27.66) | |

**Table 5.1: Colorectal cancer resectional patient characteristics from audit 19-562Q by pre- and post-intervention group**

IQR, Interquartile range; VTE, Venous thromboembolism.

[a]Including excluded patients: Pre-intervention No. = 104, Post-intervention No. = 47. [b]Chi-Squared test unless otherwise stated, [c]Mann-Whitney U test, [d]Fisher's Exact test.

*5.3.1.2 extended VTE prophylaxis compliance*

There was an 11.43% absolute increase in extended VTE prophylaxis prescription compliance from 81.25% pre- to 92.68% post-intervention (Risk difference 11.43%, 95% CI -0.26%–23.12%), and amongst the post-intervention group, 12.34% of extended VTE prophylaxis prescription compliance was attributable to the educational intervention (Attributable fraction 12.34%, 95% CI -0.43%–23.48%). However, this was not significant, P = 0.0944, see Table 5.1. Of the 15 pre-intervention patients not prescribed extended VTE prophylaxis, for most (No. = 7) no reason could be found for compliance failure. However, some (No. = 3) were due to appendicectomies converted to right hemicolectomies, and a small bowel resection (No. = 1) for neuroendocrine tumours not recognised as cancer resections. Other reasons (No. = 1 each) included electronic discharge note error, incorrect duration of VTE prophylaxis prescription, CRC not disclosed on operation note and antiplatelet medication considered adequate prophylaxis. Of the 3 post-intervention patients not prescribed extended VTE prophylaxis no reason could be found for compliance failure. Over the study period there was a 26.20% increase per calendar month in extended VTE prophylaxis prescription compliance (OR 1.26, 95% CI 0.96–1.66) however this was non-significant, P = 0.0835, see Figure 5.3.

Slight increases in valid eVTE assessments, 69.23% to 72.34%, and extended VTE prophylaxis documentation within postoperative notes, 32.50% to 36.59%, were observed between pre- and post-intervention

groups however neither were significant. There was a slight absolute decrease in valid eVTE assessments in those prescribed extended VTE prophylaxis from 44.44% to 26.21% (Risk difference -18.23%, 95% CI -42.71%–6.25%), however this was not significant, P = 0.1155, see Table 5.2. Those missing extended VTE prophylaxis documentation within the postoperative plan were significantly less likely to receive extended VTE prophylaxis at discharge, 88.89% vs 62.14%, with a 26.75% absolute decrease in extended VTE prophylaxis prescription in patients without extended VTE prophylaxis documented within the postoperative note (Risk difference -26.75%, 95% CI -44.03%–-9.48%, P = 0.0269). Therefore, amongst those prescribed extended VTE prophylaxis at discharge, 30.10% of VTE prophylaxis prescription compliance at discharge is attributable to the appropriate documentation of extended VTE prophylaxis within the postoperative plan (Attributable fraction 30.10%, 95% CI 12.70%–44.03%). see Table 5.2.

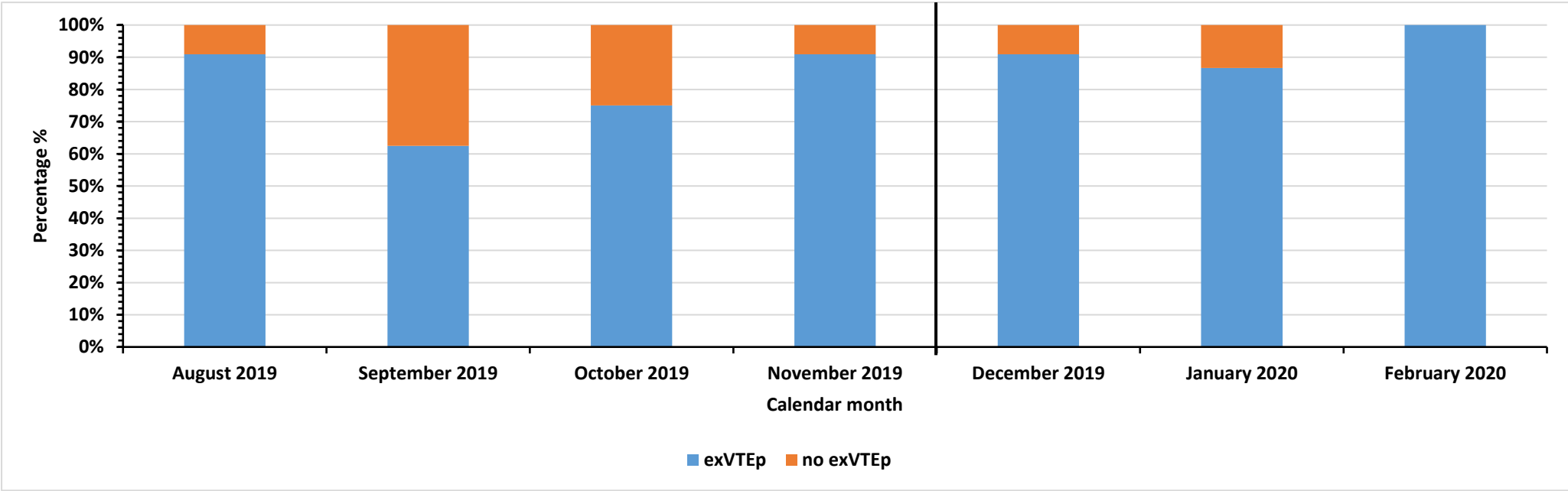



**Figure 5.3: Proportion of colorectal cancer resectional patients from service evaluation 19-562Q receiving extended venous thromboembolism prophylaxis at discharge by calendar month between August 2019 and February 2020**

exVTEp, Extended venous thromboembolism prophylaxis.

Vertical black line indicates switch from pre- to post-intervention group.

| | Extended VTE prophylaxis on discharge (No. = 103) | | No extended VTE prophylaxis on discharge (No. = 18) | | P-value[a] |
|---|---|---|---|---|---|
| | No. | (%) | No. | (%) | |
| **Age (Years) (Median (IQR))** | 66 (59 - 73) | | 67.5 (53 - 77) | | 0.7429[b] |
| **Length of Stay (Days) (Median (IQR))** | 6 (4 - 11) | | 6.5 (4 - 11) | | 0.7866[b] |
| **Admission type** | | | | | |
| **Elective** | 93 | (90.29) | 15 | (83.33) | 0.4085[c] |
| **Emergency** | 10 | (9.71) | 3 | (16.67) | |
| **Readmission** | | | | | |
| **Yes** | 38 | (36.89) | 4 | (22.22) | 0.2277 |
| **No** | 65 | (63.11) | 14 | (77.78) | |
| **Extended VTE prophylaxis within operation note** | | | | | |
| **Yes** | 39 | (37.86) | 2 | (11.11) | 0.0269 |
| **No** | 64 | (62.14) | 16 | (88.89) | |
| **Electronic VTE risk assessment valid** | | | | | |
| **Yes** | 27 | (26.21) | 8 | (44.44) | 0.1155 |
| **No** | 76 | (73.79) | 10 | (55.56) | |

**Table 5.2: Colorectal cancer resectional patient characteristics from audit 19-562Q by extended venous thromboembolism prophylaxis regimen prescription on discharge**

IQR, Interquartile range; VTE, Venous thromboembolism.

[a]Chi-Squared test unless otherwise stated, [b]Mann-Whitney U test, [c]Fisher's Exact test.

### 5.3.2 7-day abdominal venous thromboembolism prophylaxis (20-685C)

Of 169 abdominal surgeries, 94 (55.62%) were Emergency General/Other, 26 (15.38%) were Colorectal and 49 (28.99%) were HPB surgical speciality patients. 72 (42.60%) patients in total were excluded from the study, see Figure 5.2. Of those excluded: 31 were an inpatient for > 7 days, 17 underwent an abdominal procedure but not surgery, 12 were malignant or presumed malignant resections, 4 were non general surgical patients, 4 died in hospital, 2 were missing discharge summaries and 2 were prescribed long-term anticoagulation prior to surgery. Ultimately leaving a cohort of 97 abdominal surgery patients eligible for continued 7-days VTE prophylaxis at discharge.

Some patients were male (46.39%) with the median age of abdominal surgical patients 38 (IQR 29–56) years and median length of stay 2 (IQR 1–5) days. The most frequently performed operations were appendicectomy (No. = 50, 51.55%) and cholecystectomy (No. = 28, 28.87%) with most patients undergoing laparoscopic procedures (81.44%) and admitted under Emergency General/Other surgery (69.07%), see Table 5.3.

Of the 97 benign abdominal surgery patients eligible for 7-days VTE prophylaxis who were discharged prior to 1-week post-operation, none (No. = 0) were prescribed appropriate continuing VTE prophylaxis at discharge or specifically had 7-days postoperative VTE prophylaxis recorded in the postoperative plan.

| | Abdominal Surgery (No. = 97) | |
|---|---|---|
| | No. | (%) |
| **Age (Years) (Median (IQR))** | 38 (29 - 56) | |
| **Length of Stay (Days) (Median (IQR))** | 2 (1 - 5) | |
| **Sex** | | |
| **Male** | 45 | (46.39) |
| **Female** | 52 | (53.61) |
| **Operative Technique** | | |
| **Open** | 18 | (18.56) |
| **Laparoscopic** | 79 | (81.44) |
| **Surgical Subspecialty** | | |
| **Emergency General Surgery/Other** | 67 | (69.07) |
| **Colorectal Surgery** | 3 | (3.09) |
| **Hepatopancreaticobiliary Surgery** | 27 | (27.84) |
| **7-days VTE prophylaxis on discharge** | | |
| **Yes** | 0 | (0.00) |
| **No** | 97 | (100.00) |
| **7-days VTE prophylaxis within operation note** | | |
| **Yes** | 0 | (0.00) |
| **No** | 97 | (100.00) |

**Table 5.3: Characteristics of benign abdominal surgery patients eligible for continued 7-day venous thromboembolism prophylaxis from service evaluation 20-685C**

IQR, Interquartile range; VTE, Venous thromboembolism.

### 5.3.3 Chapter summary

The findings of this chapter suggest the contemporary overall proportion of surgical CRC patients receiving compliant discharge prescriptions of extended VTE prophylaxis is relatively high (85.12% (103/121)) in relation to NICE guidance, although did not meet set NHS targets. Valid eVTE assessment did not appear to effect extended VTE prophylaxis prescription however failure to properly document the need for extended VTE prophylaxis within the operative record significantly reduced compliance of its prescription at discharge (Risk difference -26.75%, 95% CI -44.03%–-9.48%, P = 0.0269). Importantly, compliance with NICE guidance on VTE prophylaxis post benign abdominal surgery was negligible (0%) meaning major focus on educational changes are needed in this cohort of surgical patients.

# Chapter 6 Discussion

This chapter discusses the results from the studies in the 4 previous chapters of this thesis. Chapter 2 reports a systematic review and meta-analysis of the incidence of VTE following CRC resection. Chapter 3 reports a cohort study on the trends in VTE risk over time following colectomy. Chapter 4 reports a cohort study on the duration and magnitude of the rate of post-discharge VTE following colorectal resection. Chapter 5 reports two service evaluations on the compliance with VTE prophylaxis guidance at discharge following CRC and abdominal surgery.

## Section 6.1 Venous thromboembolism post colorectal cancer resection

### 6.1.1 Overview

In a pooled analysis of 18 study populations this review found that the incidence rate of VTE following surgery for CRC is high in the first 30-days after surgery (195 per 1,000 person-years (95% CI 148–256)). The incidence rate decreases towards 90-days postoperatively (91 per 1,000 person-years (95% CI 56–146)). These high absolute rates are greater than previously reported VTE rates after benign general surgery.[203-205] Importantly, pooled rates were significantly higher for both follow-up lengths in those study populations within the UN Geoscheme Area of the Americas when compared to each of the subgroups of Europe, Asia and Oceania. Current international guidance

recommends patients undergoing abdominal/pelvic cancer surgery, including CRC surgery, should receive extended/up to 28-days of postoperative VTE prophylaxis.[34,50] The pooled rate of VTE following surgery we report is greater than that in those only receiving in-hospital prophylaxis in the studies from the updated Cochrane review (117 per 1,000 person-years at 30-days following surgery (0.95%)).[51] This may suggest the potential benefit of extended prophylaxis in terms of VTE risk reduction compared to harmful bleeding is still maintained despite the changes in CRC surgery particularly in the US and Asia.[237]

### 6.1.2 Strengths and limitations

This systematic review and meta-analysis has several strengths. First, it quantifies the risk of postoperative CRC VTE and is therefore comparable between different lengths of postoperative follow-up. Second, we used five validated databases without language limitation to exhaustively search available literature to ensure no papers were missed with supplementation of reference list searches of relevant review articles. The review comprises a largely globally diverse population pooling results from small to large sized studies. Third, within the quantitative synthesis the separation of studies into those of the same follow-up length allows for a more accurate analysis of VTE rates. It was predicted VTE rates in the post-surgical period would decrease the further away from time of surgery the follow-up end point was measured. Therefore, pooling only studies with the same follow-up

length would minimise heterogeneity caused by this effect, as highlighted by a previous incidence rate meta-analysis.[63]

Rates provided are derived from multiple populations with a wide range of demographic and operative variables providing an overall incidence of postoperative VTE in CRC surgery. Rates for specific populations, those deemed at higher risk of VTE e.g. elderly patients, advanced stage disease, receiving chemotherapy were not calculatable and therefore the results of this review cannot be generalised to individual subgroups of interest. This was due to the lack of specific detailed data available from included studies reporting the proportion of VTE events in these subgroups. For study specific demographic proportions see Table 2.2. Heterogeneity was high in most meta-analyses conducted with the majority obtaining an $I^2$ value >90%. This is likely due to two factors; the choice of descriptive compared to comparative epidemiological studies used where incidence rates are sensitive to minor differences in population and outcome definitions when estimating an overall statistic for a specified cohort. Secondly, large cohort sizes ultimately minimising within study variance, an effect previously reported in a similar review.[63]

High heterogeneity is not uncommon and reported to increase with increasing number of studies included within meta-analyses assessing continuous outcomes.[238] Conventionally, high $I^2$ values suggest meta-analysis should be interpreted with caution. However, when comparing descriptive study outcomes such as prevalence or incidence, arbitrary

thresholds for analysis should be avoided as it does not directly inform on the distribution of effect, particularly due to the substantially reduced within-study variances observed in these study types.[239] Although, the heterogeneity within these meta-analyses may affect the results making them similar to the arithmetic mean. This is seen within random-effects models where high heterogeneity leads to almost proportional weighting of included studies despite difference in sample size.[240]

The great differences observed within follow-up length and how VTE was assessed as an outcome following CRC surgery between the RCTs significantly affected the calculated rates of postoperative VTE. This meant the RCTs could not be incorporated into the meta-analysis as doing so would deduce little relevant information. Many studies within the quantitative synthesis spanned long time intervals where changes in surgical care and VTE prevention guidance changed. This could have affected the results of this study however on analysis by UN Geoscheme Area there were no significant trends observed between studies by increasing year of study publication date.

Within population-based cohorts it was not possible to separate symptomatic VTE and incidental VTE diagnosed on screening due to the nature in which VTE outcome was coded within databases utilised by studies. The effect of incidental VTE may have influenced the results of the analyses however the method in which population-based databases record data suggests the majority of VTE events registered are symptomatic as there were no specific VTE screening programmes

used within each cohort. The clinical relevance of incidental VTE is debated within the literature and that extended VTE prophylaxis following CRC surgery is not cost-effective and only reduces the rate of incidental and not symptomatic VTE.[104] However, meta-analysis[51] has shown the risk of symptomatic VTE is reduced following surgery with extended prophylaxis and recent studies and RCTs suggest clinical adverse outcomes following incidental and symptomatic VTE are equivalent in cancer patients.[106,108,241] The cost-effectiveness of extended VTE prophylaxis is therefore still debated although a recent study demonstrated its cost-effectiveness, despite the absolute infrequency of VTE events, following CRC surgery.[139]

### 6.1.3 Overall colorectal cancer postoperative venous thromboembolism rates

Although the 90-day rate of postoperative VTE decreases from the 30-day rate following surgery it is not dissimilar to the 30-day rate calculated from the updated Cochrane review aforementioned. This may suggest an argument for extending extended prophylaxis for a 3-month period following surgery however additional contributing factors including chemotherapy, independently a risk factor for VTE, may affect the absolute rate of VTE following CRC resection during this time period, as suggested by previous reviews.[89] This review found no statistical differences in the 1- and 3-months rates of postoperative VTE between rectal and colon cancer surgery, suggesting resection site may

not be a significant factor in the risk of VTE following CRC surgery. The difference in postoperative VTE between abdominal and pelvic resection for CRC is still debated with studies reporting higher rates of VTE following colon compared to rectal cancer resection[43,81,82] and vice versa.[83] Similarly, this review found no statistical difference between open and minimally invasive surgical techniques. This study's findings are similar to those previously reported where no difference in the risk of DVT or PE development after open vs. laparoscopic CRC surgery was found in a meta-analysis of RCTs.[161] However, the benefit of minimally invasive surgery for the prevention of VTE following CRC surgery is still debated.[83,130]

### 6.1.4 Venous thromboembolism rates by United Nations Geoscheme areas

The variation identified by UN Geoscheme Area appears attributable to studies extracted from Americas populations suggesting the risk of VTE is higher in the US than Europe. The cause of this finding is unknown, but factors may include different rates of obesity, surveillance methods for postoperative VTE or use of thromboprophylaxis. Obesity is a well-known VTE risk factor and with the prevalence of obesity significantly higher in the US compared to Europe the difference in VTE rate may be partially attributable to demographic factors.[242,243] Differences in pharmacological prophylaxis use may contribute to the findings. A national UK survey in Colorectal surgery demonstrated a high degree of

concordance, over 95% of responders, with available VTE prophylaxis guidelines.[19] However, in recent North American studies authors found up to 18% of colectomy patients were not receiving prophylaxis as per guidelines,[177] with further reports of in-hospital prophylaxis prescribing compliance rates as low as 40-70%.[171] Another explanation may stem from the global differences in healthcare systems with the out-of-pocket private insurance system of the US having an effect. A recent US database study reported only 4% of CRC surgery patients received postoperative VTE prophylaxis and Merkow et al. reported the use as low as 1.5% of Medicare beneficiaries collecting post-discharge VTE prophylaxis.[140,173] However, it may be that reimbursement directives with focus on VTE as a preventable outcome and call to action by the Centre for Disease Control and Prevention has resulted in increased surveillance of postoperative patients receiving prophylaxis.[33,244-246] This surveillance bias is discussed by Monn et al. who found 20% of PEs reported in their study were detected by Computed Tomography (CT) on the same day infection was diagnosed, leading them to believe these might have been incidental findings.[66] This surveillance bias may affect the perceived incidence of postoperative VTE in a population due to the inability within national/international databases to distinguish between clinical and incidental VTE on coding.[247]

Active surveillance for VTE in high-risk patients is gaining attention as more studies are published describing significantly higher rates of DVT among imaged individuals. In America, studies have shown hospitals with higher VTE surveillance rates have higher inpatient but not

reduced post-discharge VTE rates, and hospitals with higher quality scores have higher VTE prophylaxis rates but worse risk-adjusted VTE rates that are associated with increasing hospital VTE imaging usage.[248,249] This may suggest a reason for the observed differences in VTE rate between regions that does not assume higher rates imply a reduced quality of care. With increased surveillance comes improvement in diagnostic investigation. The availability of CT pulmonary angiography (CTPA) with a low threshold for clinical suspicion has led to the decrease of suspected patients with confirmed PE from 30% to 5% with consistent overdiagnosis since its introduction.[250-252] Recently a study found although CTPA usage is increasing so is the diagnostic yield of PE, reporting that the incidental PE rate remains low in patients undergoing CT thorax for non-PE diagnoses.[253] Suggesting the increase in VTE identification may be a consequence of improved identification of subclinical PE that would have not previously been diagnosed. This highlights that despite improvements in VTE prevention, advances in diagnostic imaging and increasing surveillance protocols may affect the observed rates of postoperative VTE.

## Section 6.2 Time trends in venous thromboembolism following colectomy

### 6.2.1 Overview

This population-based cohort describes an overall relative risk reduction of 31.25% of 30-day VTE following elective colorectal resections over the last 20 years, with no overall relative change in VTE risk after emergency resections. This decrease in VTE risk appears partially attributable to the increasing utilisation of minimally invasive surgery approximately halving the risk compared to open surgery. This is potentially due to improvements in perioperative surgical care, such as the associated use of ERAS programmes and continued focus on VTE prevention seen in this patient subgroup. This increased focus on VTE prevention through the WHO Surgical Safety Checklist and publication of guidelines on VTE prevention and extended VTE prophylaxis, although not independently affecting VTE risk, has likely in part contributed to the overall reduction in VTE rates observed. However, other factors around advancements in perioperative care seem to be important in VTE prevention. Therefore, adoption of advances in perioperative care, that have occurred in elective and or minimally invasive colectomy, is imperative in patients undergoing open Colorectal surgery, especially in the emergency setting for malignant disease, if we are to deliver further reductions in VTE in this high-risk population.

### 6.2.2 Strengths and limitations

The main strength of this large population study is the power to stratify the observed VTE time trends by type of admission, indication and operation. By using an unselected population-based cohort study we were able to present estimates that will be generalisable to other populations with universal coverage and developed healthcare systems. A further advantage of this study is that the VTE definition has previously been validated, and it captures both outpatient VTEs from primary as well as those admitted in secondary care. This thereby reduces the surveillance bias that can occur if patients are solely identified whilst hospitalised.[227,249]

A limitation of the routine data is that we were unable to assess the effect of VTE prophylaxis directly, as hospital prescribing at patient level is not currently available from NHS Digital. However, recent national audit data reports 95–96% of NHS acute admissions were risk assessed for VTE and therefore for the appropriateness of VTE prophylaxis.[46,254] This does not affect the interpretation of the results unduly as it is expected that all patient subgroups in this cohort will have prophylaxis prescribed that reflects the secular trends within the country. Although this could potentially lead to misclassification bias of those receiving extended VTE prophylaxis. Clearly, on an individual level, whether or not prophylaxis was prescribed and for how long is very important in terms of individual risk but the overview of year-on-year change in VTE risk following resection is not otherwise possible due to the need for very large numbers of patients to analyse. As with

any population-based database, there are always concerns surrounding the accuracy of recorded data. However, the databases utilised within this study have been extensively used, previously validated and contain built-in metrics to assure data quality and accuracy, including the use of a validated definition of a VTE outcome.[21,218,223,227]

### 6.2.3 Elective colectomy venous thromboembolism risks

Following elective surgery, we report annual reductions in VTE risk post minimally invasive colorectal resections. This contrasted with previous data showing no change or an increase in annual VTE risk post overall and elective malignant colectomy.[85,196,255,256] However, none of these studies reported yearly VTE rates by admission type and operative technique. Ghadban et al.[255] solely assessed in-hospital VTE events and Yhim et al.[196] examined a study interval predominantly encompassing years prior to 2010.

Interestingly, both elective benign and malignant minimally invasive VTE rates decreased year-on-year during the study even though 28-days extended VTE prophylaxis was only recommended following the malignant resections.[34,50,51] This may be related to a lower base line risk of VTE in those with benign disease compared to those with malignant disease. Furthermore, the widespread introduction of minimally invasive surgery and other perioperative care improvements that are associated with it might have overshadowed the protective effect of extended VTE prophylaxis.

Approximately two-thirds of colectomies were performed minimally invasively by the end of the study, in contrast to less than 1% at its start, in keeping with contemporary National Bowel Cancer Audit (NBOCA) data.[20] There is dispute surrounding the impact of minimally invasive colorectal resection on VTE risk as there will be a selection bias of lower risk patients being selected for this surgery. However, this selection bias may be limited as by the end of the study approximately three-quarters of patients underwent a minimally invasive procedure. Overall, meta-analysis and population-based data supports this study's finding that VTE risk is reduced post minimally invasive colectomy.[71,88,91,120,153,161] The low absolute VTE rates and yearly reduction in VTE risk in elective malignant minimally invasive resections may now suggest this subgroup no longer requires extended VTE prophylaxis. The cost-effectiveness of extended VTE prophylaxis is debated within the literature and particularly important within public health systems such as the NHS.[139,140] However, the low rates observed may be partially related to the current use of extended VTE prophylaxis in CRC resectional patients and its benefit has been demonstrated in RCTs.[95]

Alongside the increase in minimally invasive resections was the implementation of ERAS, that may in part reflect the reduction in VTE risks seen in minimally invasive colectomies. Although ERAS was not directly measured, there is evidence of its impact in this study by the reduction in inpatient length of stay from 12 (IQR 9–18) to 6 (IQR 4–11) days over 2000–2019. Therefore, this study's finding of a year-on-year

reduction in VTE risk following elective colectomy may be associated with the improved perioperative care ERAS patients receive, in addition to more minimally invasive surgery and extended VTE prophylaxis guidelines.[147] Further understanding the duration of magnitude of VTE risk in this group of patients may allow tailoring of guidance on extended VTE prophylaxis as thresholds for intervention may have changed given the studies underpinning this guidance included patients mainly undergoing open elective surgery over 15 years ago.[52] However, RCT evidence to define this further might not be feasible due to the low absolute risk of postoperative VTE and therefore large overall numbers needed to adequately power a study, suggesting large prospective cohort data might be the more realistic approach.

### 6.2.4 Emergency colectomy venous thromboembolism risks

Following emergency surgery, we found an annual reduction in VTE risk following minimally invasive benign and a year-on-year increase in VTE risk post open malignant colorectal resections. This contrasts with contemporary data reporting no differences in annual VTE risk following emergency colectomy.[257] Although the smaller numbers for emergency minimally invasive procedures mean their trends are underpowered, this again highlights that extended VTE prophylaxis alone might not be able to compensate for other developments in perioperative care.

There was an increase in year-on-year VTE risk following open emergency malignant colectomies despite guidance supporting

extended VTE prophylaxis in this subgroup. However, the ENDORSE study highlighted emergency compared to elective surgical patients were less likely to receive appropriate VTE prophylaxis.[169] Other possible explanations include the increasingly elderly population undergoing malignant Colorectal surgery and increasing complex Stage IV and metastatic disease resections that previously may not have been attempted, all of which increase VTE risk.[87,196,258,259] Additionally, those undergoing open colectomy are unlikely to be suitable for ERAS programmes. This study therefore identifies this emergency malignant group as those most in need of appropriate VTE prevention strategies.[166] National initiatives such the ACS-NSQIP in the US and National Emergency Laparotomy Audit (NELA) in the UK could help focus developments in this area and offer a mechanism to record improvements in outcomes over time for this high risk group of patients.[260,261]

## Section 6.3 Rates of post-discharge venous thromboembolism after colectomy

### 6.3.1 Overview

Overall, absolute rates of post-discharge VTE following elective benign or malignant colectomy are equivalent within the first 4-weeks post resection with weekly rates below 50 per 1,000 person-years, indicating current VTE prophylaxis guidance in these groups of patients is appropriate. Emergency benign colectomies do not routinely receive extended VTE prophylaxis, yet we show that their 4-week post-discharge VTE risk was almost 2-fold greater than those undergoing elective malignant resections that do routinely receive extended VTE prophylaxis. This suggests patients discharged after emergency benign and specifically emergency IBD resections might benefit from a period of extended VTE prophylaxis. The highest post-discharge VTE rates remain in the post emergency malignant colectomies with a greater than 3-fold increased risk of post-discharge VTE at 4-weeks post-operation compared to elective malignant resections, despite these patients already receiving extended VTE prophylaxis. This demonstrates a need for further perioperative VTE prevention strategies in this group, for example increasing minimally invasive surgery and following enhanced recovery protocols currently implemented in elective resections.

### 6.3.2 Strengths and limitations

The main strength of this large population study is the power to stratify observed post-discharge VTE rates into postoperative weeks by admission type, surgical indication, and known VTE risk factors. This allowed for the quantification to the precise week VTE rates changed following colectomy within specific subgroups of interest that are at high risk of postoperative VTE. In this study, the VTE definition has previously been validated, capturing both outpatient VTEs from primary as well as those admitted in secondary care. This thereby reduces the surveillance bias that can occur if patients are solely identified whilst hospitalised.[227,249] Furthermore, by using an unselected population-based cohort study the presented estimates will be generalisable to other populations with universal coverage and developed healthcare systems.

The study population selected underwent colectomy from 2010 onwards, all of which occurred after the introduction of national VTE prophylaxis guidelines.[34] Although a limitation of this study was the inability to assess the effect of VTE prophylaxis directly, as hospital prescribing at patient level is not currently available, that could lead to misclassification bias of those receiving extended VTE prophylaxis. However, 95–96% of NHS acute admissions were risk assessed for VTE according to recent national audit data and thus for the appropriateness of VTE prophylaxis.[46,254] Therefore, all patient groups in this cohort will have had prophylaxis prescribed in line with the trends in the country as a whole. Although, it would be desirable to have

inpatient prescribing, a national cohort large enough to allow detailed stratified results with this data is not currently available. As with any population-based database, there are always concerns surrounding the accuracy of recorded data. However, the databases utilised within this study have been extensively used, previously validated and contain built-in metrics to assure data quality and accuracy, including the use of a validated definition of a VTE outcome.[21,218,223,227]

### 6.3.3 Elective colectomy

After elective benign colectomy, weekly post-discharge VTE rates were relatively low. This is consistent with other studies that report elective benign colectomies have one of the lowest post colectomy VTE risks.[7,21] Current VTE prophylaxis guidance in this group is therefore appropriate. However, elective patients admitted for >7-days following colectomy had elevated post-discharge VTE rates to week 5 post-operation with previous data showing hospitalization for more than 1-week has a significant elevating effect on post-discharge VTE rates following colectomy.[71,88] Consequently, if guidance were to be updated, it could be tailored to address certain high-risk elective subgroups, including the elderly and those with prolonged inpatient stays, that may benefit from further VTE prevention measures such as extended VTE prophylaxis.[121]

Following elective malignant resections, post-discharge VTE rates were also low and similar to elective benign rates. This fits with contemporary

reports of VTE rates following CRC and IBD or benign resections being relatively equivalent.[85,120] A conflicting earlier analysis by Humes et al. found the VTE rate post elective malignant colectomy was greater than those with benign disease.[21] However, this may be due to the study period analysed pre-dating the introduction of extended VTE prophylaxis guidance with most patients operated on via an open approach.[83,161] The low post-discharge VTE rates we report for elective CRC resections could be a consequence of the extended 4-weeks VTE prophylaxis that international guidance already advocates. However, the risk varied by operative technique, with VTE rates in those undergoing elective malignant open resections remaining above 50 per 1,000 person-years until postoperative week 5, but patients undergoing minimally invasive colectomy were consistently at very low VTE risks. This latter group might therefore not require extended VTE prophylaxis. Despite Vedovati et al. demonstrating the protective impact of extended VTE prophylaxis within a laparoscopic CRC cohort,[95] debate surrounds the benefit of contemporary extended VTE prophylaxis use in elective CRC resection in conjunction with perioperative advancements including minimally invasive surgery and enhanced recovery protocols.[104,130,147] Furthermore, within the elective setting those aged ≤ 60 years, with inpatient durations ≤ 7 days and or no co-morbidities, the post-discharge VTE rates were further reduced. Therefore, in these low-risk subgroups extended VTE prophylaxis could potentially be omitted in elective CRC patients, thus reducing morbidity and having cost saving benefits.[140]

### 6.3.4 Emergency colectomy

After emergency benign colectomies, the post-discharge VTE risk within 4-weeks of resection was approximately 2-fold greater than those undergoing elective malignant colectomy, with the highest risk in those undergoing IBD resection and with the highest weekly post-discharge VTE rate seen in the first postoperative week. This correlates with studies showing emergency benign or IBD colectomy VTE rates are higher than those in the elective setting, including patients undergoing CRC resection that are currently considered higher risk.[21,67,85,92,125] Despite this, emergency benign resections that form the majority of emergency colectomy work (69.28%) do not receive extended VTE prophylaxis while elective malignant colectomies do. Therefore, the results of this study suggest emergency benign, and in particular IBD, admissions should receive at least 7-days VTE prophylaxis in line with current guidance and may in fact benefit from extended VTE prophylaxis.[88,116,120,137]

The highest and longest elevated weekly post-discharge VTE rates were observed following emergency malignant resections with a greater than 3-fold increased risk of post-discharge VTE within 4-weeks of colectomy compared those undergoing elective CRC surgery. This is expected and comparable with previous findings within the literature highlighting the increased VTE risk within this population.[21,87,217] These high post-discharge VTE rates persisted for the majority of the 12-week follow-up period despite guidelines recommending these patients receive 4-weeks of extended VTE prophylaxis. The relatively high

magnitude and duration of VTE rates may be secondary to the combined effects of increasing age, advanced cancer stage and adjuvant chemotherapy, commencing around 6 to 8 weeks post resection, which are known risk factors for VTE particularly within the emergency setting.[87,89,262] Further perioperative VTE prevention measures, especially in the elderly and other high-risk subgroups, might therefore benefit these patients: For example increasing emergency minimally invasive colectomy uptake and implementing emergency colorectal enhanced recovery pathways that have been shown to improve postoperative outcomes for elective patients as well as potentially increasing the period of extended VTE prophylaxis.[166,263]

## Section 6.4 Compliance with venous thromboembolism prophylaxis at discharge post-surgery

### 6.4.1 Overview

Although no significant differences were observed between pre- and post-intervention groups, the overall proportion of surgical CRC patients receiving compliant discharge prescriptions of extended VTE prophylaxis is relatively high. However, NHS Trust set targets were not reached indicating further small but necessary improvements are still needed with a focus on junior doctor education. This was not the case with respect to benign abdominal operations where major improvements and educational changes are needed to improve post-discharge VTE prophylaxis prescription with compliance currently 0%. Despite its perceived significance, valid VTE risk assessment completion did not appear to effect adherence to extended VTE prophylaxis prescription at discharge. This suggests other target measures or payment incentives are needed to accurately reflect appropriate VTE prophylaxis prescription and so improve VTE prescription compliance. One such target may be the monitoring of detailed postoperative instruction of VTE prophylaxis length within the postoperative note that was significantly associated with VTE prophylaxis prescription compliance on discharge.

### 6.4.2 Strengths and limitations

This study has several strengths, it is a prospective cohort using a continuously updated database ensuring accurate recording of data. Not only were national target outcomes, VTE risk assessments, analysed that are indirect measures of appropriate VTE prophylaxis prescription but direct outcome measurements of VTE prophylaxis at discharge were also recorded. Despite being a single centre institution, patient inclusion criteria were not excessively restrictive with outcomes measured against national guidelines. However, due to the single centre and retrospective design, the study is at risk of selection bias and the findings may not be fully generalisable and reflective of other teaching and district general hospital NHS Trusts practices within the UK. A further limitation was the inability from patient records to accurately discern reasons behind failures to prescribe appropriate VTE prophylaxis. Of note is that no sample size calculations were made due to the audit design of these studies and this may impact on the outcome of the results, increasing the potential of a type II error, suggesting a large and multicentred study is required to expand on this research question.

### 6.4.3 Compliance with extended venous thromboembolism prophylaxis post colorectal cancer resection

Following CRC resections, although not significant, the proportion of patients discharged with appropriate extended VTE prophylaxis increased and by the end of the study was close to the NHS Trust's

target of 95%. This mirrors previous reports from UK centres highlighting relatively high concordance with contemporary extended VTE prophylaxis guidelines following malignant colectomy post educational interventions for junior doctors.[176,235,236] This suggests continued active engagement with clinicians involved in VTE prophylaxis prescription is key in maintaining good compliance with prescription at hospital discharge. However, this data conflicts with a previous survey that found only 27.4% of clinicians agreed with extended post-discharge VTE prophylaxis.[19] Yet, this study was conducted soon after the introduction of current guidance and therefore the conflict in results may highlight changes in attitudes and so compliance with national guidance over the last decade, as has been shown in the US.[85,135]

Interestingly VTE assessment did not have a significant impact on extended VTE prophylaxis prescription at discharge for CRC resection patients, with a proportional increase in VTE prophylaxis prescription failure observed in those with a valid eVTE recorded. This is an intriguing finding due to the importance granted to accurate and timely VTE assessment, being both a CQUIN target and recommended by NICE for all patients with debate surrounding its improvement of in-hospital VTE prevention.[34,46,264-267] However, the current NICE VTE risk assessment does not incorporate decision making or advice on post-discharge/extended VTE prophylaxis prescription. This suggests current VTE risk assessments may need to be adapted and or other performance metrics utilised in addition to VTE risk assessment status

to increase post-discharge VTE prophylaxis compliance following CRC surgery. One such target may be the measurement of appropriately recorded extended VTE prophylaxis within the postoperative instruction that had a significant effect on the compliance of extended VTE prophylaxis prescription in this study. Current Royal College of Surgeons of England Good Surgical Practice guidance outlines the need for clear and accurate postoperative records with detailed VTE prophylaxis instruction, however, this was not observed in the majority of CRC patients.[268,269] This suggests improved documentation of VTE prophylaxis duration within the postoperative record may improve VTE prophylaxis prescription adherence at discharge, potentially by introducing a proforma highlighting the required length of prophylaxis.[270,271]

### 6.4.4 Compliance with 7-days venous thromboembolism prophylaxis post abdominal surgery

Post benign abdominal surgical resections there was a significant and complete failure of adherence to contemporary 7-days postoperative VTE prophylaxis into the post-discharge period. No other study has specifically investigated 7-days postoperative VTE prophylaxis compliance post benign abdominal operations indicating this recommendation is unlikely to be well known. This might be for several reasons: Firstly, the recommendation of 7-days postoperative VTE prophylaxis was only introduced within the 2018 NICE update on VTE guidelines compared to extended VTE prophylaxis for malignant

resections introduced in 2010, meaning less time has elapsed for national guidelines to become ingrained within local policies.[34,48] Secondly, 7-days VTE prophylaxis is currently only advocated within English NICE guidelines whereas other international guidance only recommends inpatient VTE prophylaxis for benign abdominal resections.[50] Thirdly, the potentially perceived lower risk of benign emergency general surgical operations compared with malignant colectomy.[6,203,205] However, emergency general operations have been shown to have higher rates of VTE compared with elective operations and most emergency colorectal resections are for benign pathology such as IBD.[8,153] This has led to the introduction of extended VTE prophylaxis post benign colectomy within contemporary international guidance.[137] Suggesting further efforts to improve VTE prophylaxis prescription compliance should focus on this patient subgroup and be incorporated into the educational initiatives utilised in improving extended VTE prophylaxis adherence in CRC patients.

# Chapter 7 Conclusion

## Section 7.1 Chapter conclusions

This chapter summarises the conclusions that may be drawn from the 4 original studies outlined in Chapters 2 to 5.

Chapter 2 has shown, the incidence of VTE in CRC patients after surgery is high with a persistent risk lasting more than 1-month after resection. The rates we report suggest extended prophylaxis may still be of benefit in the prevention of VTE. Globally the regional rates of VTE differ in this surgical population and this variation may be determined by differences in both demographic and clinical practice factors, such as surveillance protocols observed between populations. This suggests the rate of VTE following surgery should be assessed at a regional level when determining recommendations and guidance on its prevention following surgery. Therefore, when comparing rates of postoperative VTE against a regional standard it is necessary to acknowledge the rate observed may be influenced by these factors and what this means in terms of quality of care. To further interpret the international comparisons of postoperative VTE requires further understanding of the effect differences in surveillance practice, and therefore incidental VTE diagnosis, have on relative patient risk. More robust population studies, worldwide, are required to further investigate these geographical differences to determine valid regional incidence rates of postoperative VTE following CRC resection.

Chapter 3 has shown that over the last 20 years VTE risk following elective colorectal resections has reduced in absolute terms, specifically when compared to the VTE risk following emergency resections. This risk reduction is most likely due to changes in perioperative surgical care. This suggests future focus on improving postoperative emergency colectomy VTE rates is needed with the application of specific advances observed in the elective setting, such as emergency ERAS pathways utilising minimally invasive techniques where possible.

Chapter 4 has shown post-discharge VTE rates following elective benign and malignant colectomies are low, suggesting current international guidance on VTE prophylaxis duration is appropriate in these groups. Post-discharge VTE risk within 4-weeks of surgery following emergency benign resections, particularly in those undergoing IBD resection, is greater than in those undergoing elective malignant colectomy. This is despite emergency benign resections not receiving extended VTE prophylaxis yet comprising the majority of emergency colectomies, indicating they might benefit from extended VTE prophylaxis. Patients undergoing emergency malignant colectomy are at increased risk of post-discharge VTE despite receiving extended VTE prophylaxis. Therefore, further work on improving perioperative colorectal surgical care in the prevention of postoperative VTE needs to focus on the emergency CRC patient.

Chapter 5 has shown current compliance with extended VTE prophylaxis prescription at discharge for CRC resectional patients is

high yet requires further improvements to reach local and national targets. This is not the case for the minimum 7-days postoperative VTE prophylaxis following benign abdominal operations. VTE risk assessment does not appear to effect post-discharge VTE prophylaxis prescription compliance. Further educational initiatives and performance markers, such as the measurement of detailed documentation of VTE prophylaxis duration within postoperative records, are needed to improve appropriate post-discharge VTE prophylaxis prescription following malignant and benign operations.

## Section 7.2 Areas for future research

The findings of this thesis raise several questions for which further work is needed to help build upon its conclusions.

Chapter 2 highlighted the incidence of VTE post CRC resections is high and therefore extended VTE prophylaxis is likely still of benefit. The incidence varies globally by region, potentially due to differences in demographics between populations as well as clinical practice factors such as surveillance bias observed within different health care systems. However, no such systematic review or meta-analysis exists that characterises the rate of postoperative VTE in patients undergoing benign colorectal resections and how this varies globally and by surgical pathology. This is important as the majority of emergency colorectal resectional work that increases the risk of VTE, as demonstrated in this thesis, is for benign pathology, primarily IBD, encompassing CD and UC, and diverticular disease. This work would help quantify the risk of VTE following benign colectomy in relation to CRC resections and provide a basis for future focused stratified guidance on postoperative VTE prevention and so aid formation of guidelines on VTE prophylaxis regimen in these subgroups.

Chapter 3 emphasized the incidence of VTE following colectomy varies significantly particularly by stratification into groups of interest that are at high risk of VTE who require further interventional measures, such as patients undergoing emergency open malignant resections. Further efforts should be directed at these groups to either increase the uptake of minimally invasive surgery or, if not clinically possible, development

and utilisation of emergency Colorectal ERAS pathways should be trialled and VTE outcomes assessed. Further to stratification, outside of CRC and IBD pathologies, there is minimal evidence focusing on detailed risk factors for and the duration and magnitude of VTE incidence post colectomy for diverticular disease. The importance of this cannot be understated, with an increase in obese and elderly populations the incidence of diverticulitis and perforated diverticular disease that may require surgery has increased significantly over the last 30 years yet the impact of this on VTE incidence is not clear.[272,273]

Furthermore, a more detailed focus on the incidence of VTE and benign colorectal resections is needed. Chapter 4 demonstrated patients undergoing emergency benign resections, that do not internationally receive extended VTE prophylaxis, had higher rates of post-discharge VTE compared with those undergoing elective malignant colectomies that do. There is detailed international guidance and literature on the benefit of extended VTE prophylaxis following CRC surgery.[34,50,51] Yet, no RCT currently exists on the effect of extended 28-days vs. in-hospital/7-days postoperative VTE prophylaxis on incidence of VTE following benign colectomies. Based on similar RCTs designs,[51,178] this RCT would aim to assess the efficacy and safety of extended VTE prophylaxis using a single standard anti-coagulant preparation such as LMWH against either in-hospital VTE prophylaxis use or for a minimum 7-days post-operation. Investigators will have to set specific inclusion criteria as perioperative care factors including minimally invasive surgery and ERAS protocols will likely have an impact on VTE as an

outcome. Primary outcomes could be symptomatic VTE including VTE-related death at 4- and 12-weeks post-operation with a pre-defined definition of major bleeding as a safety outcome.[274] However, due to the infrequency of symptomatic VTEs, a pilot study to test the efficacy of extended VTE prophylaxis following benign colectomies would most likely also assess the rate of asymptomatic ultrasonography-detected DVT at both 4- and 12-weeks post-operation with pre-operative ultrasonographic screening to establish no VTE was present prior to surgery.[275]

Finally, Chapter 5 has exposed the lack of contemporary data on UK clinician adherence to international NICE guidelines with respect to both CRC extended VTE prophylaxis but most pressingly adherence to current benign abdominal surgery 7-days postoperative VTE prophylaxis. This in conjunction with the limitations in Chapters 3 and 4 that NHS Digital does not have individual HES prescription data raises the question what proportion of colorectal resectional patients receive appropriate postoperative VTE prophylaxis in line with current guidance and what proportion are truly compliant with their VTE prophylaxis regimen? This would require a repeat survey of clinicians and patients yet would be rooted in recall and response bias. However, this data is crucial as knowledge of the true compliance rate of extended VTE prophylaxis following CRC resection will help determine the efficacy this intervention has had on VTE risk following colectomy and so shape future guidance.

# Appendices

## Appendix 1 PROSPERO Registration

PROSPERO
International prospective register of systematic reviews

NHS
National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

## Systematic review

To edit the record click *Start an update* below. This will create a new version of the record - the existing version will remain unchanged.

### 1. * Review title.

Give the title of the review in English

Systematic review and meta-analysis of the risk of postoperative venous thromboembolism after surgery for colorectal malignancy

### 2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

### 3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

09/09/2019

### 4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

01/06/2020

### 5. * Stage of review at time of this submission.

Tick the boxes to show which review tasks have been started and which have been completed. Update this field each time any amendments are made to a published record.

**Reviews that have started data extraction (at the time of initial submission) are not eligible for inclusion in PROSPERO**.
If there is later evidence that incorrect status and/or completion date has been supplied, the published PROSPERO record will be marked as retracted.

This field uses answers to initial screening questions. It cannot be edited until after registration.

The review has not yet started: No

| Review stage | Started | Completed |
|---|---|---|
| Preliminary searches | Yes | Yes |
| Piloting of the study selection process | Yes | Yes |
| Formal screening of search results against eligibility criteria | No | Yes |
| Data extraction | No | Yes |
| Risk of bias (quality) assessment | Yes | Yes |
| Data analysis | Yes | Yes |

Provide any other relevant information about the stage of the review here.

Non-funded proposal
Completed and published in the journal: Diseases of the Colon & Rectum

## 6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Christopher Lewis-Lloyd

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Lewis-Lloyd

## 7. * Named contact email.

Give the electronic email address of the named contact.

chrislewislloyd@doctors.org.uk

## 8. Named contact address

**PLEASE NOTE this information will be published in the PROSPERO record so please do not enter private information, i.e. personal home address** Give the full institutional/organisational postal address for the named contact.

## 9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

(+44) 7xxxxxxxxx

## 10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Department of Gastrointestinal Surgery, National Institute for Health Research

Nottingham Digestive Diseases Biomedical Research Centre, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom

Organisation web address:

https://nddcbru.org.uk/
https://www.nuh.nhs.uk/nottingham-digestive-diseases-centre
https://www.nottingham.ac.uk/medicine/about/nddc/index.aspx

## 11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Dr Christopher Lewis-Lloyd. Department of Gastrointestinal Surgery, National Institute for Health Research
Nottingham Digestive Diseases Biomedical Research Centre, Nottingham University Hospitals NHS Trust,
Nottingham, United Kingdom
Ms Eleanor Pettitt. Department of Gastrointestinal Surgery, National Institute for Health Research
Nottingham Digestive Diseases Biomedical Research Centre, Nottingham University Hospitals NHS Trust,
Nottingham, United Kingdom
Mr Alfred Adiamah. Department of Gastrointestinal Surgery, National Institute for Health Research
Nottingham Digestive Diseases Biomedical Research Centre, Nottingham University Hospitals NHS Trust,
Nottingham, United Kingdom
Assistant/Associate Professor Collin Crooks. Department of Gastrointestinal Surgery, National Institute for
Health Research Nottingham Digestive Diseases Biomedical Research Centre, Nottingham University
Hospitals NHS Trust, Nottingham, United Kingdom
Assistant/Associate Professor David Humes. Department of Gastrointestinal Surgery, National Institute for
Health Research Nottingham Digestive Diseases Biomedical Research Centre, Nottingham University
Hospitals NHS Trust, Nottingham, United Kingdom

## 12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

Not applicable

Grant number(s)

State the funder, grant or award number and the date of award

## 13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

There are no conflicts of interest

## 14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

## 15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

Looking at the risk of venous thromboembolism (outcome) in patients with colorectal cancer (population) after their definitive colorectal surgery (intervention) for the cancer. We will look at population based studies and multi-centre clinical trials. (There is no comparator for the PICO model)

## 16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

The databases used will be the Ovid MEDLINE and Embase databases searching from database formation to August 2019 with hedge filters adapted from the SIGN RCT document. Full search strategies will be linked as an attachment closer to completion date. We will also search the Cochrane Library, US National Library of Medicine ClinicalTrials.gov and International Clinical Trials Registry Platform (ICTRP) databases. There are no language limitations.

## 17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible.

Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

Do not make this file publicly available until the review is complete

## 18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Colo-rectal cancers are neoplasms of the bowel specifically of either the colon or rectum that for curative treatment requires surgery.

Venous thromboembolism refers to the formation of a thrombus or embolus within the venous side of the vascular system. Generally either as a deep vein thrombus, usually in the lower limbs, or a pulmonary embolism i.e. a blood clot lodged in the pulmonary artery or its branches connecting to the lungs.

## 19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion: Adults aged greater than or equal to 18 years or older with a diagnosis of either colon or rectal cancer who have had definitive surgery specifically for their colorectal cancer.

Exclusion: Patients aged less than 18 years old. Patients who have not yet had surgery. Patients who have had colorectal surgery for benign disease. Patients who have undergone a completely endoscopic procedure. Patients with colorectal cancer who have undergone surgery not related to their colorectal cancer.

## 20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Any form of definitive colorectal surgery for colorectal cancer including laparoscopic and robotic techniques excluding totally endoscopic procedures.

## 21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria. Nil comparator available

## 22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated. Population based studies and multi-centre clinical trials

## 23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria. There is no geographical exclusion criteria

## 24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

The incidence of postoperative venous thromboembolism (VTE) in patients after their surgery for colorectal cancer. A patient coded as having a VTE by a study after having had and coded for having surgery for colorectal cancer.

Measures of effect

Looking at 1 month and 1 year risk of VTE in this cohort of patients.

## 25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes.
Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

None
There are no pre-specified additional outcomes however we may look at mortality or survival outcomes if they appear as an interest.

Measures of effect

Not applicable

## 26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Data exported from all databases will be pooled together with duplicates removed. Two members of the review team will independently at each stage screen titles then abstracts then full texts assessing whether the article meets the inclusion criteria for the review. If there is any discrepancy between the reviewers a third reviewer will act independently as an adjudicator. Data to be extracted will be the incidence of VTE at 30 days/1 month and 1 year post surgery.

## 27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

For RCTs we will use the Cochrane risk of bias tool.
For cohort studies we will use the modified Newcastle Ottawa scale.

## 28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data.
If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

Analyse incidence of VTE at 30 days/1 month and 1 year in each study. We will calculate the incidence rate if not provided in each study and present this as a value per 1, 000 person years. We will then pool the incidence rates from the studies to get a total incidence rate. We will report the heterogeneity and 95% confidence intervals and if $I^2$ is less than 75% perform a meta-analysis.

## 29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

We will stratify data by type of study (RCT etc.) and type of colorectal resection (right vs left hemicolectomy etc.)

## 30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

| | |
|---|---|
| Cost effectiveness | No |
| Diagnostic | No |
| Epidemiologic | No |
| Individual patient data (IPD) meta-analysis | No |
| Intervention | No |
| Living systematic review | No |
| Meta-analysis | Yes |
| Methodology | No |
| Narrative synthesis | No |
| Network meta-analysis | No |
| Pre-clinical | No |
| Prevention | No |
| Prognostic | No |
| Prospective meta-analysis (PMA) | No |
| Review of reviews | No |
| Service delivery | No |

| | |
|---|---|
| Synthesis of qualitative studies | No |
| Systematic review | Yes |
| Other | No |

Health area of the review

| | |
|---|---|
| Alcohol/substance misuse/abuse | No |
| Blood and immune system | No |
| Cancer | Yes |
| Cardiovascular | No |
| Care of the elderly | No |
| Child health | No |
| Complementary therapies | No |
| COVID-19 | No |
| Crime and justice | No |
| Dental | No |
| Digestive system | Yes |
| Ear, nose and throat | No |
| Education | No |
| Endocrine and metabolic disorders | No |
| Eye disorders | No |

| | |
|---|---|
| General interest | No |
| Genetics | No |
| Health inequalities/health equity | No |
| Infections and infestations | No |
| International development | No |
| Mental health and behavioural conditions | No |
| Musculoskeletal | No |
| Neurological | No |
| Nursing | No |
| Obstetrics and gynaecology | No |

| | |
|---|---|
| Oral health | No |
| Palliative care | No |
| Perioperative care | Yes |
| Physiotherapy | No |
| Pregnancy and childbirth | No |
| Public health (including social determinants of health) | No |
| Rehabilitation | No |
| Respiratory disorders | No |
| Service delivery | No |
| Skin disorders | No |
| Social care | No |
| Surgery | Yes |
| Tropical Medicine | No |
| Urological | No |
| Wounds, injuries and accidents | No |
| Violence and abuse | No |

## 31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

English

There is not an English language summary

## 32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved. England

## 33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them.
If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

## 34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format) No I do not make this file publicly available until the review is complete

## 35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Not applicable

## 36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Colo-rectal cancer
Colo-rectal surgery
Venous thromboembolism

## 37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.
No

## 38. Current review status.

Update review status when the review is completed and when it is published.New registrations must be
ongoing so this field is not editable for initial submission.
Please provide anticipated publication date
Review_Completed_published

## 39. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not

editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Lewis-Lloyd CA, Pettitt EM, Adiamah A, Crooks CJ, Humes DJ. Risk of Postoperative Venous Thromboembolism After Surgery for Colorectal Malignancy: A Systematic Review and Meta-analysis. Dis Colon Rectum. 2021 Apr 1;64(4):484-496. doi: 10.1097/DCR.0000000000001946. PMID: 33496485.

Give the link to the published review or preprint.
https://journals.lww.com/dcrjournal/pages/articleviewer.aspx?year=2021&issue=04000&article=00016&type=Fulltext

## Appendix 2 MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

| Reporting Criteria | Reported (Yes/No) | Reported on Page No. |
|---|---|---|
| **Reporting of Background** | | |
| Problem definition | Yes | 4 & 5 |
| Hypothesis statement | No | |
| Description of Study Outcome(s) | Yes | Table 1 |
| Type of exposure or intervention used | Yes | 5 & 6 |
| Type of study design used | Yes | 6 & 7 |
| Study population | Yes | 5 & 6 |
| **Reporting of Search Strategy** | | |
| Qualifications of searchers (e.g., librarians and investigators) | Yes | 1 |
| Search strategy, including time period included in the synthesis and keywords | Yes | 6 and Appendix 1 |
| Effort to include all available studies, including contact with authors | Yes | 6 & 7 |
| Databases and registries searched | Yes | 6 |
| Search software used, name and version, including special features used (e.g., explosion) | Yes | 6 |
| Use of hand searching (e.g., reference lists of obtained articles) | Yes | 6 |
| List of citations located and those excluded, including justification | Yes | Figure 1 |
| Method for addressing articles published in languages other than English | Yes | 6 |
| Method of handling abstracts and unpublished studies | No | |
| Description of any contact with authors | No | |
| **Reporting of Methods** | | |
| Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | Yes | 6 & 7 |

| | | |
|---|---|---|
| Rationale for the selection and coding of data (e.g., sound clinical principles or convenience) | Yes | 7 |
| Documentation of how data were classified and coded (e.g., multiple raters, blinding, and interrater reliability) | Yes | 6 & 7 |
| Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate. | No | |
| Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results | Yes | Appendix 2 |
| Assessment of heterogeneity | Yes | Figures 2 & 3 and eFigures 3 – 7 |
| Description of statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | Yes | 8 |
| Provision of appropriate tables and graphics | Yes | Table 1 and Figures 1 – 8 |
| Reporting of Results | | |
| Table giving descriptive information for each study included | Yes | Table 1 |
| Results of sensitivity testing (e.g., subgroup analysis) | Yes | Figure 2 – 8 |
| Indication of statistical uncertainty of findings | No | |
| Reporting of Discussion | | |
| Quantitative assessment of bias (e.g., publication bias) | Yes | Appendix 2 |
| Justification for exclusion (e.g., exclusion of non–English-language citations) | Yes | Figure 1 |
| Assessment of quality of included studies | Yes | Appendix 2 |
| Reporting of Conclusions | | |
| Consideration of alternative explanations for observed results | Yes | 14 – 17 |

| | | |
|---|---|---|
| Generalization of the conclusions (i.e., appropriate for the data presented and within the domain of the literature review) | Yes | 17 & 18 |
| Guidelines for future research | Yes | 18 |
| Disclosure of funding source | Yes | 1 |

## Appendix 3 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 & 3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 & 5 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 6 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6 & 7 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Appendix 1 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 6 & 7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for | 7 & 8 |

| | | | |
|---|---|---|---|
| | | obtaining and confirming data from investigators. | |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 7 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 7 & Appendix 2 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 7 & 8 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 7 & 8 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | Appendix 2 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | N/A |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Figure 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Appendix 2 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Table 1 & Appendix 4 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Figures 2 & 3, Appendix 4 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Appendix 2 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | N/A |
| **DISCUSSION** | | | |

| | | | |
|---|---|---|---|
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 13 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 13 – 15 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 16 – 18 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 1 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit: **www.prisma-statement.org**.

## Appendix 4 OVID Database search strategies

**Database: Ovid MEDLINE(R) ALL <1946 to August 20, 2019>**

**Search Strategy:**

---

1 exp Colorectal neoplasms/ (191886)

2 ((colorect* or colo rect*) adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).mp. (133188)

3 ((colon or colonic) adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).mp. (111562)

4 ((rectal* or rectum*) adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).mp. (51501)

5 exp Colonic neoplasms/ or exp Rectal neoplasms/ (105170)

6 exp Cecal neoplasms/ or exp Sigmoid neoplasms/ or exp Appendiceal neoplasms/ (9672)

7 ((sigmoid or appendiceal) adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).mp. (9234)

8 ((caec* or cec*) adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).mp. (3472)

9 lynch syndrome.mp. or exp Colorectal neoplasms, Hereditary nonpolyposis/ (5509)

10 Adenomatous Polyposis Coli.mp. or exp Adenomatous Polyposis Coli/ (9084)

11 hamartomatous polyposis.mp. or exp Peutz-Jeghers syndrome/ or exp Hamartoma syndrome, Multiple/ (3277)

12 (familial adenomatous polyposis or MYH-associated polyposis or juvenile polyposis or cowden disease).mp. (5310)

13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (266773)

14 (surger* adj3 (colorect* or colo rect* or colon* or rect* or cec* or caecum or colectom* or bowel cancer* or robotic or emergenc*)).mp. (37657)

15 exp Colorectal surgery/ or exp Cecum/ or exp Colon/ or exp Rectum/ (116527)

16 exp Colectomy/ or colectom*.mp. (25168)

17 (cecectomy or caecectomy or sigmoidectomy or sigmoidectomies or sigmoid colectomy or sigmoid colectomies or hemicolectomy or hemicolectomies or Hartmann procedure).mp. (5546)

18 (panproctocolectomy or panproctocolectomies or anterior resection or lower anterior resection or rectosigmoidectomy or rectosigmoidectomies or proctectom*).mp. (5868)

19 (abdominoperineal excision of rectum or APER or total mesorectal excision or TME or AP resection or perineal resection).mp. (5561)

20 exp Surgical oncology/ or surgical oncolog*.mp. (3248)

21 exp Proctectomy/ or abdominoperineal resection.mp. (5951)

22 exp Laparoscopy/ or exp Robotic surgical procedures/ (97361)

23 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (261120)

24 (VTE or DVT or PE).mp. (58246)

25 (thromb* adj2 (vein* or venous)).mp. (75727)

26 (venous adj stasis).mp. (1773)

27 venous thromboembolism.mp. or exp Venous thromboembolism/ or exp Thromboembolism/ or exp Pulmonary embolism/ (94740)

28 exp Venous thrombosis/ (53395)

29 (thromboembolism or venous thromb* or venous embol*).mp. (88194)

30 (deep vein thromb* or pulmonary embol* or lung embol*).mp. (62663)

31 (phlegmasia adj2 dolens).mp. (421)

32 paradoxical embolism.mp. or exp Embolism, Paradoxical/ (1657)

33 ((pulmonary or lung) adj4 (embol* or thromboembo* or microembol*)).mp. (57413)

34 (pulmonary adj infarction).mp. (863)

35 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (211715)

36 13 or 23 (480679)

37 35 and 36 (3627)

38 exp Case reports/ (2039371)

39 exp Historical article/ (390146)

40 exp Letter/ (1039676)

41 38 or 39 or 40 (3253480)

42 37 not 41 (2737)

**Database: Embase <1974 to 2019 August 21>**

**Search Strategy:**

---

1 exp colorectal tumor/ or exp colorectal cancer/ or exp colorectal carcinoma/ (187850)

2 ((colorect* or colo rect*) adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).mp. (222209)

3 ((colon or colonic) adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).mp. (157915)

4 ((rectal* or rectum*) adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).mp. (66601)

5 exp colon cancer/ or exp colon adenoma/ or exp colon tumor/ or exp colon carcinoma/ or exp colon adenocarcinoma/ (303208)

6 exp rectum carcinoma/ or exp rectum adenoma/ or exp rectum cancer/ or exp rectum tumor/ (239215)

7 exp cecum cancer/ or exp cecum tumor/ or exp cecum carcinoma/ (2138)

8 exp sigmoid cancer/ or exp sigmoid carcinoma/ (1331)

9 exp appendix tumor/ or exp appendix carcinoma/ or exp appendix cancer/ (3619)

10 ((sigmoid or appendiceal) adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).mp. (6129)

11 ((caec* or cec*) adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).mp. (3408)

12 lynch syndrome.mp. or exp hereditary nonpolyposis colorectal cancer/ (7251)

13 Adenomatous Polyposis Coli.mp. or exp colon polyposis/ (9788)

14 exp Cowden syndrome/ or exp Peutz Jeghers syndrome/ or hamartomatous polyposis.mp. (4457)

15 (familial adenomatous polyposis or MYH-associated polyposis or juvenile polyposis or cowden disease).mp. (7626)

16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (400565)

17 (surger* adj3 (colorect* or colo rect* or colon* or rect* or cec* or caecum or colectom* or bowel cancer* or robotic or emergenc*)).mp. (81373)

18 exp Colorectal surgery/ or exp Cecum/ (45282)

19 exp colon resection/ or exp colon/ or exp colon surgery/ (127247)

20 exp rectum abdominoperineal resection/ or exp rectum surgery/ or exp rectum/ or exp rectum anterior resection/ or exp rectum resection/ (57591)

21 (colectom* or cecectomy or caecectomy or sigmoidectomy or sigmoidectomies or sigmoid colectomy or sigmoid colectomies or hemicolectomy or hemicolectomies or Hartmann procedure).mp. (31966)

22 (panproctocolectomy or panproctocolectomies or anterior resection or lower anterior resection or rectosigmoidectomy or rectosigmoidectomies or proctectom*).mp. (10844)

23 (abdominoperineal resection or abdominoperineal excision of rectum or APER or total mesorectal excision or TME or AP resection or perineal resection).mp. (15826)

24 exp surgical oncology/ or exp cancer surgery/ or surgical oncolog*.mp. (300080)

25 exp laparoscopy/ or exp robotic surgical procedure/ (153249)

26 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 (656214)

27 (VTE or DVT or PE).mp. (161799)

28 (thromb* adj2 (vein* or venous)).mp. (156150)

29 (venous adj stasis).mp. (3386)

30 venous thromboembolism.mp. or exp venous thromboembolism/ (148031)

31 exp thromboembolism/ or exp lung embolism/ (458315)

32 exp vein thrombosis/ (121882)

33 (thromboembolism or venous thromb* or venous embol*).mp. (146829)

34 (deep vein thromb* or pulmonary embol* or lung embol*).mp. (132362)

35 (phlegmasia adj2 dolens).mp. (406)

36 paradoxical embolism.mp. or exp paradoxical embolism/ (2494)

37 ((pulmonary or lung) adj4 (embol* or thromboembo* or microembol*)).mp. (103643)

38 (pulmonary adj infarction).mp. (871)

39 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 (600378)

40 16 or 26 (961539)

41 39 and 40 (28618)

42 16 and 26 and 39 (2579)

43 exp case study/ (63605)

44 case report.tw. (390470)

45 exp abstract report/ or exp letter/ (1117675)

46 Conference proceeding.pt. (0)

47 Conference abstract.pt. (3532734)

48 Editorial.pt. (628185)

49 Letter.pt. (1081955)

50 Note.pt. (768523)

51 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 (6440353)

52 42 not 51 (1870)

## Appendix 5 Risk of Bias: Population/Registry studies

**Alhassan 2018**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Representativeness of Cohort (Selection) | Low risk | ACS-NSQIP data of participating hospitals in USA and Canada, with patients undergoing colorectal surgery without resection excluded. Clear cancer cohort. |
| Ascertainment of Exposure (Selection) | Low risk | Patients were identified as having colorectal surgery based on primary procedure Current Procedural Terminology (CPT) codes. |
| Outcome not present at start of study (Selection) | High risk | No demonstration that VTE had not already occurred/or was not present in population at time of surgery. |
| Comparability of Cohort (Comparability) | Unclear risk | No stratification of operation type or technique by malignancy variable yet overall does stratify by elective and laparoscopic in multivariate analysis. |
| Assessment of Outcome (Outcome) | Low risk | Standard NSQIP variable definitions were used. |
| Was follow-up long enough for outcomes to occur (Outcome) | High risk | Only 30-day follow-up. |
| Adequacy of follow-up of Cohorts (Outcome) | Low risk | All cancer cohort was followed-up. |

**Ali 2018**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Representativeness of Cohort (Selection) | Low risk | Aggregated electronic medical records from inpatients and outpatients from 26 major integrated health care systems spanning all 50 states in the United States. |
| Ascertainment of Exposure (Selection) | Low risk | Clinical data are obtained from multiple sources within the electronic medical records, including practice management systems, billing, laboratory, scheduling, and claims systems, and are matched via a proprietary engine. SNOMED-CT codes used. |
| Outcome not present at start of study (Selection) | High risk | No demonstration that VTE had not already occurred/or was not present in population at time of surgery. |

| | | |
|---|---|---|
| Comparability of Cohort (Comparability) | High risk | No stratification of operation type or technique by malignancy variable, only multivariate analysis of laparoscopy in overall colorectal surgery. |
| Assessment of Outcome (Outcome) | Low risk | Use of previously validated large population-based studies. |
| Was follow-up long enough for outcomes to occur (Outcome) | Low risk | 90-day outcomes. |
| Adequacy of follow-up of Cohorts (Outcome) | Unclear risk | Does not state how many VTE events for cancer cohort just percentage so unable to ascertain if loss in the cohort. |

**Alsubaie 2015**

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Representativeness of Cohort (Selection) | Low risk | Only patients receiving cancer surgery in the Provence of Manitoba but does define colon and rectal groups so is somewhat representative. |
| Ascertainment of Exposure (Selection) | Low risk | Use of multiple linked registries. |
| Outcome not present at start of study (Selection) | High risk | No demonstration that VTE had not already occurred/or was not present in population at time of surgery. |
| Comparability of Cohort (Comparability) | Unclear risk | No stratification of operation type or technique by malignancy for VTE outcome variable however for overall does stratify by technique. |
| Assessment of Outcome (Outcome) | Unclear risk | Uses linked DPIN data however assumes new outpatient prescriptions for LMWH were for VTE without a coded diagnosis. |
| Was follow-up long enough for outcomes to occur (Outcome) | Low risk | 90-day outcomes. |
| Adequacy of follow-up of Cohorts (Outcome) | Low risk | All colon and rectum cancer cohorts followed-up. |

**Aquina 2017**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Representativeness of Cohort (Selection) | Unclear risk | New York state patients within NYSCR and SPARCS databases with non-metastatic colonic cancer, patients excluded if died within 30 days of surgery and missing variables not relevant to review outcome. |
| Ascertainment of Exposure (Selection) | Low risk | Identified within the NYSCR and SPARCS. |
| Outcome not present at start of study (Selection) | Low risk | Postoperative complications defined as not present on admission. |
| Comparability of Cohort (Comparability) | Unclear risk | No stratification of operation type or technique by malignancy for VTE outcome variable however for overall does stratify by technique. |
| Assessment of Outcome (Outcome) | Low risk | Use of ICD-9 and ICD-10 codes. |
| Was follow-up long enough for outcomes to occur (Outcome) | High risk | 30-day follow-up for complications. |
| Adequacy of follow-up of Cohorts (Outcome) | Unclear risk | 30700 patients identified, only 24426 studied therefore >70% but <90%. |

**Braumann 2009**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Representativeness of Cohort (Selection) | High risk | Prospective multicentre registry included 24 hospitals in Germany. All patients scheduled for elective colonic resection were included in the registry, yet emergency cases removed as well as laparoscopic. |
| Ascertainment of Exposure (Selection) | Low risk | Use of a specific colon cancer registry. |
| Outcome not present at start of study (Selection) | High risk | No demonstration that VTE had not already occurred/or was not present in population at time of surgery. |
| Comparability of Cohort (Comparability) | Low risk | Specifically defines as elective open cases. |
| Assessment of Outcome (Outcome) | Low risk | Both DVT and PE defined by identification on diagnostic tests. |

| | | |
|---|---|---|
| Was follow-up long enough for outcomes to occur (Outcome) | High risk | Follow-up 30 days only. |
| Adequacy of follow-up of Cohorts (Outcome) | Low risk | Whole cohort selected analysed for VTE. |

**Davila 2005**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Representativeness of Cohort (Selection) | Unclear risk | Use of VA database and NSQIP model. all those coded as having surgery within 6 months of CRC diagnosis, so could miss some e.g. long course chemo/radiotherapy. |
| Ascertainment of Exposure (Selection) | Low risk | Use of ICD codes. |
| Outcome not present at start of study (Selection) | High risk | No demonstration that VTE had not already occurred/or was not present in population at time of surgery. |
| Comparability of Cohort (Comparability) | High risk | No stratification of operation type or technique by malignancy for VTE outcome variable. |
| Assessment of Outcome (Outcome) | Low risk | Use of ICD codes from PTF file. |
| Was follow-up long enough for outcomes to occur (Outcome) | High risk | 30-day follow-up only. |
| Adequacy of follow-up of Cohorts (Outcome) | High risk | Of 32621 CRC having surgery retrieved only 12607 analysed therefore <70%. |

**Dobbins 2014**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Representativeness of Cohort (Selection) | Low risk | Use of linked state NSW registry of first colon or rectosigmoid junction of both public and private hospitals. |
| Ascertainment of Exposure (Selection) | Low risk | Use of ICD codes and linked with multiple databases. |
| Outcome not present at start of study (Selection) | High risk | No demonstration that VTE had not already occurred/or was not present in population at time of surgery. |

| | | |
|---|---|---|
| Comparability of Cohort (Comparability) | Unclear risk | No stratification of operation type by malignancy for VTE outcome variable but does so via technique. |
| Assessment of Outcome (Outcome) | Unclear risk | Codes for both DVT and PE however must have been for re-admission, i.e. potentially those not admitted but given medication for VTE missed. |
| Was follow-up long enough for outcomes to occur (Outcome) | Low risk | 90-day follow up |
| Adequacy of follow-up of Cohorts (Outcome) | Unclear risk | Does not state how many VTE events for cancer cohort just percentage so unable to ascertain if loss in the cohort. |

**Gietelink 2016**

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Representativeness of Cohort (Selection) | Low risk | Use of national Audit cross checked by national cancer registry. |
| Ascertainment of Exposure (Selection) | Low risk | National cancer registry collection of data specifically for colorectal cancer. |
| Outcome not present at start of study (Selection) | High risk | No demonstration that VTE had not already occurred/or was not present in population at time of surgery. |
| Comparability of Cohort (Comparability) | Unclear risk | No stratification of operation type by malignancy for VTE outcome variable but does so via technique. |
| Assessment of Outcome (Outcome) | Low risk | Linkage checked by database registrars with details obtained from surgeons. |
| Was follow-up long enough for outcomes to occur (Outcome) | High risk | Only 30-day outcome follow-up. |
| Adequacy of follow-up of Cohorts (Outcome) | Low risk | 37636 identified and 35714 in analysis therefore >90%. |

**Humes 2015**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Representativeness of Cohort (Selection) | Low risk | Use of HES and CPRD linkage data for all UK - 3% sample and shown to be representative. |
| Ascertainment of Exposure (Selection) | Low risk | OPCS codes for any colectomy from HES data and ICD codes. |
| Outcome not present at start of study (Selection) | Low risk | Patients excluded if had a VTE before admission date for colectomy. |
| Comparability of Cohort (Comparability) | Low risk | Stratifies by elective/emergency but not by operative technique. |
| Assessment of Outcome (Outcome) | Low risk | VTE diagnosis was determined from medical codes in the CPRD and HES. |
| Was follow-up long enough for outcomes to occur (Outcome) | Low risk | Provides 30-day rates and 1-year rates, from author obtained 90-day rates. |
| Adequacy of follow-up of Cohorts (Outcome) | Low risk | All patients followed-up. |

**Longo 2000**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Representativeness of Cohort (Selection) | Unclear risk | All patients undergoing colectomy for cancer in VASQIP database yet 98% male. |
| Ascertainment of Exposure (Selection) | Low risk | Use of ICD-9 and CPT codes. |
| Outcome not present at start of study (Selection) | High risk | No demonstration that VTE had not already occurred/or was not present in population at time of surgery. |
| Comparability of Cohort (Comparability) | High risk | No stratification of operation type or technique by malignancy for VTE outcome variable. |
| Assessment of Outcome (Outcome) | Unclear risk | States dependent variables were 21 specific operationally defined adverse outcomes but not how these were defined in anyway, assumption of standard NSQIP. |
| Was follow-up long enough for outcomes to occur (Outcome) | High risk | Only 30-day outcome follow-up but does give mortality. |

| | | |
|---|---|---|
| Adequacy of follow-up of Cohorts (Outcome) | Low risk | Whole cohort selected analysed for VTE. |

**Molena 2015**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Representativeness of Cohort (Selection) | Low risk | ACS-NSQIP data of participating hospitals with patients undergoing cancer resection surgery with specific colorectal cohort. |
| Ascertainment of Exposure (Selection) | Low risk | Use of ICD-9 and CPT codes. |
| Outcome not present at start of study (Selection) | High risk | No demonstration that VTE had not already occurred/or was not present in population at time of surgery. |
| Comparability of Cohort (Comparability) | High risk | No stratification of operation type or technique by malignancy for VTE outcome variable. |
| Assessment of Outcome (Outcome) | Low risk | Standard NSQIP variable definitions were used. |
| Was follow-up long enough for outcomes to occur (Outcome) | High risk | Only 30-day outcome follow-up but does give mortality. |
| Adequacy of follow-up of Cohorts (Outcome) | Low risk | Whole colorectal cancer cohort selected analysed for VTE. |

**Nelson (CWG) 2015**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Representativeness of Cohort (Selection) | Unclear risk | State of Washington district only, 52 hospitals all colorectal surgery, definition of malignancy includes polyps and masses. |
| Ascertainment of Exposure (Selection) | Low risk | ICD diagnosis codes. |
| Outcome not present at start of study (Selection) | Unclear risk | Primary outcomes were 90-day new VTE diagnosis or VTE-related intervention however does not exclude those who have had a VTE. |

| | | |
|---|---|---|
| Comparability of Cohort (Comparability) | Unclear risk | No stratification of operation type or technique by malignancy for VTE outcome variable but does for overall colorectal population. |
| Assessment of Outcome (Outcome) | Low risk | Use of ICD codes on readmission and/or documented use of therapeutic anticoagulation. |
| Was follow-up long enough for outcomes to occur (Outcome) | Low risk | 90-day follow-up. |
| Adequacy of follow-up of Cohorts (Outcome) | Low risk | No data excluded and <10% missing. |

**Perdawid 2012**

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Representativeness of Cohort (Selection) | Low risk | Data from the National Colorectal Cancer Database that includes about 95% of all patients with colorectal cancer in Denmark. |
| Ascertainment of Exposure (Selection) | Low risk | Data validation carried out monthly based on comparison with the National Patient Registry. Completeness of data collection evaluated annually and estimated to be around 95%. |
| Outcome not present at start of study (Selection) | High risk | No demonstration that VTE had not already occurred/or was not present in population at time of surgery. |
| Comparability of Cohort (Comparability) | Low risk | Specifically defines as elective surgical cases, does not stratify outcome by operative technique but defines proportion. |
| Assessment of Outcome (Outcome) | Unclear risk | States postoperative outcomes from the NCCD but not how they are defined. |
| Was follow-up long enough for outcomes to occur (Outcome) | High risk | 30-day outcomes with mortality. |
| Adequacy of follow-up of Cohorts (Outcome) | Low risk | Follow-up information was complete for all included patients. |

**Reinke 2012**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Representativeness of Cohort (Selection) | Low risk | Use of ACS-NSQIP data. |
| Ascertainment of Exposure (Selection) | Low risk | Use of ICD-9 codes. |
| Outcome not present at start of study (Selection) | Low risk | State must be postoperative VTE and excluded patients missing date of VTE however doesn't state if patients with a prior VTE were excluded. |
| Comparability of Cohort (Comparability) | High risk | No stratification of operation type or technique by malignancy for VTE outcome variable. |
| Assessment of Outcome (Outcome) | Low risk | ACS-NSIQP definitions of outcomes. |
| Was follow-up long enough for outcomes to occur (Outcome) | High risk | 30-days outcome only. |
| Adequacy of follow-up of Cohorts (Outcome) | Low risk | >90% of cohort followed-up. |

**Schootman 2014**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Representativeness of Cohort (Selection) | Unclear risk | Large database of hospitals and linked with clear colon and rectal definitions but only patients aged 66 years and above and stages I to III. |
| Ascertainment of Exposure (Selection) | Low risk | HCPCS and ICD codes. |
| Outcome not present at start of study (Selection) | High risk | No demonstration that VTE had not already occurred/or was not present in population at time of surgery. |
| Comparability of Cohort (Comparability) | Unclear risk | No stratification of operation type or technique by malignancy for VTE outcome, states overall proportion of operation type. |
| Assessment of Outcome (Outcome) | Low risk | ICD codes. |

| | | |
|---|---|---|
| Was follow-up long enough for outcomes to occur (Outcome) | High risk | 30-day follow-up. |
| Adequacy of follow-up of Cohorts (Outcome) | Low risk | All patients appear to have been followed-up. |

**White 2003**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Representativeness of Cohort (Selection) | Low risk | California State database, all non-federal licensed hospitals clear colon and rectal definitions. |
| Ascertainment of Exposure (Selection) | Low risk | ICD codes. |
| Outcome not present at start of study (Selection) | Low risk | Excluded all cases that had a primary or secondary diagnosis of VTE during any hospitalization during the 182-day period (6<br>months) immediately before the index hospitalisation. |
| Comparability of Cohort (Comparability) | High risk | No stratification of operation type or technique by malignancy for VTE outcome. |
| Assessment of Outcome (Outcome) | Unclear risk | Specific and linked, potentially too specific i.e. meet criteria needs to be hospitalised for 3 days. |
| Was follow-up long enough for outcomes to occur (Outcome) | Low risk | 91-day follow-up. |
| Adequacy of follow-up of Cohorts (Outcome) | Low risk | All patients appear to have been followed-up |

**Wright 2016**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Representativeness of Cohort (Selection) | Low risk | MarketScan IBM database. |
| Ascertainment of Exposure (Selection) | Low risk | ICD-9 codes. |
| Outcome not present at start of study (Selection) | Low risk | Patients with a preoperative diagnosis of either a DVT or PE and those receiving anticoagulation prior to the |

| | | |
|---|---|---|
| | | admission for the surgical procedure were excluded from the analysis. |
| Comparability of Cohort (Comparability) | Unclear risk | No stratification of operation type but by technique for malignancy VTE outcome. |
| Assessment of Outcome (Outcome) | Unclear risk | Defines DVT and PE as VTE but not if linked data. |
| Was follow-up long enough for outcomes to occur (Outcome) | Low risk | 3-months postoperative outcomes. |
| Adequacy of follow-up of Cohorts (Outcome) | Low risk | >90% of colectomy cohort followed-up. |

**Yhim 2014**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Representativeness of Cohort (Selection) | Low risk | National database covering 97% population, 3% covered by Medical aid and also non private. |
| Ascertainment of Exposure (Selection) | Low risk | Korean ICD codes. |
| Outcome not present at start of study (Selection) | High risk | No demonstration that VTE had not already occurred/or was not present in population at time of surgery. |
| Comparability of Cohort (Comparability) | High risk | No stratification of operation type or technique by malignancy for VTE outcome. |
| Assessment of Outcome (Outcome) | Low risk | Linked codes. |
| Was follow-up long enough for outcomes to occur (Outcome) | Unclear risk | 35 days follow-up. |
| Adequacy of follow-up of Cohorts (Outcome) | Low risk | All patients appear to have been followed-up. |

## Appendix 6 Risk of Bias: Randomised Controlled Trials

**Fricker 1988**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not described in sufficient detail. |
| Allocation concealment (selection bias) | Unclear risk | Not described in sufficient detail. |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not described in sufficient detail. |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not described in sufficient detail. |
| Incomplete outcome data (attrition bias) | Low risk | Minimal attrition. |
| Selective reporting (reporting bias) | Unclear risk | Not described in sufficient detail. |

**Hata 2019**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Described in sufficient detail. |
| Allocation concealment (selection bias) | High risk | Not concealed. |
| Blinding of participants and personnel (performance bias) | High risk | Not blinded. |
| Blinding of outcome assessment (detection bias) | Low risk | Radiologists interpreted the CT scans without any identifying information about the patients. |
| Incomplete outcome data (attrition bias) | Low risk | Discussed adequately with minimal attrition. |
| Selective reporting (reporting bias) | Unclear risk | Insufficient information to permit judgment. |

**Holm 1996**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not described in sufficient detail. |
| Allocation concealment (selection bias) | Unclear risk | Not described in sufficient detail. |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not described in sufficient detail. |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not described in sufficient detail. |
| Incomplete outcome data (attrition bias) | Low risk | Minimal attrition but a third of patients excluded from original trials |
| Selective reporting (reporting bias) | Unclear risk | Not described in sufficient detail. |

**Lacy 1995**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Described in sufficient detail. |
| Allocation concealment (selection bias) | Low risk | Described in sufficient detail. |
| Blinding of participants and personnel (performance bias) | High risk | Performance bias due to knowledge of the allocated interventions by participants and personnel during the study. |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not described in sufficient detail. |
| Incomplete outcome data (attrition bias) | Low risk | Minimal attrition described. |
| Selective reporting (reporting bias) | Unclear risk | Not described in sufficient detail. |

**McLeod 2001**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random sequence generation method used. |
| Allocation concealment (selection bias) | Low risk | Code was not broken. |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blinded. |
| Blinding of outcome assessment (detection bias) | Low risk | Assessors blinded. |
| Incomplete outcome data (attrition bias) | Low risk | Minimal attrition but only just over 50% eligible participated. |
| Selective reporting (reporting bias) | Unclear risk | Not described in sufficient detail. |

**Nakagawa 2019**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Described in sufficient detail. |
| Allocation concealment (selection bias) | High risk | No allocation concealment. |
| Blinding of participants and personnel (performance bias) | High risk | No blinding. |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not clearly described. |
| Incomplete outcome data (attrition bias) | Low risk | Minimal attrition. |
| Selective reporting (reporting bias) | Unclear risk | Not described in sufficient detail. |

**Shukla 2008**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random sequence used. |
| Allocation concealment (selection bias) | High risk | No concealment. |
| Blinding of participants and personnel (performance bias) | High risk | Open label. |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not specific. |
| Incomplete outcome data (attrition bias) | Low risk | No attrition disclosed. |
| Selective reporting (reporting bias) | Unclear risk | Not described in sufficient detail. |

**Simonneau 2006**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Described in sufficient detail. |
| Allocation concealment (selection bias) | Low risk | Described in sufficient detail. |
| Blinding of participants and personnel (performance bias) | Low risk | Double blinding. |
| Blinding of outcome assessment (detection bias) | Low risk | Blinded to patient assignment. |
| Incomplete outcome data (attrition bias) | Low risk | Majority available for primary analysis. |
| Selective reporting (reporting bias) | Unclear risk | Not described in sufficient detail. |

**Stevenson 2015**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Described in sufficient detail. |
| Allocation concealment (selection bias) | Unclear risk | Not described in sufficient detail. |
| Blinding of participants and personnel (performance bias) | High risk | Not able to blind. |
| Blinding of outcome assessment (detection bias) | Low risk | Pathologists blinded. |
| Incomplete outcome data (attrition bias) | Low risk | Minimal attrition noted. |
| Selective reporting (reporting bias) | Unclear risk | Not described in sufficient detail. |

**Vedovati 2014**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random sequence described. |
| Allocation concealment (selection bias) | Unclear risk | Not described in sufficient detail. |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not described in sufficient detail. |
| Blinding of outcome assessment (detection bias) | Low risk | Blinded. |
| Incomplete outcome data (attrition bias) | Low risk | Some loss roughly over 30% from initial but minimal loss after allocation. |
| Selective reporting (reporting bias) | Unclear risk | Not described in sufficient detail. |

## Appendix 7 Description of all studies within the qualitative synthesis

| Author | Year | Country | Database/Study type | Follow-up | Study time frame | No. | Cancer | VTE type | Overall No. of VTE events | Incidence risk[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| Addae[276,bd] | 2017 | USA | NIS | inpatient | 2009-2012 | 261886 | CR | VTE | bar chart (approx. 3179) | 1.21% |
| Alcalay[65] | 2006 | USA | CACR & CA PDDS | 6-months from diagnosis | 1993-95 & 1997-99 | 46598 | CR | VTE | 932 | 2.00% |
| Alhassan[92] | 2018 | USA | ACS-NSQIP | 30-days | 2012-2016 | 101822 | CR | VTE, PE, DVT | 1948 | 1.91% |
| Ali[120] | 2018 | USA | Explorys | 7, 30 and 90-days | 1999-2017 | 32020 | CR | VTE | 1377 | 4.30% |
| Alsubaie[186] | 2015 | CAN | MCR | 90-days | 2004-2009 | 3090 | C & R | VTE | 113 | 3.66% |
| Aquina[187] | 2017 | USA | NYSCR & SPARCS | 30-days | 2004-2011 | 25537 | C | VTE | 589 | 2.31% |
| Artinyan[277] | 2015 | USA | VA SQIP & VACCR | 30-days | 1999-2009 | 12075 | CR | PE & DVT | 168 | 1.39% |
| Bellini[278,b] | 2016 | USA | ACS-NSQIP | 30-days | 2005-2012 | 56030 | CR | VTE, PE, DVT | 1118 | 2.00% |
| Braumann[188,be] | 2009 | DEU | FTCII | 30-days | 2005-2007 | 748 | C | VTE | 2 | 0.27% |
| Buchberg[83,b] | 2011 | USA | NIS | inpatient | 2002-2006 | 63,305 | CR | VTE | 823 | 1.30% |
| Chapman[279] | 2017 | USA | ACS-NSQIP | 30-days | 2005-2012 | 12828 | R | VTE, PE, DVT | 184 | 1.43% |
| Davenport[84] | 2012 | USA | ACS-NSQIP | 30-days | 2005-2009 | 21943 | CR | VTE, PE, DVT | 446 | 2.03% |
| Davila[189] | 2005 | USA | VA SQIP | 30-days | 1987-2000 | 12607 | CR | VTE | 243 | 1.93% |
| De Martino[280] | 2012 | USA | ACS-NSQIP | 30-days | 2007-2009 | 16078 | C | VTE, PE, DVT | 386 | 2.40% |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dobbins[190,d] | 2014 | AUS | NSW CCR | 90-days | 2000-2008 | 27947 | C & R | PE & DVT | 441 | 1.58% |
| El-Dhuwaib[88,c] | 2017 | GBR | HES | 2, 4, 6, 8, 10, 12-months | 2007-2008 | 19046 | CR | VTE | 492 | 2.58% |
| Ghadban[255,b] | 2019 | DEU | German DRG | inpatient (up to 17-days) | 2005-2015 | 351028 | C & R | VTE | 4356 | 1.24% |
| Gietelink[155,d] | 2016 | NLD | DSCA &NCR | 30-days | 2010-2013 | 35566 | CR | VTE | 228 | 0.64% |
| Greenblatt[281,bd] | 2011 | USA | ACS-NSQIP | 30-days | 2005-2009 | 5420 | R | VTE | 82 | 1.51% |
| Holubar[282] | 2016 | USA | ACS-NSQIP | 30-days | 2005-2010 | 6297 | R | PE & DVT | 115 | 1.83% |
| Humes[21,c] | 2015 | GBR | HES & CPRD | 1 and 3-months | 2001-2011 | 8309 | CR | VTE | 111 | 1.34% |
| Longo[191] | 2000 | USA | VA SQIP | 30-days | 1991-1995 | 5853 | C | PE & DVT | 55 | 0.94% |
| Merkow[59,b] | 2011 | USA | ACS-NSQIP | 30-days | 2006-2008 | 15204 | C & R | VTE, PE, DVT | 333 | 2.19% |
| Moghadamyeghaneh[283] | 2014 | USA | ACS-NSQIP | 30-days | 2005-2014 | 35311 | C & R | PE & DVT | 663 | 1.88% |
| Moghadamyeghaneh[284] | 2016 | USA | ACS-NSQIP | 30-days | 2012-2014 | 7786 | C | PE & DVT | 169 | 2.17% |
| Molena[192] | 2015 | USA | ACS-NSQIP | 30-days | 2005-2012 | 38898 | C | VTE | 665 | 1.71% |
| Monn[285] | 2014 | USA | ACS-NSQIP | 30-days | 2010 | 9094 | CR | VTE | 196 | 2.16% |
| Nelson (CWG)[85] | 2015 | USA | SCOAP | 90-days | 2006-2011 | 6216 | CR | VTE | 128 | 2.06% |
| Papageorge[286,bd] | 2016 | USA | ACS-NSQIP | 30-days | 2012-2013 | 11031 | C | PE & DVT | 242 | 2.19% |
| Perdawid[193,b] | 2012 | DNK | DCCG NCCR | 30-days | 2001-2008 | 9149 | C | VTE | 44 | 0.48% |
| Reinke[194] | 2012 | USA | ACS-NSQIP | 30-days | 2005-2010 | 44396 | C & R | VTE | 902 | 2.03% |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Ruff[287] | 2019 | USA | ACS-NSQIP | 30-days | 2005-2013 | 85451 | CR | VTE | 1719 | 2.01% |
| Schlottmann[288,c] | 2019 | USA | NIS | inpatient | 2008-2015 | 141641 | CR | VTE | 6266 | 4.42% |
| Schootman[195] | 2014 | USA | SEER & Medicare | 30-days | 2000-2005 | 35946 | CR | VTE | 1071 | 2.98% |
| Shapiro[26] | 2011 | USA | ACS-NSQIP | 30-days | 2005-2008 | 11243 | CR | VTE | 232 | 2.06% |
| Trepanier[139] | 2019 | USA | ACS-NSQIP | 30-days | 2012-2016 | 101822 | CR | PE & DVT | 2139 | 2.10% |
| Vendler[147,b] | 2017 | DNK | COMES | 28-days | 2008-2013 | 1893 | C | VTE | 7 | 0.37% |
| Walker[87] | 2014 | GBR | HES & CPRD | 28, 90, 180 days | 1997-2006 | 4963 | CR | VTE | 79 | 1.59% |
| White[73] | 2003 | USA | CA PDDS | 91-days | 1992-1996 | 36746 | C & R | VTE | 610 | 1.66% |
| Wright[154,d] | 2016 | USA | MarketScan IBM | 3-months | 2009-2013 | 40579 | C | VTE | 1671 | 4.12% |
| Xenos[25,d] | 2012 | USA | ACS-NSQIP | 30-days | 2005-2009 | 21943 | C & R | VTE, PE, DVT | 446 | 2.03% |
| Yhim[196] | 2014 | KOR | NHI HIRA | 5-weeks | 2007-2011 | 73961 | CR | VTE, PE, DVT | 1236 | 1.67% |
| Fricker[197] | 1988 | FRA | RCT | 4-weeks | Not specified | 6 | C | VTE, PE, DVT | 0 | 0.00% |
| Hata[198,bf] | 2019 | JPN | RCT | 16-days | 2011-2015 | 290 | CR | VTE, PE, DVT | 12[g] | 4.14%[g] |
| Holm (Stockholm I & II Trials)[200,b] | 1996 | SWE | RCT | 5-years | 1980-87 & 1987-93 | 1027 | R | VTE | 49 | 4.77% |
| Lacy[199,d] | 1995 | ESP | RCT | up to 1-year | 1993-1994 | 51 | C | VTE, PE, DVT | 0 | 0.00% |
| McLeod[43,b] | 2001 | CAN | RCT | 9-days | Not specified | 324 | CR | VTE | 50[g] | 15.38%[g] |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Nakagawa (YCOG 1404)[97,f] | 2019 | JPN | RCT | 7, and 28-days | 2015-2017 | 116 | CR | VTE, PE, DVT | 0 | 0.00% |
| Shukla[201] | 2008 | IND | RCT | 6-days | 2002-2004 | 99 | CR | VTE, PE, DVT | 0 | 0.00% |
| Simonneau[41,b] | 2006 | FRA | RCT | 12 and 60-days | 1994-1999 | 1271 | CR | VTE, PE, DVT | 17 | 1.34% |
| Stevenson (ALaCaRT)[202,bd] | 2015 | AUS | RCT | 30-days | 2010-2014 | 473 | R | VTE | 1 | 0.21% |
| Vedovati (PROLAPS)[95,bf] | 2014 | ITA | RCT | 28-days and 3-months | 2010-2012 | 225 | CR | VTE, PE, DVT | 3 | 1.33% |

Abbreviations: CWG, Colorectal Writing Group; ALaCaRT, Australasian Laparoscopic Cancer of the Rectum; USA, United States of America; CAN, Canada; DEU, Germany; AUS, Australia; GBR, United Kingdom; NLD, Netherlands; DNK, Denmark; KOR, Republic of Korea; FRA, France; JPN, Japan; SWE, Sweden; ESP, Spain; IND, India; ITA, Italy; NIS, nationwide Inpatient Sample; CACR & CA PDDS, California Cancer Registry & California Patient Discharge Data Set; ACS-NSQIP, American College of Surgeons – National Surgical Quality Improvement Program; MCR, Manitoba Cancer Registry; NYSCR SPARCS, New York State Cancer Registry & Statewide Planning and Research Cooperative System; VA SQIP & VACCR, Veterans Affairs Surgical Quality Improvement Program & Veterans Affairs Central Cancer Registry; FTCII, Fast-track Colon II; NSW CCR, NEW South Wales Central Cancer Registry; HES & CPRD, Hospital Episode Statistics & Clinical Practice Research Datalink; German DRG, German Diagnosis Related Groups; DSCA & NCR, Dutch Surgical Colorectal Audit & Netherlands Cancer Registry; SCOAP, Surgical Care and Outcomes Assessment Program; DCCG NCCR, Danish Colorectal Cancer Group National Colorectal Cancer Database; SEER & Medicare, Surveillance, Epidemiology, and End Results Program & Medicare; COMES, Copenhagen cOmplete Mesocolic Excision Study; NHI HIRA, National Health Insurance Health Insurance Review and Assessment Service; RCT, Randomised Controlled Trial; CR, Colorectal; C & R, Colon and Rectal; C, Colon;, R, Rectal; VTE, Venous Thromboembolism; DVT, Deep Vein Thrombosis; PE, Pulmonary Embolism.

[a] Values given are for the longest time period of follow-up stated.

[b] Elective only; [c] Elective and Emergency subgroup; [d] Minimally Invasive Surgery vs. Open subgroup; [e] Open surgery only; [f] Laparoscopic surgery only.

[g] Includes asymptomatic venous thromboembolism events.

All 24 studies excluded from the quantitative synthesis were database or registry cohort studies. 16 removed due to using the same database with overlapping time frames, 14 from the US and 1 each from the UK and Denmark. Of the US studies 13 used the ACS-

NSQIP and 1 the Veterans Affairs Surgical Quality Improvement Programme (VA-SQIP) databases. 4 studies were removed as they contained only inpatient data and a further 2 for using the same dataset.

**Appendix 8 ISAC Protocol 19_180RA3**

# INDEPENDENT SCIENTIFIC ADVISORY COMMITTEE (ISAC) PROTOCOL APPLICATION FORM

## PART 1: APPLICATION FORM

***IMPORTANT***

**Both parts of this application must be completed in accordance with the guidance note 'Completion of the ISAC Protocol Application Form', which can be found on the CPRD website**

**cprd.com/research-applications**

| FOR ISAC USE ONLY | |
|---|---|
| **Protocol No. - 19_180R** | **Submission date - 29 May 2020** |

| GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY |
|---|
| **1.** Study Title (Max. 255 characters)<br><br>Incidence of venous thromboembolism following colorectal resectional surgery. |

**2.** Research Area (place 'X' in all boxes that apply)

| | | | |
|---|---|---|---|
| Drug Safety | | Economics | |
| Drug Utilisation | | Pharmacoeconomics | |
| Drug Effectiveness | | Pharmacoepidemiology | |
| Disease Epidemiology | **X** | Methodological | |
| Health Services Delivery | | | |

**3.** Chief Investigator

| | |
|---|---|
| Title: | Mr |
| Full name: | David James Humes |
| Job title: | Associate Professor of Surgical Epidemiology and Honorary Consultant Surgeon |
| Affiliation/organisation: | Nottingham Digestive Diseases Centre, NIHR BRU, Division of Surgery, The University of Nottingham |
| Email address: | xxxxxxx@nottingham.ac.uk |
| CV Number (if applicable): | xxxx |

**4.** Corresponding Applicant

| | |
|---|---|
| Title: | Mr |
| Full name: | David |
| Job title: | Humes |
| Affiliation/organisation: | Nottingham Digestive Diseases Centre, NIHR BRU, Division of Surgery, The University of Nottingham |
| Email address: | xxxxxxx@nottingham.ac.uk |
| CV Number (if applicable): | xxxx |

**5.** List of all investigators/collaborators

| | |
|---|---|
| Title: | Associate Professor |
| Full name: | Colin Crooks |
| Job title: | Associate Professor of Gastroenterology |
| Affiliation/organisation: | University of Nottingham |
| Email address: | xxxxxxx@nottingham.ac.uk |
| CV Number (if applicable): | xxxx |
| Will this person be analysing the data?<br>(Y/N) | Y |

| | |
|---|---|
| Title: | Dr |
| Full name: | Christopher Lewis-Lloyd |
| Job title: | Research Fellow |
| Affiliation/organisation: | University of Nottingham |
| Email address: | xxxxxxx@exmail.nottingham.ac.uk |
| CV Number (if applicable): | |
| Will this person be analysing the data?<br>(Y/N) | Y |

[Add more investigators/collaborators as necessary by copy and pasting a new table for each investigator/collaborator]

**6.** Experience/expertise available

List below the member(s) of the research team who have experience with CPRD data.

| **Name:** | **Protocol Number/s:** |
|---|---|
| David J. Humes | 09_052, 09_053, 11_051R |

| | |
|---|---|
| Colin Crooks | |
| | |

List below the member(s) of the research team who have statistical expertise.

| **Name(s):** |
|---|
| David J. Humes |
| Colin Crooks |
| |

List below the member(s) of the research team who have experience of handling large datasets (greater than 1 million records).

| **Name(s):** |
|---|
| David J. Humes |
| Colin Crooks |
| |

List below the member(s) of the research team, or supporting the research team, who have experience of practicing in UK primary care.

| **Name(s):** |
|---|
| David J. Humes |
| Colin Crooks |
| Chris Lewis-Lloyd |

ACCESS TO THE DATA

**7.** Sponsor of the study

| | |
|---|---|
| Institution/Organisation: | The University of Nottingham |
| Address: | |

**8.** Funding source for the study

| | | | | |
|---|---|---|---|---|
| Same as Sponsor? | Yes | **X** | No | |
| Institution/Organisation: | | | | |
| Address: | | | | |

**9.** Institution conducting the research

| | | | | |
|---|---|---|---|---|
| Same as Sponsor? | Yes | **X** | No | |
| Institution/Organisation: | | | | |
| Address: | | | | |

**10.** Data Access Arrangements

Indicate with an '**X**' the method that will be used to access the data for this study:

| | |
|---|---|
| Study-specific Dataset Agreement | |

| | |
|---|---|
| Institutional Multi-study Licence | X |
| Institution Name | University of Nottingham |
| Institution Address | University Park, Nottingham, Notts, NG72RD |

Will the dataset be extracted by CPRD?

| | | | |
|---|---|---|---|
| Yes | | No | x |

If yes, provide the reference number:

**11.** Data Processor(s):

| | | |
|---|---|---|
| Processing | Yes | |
| Accessing | Yes | |
| Storing | Yes | |
| Processing area (UK/EEA/Worldwide) | | UK |
| Organisation name | | University of Nottingham |
| Organisation address | | University Park, Nottingham, Notts, NG72RD |

| | | |
|---|---|---|
| .Processing | . | |
| .Accessing | . | |
| .Storing | . | |
| .Processing area (UK/EEA/Worldwide) | | |
| .Organisation name | | |
| .Organisation address | | |

[Add more processors as necessary by copy and pasting a new table for each processor]

INFORMATION ON DATA

**12.** Primary care data (place 'X' in all boxes that apply)

| | | | |
|---|---|---|---|
| CPRD GOLD | **X** | CPRD Aurum | X |

**13.** Please select any linked data or data products being requested

**Patient Level Data** (place '**X**' in all boxes that apply)

| | | | |
|---|---|---|---|
| ONS Death Registration Data | X | CPRD Mother Baby Link | |

| | | | |
|---|---|---|---|
| HES Admitted Patient Care | X | Pregnancy Register | |
| HES Outpatient | | NCRAS (National Cancer Registration and Analysis Service) Cancer Registration Data | |
| HES Accident and Emergency | | NCRAS Cancer Patient Experience Survey (CPES) data | |
| HES Diagnostic Imaging Dataset | | NCRAS Systemic Anti-Cancer Treatment (SACT) data | |
| HES PROMS (Patient Reported Outcomes Measure) | | NCRAS National Radiotherapy Dataset (RTDS) data | |
| | | Mental Health Services Data Set (MHDS) | |

**Area Level Data** (place '**X**' in all boxes that apply)

| **Practice level (UK)** | | **Patient level (England only)** | |
|---|---|---|---|
| Practice Level Index of Multiple Deprivation (Standard) | | Patient Level Index of Multiple Deprivation | X |
| Practice Level Index of Multiple Deprivation (Non-standard) | | Patient Level Townsend Score | |
| Practice Level Index of Multiple Deprivation Domains (Non-standard) | | | |
| Practice Level Carstairs Index for 2011 Census (Excluding Northern Ireland) (Standard) | | | |
| 2011 Rural-Urban Classification at LSOA level (Non-standard) | | | |

Reference number (where applicable):

**14.** Are you requesting linkage to a dataset not listed above?

| | | | |
|---|---|---|---|
| Yes | | No | **x** |

If yes, provide the reference number:

**15.** Does any person named in this application already have access to any of these data in a patient identifiable form, or associated with an identifiable patient index?

| | | | |
|---|---|---|---|
| Yes | | No | **X** |

If yes, provide further details:

VALIDATION/VERIFICATION

**16.** Does this protocol describe an observational study using purely CPRD data?

| | | | |
|---|---|---|---|
| Yes | **X** | No | |

**17.** Does this protocol involve requesting any additional information from GPs, or contact with patients?

| | | | |
|---|---|---|---|
| Yes | | No | **X** |

If yes, provide the reference number:

# PART 2: PROTOCOL INFORMATION

| **Applicants must complete all sections listed below**<br><br>**Sections which do not apply should be completed as '*Not Applicable*' and justification provided** |
|---|
| **A)** Study Title (Max. 255 characters)<br><br>Incidence of venous thromboembolism following colorectal resectional surgery. |
| **B)** Lay Summary (Max. 250 words)<br><br>Background: Blood clots in the legs and lungs following surgery represent a potentially life-threatening complication but can be prevented. Several studies have shown that surgery to the organs in the abdomen carries a much higher risk of these clots forming. In patients for whom the surgery was performed for cancer, the risk may well be higher.<br><br>In 2010 the National institute for health and care excellence (NICE) made recommendations regarding assessment for clots, preventative measures and treatment. They recognised that age, cancer, surgery and immobility all contributed to risk of clots forming and made recommendations accordingly. Since then there have been no studies assessing the occurrence of blood clots after surgery.<br><br>Objective: To quantify the occurrence of blood clots following colorectal surgery before and after the NICE guidelines in 2010.<br><br>Design: We will use data from three large electronic health records, the Clinical Practice Research Datalink, Hospital Episode Statistics and Office of National Statistics to determine the occurrence of blood clots in the legs and lungs after surgery and the factors that contribute to their occurrence. We will compare how frequently these clots occurred before and after 2010 to determine what change if any has occurred since these guidelines came into place.<br><br>Outcomes and patient benefit: Knowing whether or not these guidelines have made a difference may improve compliance with the current recommendations and provide much needed evidence in this field. |

**C)** Technical Summary (Max. 300 words)

Background: Venous thromboembolism is an important complication after surgery and is associated with an increased risk of morbidity and mortality. In 2010 the National institute for clinical excellence (NICE) made recommendations regarding VTE assessment, prevention and treatment and CQUIN (Commissioning for Quality and Innovation) targets were introduced to promote adherence to these guidelines. They also made recommendations regarding future research directions, having acknowledged the paucity of evidence in the form of population estimates of incidence of VTE after surgery.

Since then studies into VTE, some from our group have shown that gastrointestinal surgery and in particular gastrointestinal cancer surgery carries a much larger risk of VTE. What is still lacking is evidence of how the implementation of VTE assessment and risk prevention strategies have impacted incidence.

Objective: To quantify the risk of VTE following colorectal surgery, in the 9yrs before and 9yrs after the implementation of NICE guidelines on VTE, in order to assess the impact guidelines have had on both risk and rates of VTE.

Design: The linked primary and secondary care databases (Clinical Practice Research Datalink, Hospital Episode Statistics) together with mortality data from the Office of National Statistics will be used to establish a cohort of patients undergoing colorectal resectional surgery. The incidence of VTE following colorectal surgery will be calculated as rates per 100000 person years of follow up. We will control for the confounders of age, gender, BMI, smoking, malignant and benign disease, along with emergency and elective admission and whether the procedure was performed laparoscopically.

Outcomes: We will provide population-based estimates of the incidence of VTE following colorectal surgery, comparing incidence rates pre and post 2010.

**D)** Outcomes to be Measured

- Incidence of VTE

**E)** Objectives, Specific Aims and Rationale

Rationale

There have been multiple changes in the conduct of colorectal surgery with an increase in minimally invasive techniques such as laparoscopy along with a focus on VTE prevention in the postoperative period. This study aims to determine the rates of VTE following colectomy and how they have changed over time.

Objective

What impact have the 2010 NICE guidelines and CQUIN payment framework had on rates of VTE?

Aims

- To calculate the incidence of VTE following colorectal surgery
- To measure how the incidence of VTE following colorectal surgery varies over time

**F)** Study Background

Preventable hospital acquired VTE (deep vein thrombosis and pulmonary embolus) is estimated to account for approximately 25,000 deaths per year in the UK (1). The occurrence of deep vein thrombosis (DVT) following a general surgical procedure is thought to be 10-40% with estimates of the rates of fatal pulmonary embolism (PE) ranging from 0.01-10% (2). VTE itself gives rise to significant short- and long-term morbidity, increased length of hospital stay, increased costs and mortality. Use of low molecular weight heparin in appropriately assessed patients reduces this risk by up to 60%. A multinational cross-sectional study using a survey design (the ENDORSE survey) (3) that assessed the prevalence of VTE risk in acute hospitals cares reported that the proportion of at risk surgical patients who receive appropriate VTE thromboprophylaxis was only 62-percent. In the UK VTE was made a CQUIN target in 2010/2011 and was included in the Operating Framework for England (Commissioning for Quality and Innovation) so that all English Trusts are required to ensure that 90% of their adult admissions are risk assessed for VTE, otherwise they pay a financial penalty. As VTE is considered such an important problem it was considered by NICE for guideline development. The NICE guidelines published in 2010 also highlighted the need for research on the absolute risk of VTE due to a paucity of large population estimates of this in the existing literature (1). A population-based study using routinely collected data was specifically proposed as a mechanism for establishing this.

In the past decade there has been an increased use of laparoscopic surgery and enhanced recovery programs, and increasingly surgery is performed on an older population with more comorbidities for colorectal conditions (4). All of these dramatic changes will have altered the risks of VTE following colorectal surgery and when in particular they occur. Given the less invasive nature of laparoscopic surgery a reduction in VTE rates may be expected. However prolonged activation of the coagulation system has been demonstrated following laparoscopic surgery as measured by fibrin monomers and fibrin D-Dimers at 14 days post-surgery suggesting that these patients may actually be at risk of VTE for longer than anticipated (5). Given these changes and the focus on VTE prevention since publication of the NICE guidance and introduction of the VTE CQUIN there is a clear need to provide contemporary comprehensive population-based estimates of the rates of VTE following colorectal surgery and whether rates have changed over time.

The potential impact of determining the particular postoperative time periods that are associated with higher risks following specific procedures is that there may be opportunities for preventing VTE in patients undergoing surgery for benign disease. For example, a Cochrane review concluded that the use of 4 weeks of LMWH (Low molecular weight heparin) postoperatively reduced the

incidence of VTE (for cancer surgery) by 80% OR 0.22 (95% CI 0.06-0.80) without an increase in bleeding complications and thus for those patients undergoing cancer surgery the current guidance is to administer 28 days of thromboprophylaxis (6). We have previously reported that the risk of VTE following surgery for benign colorectal conditions is as great as those undergoing surgery for malignant disease in the emergency setting suggesting this large group of patients may benefit from the use of prolonged prophylaxis which they currently do not receive (7). Previously in Nottingham we have used standalone and linked data to study VTE in inflammatory bowel disease (8), pregnancy (9), colorectal cancer (10), gastrointestinal surgery (11, 12) and cancer (13).

Time trends in VTE risk which followed the population from the Tromsø Study (Norway) suggested VTE had increased in that population despite advances in prophylaxis (14). Another from Canada found the incidence of acute venous thromboembolism remained unchanged over a 10-year period (15). Time trends in VTE risk pre and post the NICE guidelines and implementation of CQIN targets in surgical patients has not yet been studied. This study will allow us to quantify any changes in VTE risk over the time periods pre and post implementation of NICE guidance to assess changes in rates over time.

**G)** Study Type

We will undertake a descriptive historical cohort study of patients who have undergone surgery for colorectal diseases as identified by OPCS codes from HES data.

a) In the first aim we will define incidence rates of VTE following colorectal surgery at 30-days, 90-days and one year by age, gender, procedure urgency (elective/emergency), whether surgery was undertaken laparoscopically or open and by disease type defined from ICD and Read codes as benign and malignant.
b) In the second aim we will compare annual incidence rates of VTE following colorectal surgery at 30-days, 90-days and one year from 2001 to 2009 with rates from 2010-2018 accounting for the confounders of age, gender, operation urgency, method of surgery (open/laparoscopic) and whether the surgery was for malignant or benign disease.

**H)** Study Design

Population-based cohort study of the incidence of postoperative VTE following colorectal surgery.

Using OPCS codes for colorectal surgery we will identify patients undergoing surgery from HES data from 2001 to 2018. These will form the cohort for study. We will then use linked CPRD, HES and ONS data to define those who develop a VTE postoperatively using our previously published definition of VTE. In brief VTE diagnosis will be determined from medical codes in the CPRD (appendix 1 ISAC only) and HES (ICD I80 and I26). We will consider a code to represent a valid VTE event if supported by either: a prescription for an anticoagulant (code list in appendix 1 ISAC only) or other evidence of treatment in an anticoagulation clinic (medical code appendix 1 ISAC only) between 15 days before and 90 days after the VTE diagnosis, or a date of death within 30 days of the event. Additionally, an underlying cause of death of VTE will be included as evidence of a VTE diagnosis. Those with a prior VTE before surgery will be excluded from the cohort as they have an inherently increased risk of VTE.

The operative approach open or laparoscopic will be confirmed by the appropriate OPCS codes for laparoscopic approaches. Patients with a cancer diagnosis will be differentiated from benign patients using ICD 10 codes for colorectal cancer as previously published by our group and include C18, C19, C20 and C21 based on the HES data only. Comorbidity will be identified prior to the hospital admission from Read and ICD 10 codes for each individual using the Charlson index. Urgency of surgery will be defined from the HES data as elective and emergency.

**I)** Feasibility counts

From HES linked CPRD Gold data we have identified from 2000-2019 using all OPCS H codes for colectomy 100,005 unique individuals with a colectomy code in their HES record.

**J)** Sample size considerations

With 100,005 individual procedures with a previously reported incidence of VTE of 2.5% of patients undergoing colectomy we would expect 2500 VTE events in the first year of follow up. This would give us a rate of 2500 per 100,000 procedures with a precision around our estimate of 98 per 100,000 procedures at one year.

**K)** Planned use of linked data (if applicable):

HES inpatient data will be used to identify patients admitted to hospital who undergo a surgical procedure and those diagnosed with a VTE on hospital admission. The CPRD data will be used to confirm diagnosis of VTE with the aid of prescription read codes for treatment of VTE. ONS death registrations from the linked ONS data will be used to identify deaths from VTE.

**L)** Definition of the Study population

Study population – patients undergoing a first colectomy as defined by OPCS 4 codes (“H”) in HES data. Patients will be recruited who have a first colectomy code in the linked HES data from 2001-2019. Start of follow up will be the day prior to colectomy admission and will end at VTE diagnosis, the date of recording of death, transferring out of the practice, or the last collection date whichever comes first up to the first year following surgery. The index date will be the date of the first recorded colectomy code within the time period from 2001-2019 and must be within the UTS period.

Inclusion – The patient would have a minimum of 3 months data after the latest of UTS or CRD prior to colectomy date (index date).

Exclusion – Episodes of VTE prior to the index date of colectomy as patients with recurrent VTE represent a known high-risk sub-group who will have an increased incidence of VTE.

Incidence - Person time will be calculated from start of follow up (day prior to colectomy date to allow for VTE events that occur on the day of surgery) to the end date as defined. Crude incidence rates for incident VTE events will be calculated per 100,000 years of follow up for 30-day, 90-day and one-year periods. Incidence rates will be modelled before and after 2010 using Poisson regression accounting for age, gender, comorbidity, operation urgency, operation indication (benign/malignant) and method of operation (laparoscopic/open). We will assess for interaction using interaction terms and test for significance using likelihood ratio tests.

The cohort of patients undergoing surgery for digestive disease related problems will be defined by identifying all OPCS 4 codes beginning with, “H” (appendix 1 ISAC only) from the HES data.

**M)** Selection of comparison group(s) or controls

We will undertake analyses stratified by benign and malignant surgery along with those undertaken as an emergency or elective procedures.

**N)** Exposures, Outcomes and Covariates

Exposures:

Calendar time will be defined by year and time period from 2001-2009 and 2010 to 2018. Any person coded within this cohort with an ICD-10 cancer code beginning with a “C18, C19, C20 and C21” in the linked HES data or they have a medcode for colorectal cancer within the CPRD record in the same time period will be classified as having an operation for a malignancy if the diagnosis occurs within 6 months of the surgery. Admission type will be defined as elective or emergency based on HES admission code.

VTE Outcome:

A VTE diagnosis will be determined from medical codes in the CPRD (appendix 1) and HES (ICD I80 and I26). We will consider a code to represent a valid VTE event if supported by either: a prescription for an anticoagulant (code list in appendix 1) or other evidence of treatment in an anticoagulation clinic (medical code appendix 1) between 15 days before and 90 days after the VTE diagnosis, or a date of death within 30 days of the event. Additionally, an underlying cause of death of VTE will be included as evidence of a VTE diagnosis (16).

Co-variates:

The known risk factors for VTE which are likely to be recorded in electronic databases including age at index date (determined from the CPRD), body mass index (BMI) (derived from the CPRD as the first recorded BMI prior to index date), smoking (derived from the smoking status defined in CPRD as ever or never smokers prior to the index date), and comorbidity which will be defined using the Charlson index compiled from ICD codes from HES data and medcodes from CPRD prior to the index date.

**O)** Data/ Statistical Analysis

We will calculate crude and adjusted rates of VTE at 30-days, 90-days and 1-year following colorectal surgery from 2001 to 2018. We will present rates by gender, age, operation type, operation urgency (elective/emergency) and operation indication (benign/malignant). We will model rates of VTE over calendar time using Poisson regression by individual year and then by comparing rates between the time periods 2001-2009 and 2010-2018 controlling for known confounders.

**P)** Plan for addressing confounding

Incidence: We will present estimates of crude incidence rates stratified by age, sex, operation urgency, mode of surgery and indication. We will control for confounding by age, gender, smoking, BMI and comorbidity.

We will explore interactions in the models and test for their significance by using likelihood ratio tests.

**Q)** Plans for addressing missing data

Missing data is unlikely to be a particular problem in these analyses aside from those relating to covariates due to the required standardised recording of procedures. Where this is particular issue we will model categorical data that is missing as a separate category. If necessary, we will impute values for these variables and rerun our analyses to estimate the importance of the missing data on our derived estimates.

**R)** Patient or user group involvement (if applicable)

This study has been reviewed by the patient and public involvement group of the NIHR Nottingham Digestive Diseases Centre BRU previously who felt the research was timely and would be of benefit to patients. They will be involved in the discussion of results and may prove crucial in dissemination amongst patients.

**S)** Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

**Conflict of interest statement:** The researchers have no conflicts of interest to declare.

**T)** Limitations of the study design, data sources, and analytic methods

As with all observational epidemiology studies there is the possibility of unmeasured residual confounding, bias and random error generating spurious results. However, in this instance the likelihood of these problems occurring is small as the population we will select will include all people with evidence of VTE confirmed with prescription codes. Some misclassification of covariates such as smoking status and body mass index is likely but experience from previous work in this area using similar (although much older) data suggest that the magnitude of the misclassification is unlikely to affect the estimates derived unduly.

**U)** Amendment – 29/05/2020

Having examined the data, the study team has noticed a trend in the decreasing numbers of patients per year within the cohort specifically in the last 5 years from 2014 onwards. This appears attributable to the shift in general practices from the GOLD to Aurum database. To generate valid results and form accurate conclusions regarding changes in the incidence of VTE overtime it is crucial we examine the CPRD data to the fullest. The period between 2014 -2019 is of significant importance as it represents a sizable proportion of the time period in which changes to surgical technique and patient demographics took place and therefore influence the incidence of VTE post colorectal resectional surgery within the UK, as stated above (Section F). Therefore, we request access to the use of both GOLD and Aurum databases to complete this study.

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List of Appendices (ISAC only)

Appendix 1 (ISAC only)

Codes for identification of colectomy from HES data.

H041, H042, H043, H048, H049, H051, H052, H053, H058, H059, H061, H062, H063, H064, H068, H069, H071, H072, H073, H074, H078, H079, H081, H082, H083, H084, H085, H088, H089, H091, H092, H093, H094, H095, H098, H099, H101, H102, H103, H104, H105, H108, H109, H111, H112, H113, H114, H115, H118, H119, H291, H292, H293, H294, H298, H299, H331, H332, H333, H334, H335, H336, H337, H338, H339

Medcodes for anticoagulation clinic

784, 6822, 12505, 55224, 74910, 109012, 110734

Medcodes for VTE

824, 1266, 2198, 3576, 9701, 22038, 25478, 27284, 37849, 42506, 48920, 67006, 101655

Product codes for anticoagulants

45 61 833 1781 2249 2675 2676 2677 3744 3868 3895 4446

4888 4976 4995 5046 5305 5526 5747 5880 5998 6262 6478 6695

6860 6945 7154 7199 7307 7371 8466 8467 8552 8664 9140 9593

9605 9610 9640 10002 10004 10044 10072 10170 10194 10240 10469 10532

10533 11117 11372 11692 12652 12681 12974 13058 13097 13157 13210 13270

13348 13501 13502 13503 13504 13505 13568 13644 13663 13716 14099 14110

14138 14212 14308 14341 14788 14794 14851 14891 15006 15293 15376 15709

16061 16476 16530 17004 17007 17049 17484 17592 17664 17791 17965 18209

18732 19098 19280 19337 19486 19989 20010 20024 20028 20029 20153 20154

21233 21316 21365 21490 21518 22428 23078 23570 23573 23579 24896 25155

25195 25287 26146 27035 27325 28506 28593 29043 29207 29317 29318 30108

30202 30203 30396 31511 31541 31937 32511 32645 32844 33307 33558 33711

34019 34086 34087 34088 34095 34299 34416 34417 34418 34517 34526 34576

34691 34758 34864 34918 35033 35941 35955 36099 36142 36172 36196 36911

36989 37086 37131 37613 37616 37678 37704 38041 38044 38327 38536 38839

39119 39444 39503 39639 39755 39866 40143 40715 42106 42474 42853 43407

43408 43409 43655 44238 44491 44866 45911 46101 46278 46632 46678 46924

47207 47353 47397 47423 47566 47633 47646 47925 47944 48070 48134 48673

48869 48966 49578 50000 50391 50994 51006 51350 51484 51496 51509 51642

52004 52841 53350 53740 53745 53752 54066 54234 54451 54892 54927 54946

55096 55316 55490 55565 55577 55604 56166 56289 56314 56398 56640 57032

57204 58519 58594 58787 58962 59400 59578 59761 60041 60131 60188 60589

60949 61949 62150 62309 62310 62856 62902 62959 63071 63101 63146 63169

63297 63571 64133 64500 64559 64581 64678 64969 65247 65285 65462 65496

65746 65850 65876 66286 66529 66570 68591 68667 68795 69128 69194 70831

70866 71132 71196 71274 71386 71661 71746 71747 72040 72120 72394 73212

73309 73607 73642 73726 73853 73907 74257 74349 75255 75576 75798 75959

76048 76072 76358 76422 76708 76787 77043 77245 77268 77318 77559

# ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING CPRD DATA

## FEEDBACK TO APPLICANTS

| | |
|---|---|
| CONFIDENTIAL *by e-mail* | |
| PROTOCOL NO: | 19_180RA3 |

| | | | |
|---|---|---|---|
| PROTOCOL TITLE: | Incidence of venous thromboembolism following colorectal resectional surgery | | |
| APPLICANT: | Mr David James Humes<br>University of Nottingham<br>xxxxxxx@nottingham.ac.uk | | |
| APPROVED<br>☐ | APPROVED WITH COMMENTS<br>(resubmission not required)<br>☒ | REVISION/ RESUBMISSION REQUESTED<br>☐ | REJECTED<br>☐ |

INSTRUCTIONS:

*Protocols with an outcome of 'Approved' or 'Approved with comments' do not require resubmission to the ISAC.*

REVIEWER COMMENTS:

The applicants will need to be cautious in combining data across CPRD GOLD and CPRD Aurum. These are structured differently and sourced from different software systems so the recording of information may not be consistent across the two.

APPLICANT FEEDBACK:

| | |
|---|---|
| DATE OF ISAC FEEDBACK: | 16/09/2020 |
| DATE OF APPLICANT FEEDBACK: | |

***For protocols approved from 01 April 2014 onwards, applicants are required to include the ISAC protocol in their journal submission with a statement in***

***the manuscript indicating that it had been approved by the ISAC (with the reference number) and made available to the journal reviewers. If the protocol was subject to any amendments, the last amended version should be the one submitted.***

***Guidance on resubmitting applications, or making amendments to approved protocols, can be found on the CPRD website at*** *https://cprd.com/research-applications***.**

## Appendix 9 STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Checklist for Chapter 3

### STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1, 3 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 5-7 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 7 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 8 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 8-9 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 8-9 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | n/a |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 9-11 |

| | | | |
|---|---|---|---|
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 8-11 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 9-11 |
| Study size | 10 | Explain how the study size was arrived at | 8-9 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 9-11 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 11-12 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 11-12 |
| | | (*c*) Explain how missing data were addressed | n/a |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | n/a |
| | | (*e*) Describe any sensitivity analyses | 11-12 |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 13 |
| | | (b) Give reasons for non-participation at each stage | n/a |
| | | (c) Consider use of a flow diagram | n/a |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 13 |
| | | (b) Indicate number of participants with missing data for each variable of interest | n/a |

| | | | |
|---|---|---|---|
| | | (c) Summarise follow-up time (eg, average and total amount) | Tables 2 & 3 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 13-15 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 9, Tables 2 & 3 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 9-11 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 13-15 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 15 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 16 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 16-17 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 16-20 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 16-20 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 2 |

## Appendix 10 OPCS-4 (Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures version 4) and ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th Revision) codes used to identify colectomy, inflammatory bowel disease and diverticular disease

### Colectomy codes

H041, H042, H043, H048, H049, H051, H052, H053, H058, H059, H061, H062, H063, H064, H068, H069, H071, H072, H073, H074, H078, H079, H081, H082, H083, H084, H085, H088, H089, H091, H092, H093, H094, H095, H098, H099, H101, H102, H103, H104, H105, H108, H109, H111, H112, H113, H114, H115, H118, H119, H291, H292, H293, H294, H298, H299, H331, H332, H333, H334, H335, H336, H337, H338, H339

### Inflammatory bowel disease codes

K50, K500, K501, K508, K509, K51, K510, K512, K513, K514, K515, K518, K519, K520, K521, K522, K523, K528, K529

### Diverticular disease codes

K57, K570, K571, K572, K573, K574, K575, K578, K579

## Appendix 11 Chapter 3 Time Trends Stata Do File

Within this thesis, all data analysis in Stata was performed by the author. All data management performed by the author is within the Stata Do file below including merger of GOLD and Aurum datasets.

```
//// TIME TRENDS ANALYSIS

clear
cd "R:\DRS-ColorectalSurgery2019\chris\aurum_workingdata"

/// GOLD entry

clear

use "R:\DRS-ColorectalSurgery2019\chris\aurum_workingdata\cohort_vte_gold_analysis.dta"

// Rename/changes for GOLD to Aurum
gen database="Gold"
rename accept acceptable
gen robot=0
replace robot=1 if lap==2
rename charlson_score charlson_fin
gen gen_ethnicity=ethnos
rename lcd lcd_n

// Drop if NOT acceptable
tab acceptable, mis
drop if acceptable==0

// Drop if VTE before epistart date
gen epistart_n=date(epistart,"DMY")
format %td epistart_n
gen vte_pre=0
replace vte_pre=1 if vte_date<(epistart_n-1)
tab vte_pre
drop if vte_pre==1

// Gen age and year
gen mob1=mob
replace mob1=1 if mob==0
gen dayob=1
gen dob = mdy(mob1, dayob, yob)
format dob %td
browse
gen age = (epistart_n-dob)/365.25
format %td age
format age %2.0f

drop if age<18

drop if opcs=="H411"
```

```
drop if opcs=="H412"
drop if opcs=="H413"
drop if opcs=="H414"
drop if opcs=="H341"
drop if admit==2
drop if gender==3

gen year=year(epistart_n)

tab accept, mis
sum epistart_n
sum epiend_n

// Form exit date and failure date
gen epistart1=epistart_n-1
format epistart1 %d
gen exit=min(lcd_n, dod, tod)
format exit %d
gen vte_censor_date=min(exit, vte_date)
format vte_censor_date %d
gen exit2 = min(exit, vte_censor_date)
format exit2 %d

drop if epistart_n==.
drop if epiend_n==.

drop if evdate_n<epistart_n | evdate_n>epiend_n
drop if epistart1>epiend_n

drop if uts==. | crd==. | frd==. | lcd_n==.
drop if uts>epistart1
drop if crd>epistart1
drop if frd>epistart1

drop if lcd_n<=epistart1
drop if dod<=epistart1
drop if tod<=epistart1
drop if vte_censor_date<=epistart1

// Drop years 1997-1999 and 2020
tab year, mis
drop if (year<2000) | (year==2020)
tab year, mis

tab vte, mis
recode vte .=0
tab vte, mis

save "R:\DRS-ColorectalSurgery2019\chris\aurum_workingdata\cohort_vte_gold_append2.dta", replace

/// GOLD finish
/// Aurum start

clear
use "R:\DRS-ColorectalSurgery2019\chris\aurum_workingdata\cohort_aurum_analysis.dta"
```

```
102
103 // Drop if NOT acceptable
104 gen database="Aurum"
105
106 tab acceptable, mis
107 drop if acceptable==0
108
109 tab patienttypeid
110 tab id
111 drop patienttypeid id
112
113 // Drop if VTE before epistart date
114 gen vte_pre=0
115 replace vte_pre=1 if vte_date<(epistart_n-1)
116 tab vte_pre
117 drop if vte_pre==1
118
119 // Gen age and year
120 gen age = (epistart_n-ebdate_n)/365.25
121 format %td age
122 format age %2.0f
123
124 drop if age<18
125
126 drop if opcs=="H411"
127 drop if opcs=="H412"
128 drop if opcs=="H413"
129 drop if opcs=="H414"
130 drop if opcs=="H341"
131 drop if admit==2
132 drop if gender==3
133
134 tab acceptable, mis
135 sum epistart_n
136 sum epiend_n
137
138 drop if epistart_n==.
139 drop if epiend_n==.
140 drop if regstartdate_n==.
141
142 drop if evdate_n<epistart_n | evdate_n>epiend_n
143
144 gen year=year(epistart_n)
145
146 // Form exit date and failure date
147 gen epistart1=epistart_n-1
148 format epistart1 %d
149 gen exit=min(lcd_n, dod, emis_ddate_n, cprd_ddate_n)
150 format exit %d
151 gen vte_censor_date=min(exit, vte_date)
152 format vte_censor_date %d
153 gen exit2 = min(exit, vte_censor_date)
154 format exit2 %d
155
156 tab vte, mis
157 recode vte .=0
158 tab vte, mis
```

```
159
160 drop if epistart1>epiend_n
161
162 drop if lcd_n==.
163
164 drop if regstartdate_n>epistart1
165
166 drop if lcd_n<=epistart1
167 drop if dod<=epistart1
168 drop if vte_censor_date<=epistart1
169 drop if emis_ddate_n<=epistart1
170 drop if cprd_ddate_n<=epistart1
171
172 // Drop years 1997-1999 and 2020
173 tab year, mis
174 drop if (year<2000) | (year==2020)
175 tab year, mis
176
177 tab imd2015_5, mis
178 tab region, mis
179
180 /// Append GOLD data
181
182 append using cohort_vte_gold_append2.dta
183 tab database, mis
184
185 /// Define variables
186
187 gen vtenew=vte
188 replace vtenew=0 if vte_date<epistart1 | vte_date>exit2
189
190 gen vtepd=vtenew
191 replace vtepd=0 if vte_date<=epiend_n
192
193 gen vtepd30=vtepd
194 replace vtepd30=0 if vte_date>(epistart1+(365.25*0.083333333333333333333333))
195
196 gen vteip=vtenew
197 replace vteip=0 if vte_date>epiend_n
198
199 gen vte30=vtenew
200 replace vte30=0 if vte_date>(epistart1+(365.25*0.083333333333333333333333))
201
202 gen vte90=vtenew
203 replace vte90=0 if vte_date>(epistart1+(365.25*0.25))
204
205 gen vte365=vtenew
206 replace vte365=0 if vte_date>(epistart1+365.25)
207
208 // Change ethnicity, deprivation and MIS
209 tab gen_ethnicity, mis
210 encode gen_ethnicity, gen(ethnos2)
211 recode ethnos2 1=2 2=2 3=2 4=2 5=2 6=2 7=2 8=2 9=2 10=2 11=3 12=1
212 label define ethnos2 1 "White" 2 "Other" 3 "Unknown", replace
213 tab ethnos2, mis
214
215 encode gen_ethnicity, gen(ethnos3)
```

```
recode ethnos3 1=2 2=3 3=3 4=3 5=2 6=2 7=4 8=2 9=4 10=2 11=4 12=1
label define ethnos3 1 "White" 2 "Asian" 3 "Black" 4 "Other/Unknown", replace
tab ethnos3, mis

recode imd2015_5 .=99

tab lap, mis
gen lap2=lap
recode lap2 2=1
label define lap2 0 "Open" 1 "MIS"
label values lap2 lap2

gen lapcat1=lap
recode lapcat1 0=0 1=2 2=3
tab lapcat1, mis
replace lapcat1=1 if conlap==1
tab lapcat1, mis
gen lapcat2=lapcat1
recode lapcat2 0=0 1=1 2=2 3=2
label define lapcat1 0 "Open" 1 "MIS converted to Open" 2 "Laparoscopic" 3 "Robotic"
label values lapcat1 lapcat1
label define lapcat2 0 "Open" 1 "MIS converted to Open" 2 "MIS"
label values lapcat2 lapcat2
tab lapcat1, mis
tab lapcat2, mis
gen lapcat3=lapcat2
recode lapcat3 2=1
tab lapcat3, mis
label define lapcat3 0 "Open" 1 "Started MIS"
label values lapcat3 lapcat3
tab lapcat3, mis

// Indication for resection
tab can ibd, mis
gen ibd2=ibd
replace ibd2=0 if can==1
tab can dd, mis
gen dd2=dd
replace dd2=0 if can==1
tab ibd2 dd2, mis
replace dd2=0 if ibd2==1
tab can ibd2, mis
tab can dd2, mis
tab ibd2 dd2, mis
gen indicat=3
replace indicat=0 if can==1
replace indicat=1 if ibd2==1
replace indicat=2 if dd2==1
tab indicat, mis
label define indicat 0 "CRC" 1 "Inflammatory bowel disease" 2 "Diverticular disease" 3
"Other"
label values indicat indicat
tab indicat, mis

// Gen age categories and variables year, post2009 and quarter
egen agecat1=cut (age), at(0, 60 ,70, 80, 120)

```

```
gen post2009=1
replace post2009=0 if year < 2010

gen time4=.
replace time4=0 if year<=2004
replace time4=1 if year>2004 & year<=2009
replace time4=2 if year>2009 & year<=2014
replace time4=3 if year>=2015
tab time4, mis
tab year time4, mis

gen quarter=1
replace quarter=2 if (admit==0 & can==1)
replace quarter=3 if (admit==1 & can==0)
replace quarter=4 if (admit==1 & can==1)
label define qrt 1 "Emergency Benign" 2 "Emergency Malignant" 3 "Elective Benign" 4
"Elective Malignant"
label values quarter qrt

// LOS
gen los=epiend_n-epistart_n
gen los4=0
replace los4=1 if los>4
tab los4
gen los7=0
replace los7=1 if los>7
tab los7
gen los10=0
replace los10=1 if los>10
tab los10
gen los14=0
replace los14=1 if los>14
tab los14
gen los28=0
replace los28=1 if los>28
tab los28

gen loscat=0
replace loscat=1 if los<=4
replace loscat=2 if los>4 & los<=7
replace loscat=3 if los>7 & los<=14
replace loscat=4 if los>14
label define loscat 1 "<5 days" 2 "5 to 7 days" 3 "8 to 14 days" 4 ">14 days"
label values loscat loscat
tab loscat, mis

sum los, de
gen loscat2=0
replace loscat2=1 if los<=5
replace loscat2=2 if los>5 & los<=14
replace loscat2=3 if los>14
label define loscat2 1 "<=5 days" 2 "6 to 14 days" 3 ">14 days"
label values loscat2 loscat2
tab loscat2, mis

gen loscat3=0
replace loscat3=1 if los<=7
```

```
replace loscat3=2 if los>7 & los<=14
replace loscat3=3 if los>14
label define loscat3 1 "<=7 days" 2 "8 to 14 days" 3 ">14 days"
label values loscat3 loscat3
tab loscat3, mis

gen loscat4=0
replace loscat4=1 if los<=5
replace loscat4=2 if los>5 & los<14
replace loscat4=3 if los>=14
label define loscat4 1 "<=5 days" 2 "6 to 13 days" 3 ">=14 days"
label values loscat4 loscat4
tab loscat4, mis

gen loscat5=0
replace loscat5=1 if los<=6
replace loscat5=2 if los>6 & los<13
replace loscat5=3 if los>=13
label define loscat5 1 "<=6 days" 2 "7 to 12 days" 3 ">=13 days"
label values loscat5 loscat5
tab loscat5, mis

// Optype opcs
tab opcs, mis
gen optype=0
replace optype=1 if opcs=="H061"
replace optype=1 if opcs=="H062"
replace optype=1 if opcs=="H063"
replace optype=1 if opcs=="H064"
replace optype=1 if opcs=="H065"
replace optype=1 if opcs=="H068"
replace optype=1 if opcs=="H069"
replace optype=1 if opcs=="H071"
replace optype=1 if opcs=="H072"
replace optype=1 if opcs=="H073"
replace optype=1 if opcs=="H074"
replace optype=1 if opcs=="H075"
replace optype=1 if opcs=="H078"
replace optype=1 if opcs=="H079"
replace optype=1 if opcs=="H081"
replace optype=1 if opcs=="H082"
replace optype=1 if opcs=="H083"
replace optype=1 if opcs=="H084"
replace optype=1 if opcs=="H085"
replace optype=1 if opcs=="H086"
replace optype=1 if opcs=="H088"
replace optype=1 if opcs=="H089"
replace optype=2 if opcs=="H041"
replace optype=2 if opcs=="H042"
replace optype=2 if opcs=="H043"
replace optype=2 if opcs=="H048"
replace optype=2 if opcs=="H049"
replace optype=2 if opcs=="H291"
replace optype=2 if opcs=="H292"
replace optype=2 if opcs=="H293"
replace optype=2 if opcs=="H294"
replace optype=2 if opcs=="H298"
```

```
385 replace optype=2 if opcs=="H299"
386 replace optype=2 if opcs=="H051"
387 replace optype=2 if opcs=="H052"
388 replace optype=2 if opcs=="H053"
389 replace optype=2 if opcs=="H058"
390 replace optype=2 if opcs=="H059"
391 replace optype=3 if opcs=="H111"
392 replace optype=3 if opcs=="H112"
393 replace optype=3 if opcs=="H113"
394 replace optype=3 if opcs=="H114"
395 replace optype=3 if opcs=="H115"
396 replace optype=3 if opcs=="H116"
397 replace optype=3 if opcs=="H118"
398 replace optype=3 if opcs=="H119"
399 replace optype=3 if opcs=="H661"
400 replace optype=3 if opcs=="H662"
401 replace optype=3 if opcs=="H668"
402 replace optype=3 if opcs=="H669"
403 replace optype=4 if opcs=="H471"
404 replace optype=4 if opcs=="H478"
405 replace optype=4 if opcs=="H479"
406 label define optype 0 "Left" 1 "Right and Transverse" 2 "Total and Subtotal" 3 "Other" 4
"Anus"
407 label values optype optype
408 tab optype, mis
409
410 gen opsite=1
411 replace opsite=0 if opcs=="H041"
412 replace opsite=0 if opcs=="H042"
413 replace opsite=0 if opcs=="H043"
414 replace opsite=0 if opcs=="H048"
415 replace opsite=0 if opcs=="H049"
416 replace opsite=0 if opcs=="H291"
417 replace opsite=0 if opcs=="H292"
418 replace opsite=0 if opcs=="H051"
419 replace opsite=0 if opcs=="H052"
420 replace opsite=0 if opcs=="H053"
421 replace opsite=0 if opcs=="H058"
422 replace opsite=0 if opcs=="H059"
423 replace opsite=0 if opcs=="H293"
424 replace opsite=0 if opcs=="H294"
425 replace opsite=0 if opcs=="H091"
426 replace opsite=0 if opcs=="H101"
427 replace opsite=0 if opcs=="H102"
428 replace opsite=0 if opcs=="H331"
429 replace opsite=0 if opcs=="H332"
430 replace opsite=0 if opcs=="H333"
431 replace opsite=0 if opcs=="H334"
432 replace opsite=0 if opcs=="H335"
433 replace opsite=0 if opcs=="H336"
434 replace opsite=0 if opcs=="H337"
435 replace opsite=0 if opcs=="H338"
436 replace opsite=0 if opcs=="H339"
437 replace opsite=0 if opcs=="H471"
438 replace opsite=0 if opcs=="H478"
439 replace opsite=0 if opcs=="H479"
440 replace opsite=0 if opcs=="H661"
```

```
replace opsite=0 if opcs=="H662"
replace opsite=0 if opcs=="H668"
replace opsite=0 if opcs=="H669"
label define opsite 0 "Pelvic" 1 "Other"
label values opsite opsite
tab opsite, mis

gen vtedeath=0
replace vtedeath=1 if cause=="I82.8" | cause=="I26.9"

gen cantype=0
replace cantype=1 if opcs=="H041"
replace cantype=1 if opcs=="H042"
replace cantype=1 if opcs=="H043"
replace cantype=1 if opcs=="H048"
replace cantype=1 if opcs=="H049"
replace cantype=1 if opcs=="H291"
replace cantype=1 if opcs=="H292"
replace cantype=1 if opcs=="H101"
replace cantype=1 if opcs=="H102"
replace cantype=1 if opcs=="H103"
replace cantype=1 if opcs=="H104"
replace cantype=1 if opcs=="H105"
replace cantype=1 if opcs=="H106"
replace cantype=1 if opcs=="H108"
replace cantype=1 if opcs=="H109"
replace cantype=1 if opcs=="H331"
replace cantype=1 if opcs=="H332"
replace cantype=1 if opcs=="H333"
replace cantype=1 if opcs=="H334"
replace cantype=1 if opcs=="H335"
replace cantype=1 if opcs=="H336"
replace cantype=1 if opcs=="H337"
replace cantype=1 if opcs=="H338"
replace cantype=1 if opcs=="H339"
replace cantype=. if can!=1
label define cantype 0 "Colon Ca" 1 "Rectal Ca"
label values cantype cantype
tab cantype, mis

// Gen washout
gen washout2011=0
replace washout2011=1 if year>=2011 | year<2010
tab year washout2011, mis

gen washout2012=0
replace washout2012=1 if year>=2012 | year<2010
tab year washout2012, mis

/// STSET

stset vte_censor_date, origin(epistart1) failure(vtenew) scale(365.25) id(patid) exit(exit2)
drop if _t0==.

// Table 3.1
local table1 "agecat1 gender charlson_fin ethnos2 lapcat2 lapcat3 year post2009 vte30"
foreach t1 of local table1 {
```

```
bysort admit:tab `t1' can, mis chi
}

// Figures 3.1 & 3,2 (lapcat over year)
bysort admit: tab year lapcat3, mis expect col row chi

// LOS by year 3-year rolling
hist los, norm
hist los, by(quarter) norm

// Figure 3.3 (overall)
forvalues yr=2000(1)2019 {
sum los if (year==`yr' | year==(`yr'-1) | year==(`yr'+1)), de
}

// Admit
forvalues yr=2000(1)2019 {
bysort admit: sum los if (year==`yr' | year==(`yr'-1) | year==(`yr'+1)), de
}

// Admit and operative technique
// elective
forvalues yr=2000(1)2019 {
bysort lapcat3: sum los if admit==1 & (year==`yr' | year==(`yr'-1) | year==(`yr'+1)), de
}
// emergency
forvalues yr=2000(1)2019 {
bysort lapcat3: sum los if admit==0 & (year==`yr' | year==(`yr'-1) | year==(`yr'+1)), de
}

// Age by admit
forvalues yr=2000(1)2019 {
bysort admit: sum age if (year==`yr' | year==(`yr'-1) | year==(`yr'+1)), de
}

// Split follow-up into 30-days, 90-days, 1-year
stsplit year1, at(1)
stsplit mon3, at(0.25)
stsplit mon1, at(0.08333333333333333333333333)
drop if year1==1

gen personyrs=_t-_t0
tab vtenew, mis
recode vtenew .=0
tab vtenew, mis

gen pyrs2=0
replace pyrs2=(_t-0.25) if year1==0
replace pyrs2=(_t-0.08333333333333333333333333) if mon3==0
replace pyrs2=(_t) if mon1==0

/// ST RATES

// ST rate overall 30 days
strate, per (1000), if mon1==0
strate, per (1000), if mon3==0
strate, per (1000), if year1==0
```

```
strate admit, per (1000), if mon1==0
strate can, per (1000), if mon1==0
strate quarter, per (1000), if mon1==0
tab quarter if mon1==0, mis
strate quarter, per (1000), if mon3==0
strate quarter, per (1000), if year1==0
strate quarter, per (1000), if mon1==0 & lapcat3==0
strate quarter, per (1000), if mon1==0 & lapcat3==1
tab quarter lapcat3 if mon1==0, mis
strate post2009, per (1000), if mon1==0
strate lapcat2, per (1000), if mon1==0
strate indicat, per (1000), if mon1==0
strate agecat1, per (1000), if mon1==0
strate loscat2, per (1000), if mon1==0
strate loscat3, per (1000), if mon1==0
strate imd2015_5, per (1000), if mon1==0
strate charlson_fin, per (1000), if mon1==0
strate gender, per (1000), if mon1==0
strate ethnos2, per (1000), if mon1==0
strate ethnos3, per (1000), if mon1==0

// Tables 3.2 & 3.3
//ST rate 30-days
local table2 "can agecat1 gender charlson_fin ethnos2 lapcat2"
foreach t2 of local table2 {
// emergency
strate `t2', per (1000), if admit==0 & mon1==0

// elective
strate `t2', per (1000), if admit==1 & mon1==0
}

// 30 day univariable
local table2 "i.can i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat2 year"
foreach t2 of local table2 {
// emergency
poisson vtenew `t2' if admit==0 & mon1==0, e(personyrs) irr

// elective
poisson vtenew `t2' if admit==1 & mon1==0, e(personyrs) irr
}

// 30 day multivariable
local poisvar "i.can i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat2 year"
poisson vtenew `poisvar' if admit==0 & mon1==0, e(personyrs) irr

local poisvar "i.can i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat2 year"
poisson vtenew `poisvar' if admit==1 & mon1==0, e(personyrs) irr

// Figures 3.4 & 3.5 (by year (3 year rolling) 1 month post surgery overall rates)
forvalues yr=2000(1)2019 {
strate quarter, per (1000), if mon1==0 & (year==`yr' | year==(`yr'-1) | year==(`yr'+1))
}
strate year, per (1000), if mon1==0

/// FULL MODEL EFFECT MODIFICATION

```

```
// EFFECT modification proof ADMIT split by year
poisson vtenew i.can i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat3
ib1.admit##c.year if mon1==0, e(personyrs) irr
est store effectmodq1
poisson vtenew i.can i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat3 ib1.admit year if
mon1==0, e(personyrs) irr
lrtest effectmodq1

// EFFECT modification CANCER split by year
poisson vtenew can##c.year i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat3
ib1.admit##c.year if mon1==0, e(personyrs) irr
est store effectmodq2
poisson vtenew i.can i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat3
ib1.admit##c.year if mon1==0, e(personyrs) irr
lrtest effectmodq2

// EFFECT modification proof SURG TECHNIQUE and ADMIT split independantly by year
poisson vtenew can##c.year i.agecat1 i.gender i.charlson_fin i.ethnos2 lapcat3##c.year
ib1.admit##c.year if mon1==0, e(personyrs) irr
est store effectmodq3
poisson vtenew can##c.year i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat3
ib1.admit##c.year if mon1==0, e(personyrs) irr
lrtest effectmodq3

drop _est_effectmodq1 _est_effectmodq2 _est_effectmodq3

/// Final model

poisson vtenew i.can##c.year i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat3##c.year
ib1.admit##c.year if mon1==0, e(personyrs) irr

// Table 3.4
// Emergency benign open
lincom 0.lapcat3#c.year+0.admit#c.year+0.can#c.year+c.year, irr

// Emergency malignant open
lincom 0.lapcat3#c.year+0.admit#c.year+1.can#c.year+c.year, irr

// Emergency benign started MIS
lincom 1.lapcat3#c.year+0.admit#c.year+0.can#c.year+c.year, irr

// Emergency malignant started MIS
lincom 1.lapcat3#c.year+0.admit#c.year+1.can#c.year+c.year, irr

// Elective benign open
lincom 0.lapcat3#c.year+1.admit#c.year+0.can#c.year+c.year, irr

// Elective malignant open
lincom 0.lapcat3#c.year+1.admit#c.year+1.can#c.year+c.year, irr

// Elective benign started MIS
lincom 1.lapcat3#c.year+1.admit#c.year+0.can#c.year+c.year, irr

// Elective malignant started MIS
lincom 1.lapcat3#c.year+1.admit#c.year+1.can#c.year+c.year, irr

/// Proof post2009 NO effect modification (Sensitivity analysis)
```

```
poisson vtenew i.can##c.year i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat3##c.year ib1.admit##c.year i.post2009##c.year if mon1==0, e(personyrs) irr
est store test
poisson vtenew i.can##c.year i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat3##c.year ib1.admit##c.year i.post2009 if mon1==0, e(personyrs) irr
lrtest test
drop _est_test

// Sensitivity analysis test (pre/post 2010)
poisson vtenew i.can##c.year i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat3##c.year ib1.admit##c.year i.post2009 if mon1==0, e(personyrs) irr

poisson vtenew i.can##c.year i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat3##c.year ib1.admit##c.year i.post2009 if mon1==0 & washout2011==1, e(personyrs) irr

poisson vtenew i.can##c.year i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat3##c.year ib1.admit##c.year i.post2009 if mon1==0 & washout2012==1, e(personyrs) irr

// Proof post2009 NO effect modification washout2011
poisson vtenew i.can##c.year i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat3##c.year ib1.admit##c.year i.post2009##c.year if mon1==0 & washout2011==1, e(personyrs) irr
est store test
poisson vtenew i.can##c.year i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat3##c.year ib1.admit##c.year i.post2009 if mon1==0 & washout2011==1, e(personyrs) irr
lrtest test
drop _est_test

// Proof post2009 NO effect modification washout2012
poisson vtenew i.can##c.year i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat3##c.year ib1.admit##c.year i.post2009##c.year if mon1==0 & washout2012==1, e(personyrs) irr
est store test
poisson vtenew i.can##c.year i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat3##c.year ib1.admit##c.year i.post2009 if mon1==0 & washout2012==1, e(personyrs) irr
lrtest test
drop _est_test

/// Test of Risk high low category in substitution for MIS, Age and Charlson

// High vs Low
gen risk=0
replace risk=risk+2 if admit==0
replace risk=risk+2 if lapcat3==0
replace risk=risk+1 if can==1
replace risk=risk+1 if age>=60
replace risk=risk+1 if age>=70
replace risk=risk+1 if charlson_fin==1
replace risk=risk+2 if charlson_fin==2
tab risk, mis

gen risk_cut=0
replace risk_cut=1 if risk>=5
tab risk_cut, mis

gen risk2=0
replace risk2=risk2+1 if age>=60
replace risk2=risk2+1 if age>=70
replace risk2=risk2+1 if charlson_fin==1
```

```
710 replace risk2=risk2+2 if charlson_fin==2
711 tab risk2, mis
712
713 gen risk2_cut=0
714 replace risk2_cut=1 if risk2>=3
715 tab risk2_cut, mis
716
717 // Risk2
718 poisson vtenew i.risk2_cut i.can##c.year i.agecat1 i.gender i.charlson_fin i.ethnos2
i.lapcat3##c.year ib1.admit##c.year if mon1==0, e(personyrs) irr
719 est store test
720 poisson vtenew i.risk2_cut##c.year i.can##c.year i.agecat1 i.gender i.charlson_fin
i.ethnos2 i.lapcat3##c.year ib1.admit##c.year if mon1==0, e(personyrs) irr
721 lrtest test
722 drop _est_test
723
724 // Final risk2
725 poisson vtenew i.risk2_cut##c.year i.can##c.year i.agecat1 i.gender i.charlson_fin
i.ethnos2 i.lapcat3##c.year ib1.admit##c.year if mon1==0, e(personyrs) irr
726
727 // Elective benign MIS low
728 lincom 0.risk2_cut#c.year+1.lapcat3#c.year+1.admit#c.year+0.can#c.year+c.year, irr
729
730 // Elective benign MIS high
731 lincom 1.risk2_cut#c.year+1.lapcat3#c.year+1.admit#c.year+0.can#c.year+c.year, irr
732
733 // Elective benign open low
734 lincom 0.risk2_cut#c.year+0.lapcat3#c.year+1.admit#c.year+0.can#c.year+c.year, irr
735
736 // Elective benign open high
737 lincom 1.risk2_cut#c.year+0.lapcat3#c.year+1.admit#c.year+0.can#c.year+c.year, irr
738
739 // Elective maligant MIS low
740 lincom 0.risk2_cut#c.year+1.lapcat3#c.year+1.admit#c.year+1.can#c.year+c.year, irr
741
742 // Elective maligant MIS high
743 lincom 1.risk2_cut#c.year+1.lapcat3#c.year+1.admit#c.year+1.can#c.year+c.year, irr
744
745 // Elective maligant open low
746 lincom 0.risk2_cut#c.year+0.lapcat3#c.year+1.admit#c.year+1.can#c.year+c.year, irr
747
748 // Elective maligant open high
749 lincom 1.risk2_cut#c.year+0.lapcat3#c.year+1.admit#c.year+1.can#c.year+c.year, irr
750
751 // Emergency benign MIS low
752 lincom 0.risk2_cut#c.year+1.lapcat3#c.year+0.admit#c.year+0.can#c.year+c.year, irr
753
754 // Emergency benign MIS high
755 lincom 1.risk2_cut#c.year+1.lapcat3#c.year+0.admit#c.year+0.can#c.year+c.year, irr
756
757 // Emergency benign open low
758 lincom 0.risk2_cut#c.year+0.lapcat3#c.year+0.admit#c.year+0.can#c.year+c.year, irr
759
760 // Emergency benign open high
761 lincom 1.risk2_cut#c.year+0.lapcat3#c.year+0.admit#c.year+0.can#c.year+c.year, irr
762
763 // Emergency maligant MIS low
```

```
764 lincom 0.risk2_cut#c.year+1.lapcat3#c.year+0.admit#c.year+1.can#c.year+c.year, irr
765
766 // Emergency maligant MIS high
767 lincom 1.risk2_cut#c.year+1.lapcat3#c.year+0.admit#c.year+1.can#c.year+c.year, irr
768
769 // Emergency maligant open low
770 lincom 0.risk2_cut#c.year+0.lapcat3#c.year+0.admit#c.year+1.can#c.year+c.year, irr
771
772 // Emergency maligant open high
773 lincom 1.risk2_cut#c.year+0.lapcat3#c.year+0.admit#c.year+1.can#c.year+c.year, irr
774
775 gen risk3=0
776 replace risk3=risk3+2 if lapcat3==0
777 replace risk3=risk3+1 if age>=60
778 replace risk3=risk3+1 if age>=70
779 replace risk3=risk3+1 if charlson_fin>=1
780 tab risk3, mis
781
782 gen risk3_cut=0
783 replace risk3_cut=1 if risk3>=3
784 tab risk3_cut, mis
785
786 // Risk3
787 poisson vtenew i.risk3_cut i.can##c.year i.gender i.ethnos2 ib1.admit##c.year if
mon1==0, e(personyrs) irr
788 est store test
789 poisson vtenew i.risk3_cut##c.year i.can##c.year i.gender i.ethnos2 ib1.admit##c.year if
mon1==0, e(personyrs) irr
790 lrtest test
791 drop _est_test
792
793 // Final risk3
794 poisson vtenew i.risk3_cut##c.year i.can##c.year i.gender i.ethnos2 ib1.admit##c.year if
mon1==0, e(personyrs) irr
795
796 // Elective benign low
797 lincom 0.risk3_cut#c.year+1.admit#c.year+0.can#c.year+c.year, irr
798
799 // Elective benign high
800 lincom 1.risk3_cut#c.year+1.admit#c.year+0.can#c.year+c.year, irr
801
802 // Elective malignant low
803 lincom 0.risk3_cut#c.year+1.admit#c.year+1.can#c.year+c.year, irr
804
805 // Elective malignant high
806 lincom 1.risk3_cut#c.year+1.admit#c.year+1.can#c.year+c.year, irr
807
808 // Emergency benign low
809 lincom 0.risk3_cut#c.year+0.admit#c.year+0.can#c.year+c.year, irr
810
811 // Emergency benign high
812 lincom 1.risk3_cut#c.year+0.admit#c.year+0.can#c.year+c.year, irr
813
814 // Emergency malignant low
815 lincom 0.risk3_cut#c.year+0.admit#c.year+1.can#c.year+c.year, irr
816
817 // Emergency malignant high
```

```
lincom 1.risk3_cut#c.year+0.admit#c.year+1.can#c.year+c.year, irr

gen risk4=risk3
gen risk4_cut=0
replace risk4_cut=1 if risk4>=4
tab risk4_cut, mis

// Risk4
poisson vtenew i.risk4_cut i.can##c.year i.gender i.ethnos2 ib1.admit##c.year if mon1==0, e(personyrs) irr
est store test
poisson vtenew i.risk4_cut##c.year i.can##c.year i.gender i.ethnos2 ib1.admit##c.year if mon1==0, e(personyrs) irr
lrtest test
drop _est_test

// Final risk4
poisson vtenew i.risk4_cut##c.year i.can##c.year i.gender i.ethnos2 ib1.admit##c.year if mon1==0, e(personyrs) irr

// Elective benign low
lincom 0.risk4_cut#c.year+1.admit#c.year+0.can#c.year+c.year, irr

// Elective benign high
lincom 1.risk4_cut#c.year+1.admit#c.year+0.can#c.year+c.year, irr

// Elective malignant low
lincom 0.risk4_cut#c.year+1.admit#c.year+1.can#c.year+c.year, irr

// Elective malignant high
lincom 1.risk4_cut#c.year+1.admit#c.year+1.can#c.year+c.year, irr

// Emergency benign low
lincom 0.risk4_cut#c.year+0.admit#c.year+0.can#c.year+c.year, irr

// Emergency benign high
lincom 1.risk4_cut#c.year+0.admit#c.year+0.can#c.year+c.year, irr

// Emergency malignant low
lincom 0.risk4_cut#c.year+0.admit#c.year+1.can#c.year+c.year, irr

// Emergency malignant high
lincom 1.risk4_cut#c.year+0.admit#c.year+1.can#c.year+c.year, irr

/// Test effect modification Charlson and Age

// Test original final model Charlson effect modification
poisson vtenew i.can##c.year i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat3##c.year ib1.admit##c.year if mon1==0, e(personyrs) irr
est store test
poisson vtenew i.can##c.year i.agecat1 i.gender i.charlson_fin##c.year i.ethnos2 i.lapcat3##c.year ib1.admit##c.year if mon1==0, e(personyrs) irr
lrtest test
drop _est_test

// Test original final model Age effect modification
```

```
869 poisson vtenew i.can##c.year i.agecat1 i.gender i.charlson_fin i.ethnos2 i.lapcat3##c.year
ib1.admit##c.year if mon1==0, e(personyrs) irr
870 est store test
871 poisson vtenew i.can##c.year i.agecat1##c.year i.gender i.charlson_fin i.ethnos2
i.lapcat3##c.year ib1.admit##c.year if mon1==0, e(personyrs) irr
872 lrtest test
873 drop _est_test
```

## Appendix 12 STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Checklist for Chapter 4

### STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | abstract |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 2 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 2 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 3-4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 3-4 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 3-4 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | n/a |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 4-5 |

| | | | |
|---|---|---|---|
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 3-5 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 3-6 |
| Study size | 10 | Explain how the study size was arrived at | 3-4 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 4-6 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 6 |
| | | (*c*) Explain how missing data were addressed | n/a |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | n/a |
| | | (*e*) Describe any sensitivity analyses | 6 |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 7 |
| | | (b) Give reasons for non-participation at each stage | n/a |
| | | (c) Consider use of a flow diagram | n/a |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 7 |

| | | | |
|---|---|---|---|
| | | (b) Indicate number of participants with missing data for each variable of interest | n/a |
| | | (c) Summarise follow-up time (eg, average and total amount) | n/a |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 7-9 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 7-9 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 7-9 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 7-9 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 9 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 11 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 11-12 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 12-14 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 12-14 |
| **Other information** | | | |

| | | | |
|---|---|---|---|
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 1 |

## Appendix 13 Chapter 4 Post-discharge Rates Stata Do File

Within this thesis, all data analysis in Stata was performed by the author. All data management performed by the author is within the Stata Do file below including merger of GOLD and Aurum datasets.

```
//// WEEKLY RATES ANALYSIS

clear
cd "R:\DRS-ColorectalSurgery2019\chris\aurum_workingdata"

/// GOLD entry

clear

use "R:\DRS-ColorectalSurgery2019\chris\aurum_workingdata\cohort_vte_gold_analysis.dta"

// Rename/changes for GOLD to Aurum
gen database="Gold"
rename accept acceptable
gen robot=0
replace robot=1 if lap==2
rename charlson_score charlson_fin
gen gen_ethnicity=ethnos
rename lcd lcd_n

// Drop if NOT acceptable
tab acceptable, mis
drop if acceptable==0

// Drop if VTE before epistart date
gen epistart_n=date(epistart,"DMY")
format %td epistart_n
gen vte_pre=0
replace vte_pre=1 if vte_date<(epistart_n-1)
tab vte_pre
drop if vte_pre==1

// Gen age and year
gen mob1=mob
replace mob1=1 if mob==0
gen dayob=1
gen dob = mdy(mob1, dayob, yob)
format dob %td
browse
gen age = (epistart_n-dob)/365.25
format %td age
format age %2.0f

drop if age<18

drop if opcs=="H411"
```

```
drop if opcs=="H412"
drop if opcs=="H413"
drop if opcs=="H414"
drop if opcs=="H341"
drop if admit==2
drop if gender==3

gen year=year(epistart_n)

tab accept, mis
sum epistart_n
sum epiend_n

// Form exit date and failure date
gen epistart1=epistart_n-1
format epistart1 %d
gen exit=min(lcd_n, dod, tod)
format exit %d
gen vte_censor_date=min(exit, vte_date)
format vte_censor_date %d
gen exit2 = min(exit, vte_censor_date)
format exit2 %d

drop if epistart_n==.
drop if discharged_n==.

drop if evdate_n<epistart_n | evdate_n>discharged_n
drop if epistart1>discharged_n

drop if uts==. | crd==. | frd==. | lcd_n==.
drop if uts>epistart1
drop if crd>epistart1
drop if frd>epistart1

drop if lcd_n<=epistart1
drop if dod<=epistart1
drop if tod<=epistart1
drop if vte_censor_date<=epistart1

// Drop years 1997-1999 and 2020
tab year, mis
drop if (year<2000) | (year==2020)
tab year, mis

tab vte, mis
recode vte .=0
tab vte, mis

merge 1:1 patid using mets_gold.dta
drop if _merge==2
drop _merge
recode met 1=1 .=0
tab met, mis

save "R:\DRS-ColorectalSurgery2019\chris\aurum_workingdata\cohort_vte_gold_append2.dta", replace

```

```
/// GOLD finish
/// Aurum start

clear
use "R:\DRS-ColorectalSurgery2019\chris\aurum_workingdata\cohort_aurum_analysis.dta"

// Drop if NOT acceptable
gen database="Aurum"

tab acceptable, mis
drop if acceptable==0

tab patienttypeid
tab id
drop patienttypeid id

// Drop if VTE before epistart date
gen vte_pre=0
replace vte_pre=1 if vte_date<(epistart_n-1)
tab vte_pre
drop if vte_pre==1

// Gen age and year
gen age = (epistart_n-ebdate_n)/365.25
format %td age
format age %2.0f

drop if age<18

drop if opcs=="H411"
drop if opcs=="H412"
drop if opcs=="H413"
drop if opcs=="H414"
drop if opcs=="H341"
drop if admit==2
drop if gender==3

tab acceptable, mis
sum epistart_n
sum epiend_n

drop if epistart_n==.
drop if discharged_n==.
drop if regstartdate_n==.

drop if evdate_n<epistart_n | evdate_n>discharged_n

gen year=year(epistart_n)

// Form exit date and failure date
gen epistart1=epistart_n-1
format epistart1 %d
gen exit=min(lcd_n, dod, emis_ddate_n, cprd_ddate_n)
format exit %d
gen vte_censor_date=min(exit, vte_date)
format vte_censor_date %d
```

```
gen exit2 = min(exit, vte_censor_date)
format exit2 %d

tab vte, mis
recode vte .=0
tab vte, mis

drop if epistart1>discharged_n

drop if lcd_n==.

drop if regstartdate_n>epistart1

drop if lcd_n<=epistart1
drop if dod<=epistart1
drop if vte_censor_date<=epistart1
drop if emis_ddate_n<=epistart1
drop if cprd_ddate_n<=epistart1

// Drop years 1997-1999 and 2020
tab year, mis
drop if (year<2000) | (year==2020)
tab year, mis

tab imd2015_5, mis
tab region, mis

merge 1:1 patid using mets_aurum.dta
drop if _merge==2
drop _merge
recode met 1=1 .=0
tab met, mis

/// Append GOLD data

append using cohort_vte_gold_append2.dta
tab database, mis

/// Define variables

gen evdate1=evdate_n-1

gen vtenew=vte
replace vtenew=0 if vte_date<epistart1 | vte_date>exit2

gen vtepd=vtenew
replace vtepd=0 if vte_date<=discharged_n

gen vtepd30=vtepd
replace vtepd30=0 if vte_date>(epistart1+(365.25*0.08333333333333333333333333))

gen vteip=vtenew
replace vteip=0 if vte_date>discharged_n

gen vte30=vtenew
replace vte30=0 if vte_date>(epistart1+(365.25*0.08333333333333333333333333))

```

```
gen vte90=vtenew
replace vte90=0 if vte_date>(epistart1+(365.25*0.25))

gen vte365=vtenew
replace vte365=0 if vte_date>(epistart1+365.25)

// Change ethnicity, deprivation and MIS
tab gen_ethnicity, mis
encode gen_ethnicity, gen(ethnos2)
recode ethnos2 1=2 2=2 3=2 4=2 5=2 6=2 7=2 8=2 9=2 10=2 11=3 12=1
label define ethnos2 1 "White" 2 "Other" 3 "Unknown", replace
tab ethnos2, mis

encode gen_ethnicity, gen(ethnos3)
recode ethnos3 1=2 2=3 3=3 4=3 5=2 6=2 7=4 8=2 9=4 10=2 11=4 12=1
label define ethnos3 1 "White" 2 "Asian" 3 "Black" 4 "Other/Unknown", replace
tab ethnos3, mis

recode imd2015_5 .=99

tab lap, mis
gen lap2=lap
recode lap2 2=1
label define lap2 0 "Open" 1 "MIS"
label values lap2 lap2

gen lapcat1=lap
recode lapcat1 0=0 1=2 2=3
tab lapcat1, mis
replace lapcat1=1 if conlap==1
tab lapcat1, mis
gen lapcat2=lapcat1
recode lapcat2 0=0 1=1 2=2 3=2
label define lapcat1 0 "Open" 1 "MIS converted to Open" 2 "Laparoscopic" 3 "Robotic"
label values lapcat1 lapcat1
label define lapcat2 0 "Open" 1 "MIS converted to Open" 2 "MIS"
label values lapcat2 lapcat2
tab lapcat1, mis
tab lapcat2, mis
gen lapcat3=lapcat2
recode lapcat3 2=1
tab lapcat3, mis
label define lapcat3 0 "Open" 1 "Started MIS"
label values lapcat3 lapcat3
tab lapcat3, mis

// Indication for resection
tab can ibd, mis
gen ibd2=ibd
replace ibd2=0 if can==1
tab can dd, mis
gen dd2=dd
replace dd2=0 if can==1
tab ibd2 dd2, mis
replace dd2=0 if ibd2==1
tab can ibd2, mis
tab can dd2, mis
```

```
tab ibd2 dd2, mis
gen indicat=3
replace indicat=0 if can==1
replace indicat=1 if ibd2==1
replace indicat=2 if dd2==1
tab indicat, mis
label define indicat 0 "CRC" 1 "Inflammatory bowel disease" 2 "Diverticular disease" 3
"Other"
label values indicat indicat
tab indicat, mis

// Gen age categories and variables year, post2009 and quarter
egen agecat1=cut (age), at(0, 60 ,70, 80, 120)

gen post2009=1
replace post2009=0 if year < 2010

gen time4=.
replace time4=0 if year<=2004
replace time4=1 if year>2004 & year<=2009
replace time4=2 if year>2009 & year<=2014
replace time4=3 if year>=2015
tab time4, mis
tab year time4, mis

gen quarter=1
replace quarter=2 if (admit==0 & can==1)
replace quarter=3 if (admit==1 & can==0)
replace quarter=4 if (admit==1 & can==1)
label define qrt 1 "Emergency Benign" 2 "Emergency Malignant" 3 "Elective Benign" 4
"Elective Malignant"
label values quarter qrt

gen sixth=0
replace sixth=1 if (admit==1 & can==0 & indicat!=1)
replace sixth=2 if (admit==1 & can==0 & indicat==1)
replace sixth=3 if (admit==1 & can==1)
replace sixth=4 if (admit==0 & can==0 & indicat!=1)
replace sixth=5 if (admit==0 & can==0 & indicat==1)
replace sixth=6 if (admit==0 & can==1)
label define six 1 "Elective Benign Other" 2 "Elective IBD" 3 "Elective Malignant" 4
"Emergency Benign Other" 5 "Emergency IBD" 6 "Emergency Malignant"
label values sixth six
tab quarter, mis
tab sixth, mis

gen fith=0
replace fith=1 if (admit==1 & can==0)
replace fith=2 if (admit==1 & can==1)
replace fith=3 if (admit==0 & can==0 & indicat!=1)
replace fith=4 if (admit==0 & can==0 & indicat==1)
replace fith=5 if (admit==0 & can==1)
label define five 1 "Elective Benign" 2 "Elective Malignant" 3 "Emergency Benign Other" 4
"Emergency IBD" 5 "Emergency Malignant"
label values fith five
tab quarter, mis
tab sixth, mis
```

```
tab fith, mis

// LOS
gen los=discharged_n-epistart_n
gen los_postop=discharged_n-evdate_n
gen los4=0
replace los4=1 if los>4
tab los4
gen los7=0
replace los7=1 if los>7
tab los7
gen los10=0
replace los10=1 if los>10
tab los10
gen los14=0
replace los14=1 if los>14
tab los14
gen los28=0
replace los28=1 if los>28
tab los28

gen los_postop7=0
replace los_postop7=1 if los_postop>7
tab los_postop7, mis

gen loscat=0
replace loscat=1 if los<=4
replace loscat=2 if los>4 & los<=7
replace loscat=3 if los>7 & los<=14
replace loscat=4 if los>14
label define loscat 1 "<5 days" 2 "5 to 7 days" 3 "8 to 14 days" 4 ">14 days"
label values loscat loscat
tab loscat, mis

sum los, de
gen loscat2=0
replace loscat2=1 if los<=5
replace loscat2=2 if los>5 & los<=14
replace loscat2=3 if los>14
label define loscat2 1 "<=5 days" 2 "6 to 14 days" 3 ">14 days"
label values loscat2 loscat2
tab loscat2, mis

gen loscat3=0
replace loscat3=1 if los<=7
replace loscat3=2 if los>7 & los<=14
replace loscat3=3 if los>14
label define loscat3 1 "<=7 days" 2 "8 to 14 days" 3 ">14 days"
label values loscat3 loscat3
tab loscat3, mis

gen loscat4=0
replace loscat4=1 if los<=5
replace loscat4=2 if los>5 & los<14
replace loscat4=3 if los>=14
label define loscat4 1 "<=5 days" 2 "6 to 13 days" 3 ">=14 days"
label values loscat4 loscat4
```

```
tab loscat4, mis

gen loscat5=0
replace loscat5=1 if los<=6
replace loscat5=2 if los>6 & los<13
replace loscat5=3 if los>=13
label define loscat5 1 "<=6 days" 2 "7 to 12 days" 3 ">=13 days"
label values loscat5 loscat5
tab loscat5, mis

// Optype opcs
tab opcs, mis
gen optype=0
replace optype=1 if opcs=="H061"
replace optype=1 if opcs=="H062"
replace optype=1 if opcs=="H063"
replace optype=1 if opcs=="H064"
replace optype=1 if opcs=="H065"
replace optype=1 if opcs=="H068"
replace optype=1 if opcs=="H069"
replace optype=1 if opcs=="H071"
replace optype=1 if opcs=="H072"
replace optype=1 if opcs=="H073"
replace optype=1 if opcs=="H074"
replace optype=1 if opcs=="H075"
replace optype=1 if opcs=="H078"
replace optype=1 if opcs=="H079"
replace optype=1 if opcs=="H081"
replace optype=1 if opcs=="H082"
replace optype=1 if opcs=="H083"
replace optype=1 if opcs=="H084"
replace optype=1 if opcs=="H085"
replace optype=1 if opcs=="H086"
replace optype=1 if opcs=="H088"
replace optype=1 if opcs=="H089"
replace optype=2 if opcs=="H041"
replace optype=2 if opcs=="H042"
replace optype=2 if opcs=="H043"
replace optype=2 if opcs=="H048"
replace optype=2 if opcs=="H049"
replace optype=2 if opcs=="H291"
replace optype=2 if opcs=="H292"
replace optype=2 if opcs=="H293"
replace optype=2 if opcs=="H294"
replace optype=2 if opcs=="H298"
replace optype=2 if opcs=="H299"
replace optype=2 if opcs=="H051"
replace optype=2 if opcs=="H052"
replace optype=2 if opcs=="H053"
replace optype=2 if opcs=="H058"
replace optype=2 if opcs=="H059"
replace optype=3 if opcs=="H111"
replace optype=3 if opcs=="H112"
replace optype=3 if opcs=="H113"
replace optype=3 if opcs=="H114"
replace optype=3 if opcs=="H115"
replace optype=3 if opcs=="H116"
```

```
replace optype=3 if opcs=="H118"
replace optype=3 if opcs=="H119"
replace optype=3 if opcs=="H661"
replace optype=3 if opcs=="H662"
replace optype=3 if opcs=="H668"
replace optype=3 if opcs=="H669"
replace optype=4 if opcs=="H471"
replace optype=4 if opcs=="H478"
replace optype=4 if opcs=="H479"
label define optype 0 "Left" 1 "Right and Transverse" 2 "Total and Subtotal" 3 "Other" 4
"Anus"
label values optype optype
tab optype, mis

gen opsite=1
replace opsite=0 if opcs=="H041"
replace opsite=0 if opcs=="H042"
replace opsite=0 if opcs=="H043"
replace opsite=0 if opcs=="H048"
replace opsite=0 if opcs=="H049"
replace opsite=0 if opcs=="H291"
replace opsite=0 if opcs=="H292"
replace opsite=0 if opcs=="H051"
replace opsite=0 if opcs=="H052"
replace opsite=0 if opcs=="H053"
replace opsite=0 if opcs=="H058"
replace opsite=0 if opcs=="H059"
replace opsite=0 if opcs=="H293"
replace opsite=0 if opcs=="H294"
replace opsite=0 if opcs=="H091"
replace opsite=0 if opcs=="H101"
replace opsite=0 if opcs=="H102"
replace opsite=0 if opcs=="H331"
replace opsite=0 if opcs=="H332"
replace opsite=0 if opcs=="H333"
replace opsite=0 if opcs=="H334"
replace opsite=0 if opcs=="H335"
replace opsite=0 if opcs=="H336"
replace opsite=0 if opcs=="H337"
replace opsite=0 if opcs=="H338"
replace opsite=0 if opcs=="H339"
replace opsite=0 if opcs=="H471"
replace opsite=0 if opcs=="H478"
replace opsite=0 if opcs=="H479"
replace opsite=0 if opcs=="H661"
replace opsite=0 if opcs=="H662"
replace opsite=0 if opcs=="H668"
replace opsite=0 if opcs=="H669"
label define opsite 0 "Pelvic" 1 "Other"
label values opsite opsite
tab opsite, mis

gen vtedeath=0
replace vtedeath=1 if cause=="I82.8" | cause=="I26.9"

gen cantype=0
replace cantype=1 if opcs=="H041"
```

```
replace cantype=1 if opcs=="H042"
replace cantype=1 if opcs=="H043"
replace cantype=1 if opcs=="H048"
replace cantype=1 if opcs=="H049"
replace cantype=1 if opcs=="H291"
replace cantype=1 if opcs=="H292"
replace cantype=1 if opcs=="H101"
replace cantype=1 if opcs=="H102"
replace cantype=1 if opcs=="H103"
replace cantype=1 if opcs=="H104"
replace cantype=1 if opcs=="H105"
replace cantype=1 if opcs=="H106"
replace cantype=1 if opcs=="H108"
replace cantype=1 if opcs=="H109"
replace cantype=1 if opcs=="H331"
replace cantype=1 if opcs=="H332"
replace cantype=1 if opcs=="H333"
replace cantype=1 if opcs=="H334"
replace cantype=1 if opcs=="H335"
replace cantype=1 if opcs=="H336"
replace cantype=1 if opcs=="H337"
replace cantype=1 if opcs=="H338"
replace cantype=1 if opcs=="H339"
replace cantype=. if can!=1
label define cantype 0 "Colon Ca" 1 "Rectal Ca"
label values cantype cantype
tab cantype, mis

// Drop years pre 2010
drop if post2009==0
tab post2009, mis

/// STSET

stset vte_censor_date, origin(epistart1) failure(vtenew) scale(365.25) id(patid) exit(exit2)
drop if _t0==.

/// ST spliting

gen dc_time=((discharged_n-epistart1)/365.25)
gen dc_time_days=discharged_n-epistart1
gen dc_optime=((discharged_n-evdate_n)/365.25)
gen dc_optime_days=discharged_n-evdate_n
gen dif=(evdate_n-epistart1)/365.25
gen dif_days=evdate_n-epistart1
gen postop_time_vte=vte_date-evdate_n

// Spliting at post-operative week
stsplit week0, at(0) after(time=evdate_n)
stsplit week1, at(0.0192307692) after(time=evdate_n)
stsplit week2, at(0.0384615385) after(time=evdate_n)
stsplit week3, at(0.0576923077) after(time=evdate_n)
stsplit week4, at(0.0769230769) after(time=evdate_n)
stsplit week5, at(0.0961538462) after(time=evdate_n)
stsplit week6, at(0.1153846154) after(time=evdate_n)
stsplit week7, at(0.1346153846) after(time=evdate_n)
stsplit week8, at(0.1538461538) after(time=evdate_n)
```

```
stsplit week9, at(0.1730769231) after(time=evdate_n)
stsplit week10, at(0.1923076923) after(time=evdate_n)
stsplit week11, at(0.2115384615) after(time=evdate_n)
stsplit week12, at(0.2307692308) after(time=evdate_n)
drop if week12!=0
recode week0 0=0 -1=1

stsplit discharge, at(0) after(time=discharged_n)
tab discharge, mis
recode discharge 0=1 -1=0
tab discharge, mis

gen personyrs=_t-_t0
tab vtenew, mis
recode vtenew .=0
tab vtenew, mis

gen weekcat=.
replace weekcat=12 if week12==0
replace weekcat=11 if week11==0
replace weekcat=10 if week10==0
replace weekcat=9 if week9==0
replace weekcat=8 if week8==0
replace weekcat=7 if week7==0
replace weekcat=6 if week6==0
replace weekcat=5 if week5==0
replace weekcat=4 if week4==0
replace weekcat=3 if week3==0
replace weekcat=2 if week2==0
replace weekcat=1 if week1==0
replace weekcat=0 if week0==1
tab weekcat, mis

// Table 4.1
local table1 "can agecat1 gender charlson_fin ethnos2 los_postop7 sixth"
foreach t1 of local table1 {
bysort admit: tab `t1' lapcat3 if week0==1, mis col chi
}

strate if discharge==1, per (1000)
strate weekcat if discharge==1, per (1000)

// Table 4.x (NOT used inpatient VTE rates)
/*
strate, per (1000), if quarter==3 & lapcat3==0 & discharge==0
strate, per (1000), if quarter==3 & lapcat3==1 & discharge==0
strate, per (1000), if quarter==4 & lapcat3==0 & discharge==0
strate, per (1000), if quarter==4 & lapcat3==1 & discharge==0
strate, per (1000), if quarter==1 & lapcat3==0 & discharge==0
strate, per (1000), if quarter==1 & lapcat3==1 & discharge==0
strate, per (1000), if quarter==2 & lapcat3==0 & discharge==0
strate, per (1000), if quarter==2 & lapcat3==1 & discharge==0
*/

// Table 4.2
// 4 weeks post-op cumulative post-discharge VTE rates and IRR
strate quarter, per (1000), if discharge==1 & (weekcat>=1 & weekcat<=4)
```

```
610
611 // Base Elective Benign
612 poisson vtenew ib3.quarter if discharge==1 & (weekcat>=1 & weekcat<=4), e(personyrs)
irr
613
614 poisson vtenew ib3.quarter i.agecat1 i.gender i.charlson_fin if discharge==1 &
(weekcat>=1 & weekcat<=4), e(personyrs) irr
615
616 // Base Elective Malignant
617 poisson vtenew ib4.quarter if discharge==1 & (weekcat>=1 & weekcat<=4), e(personyrs)
irr
618
619 poisson vtenew ib4.quarter i.agecat1 i.gender i.charlson_fin if discharge==1 &
(weekcat>=1 & weekcat<=4), e(personyrs) irr
620
621 // Stick with Base Elective Malignant (add lapcat3 ethnos2 not los_postop7)
622 poisson vtenew ib4.quarter i.agecat1 i.gender i.charlson_fin i.lapcat3 if discharge==1 &
(weekcat >=1 & weekcat<=4), e(personyrs) irr
623
624 poisson vtenew ib4.quarter i.agecat1 i.gender i.charlson_fin i.lapcat3 i.ethnos2 if
discharge==1 & (weekcat>=1 & weekcat<=4), e(personyrs) irr
625
626 // Final model
627 poisson vtenew ib4.quarter i.agecat1 i.gender i.charlson_fin i.lapcat3 if discharge==1 &
(weekcat >=1 & weekcat<=4), e(personyrs) irr
628
629 // lapcat3 4 weeks post-op cumulative post-discharge VTE rates and IRR
630 strate lapcat3, per (1000), if discharge==1 & (weekcat>=1 & weekcat<=4)
631
632 poisson vtenew i.lapcat3 if discharge==1 & (weekcat>=1 & weekcat<=4), e(personyrs) irr
633
634 poisson vtenew i.lapcat3 i.agecat1 i.gender i.charlson_fin i.admit i.can if discharge==1 & (
weekcat>=1 & weekcat<=4), e(personyrs) irr
635
636 // 4 weeks revised sixth keep base elective malignant (sensitivity analysis)
637
638 strate sixth, per (1000), if discharge==1 & (weekcat>=1 & weekcat<=4)
639
640 // 4 weeks revised sixth keep base elective malignant (not used)
641 /*
642 poisson vtenew ib3.sixth if discharge==1 & (weekcat>=1 & weekcat<=4), e(personyrs) irr
643 poisson vtenew ib3.sixth i.agecat1 i.gender i.charlson_fin i.lapcat3 if discharge==1 &
(weekcat>=1 & weekcat<=4), e(personyrs) irr
644 */
645
646 // Base used elective and emergency "benign other"
647 poisson vtenew ib1.sixth if discharge==1 & (weekcat>=1 & weekcat<=4), e(personyrs) irr
648 poisson vtenew ib1.sixth i.agecat1 i.gender i.charlson_fin i.lapcat3 if discharge==1 &
(weekcat>=1 & weekcat<=4), e(personyrs) irr
649
650 poisson vtenew ib4.sixth if discharge==1 & (weekcat>=1 & weekcat<=4), e(personyrs) irr
651 poisson vtenew ib4.sixth i.agecat1 i.gender i.charlson_fin i.lapcat3 if discharge==1 &
(weekcat>=1 & weekcat<=4), e(personyrs) irr
652
653 /*
654 // 4 weeks revised fith keep base elective malignant (not used)
655 strate fith, per (1000), if discharge==1 & (weekcat>=1 & weekcat<=4)
```

```
656
657 poisson vtenew ib2.fith if discharge==1 & (weekcat>=1 & weekcat<=4), e(personyrs) irr
658
659 poisson vtenew ib2.fith i.agecat1 i.gender i.charlson_fin i.lapcat3 if discharge==1 &
(weekcat>=1 & weekcat<=4), e(personyrs) irr
660 */
661
662 // 4 weeks revised elective malignant split lapcat3 (not used)
663 /*
664 strate lapcat3, per (1000), if discharge==1 & (weekcat>=1 & weekcat<=4) & quarter==4
665
666 poisson vtenew i.lapcat3 if discharge==1 & (weekcat>=1 & weekcat<=4) & quarter==4,
e(personyrs) irr
667
668 poisson vtenew i.lapcat3 i.agecat1 i.gender i.charlson_fin if discharge==1 & (weekcat>=1
& weekcat<=4) & quarter==4, e(personyrs) irr
669 */
670
671 // Effect modification test
672
673 poisson vtenew ib4.quarter i.agecat1 i.gender i.charlson_fin i.lapcat3 if discharge==1 &
(weekcat >=1 & weekcat<=4), e(personyrs) irr
674 est store master
675
676 poisson vtenew ib4.quarter##i.agecat1 i.gender i.charlson_fin i.lapcat3 if discharge==1 &
(weekcat >=1 & weekcat<=4), e(personyrs) irr
677 lrtest master
678
679 poisson vtenew ib4.quarter##i.gender i.agecat1 i.charlson_fin i.lapcat3 if discharge==1 &
(weekcat >=1 & weekcat<=4), e(personyrs) irr
680 lrtest master
681
682 poisson vtenew ib4.quarter##i.charlson_fin i.agecat1 i.gender i.lapcat3 if discharge==1 &
(weekcat >=1 & weekcat<=4), e(personyrs) irr
683 lrtest master
684
685 poisson vtenew ib4.quarter##i.lapcat3 i.agecat1 i.gender i.charlson_fin if discharge==1 &
(weekcat >=1 & weekcat<=4), e(personyrs) irr
686 lrtest master
687 drop _est_master
688
689 // Effect modification test revised sixth
690
691 poisson vtenew ib3.sixth i.agecat1 i.gender i.charlson_fin i.lapcat3 if discharge==1 &
(weekcat>=1 & weekcat<=4), e(personyrs) irr
692 est store master
693
694 poisson vtenew ib3.sixth##i.agecat1 i.gender i.charlson_fin i.lapcat3 if discharge==1 &
(weekcat>=1 & weekcat<=4), e(personyrs) irr
695 lrtest master
696
697 poisson vtenew ib3.sixth##i.gender i.agecat1 i.charlson_fin i.lapcat3 if discharge==1 &
(weekcat>=1 & weekcat<=4), e(personyrs) irr
698 lrtest master
699
700 poisson vtenew ib3.sixth##i.charlson_fin i.agecat1 i.gender i.lapcat3 if discharge==1 &
(weekcat>=1 & weekcat<=4), e(personyrs) irr
```

```
lrtest master

poisson vtenew ib3.sixth##i.lapcat3 i.agecat1 i.gender i.charlson_fin if discharge==1 &
(weekcat>=1 & weekcat<=4), e(personyrs) irr
lrtest master
drop _est_master

// Mets test (sensitivity analysis)
tab met if week0==1, mis
tab met admit if week0==1, mis row col chi
tab icd_met if week0==1, mis

// 4 weeks revised mets base non-metastatic
// Overall
strate met, per (1000), if discharge==1 & (weekcat>=1 & weekcat<=4) & can==1

poisson vtenew i.met if discharge==1 & (weekcat>=1 & weekcat<=4) & can==1,
e(personyrs) irr

poisson vtenew i.met i.admit i.agecat1 i.gender i.charlson_fin i.lapcat3 if discharge==1 &
(weekcat>=1 & weekcat<=4) & can==1, e(personyrs) irr

// Elective
strate met, per (1000), if discharge==1 & (weekcat>=1 & weekcat<=4) & quarter==4

poisson vtenew i.met if discharge==1 & (weekcat>=1 & weekcat<=4) & quarter==4,
e(personyrs) irr

poisson vtenew i.met i.admit i.agecat1 i.gender i.charlson_fin i.lapcat3 if discharge==1 &
(weekcat>=1 & weekcat<=4) & quarter==4, e(personyrs) irr

// Emergency
strate met, per (1000), if discharge==1 & (weekcat>=1 & weekcat<=4) & quarter==2

poisson vtenew i.met if discharge==1 & (weekcat>=1 & weekcat<=4) & quarter==2,
e(personyrs) irr

poisson vtenew i.met i.admit i.agecat1 i.gender i.charlson_fin i.lapcat3 if discharge==1 &
(weekcat>=1 & weekcat<=4) & quarter==2, e(personyrs) irr

// Met effect modification (No effect modifcation seen between mets and admit or
lapcat3)
poisson vtenew i.met i.admit i.agecat1 i.gender i.charlson_fin i.lapcat3 if discharge==1 &
(weekcat>=1 & weekcat<=4) & can==1, e(personyrs) irr
est store master

poisson vtenew i.met##i.admit i.agecat1 i.gender i.charlson_fin i.lapcat3 if discharge==1
& (weekcat>=1 & weekcat<=4) & can==1, e(personyrs) irr
lrtest master

poisson vtenew i.met##i.lapcat3 i.admit i.agecat1 i.gender i.charlson_fin if discharge==1
& (weekcat>=1 & weekcat<=4) & can==1, e(personyrs) irr
lrtest master
drop _est_master

// Figure 4.2
strate weekcat, per (1000), if quarter==1 & discharge==1
```

```
747 strate weekcat, per (1000), if quarter==2 & discharge==1
748 strate weekcat, per (1000), if quarter==3 & discharge==1
749 strate weekcat, per (1000), if quarter==4 & discharge==1
750 bysort quarter: sum los_postop if weekcat==0, de
751
752 // Figure 4.3
753 strate weekcat, per (1000), if quarter==4 & lapcat3==0 & discharge==1
754 strate weekcat, per (1000), if quarter==4 & lapcat3==1 & discharge==1
755 bysort lapcat3: sum los_postop if weekcat==0 & quarter==4, de
756
757 // Figure 4.4 (sensitivity analysis, revised Figure 4.2)
758 strate weekcat, per (1000), if sixth==1 & discharge==1
759 strate weekcat, per (1000), if sixth==2 & discharge==1
760 strate weekcat, per (1000), if sixth==3 & discharge==1
761 strate weekcat, per (1000), if sixth==4 & discharge==1
762 strate weekcat, per (1000), if sixth==5 & discharge==1
763 strate weekcat, per (1000), if sixth==6 & discharge==1
764 bysort sixth: sum los_postop if weekcat==0, de
765
766 // Figure 4.5 (sensitivity analysis)
767 gen agecat60=0
768 replace agecat60=1 if age>60
769 replace agecat60=. if age==.
770 label define age60 0 "<=60" 1 ">60"
771 label values agecat60 age60
772 tab agecat60 if week0==1 & discharge==0, mis
773
774 strate weekcat, per (1000), if admit==1 & agecat60==1 & discharge==1
775 strate weekcat, per (1000), if admit==1 & agecat60==0 & discharge==1
776 strate weekcat, per (1000), if admit==0 & agecat60==1 & discharge==1
777 strate weekcat, per (1000), if admit==0 & agecat60==0 & discharge==1
778 bysort agecat60: sum los_postop if weekcat==0 & admit==1, de
779 bysort agecat60: sum los_postop if weekcat==0 & admit==0, de
780
781 // agecat60 4 weeks post-op cumulative post-discharge VTE rates and IRR
782 strate agecat60, per (1000), if discharge==1 & (weekcat>=1 & weekcat<=4)
783
784 poisson vtenew i.agecat60 if discharge==1 & (weekcat>=1 & weekcat<=4), e(personyrs)
irr
785
786 poisson vtenew i.agecat60 i.gender i.charlson_fin i.lapcat3 i.admit i.can if discharge==1 &
(weekcat>=1 & weekcat<=4), e(personyrs) irr
787
788
789 // Figure 4.6 (sensitivity analysis)
790 gen charlson_bin=0
791 replace charlson_bin=1 if charlson_fin>=1
792 replace charlson_bin=. if charlson_fin==.
793 label define ccs2 0 "0" 1 ">=1"
794 label values charlson_bin ccs2
795 tab charlson_fin if week0==1 & discharge==0, mis
796 tab charlson_bin if week0==1 & discharge==0, mis
797
798 strate weekcat, per (1000), if admit==1 & charlson_bin==1 & discharge==1
799 strate weekcat, per (1000), if admit==1 & charlson_bin==0 & discharge==1
800 strate weekcat, per (1000), if admit==0 & charlson_bin==1 & discharge==1
801 strate weekcat, per (1000), if admit==0 & charlson_bin==0 & discharge==1
```

```
bysort charlson_bin: sum los_postop if weekcat==0 & admit==1, de
bysort charlson_bin: sum los_postop if weekcat==0 & admit==0, de

// charlson_bin 4 weeks post-op cumulative post-discharge VTE rates and IRR
strate charlson_bin, per (1000), if discharge==1 & (weekcat>=1 & weekcat<=4)

poisson vtenew i.charlson_bin if discharge==1 & (weekcat>=1 & weekcat<=4),
e(personyrs) irr

poisson vtenew i.charlson_bin i.agecat1 i.gender i.lapcat3 i.admit i.can if discharge==1 &
(weekcat>=1 & weekcat<=4), e(personyrs) irr


// Figure 4.7 (sensitivity analysis)
strate weekcat, per (1000), if admit==1 & discharge==1 & los_postop7==0
strate weekcat, per (1000), if admit==1 & discharge==1 & los_postop7==1
strate weekcat, per (1000), if admit==0 & discharge==1 & los_postop7==0
strate weekcat, per (1000), if admit==0 & discharge==1 & los_postop7==1
bysort los_postop7: sum los_postop if weekcat==0 & admit==1, de
bysort los_postop7: sum los_postop if weekcat==0 & admit==0, de

// los_postop7 4 weeks post-op cumulative post-discharge VTE rates and IRR
strate los_postop7, per (1000), if discharge==1 & (weekcat>=1 & weekcat<=4)

poisson vtenew i.los_postop7 if discharge==1 & (weekcat>=1 & weekcat<=4),
e(personyrs) irr
poisson vtenew i.los_postop7 i.agecat1 i.gender i.charlson_fin i.lapcat3 i.admit i.can if
discharge==1 & (weekcat>=1 & weekcat<=4), e(personyrs) irr
```

## Appendix 14 Chapter 5 Venous Thromboembolism Compliance Stata Do File

Within this thesis, all data analysis in Stata was performed by the author. All data management performed by the author is within the Stata Do file below

```
//// CRC VTE COMPLIANCE ANALYSIS

clear
cd "C:\Users\mzxcl1\OneDrive - The University of Nottingham\mzxcl1\mzxcl1 (UON2Users031)\CRC exVTEp TTO Audit\CRC"
use "crc_exvtep_2"

// Table 5.1
bysort group: sum age if exclude==0, de
ranksum age if exclude==0, by(group)
bysort group: sum los if exclude==0, de
ranksum los if exclude==0, by(group)

tab admit1 group if exclude==0, mis col chi exact row expect
tab readmit1 group if exclude==0, mis col chi exact row expect
tab exvtep1 group if exclude==0, mis col chi exact row expect
tab opnotevte1 group if exclude==0, mis col chi exact row expect
tab evte2 group, mis col chi exact row expect

cs admit2 group if exclude==0, exact
cs readmit2 group if exclude==0
cs exvtep1 group if exclude==0
cs opnotevte2 group if exclude==0
/* negative reverse */
cs evte2 group

// Table 5.2
bysort exvtep1: sum age if exclude==0, de
ranksum age if exclude==0, by(exvtep1)
bysort exvtep1: sum los if exclude==0, de
ranksum los if exclude==0, by(exvtep1)

tab admit1 exvtep1 if exclude==0, mis col chi exact row expect
tab readmit1 exvtep1 if exclude==0, mis col chi exact row expect
tab opnotevte1 exvtep1 if exclude==0, mis col chi exact row expect
tab evte2 exvtep1 if exclude==0, mis col chi exact row expect

cs admit2 exvtep1 if exclude==0, exact
/* negative reverse */
cs readmit2 exvtep1 if exclude==0
cs opnotevte2 exvtep1 if exclude==0
cs evte2 exvtep1 if exclude==0
/* negative reverse */

// Figure 3
```

```
45 tab month2 exvtep1 if exclude==0, mis col chi row expect
46 logistic exvtep1 month2 if exclude==0
47 est store master
48 logistic exvtep1 if exclude==0
49 lrtest master
50 drop _est_master
```

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