# STATISTICAL REANALYSIS OF VASCULAR EVENT OUTCOMES IN PRIMARY AND SECONDARY VASCULAR PREVENTION TRIALS

OPTIMISING THE ANALYSIS OF VASCULAR PREVENTION TRIALS

(OA – PREVENTION)

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# ABSTRACT

Randomised controlled trials in vascular prevention typically use binary events as the primary outcome. However, this practice is statistically inefficient and gives no indication of the severity of the event. Hypothetically, outcomes could be polychotomised, with ordering determined by severity.

The primary aim of this study was to identify the most efficient type of outcome and analysis technique using individual patient data from randomised controlled trials. Another aim was then to review the use of these approaches on other vascular event outcomes; done using data from the TARDIS trial, the first trial to use an ordinal event measure as the primary outcome. An additional consideration was that some trials use a composite outcome as the primary measure. Therefore, a third aim was to determine if severity data can be incorporated here as well and whether to analyse these novel outcomes using standard methods or global analysis techniques, which can analyse multiple outcome measures at once to determine an overall effect.

Chief investigators of vascular prevention trials were asked to share individual participant data. Binary and ordinal extensions of vascular

outcomes were then developed and analysed using methods including binary logistic regression, bootstrapping, Chi-Square, Cochran-Armitage trend test, Cox proportional hazards, Mann-Whitney U, median test, multiple linear regression, ordinal logistic regression, t-test and the Win Ratio test. Regressions were performed adjusted and unadjusted. Global analysis techniques included the Wei-Lachin test (for ordinal/continuous outcomes), the Wald test (for binary outcomes) and the Hotelling's $T^2$ test (for continuous outcomes). Once the appropriate tests has been performed the resulting p-values were ordered within each trial set and given a rank, with the smallest p-value given the top rank. For the primary and global analyses the Freidman and Duncan's multiple range tests were then performed to identify significant differences between statistical methods. In the case of the TARDIS trial analysis, the ranks of the p-values were compared using heat maps.

Data from 35 trials (257,749 patients) were shared, thirteen trials had multiple comparator arms, resulting in 59 datasets. The most commonly shared outcomes were stroke, myocardial infarction (MI) and bleeding. When compared against analysis methods performed on their binary counterparts (event/no-event), the analyses performed on the extended outcomes tended to be more efficient;

e.g. Mann-Whitney U for stroke and MI outcomes (both $p<0.0001$) and multiple regression for bleeding event outcomes ($P<0.0001$).

As for the TARDIS analysis, ordinal versions of vascular event outcomes were created in 3096 participants for stroke, MI, major cardiac events, bleeding events, serious adverse events and venous thromboembolism (VTE), with 32 outcomes being created overall (29 in the subgroup population due to the absence of VTE events). Overall, tests run on the ordinal outcome appeared more efficient for 20/32 (63%) of the analyses in comparison with binary tests. 764 (24.7%) participants were recruited within 24 hours of a mild stroke/TIA; again, tests run on ordinal outcome were superior in 27/29 (93%) of the comparisons.

For the analysis including global analysis techniques, of the 35 trials shared, 24 (158,901 patients) had outcome data for both stroke and MI. From these 24 trials it was possible to develop 35 comparator datasets, as 5 of the trials had multiple intervention arms. With the introduction of further levels based on severity (that is, 4 or 5-level stroke with 3-level MI), the Wei-Lachin test had the smallest average rank and therefore appeared to be more efficient statistically than those that analysed the composite outcomes ($p<0.0001$).

This study found that methods that are used when analysing polychotomised outcomes appear to be more efficient than those used for binary outcomes. This was shown for both the primary analysis and the secondary TARDIS analysis. Based on this, there could be a potential role for using ordinal outcomes in vascular prevention trials. Furthermore, the global analysis suggested that, where there are multiple outcomes of interest, there could also be benefits to basing the primary measure on global techniques, as they appeared to be more efficient statistically.

# DECLARATION

The research reported in this thesis was conducted at the University of Nottingham, Stroke Trials Unit, Mental Health & Clinical Neurosciences, between May 2013 and May 2022. I declare that the work is my own and has not been submitted for a degree at another University.

Lisa Jane Woodhouse

Nottingham

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# LIST OF COLLABORATORS

The following collaborators shared individual patient data from their trial, and commented on draft manuscripts:

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**NB:** Data were shared after submission of formal application or request to the collaborators highlighted in bold.

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**Links for data repositories used by this study**

Boehringer Ingelheim[†] and GlaxoSmithKline data were accessed via: www.clinicalstudydatarequest.com

IST-1: https://trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-12-101

MERCK: http://engagezone.msd.com/ds_documentation.php

NHLBI: https://biolincc.nhlbi.nih.gov/home/

NINDS: https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-Research/Archived-Clinical-Research-Datasets

[†]Trial data from Boehringer Ingelheim is no longer available via www.clinicalstudydatarequest.com.

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADL | Activities of daily living |
| ACT | Anticoagulants |
| AF | Atrial fibrillation |
| AHT | Antihypertensives |
| ANOVA | Analysis of variance |
| APT | Antiplatelets |
| BLR | Binary logistic regression |
| CEA | Carotid endarterectomy |
| CHANCE | Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events trial |
| CI | Chief Investigator |
| CPH | Cox Proportional Hazards |
| CT | Computerised tomography |
| DMC | Data Monitory Committee |
| DVT | Deep Vein Thrombosis |
| ECG | Electrocardiogram |
| EQ-5D | EuroQol – 5 Dimension |
| FAST | Face-Arm-Speech Test |
| GL | Glucose lowering |
| GOS | Glasgow Outcome Scale |
| HDL | High Density Lipoproteins |

| | |
|---|---|
| HRT | Hormone Replacement Therapy |
| IPD | Individual patient data |
| LACI | Lacunar infarct |
| LDL | Low Density Lipoproteins |
| MACE | Major Adverse Cardiovascular Events |
| MI | Myocardial infarction |
| MLR | Multiple linear regression |
| mRS | modified Rankin Scale |
| MWU | Mann-Whitney U test |
| NFS | Non-fatal stroke |
| NHLBI | National Heart, Lung, and Blood Institute |
| NIHSS | National Institute of Health Stroke Scale |
| NINDS | National Institute of Neurological Disorders and Stroke |
| NSTEMI | Non-ST-Segment Elevation Myocardial Infarction |
| OA-Prevention | Optimising the Analysis of vascular Prevention trials |
| OAST | Optimising Analysis of Stroke Trials |
| OLR | Ordinal logistic regression |
| PACI | Partial anterior circulation infarcts |
| PAD | Peripheral arterial disease |
| PE | Pulmonary embolism |

| | |
|---|---|
| POCI | Posterior circulation infarcts |
| POINT | Platelet-Oriented Inhibition in New TIA and minor ischemic stroke trial |
| RVD | Renal vascular disease |
| SAE | Serious adverse event |
| SF-36 | Short-form 36 health survey |
| SR | Sinus rhythm |
| STEMI | ST-Segment Elevation Myocardial Infarction |
| TACI | Total anterior circulation infarcts |
| TARDIS | Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke trial |
| TIA | Transient ischaemic attack |
| VTE | Venous thromboembolism |
| WHO | World Health Organisation |

*For my family,*

*"I may not have gone where I intended to go, but I think I have ended up where I needed to be."*

*Douglas Adams*

# CHAPTER 1

# INTRODUCTION

**List of publications contributing to this chapter**

Philip M W Bath, Aimee Houlton, Lisa Woodhouse, et al. Statistical analysis plan for the 'Efficacy of Nitric Oxide in Stroke' (ENOS) trial. Int J Stroke. 2014 Apr; 9(3):372-4. doi: 10.1111/ijs.12235. Epub 2014 Mar 3.

ENOS Investigators. Baseline characteristics of the 4011 patients recruited into the 'Efficacy of Nitric Oxide in Stroke' (ENOS) trial. Int J Stroke. 2014 Aug; 9(6):711-20.

Philip M W Bath, Lisa Woodhouse, Polly Scutt, et al. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. The Lancet, Volume 385, Issue 9968, 617 – 628. Published: October 21, 2014, DOI: https://doi.org/10.1016/S0140-6736(14)61121-1

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Philip M Bath, Lisa J Woodhouse, Jason P Appleton, et al. Antiplatelet therapy with aspirin, clopidogrel, and dipyridamole versus clopidogrel alone or aspirin and dipyridamole in patients with acute cerebral ischaemia (TARDIS): a randomised, open-label, phase 3 superiority trial. Lancet. 2018 Mar 3; 391(10123):850-859. doi: 10.1016/S0140-6736(17)32849-0. Epub 2017 Dec 20.

Jason P Appleton, Polly Scutt, Mark Dixon, Harriet Howard, Lee Haywood, Diane Havard, Trish Hepburn, Tim England, Nikola Sprigg, Lisa J Woodhouse, Joanna M Wardlaw, Alan A Montgomery, Stuart Pocock, Philip M Bath. Ambulance-delivered transdermal glyceryl trinitrate versus sham for ultra-acute stroke: Rationale, design and protocol for the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2) trial (ISRCTN26986053). Int J Stroke. 2019 Feb; 14(2):191-206. doi: 10.1177/1747493017724627. Epub 2017 Aug 1.

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Lisa J. Woodhouse, Jason P. Appleton, Polly Scutt, Lisa Everton, Gwenllian Wilkinson, Valeria Caso, et al. Effect of continuing versus stopping pre-stroke antihypertensive agents within 12 h on outcome after stroke: A subgroup analysis of the efficacy of nitric oxide in stroke (ENOS) trial. eClinicalMedicine, Volume 44, 2022, 101274, ISSN 2589-5370. https://doi.org/10.1016/j.eclinm.2022.101274.

# 1 Introduction

In recent years, major advances have been made in the primary and secondary prevention of vascular events, with the introduction of effective intervention strategies (based on blood pressure lowering, antithrombotic agents and lifestyle modification). Furthermore, in parallel with this, the absolute risk of the recurrence of vascular events has fallen rapidly over time. As absolute event rates are a key component in calculating sample sizes for binary event outcomes (e.g. stroke / no stroke), which are typically used in vascular prevention trials, lower rates mean larger trials [1]. In addition to this, another pressure on performing vascular prevention trials is that there has been an increase in the numbers of trials being undertaken, due to new therapies being tested. This combination of more and larger trials means that it is becoming increasingly difficult to find enough patients to enrol into new trials. This means new strategies are needed to reduce trial sample sizes and to amplify the potential to demonstrate benefit.

One possible approach would be to analyse vascular prevention trials in a way that does not lose clinically relevant data. As previously stated most vascular prevention trials compare binary event rates between the treatment and control group. However,

certain vascular events, such as stroke or myocardial infarction, can be fatal or non-fatal. This means that trichotomous outcomes (i.e. no event / non-fatal event / fatal event) could be analysed instead. Also, this approach could be further extended to four or even five level outcomes (e.g. in the case of stroke – no event / transient ischaemic attack / mild non-fatal stroke / severe non-fatal stroke / fatal stroke). Analysis of this type of ordered categorical event (or ordinal outcome) is typically more efficient than that of dichotomous outcomes. This opens up the potential for reducing trial sample size whilst also increasing the possibility of finding small clinically relevant benefits. Such structuring of vascular event outcomes assumes that the ordering of events is meaningful; i.e. fatal vascular events are considered more severe than non-fatal events. This means that ordinal outcomes may be more informative to patients and healthcare professionals than binary ones. Therefore, this study will report on comparisons of the relative efficiencies of using and analysing binary and ordinal outcomes from vascular prevention trials.

## 1.1 Vascular Events

The term vascular event covers a broad spectrum of different types of event, including stroke, transient ischaemic attack, myocardial

infarction, angina, bleeding events and venous thromboembolism. The following includes a description of these types of vascular event and the risk factors that are associated with them.

### 1.1.1 Type of event

#### 1.1.1.1 Stroke

According to the World Health Organisation (WHO) a stroke is defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death) with no other cause other than a vascular origin" [2]. When a stroke occurs the supply of blood to an area of the brain can be disrupted, which can cause damage to brain cells. This damage can lead to problems with certain bodily functions. The severity of the damage caused by a stroke can vary dramatically, from recovery in a day to severe disability or death [3].

The word "stroke" can actually be considered as a collective term for various types of brain injury, of which there are two main types:

ischaemic (caused by inadequate blood flow) and haemorrhagic (caused by a bleed). The following describes these two main types of stroke.

Ischaemic stroke

Ischaemic strokes typically account for around 85% of strokes in the UK [4, 5]. This type of stroke tends to occur when an artery, which supplies blood to the brain, becomes blocked and so interrupts the brain's blood supply. The prevention of blood getting to the brain starves the brain tissue, which can lead to cell death. This is known as a cerebral infarction. In all, an ischaemic stroke can be attributed to one of the following four causes;

1. An Embolism: this is where a blood clot, which has formed in a separate part of the body (typically the heart), travels to the brain via the bloodstream. This type accounts for 20% of ischaemic strokes.

2. Thrombosis: this is where a clot has formed either in a main artery leading to the brain or in the brain itself. This accounts for around 50% of all ischaemic strokes.

3. Lacunar stroke: this type of ischaemic stroke occurs when small vessels, which are deep within the brain, have become blocked. Around 25% of ischaemic strokes tend to be of this type.

4. The remaining 5% of ischaemic strokes are accounted for by other causes such as arterial dissection, infective endocarditis and arteritis.

Haemorrhagic stroke

Haemorrhagic strokes are less common than ischaemic strokes, accounting for around 15% of all strokes. This type of stroke is caused when a blood vessel bursts. There are two main types of haemorrhagic stroke, intracerebral haemorrhage and subarachnoid haemorrhage [6]. Intracerebral haemorrhage occurs when a vessel within the brain bursts and blood leaks out into the brain tissue at high pressure causing damage to cells and brain swelling. This type accounts for around two thirds of the overall rate of haemorrhagic strokes. Subarachnoid haemorrhage is caused by a blood vessel near the surface of the brain bursting and blood leaking into the subarachnoid space, which is the area between two of the layers of

membranes that protect the brain from the skull and is filled with cerebrospinal fluid.

Impact of stroke

Each year in the United Kingdom there are around 110, 000 new cases of stroke, which contributes to 11% of the national mortality statistics [7, 8]. Around 300, 000 people are living with the consequences of a stroke, a third of whom require daily assistance with personal care.

Strokes can effect different people in a diverse number of ways; depending on the type of stroke suffered, the area of the brain which is affected and the severity of the stroke. However, there are some common symptoms, such as numbness or weakness of the face, arm and / or leg (typically occurring on one side of the body), confusion, problems with speech, vision problems, dizziness and sudden severe headaches. The Face-Arm-Speech-Time test (FAST) was developed, in the late 1990's, to help quicken the process of identifying people who are suffering from a stroke. This test, as the name implies, involves checking the individual for facial weakness, weakness in the arms and problems with speech. Other, less

common, symptoms of stroke include nausea, fever, vomiting, loss of consciousness, fainting and convulsions [9].

#### 1.1.1.2 Transient Ischaemic Attack

A transient ischaemic attack (TIA) is typically caused by a temporary disruption in the blood supply to part of the brain [10]. Common causes of this type of disruption to the blood supply are atherosclerosis (where blood vessels have become thickened, hard and less elastic due to a build-up of fatty deposits, or plaques, on the inner lining), blood clots and haemorrhages. This disruption results in a lack of oxygen to the brain, which can cause symptoms similar to that of a stroke.

A TIA is another of the initial clinical diagnoses suspected when there has been an acute onset focal neurological deficit with a likely vascular origin [7, 8]. Typically the symptoms of a TIA last for less than 60 minutes, however, the WHO definition permits symptoms to persist up to 24 hours. The lifetime prevalence of TIA is 5 per 1000 population and 17% of TIA patients will suffer a stroke in the following three months. The risk of stroke for some patients is as high as 1 in 3 during the first week after their TIA symptoms [7, 8].

#### 1.1.1.3 Myocardial Infarction

According to NICE guidelines [11], myocardial infarction (MI) is one of the most dramatic presentations of coronary artery disease. It is typically caused by a blockage of a coronary artery, which produces tissue death and consequently the typical features of a heart attack (e.g. severe chest pain). There are two separate types of MI, according to the changes they produce on an electrocardiogram (ECG). These two types include:

1. ST-segment elevation myocardial infarction (STEMI). This is generally caused by a complete and persisting blockage of an artery.

2. Non-ST-segment elevation myocardial infarction (NSTEMI). This type is caused by the partial or intermittent blockage of an artery.

In 2011 / 2012, in England and Wales, more than 79, 000 hospital admissions were caused by MI. Treatments for MI typically include angiotensin-converting enzyme (ACE) inhibitors, dual antiplatelet therapy (usually aspirin plus a second antiplatelet agent), beta blockers and statins.

#### 1.1.1.4 Angina

Angina is chest pain, or constricting discomfort, caused by an insufficient blood supply to the myocardium (the muscular tissues of the heart).[12] It is usually caused by coronary artery disease. However, it can also be caused by valvular disease (such as aortic stenosis, which is a narrowing of the exit of the left ventricle of the heart), hypertrophic obstructive cardiomyopathy (where the muscle walls of the heart thicken, effecting the left ventricle and the septum), or hypertensive heart disease, though these causes are less common. There are two types of angina, namely stable and unstable angina. Stable angina typically occurs predictably with emotional stress or physical exertion, and can be relieved within minutes by resting or through use of medication. Unstable angina is new onset angina, or an abrupt deterioration of previously stable angina, often occurring at rest. This form of angina usually requires immediate admission or referral to hospital.

Treatments for angina include sublingual glyceryl trinitrate, beta-blockers and calcium channel blockers. Angina is also a risk factor for further cardiovascular events. Patients with stable angina may also be prescribed antiplatelet therapy or angiotensin-converting enzyme (ACE) inhibitor treatment for the prevention of secondary cardiovascular events.[12]

#### 1.1.1.5 Bleeding events

Advances in medical treatments (such as antithrombotic therapy) have led to a reduction in the recurrence of ischaemic events and death in patients with acute coronary syndromes (e.g. MI, unstable angina). However, the use of a combination of multiple antithrombotic therapies is also associated with an increased risk of bleeding events. Complications of a haemorrhagic nature typically occur with a frequency of 1 to 10 percent during treatment for acute coronary syndromes. Bleeding is in itself associated with an increased risk of further vascular adverse events [13].

The classification of bleeding events in vascular prevention trials can depend on the type of intervention used and the outcome event, which has led to a lack of strict uniformity in the definitions of bleeding (i.e. minor to major bleeding). Nevertheless, current bleeding definitions tend to be made up of laboratory parameters (such as decreases in haemoglobin and haematocrit scores) and clinical events (including the need for transfusion or surgery).

#### 1.1.1.6 Venous Thromboembolism

Venous thromboembolism (VTE) occurs when thrombus (a blood clot) is formed in a vein, which can dislodge from its site of origin and travel to another site in the body (embolism) [7, 8]. Usually blood clots tend to form in the deep veins of the legs, i.e. deep vein thrombosis (DVT). If dislodged the blood clot can then travel to the lungs, which results in the patient suffering a pulmonary embolism (PE), which can be fatal. Incidence of VTE can range from 10 to 20% in general medical patients to 80% in trauma patients, spinal injury patients and patients in the intensive care unit.

Treatment of VTE typically consists of two different methods: the use of anticoagulants (such as heparin) or having an inferior vena cava filter inserted. Elastic compression stockings can also be used in the prevention of VTE.

### 1.1.2 Risk factors

There are many risk factors which can be associated with vascular events. There are some risk factors, such as age, which cannot be changed. However, there are others that can be treated or altered. These types of risk factors (often called modifiable risk factors),

include hypertension, diabetes, high cholesterol, smoking and alcohol [14].

#### 1.1.2.1 Age

Simply getting older is a risk factor for suffering a vascular event. The risk of stroke doubles every decade after the age of 55 [14]. However, it should be understood that approximately 25% of strokes occur in people aged under 65, 40 to 50% of which will be haemorrhagic [15].

#### 1.1.2.2 Previous vascular event

Suffering from a recent vascular event should also be counted as a risk factor for suffering a further vascular event. For example, having a stroke or a TIA increases the risk of having a recurrent stroke. A population based study discovered that after a TIA or minor stroke the risk of recurrence was around 8 to 12% at seven days, 12 to 15% at one month and at three months it was 17 to 19% [16]. In this study it was also found that the higher rates of

recurrence were seen in those participants who had suffered a more severe vascular event.

#### 1.1.2.3 Hypertension

High blood pressure, or hypertension, is defined by the World Health Organisation as a systolic blood pressure of 140 mmHg or above and / or a diastolic blood pressure of 90 mmHg or above. Systolic blood pressure is the maximum pressure in the arteries when the heart contracts, whereas diastolic blood pressure is the minimum pressure in the arteries between the contractions of the heart.

Worldwide there are about 970 million people who suffer from hypertension [14] and the World Health Organisation rates hypertension as one of the most important risk factors for premature death. Hypertension is also a major risk factor for coronary heart disease and cerebrovascular disease. Approximately 50% of ischaemic strokes are caused by this risk factor and people with hypertension also have a higher probability of suffering a haemorrhagic stroke.

One of the main reasons why hypertension is such an important risk factor for vascular events is that it puts stress on on the body's blood vessels, which leads to them becoming blocked or weakened. Hypertension can cause atherosclerosis and narrowing of the blood vessels. This makes them more susceptible to becoming blocked, either by blood clots or bits of fatty material from the lining of the blood vessel wall. Furthermore, damage to the arteries caused by hypertension can create weak sections that are likely to rupture or thin areas which can cause the wall of the artery to balloon out (an aneurysm).

#### 1.1.2.4 Diabetes

Diabetes is a condition where the concentration of glucose in the blood is too high as the body is not able to use it effectively [17]. This can be due to the fact that the pancreas is not producing any insulin (Type I diabetes). However, it can also occur because not enough insulin has been produced, or because the insulin, which has been produced, does not work properly (Type II diabetes).

In the UK, there are around 3.2 million people who are diagnosed with diabetes and a predicted 630, 000 who have this condition, but are unaware of it. Type II diabetes is a major risk factor for

coronary heart disease and stroke [14]. That is, people with diabetes are twice as likely to develop cardiovascular disease as those who don't suffer from this condition. Diabetes can also increase the risk of ischaemic stroke by two- to four- fold, although the risk of haemorrhagic strokes is similar to that of the general population [7, 8]. Furthermore, following a stroke, people with diabetes are more likely to die or suffer from a severe residual disability. Risk of TIA is also increased in people who suffer from diabetes, between two to six times higher.

A reason why diabetes is such a major risk factor for vascular events is that hypertension, abnormal blood lipids and obesity, which are all risk factors in their own right, occur more frequently in people with this condition. Diabetes, similarly to hypertension, contributes to the formation of atherosclerosis.

#### 1.1.2.5 High levels of cholesterol and / or lipids

Cholesterol is a soft, waxy substance that can be found amongst the lipids (or fats) in the blood stream and within the body's cells [14] . It is important for healthy bodily functions. Cholesterol is transported through our blood by lipoproteins: high-density lipoproteins (HDL) and low-density lipoproteins (LDL).

High levels of LDL cholesterol in the blood stream are associated with higher risk of atherosclerosis, which as described before, increases the probability of suffering a MI or an ischaemic stroke. On the other hand HDL cholesterol reduces the probability of suffering from cardiovascular disease as it carries the cholesterol away from the blood stream.

High levels of lipids in the blood stream are also a risk factor for vascular events. The most common type of fat in the body is triglyceride. High levels of this substance in the blood stream, similarly to high levels of cholesterol, can increase the risk of a cerebrovascular or cardiovascular event. This is due to the fact that high levels of triglyceride in the blood can also lead to atherosclerosis.

In order to reduce the probability of suffering a vascular event caused by high levels of cholesterol and / or lipids, recommended levels of cholesterol and triglycerides have been determined [14, 18-20]. These levels can be seen in Table 1.1.

**Table 1.1 Recommended levels of cholesterol and triglyceride in UK and America**

| | UK guidelines | American guidelines |
|---|---|---|
| Optimal total cholesterol | < 5.0 mmol/l | < 200 mg/dL |
| LDL-cholesterol | < 3.0 mmol/l | ≤ 70 mg/dL |
| HDL-cholesterol | > 1.0 mmol/l for men<br>> 1.2 mmol/l for women | ≥ 60 mg/dL |
| Triglyceride | < 1.7 mmol/l fasting<br>< 2.3 mmol/l non-fasting | < 150 mg/dL |

mmol/l: millimoles per litre, mg/dL: milligrams per decilitre

#### 1.1.2.6 Atrial fibrillation

Atrial fibrillation, or AF, can be classified as an irregular heart rhythm. This condition affects up to 800,000 people, in the UK [15]. Furthermore, the likelihood of suffering from this condition increases with age [21, 22].

People with AF or a history of AF are at much higher risk of suffering the occurrence or recurrence of a vascular event than people without, leading to a fivefold increase in risk. Approximately 12,500 strokes a year can be directly attributed to AF and a quarter of stroke patients admitted to hospital are in AF.

Appropriate treatment of this condition however, could prevent around 4,500 strokes and about 3,000 deaths each year.

#### 1.1.2.7 Smoking

The use of tobacco, whether it is smoking or chewing tobacco, is also a risk factor for certain vascular events [14]: for instance, the risk of stroke for smokers is double that of non-smokers [15]. This risk can be amplified by smoking heavily, being female, or if smoking was started at a young age. Passive smoking can also lead

to an increased risk for suffering a vascular event. However, if tobacco use is stopped, then this risk can reduce significantly, regardless of the length of time it was previously used [14].

There are various reasons for why smoking can cause an increased risk of vascular events. Firstly, cigarette smoke can affect the body's cholesterol levels as it reduces the level of HDL-cholesterol in the bloodstream and increases the level of LDL-cholesterol [23]. Secondly, toxic chemicals (such as carbon monoxide, formaldehyde and hydrogen cyanide), which are inhaled when smoking and transferred by the lungs to the blood stream, can change and damage cells all around the body. For instance, high levels of carbon monoxide in the blood stream can cause damage to the cells in the artery walls and there are other chemicals that can affect the stickiness of the blood and the production of platelets causing an increase in the formation of blood clots. This can lead to an increased risk of atherosclerosis. Lastly, smokers are also more likely to develop hypertension than non-smokers.

#### 1.1.2.8 Alcohol

People who regularly consume a large amount of alcohol are also at a higher risk of vascular events. For example, customarily

consuming large amounts of alcohol can lead to a threefold increase in the risk of stroke [15]. In an article by the Stroke Association, excessive drinking is defined as when more than six to eight units are consumed in any one day [24].

One reason why regularly drinking large amounts of alcohol has such an effect on the risk of vascular events, such as stroke, is that it contributes to diseases which affect the circulation of the blood, such as hypertension and diabetes [24]. For instance, excessive drinking can not only raise blood pressure (causing hypertension) but it can also increase the risk of becoming overweight (due to the fact that alcoholic drinks are high in calories), which increases the risk for type II diabetes. It can also raise the levels of cholesterol and triglycerides in the blood and trigger atrial fibrillation. Furthermore, alcohol can cause a rise in the level of a substance called homocysteine in the blood, which can increase the risk of blood clotting and atherosclerosis [24].

## 1.2 Vascular Prevention Trials

A prevention trial is designed to intervene in a population at risk for a specified disease [25]. They typically compare a proposed intervention with standard healthcare. There are two separate types

of vascular prevention trials. For instance, there are those which investigate the prevention of suffering a first vascular event (primary prevention studies). There are also those which investigate the prevention of a second recurrent event occurring (secondary prevention trials).

### 1.2.1 Primary prevention trials

Primary prevention trials customarily assess whether a new intervention is able to reduce the risk of a disease developing in individuals who are disease free. In this type of trial, an individual who is defined as having a high risk for first occurrence of a specified disease are treated with a drug, device or procedure to prevent the disease from transpiring. For example, in patients with high blood pressure (or high cholesterol), a primary prevention trial using blood pressure lowering drugs (or cholesterol lowering drugs) can assess whether this type of intervention can reduce the incidence of a vascular event, such as a stroke or MI, or death caused by this vascular event. In cases such as this, patients who are entered into the trial might be at higher risk but typically are free of symptoms for the disease and so will not be seeking medical assistance. Therefore, this means that recruitment strategies for this type of trial tend to target otherwise healthy individuals.

### 1.2.2 Secondary prevention trials

Trials in secondary prevention typically evaluate whether a proposed intervention is capable of preventing the recurrence of a disease in a population who have had a defining event. For example, a secondary prevention trial might assess whether a drug, such as a beta blocker, reduces the risk of the second occurrence of a vascular event after surviving the first. In the "Early use of Existing Preventative Strategies for Stroke" (or EXPRESS) study, it was discovered that early treatment after TIA or minor stroke could reduce the risk of early recurrence by 80% [26].

In the prevention of secondary vascular events there are various treatment options available, which depend on the initial cause of the primary event. For instance, if the vascular event was caused by a blood clot (such as an ischaemic stroke) there are medications available that could prevent the formation of further clots and therefore reduce the risk of a recurrence of this event. In stroke, aspirin is the most widely used treatment of this type as it has been known to reduce the risk of further strokes by 13 to 22% [27]. Alternative antiplatelet therapies, e.g. dipyridamole and clopidogrel, work in a similar manner.

Anticoagulants, such as warfarin, are another type of medication which can be used to prevent further blood clots from forming, though this treatment is typically used in patients where the vascular event was caused by a blood clot from the heart. In a systematic review of anticoagulant versus antiplatelet (secondary prevention) trials,[28] participants who were randomised anticoagulants were 33% less likely to suffer a recurrent vascular event. Furthermore, in the "Birmingham Atrial Fibrillation Treatment of the Aged Study" (BAFTA) treatment with warfarin significantly reduced the risk of recurrent events in patients over 75 when compared with aspirin: 1.8% per year in the warfarin group compared to 3.8% per year in the aspirin group (p=0.003) [21].

Carotid endarterectomy (surgery) is another possible treatment method for the prevention of further vascular events. This type of surgery is typically performed on those whose primary event was caused by a partially blocked blood vessel in the neck. In a systematic review of carotid endarterectomy (versus treatment with medication) trials for asymptomatic carotid stenosis,[29] surgery significantly reduced the risk of stroke and death (relative risk 0.69, 95% confidence interval 0.57 to 0.83). Also, in a study of carotid surgery, the "North American Symptomatic Carotid Endarterectomy Trial" (or NASCET), surgery reduced the absolute risk of recurrent stroke by 17% [30].

In comparison to primary prevention trials, secondary prevention trials require a separate recruitment strategy since the participants for these trials are identified through an event.

### 1.2.3 Typical interventions used in vascular prevention trials

There are various different types of intervention that are commonly used in either primary or secondary vascular prevention trials.

#### 1.2.3.1 Antihypertensives

Hypertension (subsection 1.1.2.3) is one of the major modifiable risk factors for stroke and other vascular events [31]. Trials have shown that there are benefits to lowering blood pressure with antihypertensives. These benefits have been well established for primary and secondary prevention of cardiovascular mortality and morbidity [32-34]. There are several classes of antihypertensive medication; such as diuretics, alpha blockers, beta blockers, ACE inhibitors, Angiotensin II receptor antagonists, calcium channel

blockers, alpha-2 receptor agonists, renin inhibitors and vasodilators.

#### 1.2.3.2 Statins (Lipid lowering)

There is strong evidence that reducing serum cholesterol levels in patients with established coronary heart disease reduces recurrence. Furthermore, results of previous studies have shown that statin based therapies can protect patients, with or without a history of coronary heart disease, from suffering an ischaemic stroke in the future [35, 36].

#### 1.2.3.3 Antiplatelets

It is well known that, for patients who have suffered an MI, stroke or TIA, long term treatment with antiplatelet agents (e.g. aspirin, dipyridamole or clopidogrel) reduces the yearly risk of serious vascular events (non-fatal stroke, non-fatal MI or vascular death) by approximately a quarter.[27] Side effects, such as bleeding complications and gastrointestinal problems are associated with this type of therapy, but the benefit of this type of treatment could be

seen as greater in magnitude than the risks [27]. However, in primary prevention, the balance between benefits and risks is less clear as the absolute magnitude of risk reduction is usually lower compared to the results in secondary prevention [37].

#### 1.2.3.4 Anticoagulation

The benefits of oral anticoagulants has been well established in the primary and secondary prevention (and also in the treatment) of a variety of conditions including AF, pulmonary embolism, venous thromboembolism, congestive heart failure, stroke (except for haemorrhagic stroke) and MI. An important note is that Direct Oral Anticoagulants (DOACs), are now more commonly initiated than warfarin for prevention in AF.[38] It should be understood though, that anticoagulation therapy needs to be monitored carefully (haemorrhage management and adjusted dose targeting an international normalised ratio [INR] of 2 – 3). However, if this has been done, this form of treatment has been proven to be safe [39].

#### 1.2.3.5 Surgery

Surgery such as endarterectomy or angioplasty, with or without vascular stenting, is commonly used to treat conditions that involve a narrowing or blockage of arteries or veins throughout the body. Such conditions include carotid artery stenosis [40, 41] coronary artery disease, peripheral arterial disease or renal vascular hypertension.

#### 1.2.3.6 Post-Menopausal hormone replacement therapy

Pre-menopausal women have a lower risk of suffering a stroke than men of the same age. However, after the menopause the incidence of stroke in women increases rapidly. This therefore suggests that hormones play an important role in stroke occurrence [42]. Two meta-analyses of completed trials assessing the effect of post-menopausal hormone replacement therapy have revealed an increased risk of stroke, particularly of the ischaemic type [43, 44]. There is however no evidence of a relationship between hormone replacement therapy and MI.

#### 1.2.3.7 Vitamins

Elevated serum homocysteine levels have been found to be linked to an increased risk of vascular disease. Studies have also shown that daily supplementation with B vitamins can help to reduce homocysteine levels. However, the potential protective effect of B vitamins in patients who have had a stroke or transient ischaemic attack has not been proven [45]. Regarding the effect of antioxidant vitamins, such as vitamin E, vitamin C and beta carotene, randomised trials have largely failed to support an effect on risk of cardiovascular disease [46].

### 1.2.4 Current problems with vascular prevention trials

An issue with primary vascular prevention trials is that the proportion of potentially eligible patients with the comorbidity of interest is likely to be quite low.[25] This means that large numbers of patients will need to be screened for eligibility and willingness to participate in order to get the desired sample size. Secondary prevention trials, similarly to primary prevention trials, often require large sample sizes due to low recurrence rates. However, they are

dissimilar in that there may be quite a large number of eligible participants for secondary prevention trials.

Since the individuals typically recruited to primary prevention trials are, for the moment, disease free, the sample size of the trial must account for the possibility that adherence with prophylaxis is likely to be low. This means that sample sizes need to be quite large in order to account for this potential for non-adherence and for the trial to be sensitive enough to detect the effect of the intervention. Similarly in secondary prevention trials, whilst patients may have been diagnosed with a vascular event, they may still not fully adhere with their randomised intervention. This, in concordance with primary prevention trials, will lead to the need for a large sample size so that the trial is sensitive to the effect of the proposed intervention.

Non-adherence with randomised treatment is a considerable issue if the resulting analysis is undertaken on a per-protocol population. This is due to the fact that data from participants who did not adhere to the trial's treatment protocol are removed. However, it can also cause problems if the analysis is undertaken on an intention to treat population (where all participants are analysed according to their randomisation). That is, non-adherence to

randomised treatment can lead to the treatment effect being diluted out.

## 1.3 Outcomes

An outcome can be classified as "a change in a patient's current and future health status that can be attributed to antecedent care" [47]. It is important to collect outcomes after a vascular event as they can be used to assess an individual patient's progress (or to compare groups of patients). For instance, an outcome can be used, in a clinical trial, to discern if there is a difference between a new treatment and a standard treatment after a set length of time. There are various different types of outcome measure that can be used, such as quality of life (a complex subjective measure) or mortality (an objective measure). The kinds of outcome measures that are more typically used in vascular prevention trials are binary objective measures (e.g. stroke / no stroke) and binary composite measures (e.g. stroke, death or MI / no event). It is these measures that are more often than not used for the primary outcome. However, functional outcome data, used to assess recovery, can also be collected during vascular prevention trials (e.g. from the modified Rankin Scale).

### 1.3.1 Composite outcome

Over the past two decades, improvements in medical care have reduced the frequency with which patients with common conditions such as MI develop subsequent events [48, 49]. This news is welcome for patients, however, lower event rates will present challenges for investigators. These will include the need for larger sample sizes and longer follow up times in order to test new treatments for incremental benefit. This has led to studies using composite outcomes as their primary endpoint.

Composite outcomes typically consist of two or more components [50], for example, death, stroke or MI. A patient who has suffered any one of the events specified by the components is therefore considered to have experienced the composite outcome. The use of a composite outcome as an end point in vascular prevention trials is commonly justified by the belief that the effect of the treatment on each of the components will be similar and that the patients will ascribe similar importance to each separate component of the outcome.

One of the main advantages, which supports the use of composite outcomes, is that it increases statistical efficiency due to the higher event rates. This should in turn reduce the sample size

requirement, costs and time. It can also help investigators to avoid the arbitrary choice between several principal outcomes which represent a similar disease process. Another advantage is that it is a way to assess the efficacy of patient reported outcomes which address more than one aspect of a patient's health status.

Composite outcomes can, unfortunately, be misleading. This statement is particularly true when considering the fact that treatment effects can vary across components with diverse clinical importance. For instance, if a treatment led to a large reduction in stroke or death, this could mean that the drug resulted in fewer strokes and deaths. However, it is also probable that the composite outcome was driven entirely by a decrease in the number of strokes, with there being no change at all (or worse an increase) in the number of deaths. Therefore, it is easy to misinterpret the findings of studies which use composite outcomes as the primary endpoint. This was shown to be true in a review of cardiovascular trials, which used composite end points as an outcome, by Ferreira-Gonzalez [51]. Another issue with composite outcome measures is that they do not reflect the severity of the individual events. For example, death is a more severe outcome than hospitalisation, but a composite outcome of the two events would not reflect this, simply that one of the two events has occurred.

### 1.3.2 Functional outcome

The International Classification of Impairments, Disabilities and Handicaps was published in 1980 by the WHO [52]. It was produced in order to provide a framework against which information that clarified the consequences of disease could be organised [53]. This publication was later updated (in 2001) and was renamed the International Classification of Functioning, Disability and Health [54]. In the 2001 publication, disability was defined as an umbrella term for any impairments, activity limitations and participation restrictions. Impairment was defined as being any abnormality or loss of physiological, psychological or anatomical structure or function (e.g. limb weakness).

#### 1.3.2.1 Frequently used functional outcome scales

Functional outcome scales typically take the form of a number of predetermined levels on an ordinal scale, which normally ranges from the worst possible state to the best possible state. They can either be made up of a set of questions that give a patient a score when answered or each level of the scale can have its own clear definition. In vascular prevention research, functional outcome scales typically measure impairment or disability.

There are various different types of functional outcome scales that can be used to measure disability and impairment. One of these scales, which is typically used in stroke research, is discussed in detail below.

Modified Rankin Scale (mRS)

In 1957, the Rankin Scale was originally developed as a five level scale from research undertaken on the prognosis of stroke [55]. This scale is a simple and fairly crude measure of handicap. The Rankin Scale was then modified in 1991, for use in the UK-TIA study to account for cognitive defects and language disorders [56].

The modified Rankin Scale (mRS) is used regularly in stroke research, which is probably down to its ease of administration and time efficiency. Table 1.2 provides an overview of the modified Rankin Scale scores. Historically, when the analysing the mRS outcome, this scale has typically been dichotomised. This is in order to compare participants with a good outcome with those with a poor one. A review of studies by Sulter [57], which used this outcome measure, discovered that usually a good outcome was defined as a participant either having a mRS score of ≤2 or ≤1. This particular

finding raises some concern, as it has since been found that a valid dichotomy was actually at ≤3 [58]. The mRS outcome measure is typically used to measure handicap, although there are many who believe that the scale actually measures disability [59].

The study by de Haan in 1995 also discovered that the results from the mRS outcome measure were strongly associated with mobility, disability in daily and instrumental activities, and living arrangements. It was also found that there was a low association between the mRS outcome and cognitive and social functioning. The most important explanatory factor of the mRS outcome scores was discovered to be Activities of Daily Living (ADL). Finally, it was concluded by this study that this scale should be used as a measure of physical disability and functional health and not as a measure of handicap.

The reliability of the mRS outcome measure is relatively well documented. In a study by van Swieten [60], which investigated inter rater agreement, it was found that out of a hundred pairs of raters, sixty five of those agreed on the level of disability and functional health. It has also been discovered that giving the rater a structured interview to follow helps to improve the reliability of the mRS score further [61]. However, little is actually known about the validity of the mRS outcome measure [62]. Also, due to the

simplicity of the mRS outcome measure, this outcome can be thought of as having low sensitivity.

**Table 1.2 Modified Rankin Scale**

| mRS score | Description |
|---|---|
| 0 | No symptoms |
| 1 | No significant disability despite symptoms; able to carry out all usual duties and activities |
| 2 | Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance |
| 3 | Moderate disability; requiring some help (e.g. with shopping / managing affairs) but able to walk without assistance |
| 4 | Moderately severe disability; unable to walk without assistance and unable to attend own bodily needs without assistance |
| 5 | Severe disability; bedridden, incontinent and requiring constant nursing care and attention |
| 6 | Dead |

#### 1.3.2.2 Issues with functional outcome scale data

Typically outcome scales are ordinal in nature. The main feature of ordinal data is that it expresses an increasing or decreasing order to the extent of some observable phenomenon. For example, when gauged as primary / secondary / college / undergraduate / postgraduate, education can be considered as an ordered categorical scale. Data from outcome scales such as the mRS, which produce numbered ordered categories, can often be mistaken for continuous data, but the values from these scales are just indicating the order and not actual numeric values. Another feature of data from functional outcome scales is the distribution. For instance, data from the mRS has acute floor and ceiling effects. This is due to the fact that around a third of patients will have recovered completely (giving them a score of 0) and another third will have died (scoring 6). All remaining patients will be spread out across the rest of the scale. This atypical type of distribution means that it is usually not valid to use standard parametric methods of analysis such as comparing means and therefore a non-parametric approach should be used.

## 1.4 Areas using ordinal scales

The hypothesis that the use of a binary / dichotomised scale as an outcome measure is not always suitable has been tested before in other areas of research. Three such areas, where this has been tested before are quality of life outcome measures, traumatic brain injury trials and acute stroke trials.

### 1.4.1 Quality of Life

It is now quite common for trials to include a quality of life assessment as an outcome. This is due to the fact that quality of life is thought of as being more important to the patient. Therefore it will also be a significant factor when investigating the effectiveness of a new treatment / intervention.

Structurally, quality of life outcome scales tend to be ordinal or continuous. Studies that have investigated the analysis of these quality of life scales could thus be very helpful in developing the analysis methods of ordinal vascular outcomes. A commonly used quality of life outcome measure is the Short-Form 36 health survey (SF-36) as a measure for quality of life. The SF-36 consists of 36

questions on eight separate domains of quality of life (e.g. social function), which results in a score of 0 to 100, 100 meaning good health [63]. Another commonly used quality of life scale is the European quality of life-5 dimensions (EQ-5D) [64].

Most of the work undertaken in optimising the analysis of quality of life outcomes has researched comparing the sample sizes needed if diverse analysis methods are applied to data. This style of analysis is equivalent to investigating the power of a test (i.e. the more power a test has the smaller the sample size will be). One study,[65] indicated that analysis methods that depend on the assumptions of normality are probably not appropriate for quality of life data as these methods can lead to under- or over- estimated sample sizes. This suggests that methods that don't make suppositions about the distribution of the data should be used instead. However, it has also been argued that if the scale has multiple categories (at least 7), then methods such as the t-test (a test in which normality is assumed) can be thought of as reliable. If a scale has less than seven categories though ordinal logistic regression should be used [66, 67].

Bootstrapping the mean rank is another method, which has been assessed as a route for analysing quality of life data [68]. In this case however, it has been discovered that this method wasn't more

powerful than other methods. Therefore, given the complexity of the bootstrapping method its use shouldn't be endorsed for the analysis of quality of life data [69].

### 1.4.2 Traumatic Brain Injury

Trials of traumatic brain injury also use an ordinal scale as the primary outcome. That is, they tend to use the Glasgow Outcome Scale (GOS), which is a 5 level scale, where 1 indicates death and 5 indicates fully recovered [70]. One study, which has investigated ways of improving the design and analysis of traumatic brain injury studies, is the "International Mission for Prognosis and Clinical Trial" (IMPACT) study [71]. One of the aims of this study was to investigate the possibility of enhancing the analysis of GOS data. In the past it was very common for trials in traumatic brain injury to dichotomise the outcome scales into unfavourable and favourable groups. This approach has been criticised by the IMPACT study as this means that patients with severe injury don't contribute to the final outcome due to that fact that their improvement will be limited and will almost definitely not cross into the pre-specified range for a favourable outcome [72].

Instead the IMPACT study proposed the use of a patient specific outcome measure (where instead of taking a single definition of a "good" outcome for all patients, the definition is tailored to each individual patient's baseline prognosis on entry to the trial) based on the work of Berge and Barer [73]; this type of outcome has been termed as a "sliding dichotomy". This outcome measure was assessed by comparing it to ordinal logistic regression analysis on data taken from two complete clinical trials. The method of ordinal logistic regression is similar to that of binary logistic regression, but it does not require the data to be dichotomised. However, this method does make the assumption of 'proportional odds'; that is, it assumes that the odds ratio for the treatment covariate is the same for each transition of the scale. Using the mRS outcome measure as an example, this method assumes that the odds of shifting from a mRS score of 5 to 4 are equivalent to that of shifting from a score of 2 to 1.

This work was then further extended by including prognostic factors in the model, such as age, baseline motor score, and baseline computerised tomography (CT) scan to divide patients into tertiles of risk (each risk group was then given its own definition for a favourable outcome). From this analysis it was discovered that the sliding dichotomy analysis was actually more sensitive than the ordinal logistic regression method. Therefore, since this discovery,

this type of analysis has been used in trials of traumatic brain injury [74, 75].

Another area of the IMPACT study, which dealt with the analysis of ordinal outcomes, investigated accounting for certain covariates. In this case, it was discovered that if seven important prognostic factors were adjusted for, then sample size could be reduced by 25% [76].

### 1.4.3 Acute stroke - Optimising the Analysis of Stroke Trials

The international collaboration 'Optimising the Analysis of Stroke Trials' (OAST), was a study that concentrated on optimising the analysis of functional outcomes in acute stroke trials.

The functional outcomes that were studied in OAST included the Barthel Index (BI), the modified Rankin Scale (mRS) and "3 questions" (3Q) [77]. The BI, mRS and 3Q outcomes are all of an ordinal nature. However, prior to the OAST research study these outcomes were traditionally analysed as dichotomous outcome measures. For instance, the mRS is a 7-level outcome measure, where 0 represents individuals who are fully independent and 6

indicates death. This outcome is traditionally analysed as good outcome versus bad outcome, such as independent (0 - 2) versus dead or dependent (3 - 6).

The OAST study sought individual patient data from randomised controlled trials assessing functional outcome after stroke. Information on patient demographics, stroke severity and functional outcome were requested from the chief investigators of each identified eligible trial. Each trial dataset was then analysed using several statistical methods for assessing treatment effect. The results of each method were then ordered within each trial and given a rank, with the lowest rank given to the method which produced the most significant result (that is, the largest z score). A two-way analysis of variance test was then used to see on average which statistical method had produced the lowest ranks. The statistical methods were then ordered in terms of their efficacy in determining treatment effects. The OAST study also assessed how many statistically significant results each method found at the 5% level.

A total of fifty five trials comparing active versus control treatment were included. Thirty eight of these trials shared individual patient data and nine datasets were built from summary data extracted from publications. Six trials had two active treatment groups and

one had three active groups so a further eight comparisons were available. The OAST study concluded that the most efficient statistical methods were ones which involved the full ordinal scale of the data rather than those which collapsed the data into two or more groups. The methods which were found to be most efficient were ordinal logistic regression, t-test, robust rank test and bootstrapping the difference in mean rank.

The OAST study also compared the sample size estimations obtained using the different methods based on dichotomous and ordinal outcomes [78]. Five methods of sample size calculation were compared: comparing ordinal data (Whitehead), comparing means, comparing proportions (in the case of good outcome versus bad outcome), comparing proportions (excellent outcome versus bad outcome) and comparing medians. Each method of sample size calculation was used on each of the trial datasets. The sample sizes calculated using each method were then compared using ranks as described before. It was found that, compared to the traditional method of comparison of proportions based on a good outcome, the ordinal method and the comparison of means methods produced significantly lower sample sizes than the other approaches, reducing sample size by 28% and 30% respectively. The comparison of median method was found to produce significantly larger sample sizes by increasing the size required by 12%.

Finally, the OAST study investigated the effect of adjusting for prognostic factors in ordinal logistic regression models using functional outcomes from stroke trials [79]. For this OAST used individual patient data from twenty three trials. Additional data was simulated using the study data. This was achieved by running 10,000 simulations for each of the twenty three trials and at three levels of imputed treatment effect. Two ordinal logistic regression models with functional outcomes as the dependent variable were compared; the first using treatment only as a covariate, the second containing sex, age, baseline severity of qualifying event and treatment. Sample size was found to decrease by 35 - 38% when the second (adjusted) model was used compared to the first (unadjusted) model. Therefore, it was concluded the adjustment for prognostic factors in acute stroke studies can reduce sample size for a given power or conversely increase power for a given sample size.

As it is clear that there isn’t a consistent method for the analysis of vascular prevention data, it was hypothesised that the work presented in this thesis (titled the OA-Prevention collaboration study), could follow a similar structure as that used in the OAST study.

## 1.5 Previous work in vascular prevention trials

In 2008, a research study was undertaken by Bath et al. [80], using summary vascular prevention data (taken from research papers), to investigate the optimisation of the analysis of vascular prevention trials.

This particular study sought summary patient data from randomised controlled trials assessing primary or secondary prevention, which were either positive or negative according to the trial publication, or were included in a meta-analysis showing benefit or harm. Overall, 101 vascular prevention trials were included (416, 020 subjects), 35 of which were primary prevention trials and 66 were secondary.

The numbers of subjects, at the end of each trial's follow-up, having had a stroke (fatal, non-fatal, severe, mild TIA), MI (fatal, non-fatal), composite vascular event, or bleeding event (major, minor, no bleeding) were obtained, where available, for each treatment group from the primary trial publication. In the cases of factorial trials or trials which had more than two treatment groups, the gathered summary data were analysed for each active component versus control. Data from each trial was assessed, where possible, by intention to treat.

Once collected, each dataset (representing a treatment comparison) was analysed using various statistical analysis methods. These methods included Pearson's Chi-Square test, the Mann-Whitney U test, Bootstrapping (difference in the mean rank), Ordinal logistic regression, Robust ranks test, Cochran-Armitage trend test, t-test, and the Median test. After each data set was analysed using each method the results were then ordered within each trial and given a rank. The lowest rank was given to the test which produced the smallest probability value within that trial. A 2-way analysis of variance test was then performed to assess which statistical test produced the lowest ranks (i.e. the most statistically significant values). The Duncan multiple range test was then used to assess the ordering of the tests and determine where significant differences between tests were present.

The conclusions of this study were that statistical tests which used ordered categorical data were more efficient and were also more likely to yield reliable results than binary tests. For instance, in the case of stroke it found that the results of the statistical tests differed significantly with 3-level data; ordinal analyses ranked above binary approaches with the Mann-Whitney U tests, bootstrapping (difference in mean rank) and ordinal logistic regression being significantly better than other methods. Similar results were also seen for 4-level stroke data.

However, the above analyses did not use individual patient data and so it was not possible to perform adjusted analyses.

The results of this analysis led to the formation of the OA-Prevention collaboration study, the purpose of which was to build upon this work, using individual patient data, to try to confirm its findings.

## 1.6 Aims of this study

This study had a number of primary and secondary objectives, which are discussed in the subsections below.

### 1.6.1 Primary objectives

The primary objective of this study is to improve the statistical analysis of outcome measures that are associated with vascular prevention trials. This can be described by the following aims:

1) To evaluate the possibility of deriving polychotomous vascular event outcomes based on the severity of the event using individual patient level data from randomised controlled trials of patients with or at risk of vascular events

2) To compare and identify the most efficient statistical analysis methods for analysing vascular event outcomes

3) To assess the use of adjusting for covariates as it may be beneficial to adjust for imbalances in baseline characteristics or take into account prognostic variables.

4) To assess how use of an ordinal vascular event outcome measure could impact the sample sizes of vascular prevention trials

### 1.6.2 Secondary Objectives

This study also has a number of secondary objectives, which are outlined below.

1) To discuss the experiences of requesting and accessing individual patient data from completed randomised controlled trials in vascular prevention medicine.

2) Further reviewing the statistical approaches utilised for the primary objective using data from the Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke (TARDIS) trial,[81] which was the first prevention trial to use an ordinal event outcome as the primary. As part of this trial, data on other vascular events and their severity were also collected. It was therefore possible to review statistical methods for these event outcomes.

To consider the case of where the occurrence of more than one type of event are of importance. In situations such as these, trials tend to use a binary composite outcome as the primary. Another secondary aim of this work therefore is to ascertain if it is suitable to include severity information in composite outcomes as well. Furthermore, there are certain statistical techniques that can analyse the individual effects of an intervention on multiple outcomes at once to determine a 'global' effect. It would therefore be of interest to determine if these methods would be more efficient than those that are typically used to analyse composite outcomes.

# CHAPTER 2

# METHODS

# STUDY METHODS

**List of publications associated with this chapter**

Lisa J Woodhouse, Alan A Montgomery, Philip M Bath. Improving the statistical analysis of vascular prevention trials: statistical reanalysis of vascular event outcomes in primary and secondary vascular prevention trials. The optimising the analysis of vascular prevention trials collaboration (OA-Prevention). PROSPERO 2019 CRD42019120064. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019120064

# 2 Methods

## 2.1 Introduction

In this chapter there is a description of the general methods that were undertaken for subsequent chapters. In particular the objectives of this chapter are to discuss in detail: the identification and collection of data from eligible randomised controlled trials; the setting up of the trial database; the development of ordinal vascular event outcome measures; the various types of statistical analysis techniques that were used; and finally the identification process for finding the most efficient analysis method.

In regards to the last point mentioned in the previous paragraph, it should be noted that, for the purposes of this study, the most efficient analysis will be the statistical method that is capable of discerning the largest difference between the comparator arms. In this instance, the ability of a test to discern a difference will be determined using the p-values. It is understood that the use of p-values, rather than quantifying effects to compare the performance of methods and drawing conclusions is a limitation as evidence-based is typically based on a measure of effect and its

corresponding confidence interval. Decision-making is characteristically only partly influenced by p-values. However, their use was necessary for this study as different tests produce different quantifying effects and p-values offer a common currency. In addition to this, the ranking of p-values within comparisons is likely to be very similar to the ranking of standardized effect sizes.

Other methods that are chapter specific will be discussed in the relevant chapter.

## 2.2 Data collection process

### 2.2.1 Identification of eligible data

Eligible studies were identified electronically through search engines including the Cochrane Library and PubMed (to the end of 2016). Further information on the search strategy is given in Table 2.1. Eligible trials were defined as being randomised controlled trials, which included participants with or at risk of vascular events, and had vascular event data post baseline. The trials also had to be either positive or negative according to the trial publication, or

included in a meta-analysis showing benefit or harm. Once a trial was established as being an eligible, the Chief Investigators or appropriate representative (e.g. funding institution, pharmaceutical company) was then contacted with a request to share data from their clinical trial either via an invitation letter (Appendix A) or a formal online application. Further information on the data collection process can be found in Chapter 3. The data requested included demographics / risk factors, clinical details / trial design and outcome / safety measures. Subsection 2.2.2 provides a full description of the data requested from potential collaborators.

**Table 2.1 Search strategy for eligible trials**

| Search terms | Combinations |
|---|---|
| 1. "Prevention" | |
| 2. "Primary prevention" | |
| 3. "Secondary prevention" | |
| 4. "Vascular" | & (1) or (2) or (3) |
| 5. "Cardiovascular" | & (1) or (2) or (3) |
| 6. "Cerebrovascular" | & (1) or (2) or (3) |
| 7. "Stroke" | & (1) or (2) or (3) |
| 8. "TIA" | & (1) or (2) or (3) |
| 9. "Myocardial Infarction" | & (1) or (2) or (3) |
| 10. "Angina" | & (3) & (16) or (19) or (24) |
| 11. "Bleeding" | & (16) or (22) |
| 12. "Venous thromboembolism" | & (1) & (22) |
| 13. "Carotid endarterectomy" | & (1) |
| 14. "Carotid stenting" | & (1) |
| 15. "Carotid stenosis" | & (13) or (14) |
| 16. "Antiplatelets" | & (1) or (2) or (3) & (6) or (7) |
| 17. "Aspirin" | & (6) or (7) or (8) |
| 18. "Clopidogrel" | & (6) or (7) or (8) |

| | | |
|---|---|---|
| 19. | "Statins" | & (1) & (5) or (6) or (7) or (9) |
| 20. | "Lipid lowering" | & (2) & (5) or (6) or (7) or (9) |
| 21. | "Hyperlipidaemia" | & (2) & (5) or (6) or (7) or (9) |
| 22. | "Anticoagulants" | & (1) or (2) or (3) & (5) or (6) or (7) or (9) |
| 23. | "Atrial fibrillation" | & (1) or (2) & (22) |
| 24. | "Antihypertensives" | & (1) or (2) or (3) & (5) or (6) or (7) or (9) |
| 25. | "Hypertension" | & (2) & (5) or (6) or (7) or (9) & (24) |
| 26. | "Glucose lowering" | & (1) & (5) or (6) or (7) or (9) & (27) |
| 27. | "Diabetes" | & (2) & (5) or (6) or (7) or (9) & (26) |
| 28. | "B Vitamins" | & (5) or (6) or (7) |
| 29. | "Hormone replacement therapy" | & (5) or (6) or (7) or (9) |

### 2.2.2 Trial data

Collaborators were asked to share individual patient data from each trial for the following variables (where data items were available):

Demographics / risk factors / clinical details

- Age (years)
- Sex (male, female)
- History of hypertension (yes, no)
- Diabetes mellitus (yes, no)
- Hyperlipidaemia (yes, no)
- Smoking status (yes, no; or current, former, never)
- Previous MI (yes, no)
- Previous Ischaemic Heart Disease (yes, no)
- Previous stroke (yes, no)
- Peripheral arterial disease (yes, no)
- Carotid stenosis (yes, no)
- (un)stable angina (yes, no)
- Atrial fibrillation (yes, no)

Clinical details / trial design

- Index event (none, stroke / type, MI / type, atrial fibrillation, peripheral arterial disease [PAD], renal vascular disease [RVD]).
- Time since index event (if a secondary prevention trial) - for covariate adjustment, baseline blood pressure, cholesterol, glucose, AF / Sinus rhythm (SR), or degree of carotid stenosis (depending on trial's aim).
- Indication for trial (stroke, MI, hypertension, hypercholesterolemia).
- Randomisation group (active treatment, control).
- Randomisation date.
- Start date of intervention.
- Length of follow-up.

Outcome / Safety (All events of type)

- Stroke / TIA: Fatal, severity if non-fatal (severe, moderate, mild; or modified Rankin Scale; or discharge disposition e.g. nursing home, care home, sheltered housing, home with carer, home), TIA. When the event occurred: time to event from randomisation or date of event. Type of event:

haemorrhage, ischaemic (cardioembolic, large artery, small vessel disease, other); LACI, PACI, POCI, TACI.

- MI: Fatal; type if non-fatal (STEMI + heart failure, STEMI, NSTEMI, unstable angina, stable angina). Time to event.
- Adverse events: Fatal; non-fatal-serious; other. Time to event.
- Bleeding: Fatal; major non-fatal; moderate; minor. Time to event.
- Renal failure: Fatal; dialysis; no dialysis. Time to event.
- Venous thromboembolism (VTE): Fatal; non-fatal pulmonary embolism (PE); deep vein thrombosis (DVT). Time to event.
- Revascularisation: Fatal; non-fatal.
- Cognition: MMSE or equivalent.
- Dementia: Fatal; non-fatal.
- Death: (yes, no); cause of death.

These variables allow for both unadjusted and adjusted analyses. The data could be sent in any commonly used format, e.g. Excel, SPSS, or SAS.

### 2.2.3 Collection of data

If the collaborator agreed to share their data, they were provided with a copy of the study's protocol (Appendix B) and a data / material transfer agreement was developed and signed.

The individual patient data received from chief investigators was then converted into a standard format (i.e. standard variable naming, coding, [Appendix C – Data dictionary]) and each database was assigned a unique trial identifier.

## 2.3 Statistical methodology

In this section there is a description of the outcomes and analysis methods that were used in this study. Analyses were carried out in SAS (version 9.3 / 9.4).

### 2.3.1 Formation of outcome measures

Vascular prevention trials typically count outcomes as dichotomous events, even though this is inefficient statistically and gives no

indication as to the severity of recurrent events. It is therefore hypothesised that these vascular event outcomes can be polychotomised with ordering determined by severity. Table 2.2 shows how this might be accomplished for various types of vascular events.

The choice of which outcome scale to use will depend, in part, on its reliability and ease of measurement. Statistically, five to nine levels will be more efficient than having fewer [82]. Clinically however, it will be difficult to differentiate more than nine levels [83]. The underlying assumption in using such ordered categorical outcomes is that treatments will have benefit across the range of event severity. That is, the intervention will reduce the number of severe strokes by making them less severe, and reduce the number of mild strokes by preventing them all together; when present, this delivers the assumption of 'proportionality of odds'.

**Table 2.2 Potential ordinal outcome structures**

| Outcome | Levels | Structure |
|---|---|---|
| Stroke | 3 level | Fatal / non-fatal / no stroke |
| | 4 level | Fatal / severe (dependent) / mild (independent) / no stroke |
| Stroke / TIA | 4 level | Fatal / severe / TIA / no stroke - TIA |
| | 5 level | Fatal / severe / mild / TIA / no stroke - TIA |
| | 5 level | Fatal / severe (mRS 2 - 5) / mild (mRS 0,1) / TIA / no stroke - TIA |
| | 6 level | Fatal / severe (mRS 4,5) / moderate (mRS 2,3) / mild (mRS 0,1) / TIA / no stroke - TIA |
| | 9 level | Fatal / mRS=5 / mRS=4 / mRS=3 / mRS=2 / mRS=1 / mRS=0 / TIA / no stroke - TIA |
| MI | 3 level | Fatal / non-fatal / no event |
| | 4 level | Fatal / non-fatal / angina / no event |
| | 6 level | Fatal / MI + heart failure / STEMI + no heart failure / NSTEMI / unstable angina / none |

| | | |
|---|---|---|
| Vascular | 3 level | Fatal stroke or MI / non-fatal stroke or MI / no event |
| | 4 level | Fatal stroke or MI / non-fatal stroke or MI / TIA or angina / no event |
| Bleeding | 3 level | Fatal / non-fatal major / no bleeding |
| | 4 level | Fatal / major / moderate-mild / no bleeding |
| | 5 level | Fatal / major / moderate / mild / no bleeding |

### 2.3.2 Statistical analysis methods

In this subsection there will be an outline of the individual statistical analysis methods that were chosen to analyse the vascular event outcomes in each of the trials. A range of univariate and multivariate tests were used.

The rationale for choosing these methods in particular was based on a number of considerations. First, it was decided that this study should include methods that have previously been or are currently used for vascular prevention trials. Therefore, when reviewing publications for suitable trials, information was also gathered on the main analysis method used. This lead to the decision to include the Chi-Square test, binary logistic regression and Cox proportional hazards models. Second, it was also decided that this study should include methods that were used in the previous work by Bath et al. [80]. This led to the inclusion of ordinal logistic regression, the Mann-Whitney U test, the Median test, the Cochran-Armitage trend test, the t-test and bootstrapping the difference in mean rank. Third, as this study would be using IPD, it was decided that covariate adjusted versions of the regression analyses would be used for this study as well. Furthermore, for completeness adjusted multiple linear regression would be used as the univariate analyses included the t-test. Lastly, it was thought that it may be of interest

to include a newer method that is not as commonly known, that can be used to analyse vascular event data. This led to the inclusion of the Win Ratio test.

It should be understood that not all of the chosen tests are suitable for the types of outcomes being analysed here (e.g. t-test). However, given the fact that these methods were used in the previous study,[80] it was decided that they should also be included for this work. A description of the methods used and their advantages and disadvantages will therefore be provided in the following sections.

In regards to univariable analysis of the OA-Prevention data, the following statistical approaches for analysing dichotomous, nominal and ordered data were used [84-86].

#### 2.3.2.1 Fisher's Exact / Chi-square test

Both of these tests are comparison of proportions tests for binary data and are common methods. In this study these tests are used under three distinct conditions:

2x2 test: event versus no event

2x2 test: fatal event versus no fatal event

2xN test (unordered data): e.g. fatal versus non-fatal versus no event (3-level outcome), fatal versus severe non-fatal versus minor non-fatal versus no event (4-level)

Due to the differing natures of the trials and event outcomes collected not all of these comparisons could be carried out for all trials. For example, in some trials only limited information is collected on the severity of the event (i.e. whether it was fatal or not), therefore these trials were not included where higher (more than 3) level outcomes were assessed.

#### 2.3.2.2 Cochran-Armitage trend test

This test is similar to the Chi-square test but it takes into account the ordering across categories [87]. For instance, the table below shows a possible summary of data gathered from a trial assessing two treatments using an ordinal event outcome ranging from 0 (no event) to *k* (fatal event).

| Treatment | Event outcome | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | i | k | Total |
| Active (1) | $n_{10}$ | $n_{11}$ | $n_{1i}$ | $n_{1k}$ | $n_{1+}$ |
| Control (0) | $n_{00}$ | $n_{01}$ | $n_{0i}$ | $n_{0k}$ | $n_{0+}$ |
| Total | $n_{+0}$ | $n_{+1}$ | $n_{+i}$ | $n_{+k}$ | $n_{++}$ |

In this case the Cochran-Armitage trend test assesses whether there is a linear trend in binomial proportions across the levels of the ordinal event outcome. The test statistic for this test is given by the following formula, where s denotes the outcome score

$$z^2 = \left(\frac{b^2}{p_{1+}p_{0+}}\right)\sum_i n_{+i}(s_i - \bar{s})^2$$

Where

$p_{1+} = \frac{n_{1+}}{n_{++}}$, $\bar{s} = \frac{\sum_i n_{+i}s_i}{n}$, $b = \frac{\sum_i n+i(p_{1|i}-p_{1+})(s_i-\bar{s})}{\sum_i n_{+i}(s_i-\bar{s})^2}$, $p_{0+} = 1 - p_{1+}$ and $p_{1|i}$ is the observer sample proportion of response 1.

#### 2.3.2.3 Mann-Whitney U (MWU) two-sample test

This test, which is also referred to as the Wilcoxon test, is the nonparametric equivalent of the t-test and tests whether two independent groups have been drawn from the same population. Here the version of the test that allows for adjustment for ties was used, as there will be patients who suffer the same type of event outcome, which are also of a similar severity. [84-86, 88]

#### 2.3.2.4 t-test

This test assesses whether the means of the two independent samples are equal. It is a parametric test which makes the assumption that the samples are normally distributed. This particular tests can be used under two separate conditions; either assuming that the variance is equal (pooled test) or unequal (unpooled test). For this study the unpooled version of the test was used.

#### 2.3.2.5 Bootstrapping the mean rank

This method can be computationally intensive and involves resampling data from a given data set [68, 89]. The main advantage of using the bootstrapping method over others is that it does not make any assumptions about the distribution of the data. For this study, the following steps were undertaken to perform the bootstrap procedure (this was done for each trial comparator dataset):

1. Take a comparator dataset, with N observations and a sample size of A in the control group and B in the treated group

2. Draw a new sample (with replacement) of size N – the use of replacement means that some of the original observations may appear in the new sample more than once and some may not appear at all

3. The first A values are assigned to the control group and the next B values to the treatment group

4. Estimate the parameter of interest and store the result

5. Repeat steps 2 and 3 many times (in this case three sets of 3,000 iterations were used)

6. Compare the distribution of the stored results to the actual point estimate from the original data set

#### 2.3.2.6 Win Ratio test

The Win Ratio test is a relatively new method for analysing composite endpoints, which gives appropriate priority to the more clinically important event (e.g. fatal event) [90]. In this test, patients in the active and control groups are formed into matched pairs based on their risk profiles. For example, consider a composite endpoint of fatal stroke and hospitalisation for non-fatal stroke in stroke trials. For each matched pair, the active treatment patient is labelled a 'winner' or a 'loser' depending on who had a fatal stroke first. If neither had a fatal stroke, then they can only be labelled a 'winner' or 'loser' depending on who was hospitalised for non-fatal stroke first. Otherwise, if neither of the pair suffered either of the events, they are considered tied. The Win ratio is the total number of winners divided by the total numbers of losers. If it is not possible to form matched pairs then alternatively an unmatched pairs version of the method can be used instead.

#### 2.3.2.7 Median test

The median test analyses whether two independent groups have been drawn from a population with the same median. Even though this test is typically considered as a non-parametric test it is basically a Chi-Square test that uses the combined median to determine where the data are collapsed into two groups [84-86, 88].

#### 2.3.2.8 Binary logistic regression (BLR)

Binary logistic regression (BLR) is an analysis method that is used with a dichotomous outcome measures (i.e. Yes / No or No event / Event). This method is used for a wide variety of applications, including vascular prevention trials. BLR has the following format.[91]

For a binary outcome measure *Y* and explanatory variable *X*, let $\pi(x) = P(Y=1|X=x) = 1-P(Y=0|X=x)$. The BLR model is

$$\pi\,(x) = \frac{\exp(\alpha + \beta x)}{1 + \exp(\alpha + \beta x)},$$

Equivalently, the log odds (i.e. *logit*) has the following linear relationship

$$logit\,[\pi(x)] = log\frac{\pi(x)}{1-\pi(x)} = \alpha + \beta x.$$

In this model, the sign of $\beta$ determines whether $\pi(x)$ is increasing or decreasing as $x$ increases.

#### 2.3.2.9 Ordinal logistic regression (OLR)

This method can be used when the outcome is categorical and ordered and is also referred to as the proportional odds model (proportional odds being the main assumption of OLR) and the cumulative logit model. OLR is quite similar to BLR but simultaneously estimates multiple endpoints instead of just one. In this case the number of endpoints that are estimated is equal to the total number of ordered categories minus 1. For instance, in the case of a 5-level stroke outcome (No event / Minor stroke / Moderate stroke / Major Stroke / Fatal stroke) OLR would compare the following categories: No event versus Minor, Moderate, Major, Fatal; No event, Minor versus Moderate, Major, Fatal; No event,

Minor, Moderate versus Major, Fatal; and No event, Minor, Moderate, Major versus Fatal.

OLR only provides one overall estimate for each covariate in the model and not one for each possible end point. This means that the model assumes that the overall odds ratio is constant irrespective of which endpoint is used.[92]

The following shows the format for the OLR model

$$\Pr(Y \leq y_j \mid x) = \frac{\exp(a_j - x'\beta)}{1 + \exp(a_j - x'\beta)},$$

where *j=1, 2, …, k.*

In this model the regression coefficient $\beta$ is not dependent on the level of the response variable (*j*). This suggests that the relationship between *x* and *Y* is actually independent of *j*; this independence is more commonly known as the "proportional odds assumption".

#### 2.3.2.10 Multiple linear regression (MLR)

Multiple linear regression is an extension of simple linear regression and is typically used with continuous data. This form of regression

attempts to model the relationship between two or more explanatory variables and a response variable by fitting a linear equation to the observed data. For instance, the population regression line for p explanatory variables ($x_1$, $x_2$ to $x_p$) is defined as

$$\mu_y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p.$$

This describes how mean response $\mu_y$ changes with the explanatory variables. The values observed for y vary about their means ($\mu_y$) and are expected to have the same standard deviation ($\sigma$). As the observed values for y fluctuate about their means, the multiple regression model also requires a term for this variation, typically referred to as the residual error ($\varepsilon$). The residual error term represents the deviations of the observed values of y from their means, which are normally distributed with a mean of zero and variance $\sigma$. Formally the model for multiple linear regression, for n observations, can be represented by the following formula

$$y_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_p x_{ip} + \varepsilon_i$$

for i=1, 2, 3 …, n.

#### 2.3.2.11 Cox proportional hazards regression (CPH)

Cox proportional-hazards (CPH) is essentially a regression model that is commonly used to investigate the association between the survival time of patients and a predictor variable(s).[93] This model allows researchers to examine how certain factors may influence the rate (typically referred to as the hazard rate) of an event occurring at a particular point in time. The CPH model has the following formula

$$h(t) = h_0(t) \times \exp\left(b_1 x_1 + b_2 x_2 + \cdots + b_p x_p\right)$$

where t represents the survival time, h(t) is the hazard function determined by a set of covariates ($x_1$, $x_2$, …, $x_p$) and $h_0$ is the baseline hazard.

Chi-square and MWU tests will be corrected for continuity, a conservative approach; MWU will also be adjusted for ties. Each data set was analysed using each test and the p-value collected. Certain statistical approaches relating to the analysis of dichotomous and ordinal data (BLR, OLR, MLR and CPH) were performed both with and without adjustment for baseline

covariates. A review of these analysis methods can be found in Table 2.3.

**Table 2.3 Review of statistical analysis methods**

| Analysis method | Statistical assumptions | Advantages | Disadvantages |
|---|---|---|---|
| Binary logistic regression | • No assumptions made about explanatory variables | • Can adjust for covariates | • Large number of observations required |
| Cox proportional hazards | • Proportionality of hazards over time<br>• Censoring of observations is unrelated to prognosis | • Can adjust for covariates | • If assumptions of the model not met then subsequent analyses and risk estimates will possibly be biased |
| Fisher's exact / Chi-Square ($\chi^2$) | • Chi-Square – Overall total count is > 40 or overall total count is between 20 and 40 and the expected value of each exposure – outcome category is greater than 5 (if this isn't satisfied | • Simple to implement<br>• Easy to interpret | • Cannot adjust for covariates<br>• Non informative as does not produce effect estimate only a p-value |

| | | | |
|---|---|---|---|
| | Fisher's exact test should be used) | | • Does not take into account ordering of categories within the outcome |
| Cochran-Armitage trend test | • Similar to the Chi-square test but it takes into account the ordering across categories | • Easy to interpret | • Cannot adjust for covariates |
| Ordinal logistic regression | • Response is ordinal<br>• Proportionality of odds | • Can adjust for covariates | • If assumptions of the model not met then subsequent analyses and odds estimates will possibly be wrong |
| Mann-Whitney U test | • Non-parametric test<br>• Response is ordinal / continuous<br>• Observations from both groups are independent of one another | • Easy to interpret | • Cannot adjust for covariates<br>• Non informative as does not produce effect estimate only a p-value |
| Median test | • Non-parametric test | • Easy to interpret | • Cannot adjust for covariates |

| | | | |
|---|---|---|---|
| | • Considers the position of each observation relative to the overall median. | | • Inefficient (low power) to detect differences if sample size is large. |
| t-test | • Response is continuous<br>• Homogeneity of variances | • Easy to interpret | • Cannot adjust for covariates |
| Multiple linear regression | • Response is continuous<br>• Linear relationship<br>• Homogeneity of variances<br>• No or little multicollinearity | • Can adjust for covariates | • Assumes linear relationship<br>• Sensitive to outliers |
| Win Ratio test | • Response is binary<br>• Accounts for clinical priorities of endpoints | • Prioritizes the more major component of the outcome<br>• Easy to interpret | • New method<br>• Doesn’t use the precise times from randomisation to event occurrence |

| | | | |
|---|---|---|---|
| Bootstrapping the mean rank | • None | • No assumptions made about the distribution of the data | • Cannot adjust for covariates (though is possible if performing bootstrap regression models)<br>• Can be computationally intensive<br>• Doesn’t provide a meaningful point estimate |

### 2.3.3 Global analysis methods

In this subsection there is an outline of the global statistical analysis methods that were used to analyse combinations of vascular event outcomes in the trials that recorded more than one type of vascular event.

#### 2.3.3.1 Wald test

The term Wald test covers a wide array of applications, however in this instance it refers to the methods of Lefkopoulou et al [94], which were generalised from the work of Pocock et al [95]. This test is used to analyse the effect of an intervention on multiple binary outcome measures. It uses generalised estimating equations to take the correlations between the binary outcomes into account, and assuming a common intervention effect, can be used to calculate a Wald test statistic. This approach also has the advantage of providing an odds ratio and 95% confidence interval, which is a result that clinicians are familiar with. When comparing two groups (e.g. intervention vs control), this test gives an odds ratio for a favourable outcome based on each of the binary outcomes (i.e. a global odds ratio).

#### 2.3.3.2 Hotelling's $T^2$ test

Hotelling's $T^2$ is a classic global analysis approach that is typically used to test whether treatment groups differ in any way with respect to multiple continuous outcomes. [96] It is the multivariate analogue of the Student's t-test. However, this test does not take into account the directionality of the effect; that is, it does not test for a favourable treatment. For instance, if treatment was superior to control for outcome A, but control was actually superior to treatment for outcome B, this test could reject the null hypothesis that the two groups had equal efficacy, even though neither group is uniformly better than the other.

#### 2.3.3.3 Wei-Lachin test

The Wei-Lachin test [97] is not a new approach, however, it is not as commonly used for global analysis as perhaps the Wald and Hotelling's $T^2$ tests are. This particular test can be used to analyse multiple outcomes that are either ordinal or continuous. Unlike the Hotelling's $T^2$ test, discussed in section 2.3.3.2, the Wei-Lachin test does take the direction of effect into account. This approach produces an individual Mann-Whitney difference statistic (probability of treatment being superior – probability of control being superior),

with a 95% confidence interval, for each of outcome measures included and an overall estimate. As opposed to an odds ratio, which is centred around 1, the Mann-Whitney difference is centred around 0.

### 2.3.4 Comparison of analysis tests

Each trial comparator dataset was analysed using each statistical approach. The most efficient test was identified as the test which discerned the largest difference between the comparison groups (i.e. the test that produced the smallest p-value). Therefore, The results of the tests for the ordinal outcome and the binary counterpart were then ordered within each dataset and given a rank (e.g. numbers 1 to n), with the smallest rank given to the test that produced the smallest probability value (i.e. 2-sided p-value, with the exception of 2xN Chi-Square) within that dataset.

For both the primary and the global analysis chapters, a 2-way analysis of variance, Friedman's ANOVA, test was then used to see if there was a difference in the efficiency, or capability to discern the largest difference, of each of the tests. If the ANOVA test was significant, the statistical tests were then ordered in terms of their efficiency in identifying treatment effects through the use of

Duncan's multiple range test [98]. As for the TARDIS trial analysis chapter, the ranks of the p-values were compared using heat maps.

The number of statistically significant (at 5%) results each test found were also assessed for the TARDIS and Global analysis chapters.

### 2.3.5 Assessments of validity and reliability

For the primary analysis chapter, to assess the validity and reliability of the results, a number of supplementary analyses were also carried out. One of the first supplementary analyses undertaken was to repeat the comparison of the statistical approaches within subgroups of trials that shared similar characteristics. This was done so that it could be assessed whether certain methods were more efficient for certain types of trials. Another supplementary analysis involved generating sample sizes using the formulas for the ordinal / continuous statistical tests and comparing them to those generated using a formula for a binary proportions test. This was performed in an effort to determine the effect of outcome / method choice on sample size. The statistical assumptions of the more efficient tests were also assessed to

determine if the use of these tests in these circumstances were appropriate.

The sensitivity, or type I error, of the two most efficient statistical tests (i.e. with the smallest mean rank) were also assessed. This was performed using ordinal vascular outcomes from ten randomly selected comparator datasets. For each of those selected datasets a dummy treatment variable with a neutral treatment effect was created so that any treatment difference could only occur by chance. Then, 1000 sample datasets were derived from each of the selected datasets, using random sampling with replacement. Tests that maintained an acceptable proportion of type I errors should only expect to show a significant result in around fifty of the 1000 sample data sets.

# CHAPTER 3

# RESULTS

# DATA SHARING

**List of publications associated with this chapter**

Polly Scutt*, Lisa Woodhouse*, Alan Montgomery, Philip Bath. Data sharing: highs and lows of accessing individual patient data from completed trials for optimising the analysis of trials. UK Stroke Forum 2016 – Poster.

Scutt P*, Woodhouse LJ*, Montgomery AA, et al. Data sharing: experience of accessing individual patient data from completed randomised controlled trials in vascular and cognitive medicine. *BMJ Open* 2020; 10:e038765. doi: 10.1136/bmjopen-2020-038765.

*equal first author

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The research conducted for the main publication associated with this chapter was done in collaboration with Polly Scutt, who led the Optimising the Analysis of Cognition trials (OA-Cog) study.
However, the research detailed below describes the experiences of the OA-Prevention study only.

# 3 Data Sharing

## 3.1 Background

It is the purpose of clinical research to not only improve the treatment and outcomes of patients, but to also do this ethically and efficiently with the smallest possible sample of patients subjected to experimental therapies in trials. The sharing of individual patient data (IPD) from completed trials can allow multiple questions to be answered, which prevents the unnecessary exposure of further patients. In fact, there is now increasing expectation that researchers should share IPD from their completed trials when requested. Funding institutions for clinical trials, such as the UK Medical Research Council and the US National Institutes of Health [99, 100] require that researchers consent to sharing their IPD before funding is granted. Furthermore, the International Committee of Medical Journal Editors [101] now requires the researcher to indicate their intention to share IPD, in order for the main trial paper to be published. This is promoted by journals such as the British Medical Journal and the Public Library of Science (PLoS) journals.[102, 103] Regarding commercially funded trials, there are some sponsors that openly share IPD.[104-106]

Nonetheless, even with the existence of these policies, investigators requiring IPD still face challenges in accessing it.[107] A survey of academics, who were corresponding authors of published clinical trials, suggested that 88% were in favour of data sharing, with 75% also indicating that it should be mandatory.[108] However, this survey also discovered that only 18% of these academics were actually required to share data by the trial funder, and of these, only 57% had shared their data.[108]

In this chapter, there will be a discussion of the experience of obtaining trial IPD for the OA-Prevention study. Prior to commencing the data sharing phase the study protocol was finalised and a research ethics committee waiver was obtained.

## 3.2 Methods

### 3.2.1 Eligibility criteria and researcher contact

Trials were eligible for inclusion in the OA-Prevention study if the primary analysis was statistically significant with a p-value < 0.05,

showing either benefit or harm, or were included in a systematic review showing statistically significant benefit or harm overall. Trials were excluded if they were not randomised, were neutral ($p \geq 0.05$) within a neutral review, did not collect outcome data required in the studies (e.g. the severity of the vascular event outcome), or met at least two of the following conditions: < 50 participants; published before 1995; full publication of the primary analysis was unavailable.

Once a trial was deemed eligible the lead researcher or corresponding author was contacted by email, letter or via an online application form. If an email address was not provided in the trial publication or the email address was no longer active, attempts were then made to identify current contact information. Methods included internet searches for more recent publications by the same author, or for other authors from the primary publication, or by contacting the researcher's institution as listed in the publication. If no response was received within four weeks, a reminder email was sent to the same email address. Reminders were sent up to four times with a minimum of four weeks between each reminder.

The researchers contacted were requested to share data on patient demographics (e.g. age, sex); medical history (e.g. history of hypertension etc.); baseline clinical data (e.g. stroke type, blood

pressure, functional status); outcome measures (e.g. vascular events and event dates); and trial characteristics (e.g. randomisation group, length of follow-up). Once received, the individual patient data were combined into one master database with each trial given a unique identifier.

### 3.2.2 Data sharing mechanisms

There are multiple methods that exist for sharing data. The IPD could be published within the main paper (only relevant for trials with a small sample size), published directly on the web with full open access, sent by the lead researcher directly as a data file either via USB / CD or by email (usually with encryption to protect confidentiality), accessed through an academic collaboration data repository, or accessed via a website hosting both the trial data and statistical packages so that analyses have to be performed on the remote server.

### 3.2.3 Outcomes

The main aim for this research was to describe the process of obtaining IPD from trials fulfilling the criteria of the OA-Prevention study. Secondary outcomes included type of response (positive or negative) and rates of non-response. The following trial characteristics were compared between those that did or did not make IPD available: year of publication, sample size and sponsor type. Reasons for not sharing IPD, where given, were also collected and reviewed. Data regarding time from initial contact date to receipt of trial data, were also collected and analysed. Data are tabulated and shown as number and percent or median with 25th and 75th centiles.

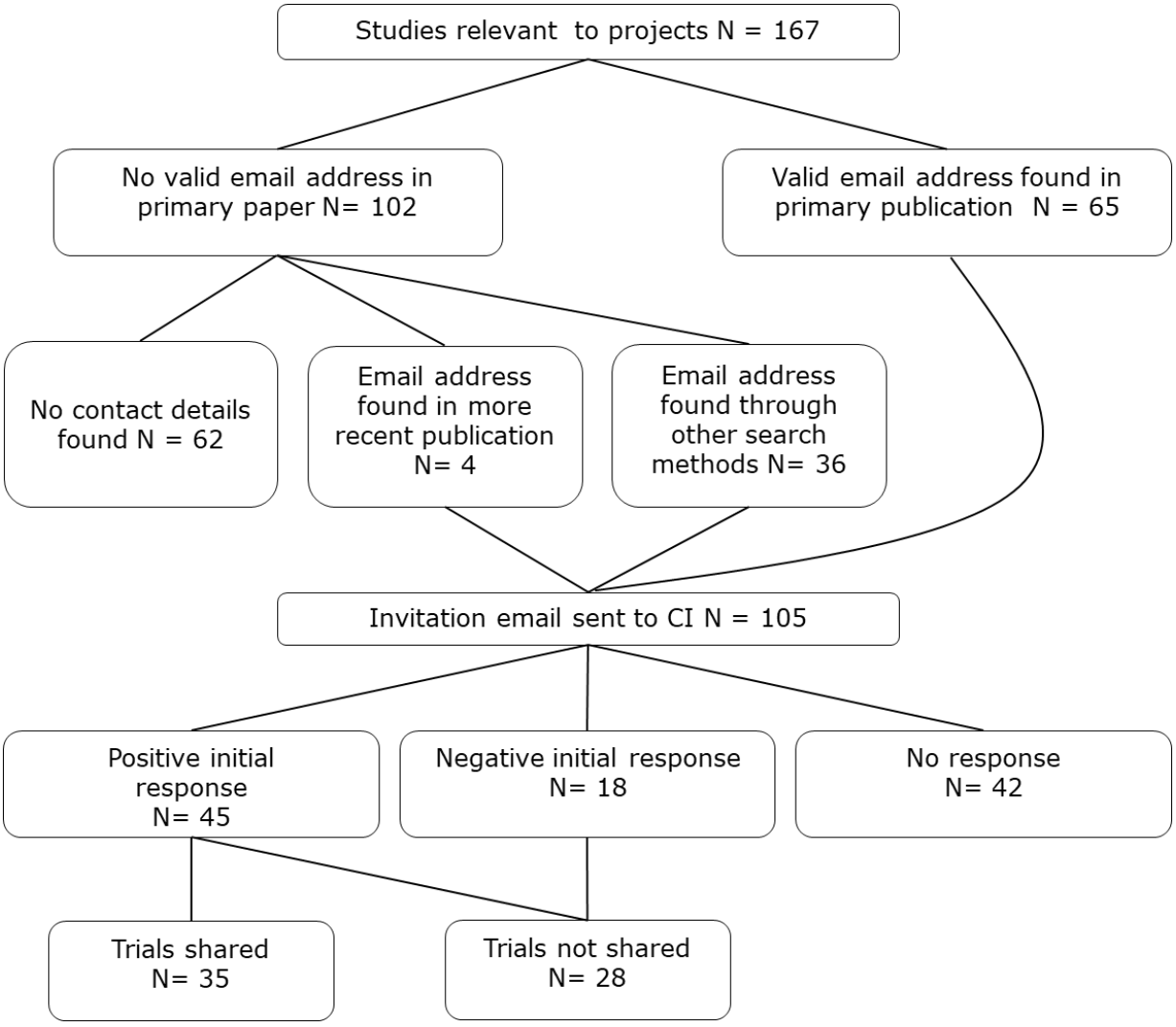
## 3.3 Results

### 3.3.1 Identified trials

Of 167 trials identified as being relevant to the OA-Prevention study, an active email address for the lead researcher or a corresponding author was provided in the primary publication for 65

(39%, Figure 3.1) and was either not given or inactive for 102 trials. Of the 102 trials, different active email addresses were identified for 40 from secondary publications, other authors, the lead researcher's institution, or web searches. No email address was found for researchers of 62 trials. Invitation emails were sent to the lead researcher of the resulting 105 trials.

**Figure 3.1 Flow diagram for contacting authors and receiving data**



### 3.3.2 Obtaining data

Of 105 invitations sent, a positive initial response was received from 45 researchers (43%), from whom 35 usable trial datasets were eventually obtained. Data was actually obtained from a repository for a 36$^{th}$ trial, however, when reviewed was found to be missing treatment information. The repository was contacted regarding this, but unfortunately this data was not available and therefore this trial had to be excluded from this study. In spite of further reminders, the remaining 9 researchers did not follow through on their initial willingness to share data. Another 42 (40%) researchers did not respond despite evidence that the email address was still in use and multiple reminders being sent. Finally, 18 (17%) researchers directly declined to share their data; reasons for declining included "non-availability of data" and non-availability of the researcher (death, retirement, moved into another scientific field). A full list of reasons given for not sharing usable IPD can be seen in Table 3.1.

**Table 3.1 Reasons given for not sharing IPD**

| **Reasons** | **N=28** |
|---|---|
| Lack of communication after initial positive response | 9 |
| Data not available | 5 |
| Unsure whether to share data | 5 |
| Lead researcher retired / left field of study | 2 |
| Contract issues | 2 |
| Lead researcher unable to take project on / too busy to collaborate | 2 |
| Lack of enthusiasm for our pooling projects | 1 |
| Policy not to release IPD | 1 |
| Missing treatment information | 1 |

### 3.3.3 Timings

The median time from sending the first email to successfully receiving data in this study was 242 [25th, 75th centile: 21.5, 405] days. This varied between the different methods for sharing data and data source (commercial website / lead researcher / academic repository; Figures 3.2 and 3.3). Time from initial contact to receiving a copy of data was shorter if sent via email or USB (median 86, 25th, 75th centile 20 - 405 days), but was longer if shared via an online platform (median 336, 25th, 75th centile 315 - 357 days) (Figure 3.2). If the data source was a commercial website the median time from first request to data being shared was 336 [25th, 75th centile: 273, 336] days, for lead researcher it took 169 [25th, 75th centile: 6.5, 495.75] days and for academic repository 23 [25th, 75th centile: 20, 221.5] days (Figure 3.3).

**Figure 3.2 Boxplot showing the time, in days, from first data request sent to receiving the data, by method of sharing**

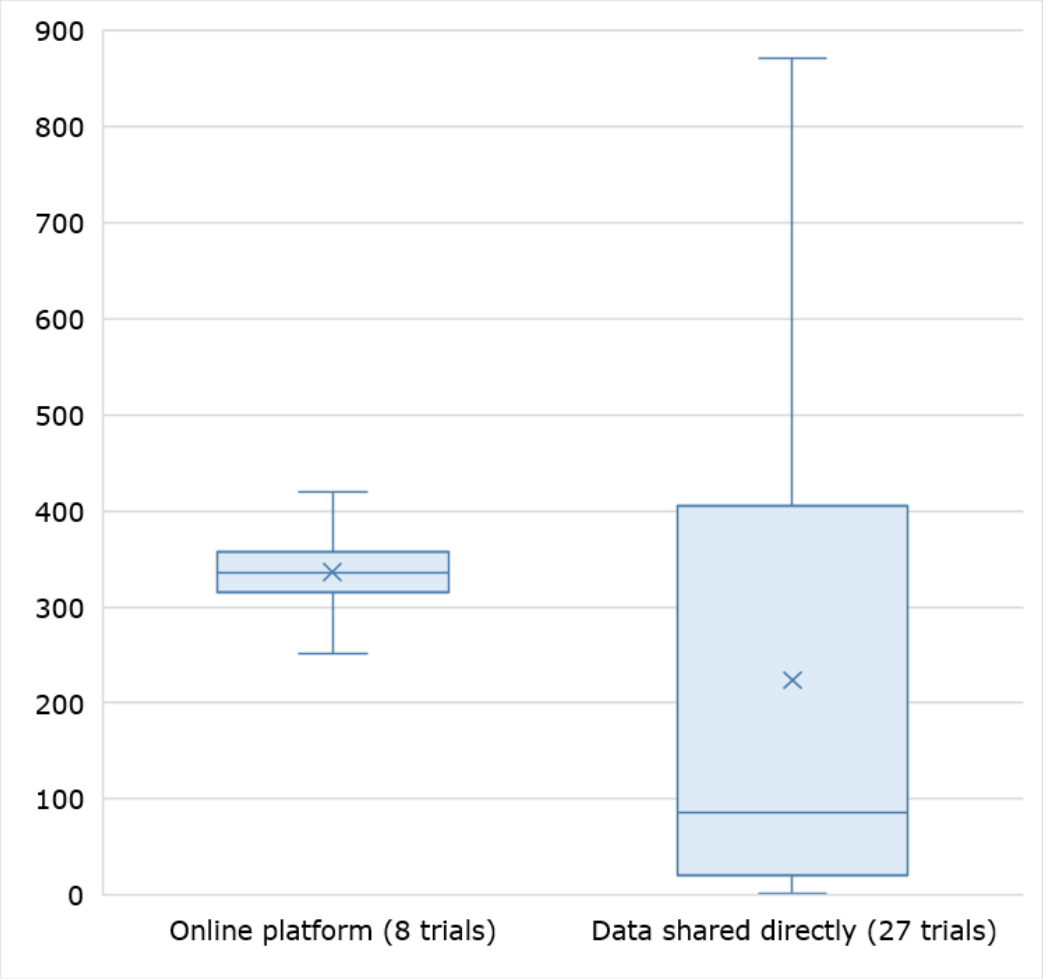
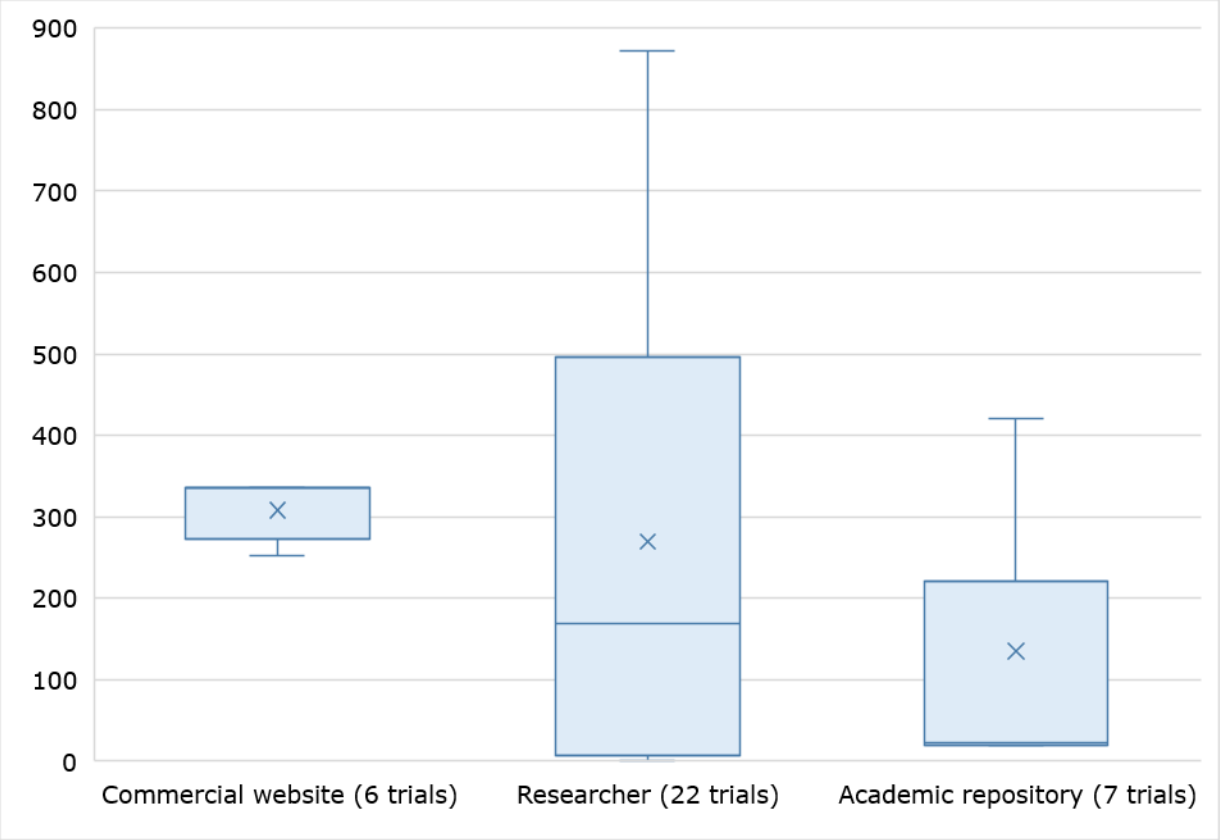


**Figure 3.3 Boxplot showing the time, in days, from first data request sent to receiving the data, by source**



### 3.3.4 Methods of data sharing

The various methods used for sharing data will be discussed in this section and the advantages and disadvantages associated with them are given in Table 3.2. In some cases, data are shared directly with, and analysed by, the researcher. A number of pharmaceutical companies have committed to sharing their data via hosted servers: e.g. Clinical Study Data Request data repository.[109] In contrast to other sharing methodologies, analyses for these trials are performed on a host server using specified software (e.g. SAS).

#### 3.3.4.1 Dataset published online

Data from completed trials may be published online so they can be accessed free of charge, with no application to the data holder required. Data from the IST trial have been published in this way along with a data dictionary which describes the dataset, including variable names and codes.[110] The trial dataset was downloaded directly from the supplementary material of the publication and was immediately ready to analyse.

#### 3.3.4.2 Dataset provided by the lead researcher on request

Researchers may store data at their institution and oversee the data sharing process each time there is a request. Typically, this required an email to the lead researcher, including details about the study. If agreed, transfer of data was made under a data sharing agreement with signature by both the data holder and user. The researcher then provided the data in an analysable format such as an Excel spreadsheet or SPSS data file. In most cases, a description of the dataset was provided along with the data. Researchers were usually willing and able to provide answers to follow-up queries.

#### 3.3.4.3 Academic collaboration repository

A number of academic collaborations exist to facilitate data sharing of randomised controlled trials in a particular disease area. The collaboration is approached via email and an on-line application form; the form requests details of the study's hypothesis, analysis methods, which trials are required, and contact details of those wishing to have access to the data. The application is reviewed by the collaboration's steering committee and, following approval, the

data are provided in an analysable format. Examples include the NINDS [111] and NHLBI [112].

#### 3.3.4.4 Commercial website

A number of pharmaceutical companies share their data via externally hosted servers: Clinical Study Data Request data repository (www.clinicalstudydatarequest.com). [109] Examples include the PRoFESS and JASAP trials. Access is requested via an on-line application form, this requiring information on the study's overview, rationale, aims and analysis methods, plans for dissemination of results, and names of those wishing to access data. Once approved, a three-way contract between the commercial site, the company who own the data, and the institution wishing to obtain the data is required. The process of negotiating the contract took several months, after which access to the remote analysis platform was granted. Some time was needed to set up access to the system and for the data user to become familiar with it. Statistical analysis code (written using SAS 9.3 / 9.4) was uploaded and run on the remote server. Download of results (typically point estimates, confidence intervals and significance values) had to be approved by the data-owning company (presumably to prevent a direct export of the IPD). Approval could take a few hours to a few

days, after which the results could be exported. During the course of this study, two of the pharmaceutical companies that had agreed to share data via this method decided to withdraw all data from the repository, causing issues with data access and required revision of the original contracts.

**Table 3.2 Advantages and disadvantages of methods for sharing IPD**

| Method of data sharing | Example(s) | Advantages | Disadvantages | Trials shared |
|---|---|---|---|---|
| IPD published on web | IST aspirin / heparin [110] | Free. Quick and easy to access. No application required. No effort required by data owner once data are published. | No formal support by lead researcher. | 1 |
| Lead researcher holds IPD, and provides on request | EAFT [113] | Free. Minimal resources required once dataset has been prepared for sharing. Lead researcher has complete control over who the data is shared with. | Requires active participation by lead researcher, i.e. need time to share data and approve each request. Assumes lead researcher can still be contacted. Quality of data and accompanying materials shared are variable. | 21 |

| | | | | |
|---|---|---|---|---|
| Academic collaboration data repository | National Institute of Neurological Disorders and Stroke (NINDS) [111], National Heart, Lung, and Blood Institute (NHLBI) [112] | Short application process. Responses to requests are usually quick. Application process allows more control over who has access to data. Once data has been prepared, minimal further input is required from the data owner. | NINDS, NHLBI require evidence of Research Ethics Committee approval or waiver. IPD may not be complete. | 7 |
| Commercial website | Clinical study data request.com.[109] Merck. [114] | Apply for data from multiple companies. Pharmaceutical companies can share data from their clinical trials via | Long application process and waiting time for response. Data analysed within the repository, requiring upload of analysis code. Often platform only allows access to one statistical software | 6 |

| | | |
|---|---|---|
| | an independently monitored online system. | package making the data inaccessible to researchers without the necessary skills. Companies choose what data to share. Complicated, technically-challenging, and time-consuming process. Assumes that remote analyses will give the same results as those obtained locally. |

### 3.3.5 Characteristics of trials received versus not received

In a comparison between positive, negative and non-responders, there was evidence of a difference in year of study publication (p=0.044). Non-responses tended to be from newer studies (median [25th, 75th centile]: 2005 [2002, 2009]), compared to positive (2002 [1997, 2007]) and negative responses (2003 [2000, 2005]). However, there was no evidence to suggest an association between year of study publication and whether IPD were eventually shared (data shared median year 2001 [1996, 2007] vs data not shared 2004 [2001, 2008], p=0.085). Median [25th, 75th centile] sample size for trials where data were shared (4396 [1316, 10251]) was similar to those not shared (3103 [1100, 9711], p=0.45). There was also no strong evidence that study size was associated with positive (4159 [1309, 9014]), negative 5465 [2757, 18624]) or no response 3025.5 [1095, 9193], p=0.19) from study authors.

### 3.3.6 Quality of the data shared

The quality of the data shared was mixed. On more than one occasion datasets were sent missing key variables that had been

requested in the original application. This meant that further contact with the lead researcher was required to confirm why this data was missing and whether it was available for sharing, which was a time consuming issue. Occasionally data were also sent with the variable headings and codes written in another language, without a data dictionary. This made it harder to identify the variables needed for the studies and increased the time it took to merge with the other IPD. Another approach used was to share all the trial's data in its raw format. If shared with a well written data dictionary this was not a problem, however, this was not always the case. One message discerned from this process is that even though inclusion of a well written and linked data dictionary is key in data sharing, this is variably done in practice.

## 3.4 Discussion

Despite difficulties in accessing data, there were researchers who were enthusiastic and forthcoming with support for this study and with sharing their data for 35 trials. There are now several different mechanisms for data sharing available to researchers, a number of which were used to share data with this study. Unfortunately, there was also a high non-response rate, with 40% of lead researchers not responding despite multiple attempts to make contact.

The difficulties experienced as part of this study have also been encountered by others conducting research that required individual patient data from completed trials to be shared. One project,[107] reported that of thirty eligible trials, six had no contact information for the lead researcher. Of the remaining 24 trials, the lead researchers for 18 (75%) failed to respond, and 5 (21%) chose not to share their data. It could be inferred from this that data sharing may not be a high priority for many researchers.

However, there is now the expectation that researchers should be able to make a copy of their trial data available when requested. For instance, some journals, such as the British Medical Journal,[102] now have a requirement that researchers make their trial data available for sharing in order for their research to be published. Furthermore, there are others that also require that the researchers include a data availability statement in the final publication (PLoS [103]). Funding bodies, such as the US National Institutes of Health and UK Medical Research Council [99, 100] also now require that researchers agree to share their data within a certain timeframe of completion of the trial. However, they do not encourage researchers of older trials to share their data.

Even though it is expected that researchers should be able to share data when requested, it should also be understood that there are still some barriers that may prevent researchers from actually being able to do this. For instance, the preparation of data for sharing, which ideally means creating an anonymised analysis ready dataset and accompanying data dictionary, will require a lot of time and effort to be put in by the trial team once the trial has finished. However, not all funders provide support or funding for this process, which can lead to a cost for the trial team. Furthermore, sponsors often do not provide administrative or contractual support for sharing, and may be reluctant to do so if there are intellectual property implications. This means that even though researchers may actually want to share their data with other investigators, they are not able to without substantial cost (in money and time) to themselves.

One of the main barriers to accessing IPD from trials for this study was non-response from lead researchers. That journals now require a contact email address with every publication may help, however, it does not fully solve the problem, as this study has found. While there is a general consensus that IPD from trials should be made available for sharing, in reality, requests that are sent for data sharing can be either missed or ignored. It is also very important that researchers should be able to access older data. Even if the

lead researcher for a trial moves on, it should then become the responsibility of the institution to continue support for potential data sharing. Ideally, it could be made mandatory that the data holder's contact details are made available in the primary publication and perhaps in the trial's registry information as well. A common reason for not sharing IPD is lack of resources for preparing the data, as seen in a survey of trialists.[108] However, there are some methods for sharing data that do not require too much input from the data owner once the initial effort of preparing the data is done. For instance, the data owner can make use of commercial websites and academic trial repositories. Storing a trial's IPD within a repository can also take the responsibility of having to approve requests for sharing away from the lead researcher. This, however, can be an expensive approach and may not be suitable for all trialists. It is important that resources should be made available to researchers to ensure that data can be archived properly and data sharing can take place once a trial is completed. In order to assist trialists with this, it would be advantageous if a universal set of standards for preparation, storage and sharing of data could be established and also promoted by institutions that mandate the sharing of IPD after publication. One other concern that researchers could have is that the data from their trial may not be used in and appropriate manner. Therefore when submitting a request a researcher should make sure to provide full details regarding why the trial IPD are

requested; how the data will actually be used and stored; how the results of the analysis will eventually be published and whether the trialists will be included as co-authors; and lastly how and when the data will be destroyed once the research is complete. Formal data / material sharing agreements or contracts should also be used for data security purposes. Another consideration is that the patients who take part in the trials may also have concerns about how their data will be used in the future. It is therefore essential that during the consent process patients are made aware about whether their data could be shared with other researchers once the trial is complete and in what context. Guidance on data sharing and informed patient consent for trialists has been published by the MRC.[115]

One of the strengths of this research is that The OA-Prevention Study identified a large number of eligible trials across its specified disease area, resulting in a large number of researchers being contacted. Additionally, the trials which were requested had both academic and commercial sponsors, no restriction on country of origin and covered a reasonably wide timeframe (1985 to 2017). Therefore the results of this study are likely to reflect a common experience in data sharing in vascular research. Limitations of this study's approaches include the use of email or letter only when contacting authors, due to the availability of resources. Contact

methods such as telephone or face to face were not used for this study and could have potentially led to a different outcome for some trials. Furthermore, it was not possible to survey researchers who were non-responders to requests, so any potential reasons for not sharing data should be considered as speculation. This is unfortunate, as it means that the true barriers to data sharing are not, at this moment in time, fully known.

## 3.5 Conclusions

To summarise, there still are many barriers that need to be surmounted in order to enable further collaboration and sharing between researchers. These barriers include: non-response to requests by researchers; the reluctance of some researchers to share data; and also the lack of available resources for researchers for data sharing (as not all funders or sponsors support this). This makes pooling data for meta-analyses and studies such as this one challenging to undertake. Based on this experience, the sharing of IPD appears to can, on occasion, depend on the enthusiasm of the lead researcher, despite it being generally agreed that accessing IPD should be easier. This is a worrying issue, as it means that the trial results cannot be verified by an independent researcher. Even more worrying is the fact that it also means that more patients

could be subjected to experimental treatments when there is data that is already available. Given that patients have taken a risk by volunteering to participate in research, it is therefore the responsibility of researchers to gain as much knowledge as possible from the data that has been provided. Therefore, if the patient has consented to their data being used for further study, then the researcher, sponsor and funder have a responsibility to ensure this is done. Given that some sponsors and funders already provide resources to assist with data sharing, which has led to improvements in this process, it seems justifiable to recommend that other sponsors and funders, who currently do not offer these services, consider providing the same type of support for their funded studies. Nonetheless, whether the current expectations of certain journals and funders for researchers and authors to share their IPD will improve the current situation remains to be established.

# CHAPTER 4

# RESULTS

# OA-PREVENTION STUDY

**List of publications associated with this chapter**

Lisa J Woodhouse, Alan Montgomery, Philip M W Bath; for the OA-Prevention collaborators. The optimising the analysis of vascular prevention trials project (OA-PREVENTION). European Stroke Organisation Conference (ESOC Glasgow) 2015 – Poster (ongoing).

Lisa J Woodhouse, Alan Montgomery, Philip M W Bath; for the OA-Prevention collaborators. Can we improve the statistical analysis of vascular prevention trials?: results from the Optimising the analysis of vascular Prevention trials (OA-PREVENTION) collaboration. European Stroke Organisation Conference (ESOC Gothenburg) 2018 – Poster.

Lisa J Woodhouse, Alan Montgomery, Philip M W Bath; for the OA-Prevention collaborators. Can we improve the statistical analysis of vascular prevention trials?: results from the Optimising the analysis of vascular Prevention trials (OA-PREVENTION) collaboration. UK Stroke Forum 2018 – Poster (Winner of Poster Tour 9 - Acute Care session 5).

The Optimising the Analysis of vascular Prevention trials (OA-Prevention) Collaboration. Statistical reanalysis of vascular event outcomes in primary and secondary vascular prevention trials. BMC Med Res Methodol 21, 218 (2021). https://doi.org/10.1186/s12874-021-01388-6

# 4 OA-Prevention study

This chapter will report the main findings of the OA-Prevention study.

## 4.1 Introduction

Effective prevention of vascular events lies in the management of modifiable risk factors, and also treating the causes of an initial event in the case of secondary prevention. There are numerous prevention strategies to reduce the risk of cardiovascular outcome events such as stroke, myocardial infarction (MI) and bleeding. These strategies include reducing blood pressure [31-33] and cholesterol [35, 36], and the use of antiplatelets [27, 37], anticoagulation [39], surgery [40, 41], and vitamins [45, 46] to improve outcome. Some interventions may be hazardous and increase vascular risk, for example hormone replacement therapy (HRT) [42, 43].

Effective prevention, whether primary or secondary, results in a lower absolute risk of vascular events. As absolute event rates are a key component in calculating sample sizes for binary event

outcomes, lower event rates mean larger, longer and more expensive clinical trials [116]. Further, there has been an increase in the numbers of clinical trials being undertaken, due to new therapies being tested. This combination of more and larger clinical trials means recruitment of the required number of participants is a difficult and competitive process.[117] Therefore, new strategies are needed to reduce clinical trial sample size, which will reduce costs, time to completion and number of participants exposed to risks.

One possible approach is to analyse vascular prevention trials in a way which incorporates more data that could also be considered as clinically relevant. Most vascular prevention trials compare binary event rates between the treatment and control group. However, vascular event outcomes such as stroke, myocardial infarction (MI) and bleeding, can be fatal or non-fatal, this generating trichotomous outcomes (a variable with three levels; i.e. fatal event / non-fatal event / no event). Further, non-fatal events may have different severities, so that further extensions to the ordinal outcome may be included to generate four or more levels of outcomes.[80, 118] Analysis of this type of ordered categorical event is likely to be more efficient statistically than that of dichotomous outcomes. This opens up the potential for reducing trial sample size or detecting smaller but still clinically-relevant benefits. Such structuring of

vascular event outcomes assumes that the ordering of events is meaningful, i.e. fatal vascular events are considered more severe than non-fatal events. Ordered categorical outcomes could also be more informative to participants and healthcare professionals than binary ones,[80] e.g. rather than saying that an intervention reduces the risk of stroke, we can say that it reduces both stroke and the severity of stroke events.

An empirical analysis of published summary data taken from the primary publications of 101 vascular prevention trials that supported the above concepts was performed previously.[80] Here, this chapter reports a prospective study based on analysis of individual participant data. Specifically, this study compared the relative statistical efficiencies of ordinal versus binary outcomes as part of the Optimising the Analysis of vascular Prevention trials Collaboration. Although the use of statistical approaches for ordinal data is well defined in the methodological literature, its use for designing and analysing vascular prevention trials is novel. In this chapter there will also be a report on the effect of adjusting for baseline characteristics on the efficiency of the analysis methods.

## 4.2 Methods

### 4.2.1 Identification of trials

Individual participant data was sought from randomised controlled trials assessing the primary and secondary prevention of vascular events. Potentially eligible studies were identified electronically through search engines including the Cochrane Library and PubMed (to the end of 2016). The use of relevant filters within these search engines was also utilised to help narrow the search for randomised controlled trials. More information on the search process is given in Chapter 2. Once trials were identified, the abstracts were reviewed (and results sections if necessary) to determine if the trial was eligible. Trials were included if they showed benefit or harm according to the trial publication, or were included in a meta-analysis showing benefit or harm. Trials were excluded if they were neutral (showed no significant effect on the primary outcome) and were part of a neutral meta-analysis. Trials were also excluded if they only collected data relating to the occurrence of events and not any information regarding the severity of the event.

### 4.2.2 Data sharing

For each eligible study, lead researchers were contacted by email that included the study protocol and invited to join the collaboration and share their data. Up to four reminders were sent if the researcher did not respond. In some cases, data were obtained via application to data repositories maintained either by the trial funding body (e.g. National Institute of Neurological Disorders and Stroke; National Heart, Lung and Blood Institute) or consortium websites hosting commercial trial data (clinicalstudydatarequest.com).

### 4.2.3 Trial data

Shared data included information on participant demographics (age, sex, medical history), trial design (setting, intervention, length of follow-up) and vascular events / outcomes (stroke, MI, bleeding), including information on the severity of those events (fatal, non-fatal, severe, mild). In trials where there were more than two treatment groups (e.g. factorial trials), outcomes were analysed for each treatment comparison that had been performed in the trial's main publication. Data were analysed according to allocated

treatment using observed outcome data only and no imputation was performed.

### 4.2.4 Statistical analysis

After reviewing published vascular prevention trials and the consideration of other methods for analysing ordinalised outcomes, fifteen different statistical methods were chosen for analysing treatment effects (see section 2.3.2 for further details). Methods included binary logistic regression (adjusted), Cox Proportional hazards (adjusted and unadjusted) and Chi-Square test for the binary outcome measures, and 2xN Chi-square test, Cochran-Armitage trend test, ordinal logistic regression (adjusted and unadjusted), Mann-Whitney U test, Median test, t-test, multiple linear regression (adjusted) and bootstrapping the mean rank for the ordinal outcomes.[68, 84-87] The Win-ratio test, which is a method where multiple binary outcomes, with varying levels of clinical importance, can be analysed together to determine a 'Win ratio' (calculated as total number of wins/ total number of losses), was also used for this study.[90] For regression-based analyses, both unadjusted and adjusted analyses were performed; adjustments were made for variables common to all data sets: age, sex and history of diabetes. No transformations of outcome were

performed for any of the analysis methods. Analyses were carried out in SAS (version 9.3 / 9.4).

### 4.2.5 Comparison of statistical tests

Each trial comparator dataset was analysed using each statistical approach; an example of the application of this methodology can be seen in Table 4.1. The most efficient test was identified as the test which discerned the largest difference between the comparison groups (i.e. the test that produced the smallest p-value). The results of the tests for the ordinal outcome and the binary counterpart were then ordered within each dataset and given a rank (numbers 1 to 15), with the smallest rank given to the test that produced the smallest probability value (i.e. 2-sided p-value, with the exception of the 2xN Chi-Square) within that dataset. A 2-way analysis of variance test, ANOVA – Friedman with adjustment for ties, [119] was used to determine if there was a difference between the average ranking of each test across the datasets. If the ANOVA test was significant, Duncan's multiple range test [98] was then performed to assess the ordering of tests and to assess where significant differences between tests were present. The results of the Duncan's multiple range test for the 3-level extensions of the MI and bleeding outcomes were then more closely inspected. As for the

stroke outcomes, the stroke / TIA 4-level outcome was chosen for closer inspection, rather than the 3-level, as it contained more severity information and the fact that there were more comparator datasets available for it than for any of the other stroke outcomes. Furthermore, for this outcome boxplots were created to show the distributions of the p-value rankings and the p-values themselves, respectively, across all of the available comparator datasets, for each analysis technique used.

**Table 4.1 Example analysis process – based on 4-level outcome (fatal stroke / non-fatal stroke / TIA / no event)**

1. For each of the datasets with available data regarding fatal stroke, non-fatal stroke and TIA the following outcomes were created:

    a. **Binary (event / no event)** – analysed using: Unadjusted – Chi-Square test; Adjusted – binary logistic regression
    b. **Binary (fatal event / no fatal event)** – analysed using Chi-Square test and used for the Win ratio test
    c. **Binary (non-fatal event / no non-fatal event)** – for use in the Win ratio test only
    d. **Binary (TIA / no TIA)** – for use in Win ratio test only
    e. **Binary time to event** – analysed using: Unadjusted – Cox Proportional hazards; Adjusted – Cox proportional hazards
    f. **Ordinal 4-level**– analysed using: Unadjusted – ordinal logistic regression, Mann-Whitney U test, Cochran-Armitage trend test, Median test, Chi-Square test, t-test, and bootstrapping of the mean rank; Adjusted – ordinal logistic regression and multiple linear regression.

2. For each dataset:
    a. All of the tests are performed on the corresponding outcome and the p-values are extracted to a new dataset, e.g.

| Dataset | Chi-Square (Fatal) | Chi-Square (Binary) | Adjusted BLR | Adjusted CPH | Adjusted OLR | Adjusted MLR | Un-adjusted CPH | C-A trend test | Chi-Square (Ordinal) | Un-adjusted OLR | t-test | Mann-Whitney U | Median test | Boot-strapping | Win ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| X | 0.91 | 0.0074 | 0.0052 | 0.0039 | 0.0011 | 0.0027 | 0.0049 | 0.0031 | 0.43 | 0.0014 | 0.0030 | 0.0013 | 0.0017 | 0.0037 | 0.024 |

    b. Then each of the p-values is ranked 1 to 15, from smallest to largest, e.g.

| Dataset | Chi-Square (Fatal) | Chi-Square (Binary) | Adjusted BLR | Adjusted CPH | Adjusted OLR | Adjusted MLR | Un-adjusted CPH | C-A trend test | Chi-Square (Ordinal) | Un-adjusted OLR | t-test | Mann-Whitney U | Median test | Boot-strapping | Win ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| X | 15 | 12 | 11 | 9 | 1 | 5 | 10 | 7 | 14 | 3 | 6 | 2 | 4 | 8 | 13 |

3. This process is completed for all 35 comparator datasets and these are then aggregated into a single dataset, e.g.

| Dataset | Chi-Square (Fatal) | Chi-Square (Binary) | Adjusted BLR | Adjusted CPH | Adjusted OLR | Adjusted MLR | Un-adjusted CPH | C-A trend test | Chi-Square (Ordinal) | Un-adjusted OLR | t-test | Mann-Whitney U | Median test | Boot-strapping | Win ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| X | 15 | 12 | 11 | 9 | 1 | 5 | 10 | 7 | 14 | 3 | 6 | 2 | 4 | 8 | 13 |
| Y | 15 | 13 | 10 | 11 | 3 | 6 | 12 | 5 | 14 | 2 | 7 | 1 | 8 | 9 | 4 |
| ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ |

4. This new dataset is then analysed using Friedman's ANOVA and the Duncan's test to determine if there is a difference in the average ranking of each test and the ordering / grouping of tests respectively.

5. This process is repeated for each of the derived ordinal outcomes.

### 4.2.6 Assessments of validity and reliability

For this study, a number of supplementary analyses were performed to assess the validity and reliability of the results. Firstly, the comparison of the statistical approaches was repeated within subgroups of trials that shared similar characteristics to assess whether certain methods were more efficient for certain types of trials. Secondly, sample sizes generated using the formulas for the ordinal / continuous statistical tests were compared to those generated using a formula for binary proportions test to determine the effect of outcome / method choice on sample size. Thirdly, the statistical assumptions of the tests were assessed to determine if the use of these tests in these circumstances was appropriate.

The sensitivity, or type I error, of the two most efficient statistical tests (that is, those with the smallest mean ranks) were also assessed using ordinal vascular outcomes from ten randomly selected comparator datasets. For each of the selected comparator datasets a dummy treatment variable with a neutral treatment effect was created so that any treatment difference could only occur by chance. Once the dummy variable had been created, 1000 sample datasets were generated from each of the comparator datasets, using random sampling with replacement. Tests maintaining an acceptable proportion of type I errors would only

expect to see a significant result in around 50 of the 1000 sample data sets.

## 4.3 Results

### 4.3.1 Trial characteristics

Of 167 identified trials (Figure 4.1), data were shared with the OA-Prevention Collaboration for 35 trials; including 254,223 participants, Tables 4.2 and 4.3. Reasons for not obtaining data included inability to contact the chief investigator or other investigators (e.g. the emails bounced); chief investigators did not respond to requests for data sharing despite multiple attempts and when emails had not bounced; chief investigators explicitly chose not to share their data; and trial data were not available in a usable format, a problem particularly for some older trials. Of the included trials, 15 were primary prevention and 20 secondary prevention (Table 4.4). Interventions included anticoagulants (ACT; eight trials), antihypertensives (AHT; eight trials), antiplatelets (APT; seven trials), carotid stenting / endarterectomy (CEA; three trials), glucose lowering (GL; one trial), hormone replacement therapy

(HRT; two trials), statins (four trials) and vitamins (two trials). From the 35 trials, a total of 59 comparator datasets were derived with 13 trials having more than two comparator arms (Figure 4.1). Further information regarding the included trials is given in Tables 4.2 and 4.3.

**Figure 4.1 Flow diagram – Identification of included trials**

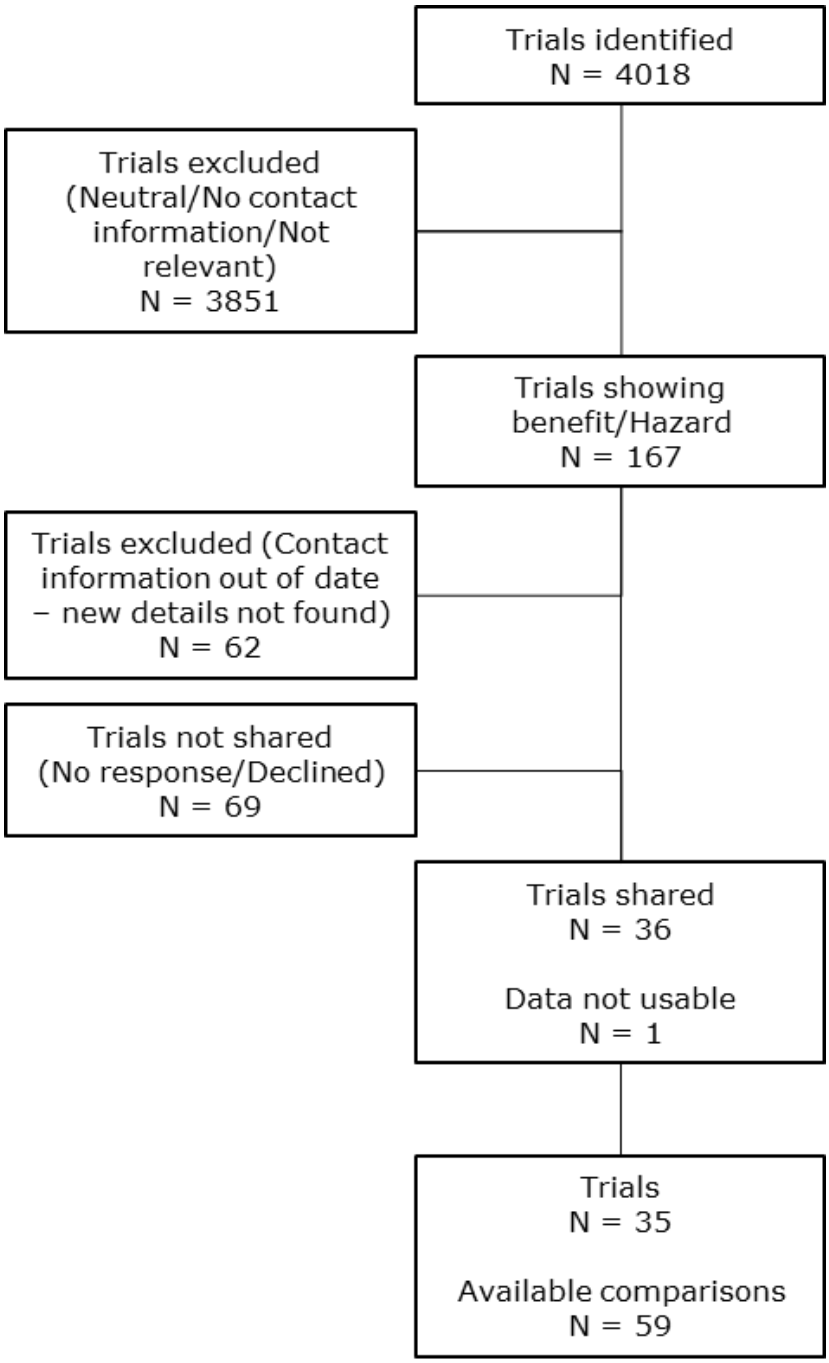


**Table 4.2 List of included trials by indication and whether primary or secondary prevention**

| Intervention | Type of trial | |
|---|---|---|
| | Primary | Secondary |
| Antiplatelets | | Dutch-TIA† [120]<br>ESPRIT† [121]<br>ESPS 1 [122]<br>ESPS 2 [123]<br>JASAP [124]<br>PROFESS [125]<br>TARDIS [81] |
| Anticoagulants | BAFTA [21]<br>APOLLO [126]<br>PETRO [127]<br>RE-LY [128] | EAFT [113]<br>OASIS-6 [129]<br>SPIRIT [130]<br>IST-1* [110] |
| Antihypertensives | ALLHAT [131]<br>EWPHE [132]<br>INDANA MRC 1 [133]<br>INDANA MRC 2 [134]<br>SHEP [135]<br>SYST-EUR [136] | PROGRESS [137]<br>ENOS* [138] |
| Carotid Endarterectomy | ACAS [139] | EVA-3S [140]<br>NASCET [30] |

| | | |
|---|---|---|
| Vitamins | | VISP [141]<br>VITATOPS [45] |
| HRT[1] | WHI 1 [142]<br>WHI 2 [143] | |
| Statins | AFCAPS / TEXCAPS [144] | 4S [145]<br>LIPID [146]<br>CARE [147] |
| Glucose lowering | ACCORD [148] | |

[1]HRT: Hormone replacement therapy.

*Acute trials that collected data on vascular events.

†Participants in these trials could also be randomised to receive either an antihypertensive (DUTCH-TIA) or an anticoagulant (ESPRIT). Trials have been listed according to their primary intervention.

**Table 4.3 Information on included trials**

| Trial | Year | Class | Treatment | Control | Size | Length of follow-up | Data source |
|---|---|---|---|---|---|---|---|
| 4S [145] | 1994 | Statins | Simvastatin | Placebo | 4444 | 5.4 years | Merck |
| ACAS [139] | 1995 | CEA | CEA | No surgery | 1662 | 2.7 years | NINDS |
| ACCORD [148] | 2008 | GL | Intensive GL | Standard | 10251 | 3.5 years | NHLBI |
| AFCAPS / TEXCAPS [144] | 1998 | Statins | Lovastatin | Placebo | 6605 | 5.2 years | Merck |
| ALLHAT [131] | 2002 | AHT | CCB or ACE-I | Diuretic | 33357 | 4.9 years | NHLBI |
| APOLLO [126] | 2007 | ACT | FS | Placebo | 1309 | 1 month | CTDR |
| BAFTA [21] | 2007 | ACT | Warfarin | A | 973 | 2.7 years | CI |
| CARE [147] | 1996 | Statins | Pravastatin | Placebo | 4159 | 5 years | CI |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| DUTCH-TIA [120] | 1991 | APT | A (283mg per day) / BB | A (30mg per day) / Placebo | 3131 | 2.6 years | CI |
| EAFT [113] | 1993 | ACT | ACT or Aspirin | Placebo | 1007 | 2.3 years | CI |
| ENOS [138] | 2014 | AHT | GTN | No GTN | 4011 | 3 months | CI |
| ESPRIT [121] | 2007 | APT | AD / ACT | A | 1068 | 4.6 years | CI |
| ESPS 1 [122] | 1990 | APT | AD | Placebo | 2500 | 2 years | CI |
| ESPS 2 [123] | 1996 | APT | A, D or AD | Placebo | 6602 | 2 years | CI |
| EVA-3S [140] | 2006 | CEA | CEA | Stenting | 527 | 4 years | CI |
| EWPHE [132] | 1985 | AHT | H + T | Placebo | 840 | 4.7 years | CI |
| INDANA MRC1 [133] | 1985 | AHT | Bendro or Prop | Placebo | 17354 | 5 years | CI |
| INDANA MRC2 [134] | 1992 | AHT | Diuretic or BB | Placebo | 4396 | 5.8 years | CI |
| IST-1 [110] | 1997 | ACT | Heparin | No heparin | 19435 | 6 months | Online |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| JASAP [124] | 2011 | APT | Aggrenox | A | 1294 | 4 months | CTDR |
| LIPID [146] | 1998 | Statins | Pravastatin | Placebo | 9014 | 6.1 years | CI |
| NASCET [30] | 1998 | CEA | CEA | No surgery | 2267 | 5 years | NINDS |
| OASIS-6 [129] | 2006 | ACT | FS | Placebo / Heparin | 12092 | 6 months | CTDR |
| PETRO [127] | 2007 | ACT | Dabigatran | Warfarin | 502 | 3 months | CTDR |
| PROFESS [125] | 2008 | APT | AD | C | 20332 | 2.5 years | CTDR |
| PROGRESS [137] | 2001 | AHT | Perindopril | Placebo | 6105 | 4 years | CI |
| RE-LY [128] | 2009 | ACT | Dabigatran | Warfarin | 18113 | 2 years | CTDR |
| SHEP [135] | 2000 | AHT | Chlorthalidone | Placebo | 4736 | 4.5 years | NHLBI |
| SPIRIT [130] | 1997 | ACT | ACT | A | 1316 | 14 months | CI |
| SYST-EUR [136] | 1997 | AHT | Nitrendipine | Placebo | 6403 | 2 years | CI |
| TARDIS [81] | 2017 | APT | ACD | AD or C | 3996 | 3 months | CI |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| VISP [141] | 2004 | Vitamins | High FA, $B_6$ + $B_{12}$ | Low FA, $B_6$ + $B_{12}$ | 3680 | 2 years | NINDS |
| VITATOPS [45] | 2010 | Vitamins | B vitamins | Placebo | 8164 | 3.4 years | CI |
| WHI 1 [142] | 2002 | HRT | Estrogen + Progestin | Placebo | 16608 | 5.2 years | CI |
| WHI 2 [143] | 2004 | HRT | Estrogen | Placebo | 10739 | 5.2 years | CI |

ACT: Anticoagulants, AHT: Antihypertensives, APT: Antiplatelets, CEA: Carotid Endarterectomy, GL: Glucose lowering, HRT: Hormone replacement therapy, CCB: Calcium channel blocker, ACE-I: Angiotensin-converting enzyme inhibitor, FS: Fondaparinux Sodium, A: Aspirin, D: Dipyridamole, C: Clopidogrel, H + T: Hydrochlorothiazide plus Triamterene, Bendro: Bendroflumethiazide, Prop: Propranolol, BB: Beta blocker, FA: Folic acid, CI: Chief Investigator, CTDR: clinical trials data repository, NHLBI: National Heart, Lung and Blood Institute, NINDS: National Institute of Neurological Disorders and Stroke.

### 4.3.2 Participant Characteristics

Baseline characteristics of the 254,223 participants are provided in Table 4.4. For secondary prevention trials, one had information on qualifying event missing, and two did not have time to randomisation data. The most consistently collected baseline data included information on age, sex and history of diabetes. Baseline characteristics differed between intervention types, including age (statin trials, mean 59 years, anticoagulation 69 years); female sex (statin 16%, HRT 100%); history of diabetes (statin 7%, glucose lowering 100%); history of hypertension (statins 34%, antihypertensive 95%); and time to randomisation (for secondary prevention trials, anticoagulation 3 days, statins 507 days).

**Table 4.4 Characteristics of trial participants by type of intervention**

| | Trials | All | ACT | AHT | APT | CEA | GL | HRT | Statins | Vitamins | P |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **All** | | | N=8 | N=8 | N=7 | N=3 | N=1 | N=2 | N=4 | N=2 | |
| Primary (%) | 15 | | 4 (36.7%) | 6 (40.0%) | 0 | 1 (6.7%) | 1 (6.7%) | 2 (13.3%) | 1 (6.7%) | 0 | |
| Secondary (%) | 20 | | 4 (20%) | 2 (10.0%) | 7 (35.0%) | 2 (10.0%) | 0 | 0 | 3 (15.0%) | 2 (10.0%) | |
| **Baseline** | | | | | | | | | | | |
| Number | 35 | 254223 | 54713 | 81058 | 39714 | 5074 | 10251 | 27347 | 24222 | 11844 | |
| Age | 35 | 65.1 (30.5) | 69.0 (11.7) | 64.6 (51.9) | 66.0 (9.6) | 66.6 (8.2) | 62.8 (6.6) | 63.4 (7.2) | 59.3 (8.1) | 63.7 (12.1) | <0.0001 |
| Sex, Female (%) | 35 | 117222 (46.1%) | 21063 (38.5%) | 39213 (48.4%) | 14697 (37.0%) | 2711 (53.4%) | 3952 (38.6%) | 27347 (100%) | 3916 (16.2%) | 4323 (36.5%) | <0.0001† |
| Medical History (%) | | | | | | | | | | | |
| Diabetes | 34 | 51131 (20.1%) | 7030 (12.9%) | 17143 (21.2%) | 8897 (22.4%) | 1135 (22.4%) | 10251 (100%) | 1980 (7.2%) | 1725 (7.1%) | 2970 (25.3%) | <0.0001‡ |
| Hypertension | 32 | 153427 (69.6%) | 22771 (67.0%) | 76550 (94.5%) | 25871 (65.2%) | 3212 (63.3%) | - | 8433 (34.0%) | 8141 (33.6%) | 8449 (72.0%) | <0.0001 |
| Hyperlipidaemia | 17 | 27627 (29.8%) | 96 (9.6%) | 1019 (15.4%) | 14757 (37.3%) | 1291 (37.8%) | - | 3366 (13.7%) | 4444 (40.2%) | 2654 (41.7%) | <0.0001 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| IHD | 12 | 27850 (30.6%) | - | 8813 (24.0%) | 6724 (20.7%) | 1970 (38.8%) | - | - | 9014 (100%) | 1329 (17.0%) | <0.0001¥ |
| Stroke | 28 | 21645 (12.6%) | 3403 (9.6%) | 5375 (13.9%) | 8707 (23.9%) | 717 (21.0%) | 630 (6.1%) | 306 (1.1%) | 369 (4.1%) | 2138 (18.2%) | <0.0001 |
| MI | 25 | 22069 (13.6%) | 5073 (14.4%) | 704 (2.1%) | 2720 (7.7%) | 640 (18.8%) | 1590 (15.5%) | 634 (2.3%) | 10708 (60.8%) | - | <0.0001 |
| Smoking, Current | 31 | 48441 (20.9%) | 7030 (21.0%) | 17515 (21.9%) | 10211 (25.8%) | 1471 (29.0%) | 1247 (12.2%) | 2831 (10.5%) | 3496 (14.4%) | 4640 (39.5%) | <0.0001 |
| Alcohol | 12 | 27897 (41.3%) | 6373 (34.2%) | 4754 (48.0%) | 10984 (40.5%) | 561 (33.8%) | - | - | 3098 (46.9%) | 2127 (59.4%) | <0.0001 |
| SBP | 31 | 145.8 (23.1) | 143.5 (27.1) | 155.2 (19.8) | 147.4 (20.2) | 146.1 (19.3) | - | 128.7 (17.6) | 136.5 (18.8) | 141.5 (20.9) | <0.0001 |
| DBP | 30 | 83.3 (12.0) | 79.5 (12.8) | 87.7 (11.1) | 84.9 (11.7) | 80.1 (10.0) | - | 76.0 (9.2) | 80.3 (10.4) | 81.6 (12.1) | <0.0001 |
| HR | 14 | 73.1 (13.7) | 75.1 (15.8) | 77.5 (11.6) | 73.2 (12.4) | 73.1 (10.6) | - | - | 67.8 (11.1) | - | <0.0001 |
| **Secondary** | | | | | | | | | | | |
| Qualifying event (%) | | | | | | | | | | | |
| Stroke | 19 | 71178 (66.4%) | 19779 (60.9%) | 5632 (85.2%) | 34071 (85.8%) | 1571 (46.0%) | - | - | - | 10125 (86.1%) | <0.0001 |
| MI | 19 | 25528 (22.9%) | 12090 (37.2%) | - | - | - | - | - | 1348 (76.3%) | - | <0.0001 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| TIA | 19 | | | 974 | 5497 | 1759 | | | | 1402 | <0.0001 |
| | | 9979 (9.3%) | 347 (1.1%) | (14.7%) | (13.8%) | (51.6%) | - | - | - | (11.9%) | |
| OTR | 18 | | | 418.0 | | | | | 507.4 | | <0.0001 |
| | | 91.2 (246.2) | 3.2 (12.9) | (439.6) | 31.0 (163.5) | 47.9 (43.6) | - | - | (317.0) | 60.2 (178.0) | |

ACT: anticoagulants; AHT: antihypertensives; APT: antiplatelets; CEA: carotid endarterectomy; DBP: diastolic blood pressure; GL: glucose lowering; HRT: hormone replacement therapy; IHD: ischaemic heart disease; MI: myocardial infarction; HR: heart rate; OTR: onset to randomisation; SBP: systolic blood pressure; TIA: transient ischaemic attack. Percentages (%) are out of the total number of participants with available data. Comparisons by Chi-Square test and ANOVA. †Excluding HRT group. ‡Excluding GL group. ¥Excluding Statins group.

### 4.3.3 Stroke

The derived categorical stroke outcomes ranged between 3-, 4-, 5- and 8- levels; addition of TIA increased this to 4-, 5-, 6- and 9- levels (Table 4.5). Comparison of analyses for all levels of stroke outcome found that ordinal analyses were rated higher than binary for 4 and more levels (Table 4.6). For the 3-level stroke outcome review, ordinal and binary analysis methods appeared to have similar efficiency with adjusted binary logistic regression being rated the most efficient analysis method. Further, adjusted analyses were more efficient with lower ranks then their univariate counterparts, e.g. for OLR, CPH (Table 4.6). The results of performing the Duncan's multiple range test on the Stroke / TIA 4-level outcome can be seen in Table 4.7. Ordinal analyses were rated superior to binary, with the most efficient being the Mann-Whitney U test and ordinal logistic regression (both unadjusted and adjusted); Table 4.7, Figure 4.2.

**Table 4.5 Ordered categorical severity levels for stroke, myocardial infarction, major adverse cardiovascular events and bleeding, and the number of datasets for each outcome**

| Levels | Stroke | MI | MACE | Bleeding |
|---|---|---|---|---|
| 3 | Fatal / non-fatal / none (n=56) | Fatal / non-fatal / none (n=47) | Fatal / non-fatal / none (n=47) | Fatal / non-fatal / none (n=32) |
| 4 | Fatal / severe / moderate-mild / none (n=23) | | | Fatal / severe / moderate-mild / none (n=26) |
| 4 | Fatal / non-fatal / TIA / none (n=35) | | | |
| 5 | Fatal / severe / moderate / mild / none (n=16) | | | Fatal / severe / moderate / minor / none (n=13) |
| 5 | Fatal / severe / moderate-mild / TIA / none (n=17) | | | |
| 6 | Fatal / severe / moderate / mild / TIA / none (n=13) | | | |
| 8 | Fatal / mRS=5 / mRS=4 / mRS=3 / mRS=2 / mRS=1 / mRS=0 / none (n=12) | | | |
| 9 | Fatal / mRS=5 / mRS=4 / mRS=3 / mRS=2 / mRS=1 / mRS=0 / TIA / none (n=12) | | | |

MI: Myocardial infarction; MACE: Major cardiovascular events; mRS: modified Rankin Scale.

## Table 4.6 Rating of statistical tests

| | | | | Rating of tests relative to each other | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Comparator | | | Adj. | | | | | Adj. | Adj. | Adj. | | | | | | | |
| **Outcome** | **Levels†** | **datasets** | **P** | **MWU** | **OLR** | **WR** | **OLR** | **BS** | **MLR** | **BLR** | **CPH** | **TT** | **CAT** | **CPH** | **MT** | **CSB** | **CSO** | **CSF** |
| Stroke | 3 | 56 | <0.0001 | **2** | **4** | **3** | 7 | 9 | 10 | **1** | **5** | 13 | 12 | **6** | 11 | 8 | 14 | 15 |
| | 4 | 23 | <0.0001 | **2** | **3** | **1** | **6** | 10 | 12 | **4** | **5** | 11 | 13 | **7** | 8 | 9 | 14 | 15 |
| | 5 | 16 | 0.0002 | **2** | **3** | **1** | **6** | **8** | 12 | **4** | **5** | 11 | 13 | **7** | 10 | 9 | 14 | 15 |
| | 8 | 12 | 0.0115 | **3** | **2** | **1** | **7** | **8** | 10 | **4** | **5** | 13 | 14 | **6** | 9 | 11 | 12 | 15 |
| Stroke / TIA | 4 | 35 | <0.0001 | **1** | **3** | **5** | **2** | **4** | 8 | 10 | 12 | 7 | **6** | 11 | 9 | 13 | 14 | 15 |
| | 5 | 17 | <0.0001 | **1** | **3** | 9 | **7** | **2** | **4** | 10 | 11 | **6** | **5** | 12 | **8** | 13 | 14 | 15 |
| | 6 | 13 | <0.0001 | **1** | **2** | 9 | **3** | **6** | **4** | 10 | 11 | **7** | **8** | 12 | **5** | 13 | 14 | 15 |
| | 9 | 12 | <0.0001 | **1** | **2** | 7 | **3** | **4** | **6** | 11 | 10 | 8 | 9 | 12 | **5** | 14 | 13 | 15 |
| MI | 3 | 47 | 0.010 | **1** | **6** | 12 | **5** | **2** | **7** | **8** | 11 | **4** | **3** | 10 | 14 | 13 | **9** | 15 |
| Bleeding | 3 | 32 | <0.0001 | **4** | **9** | **3** | 11 | **7** | **1** | **8** | **6** | **5** | **2** | **10** | 15 | 14 | 14 | 13 |
| | 4 | 26 | 0.035 | **3** | **7** | **5** | **8** | **2** | **1** | **10** | **9** | **6** | **4** | 11 | 13 | 14 | 12 | 15 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 5 | 13 | 0.032 | **6** | **8** | **5** | **3** | **2** | **1** | **11** | **7** | **4** | **10** | **12** | 15 | 14 | **9** | 13 |
| Vascular | 3 | 47 | <0.0001 | **2** | **3** | **5** | **6** | 10 | 8 | **1** | **4** | 11 | 12 | **7** | 13 | 9 | 14 | 15 |

The numbers in bold represent the tests that are the most efficient and do not differ statistically from one another. The P-value is from the results of the Friedman ANOVA. The order of the rating of test is based on the mean rank calculated by the Duncan's multiple range test; the most efficient test (i.e. the test with the smallest mean rank) is rated the best with a score of 1 and the least efficient with a score of 15.

Adj.: adjusted; BLR: binary logistic regression; BS: bootstrapping; CAT: Cochran-Armitage trend test; CPH: Cox proportional hazards; CSB: Chi-square binary event outcome; CSF: Chi-square binary fatal event outcome; CSO: Chi-square ordinal event outcome; MLR: multiple linear regression; MT: median test; MWU: Mann-Whitney U test; OLR: ordinal logistic regression; TT: t-test; Vascular: combination of stroke and MI; WR: Win ratio test.

[†]Defined in Table 4.5.

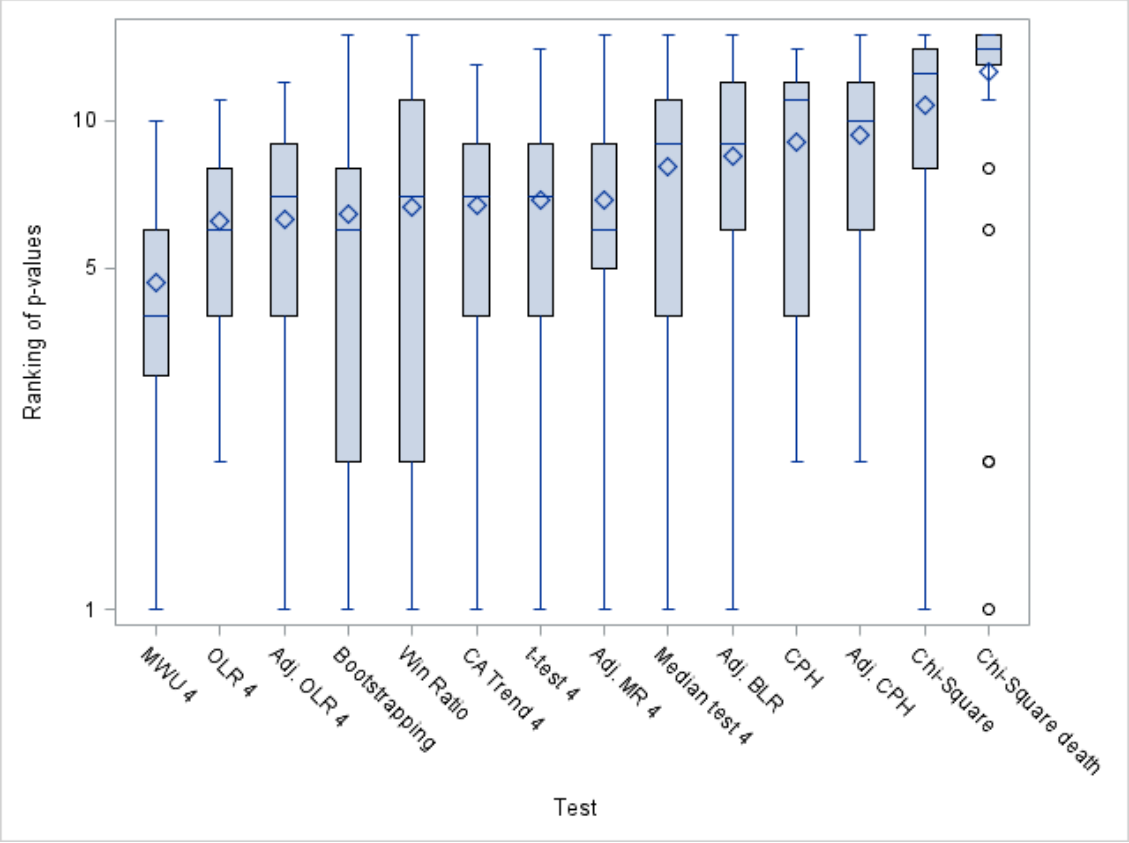
**Table 4.7 Results from the Duncan's test analysis of p-value ranks for 4-level stroke / TIA based on 35 comparator datasets (p<0.0001)**

| Test | | | | | | | Mean rank |
|---|---|---|---|---|---|---|---|
| MWU 4 | A | | | | | | 4.69 |
| OLR 4 | A | B | | | | | 6.26 |
| Adj. OLR 4 | A | B | C | | | | 6.31 |
| Bootstrapping | A | B | C | | | | 6.43 |
| Win Ratio | A | B | C | | | | 6.69 |
| CA Trend 4 | A | B | C | | | | 6.71 |
| t-test | | B | C | | | | 6.89 |
| Adj. MLR 4 | | B | C | | | | 6.91 |
| Median test 4 | | B | C | D | | | 8.06 |
| Adj. BLR | | | C | D | E | | 8.49 |
| CPH | | | | D | E | | 9.06 |
| Adj. CPH | | | | D | E | F | 9.34 |
| Chi-square 2 | | | | | E | F | 10.37 |
| Chi-square 4 | | | | | | F | G | 11.14 |
| Chi-square Death | | | | | | | G | 12.66 |

BLR: binary logistic regression; CA trend: Cochran-Armitage trend test; CPH: Cox proportional hazards model; MLR: multiple linear

regression; MWU: Mann-Whitney U test; OLR: ordinal logistic regression.

**Figure 4.2 Box plot showing distribution of p-value ranks by test – stroke / TIA 4-level**



### 4.3.4 Myocardial Infarction

Data on 3-level MI (fatal / non-fatal / none) were available for 33 trials (47 comparator datasets). Comparison of analysis methods suggested that there was a significant difference between the tests (p=0.010) and that ordinal / continuous approaches were rated more efficient than binary methods, with the exception of adjusted binary logistic regression (Table 4.6, Table 4.8).

### 4.3.5 Bleeding

Bleeding data were available for 15 (43%) trials and it was possible to create 3-, 4- and 5- level outcomes (for 32, 26, and 13 comparator datasets respectively); Table 4.5. For each of these three bleeding outcomes, ordinal / continuous analyses were more efficient than binary methods. Adjusted multiple linear regression, was the top-rated analysis in each case (Table 4.6, Table 4.9).

**Table 4.8 Duncan's test analysis of p-value ranks for 3-level myocardial infarction based on 47 comparator datasets (p=0.010)**

| Test | | | | | | Mean rank |
|---|---|---|---|---|---|---|
| MWU 3 | A | | | | | 6.04 |
| Bootstrapping | A | B | | | | 6.47 |
| CA trend 3 | A | B | C | | | 6.62 |
| t-test 3 | A | B | C | | | 6.91 |
| OLR 3 | A | B | C | | | 6.94 |
| Adj. OLR 3 | A | B | C | | | 7.09 |
| Adj. MLR 3 | A | B | C | | | 7.09 |
| Adj. BLR | A | B | C | | | 7.55 |
| Chi-Square 3 | A | B | C | | | 8.02 |
| CPH | | B | C | | | 8.21 |
| Adj. CPH | | | C | D | | 8.53 |
| Win ratio | | | C | D | | 8.55 |
| Chi-square 2 | | | | D | E | 10.17 |
| Median test 3 | | | | | E | 10.89 |
| Chi-square Death | | | | | E | 10.91 |

MWU: Mann-Whitney U test, OLR: ordinal logistic regression: CA trend: Cochran-Armitage trend test, MLR: multiple linear regression, BLR: binary logistic regression, CPH: Cox proportional hazards.

**Table 4.9 Duncan's test analysis of p-value ranks for 3-level bleeding based on 32 comparator datasets (p<0.0001)**

| Test | | | | Mean rank |
|---|---|---|---|---|
| Adj. MLR 3 | A | | | 5.38 |
| CA trend 3 | A | B | | 5.91 |
| Win Ratio | A | B | | 6.28 |
| MWU 3 | A | B | | 6.72 |
| t-test | A | B | | 6.75 |
| Adj. CPH | A | B | | 6.84 |
| Bootstrapping | A | B | | 7.00 |
| Adj. BLR | A | B | | 7.09 |
| Adj. OLR 3 | A | B | | 7.13 |
| CPH | A | B | | 7.56 |
| OLR 3 | | B | | 7.97 |
| Chi-square (death) | | | C | 10.97 |
| Chi-square 2 | | | C | 11.03 |
| Chi-square 3 | | | C | 11.31 |
| Median test 3 | | | C | 12.06 |

MWU: Mann-Whitney U test, OLR: ordinal logistic regression: CA trend: Cochran-Armitage trend test, MLR: multiple linear regression, BLR: binary logistic regression, CPH: Cox proportional hazards.

### 4.3.6 Major adverse vascular event (MACE, composite vascular event)

A composite outcome (fatal stroke or MI / non-fatal stroke or MI / none) was derived for 33 trials; 47 comparator datasets. This outcome was constructed under the assumption that the 'worst' event would be taken rather than the 'first' event. For instance, if a participant has had a non-fatal stroke, but then later also has a fatal MI, then the fatal MI would be used for the composite outcome. The comparison of analyses (Table 4.6) suggested that there was a significant difference between the tests ($p<0.0001$). The most efficient method appeared to be adjusted binary logistic regression, however this approach did not differ significantly from the Mann-Whitney U test and adjusted and unadjusted ordinal logistic regression suggesting that ordinal approaches were just as efficient as binary methods.

### 4.3.7 Subgroup analysis

The results of the comparisons using the 4-level stroke / TIA outcome, for subgroups including type of trial, and the main intervention can be seen in Table 4.10 and Figure 4.3; insufficient data were present for glucose lowering and vitamin based trials.

The differences between the tests were significant for each of the trial type subgroups (both $p<0.0001$) and the top performing analyses appeared to be Mann-Whitney U test, the Win ratio test, adjusted ordinal logistic regression and the Cochran-Armitage trend test. Analysis methods also differed for interventions, including ACT, AHT, APT, CEA and statins, with the best rated being the Mann-Whitney U test, bootstrapping, the Win ratio test and adjusted ordinal logistic regression.

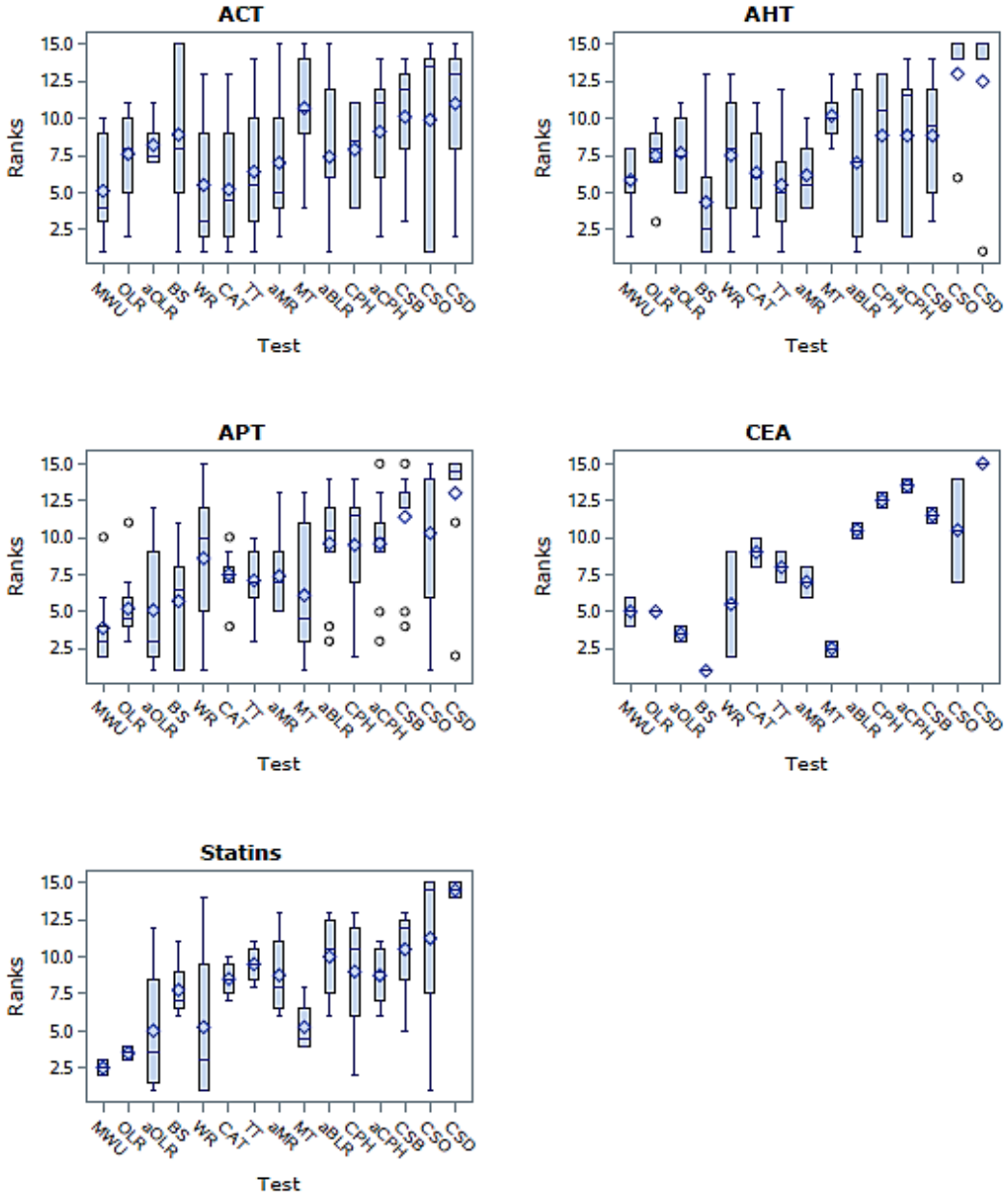
**Table 4.10 Rating of tests by subgroups for stroke / TIA 4-level (35 comparator datasets)**

| | | | Rating of tests relative to each other | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subgroup** | **Comparator datasets** | **P-value** | **MWU** | **Adj. OLR** | **WR** | **OLR** | **BS** | **Adj. MLR** | **Adj. BLR** | **Adj. CPH** | **TT** | **CAT** | **CPH** | **MT** | **CSB** | **CSO** | **CSF** |
| *Trial type* | | | | | | | | | | | | | | | | | |
| Primary | 15 | <0.0001 | **1** | **6** | **3** | **7** | **8** | **4** | 9 | 12 | **5** | **2** | 11 | 10 | 13 | 15 | 14 |
| Secondary | 20 | <0.0001 | **1** | **4** | 5 | **3** | **2** | 9 | 10 | 12 | 6 | 8 | 11 | 7 | 14 | 13 | 15 |
| *Main* | | | | | | | | | | | | | | | | | |
| *Intervention* | | | | | | | | | | | | | | | | | |
| ACT | 10 | 0.0089 | **1** | **9** | **3** | **7** | **10** | **5** | **6** | **11** | **4** | **2** | **8** | 14 | 13 | 12 | 15 |
| AHT | 6 | 0.011 | **3** | **9** | **7** | **8** | **1** | **4** | **6** | **10** | **2** | **5** | **11** | 13 | **12** | 15 | 14 |
| APT | 10 | <0.0001 | **1** | **2** | 9 | **3** | **4** | **7** | 12 | 11 | **6** | **8** | 10 | **5** | 14 | 13 | 15 |
| CEA | 2 | <0.0001 | **5** | **3** | **6** | **4** | **1** | 7 | 11 | 14 | 8 | 9 | 13 | **2** | 12 | 10 | 15 |
| HRT | 2 | 0.35 | 4 | 2 | 1 | 5 | 10 | 3 | 12 | 6 | 7 | 8 | 11 | 9 | 13 | 15 | 14 |
| Statins | 4 | 0.0011 | **1** | **3** | **4** | **2** | **6** | 9 | 12 | 8 | 11 | 7 | 10 | **5** | 13 | 14 | 15 |

The numbers in bold represent the tests are the most efficient and do not differ statistically from one another. The P-value is from the results of the Friedman ANOVA. The order of the rating of test is based on the mean rank calculated by the Duncan's multiple range test; the most efficient test (i.e. the test with the smallest mean rank) is rated the best with a score of 1 and the least efficient with a score of 15.

ACT: anticoagulants, Adj.: adjusted, AHT: antihypertensives, APT: antiplatelets, BLR: binary logistic regression, BS: bootstrapping, CAT: Cochran-Armitage Trend test, CEA: carotid Endarterectomy, CPH: Cox proportional hazards, CSB: Chi-square binary event outcome, CSF: Chi-square binary fatal event outcome, CSO: Chi-square ordinal event outcome, HRT: hormone replacement therapy, MWU: Mann-Whitney U test, MT: median test, MLR: multiple linear regression, OLR: ordinal logistic regression, TT: t-test, Vascular: combination of stroke and MI, WR: Win ratio test.

**Figure 4.3 Box plot showing distribution of ranks by subgroups for 4-level stroke / TIA**



### 4.3.8 Sample size comparisons

The comparisons between sample sizes generated for the binary stroke outcome and the 4-level stroke / TIA outcome can be seen in Table 4.11. Sample size estimates were generated for ordinal logistic regression,[149] Mann-Whitney U test[150] and t-test[151], and compared with binary comparison of proportions.[152] In 13 comparator datasets and relative to binary sample size estimation, sample sizes were reduced by 34% for ordinal logistic regression and 82% for the Mann-Whiney U test and t-test.

### 4.3.9 Sensitivity analyses and Statistical assumptions

The statistical assumptions for ordinal logistic regression (checked using the score test for proportional odds) were upheld ($p>0.05$) in 51/56 (91%) datasets with 3-level stroke data and 30/35 (86%) datasets with the 4-level Stroke / TIA outcome. The sensitivity analysis assessing type I error, was performed on the 3-, 5- and 8-level stroke outcome, the 3-level MI outcome and the 4-level bleeding outcome. This analysis did not find any evidence of increased type I error rate for the Mann-Whitney U test or ordinal logistic regression (Table 4.12).

**Table 4.11 Sample size comparisons (Stroke / TIA 4-level)**

| | Sample size | | | | Multiplier | | | |
|---|---|---|---|---|---|---|---|---|
| **Dataset** | **Binary** | **Ordinal** | **MWU** | **t-test** | **Binary** | **Ordinal** | **MWU** | **t-test** |
| 1 | 4528 | 4052 | 1194 | 1196 | 1 | 0.89 | 0.26 | 0.26 |
| 2 | 17986 | 11970 | 3326 | 3904 | 1 | 0.67 | 0.18 | 0.22 |
| 3 | 15292 | 10072 | 2744 | 2828 | 1 | 0.66 | 0.18 | 0.18 |
| 4 | 5436 | 2382 | 704 | 898 | 1 | 0.44 | 0.13 | 0.17 |
| 5 | 25090 | 8666 | 2426 | 3362 | 1 | 0.35 | 0.097 | 0.13 |
| 6 | 30450 | 10164 | 2958 | 5070 | 1 | 0.33 | 0.097 | 0.17 |
| 13 | 13510 | 12610 | 3806 | 3754 | 1 | 0.93 | 0.28 | 0.28 |
| 18 | 23090 | 22110 | 6486 | 7194 | 1 | 0.96 | 0.28 | 0.31 |
| 30 | 15934 | 1582 | 442 | 566 | 1 | 0.099 | 0.028 | 0.036 |
| 31 | 6934 | 1952 | 608 | 802 | 1 | 0.28 | 0.088 | 0.12 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 32 | 115114 | 63792 | 17482 | 19952 | 1 | 0.55 | 0.15 | 0.17 |
| 33 | 15198 | 10862 | 3388 | 3450 | 1 | 0.71 | 0.22 | 0.23 |
| 55 | 37646 | 37456 | 10924 | 12186 | 1 | 0.99 | 0.29 | 0.32 |
| Median (Q1 - Q3) | - | - | - | - | - | 0.66 (0.35 - 0.89) | 0.18 (0.097 - 0.26) | 0.18 (0.17 - 0.26) |

MWU: Mann-Whitney U test; Q1: lower 25% quartile; Q3: upper 75% quartile.

**Table 4.12 Type 1 error analyses**

| | | | MWU | | OLR | |
|---|---|---|---|---|---|---|
| **Outcome** | **Level** | **Comparator dataset** | **N samples** | **P** | **N samples** | **P** |
| Stroke | 3 | ALLHAT [131] | 57/1000 | 0.15 | 57/1000 | 0.15 |
| | 3 | INDANA MRC1 [133] | 52/1000 | 0.61 | 50/1000 | 1.00 |
| | 5 | ACAS [139] | 48/1000 | 1.00 | 47/1000 | 1.00 |
| | 5 | EAFT [113] | 53/1000 | 0.33 | 51/1000 | 0.44 |
| | 8 | ESPS-2 [108] | 50/1000 | 1.00 | 50/1000 | 1.00 |
| | 8 | NASCET [30] | 50/1000 | 1.00 | 50/1000 | 1.00 |
| MI | 3 | LIPID [133] | 54/1000 | 0.28 | 54/1000 | 0.28 |
| | 3 | SHEP [135] | 37/1000 | 1.00 | 37/1000 | 1.00 |
| Bleeding | 4 | SPIRIT [130] | 49/1000 | 1.00 | 49/1000 | 1.00 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 4 | TARDIS [81] | 46/1000 | 1.00 | 46/1000 | 1.00 |

MWU: Mann-Whitney U test; OLR: ordinal logistic regression.

## 4.4 Discussion

This study found that it is more efficient statistically to analyse vascular event data as several categories ordered by severity rather than as dichotomous event / no event data. The findings applied to both primary and secondary prevention trials, and to a variety of intervention types including blood pressure and lipid lowering, antithrombotics and carotid endarterectomy. The analysis approaches that performed best included the Mann-Whitney U test, ordinal logistic regression, bootstrapping the mean rank, the Win ratio test and, for some ordinal scales, multiple linear regression (adjusted). In general, statistical regression models were more efficient if adjusted for prognostic factors than if performed unadjusted. Using ordinal outcome data and efficient analyses did not carry a risk of false positive findings. Finally, sample size estimations for ordered outcomes were significantly lower than for dichotomous events. These results extend the previous work based on published trial summary data.[80] Overall, based on this research, this study would recommend the use of adjusted OLR (or generalised OLR if the proportionality of odds assumption fails) for the analysis of ordered categorical event outcomes. This is due to the fact that parametric tests are more powerful than their non-parametric equivalents, it is possible to adjust for important prognostic covariates and this test it capable of producing a

meaningful estimate of effect (i.e. odds ratio and confidence intervals) that researchers will be familiar with.

In this study, there were two methods - the Mann-Whitney U test and Win ratio test - which often appeared to be more efficient than the others. Although neither can be adjusted for covariates, extensions of these methods do allow for covariate adjustment.[153-156] Furthermore, though shown not to be as efficient as the ordinal methods, there are extensions that could be applied to the Cox proportional hazards model that enable adjustment for covariates in a manner that does not require the proportional hazards assumption for covariates.[157]

The premise of this study is that an effective, or even hazardous, treatment alters both the risk and severity of an event. Although novel when considered across vascular prophylaxis, individual trials and meta-analyses have found this before, as seen in the Heart Protection Study with simvastatin,[158] and for HRT.[159]

This study has a number of strengths. First, the study used individual participant data, not summary data, thereby allowing covariate adjusted analyses. Second, trials included both primary and secondary prevention studies and multiple intervention types thereby increasing the external validity of the findings. Third,

ordered categorical outcomes have embedded dichotomies for poorer versus better outcome; for example, event versus no event, or major event versus no major event and so on. Therefore, if statistical significance is shown, further closed testing methods can be applied to present results for the important dichotomies; this would be particularly useful for a trichotomous outcome for which the two embedded dichotomies are of primary interest.

However, there are also a number of limitations apparent. First, individual data were not shared for a majority of identified trials, a common problem in data pooling projects. Although non-availability of data might cause a systematic bias, the included trials involved both primary and secondary prevention studies, and a range of different interventions. Second, trials typically did not include sufficient information to allow 4 or more levels of ordinal data to be generated for MI and bleeding; some stroke trials allowed ordinal outcomes to be generated up to 9 levels. In principle, MI could be further categorised with the addition of unstable angina and angina, and MI could be divided into ST-elevation and non-ST elevation. Third, for the trials that had comparisons of two (or more) intervention groups to the same control group, the rankings of the p-values are not independent. However, this issue is unlikely to have had a significant impact on the final results because the rankings of methods were done within the respective comparisons.

Fourth, the use of p-values (rather than quantifying effects) to compare the performance of methods and drawing conclusions is also a limitation as evidence-based decision-making is only partly influenced by p-values. However, this was necessary as different tests produce different quantifying effects and p-values offer a common currency. Furthermore, the ranking of p-values within comparisons is likely to be very similar to the ranking of standardized effect sizes. Last, there are other comparison methods that could be considered more suitable than the Freidman's ANOVA and the Duncan's test, such as a more generally applicable version of Friedman's ANOVA test and a multivariate extension of the Wilcoxon signed ranks test [160], although each method has its own limitations. Nevertheless, these approaches were also utilised, for the same purpose, in the published Optimising the analysis of Acute Stroke Trials collaboration [161].

## 4.5 Conclusions

In summary, vascular outcomes can be ordered categorical variables with ordering determined by the severity of the vascular event. This improves statistical efficiency as well as providing additional information for participants, public and healthcare practitioners. The approach appears to be relevant to all tested

vascular interventions and outcomes (stroke, MI, major adverse cardiovascular events, bleeding). Further, where applicable, adjusted analyses add further statistical efficiency. The use of ordinal outcomes as primary outcomes could also lead to significant reductions in sample size. Future vascular prevention trials should consider whether to use ordered categorical outcomes and the statistical methods associated with those. If this approach is chosen the resulting trials could be smaller whilst retaining their original power, and would test the effect of interventions on severity, not just the absolute number of events. Implementation of this approach might then lead to smaller, shorter and less expensive vascular prophylaxis trials.

# CHAPTER 5

# RESULTS

# TARDIS TRIAL RE-ASSESSMENT

**List of publications associated with this chapter**

Lisa J Woodhouse, Alan A Montgomery, Stuart Pocock, Marilyn James, Anna Ranta and Philip M Bath; for the TARDIS Investigators. Optimising the analysis of vascular prevention trials: re-assessment of the TARDIS trial, the first prevention trial to adopt an ordinal primary outcome measure. (Submitted for publication – Contemporary Clinical Trials Communications, 2021)

Lisa J Woodhouse, Alan A Montgomery, Stuart Pocock, Marilyn James, Anna Ranta and Philip M Bath; for the TARDIS Investigators. Optimising the analysis of vascular prevention trials: re-assessment of the TARDIS trial, the first prevention trial to adopt an ordinal primary outcome measure. European Stroke Organisation Conference (ESOC Lyon) 2022 – Poster.

Others:

Philip M W Bath, Katie Robson, Lisa J Woodhouse, et al. Statistical analysis plan for the 'Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke' (TARDIS) trial. Int J Stroke. 2015 Apr; 10(3):449-51. doi: 10.1111/ijs.12445. Epub 2014 Dec 30.

Philip MW Bath, Jason P Appleton, Maia Beridze, Hanne Christensen, Robert A Dineen, Lelia Duley, Timothy J England, Stan Heptinstall, Marilyn James, Kailash Krishnan, Hugh S Markus, Stuart Pocock, Annemarei Ranta, Thompson G Robinson, Katie Flaherty, Polly Scutt, Graham S Venables, Lisa J Woodhouse, Nikola Sprigg. Baseline characteristics of the 3096 patients recruited into the 'Triple Antiplatelets for Reducing Dependency after Ischemic Stroke' trial. Int J Stroke. 2016 Nov 3. pii: 1747493016677988.

Philip M Bath, Lisa J Woodhouse, Jason P Appleton, et al. Antiplatelet therapy with aspirin, clopidogrel, and dipyridamole versus clopidogrel alone or aspirin and dipyridamole in patients with acute cerebral ischaemia (TARDIS): a randomised, open-label, phase 3 superiority trial. Lancet. 2018 Mar 3; 391(10123):850-859. doi: 10.1016/S0140-6736(17)32849-0. Epub 2017 Dec 20. PMID: 29274727; PMCID: PMC5854459.

Philip M Bath, Lisa J Woodhouse, Jason P Appleton, et al. Triple versus guideline antiplatelet therapy to prevent recurrence after acute ischaemic stroke or transient ischaemic attack: the TARDIS RCT. Health Technol Assess. 2018 Aug; 22(48):1-76. doi: 10.3310/hta22480.

# 5 TARDIS: A re-assessment

## 5.1 Introduction

As discussed in the previous chapter, the use of effective primary and secondary prevention strategies reduces the absolute risk of vascular events. As absolute event rates are a fundamental part of sample size calculations for binary events, a reduction in event numbers necessitates that clinical trials must be larger and / or run for longer and so expose more patients to risks and be more expensive.[116] Further, there has also been an increase in the numbers of trials being undertaken as more therapies are developed and need testing. The combination of these two factors means that recruitment of the required number of patients is a challenging and competitive process.[117] New approaches therefore are needed to reduce the sample size of clinical trials, which in turn will reduce costs, completion times and the number of patients exposed to risks.

In the previous chapter, there was an assessment of whether it is more efficient to have an ordinalised vascular event outcome, incorporating event severity (e.g. fatal / severe / mild), rather than

the traditional binary event / no event outcome as the primary measure. The Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke (TARDIS) trial was the first vascular prevention trial to prospectively use ordinal primary efficacy and safety outcome measures, and also recorded ordinal data for other outcomes.[81] The trial compared intensive antiplatelet therapy (combined aspirin, clopidogrel and dipyridamole) with guideline antiplatelet therapy (either combined aspirin and dipyridamole, or clopidogrel alone) in patients with acute non-cardioembolic ischaemic stroke (of any severity) or transient ischaemic attack (TIA) and recruited within 48 hours of onset. Although intensive antiplatelet therapy did not reduce recurrence as compared with guideline therapy, a significant increase in bleeding was present with intensive antiplatelets.[81] Overall, the trial was neutral and there was no net balance in favour of hazard or benefit. These results differ from the Clopidogrel in High-Risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial and POINT trials which reported that treatment with combined aspirin and clopidogrel was associated with a lower risk of recurrent stroke events by 90 days in patients with minor ischaemic stroke or TIA when enrolled within 24 and 12 hours of onset respectively.[162, 163]

This chapter will report a pre-planned re-analysis of TARDIS comparing the efficiency of ordinal and binary statistical approaches. This has been done across the whole TARDIS population and then in a subgroup of participants that match those in CHANCE, i.e., those recruited within 24 hours of a mild stroke (National Institutes of Health stroke scale, NIHSS ≤ 3) or TIA.

## 5.2 Methods

### 5.2.1 TARDIS design

TARDIS was a prospective, randomised, open-label, blinded-endpoint trial conducted across four countries at 106 sites. The protocol, statistical analysis plan, baseline characteristics of the participants and primary results have been published previously.[81, 164-166] Briefly, adult patients aged 50 years or older were eligible for inclusion if they were at risk of a recurrent ischaemic event and had had either a non-cardioembolic ischaemic stroke (with limb weakness, dysphasia and / or hemianopia, and of any severity on the NIHSS) or a non-cardioembolic TIA (with at least ten minutes of limb weakness or isolated dysphasia).

Participants had to be randomised within 48 hours of onset. TARDIS was approved by national and / or local ethics committees and national competent authorities in each participating country, was registered (ISRCTN47823388) and was adopted in the UK by the National Institute of Health Research (NIHR) Stroke Research Network. Participants gave written consent, or written proxy consent from a relative, carer or friend if they lacked capacity.

Participants were randomised to intensive antiplatelet therapy comprising combined aspirin (300 mg load then 50-150mg daily), clopidogrel (300 mg load then 75 mg daily) and dipyridamole (200 mg twice daily modified release) or to guideline therapy comprising either clopidogrel alone or combined aspirin and dipyridamole;[81] the use of two control antiplatelet strategies reflected national guidelines and licenses at the time of the trial. Randomised antiplatelet drugs were then given for 30 days, after which participants were treated according to local guidelines.

### 5.2.2 Ordinal efficacy and safety outcomes

The final follow-up was performed centrally at 90 days by telephone from the coordinating centre in each country, with the assessor blinded to treatment allocation. The primary efficacy outcome

comprised recurrence and its severity assessed using a six-level ordered categorical scale based in part on the modified Rankin Scale (mRS): fatal stroke (mRS 6), non-fatal severe stroke (mRS 4 or 5), moderate stroke (mRS 2 or 3), mild stroke (mRS 0 or 1), TIA, and neither stroke nor TIA.[81] Identification of recurrent cerebrovascular events was triangulated between reporting by the investigator, participant and general practitioner. The primary safety outcome was bleeding and its severity assessed using a five level ordered categorical scale: fatal, major, moderate, minor and none.[81] The definitions of fatal, major and moderate bleeding were according to the International Society on Thrombosis and Haemostasis and are based on severity, site of bleeding, fall in haemoglobin and need for transfusion.[167] Other outcomes collected or derived, with severity information, included myocardial infarction (MI), angina, cardiac events, venous thromboembolism (VTE), serious adverse events (SAEs) and major adverse cardiovascular events (MACE). For the purposes of this analysis MACE was a composite outcome made up of any vascular death, MI and stroke, though, as mentioned previously (see section 1.3.1) composite outcomes do have disadvantages. It should also be noted that the MACE ordinal outcomes were constructed under the assumption that the 'worst' event would be taken rather than the 'first' event. For instance, if a participant has had a non-fatal stroke, but then later also has a fatal MI, then the fatal MI would be used

for the composite outcome. The primary efficacy and safety outcomes and SAEs (including cause-specific case-fatality) were validated and categorised by expert adjudicators who were blinded to treatment assignment. Participants who did not receive their allocated treatment or did not adhere to the protocol were still followed up in full at day 90 and included in all analyses.

### 5.2.3 Mild stroke / TIA

A pre-specified sub-group of participants matching those in CHANCE was created as those with an index event of mild stroke (NIHSS<4) or TIA with randomisation within 24 hours.[162]

### 5.2.4 Statistical testing

Fifteen methods for analysing binary and ordered categorical outcomes were used for assessing treatment effects (see section 2.3.2 for the rationale behind the choice of these methods). Methods included the Chi-Square test (used for binary outcomes, binary fatal outcomes and ordinal outcomes), binary logistic regression (BLR, adjusted, for binary outcomes), Cox proportional

hazards models (CPH, adjusted and unadjusted, for binary outcomes), Cochran-Armitage Trend test (for ordinal outcomes), Mann-Whitney U test (for ordinal outcomes), median test (for ordinal outcomes), ordinal logistic regression (OLR, adjusted and unadjusted, for ordinal outcomes), bootstrapping the mean rank (for ordinal outcomes), t-test (for ordinal outcomes), multiple linear regression (MLR, adjusted, for ordinal outcomes) and the Win Ratio test.[68, 84, 86, 87, 90] For the adjusted analyses the covariates comprised age, sex, pre-morbid function, systolic blood pressure, syndrome (OSCP classification), previous antiplatelet therapy (number of tablets), use of gastroprotection, use of low dose heparin, time to randomisation, NIHSS and treatment with alteplase.[81]

For each ordinal outcome, the results of the ordinal and continuous outcome tests used were compared with the results of the tests performed on the counterpart binary outcome. The most efficient test was defined as the test which discerned the largest difference between the comparison groups (i.e. the test that produced the smallest p-value). Therefore, the results of the tests run on the ordinal and binary outcomes were ranked, with the result with the smallest p-value being given the smallest rank; i.e. the highest rank of 1. Once the ranking of the tests had been determined for each outcome comparison the results were then tabulated and displayed

as a heat map of rankings. This made it possible to determine any trends in the ranking of tests. The proportion of significant results ($p<0.05$) for each test, across the different outcomes, was also calculated.

### 5.2.5 Statistical analyses

Data are number (%), median [25th, 75th quartiles] or mean (standard deviation, SD). No adjustment was made for multiplicity of testing for secondary analyses. All analyses were by the intention to treat principle for all comparisons. Statistical analyses were performed using SAS software (version 9.4).

## 5.3 Results

### 5.3.1 Patient characteristics

TARDIS commenced recruitment on 7th April 2009 but was halted on the 18th March 2016 on the advice of the trial's independent Data Monitoring Committee (DMC).[81] The DMC reported a

significant increase in major bleeding without a significant reduction in stroke. In the published analysis, the absolute numbers of stroke and bleeding events were similar.[81] The rate of TIA was lower with triple antiplatelet therapy. Of the 3096 participants (intensive group 1556 [50.3%]; guideline 1540 [49.7%]), 2143 participants (69.2%) were recruited with a diagnosis of ischaemic stroke with the remaining 30.8% having a TIA (Table 5.1). The median time from onset to recruitment was 29.3 hours [quartiles: 21.8, 39.6 hours] with 764 (24.7%) recruited within 24 hours of a mild stroke (305, 39.9%) or TIA (459, 60.1%).

**Table 5.1 Baseline characteristics of the TARDIS participants overall and within the mild / TIA ≤24 hour subgroup**

| | TARDIS | | | Mild / TIA ≤24 hour subgroup | | |
|---|---|---|---|---|---|---|
| | All | Intensive | Guideline | All | Intensive | Guideline |
| Participants | 3096 | 1556 | 1540 | 764 | 385 | 379 |
| Age (years) | 69.0 (10.1) | 69.1 (9.9) | 68.9 (10.3) | 69.0 (10.0) | 69.3 (9.7) | 68.8 (10.2) |
| Sex, male (%) | 1945 (63) | 982 (63) | 963 (63) | 482 (63) | 256 (66) | 226 (60) |
| mRS, pre-morbid | 0.0 [0.0, 0.0] | 0.0 [0.0, 0.0] | 0.0 [0.0, 0.0] | 0.0 [0.0, 0.0] | 0.0 [0.0, 0.0] | 0.0 [0.0, 0.0] |
| Time OTR (hours) | 29.3 [21.8, 39.6] | 29.3 [21.7, 39.7] | 29.3 [21.9, 39.5] | 17.3 [9.5, 21.5] | 17.7 [10.5, 21.6] | 16.9 [8.9, 21.5] |
| Medical history (%) | | | | | | |
| Smoking, current | 784 (26) | 404 (26) | 380 (25) | 151 (20) | 72 (19) | 79 (21) |
| Hypertension | 1824 (59) | 930 (60) | 894 (58) | 440 (58) | 225 (58) | 215 (57) |
| Hyperlipidaemia | 1317 (44) | 655 (44) | 662 (45) | 344 (47) | 161 (43) | 183 (51) |
| Diabetes | 590 (19) | 280 (18) | 310 (20) | 142 (19) | 65 (17) | 77 (20) |
| Stroke | 348 (11) | 189 (12) | 159 (10) | 75 (10) | 46 (12) | 29 (8) |
| Ischaemic heart disease | 403 (13) | 196 (13) | 207 (13) | 83 (11) | 39 (10) | 44 (12) |
| Peripheral artery disease | 70 (2) | 40 (3) | 30 (2) | 16 (2) | 7 (2) | 9 (2) |
| Bleed, major | 19 (1) | 9 (1) | 10 (1) | 4 (1) | 2 (1) | 2 (1) |
| Clinical features | | | | | | |

| | TARDIS | | | Mild / TIA ≤24 hour subgroup | | |
|---|---|---|---|---|---|---|
| | All | Intensive | Guideline | All | Intensive | Guideline |
| NIHSS (/42) | 2.8 (3.6) | 2.9 (3.7) | 2.7 (3.5) | 1.0 (1.2) | 1.0 (1.3) | 0.9 (1.2) |
| OCSP, TACI (%) | 181 (6) | 86 (6) | 95 (6) | 6 (1) | 4 (1) | 2 (1) |
| Systolic BP (mmHg) | 143.5 (18.2) | 143.4 (17.8) | 143.6 (18.5) | 145.9 (18.0) | 146.2 (17.7) | 145.5 (18.3) |
| Weight (kg approx.) | 75.3 (16.6) | 75.5 (16.7) | 75.1 (16.5) | 75.8 (16.4) | 76.2 (16.2) | 75.4 (16.6) |
| Qualifying event (%) | | | | | | |
| Ischaemic stroke | 2143 (69) | 1076 (69) | 1067 (69) | 305 (40) | 152 (39) | 153 (40) |
| TIA | 953 (31) | 480 (31) | 473 (31) | 459 (60) | 233 (61) | 226 (60) |
| Treatment (%) | | | | | | |
| Prior AP(s) | 1080 (35) | 557 (36) | 523 (34) | 262 (34) | 137 (36) | 125 (33) |
| Prior heparin | 7 (0) | 2 (0) | 5 (0) | 1 (0) | 0 (0) | 1 (0) |
| Alteplase | 341 (11) | 169 (11) | 172 (11) | 1 (0) | 0 (0) | 1 (0) |
| AP + Alteplase | 196 (6) | 97 (6) | 99 (6) | 0 (0) | 0 (0) | 0 (0) |
| Randomised AP | | | | | | |
| ACD | 1556 (50) | 1556 (100) | 0 (0) | 385 (50) | 385 (100) | 0 (0) |
| AD | 691 (22) | 0 (0) | 691 (45) | 204 (27) | 0 (0) | 204 (54) |
| Clopidogrel | 849 (27) | 0 (0) | 849 (55) | 175 (23) | 0 (0) | 175 (46) |
| Imaging (%) | | | | | | |
| Compatible lesion | 1051 (40) | 533 (40) | 518 (39) | 156 (26) | 70 (24) | 86 (28) |
| Mass effect | 514 (49) | 266 (50) | 248 (48) | 70 (45) | 35 (50) | 35 (41) |
| ASPECTS [/10] | 8.0 [7.0, 9.0] | 8.0 [7.0, 9.0] | 8.0 [7.0, 9.0] | 9.0 [7.0, 9.0] | 9.0 [7.0, 9.0] | 8.0 [7.0, 9.0] |

| | TARDIS | | | Mild / TIA ≤24 hour subgroup | | |
|---|---|---|---|---|---|---|
| | All | Intensive | Guideline | All | Intensive | Guideline |
| Atrophy | 2448 (93) | 1218 (92) | 1230 (93) | 576 (95) | 280 (95) | 296 (95) |
| Leukoaraiosis | 1054 (40) | 534 (41) | 520 (40) | 221 (36) | 110 (37) | 111 (36) |
| Old stroke | 1595 (61) | 807 (61) | 788 (60) | 349 (57) | 173 (58) | 176 (56) |

ACD: Aspirin, Clopidogrel & Dipyridamole; AD: Aspirin & Dipyridamole; AP: antiplatelets; ASPECTS: Alberta stroke programme early CT score; OTR: onset to randomisation; TIA: transient ischaemic attack.

### 5.3.2 Creation of ordinal outcomes

In addition to the 6-level primary efficacy and 5-level primary safety outcomes used for the original analysis,[81] further ordered categorical outcomes were created using the available data. The new outcomes included 3 to 6, 8 and 9-level stroke / TIA measures, 3 to 7 level myocardial infarction / angina events, and 3 to 5 level events relating to bleeding, major adverse cardiac events (MACE), venous thromboembolism (VTE) and serious adverse events (SAEs) (Table 5.2). These ranged in each case between no event and a fatal outcome.

**Table 5.2 Ordered categorical severity levels for vascular event outcomes**

| Levels | Stroke (some include TIA) | MI (some include angina) | Bleeding, Cardiac event, MACE, VTE, SAE |
|---|---|---|---|
| 2 | Event / none | Event / none | Event / none |
| 2 | Fatal event / non-fatal + no event | Fatal event / non-fatal + no event | Fatal event / non-fatal + no event |
| 3 | Fatal / non-fatal / none | Fatal / non-fatal / none | Fatal / non-fatal / none |
| 4 | Fatal / severe / moderate-mild / none | Fatal / severe / moderate-mild / none | Fatal / severe / moderate-mild / none |
| 4 | Fatal / non-fatal / TIA / none | Fatal / non-fatal / angina / none | |
| 5 | Fatal / severe / moderate / mild / none | Fatal / severe / moderate / minor / none | Fatal / severe / moderate / minor / none |
| 5 | Fatal / severe / moderate-mild / TIA / none | Fatal / severe / moderate-mild / angina / none | |
| 5 | | Fatal / non-fatal / unstable angina / stable angina / none | |
| 6 | Fatal / severe / moderate / mild / TIA / none | Fatal / severe / moderate / mild / angina / none | |
| 6 | | Fatal / severe / moderate-mild / unstable angina / stable angina / none | |
| 7 | | Fatal / severe / moderate / mild / unstable angina / stable angina / none | |

| | |
|---|---|
| 8 | Fatal / mRS=5 / mRS=4 / mRS=3 / mRS=2 / mRS=1 / mRS=0 / none |
| 9 | Fatal / mRS=5 / mRS=4 / mRS=3 / mRS=2 / mRS=1 / mRS=0 / TIA / none |

MI: Myocardial infarction; MACE: Major cardiovascular events; mRS: modified Rankin Scale; SAE: Serious adverse event; TIA: Transient ischaemic attack; VTE: Venous thromboembolism.

### 5.3.3 Outcomes and ranks of tests – All participants

Overall, 3070 (99.2%) participants had data relating to stroke, TIA, MI, angina, cardiac events, MACE and VTE, 3072 (99.2%) for bleeding and 3074 (99.3%) for SAEs (Table 5.3).

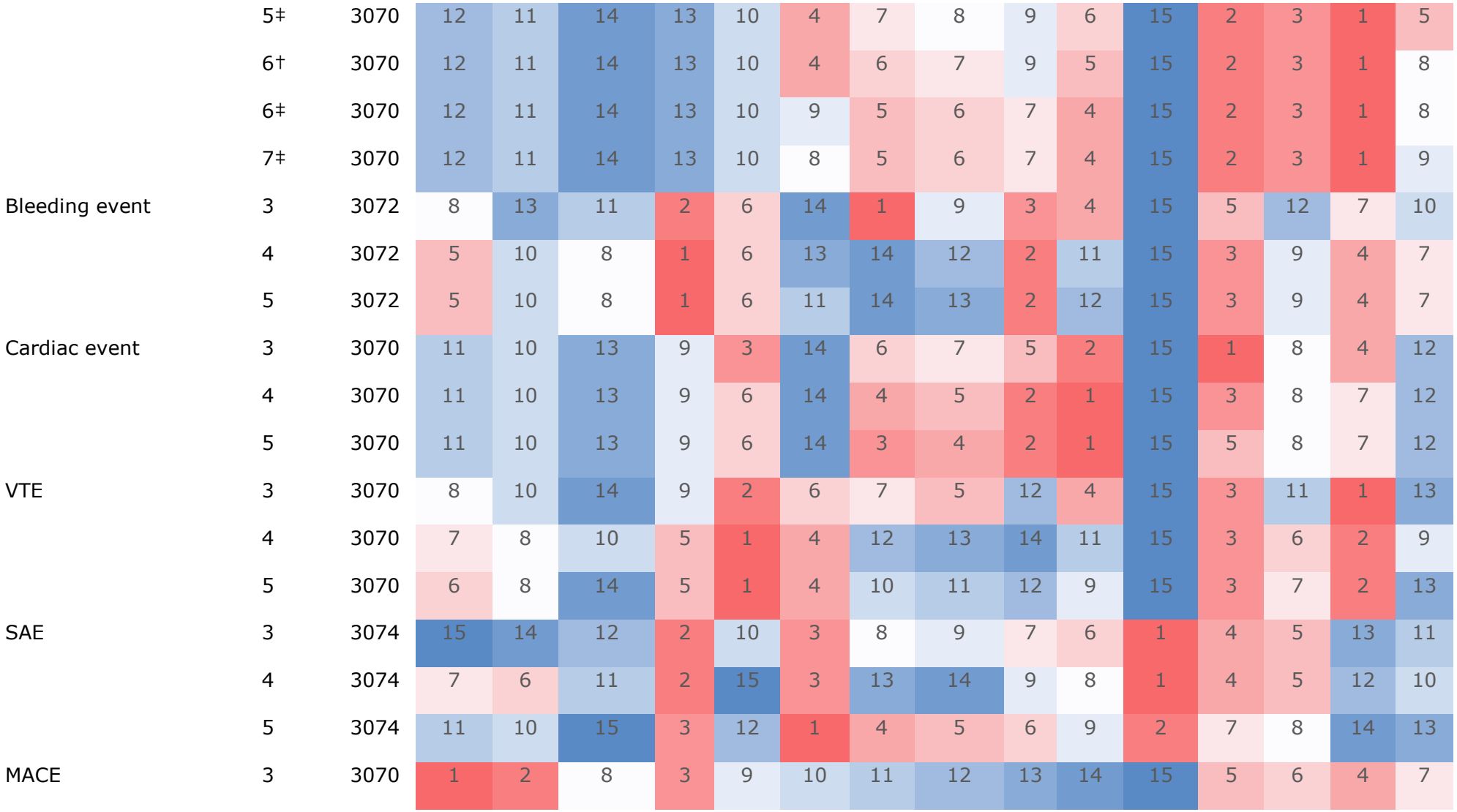
For 20/32 (63%) outcome comparisons, tests run on the ordinal outcome had the smallest rank. In 7 (35%) of those 20 outcome comparisons, the Mann-Whitney U test appeared to be the most efficient test, that is the test with the smallest rank, for events such as stroke including TIA, stroke and MACE. Adjusted MLR was then the test with the smallest rank for 5/20 (25%) outcome comparisons, for events including MI and cardiac events. Following that was OLR, which was the test with the lowest rank for 3/20 (15%) outcome comparisons, with each comparison undertaken on a stroke outcome. Adjusted OLR was then the test with the smallest rank for 2/20 (10%) of the outcome comparisons, with each comparison being performed on a VTE outcome. The Median test, ordinal Chi-Square test and Cochran-Armitage trend test each had the lowest rank for 1/20 (5%) of the outcome comparisons, for events including bleeding, SAEs and MACE.

The test with the largest proportion of significant results was the Median test with 13% (Table 5.3). The rest of the tests, with the

exception of the fatal Chi-Square, had a 9% significant proportion rate.

**Table 5.3 Heat map showing rankings of tests for each outcome in all participants.**

| Outcome | Levels | N | MWU | OLR | Median | WR | Adj. OLR | Ord. Chi | CAT | t-test | BS | Adj. MLR | Fatal Chi | Adj. CPH | CPH | Adj. BLR | Bin Chi |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stroke, including TIA | 4 | 3070 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
| | 5 | 3070 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
| (Primary outcome) | 6 | 3070 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 11 | 10 | 12 | 13 | 14 | 15 |
| | 9 | 3070 | 1 | 2 | 3 | 4 | 5 | 6 | 10 | 11 | 13 | 14 | 7 | 8 | 9 | 12 | 15 |
| Stroke | 3 | 3070 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
| | 4 | 3070 | 9 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 10 | 11 | 13 | 14 | 15 | 12 |
| | 5 | 3070 | 11 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 13 | 14 | 15 | 12 |
| | 8 | 3070 | 2 | 1 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 13 | 14 | 15 | 12 |
| MI | 3 | 3070 | 8 | 10 | 13 | 9 | 2 | 14 | 3 | 4 | 5 | 1 | 15 | 7 | 11 | 6 | 12 |
| | 4 | 3070 | 8 | 10 | 13 | 9 | 4 | 14 | 2 | 3 | 5 | 1 | 15 | 7 | 11 | 6 | 12 |
| | 5 | 3070 | 8 | 10 | 13 | 9 | 5 | 14 | 2 | 3 | 4 | 1 | 15 | 7 | 11 | 6 | 12 |
| MI, including angina | 4† | 3070 | 12 | 11 | 14 | 13 | 10 | 4 | 7 | 8 | 9 | 6 | 15 | 2 | 3 | 1 | 5 |
| | 5† | 3070 | 12 | 11 | 14 | 13 | 10 | 9 | 6 | 7 | 8 | 4 | 15 | 2 | 3 | 1 | 5 |


5‡ 3070 12 11 14 13 10 4 7 8 9 6 15 2 3 1 5
6† 3070 12 11 14 13 10 4 6 7 9 5 15 2 3 1 8
6‡ 3070 12 11 14 13 10 9 5 6 7 4 15 2 3 1 8
7‡ 3070 12 11 14 13 10 8 5 6 7 4 15 2 3 1 9
Bleeding event 3 3072 8 13 11 2 6 14 1 9 3 4 15 5 12 7 10
4 3072 5 10 8 1 6 13 14 12 2 11 15 3 9 4 7
5 3072 5 10 8 1 6 11 14 13 2 12 15 3 9 4 7
Cardiac event 3 3070 11 10 13 9 3 14 6 7 5 2 15 1 8 4 12
4 3070 11 10 13 9 6 14 4 5 2 1 15 3 8 7 12
5 3070 11 10 13 9 6 14 3 4 2 1 15 5 8 7 12
VTE 3 3070 8 10 14 9 2 6 7 5 12 4 15 3 11 1 13
4 3070 7 8 10 5 1 4 12 13 14 11 15 3 6 2 9
5 3070 6 8 14 5 1 4 10 11 12 9 15 3 7 2 13
SAE 3 3074 15 14 12 2 10 3 8 9 7 6 1 4 5 13 11
4 3074 7 6 11 2 15 3 13 14 9 8 1 4 5 12 10
5 3074 11 10 15 3 12 1 4 5 6 9 2 7 8 14 13
MACE 3 3070 1 2 8 3 9 10 11 12 13 14 15 5 6 4 7

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | 3070 | 1 | 2 | 8 | 3 | 9 | 14 | 10 | 11 | 12 | 13 | 15 | 5 | 6 | 4 | 7 |
| 5 | 3070 | 2 | 3 | 1 | 4 | 9 | 14 | 10 | 11 | 12 | 13 | 15 | 6 | 7 | 5 | 8 |
| Proportion of significant results (%) | | 9 | 9 | 13 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 0 | 9 | 9 | 9 | 9 |

†Includes a composite of stable and unstable angina as a level. ‡Includes stable and unstable angina as separate levels.

Adj.: adjusted; Bin: binary; BLR: binary logistic regression; BS: bootstrapping; CAT: Cochran-Armitage trend test; CPH: Cox proportional hazards; CSB: Chi-square binary event outcome; CSF: Chi-square binary fatal event outcome; CSO: Chi-square ordinal event outcome; MACE: Major Adverse Cardiovascular event; MI: myocardial infarction; MLR: multiple linear regression; MT: median test; MWU: Mann-Whitney U test; OLR: ordinal logistic regression; Ord.: Ordinal; TT: t-test; SAE: Serious Adverse Event; VTE: Venous thromboembolism; WR: Win ratio test.

### 5.3.4 Outcomes and ranks of tests – the Mild stroke / TIA, ≤24 hour subgroup

Out of the 764 participants in this subgroup, 755 (98.8%) had outcome data regarding stroke, TIA, MI, angina, cardiac events and MACE (Table 5.4). Furthermore, 756 (99.0%) participants had data regarding bleeding events and SAEs. It was not possible to perform outcome analyses for VTE as no events occurred in this population of participants.

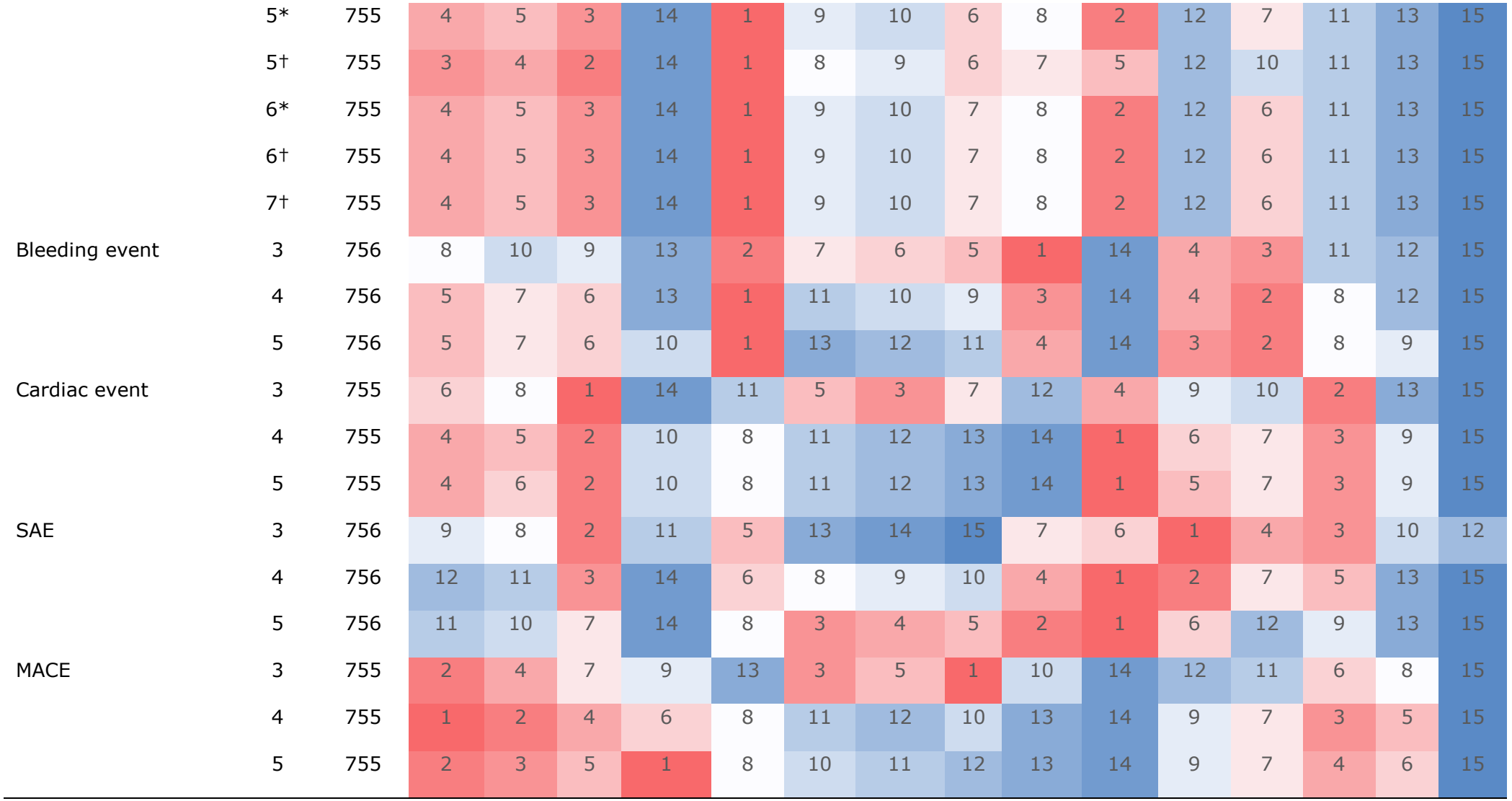
For 27/29 (93%) outcome comparisons, tests run on the ordinal outcome had the smallest rank. Of those 27, adjusted OLR was the test with the smallest rank for 8 (30%) outcome comparisons, for outcomes such as MI including angina and bleeding events. Following that was the ordinal Chi-Square test, which was the test with the lowest rank in 6 (22%) of the outcome comparisons, for event outcomes including MI, cardiac events and SAEs. The Mann-Whitney U test came next, being the test with the lowest rank in 5 (19%) outcome comparisons, for event outcomes such as stroke including TIA and MACE. In 4 (15%) outcome comparisons the test with the lowest rank was the Cochran-Armitage trend test, with all comparisons being performed for a stroke outcome. Bootstrapping was then the test with the lowest rank in 2 (7%) of the outcome comparisons, for outcomes relating to MI events and MACE. As for

MLR and the Median test, these methods were each the test with the lowest rank for 1 (4%) of the outcome comparisons, for events including bleeding and MACE.

The tests with the largest proportions of significant results were Mann-Whitney U test, adjusted and unadjusted ordinal logistic regression and the Win Ratio test, each having a proportion of 34% (Table 5.4).

**Table 5.4 Heat map showing rankings of tests for each outcome in Minor stroke / TIA participants recruited within 24 hours**

| Outcome | Levels | N | MWU | OLR | WR | Median | Adj. OLR | CAT | t-test | BS | Adj. MLR | Ord. Chi | Adj. CPH | Adj. BLR | CPH | Bin Chi | Fatal Chi |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stroke, including TIA | 4 | 755 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
| | 5 | 755 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
| (Primary outcome) | 6 | 755 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
| | 9 | 755 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
| Stroke | 3 | 755 | 5 | 6 | 9 | 13 | 10 | 1 | 3 | 2 | 11 | 14 | 4 | 7 | 8 | 12 | 15 |
| | 4 | 755 | 6 | 7 | 11 | 13 | 10 | 1 | 2 | 3 | 4 | 14 | 5 | 8 | 9 | 12 | 15 |
| | 5 | 755 | 5 | 7 | 10 | 13 | 11 | 1 | 2 | 3 | 4 | 14 | 6 | 8 | 9 | 12 | 15 |
| | 8 | 755 | 5 | 6 | 10 | 13 | 8 | 1 | 2 | 3 | 4 | 14 | 7 | 9 | 11 | 12 | 15 |
| MI | 3 | 755 | 9 | 4 | 10 | 14 | 3 | 6 | 7 | 1 | 11 | 5 | 12 | 2 | 8 | 13 | 15 |
| | 4 | 755 | 9 | 8 | 11 | 14 | 7 | 3 | 4 | 2 | 5 | 1 | 12 | 6 | 10 | 13 | 15 |
| | 5 | 755 | 9 | 8 | 11 | 14 | 7 | 3 | 4 | 2 | 5 | 1 | 12 | 6 | 10 | 13 | 15 |
| MI, including angina | 4* | 755 | 3 | 4 | 2 | 14 | 1 | 8 | 9 | 7 | 6 | 5 | 12 | 10 | 11 | 13 | 15 |


5* 755 4 5 3 14 1 9 10 6 8 2 12 7 11 13 15
5† 755 3 4 2 14 1 8 9 6 7 5 12 10 11 13 15
6* 755 4 5 3 14 1 9 10 7 8 2 12 6 11 13 15
6† 755 4 5 3 14 1 9 10 7 8 2 12 6 11 13 15
7† 755 4 5 3 14 1 9 10 7 8 2 12 6 11 13 15
Bleeding event 3 756 8 10 9 13 2 7 6 5 1 14 4 3 11 12 15
4 756 5 7 6 13 1 11 10 9 3 14 4 2 8 12 15
5 756 5 7 6 10 1 13 12 11 4 14 3 2 8 9 15
Cardiac event 3 755 6 8 1 14 11 5 3 7 12 4 9 10 2 13 15
4 755 4 5 2 10 8 11 12 13 14 1 6 7 3 9 15
5 755 4 6 2 10 8 11 12 13 14 1 5 7 3 9 15
SAE 3 756 9 8 2 11 5 13 14 15 7 6 1 4 3 10 12
4 756 12 11 3 14 6 8 9 10 4 1 2 7 5 13 15
5 756 11 10 7 14 8 3 4 5 2 1 6 12 9 13 15
MACE 3 755 2 4 7 9 13 3 5 1 10 14 12 11 6 8 15
4 755 1 2 4 6 8 11 12 10 13 14 9 7 3 5 15
5 755 2 3 5 1 8 10 11 12 13 14 9 7 4 6 15

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Proportion of significant results (%) | 34 | 34 | 34 | 31 | 34 | 31 | 31 | 31 | 14 | 3 | 21 | 21 | 21 | 21 | 0 |

*Includes a composite of stable and unstable angina as a level. †Includes stable and unstable angina as separate levels.

Adj.: adjusted; BLR: binary logistic regression; BS: bootstrapping; CAT: Cochran-Armitage trend test; CPH: Cox proportional hazards; CSB: Chi-square binary event outcome; CSF: Chi-square binary fatal event outcome; CSO: Chi-square ordinal event outcome; MACE: Major Adverse Cardiovascular event; MI: myocardial infarction; MLR: multiple linear regression; MT: median test; MWU: Mann-Whitney U test; OLR: ordinal logistic regression; TT: t-test; SAE: Serious Adverse Event; VTE: Venous thromboembolism; WR: Win ratio test.

## 5.4 Discussion

For this analysis, 32 ordinal versions of vascular event outcomes were created for stroke, MI, bleeding events, cardiac events, MACE, SAEs and venous thromboembolism. For both TARDIS overall and in participants with mild stroke / TIA, the tests performed on the ordinal vascular outcomes tended to more efficient statistically than binary outcome analyses; the Mann-Whitney U test, ordinal logistic regression, Win Ratio, Cochran-Armitage trend test and adjusted multiple linear regression all were associated with the smallest ranks for at least some outcomes. Comparing the statistical tests in the subgroup of participants with minor stroke or TIA and randomised within 24 hours was important since these parameters matched the positive CHANCE trial.[162] The population adhering to the POINT trial inclusion criteria [163] were not assessed as few TARDIS participants were actually recruited within 12 hours.

From an implementation perspective, trialists should consider the prospective collection of information on event severity as well as event numbers for stroke, MI, MACE / cardiac events, VTE, bleeding and adverse events; theoretically, these approaches should work for other medical conditions that have ordered categorical scales such as heart, liver, renal and respiratory failure. In general, this will enhance the statistical power of analyses (or allow smaller sample

sizes). Unadjusted analyses can use the MWU or Win Ratio tests; similarly, covariate adjusted analyses can use OLR (or MLR if the assumption of proportionality fails). However, based on the research presented in this and the previous chapter, this study would recommend the use of adjusted OLR (or generalised OLR if the proportionality of odds assumption fails) for the analysis of ordered categorical event outcomes. The main reasons for use of this approach include the fact that parametric tests are more powerful than their non-parametric equivalents, it is possible to adjust for important prognostic covariates and this test is capable of producing a meaningful estimate of effect (i.e. odds ratio and confidence intervals) that researchers will be familiar with.

To date, TARDIS remains the only vascular prevention trial to have prospectively chosen an ordinal outcome although secondary or post hoc analyses of ordered categorical outcomes have been reported previously.[80, 118, 159, 168-170]

This analysis had several strengths, for instance, TARDIS had a large sample size (more than 3,000 participants), concealment of treatment assignment and assessment prospectively of multiple event outcomes. The trial also collected data regarding patient characteristics thereby allowing for covariate adjusted analyses. Lastly, ordinal outcomes have embedded dichotomies for worse

versus better outcome. For instance, event versus no event, major event versus no major event and so on. This means that if statistical significance is shown, further closed testing methods can be applied to present results for the important dichotomies.

However, there were limitations. Firstly, treatment was administered in an open-label design which could have increased the reporting of known adverse events. Secondly, recruitment to the TARDIS trial was stopped early following recommendation by the independent data monitoring committee which will have impacted the statistical power. Last, another limitation is the use of p-values to compare the efficiency of methods and drawing conclusions as evidence-based decision-making is not predominantly influenced by p-values. However, this approach was necessary since different statistical methods produce different quantifying effects and p-values are a common output. Additionally, the ranking of p-values within comparisons is very similar to the ranking of standardised effect sizes.

## 5.5 Conclusions

In summary, the results of this analysis show that vascular event outcomes can be ordinal with the inclusion of severity information.

This approach increases statistical efficiency and will also provide further information for participants, public and healthcare practitioners. In this particular analysis the methods used appeared to be relevant for the majority of the tested vascular outcomes.

# CHAPTER 6

# RESULTS

# COMPOSITE OUTCOMES AND

# GLOBAL ANALYSIS TECHNIQUES

**List of publications associated with this chapter**

Lisa J Woodhouse, Alan A Montgomery, Barry R Davies, Graeme J Hankey, Adrienne Kirby, Johnathan Mant, Jean-Louis Mas, Jan A Staessen, Andrew Tonkin and Philip M Bath; for the OA-Prevention Collaboration. Reanalysis of vascular event outcomes in prevention trials using global analysis methods. (To be submitted to Hypertension, 2022)

Lisa J Woodhouse, Alan A Montgomery, and Philip M Bath; for the OA-Prevention Collaboration. Reanalysis of vascular event outcomes in prevention trials using global analysis methods. European Stroke Organisation Conference (ESOC Lyon) 2022 – Presentation: Scientific Communications session – Secondary prevention.

# 6 Composite outcomes and use of global analysis techniques

## 6.1 Introduction

Successful primary and secondary prevention of vascular events requires the management of modifiable risk factors. Typically, preventive approaches after stroke or other vascular events encompasses blood pressure [31-33], lipid lowering [35, 36], antiplatelet [27, 37] or anticoagulant [39] therapy, surgery [40, 41] and possibly, vitamins [45, 46].

Advances in preventive treatment have resulted in a decline in the absolute risk of vascular events. As event rates are a key component of sample size calculations for binary outcomes, lower rates necessitate larger, longer-lasting and more expensive trials.[116] With ever-increasing new therapies, there has been a parallel increase in the number of trials undertaken. This combination of more and larger trials means that it is increasingly difficult to recruit sufficient numbers of patients in new trials.[117]

Therefore, new strategies are needed to permit robust testing of therapies in such trials.

In the primary analysis chapter (Chapter 4), my research assessed whether ordinal event outcomes, incorporating both event frequency and severity, are more efficient than binary versions. This research was performed on the premise that events can be fatal or non-fatal, minor or severe, generating the possibility for ordered categorical outcomes with 3 or more levels. Additionally, there is the notion that ordinal outcomes would be clinically more informative than binary versions.[80] For example, rather than only reporting that an intervention reduces the risk of an event, we can say that it reduces both the event rate and its severity. Overall, the research undertaken in Chapter 4 suggested that the analysis of ordinalised outcomes appeared to be more efficient statistically than that of binary (event / no event) outcomes.

However, one other possible approach to deal with low absolute event rates is to use a binary composite vascular outcome (any of the chosen events / none) as the primary measure, e.g. composites of any stroke, myocardial infarction or vascular death, or stroke or systemic embolism.[45, 128] Using a composite outcome increases the absolute event rate but does not provide information on the severity of the events. Alternatively, global analysis techniques

allow testing of the effect of an intervention on multiple outcomes at once to determine an overall result, e.g. analysis of stroke and myocardial infarction.

In this chapter there will be an assessment of whether analyses based on ordinal composite or global outcomes are more efficient than equivalents based on binary events.

## 6.2 Methods

### 6.2.1 Identification of trials

Individual patient data was sought from randomised controlled trials assessing the primary and secondary prevention of vascular events. Further information on the search strategy is provided in Chapter 2. Briefly, eligible studies were identified electronically through search engines including the Cochrane Library and PubMed.

### 6.2.2 Trial data

Data were requested for patient demographics, trial design and vascular events / outcomes, including information on severity. In trials where there were more than two treatment groups, outcomes were analysed for each treatment comparison that had been performed in the trial's main publication. Data were analysed according to allocated treatment using observed outcome data only. No imputation of missing data was performed.

### 6.2.3 Formation of outcomes

Ordinal outcomes were created for stroke, 3, 4 and 5-levels (i.e. no event / non-fatal stroke / fatal stroke, no event / TIA / non-fatal stroke / fatal stroke and no event / TIA / minor stroke / severe stroke / fatal stroke respectively); myocardial infarction, 3-levels (no event / non-fatal MI / fatal MI); and composite outcomes, 3-levels (no event / non-fatal event / fatal event).

### 6.2.4 Statistical analysis

Analyses included Chi-Square test and binary logistic regression for binary outcomes and ordinal logistic regression and Mann-Whitney U test for ordinal composite outcomes.[84, 85, 88, 91, 92] Global analyses included the Wald test for binary outcomes [94, 95] and the Wei-Lachin and Hotelling's $T^2$ tests for ordinal outcomes.[96, 97] The Wald test allows for the assessment of the effect of an intervention on multiple binary event outcomes at once. The Wei-Lachin test assesses the effect of an intervention on multiple categorical or continuous outcomes; this test takes account of the directionality of effect on each outcome. The Hotelling's $T^2$ test assesses the effect of an intervention on multiple continuous outcomes and determines an overall effect; however, it does not take directionality of effect into account. The Wald and Wei-Lachin tests produce estimates of effect - odds ratio and Mann-Whitney difference respectively - with corresponding confidence intervals, whereas the Hotelling's $T^2$ produces a test statistic. All analyses were carried out in SAS (version 9.4).

### 6.2.5 Comparison of statistical tests

Each comparison was analysed using each statistical analysis method. The most efficient analysis method was the test which discerned the largest difference between the comparison groups (i.e. the test that produced the smallest p-value). Therefore, the resulting outputs were then ordered within each comparison and given a rank, with the smallest rank given to the test that produced the smallest probability value. A mean rank was then calculated for each test across all of the available comparisons. A 2-way analysis of variance test (ANOVA, Friedman with adjustment for ties [119]) was used to determine if there was a difference in the average rank of each test. If the result of the ANOVA test was significant, the Duncan's multiple range test [98] was then used to determine the ordering of tests, and to find if significant differences were present between tests. The proportion of statistically significant results each test produced was also assessed.

## 6.3 Results

### 6.3.1 Trial characteristics

Of 35 trials that had shared data, 24 (69%; 158,901 participants) had data regarding stroke and myocardial infarction (Figure 6.1). The majority of the included trials were secondary prevention with nine being primary prevention trials (Table 6.1). Interventions included anticoagulants (ACT; two trials), antihypertensive agents (AHT; eight trials), antiplatelets (APT; five trials), carotid endarterectomy (CEA: three trials), hormone replacement therapy (HRT; two trials), statins (two trials) and vitamins (one trial). From the 24 trials, a total of 35 comparisons were derived as five of the trials had more than two intervention arms (Figure 6.1).

**Figure 6.1 Study flow diagram**

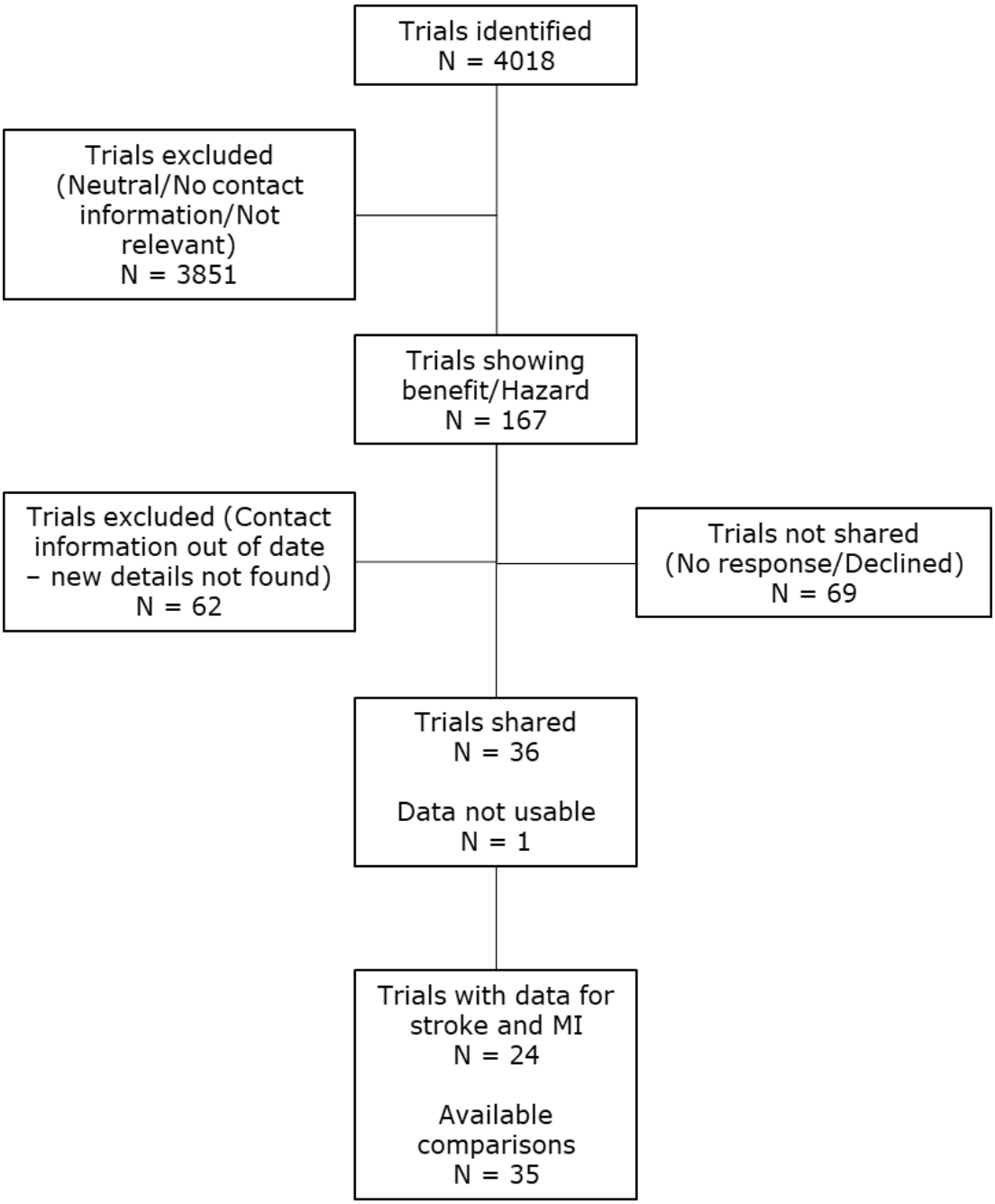


**Table 6.1 Characteristics of included trials**

| Trial | Year | Class | Treatment | Control | Size | Length of follow-up | Data source |
|---|---|---|---|---|---|---|---|
| ACAS [139] | 1995 | CEA | CEA | No surgery | 1662 | 2.7 years | NINDS |
| ALLHAT [131] | 2002 | AHT | CCB or ACE-I | Diuretic | 33357 | 4.9 years | NHLBI |
| CARE [147] | 1996 | Statins | Pravastatin | Placebo | 4159 | 5 years | CI |
| DUTCH-TIA [120] | 1991 | APT | A (283mg per day) / BB | A (30mg per day) / Placebo | 3131 | 2.6 years | CI |
| EAFT [113] | 1993 | ACT | ACT or Aspirin | Placebo | 1007 | 2.3 years | CI |
| ENOS [138] | 2014 | AHT | GTN | No GTN | 4011 | 3 months | CI |
| ESPRIT [121] | 2007 | APT | AD / ACT | A | 1068 | 4.6 years | CI |
| ESPS 1 [122] | 1990 | APT | AD | Placebo | 2500 | 2 years | CI |
| ESPS 2 [123] | 1996 | APT | A, D or AD | Placebo | 6602 | 2 years | CI |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| EVA-3S [140] | 2006 | CEA | CEA | Stenting | 527 | 4 years | CI |
| EWPHE [132] | 1985 | AHT | H + T | Placebo | 840 | 4.7 years | CI |
| INDANA MRC1 [133] | 1985 | AHT | Bendro or Prop | Placebo | 17354 | 5 years | CI |
| INDANA MRC2 [134] | 1992 | AHT | Diuretic or BB | Placebo | 4396 | 5.8 years | CI |
| IST-1 [110] | 1997 | ACT | Heparin | No heparin | 19435 | 6 months | Online |
| LIPID [146] | 1998 | Statins | Pravastatin | Placebo | 9014 | 6.1 years | CI |
| NASCET [30] | 1998 | CEA | CEA | No surgery | 2267 | 5 years | NINDS |
| PROGRESS [137] | 2001 | AHT | Perindopril | Placebo | 6105 | 4 years | CI |
| SHEP [135] | 2000 | AHT | Chlorthalidone | Placebo | 4736 | 4.5 years | NHLBI |
| SPIRIT [130] | 1997 | ACT | ACT | A | 1316 | 14 months | CI |
| SYST-EUR [136] | 1997 | AHT | Nitrendipine | Placebo | 6403 | 2 years | CI |
| TARDIS [81] | 2017 | APT | ACD | AD or C | 3996 | 3 months | CI |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| VISP [141] | 2004 | Vitamins | High FA, $B_6$ + $B_{12}$ | Low FA, $B_6$ + $B_{12}$ | 3680 | 2 years | NINDS |
| VITATOPS [45] | 2010 | Vitamins | B vitamins | Placebo | 8164 | 3.4 years | CI |
| WHI 1 [142] | 2002 | HRT | Estrogen + Progestin | Placebo | 16608 | 5.2 years | CI |
| WHI 2 [143] | 2004 | HRT | Estrogen | Placebo | 10739 | 5.2 years | CI |

ACT: Anticoagulants, AHT: Antihypertensives, APT: Antiplatelets; BB: ß-blocker; CEA: Carotid Endarterectomy, HRT: Hormone replacement therapy, CCB: Calcium channel blocker, ACE-I: Angiotensin-converting enzyme inhibitor, A: Aspirin, D: Dipyridamole, C: Clopidogrel, H + T: Hydrochlorothiazide plus Triamterene, Bendro: Bendroflumethiazide, Prop: Propranolol, BB: Beta blocker, FA: Folic acid, CI: Chief Investigator, NHLBI: National Heart, Lung and Blood Institute, NINDS: National Institute of Neurological Disorders and Stroke.

### 6.3.2 Patient Characteristics

The baseline characteristics of participants included in this analysis are provided in Table 6.2. All trials collected baseline age (mean 64 [SD 10] years), sex (female 53%), history of diabetes (17%) and history of hypertension (72%). The least commonly collected characteristics included history of ischaemic heart disease (11 trials), current alcohol intake (seven trials) and heart rate (seven trials). In regards to the secondary prevention trials, one was missing qualifying event data and another, time from onset to randomisation data. All baseline characteristics differed between the separate intervention types (Table 6.2).

## Table 6.2 Characteristics of trial participants by type of intervention

| | Trials | All | ACT | AHT | APT | CEA | HRT | Statins | Vitamins | P |
|---|---|---|---|---|---|---|---|---|---|---|
| **All** | | **N=24** | **N=2** | **N=8** | **N=5** | **N=3** | **N=2** | **N=2** | **N=2** | |
| Primary (%) | | 9 | 0 | 6 | 0 | 1 | 2 | 0 | 0 | |
| Secondary (%) | | 15 | 2 | 2 | 5 | 2 | 0 | 2 | 2 | |
| **Baseline** | | | | | | | | | | |
| Number | | 158901 | 2318 | 81058 | 18087 | 5074 | 27347 | 13173 | 11844 | |
| Age | 24 | 64.0 (9.9) | 67.4 (10.6) | 64.2 (10.0) | 65.9 (10.8) | 66.6 (8.2) | 63.4 (7.2) | 60.1 (8.8) | 63.7 (12.1) | <0.0001 |
| Sex, Female (%) | 24 | 83619 (52.6%) | 916 (39.5%) | 39213 (48.4%) | 7017 (38.8%) | 2711 (53.4%) | 27347 (100.0%) | 2092 (15.9%) | 4323 (36.5%) | <0.0001 |
| Medical History (%) | | | | | | | | | | |
| Diabetes | 24 | 27511 (17.3%) | 285 (12.3%) | 17143 (21.2%) | 2630 (14.5%) | 1135 (22.4%) | 1980 (7.2%) | 1368 (10.4%) | 2970 (25.3%) | <0.0001 |
| Hypertension | 24 | 112882 (72.3%) | 1028 (44.4%) | 76550 (94.5%) | 9679 (53.7%) | 3212 (63.3%) | 8433 (34.0%) | 5531 (42.0%) | 8449 (72.0%) | <0.0001 |
| Hyperlipidaemia | 13 | 12834 (21.4%) | 96 (9.6%) | 1019 (15.4%) | 4408 (24.5%) | 1291 (37.8%) | 3366 (13.7%) | - | 2654 (41.7%) | <0.0001 |
| IHD | 11 | 24546 (34.7%) | - | 8813 (24.0%) | 3420 (28.2%) | 1970 (38.8%) | - | 9014 (100.0%) | 1329 (17.0%) | <0.0001 |
| Stroke | 20 | 13843 (12.9%) | 188 (8.1%) | 5375 (13.9%) | 4750 (32.0%) | 717 (21.0%) | 306 (1.1%) | 369 (4.1%) | 2138 (18.2%) | <0.0001 |
| MI | 17 | 10714 (11.3%) | 204 (8.8%) | 704 (2.1%) | 1354 (9.0%) | 640 (18.8%) | 634 (2.3%) | 7178 (54.5%) | - | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Smoking, Current | 23 | 34436 (21.9%) | 780 (33.8%) | 17515 (21.9%) | 5659 (31.4%) | 1471 (29.0%) | 2831 (10.5%) | 1540 (11.7%) | 4640 (39.5%) | <0.0001 |
| Alcohol | 7 | 10505 (50.9%) | - | 4754 (48.0%) | 3063 (55.7%) | 561 (33.8%) | - | - | 2127 (59.4%) | <0.0001 |
| SBP | 22 | 147.5 (22.6) | 153.6 (24.0) | 155.2 (19.8) | 151.7 (23.1) | 146.1 (19.3) | 128.7 (17.6) | 134.1 (19.1) | 141.5 (20.9) | <0.0001 |
| DBP | 22 | 84.4 (12.0) | 88.6 (12.7) | 87.7 (11.1) | 86.5 (12.6) | 80.1 (10.0) | 76.0 (9.2) | 80.5 (10.8) | 81.6 (12.1) | <0.0001 |
| HR | 7 | 73.2 (12.5) | - | 77.5 (11.6) | 72.6 (14.3) | 73.1 (10.6) | - | 68.9 (10.9) | - | <0.0001 |
| **Secondary** | | | | | | | | | | |
| Qualifying event (%) | | | | | | | | | | |
| Stroke | 14 | 30544 (56.5%) | 772 (77.1%) | 5632 (85.2%) | 12444 (68.8%) | 1571 (46.0%) | - | - | 10125 (86.1%) | <0.0001 |
| MI | 14 | 9913 (18.3%) | - | - | - | - | - | 9913 (75.3%) | - | <0.0001 |
| TIA | 14 | 9861 (18.2%) | 229 (22.9%) | 974 (14.7%) | 5497 (30.4%) | 1759 (51.6%) | - | - | 1402 (11.9%) | <0.0001 |
| OTR (Days) | 14 | 172.6 (331.4) | 36.1 (35.8) | 418.0 (439.6) | 32.1 (242.1) | 47.9 (43.6) | - | 507.4 (317.0) | 60.2 (178.0) | <0.0001 |

ACT: Anticoagulants, AHT: Antihypertensives, APT: Antiplatelets, IHD: Ischaemic heart disease, MI: Myocardial infarction, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate and TIA: Transient ischaemic attack, OTR: Onset to randomisation. Percent's (%) are out of the total number of participants with available data. Comparisons performed using ANOVA or Chi-Square test.

### 6.3.3 Outcome analysis comparison for binary and 3-level outcomes

Binary and 3-level stroke, MI and composite outcomes were derived for all of the available comparisons. When the ranks of the global and standard methods were compared using the Freidman test, the results showed that there was evidence of a significant difference present between the tests ($p<0.0001$). Table 6.3 shows the results of the Duncan's multiple range test. Global analysis techniques appeared to be as efficient as the standard methods, with the Wei-Lachin test being the second most efficient after binary logistic regression (Table 6.3). When assessing the proportions of significant results, the tests with the highest proportion (51%) were the three global analysis methods (Table 6.3).

**Table 6.3 Comparison of ranks of p-values for 3-level stroke and 3-level MI (35 comparisons; Freidman's ANOVA p<0.0001)**

| Test | | | | | | | Mean rank | Proportion of significant results |
|---|---|---|---|---|---|---|---|---|
| BLR | A | | | | | | 3.29 | 49% |
| Wei-Lachin | A | B | | | | | 3.63 | 51% |
| MWU | A | B | | | | | 3.71 | 46% |
| Wald | A | B | C | | | | 4.06 | 51% |
| OLR | | B | C | D | | | 4.51 | 46% |
| Hotelling's $T^2$ | | | C | D | | | 5.06 | 51% |
| Chi-Square | | | | D | | | 5.43 | 46% |
| BLR (fatal) | | | | | E | | 7.03 | 14% |
| Chi-Square (fatal) | | | | | | F | 8.29 | 11% |

BLR: binary logistic regression; MWU: Mann-Whitney U test; OLR: ordinal logistic regression
**NB:** Within any band tests do not differ statistically from one another

### 6.3.4 Outcome analysis comparison for binary and 3 / 4-level outcomes

Based on the available data it was possible to derive and analyse 3- and 4-level stroke outcomes, a 3-level MI outcome, and 3-level composite outcomes for 20 (57%) of the comparisons. There was evidence of a difference between the test ranks ($p<0.0001$). The test with the smallest average rank was the Wei-Lachin global analysis technique which was performed on the 4-level stroke and 3-level MI outcomes (Table 6.4). In the assessment of the proportions of significant results the tests with the highest proportion (70%) were the Wei-Lachin test and the Hotelling's $T^2$ test, which were performed on the 4-level stroke and 3-level MI outcomes (Table 6.4).

**Table 6.4 Comparison of ranks of p-values for 3 / 4-level stroke and 3-level MI (20 datasets; Freidman's ANOVA p<0.0001)**

| Test | | | | | | Mean rank | Proportion of significant results |
|---|---|---|---|---|---|---|---|
| Wei-Lachin (Stroke 4l / MI 3l) | A | | | | | 2.95 | 70% |
| BLR (event) | A | B | | | | 4.40 | 55% |
| MWU (Stroke 3l / MI 3l) | | B | C | | | 4.80 | 55% |
| Hotelling's $T^2$ (Stroke 4l / MI 3l) | | B | C | | | 4.85 | 70% |
| Wei-Lachin (Stroke 3l / MI 3l) | | B | C | | | 5.05 | 60% |
| Wald (event) | | B | C | D | | 5.35 | 60% |
| OLR (3l Stroke & MI) | | B | C | D | | 5.75 | 55% |
| Chi-Square | | | C | D | | 6.65 | 55% |
| Hotellings $T^2$ (Stroke 3l / MI 3l) | | | | D | | 6.95 | 55% |
| BLR (fatal) | | | | | E | 9.10 | 15% |
| Chi-Square (fatal) | | | | | E | 10.15 | 10% |

3l: 3-level outcome(s), 4l: 4-level outcome, BLR: binary logistic regression, MWU: Mann-Whitney U test, OLR: ordinal logistic regression
**NB:** Within any band tests do not differ statistically from one another

### 6.3.5 Outcome analysis comparison for binary and 3 / 5-level outcomes

It was possible to create 3- and 5-level stroke outcomes, a 3-level MI outcome, and 3-level composite outcomes in 11 (31%) of the comparisons. When compared using the Freidman test, there was evidence of a significant difference between the tests ($p<0.0001$). The test with the smallest average rank was the Wei-Lachin global analysis technique which was performed on the 5-level stroke and 3-level MI outcomes (Table 6.5). The assessment of the proportions of significant results showed that the test with the highest proportion (73%) was the Wei-Lachin test, which was performed on the 5-level stroke and 3-level MI outcomes (Table 6.5).

**Table 6.5 Comparison of ranks of p-values for stroke 3 / 5-level and MI 3-level (11 datasets; Freidman's ANOVA p<0.0001)**

| Test | | | | | | Mean rank | Proportion of significant results |
|---|---|---|---|---|---|---|---|
| Wei Lachin (Stroke 5l / MI 3l) | A | | | | | 2.64 | 73% |
| Hotellings $T^2$ (Stroke 5l / MI 3l) | A | B | | | | 3.27 | 64% |
| BLR | A | B | C | | | 4.09 | 45% |
| Wald | A | B | C | D | | 4.82 | 55% |
| Wei-Lachin (Stroke 3l / MI 3l) | | B | C | D | | 5.18 | 55% |
| MWU (3l Stroke & MI) | | | C | D | | 6.09 | 45% |
| Hotellings $T^2$ (Stroke 3l / MI 3l) | | | | D | | 6.73 | 55% |
| Chi-Square | | | | D | | 6.73 | 45% |
| OLR (Stroke 3l / MI 3l) | | | | D | | 7.00 | 45% |
| BLR (fatal) | | | | | E | 9.18 | 0% |
| Chi-Square (fatal) | | | | | E | 10.27 | 0% |

3l: 3-level outcome(s), 5l: 5-level outcome, BLR: binary logistic regression, MWU: Mann-Whitney U test, OLR: ordinal logistic regression
**NB:** Within any band tests do not differ statistically from one another

## 6.4 Discussion

When analysing multiple event outcomes global analysis techniques were more than or as efficient statistically as methods that are typically used for composite outcomes. These techniques also allowed for severity information to be incorporated into the outcome measures. Furthermore, when assessing the proportions of significant results for each comparison, it was the global methods that tended to have the higher proportions. Overall, when compared with the other approaches, the most appropriate techniques appeared to be the Wei-Lachin test and the Wald test.

A premise of this study is that severity can be incorporated into vascular event outcomes of prevention trials where multiple types of event are of interest, demonstrated previously for singular vascular event outcomes in the primary analysis chapter (Chapter 4).

The research described in this chapter had several strengths. Firstly, it used individual patient data from randomised controlled trials, not summary data taken from the primary publications. Second, both primary and secondary prevention trials, multiple intervention types and stroke and MI as outcomes were included; hence, the results are relevant to a large range of vascular

prevention trials. Third, the ordinal outcome measures embed binary outcomes within them; therefore, if statistical significance is shown for the ordinal measure, further closed testing methods can be applied to the important dichotomies; this would be particularly useful for a trichotomous outcome for which the two embedded dichotomies are of primary interest.

Nevertheless, there are also some limitations to this research. As chapter 3 indicated, it was not possible, for several reasons, to collect IPD for all of trials identified as being potentially suitable. Even though unavailability of data might lead to systematic bias, the trials included in this study comprised both primary and secondary prevention studies, and a variety of interventions. Secondly, the availability of data regarding multiple types of event varied considerably between trials, which limited the number of trials available for analysis. Thirdly, information on event severity was also limited so it was not possible to create outcomes of more than 5-levels. Fourth, for trials that had comparisons of multiple intervention groups to the same control group, the rankings of the p-values are not independent. Nonetheless, this is not likely to have influenced the results materially since the rankings were done within the respective comparisons. Fifth, the use of p-values is a disadvantage since evidence-based decision-making is usually based on an estimate of effect and corresponding confidence

interval and only partially influenced by p-values. However, this was a necessary step as different methods estimate different effects and p-values are a common output. Additionally, the ranking of p-values within comparisons should be similar to the ranking of standardized effect sizes. Lastly, there are other comparative techniques that could be considered better suited than the Freidman's ANOVA and the Duncan's test. These include the more generally applicable version of Friedman's ANOVA test and a multivariate extension of the Wilcoxon signed-ranks test,[160] although these methods have their own limitations. However, Freidman's ANOVA and the Duncan's test were used in the published Optimising the analysis of Acute Stroke Trials collaboration.[161]

## 6.5 Conclusions

In summary, reporting global tests adds summary information on overall treatment effects. Further, it may be advantageous to base the primary outcome on a global analysis since global tests are statistically more efficient; in this case, individual outcomes would be presented in pre-specified secondary analyses. The Wei-Lachin test may be preferred since it allows analysis of ordinal and continuous variables; in contrast, the Wald test only analyses binary

outcomes, and the Hotellings $T^2$ test does not take account of direction of effect.

# CHAPTER 7

# DISCUSSION

# 7 Discussion

## 7.1 Introduction

The term vascular event encompasses a vast number of different types of event, such as stroke, myocardial infarction, transient ischaemic attack, venous thromboembolism and bleeding, to name a few. It can be understood that each of these events can vary in their symptoms and severity. For instance, in stroke common symptoms include numbness or weakness of the face, confusion and limb weakness, whereas common symptoms for myocardial infarction include severe chest pain. There are various different risk factors that can be associated with these events, such as simply getting older, hypertension, diabetes, having suffered a previous vascular event and so on.

Prevention trials are designed to intervene in a population at risk for a particular disease. In the case of the prevention of vascular events there are two separate types of trial, primary and secondary. Primary prevention trials typically assess whether a new intervention is able to prevent a first vascular event. Secondary prevention trials on the other hand assess whether the new

intervention is able to prevent the recurrence of a vascular event. In both types of vascular prevention trial there are various types of intervention methods that are typically used. The most common forms of intervention that are classically used in vascular prevention trials include antihypertensives, lipid lowering therapy (e.g. statins), antiplatelets, anticoagulants, surgery, post-menopausal hormone replacement therapy and vitamins.

Effective primary and secondary prevention has resulted in a lower absolute risk of vascular events. As absolute event rates are a key component in calculating sample sizes for binary event outcomes, lower event rates mean larger, longer and more expensive clinical trials. Further, there has been an increase in the numbers of clinical trials being undertaken, due to new therapies being tested. This combination of more and larger clinical trials means recruitment of the required number of participants is a difficult and competitive process. Therefore, new strategies are needed to reduce clinical trial sample size, which will reduce costs, time to completion and number of participants exposed to risks.

A possible approach to combat this would be to analyse vascular prevention trials in a way which incorporates more data that could also be considered as clinically relevant. Most vascular prevention trials compare binary event rates (event / no event) between the

treatment and control group. However, vascular event outcomes can be fatal or non-fatal, this generating trichotomous outcomes (a variable with three levels; i.e. fatal event / non-fatal event / no event). Further, non-fatal events may have different severities, so that further extensions to the ordinal outcome may be included to generate four or more levels of outcomes. Analysis of this type of ordered categorical event is likely to be more efficient statistically than that of dichotomous outcomes. This opens up the potential for reducing trial sample size or detecting smaller but still clinically-relevant benefits. Such structuring of vascular event outcomes assumes that the ordering of events is meaningful; that is, fatal vascular events are considered more severe than non-fatal events. Ordered categorical outcomes could also be more informative to participants and healthcare professionals than binary ones. For example, rather than saying that an intervention reduces the risk of stroke, we can say that it reduces both stroke and the severity of stroke events.

The OA-Prevention study reports a prospective study based on analysis of individual participant data. Specifically, the relative statistical efficiencies of ordinal versus binary outcomes were reported as part of the Optimising the Analysis of vascular Prevention trials Collaboration. Although the use of statistical approaches for ordinal data is well defined in the methodological

literature, its use for designing and analysing vascular prevention trials is novel.

In the following sections there will be a discussion of the main findings of this study, including the experiences of data sharing, the primary analysis, the TARDIS re-analysis and the global analysis. There will also be a reflection on these, and suggested places for further work.

## 7.2 The OA-Prevention Study

Overall, the premise of this study was that an effective, or even hazardous, treatment can alter both the risk and severity of an event. Although this idea is novel when considered across vascular prophylaxis, individual trials and meta-analyses have found this before, as seen in the Heart Protection Study with simvastatin,[158] and for hormone replacement therapy.[44]

My research has demonstrated that it appears to be more, or as, efficient statistically to analyse vascular event data as several categories ordered by severity rather than as dichotomous event / no event data. My findings appeared to apply to both primary and secondary prevention trials, and to a variety of intervention types

including blood pressure and lipid lowering, antithrombotics and carotid endarterectomy.

Although there were difficulties in accessing data for this study, there were researchers who were enthusiastic and forthcoming with support for this analysis and with sharing their data, which led to this study receiving IPD from 35 vascular prevention trials. There are a variety of different procedures available to researchers for sharing data, a number of which were used to share data with the OA-Prevention study. Unfortunately, there was also a high non-response rate with 40% lead researchers not responding to an email invitation despite multiple attempts to make contact. There was also a number of researchers (28, 27%) who chose not to share their trial data with this study.

In regards to the primary analysis shown in Chapter 4, the most appropriate analysis approaches included the Mann-Whitney U test, ordinal logistic regression, bootstrapping, the Win ratio test and, for some ordinal scales, multiple linear regression (adjusted). In general, statistical regression models were more efficient if adjusted for prognostic factors than if performed unadjusted. Using ordinal outcome data and efficient analyses did not carry a risk of false positive findings. Finally, sample size estimations for ordered outcomes were significantly lower than for dichotomous events.

In the case of the TARDIS re-analysis in Chapter 5, for both the overall and the mild stroke / TIA ≤24 hour subgroup populations, the tests performed on the ordinal vascular outcomes again tended to more efficient statistically than binary outcome analyses; the Mann-Whitney U test, ordinal logistic regression, Win Ratio, Cochran-Armitage trend test and adjusted multiple linear regression all were associated with the smallest ranks for at least some outcomes.

As for the global analysis review in Chapter 6, global analysis techniques were more efficient statistically when analysing multiple event outcomes and allowed severity information to be incorporated into the outcome measures. Furthermore, when assessing the proportions of significant results for each comparison, it was the global methods that tended to have the higher proportions than traditional methods. Overall, when compared with the other approaches, the most appropriate techniques appeared to be the Wei-Lachin test and the Wald test.

## 7.3 Discussion of results in context of literature

The OA-Prevention study is the largest IPD pooling study, to date, in vascular prevention to look at improving the statistical analysis of vascular prevention trials. Previous research has focussed on re-analysing data from one trial or one type of trial for a particular intervention. The quirks and complexity of data from vascular prevention trials means that using 'real-life' data from many situations is beneficial. Also, other studies have focussed on only certain types of prevention trial, whereas this study includes data on primary and secondary prevention trials, and also encompasses more than one type of intervention.

Another area where this work contributes to the literature is the discussion on data sharing. Though it is widely accepted that data sharing for IPD meta-analyses is good practice, researchers may still struggle when trying to acquire the necessary data. However, this study has shown that there are now multiple methods available for obtaining data, which should make it easier for future researchers to undertake these types of analyses.

Though the use of an ordinal outcome measure in vascular prevention trials is a new one, and has only been implemented for one trial, this study should hopefully incline researchers to consider

the use of this type of outcome for future trials. At the very least it should provide a point of discussion for improving the design and analysis of future trials and could form a basis for other work looking into further improvement measures.

Even though this is a novel approach for vascular prevention trials, the idea of using an ordinal measure as the primary outcome, and a suitable analysis method, is not new concept. As mentioned in section 1.4, there other areas of research, such as traumatic brain injury and acute stroke, which have also reported that the analysis of ordinal (or continuous) outcome are more 'efficient' than the analysis of a binary outcome. In line with the OA-Prevention collaboration findings, both of the associated research collaborations in these areas reported that statistical power could be increased by using this approach.

The aim of this study was to try to determine if it was possible to make the statistical analysis of vascular prevention trials more efficient and therefore make the trials themselves more efficient. For instance, if ordinal outcomes and methodologies were shown to be more efficient than binary, then this could lead to a reduction in trial sample sizes, reducing costs and the number of participants required to test an intervention. However, there are other concepts to consider, apart from reductions in trial sample size, when it

comes to how to make trials more efficient.[171] For instance, at the planning stage, there needs to be a thorough consideration of all the available (or accessible) scientific knowledge and an examination of multiple scenarios to anticipate any potential risks and expected results. This can be achieved through the use of computational simulations of trial results under various scenarios that test the fragility of assumptions and weigh the advantages and disadvantages of different design strategies.[172] The choice of the design of a trial can be very important in regards to efficiency. For instance, factorial designs are a more efficient design if there is more than one intervention that need to be tested for the same condition and population of patients. Adaptive trial designs are another innovation in clinical trials that have the potential to improve both the efficiency of trials and the outcome of patients.[173] In essence, adaptive trial designs allow information collected during the trial to be used to alter the design in order to optimise it.[173] There are of course other considerations that can be made in terms of trial efficiency, such as suitable methods for trial delivery and monitoring. In fact, in order to further improve the efficiency of clinical trials, the National Institute for Health and Care Research has an 'Annual efficient studies funding call' for clinical trials units to support the development of more efficient, faster innovative studies.[174] Overall, in terms of how to make trials

efficient, there are multiple other considerations that can be made as well as statistical analysis and sample size.

## 7.4 Strengths and limitations of this research

This research had a number of strengths and limitations, which are detailed in the subsections below.

### 7.4.1 Strengths

This study had a number of strengths. First, OA-Prevention was a very large data pooling study. Data were shared with the collaboration for 35 trials, including records for 254,223 participants. Second, the trials included covered both primary and secondary prevention studies and multiple types of treatment intervention. Fifteen of the included trial were primary prevention and twenty were secondary prevention. The treatment interventions covered by these trials included anticoagulants, antihypertensives, antiplatelets, carotid stenting / endarterectomy, glucose lowering, hormone replacement therapy, statins and vitamins. Therefore, the

data collected for this study should be good representation of vascular prevention research. Such variability in type of trial and intervention also increases the external validity of the findings. Third, individual participant data, not summary data, was used thereby allowing covariate adjusted analyses. This is important as adjustment for covariates can increase statistical power if imbalances in prognostic variables are present and reduces the variability in the data so that more precise comparisons of treatment can be made.[175] Fourth, the ordered categorical outcomes created also have embedded dichotomies for poorer versus better outcome. For example, event versus no event or major event versus no major event and so on. Therefore, if statistical significance is shown, further closed testing methods can be applied to present results for the important dichotomies; this would be particularly useful for a 3-level outcome for which the two embedded dichotomies are of primary interest. Furthermore, in regards to the TARDIS re-assessment in Chapter 5, there is the fact that the trial had a large sample size (over 3,000 participants), concealment of treatment assignment and assessment prospectively of multiple event outcomes.

### 7.4.2 Limitations

However, there are also a number of limitations apparent for this study. First, individual data were not shared for a majority of identified trials, a common problem in data pooling projects, as identified in Chapter 3. Non-availability of data could lead to systematic bias, such as inclusion of only certain types of trial and trial intervention. However, as previously mentioned, the included trials involved both primary and secondary prevention studies, and a range of different interventions. Second, trials typically did not include sufficient information to allow four or more levels of ordinal data to be generated for MI, bleeding and composite outcomes; some stroke trials allowed ordinal outcomes to be generated up to 9 levels. In principle, MI could be further categorised with the addition of unstable angina and angina, and MI could be divided into ST-elevation and non-ST elevation. Third, for the trials that had comparisons of two (or more) intervention groups to the same control group, the rankings of the p-values are not independent. However, this issue is unlikely to have had a significant impact on the final results because the rankings of methods were done within the respective comparisons. Fourth, the use of p-values (rather than quantifying effects) to compare the performance of methods and drawing conclusions is also a limitation as evidence-based is typically based on a measure of effect and its corresponding

confidence interval. Decision-making is characteristically only partly influenced by p-values. However, their use was necessary for this study as different tests produce different quantifying effects and p-values offer a common currency. In addition to this, the ranking of p-values within comparisons is likely to be very similar to the ranking of standardized effect sizes. Fifth, there are other comparison methods that could be considered more suitable than the Freidman's ANOVA and the Duncan's test. For instance, there is a more generally applicable version of Friedman's ANOVA test and a multivariate extension of the Wilcoxon signed ranks test.[160] However, each of these methods also have their own limitations. Nevertheless, the Freidman's ANOVA and the Duncan's test were also employed, for the same purpose, in the main publication of the Optimising the analysis of Acute Stroke Trials collaboration study.[161] Last, one limitation that will need to be considered at the design stage of trials is that with the use of an ordinal outcome as the primary, it won't be possible to go back to a binary outcome as the sample size will not be large enough to attain the necessary power.

## 7.5 Implications for practice / research

From an implementation perspective, trialists should consider the prospective collection of information on severity as well as absolute numbers for events such as stroke, myocardial infarction, cardiac events, venous thromboembolism, bleeding and other adverse events; theoretically, these approaches should work for other medical conditions that have ordered categorical scales such as heart, liver, renal and respiratory failure. In general, this will enhance the statistical power of analyses (or allow smaller sample sizes).

It is understood that there may be situations when a binary outcome is preferable or the only option. For instance, where the outcome of interest is mortality, or where the complete avoidance of an event might be required for the treatment to be considered as cost-effective. Furthermore, there is also the potential for controversy over what type of outcome researchers would accept as sufficient evidence to indicate that change of practice is required. Nevertheless, this does not mean there will not be situations where the type of approach recommended by this study might be valid.

Of all the methods undertaken in chapters 4 and 5, the OA-Prevention study would suggest the use of a covariate adjustable

analysis approach (such as OLR) for the analysis of an ordinalised vascular event outcome. Even though the MWU test did also perform well in this study, this approach has obvious limitations which should dissuade researchers from its use. For instance, there is the fact that this test does not produce an estimate of effect, which is a major issue as researchers are rarely interested in a significance test alone. There is also the problem that this analysis approach does not allow for the adjustment of covariates. This would mean that important prognostic factors would not be taken into account in the final analysis. Furthermore, parametric tests tend to have more statistical power than their non-parametric equivalents.

To date, the TARDIS trial remains the only vascular prevention trial to have prospectively chosen an ordinal outcome although secondary or post hoc analyses of ordered categorical outcomes have been reported previously.[80, 118, 159, 168-170]

The OA-Prevention study is promoting the use of ordinal analyses to vascular prevention trialists. While applying ordinal methods improves the analysis of vascular prevention trials, this choice to use such an outcome will also complicate the ability of future researchers to undertake meta-analyses. The trials that use the traditional binary outcomes will present the number and percentage

of patients who fall into each outcome category by treatment group. These numbers can be easily extracted from the publications and used for a binary meta-analyses based on summary data. This means that trialists will need to display the number and percentage of patients falling into each category on the ordinal event scale being used in order to allow for ordinal meta-analyses. Examples of this can be seen in tables 7.1 and 7.2, taken from the TARDIS trial main publication, which show the distributions of the primary efficacy (ordinal recurrence) and primary safety (ordinal bleeding) outcomes respectively.

**Table 7.1 Primary efficacy outcome taken from the TARDIS trial manuscript**

| | Intensive antiplatelet therapy (n=1556) | Guideline antiplatelet therapy (n=1540) | Adjusted cOR or HR (95% CI) | p value |
|---|---|---|---|---|
| **Primary outcome** | | | | |
| Number of patients | 1540 | 1530 | .. | .. |
| Ordinal stroke or TIA | 93 (6%) | 105 (7%) | 0·90 (0·67–1·20) | 0·47 |
| Death (mRS 6) | 13 (1%) | 7 (<1%) | 1·92 (0·76–4·84) | 0·17 |
| mRS 4–5 | 11 (1%) | 9 (1%) | .. | .. |
| mRS 2–3 | 22 (1%) | 23 (2%) | .. | .. |
| mRS 0–1 | 15 (1%) | 18 (1%) | .. | .. |
| TIA | 32 (2%) | 48 (3%) | .. | .. |
| No stroke or TIA | 1447 (94%) | 1425 (93%) | .. | .. |

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**Table 7.2 Primary safety outcome taken from the TARDIS trial manuscript**

| | Intensive antiplatelet therapy (n=1556) | Guideline antiplatelet therapy (n=1540) | Adjusted cOR or HR (95% CI) | p value |
|---|---|---|---|---|
| **Bleeding (safety analysis)** | | | | |
| Ordinal bleeding (cOR) | 305/1541 (20%) | 139/1531 (9%) | 2·54 (2·05–3·16) | <0·0001 |
| Fatal[20] | 8/1541 (1%) | 3/1531 (<1%) | 3·48 (0·89–13·63) | 0·074 |
| Major | 31/1541 (2%) | 14/1531 (1%) | .. | .. |
| Moderate | 25/1541 (2%) | 13/1531 (1%) | .. | .. |
| Mild | 241/1541 (16%) | 109/1531 (7%) | .. | .. |
| None | 1236/1541 (80%) | 1392/1531 (91%) | .. | .. |

Reprinted from The Lancet, 391, 850-59. Bath PM et al. Antiplatelet therapy with aspirin, clopidogrel, and dipyridamole versus clopidogrel alone or aspirin and dipyridamole in patients with acute cerebral ischaemia (TARDIS): a randomised, open-label, phase 3 superiority trial. Copyright (2018); The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

## 7.6 Further Work

There are still some unanswered questions around the analysis of vascular prevention trials and therefore there are ways this study could be built upon.

In this study there were two methods, the Mann-Whitney U test and Win ratio test, which often appeared to be more efficient than the others. Although neither can be adjusted for covariates, there are extensions of these methods that do allow for covariate adjustment.[153-156] Furthermore, though shown not to be as efficient as the ordinal methods, there are extensions that could be applied to the Cox proportional hazards model that enable adjustment for covariates in a manner that does not require the proportional hazards assumption for covariates.[157] Further work, could be done to review these extensions, and other methods perhaps, to determine their efficiency respective to the methods already used.

Due to the lack of available data it was only possible to perform analyses for certain vascular event outcomes, such as venous thromboembolism, within one trial (TARDIS, Chapter 5). Further work could therefore look into these outcomes and perform the required analyses to confirm that ordinal outcomes and statistical

methods are more efficient. This would require collecting more individual patient data for more trials of these types of events.

## 7.7 Conclusions

In summary, vascular outcomes can be ordinal variables with ordering determined by the severity of the vascular event. This improves statistical efficiency as well as providing additional information for participants, public and healthcare practitioners. The approach appears to be relevant to all tested vascular interventions and outcomes (stroke, MI, major adverse cardiovascular events, bleeding). Further, where applicable, adjusted analyses add further statistical efficiency. The use of ordinal outcomes as primary outcomes could also lead to significant reductions in sample size. Future vascular prevention trials should consider whether to use ordered categorical outcomes and the statistical methods associated with those. If this approach is chosen the resulting trials could be smaller whilst retaining their original power, and would test the effect of interventions on severity, not just the absolute number of events. Implementation of this approach might then lead to smaller, shorter and less expensive vascular prophylaxis trials.

These findings were also supported by the TARDIS re-analysis, which again suggested that vascular outcomes can be ordinal with the inclusion of severity information. The methods used in this analysis appeared to be relevant for the majority of the tested vascular outcomes.

As for the analysis of ordinal vascular event outcomes, the method that this study would promote is OLR. This is due to the fact that parametric tests are more powerful than their non-parametric equivalents, it is possible to adjust for important prognostic covariates and this test is capable of producing a meaningful estimate of effect (i.e. odds ratio and confidence intervals) that researchers will be familiar with. Of course there are limitations with this method, the main one being what to do when the assumption of the proportionality of odds fails. If this occurs, other methods should be considered as subsequent analyses and odds estimates will be wrong. One such method is generalised OLR, which is a more complicated model that fits a separate set of regression coefficients for each comparison.[176] Adjusting for covariates, though widely accepted in practice, can also cause problems. For instance, issues can arise if there are missing data, as this could mean there are participants who cannot be included in the primary analysis. Methods like imputation can be used in this instance, but it is not a suitable solution if the majority of data is missing. Issues can also

be caused by overpopulation of the model, that is, the use of multiple covariates. This can cause problems with model convergence and fit (i.e. overfitting). It is therefore recommended that the choice of which prognostic factors to use as covariates within a model should be considered very carefully.

In regards to the use of global analysis techniques when more than one outcome is of interest, reporting the results of these tests adds summary information on overall treatment effects. Further, it may be advantageous to base the primary outcome on a global analysis since global tests are statistically more efficient; in this case, individual outcomes would be presented in pre-specified secondary analyses. The Wei-Lachin test may be preferred since it allows analysis of ordinal and continuous variables. In contrast, the Wald test only analyses binary outcomes, and the Hotellings $T^2$ test does not take account of direction of effect.

Although finding that ordinal methods appear to be more statistically efficient than those which analyse binary outcomes is not surprising or novel in the statistical community, the novelty of this work is in the application to vascular prevention data. As previously stated, only one prevention trial to date has used an ordinal method of analysis for their primary outcome, and although statistical analysis is receiving more interest in the field of vascular

prevention, most studies still choose their method of analysis based on hearsay or the results of previous trials. The OA-Prevention study is a rigorous and thorough examination of the available methods of analysis and the results can therefore be used reliably in future trials.

Changing the design and analysis of vascular prevention trials to improve statistical power gives new effective interventions the best possible chance of being used in everyday medicine, both reducing the number of people needed to be involved in clinical trials and potentially the number of trials needed.

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# 9 Appendices

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**Appendix A – OA-Prevention study Invitation Letter**

Dear …,

I am writing on behalf of Professor Philip Bath (University of Nottingham) and myself. We are designing, with others, an assessment of vascular prevention trials with the aim of optimising the statistical analysis of these (see attachment – OA-Prevention Newsletter MONTH YEAR).

Prevention trials typically count outcomes as dichotomous events (e.g. stroke – no stroke) although this is inefficient statistically and gives no indication on the severity of recurrent events. We hypothesise that vascular events may be polychotomised with ordering determined by severity, e.g. stroke categorised as fatal-severe-mild-TIA-no stroke. In our pilot study using published summary trial data, ordinal analysis of these ordered categorical outcomes was more efficient statistically than current binary approaches (see attachments – Bath et al. Stroke 2008 39 2817-2823). We plan to further test this concept using individual patient data from the same trials, not least because many publications do not provide sufficient granular data. We will identify relevant trials

and generate ordered vascular outcomes. We will then compare binary and ordinal statistical methods of analysis, both unadjusted and adjusted, then compare sample size estimates and number-needed-to-treat for these trials using published binary and ordinal methods. If these ordinal approaches are superior, future trials should consider using stroke and other vascular outcomes as ordered categories, and should be analysed using ordinal (or even linear) statistical tests. Using this approach, future trials could potentially be smaller (thereby reducing trial costs and competition for patient recruitment) and provide extra information on the effect of treatment on the severity, as well as frequency of vascular events. This information will be vital for patients, carers, healthcare professionals, and Government.

We are writing to invite you, as someone leading a relevant trial assessing vascular prevention (**trial name**), to join an international collaboration looking at the optimisation of analysis of vascular prevention trials. (This project follows on from a similar one looking at how to best analyse functional outcome after stroke - the 'Optimising Analysis of Stroke Trials' [OAST] Collaboration which has published several papers - see other attachments.)

What the project needs is the individual patient data for certain key variables relating to:

- Demographics
- Risk factors
- Clinical details
- Trial design
- Outcomes
- Safety measures

It is possible that you will not have data for all the above variables. If you have data for other vascular measures, then we can try the same approach for those e.g. deep vein thrombosis, pulmonary embolism, heart failure or renal failure. The use of these variables (or as many as that are available) will allow both univariate and covariate adjusted approaches to be assessed. Data, and their description, can be sent by email in a spreadsheet (Excel, SPSS, SAS, etc.) or by CD. We can re-format the data to make it fit our database as needed.

The results of analyses for individual trials will NOT be published (since you and other investigators have already done this); rather, the results of different analysis methods across trials will be compared and published. All collaborators will see the final results and manuscript for comment/interpretation, and the results will be published under the banner of OA-Prevention with the collaboration listed by name at the end. See the attached OAST acute papers illustrating these approaches. We should add that our group in Nottingham has considerable experience in working with individual subject data (including projects such as BASC, DISC, NEMAS, OAST, OT, PROGESTERONE), and of protecting the interests of the collaborators who shared that data. Finally, we should confirm that your data will not be used for any purpose other than to do with OA-Prevention.

We believe that this study may be very influential in the design and analysis of future trials that assess vascular prevention in patients with or at risk of vascular disease. We do hope that you will be interested and willing to collaborate by sharing your data and helping in interpretation of the results and their publication. If you are interested and willing please let us know and I will forward the protocol.

Kind regards,

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## Appendix B – OA-Prevention study Protocol

*Version 1.4 – Date: 16th September 2013*

# Improving the statistical analysis of vascular outcomes in randomised controlled trials including patients with or at risk of vascular disease

## The 'Optimising the Analysis of vascular trials - Prevention' Collaboration

## (OA-Prevention)

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## AIMS

1. To identify the most efficient statistical analysis technique for analysing global vascular prevention data (e.g. stroke or MI severity) from randomised controlled trials including patients with or at risk of vascular events.

2. To assess the implication of choosing particular methods of analysis on trial sample size.

3. To assess the implication of adjusting analyses for baseline prognostic factors on sample size.

## BACKGROUND

According to the world health organization (WHO), the incidence of vascular events, including conditions such as coronary heart disease (angina and myocardial infarction (MI)), stroke or peripheral arterial disease (PAD), seems to be globally declining, mainly because of efforts to reduce blood pressure, but is still the worldwide leading cause of mortality and major cause of serious disability.

In the year 2008, approximately 17.3 million people died from cardiovascular diseases (CVDs), representing 30% of all global

deaths. Of these deaths, an estimated 7.3 million were due to coronary heart disease and 6.2 million were due to stroke. As well, at least 20 million people survive heart attacks and strokes every year, a significant proportion of them requiring costly clinical care, which puts a huge burden on long-term care resources. By 2030, at least 23.6 million people are estimated to die from CVDs, mainly from heart disease and stroke. These are projected to remain the single leading causes of death.

Effective vascular prevention lies in the management of modifiable risk factors as well as treating the causes of the initial event for secondary prevention. There are numerous prevention strategies to reduce the risk of MI, stroke and other vascular events. Most of them apply to all vascular events e.g. reducing blood pressure [1-3], reducing cholesterol [4, 5], antiplatelets [6, 7], anticoagulation [8], surgery [9, 10], and vitamins [11, 12]. In contrast, some interventions are hazardous, e.g. hormone replacement therapy (HRT) [13, 14] in stroke prevention.

**High Blood Pressure**

Hypertension is the major modifiable risk factor for stroke and other vascular events [1], and the benefits of lowering blood pressure

(BP) for primary and secondary prevention of cardiovascular mortality and morbidity are well established [2, 3].

**High Cholesterol**

Strong evidence denotes benefit from reducing serum cholesterol levels in patients with established coronary heart disease (CHD). Furthermore results of previous studies have shown that statin-based therapies protect patients, with or without history of CHD, from ischemic stroke or TIA [4, 5].

**Antiplatelet**

It is well known that for patients who had a myocardial infarction (MI), stroke, or TIA, long term treatment with antiplatelet agents (e.g. aspirin) reduces the yearly risk of serious vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death) by approximately a quarter. Side effects such as bleeding complications and gastrointestinal problems were associated, but the benefits of antiplatelet therapy were greater in magnitude than the risks [6].

However in primary prevention, the balance between benefits and risks is less clear as the absolute magnitude of risk reduction is usually lower compared to the results in secondary prevention [7].

## Anticoagulation

The benefits of oral anticoagulants has been established in primary and secondary prevention (and also in treatment) in a variety of conditions including atrial fibrillation (AF), pulmonary embolism (PE), deep vein thrombosis (DVT), venous thromboembolism (VTE), congestive heart failure, stroke (except haemorrhagic stroke) or myocardial infarction (MI). Although anticoagulation therapy needs to be carefully monitored (haemorrhage management and adjusted-dose targeting an international normalised ratio [INR] of 2-3), if done so, it has been proven to be safe [8].

## Surgery

Surgeries such as endarterectomy or angioplasty with or without vascular stenting is commonly used to treat conditions that involve a narrowing or blockage of arteries or veins throughout the body, such as carotid artery stenosis [9, 10], coronary artery disease, narrowing of large arteries due to atherosclerosis, peripheral artery disease (PAD) or renal vascular hypertension.

## Post-Menopausal hormone replacement therapy (HRT)

Pre-menopausal women have a lower risk of stroke than men of the same age, and the incidence of stroke in women increases rapidly after the menopause which would suggest that hormones play an important role in stroke occurrence [13]. However a meta-analysis of completed trials assessing the effect of post-menopausal hormone replacement therapy (HRT) has revealed an increased risk of stroke particularly of ischaemic type [14]. Concerning prevention of MI, there is no evidence of any relationship with HRT.

## Vitamins

Elevated serum homocysteine levels have been found to be linked to increased risk of vascular disease. Studies have shown that daily supplementation with B vitamins can reduce homocysteine levels. However the potential protective effect of B vitamins in patients who have had a stroke or transient ischaemic attack (TIA) has not been proven [11]. Concerning the effect of antioxidant vitamins such as vitamin E, vitamin C and beta carotene, randomized trials have largely failed to support an effect on risk of cardiovascular disease (CVD) [12].

## Statistical analysis of vascular events

Prevention trials typically count outcomes as dichotomous events (e.g. stroke-no stroke) although this is inefficient statistically and gives no indication on the severity of recurrent events. It is hypothesised that vascular events may be polychotomised with ordering determined by severity, e.g. stroke categorised as fatal-severe-mild-TIA-no stroke. In the OA-P pilot [15] study using published summary trial data, ordinal analysis of these ordered categorical outcomes was more efficient statistically than current binary approaches.

It is planned to further test this concept using individual patient data from the same trials, not least because many publications do not provide sufficient granular data. Relevant trials will be identified and ordered vascular outcomes will be generated. Binary and ordinal statistical methods of analysis will be then compared, both unadjusted and adjusted, then compared sample size estimates and number-needed-to-treat for these trials using published binary and ordinal methods. If these ordinal approaches are superior, future trials should consider using stroke and other vascular outcomes as ordered categories, and should be analysed using ordinal (or even linear) statistical tests. Using this approach, future trials could potentially be smaller (thereby reducing trial costs and competition for patient recruitment) and provide extra information on the effect

of treatment on the severity, as well as frequency of vascular events. This information will be vital for patients, carers, healthcare professionals, and Government.

It is hypothesised that vascular events may be polychotomised with ordering determined by severity:

- 3 stroke levels: Fatal / non-fatal / no stroke
- 4 stroke levels: Fatal / severe (dependent) / mild (independent) / no stroke
- 4 stroke/TIA levels: Fatal / severe / TIA / no stroke-TIA
- 5 stroke/TIA levels: Fatal / severe / mild / TIA / no stroke-TIA
- 5 stroke/TIA levels: Fatal / severe (mRS 2-5) / mild (mRS 0, 1) / TIA / no stroke-TIA [This is the primary outcome in the on-going BHF TARDIS trial; PB is CI.]
- 6 stroke/TIA levels: Fatal / severe (mRS 4, 5) / moderate (mRS 2, 3) / mild (mRS 0, 1) / TIA / no stroke-TIA
- 9 stroke/TIA levels: fatal / mRS=5 / mRS=4 / mRS=3 / mRS=2 / mRS=1 / mRS=0 / TIA / no stroke-TIA

- 3 MI levels: Fatal / non-fatal / no event

- 4 MI levels: Fatal / non-fatal / angina / no event

- 6 MI levels: Fatal / MI + heart failure / STEMI + no heart failure / NSTEMI / unstable angina / none

- 3 vascular levels: Fatal stroke or MI / non-fatal stroke or MI / no event

- 4 vascular levels: Fatal stroke or MI / non-fatal stroke or MI / TIA or angina / no event

- 4 renal failure levels: Fatal / dialysis / no dialysis / no event

- 4 venous thromboembolism (VTE) levels: Fatal / non-fatal pulmonary embolism (PE) / deep vein thrombosis (DVT) / no event

- 3 serious adverse event levels: Fatal / non-fatal serious / no event

- 4 serious adverse event levels: Fatal / severe / moderate-mild / no event

- 5 serious adverse event levels: Fatal / severe / moderate / mild / no event

- 3 bleeding levels: Fatal / non-fatal major / no bleeding

- 4 bleeding levels: Fatal / major / moderate-mild / no bleeding

- 5 bleeding levels: Fatal / major / moderate / mild / no bleeding

The choice of ordinal scale will depend, in part, on its reliability and ease of measurement. Statistically, 5-9 levels will be more efficient than having fewer [16]; clinically, it will be difficult to differentiate more than 9 levels [17]. The underlying assumption in using such ordered outcomes is that treatments will have benefit across the range of event severity, i.e. the intervention will reduce the number of severe strokes by making them less severe, and reduce the number of mild strokes by preventing them all together; when present, this delivers the assumption of 'proportionality of odds', as seen for the majority of trials in OAST-A [18-21] and the OA-P pilot [15].

A number of advantages are likely to accrue with ordinal analysis of ordered outcome scales as compared with conventional binary analysis of dichotomous outcomes:

- Ordinal analysis is more efficient (powerful) statistically, i.e. confidence intervals are narrower and p-values smaller (as it was showed in acute stroke [18]).

- Ordinal analyses may be more efficient than time to event analyses (e.g. log rank test) since these offer little advantage over dichotomous approaches when event rates are low (e.g. <14%).

- Calculated sample sizes for ordinal scales are smaller, as showed in acute stroke [19].

- Calculated numbers needed to treat (NNT) are smaller, i.e. more subjects will be seen to benefit, as it was showed in acute stroke and in one secondary prevention trial (ESPS-2) [21].

- Ordered outcomes convey to patients, carers, healthcare practitioners and Government that interventions alter both severity and frequency of outcomes. Reductions in stroke severity are important economically since healthcare costs are much higher with severe non-fatal events.

- Hazardous interventions are easier to identify if ordered outcomes are assessed, as seen with HRT (stroke [14]) and chronic antiplatelets (bleeding [22]).

It has been argued that ordinal scales with sufficient numbers of levels, e.g. 7 or more, should be analysed using continuous (parametric) approaches, particularly if the dataset is large (so that large-sample normal approximations become valid). Nevertheless, ordinal data is often skewed and kurtotic which will reduce the power advantage of parametric over non-parametric approaches.

**Optimising the Analysis of Stroke Trials - Acute (OAST-A)**

The proposed work is derived from the international collaborative study, 'Optimising the Analysis of Stroke Trials' (OAST-A) project [18-21]. Few treatments exist for acute stroke (alteplase, hemicraniectomy, aspirin, stroke units) in spite of numerous trials; a contributing factor is that the analysis of trials has usually been suboptimal since most analysed the 7-level mRS or 22-level Barthel Index as dichotomous outcomes (dead or dependent vs. independent).

In OAST-A, individual patient data were shared by 55 trial groups. When compared with dichotomous approaches, ordinal tests (especially ordinal logistic regression, robust ranks test [RRT]) were more efficient statistically [18] providing either extra power for a given sample size, or a smaller sample size for a given power [19]. The use of these more efficient statistical analyses may increase the chances of finding treatments for acute stroke in the future and modern trials are using them.

**Optimising the Analysis of Stroke Trials - Prevention (OA-P) pilot data**

The analysis of completed vascular prevention trials has been piloted using ordinal outcomes [15]. Published summary data from 85 primary and secondary prevention trials (335,305 patients) were used. Ordinal analytical methods were superior (more efficient statistically) to dichotomous approaches, including: bootstrap of the mean (3000 cycles/3 iterations), MWU (table 1), RRT, and OLR. Insufficient data were available for 4/5-level ordering to formally assess these but they tended to be superior to 3-level outcomes [16].

**Table 1: Comparison of ordinal (Mann-Whitney U test) and dichotomous (Chi-square) analyses: p-values**

| Levels † | 2-levels | 3-levels | 4-levels (no TIA) | 4-levels (TIA) | 5-levels (TIA) |
|---|---|---|---|---|---|
| PPP [23] | 0.2932 | 0.2244 | 0.2243 | 0.0641 | 0.0647 |
| SPAF/aspirin [24] | 0.0291 | 0.0220 | 0.0231 | 0.0077 | 0.0081 |

**Effect on sample size**

Dichotomous and the Whitehead ordinal sample size estimation [16] were compared for the outcome of stroke using published 3-level summary data from example trials (power=90%, significance=5%). Trial sizes were smaller if ordinal analysis of an ordered categorical scale had been used (table 2). The addition of extra levels would likely further reduce size; so that trials would need to be larger by 33%, 13%, 7% and 4% with 2, 3, 4 and 5 levels respectively, as compared with 6 levels [25].

**Table 2: Sample size estimates for 4 positive vascular prevention trials**

| Trial | Actual size | 2-levels, dichotomous | 3-levels, Whitehead [16] | Change % |
|---|---|---|---|---|
| ESPS [26] | 2,500 | 1,476 | 1,358 | -8.0 |
| HOPE [27] | 9,297 | 7,622 | 7,218 | -5.3 |
| HPS [28] | 20,536 | 9,326 | 8,940 | -4.1 |
| SPAF/aspirin [29] | 1,120 | 2,318 | 2,150 | -7.2 |

**Effect on Number Needed to Treat (NNT)**

NNTs are widely used for explaining the magnitude of effect an intervention has and form an important part of health economic analyses. Methods for calculating NNTs from ordinal or continuous data [21, 29, 30] have been developed; Using these approaches, the NNT for alteplase (derived from the NINDS rt-PA trial) was 8.4 when analysed using dichotomous mRS data (0-2 vs 3-6) but only 3.1 (95% CI, 2.6-3.6) when based on ordered mRS data [17]. NNTs derived from ordered and dichotomous outcomes in vascular prevention trials will be compared.

## METHODS

The general approach used in the OAST-A project will be followed.

### Trial Data

Collaborative chief investigators are asked to share individual patient data from each trial for the following variables (where data items are available):

### Demographics/risk factors/clinical details

- Age (years).
- Sex (male, female).
- History of hypertension (yes, no).
- Diabetes mellitus (yes, no).
- Hyperlipidaemia (yes, no).
- Smoking status (yes, no; or current, former, never).
- Previous MI (yes, no).
- Previous Ischaemic Heart Disease (yes, no).

- Previous stroke (yes, no).
- Peripheral arterial disease (yes, no).
- Carotid stenosis (yes, no).
- (un)stable angina (yes, no).
- Atrial fibrillation (yes, no).

**Clinical details/trial design**

- Index event (none, stroke/type, MI/type, atrial fibrillation, peripheral arterial disease [PAD], renal vascular disease [RVD]).
- Time since index event (if a secondary prevention trial) - for covariate adjustment, baseline blood pressure, cholesterol, glucose, AF/SR, or degree of carotid stenosis (depending on trial's aim).
- Indication for trial (stroke, MI, hypertension, hypercholesterolemia…).
- Randomisation group (active treatment, control).
- Randomisation date.
- Start date of intervention.

- Length of follow-up.

**Outcome/Safety (All events of type)**

- Stroke/TIA: Fatal, severity if non-fatal (severe, moderate, mild; or modified Rankin Scale; or discharge disposition e.g. nursing home, care home, sheltered housing, home with carer, home); TIA. Time to event. Type of event: haemorrhage, ischaemic (cardioembolic, large artery, small vessel disease, other); LACI, PACI, POCI, TACI.

- MI: Fatal; type if non-fatal (STEMI + heart failure, STEMI, NSTEMI, unstable angina, stable angina). Time to event.

- Adverse events: Fatal; non-fatal-serious; other. Time to event.

- Bleeding: Fatal; major non-fatal; moderate; minor. Time to event.

- Renal failure: Fatal; dialysis; no dialysis. Time to event.

- Venous thromboembolism (VTE): Fatal; non-fatal pulmonary embolism (PE); deep vein thrombosis (DVT). Time to event.

- Revascularisation: Fatal; non-fatal.
- Cognition: MMSE or equivalent.
- Dementia: Fatal; non-fatal.
- Death: (yes, no); cause of death.

These variables will allow for both unadjusted and adjusted analyses. The data can be sent in any commonly used format, e.g. Excel, SPSS, and SAS.

**Statistical approaches**

Univariate analyses - compare ordinal, nominal and dichotomous approaches

Statistical approaches for analysing dichotomous, nominal and ordered data will be compared [18, 31-33]:

(i) Fisher's Exact test/Chi-square – binary data.

(ii) Fisher-Freeman-Halton test/Chi-square - unordered multi-level data; [this will provide a 'negative' control for ordered tests.]

(iii) Cochran-Armitage trend test.

(iv) MWU two-sample test.

(v) Robust Ranks Test [34].

(vi) t test (pooled).

(vii) t test (unpooled/Welsh).

(viii) Bootstrap of difference in mean rank (3 x 3000 cycles [35, 36]).

Chi-square and MWU tests will be corrected for continuity, a conservative approach; MWU will also be adjusted for ties. Each data set will be analysed using each test and the z score obtained (as in OAST-A [18]). [Other non-parametric tests will not be used since they have assumptions which will not be appropriate (e.g. Wald-Wolfowitz runs test is inappropriate if multiple ties are present).]

Multiple variable analyses - compare ordinal and dichotomous approaches

Where relevant, statistical approaches relating to the analysis of dichotomous and ordinal data with and without adjustment for

baseline covariates will be performed. These approaches will parallel and be compared with the above univariate tests:

(i) logistic regression (binary events);

(ii) ordinal logistic regression;

(iii) Cochran-Mantel-Haenszel test [37];

(iv) multiple linear regression;

(v) Cox regression (binary time to event data).

**Comparison of statistical tests**

Each data set will be analysed using each statistical approach. These results will then be ordered within each trial and given a rank, with the lowest rank given to the test which produced the most significant result, i.e. the smallest p-value, within that trial. A 2-way analysis of variance test will then be used to see on average which statistical test had produced the lowest ranks. The statistical tests will be then ordered in terms of their efficiency in identifying treatment effects. The number of statistically significant (at 5%) results each test found will be also assessed.

To assess the validity and reliability of the results, a number of supplementary analyses will be carried out:

1. Comparison of statistical tests within subgroups of trials sharing similar characteristics (although there may not be enough trials to allow this for all subgroups)

2. Assessment of statistical assumptions underlying the tests

3. Assessment of the sensitivity of the tests to ensure that treatment effects are only detected when they truly existed (the type 1 error rate).

Analyses will be carried out in SAS (version 9.3 or later) and significance will be taken at $P<0.05$.

**Data sharing**

Collaborators will be sharing data under a formal data sharing agreement with the OA-Prevention collaboration and with no other group or individual. Specifically, OA-Prevention will not share data with any third party. Data will be stored on a secure computer in a locked room. The computer is backed up daily to a central University server.

**Publication**

The results of analyses for individual trials will NOT be published (since individual Collaborators have already done this); rather, the results of different analysis methods across the trials will be compared and published. As a result, individual trials will not be identifiable. The results will be published under the banner of OA-Prevention with the collaboration listed by name. Collaborators (a maximum of two per trial) will be listed in the acknowledgments by trial. The papers will be written by a 'Publication Committee' and then distributed to all Collaborators for comment, interpretation, changes, additions etc. The results will be submitted to major vascular conference(s) for presentation, and submitted for publication in major quality peer-reviewed journal(s). Data will not be used for any purpose other than to do with OA-Prevention. The OAST-A papers were published using this approach.

**Experience of the Nottingham Stroke Trials Unit**

STU has considerable experience in working with individual subject data within collaborations such as OA-Prevention. This includes projects such as BASC (blood pressure in acute stroke collaboration) [38-42], DISC (dipyridamole in stroke collaboration) [43, 44], NEMAS (NXY-059, animal data ) [45], OAST-A (optimising the analysis of stroke trials in acute phase) [18-21], OA-P pilot

(optimising the analysis of stroke trials in prevention) [15], OT (community occupational therapy) [46], OA-COG (optimising the analysis of cognition) [on-going project not published yet], PROGESTERONE (Progesterone as a neuro protectant in stroke) [47], and of protecting the interests of the collaborators who shared their data.

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## Appendix C – OA-Prevention data dictionary

| VARIABLE | COMMENTS |
|---|---|
| study | Name of trial |
| trialc | Name of comparison dataset |
| trial | ID number of comparison dataset |
| trial_number | Patient ID number |
| treatc | Treatment group Character variable |
| treat | Treatment group: 1=Treatment, 2=Control |
| type | Intervention type: ACT, AHT, APT, CEA, Vitamins, Statins, GL, HRT |
| primary | Primary prevention trial: 1=yes, 0=no |
| secondary | Secondary prevention trial: 1=yes, 0=no |
| **Baseline Characteristics** | |
| gender | sex:1=male 0=female |
| age | years |
| qe_onset_date | Date of qualifying event |

| | |
|---|---|
| date_of_report | Randomisation date |
| timetorand | Time to randomisation (days) |
| smoking | Smoking status: current C, past P, never N, unknown U |
| alcohol | status: 1=yes, 0=no |
| hx_of_ihd | history of ischaemic heart disease: 1=yes, 0=no |
| hx_of_mi | history of myocardial infarction: 1=yes, 0=no |
| hx_of_hyperten | history of hypertension: 1=yes, 0=no |
| hx_of_hyperlipid | history of hyperlipidaemia: 1=yes, 0=no |
| hx_of_dm | history of diabetes: 1=yes, 0=no |
| hx_of_cf | history of cardiac failure: 1=yes, 0=no |
| hx_of_cd | history of cardiovascular disease: 1=yes, 0=no |
| hx_of_af | history of atrial fibrillation: 1=yes, 0=no |
| hx_of_va | history of ventricular arrhythmia: 1=yes, 0=no |

| | |
|---|---|
| hx_of_prev_stroke | history of previous stroke: 1=yes, 0=no |
| hx_of_claud | history of claudication: 1=yes, 0=no |
| sbp0 | baseline systolic blood pressure |
| dbp0 | baseline diastolic blood pressure |
| hr0 | baseline heart rate |
| final_diagnosis | Diagnosis of Qualifying event: stroke, TIA, MI etc. |
| **Vascular event outcome data** | |
| stroke_date | Date of stroke |
| mi_date | Date of MI |
| bleed_date | Date of bleed |
| isc_date | Date of ischaemic event |
| ove_date | Date of other vascular event |
| vasdth_date | Date of vascular death |
| tia_date | Date of TIA |
| death_date | Date of death |
| cf_date | Date of cardiac failure |

| | |
|---|---|
| dead | status: 1=yes, 0=no |
| stroke_death | Fatal stroke:1=yes, 0=no |
| mi_death | Fatal MI:1=yes, 0=no |
| cf_death | Fatal CF:1=yes, 0=no |
| bleed_death | Fatal bleeding: 1=yes, 0=no |
| vte_death | Fatal VTE: 1=yes, 0=no |
| rf_death | Fatal renal failure: 1=yes, 0=no |
| rf | renal failure: 1=yes, 0=no |
| rf_dialysis | 1=yes, 0=no |
| bleeding | Bleeding event: 1=yes, 0=no |
| minor_bleed | Minor bleeding event: 1=yes, 0=no |
| moderate_bleed | Moderate bleeding event: 1=yes, 0=no |
| major_bleed | Major bleeding event: 1=yes, 0=no |
| tia | Transient Ischaemic Attack: 1=yes, 0=no |
| mi | Myocardial Infarction: 1=yes, 0=no |
| stemi | ST-segment elevation MI: 1=yes, 0=no |

| | |
|---|---|
| nstemi | Non-ST-segment elevation MI: 1=yes, 0=no |
| angina | Angina: 1=yes, 0=no |
| unstable_angina | Unstable angina: 1=yes, 0=no |
| stable_angina | Stable angina: 1=yes, 0=no |
| minor_mi | Minor MI: 1=yes, 0=no |
| moderate_mi | Moderate MI: 1=yes, 0=no |
| major_mi | Major MI: 1=yes, 0=no |
| cf | Cardiac failure: 1=yes, 0=no |
| minor_cf | Minor CF: 1=yes, 0=no |
| moderate_cf | Moderate CF: 1=yes, 0=no |
| major_cf | Major CF: 1=yes, 0=no |
| stroke | Stroke: 1=yes, 0=no |
| minor_stroke | Minor stroke: 1=yes, 0=no |
| moderate_stroke | Moderate stroke: 1=yes, 0=no |
| major_stroke | Major stroke: 1=yes, 0=no |
| mrs_stroke | mRS class of stroke [0-6] |

| | |
|---|---|
| ischaemic_event | Ischaemic event: 1=yes, 0=no |
| revascular | Revascularisation: 1=yes, 0=no |
| revascular_death | Death caused by revascularisation: 1=yes, 0=no |
| vte | Venous thromboembolism: 1=yes, 0=no |
| other_ve | Other vascular event: 1=yes, 0=no |
| retinal_ve | Retinal vascular event: 1=yes, 0=no |
| pulmonary_embolism | Pulmonary embolism: 1=yes, 0=no |
| pa_occlusion | Peripheral artery occlusion: 1=yes, 0=no |
| dvt | Deep vein thrombosis: 1=yes, 0=no |
| vascular_death | Vascular death: 1=yes, 0=no |
| sae_death | Fatal SAE: 1=yes, 0=no |
| sae | Serious adverse event: 1=yes, 0=no |
| ae | Adverse event: 1=yes, 0=no |
| timetostroke | Time to stroke (years) |
| timetomi | Time to mi (years) |
| timetodeath | Time to death (years) |

| | |
|---|---|
| timetorf | Time to renal failure (years) |
| timetocf | Time to cardiac failure (years ) |
| timetotia | Time to TIA (years) |
| timetorevasc | Time to revascularisation (years) |