The efficacy and safety of aspirin in individuals with and without diabetes: A collaborative meta-analysis of individual participant data from randomised trials

A thesis submitted for the degree of Master of Science by Research

Trinity Term 2014

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DEDICATION

To my wife, Michelle, without whose love and support this thesis would not be possible.

ABSTRACT

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Background: Whether aspirin is of net clinical benefit for the primary prevention of vascular events in those at high risk, such as some people with diabetes, is uncertain.

Methods: Individual participant data from 26 randomised trials (123,361 individuals, 760,000 person-years) assessing aspirin versus control in people with and without diabetes were included. Major outcomes included serious vascular events (SVE: myocardial infarction, stroke or vascular death) and major extracranial bleeding (MEB).

Findings: In the primary prevention setting, aspirin reduced SVE (0.65% vs 0.71% per year; relative risk (RR) 0.90 [95% confidence interval (CI) 0.85-0.96]; p=0.0006) and increased MEB (0.10% vs 0.07% per year; RR 1.52 [95% CI 1.30-1.78]; p<0.0001). These proportional effects were similar in people with and without diabetes (χ^2_1 =0.74, p=0.39 and χ^2_1 =1.00, p=0.32 respectively). Estimated absolute effects of aspirin according to diabetes status and vascular risk suggested that some people, particularly those with diabetes and 5-year risk >5%, may derive net clinical benefit in the primary prevention setting. At a 5-year risk level of 5-10%, for example, people without diabetes might have a 1.6% (95% CI 1.1-2.1) reduction in 5-year SVE balanced against a 0.5% (95% CI 0.3-0.8) increase in 5-year MEB. In comparison, people with diabetes and 5-year risk of 5-10% might have a 1.7% (95% CI 1.2-2.2) reduction in 5-year SVE balanced against a 0.3% (95% CI 0.1-0.4) increase in 5-year MEB. Even if an approximate halving of baseline vascular risk by modern preventative measures such as statins is factored in before aspirin therapy is considered, aspirin may still have a worthwhile net clinical benefit in such people at least at moderate vascular risk.

Interpretation: Some people without previous disease but at higher vascular risk, such as people with diabetes and 5-year risk >5%, may derive net clinical benefit from aspirin. Further direct randomised evidence in these individuals will help clarify the balance of risks and benefits.

FOREWORD

Since 2011, I have collaborated with, and later joined, Professor Colin Baigent, Associate Professor Jonathan Emberson and the Vascular Overviews Group at the Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford.

It has been a remarkable opportunity to work with the renowned Antithrombotic Trialists' (ATT) Collaboration that is coordinated by this group. The material contained in this thesis, from part of my time working with the ATT Collaboration, constitutes a large-scale meta-analysis of individual participant data assessing the efficacy and safety of aspirin in individuals with and without diabetes mellitus. The results of this systematic overview have come about from a substantial, collaborative and international effort involving many researchers and participants from numerous randomised controlled trials of aspirin.

Within with the Vascular Overviews Group, I assisted with the day-to-day running of the ATT Collaboration, under the supervision of Professor Baigent and Associate Professor Emberson. This involved assisting a team in Oxford (including research assistants, statisticians, programmers and administrative staff), planning for the establishment of international steering committees and working groups, drafting and developing study protocols and data request forms, conducting electronic searches with the ATT Secretariat, and working with statisticians on the calculation and presentation of results, including those for the present thesis. The discussion, interpretation and implications of this work are my own.

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This thesis, and the results within it, would not have been possible without the help and assistance of many people.

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My wife Michelle – My remarkable time at Oxford has not been without many and multifaceted challenges. Facing these without your love, support, patience and more would certainly not have been possible, and for that I cannot thank you enough.

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CHAPTER 1: DIABETES AND CARDIOVASCULAR DISEASE

1.1 The global epidemiology of diabetes

As of 2013, it has been estimated by the International Diabetes Federation that there are 382 million people globally with diabetes, and this is estimated to rise to almost 592 million by 2035.[1] Similar figures have been reported by a number of other investigators in comparable reports.[2-4] While the number of people with type 2 diabetes – which accounts for 85 to 95 percent of patients with diabetes – is increasing in every country, approximately 80 percent of all people with diabetes currently live in low- and middle-income countries, presenting challenges for healthcare delivery.[1] In 2013, the top five countries with the most number of people with diabetes were China (98.4 million), India (65.1 million), the United States (24.4 million), Brazil (11.9 million) and Russia (10.9 million). Of great concern is the fact that 175 million people worldwide with diabetes are estimated to be undiagnosed.[1] In addition to the increasing total number, the prevalence of both type 1 and type 2 diabetes continues to increase. The global prevalence of diabetes in adults 20-79 years of age is currently estimated to be 8.3% and is forecast to increase to 10.1% by 2035.[1] There is little gender difference in the global prevalence of diabetes; 51% of adults with diabetes are male and this is expected to remain stable.[1]

The most important factor underlying these deleterious trends is central obesity. The epidemic of obesity is global, affecting developed and increasingly developing nations. This has been fuelled particularly by the widespread availability of high fat and high energy-containing food, the marketing of such food products and the

increasingly sedentary nature of modern lifestyles. Obesity is a key risk factor for type 2 diabetes and, together with its adverse effect on blood pressure, lipids and respiratory function, has a strong influence on the development of cardiovascular disease. It has been estimated that approximately 60% of diabetes can be attributed to a body mass index (BMI) above 21 kg/m^2.[5] While the absolute prevalence of type 2 diabetes in each category of BMI may vary by ethnicity, there are comparable proportional increases in the prevalence of type 2 diabetes with increasing BMI. As is well established, however, obesity is a complex condition that is associated with significant morbidity and mortality from not only diabetes and cardiovascular disease, but also, a myriad of other obesity-related conditions.

Due to the ongoing management required of diabetes, the microvascular (retinopathy, neuropathy and nephropathy) and macrovascular (ischaemic heart disease, cerebrovascular disease and peripheral vascular disease) effects of diabetes and other associated complications, diabetes confers significant morbidity and mortality on affected patients. For example, people with type 2 diabetes lose on average 5-10 years of life from the year of diagnosis.[6] When the implications of such morbidity and mortality are scaled to the large proportion of the population affected, diabetes imposes a substantial burden on society. From the Global Burden of Disease Study 2010, it is estimated that diabetes accounts for 1.9% of all global disability-adjusted life years.[7] In 2010, a total of 1.3 million deaths were attributable to diabetes, an increase of 92.7% compared to 1990.[8] In the United States alone, it is estimated that the total estimated cost of diagnosed diabetes was US242 billion in 2012.[9] Healthcare for people with diagnosed diabetes accounted for one-fifth of all

health expenditure. While these estimates include those associated with reduced societal productivity, they do not account for that cost attributable to pain and suffering, nonpaid caregivers and burden on people with undiagnosed diabetes. Thus, these staggering figures are still likely to be underestimates.

1.2 Cardiovascular disease in people with diabetes

Cardiovascular disease remains the leading cause of mortality globally, representing more than 30% of deaths.[10] These deaths are largely due to coronary heart disease and stroke, and over 80% of cardiovascular disease deaths occur in low- and middle-income countries.

Diabetes and pre-diabetes are important risk factors for cardiovascular disease.[11, 12] As confirmed by many prospective studies, people with diabetes have a twofold higher risk of developing cardiovascular disease relative to those without diabetes.[11, 13] The significance of diabetes has furthermore gained notoriety from studies showing a comparable risk of myocardial infarction and coronary mortality between people with diabetes and people without diabetes but with prior myocardial infarction.[14] Although there is a wide spectrum of cardiovascular risk amongst people with diabetes, such studies have led to diabetes often being referred to as a coronary heart disease equivalent.[15, 16] Furthermore, as a result of the rising prevalence of diabetes, there has been a 60% increase in the attributable risk ratio for cardiovascular disease associated with diabetes, with the contribution from other risk factors either remaining constant or falling.[17] While microvascular complications of diabetes (retinopathy, neuropathy and nephropathy) are significant causes of

morbidity and mortality, it is the macrovascular disease associated with diabetes which has greatest impact on overall mortality.

1.2.1 Cardiovascular risk factors in people with diabetes

Patients with diabetes have a significant number of other risk factors for cardiovascular disease, including hypertension, obesity and lipid abnormalities. These are often already present in people with prediabetes prior to the diagnosis or development of overt type 2 diabetes; in fact, complications are not uncommonly already present at the time of diagnosis and can be found in a not insignificant proportion of individuals with specific screening investigations.[18-21] The co-occurrence of certain metabolic risk factors for both type 2 diabetes and cardiovascular disease is termed the metabolic syndrome. While debate exists as to whether the metabolic syndrome as it is currently defined confers additional risk beyond its individual components, the real clustering of these components is accepted, evidencing the close relationship between insulin resistance and these other risk factors.[22] Individual with metabolic syndrome are thus at high risk of developing both type 2 diabetes and overt cardiovascular disease.

1.2.2 Hyperglycaemia and macrovascular disease

Hyperglycaemia plays an important role in the development of vascular complications in people with diabetes. Numerous studies support the correlation between chronic hyperglycaemia and greater rates of cardiovascular disease.[23-25] As an example, one meta-analysis of 13 prospective cohort studies suggests that there is an 18% proportional increase of any cardiovascular event for every one

percentage point increase in glycated haemoglobin.[23] In keeping with this, management of hyperglycaemia with tight glycaemic control has been shown to protect against both microvascular and cardiovascular disease in the DCCT/EDIC study for type 1 diabetes.[26, 27] While large trials (e.g. ACCORD, ADVANCE and VADT) have failed to show that tight glycaemic control reduces cardiovascular events in people with longstanding type 2 diabetes, post-trial follow-up of the UKPDS suggests that tight glycaemia control does reduce macrovascular complications in newly diagnosed patients with type 2 diabetes.[28-32]

1.2.3 Mechanisms of accelerated atherosclerosis

Atherosclerosis is accelerated in people with diabetes and underlies its epidemiological association with premature cardiovascular disease. While the risk factors that often cluster with diabetes in the metabolic syndrome account for some of the increased incidence, diabetes confers additional risk beyond that seen with metabolic syndrome alone.[33] This suggests that hyperglycaemia must play a key role in atherogenesis, and is supported by evidence suggesting benefits from glycaemic control mentioned previously.

Hyperglycaemia in people with diabetes results in modification of molecules in the arterial wall by glycation. The result of this process are advanced glycation end-products; these have a range of atherogeneic effects including mechanical wall dysfunction, trapping of blood components, and causing broad perturbations in cell pathways that generates matrix and vessel wall growth.[34]

The endothelium can also be subject to insults which, when resulting in excessive inflammatory and proliferative responses, can lead to the development of atherosclerosis. Accumulating evidence suggests that endothelial dysfunction is, in fact, an initial step in atherosclerosis and can be detected before structural changes noted.[35] Commensurate with this is the fact that people with diabetes exhibit abnormalities in endothelial function in the absence of overt atherosclerosis or other cardiovascular risk factors.[36-41] While such dysfunction worsens with increasing duration of diabetes, impairment with acute hyperglycaemia can be seen even in those with normal fasting plasma glucose.[42] There are a number of possible mechanisms for these observations. The synthesis and release of nitric oxide is a key regulator of endothelial function. Hyperglycaemia reduces nitric oxide production by inhibiting the activation of endothelial nitric oxide synthase and generating reactive oxygen species.[43] Decreased nitric oxide and increased oxidative stress activates transcription factors such as nuclear factor κB and activator protein 1 that regulate genes mediating atherogenesis by the recruitment of lymphocytes and monocytes into the vascular wall.[44] In addition to effects on nitric oxide biology, diabetes increases the production of endothelin-1 and other vasoconstrictors which activate receptors on vascular smooth muscle cells to induce vasoconstriction.[45] Once plaque formation occurs, diabetes also contributes to plaque instability through collagen breakdown and subsequent rupture.[46]

In addition to the contribution of platelet dysfunction to abnormal thrombogenesis (discussed later), people with diabetes also have abnormal coagulation and fibrinolysis. There is an elevation of several coagulation factors such as fibrinogen,

factor VII, factor VIII, factor XI, factor XII, kallikrein, and von Willebrand factor, and decreases in anticoagulants such as antithrombin III and protein C.[47-49] Increased levels of plasminogen activator inhibitor type 1 also contributes to impaired fibrinolysis.[48] As a result, thrombi are more easily generated and less readily removed in people with diabetes.

1.2.4 Platelet dysfunction in diabetes

In people with diabetes, platelets have been shown to have several dysregulated signalling pathways via both receptor and downstream intracellular signaling abnormalities.[50, 51] The resulting greater platelet reactivity has been speculated to be in-part responsible for not only the greater risk of vascular events in people with diabetes, but also, the attenuated platelet response measures to antiplatelet agents that has been previously observed.[52] This is discussed in more detail in Chapter 3.

1.3 Reducing cardiovascular disease in diabetes

Given the global epidemic of diabetes, strategies to reduce the burden of cardiovascular disease associated with diabetes are of great public health importance. Individuals with diabetes who have already suffered occlusive vascular events benefit from strategies that have well established roles in the general secondary prevention of cardiovascular disease; these include antiplatelet therapy, antihypertensive agents, lipid-lowering medications and lifestyle changes. Glycaemic control in those with diabetes is likely to be of additional benefit. Importantly, however, is the majority of individuals with diabetes that do not have, but are at

heightened risk of developing, cardiovascular disease and subsequently occlusive vascular events; careful management to reduce their risk requires similar attention.

1.3.1 Antiplatelet therapy

The benefits of long-term antiplatelet therapy (chiefly aspirin) in the secondary prevention of cardiovascular disease is well established, and evidence to date suggests that the proportional reductions in major vascular events such as myocardial infarction, stroke and vascular death seem similar irrespective of the presence or absence of diabetes.[53] The use of aspirin in people with diabetes but no previous occlusive vascular events, however, is less clear. A discussion on this topic is presented in further detail in Chapter 3.

1.3.2 Blood pressure lowering

Elevated blood pressure is perhaps the most important risk factor for premature cardiovascular disease given its greater global prevalence compared to other risk factors.[54] In people with diabetes, hypertension is a common finding though the pattern differs between type 1 and type 2 diabetes. While often present at the time of diagnosis in type 2 diabetes, its onset is later and coincident with nephropathy in type 1 diabetes.[55] Multiple randomized trials have demonstrated that blood pressure lowering with several classes of antihypertensive agents such as angiotensin converting enzyme inhibitors, calcium antagonists, diuretics and beta-blockers reduce cardiovascular events, and the effects of blood pressure lowering regimens are broadly comparable for people with and without diabetes.[56] Debate continues to exist, however, on optimal blood pressure goals. While previous guidelines

recommended a target blood pressure of less than 130/90 mmHg in those with diabetes, more recent evidence – in particular from the large ACCORD trial – suggests there may be minimal additional benefit, except for some reduction in stroke, with intense blood pressure lowering.[57-59] As a result, current guidelines suggest a target of less than 140/90 mmHg in people with diabetes.[60]

1.3.3 Lipid lowering

Lipid-lowering, chiefly with statin therapy, has been shown to safely reduce cardiovascular events regardless of baseline lipid profile and other baseline characteristics.[61] Both types of diabetes are associated with dyslipidaemia, and prospective data from many randomized trials have conclusively established that statin therapy has similar proportional benefits in a range of people with diabetes, irrespective of baseline lipid profile and the presence of established cardiovascular disease. [62] It has been suggested, therefore, that given the benefits far outweigh the risks of any hazards, all adults with diabetes at sufficiently high risk of vascular events should consider statin therapy.

1.3.4 Glycaemic control

Glycaemic control is of established benefit in preventing progression of microvascular complications (retinopathy, nephropathy and neuropathy) in both types of diabetes. [26, 28, 63] Greater reductions in glycated haemoglobin are associated with improved outcomes with no apparent threshold effect, though the benefit of intensive glycaemic control needs to be weighed against the risks of hypoglycaemia. While the importance of tight glycaemic control has been shown to protect against

cardiovascular disease in type 1 diabetes, the results of trials in type 2 diabetes did not show in-trial reductions in overall cardiovascular events as discussed above (though post-trial follow-up of the UKPDS cohort did show reductions in macrovascular events with intensive glucose lowering therapy).[29] Importantly, this benefit was seen despite the loss of between-group differences in glycated haemoglobin after the first year following trial completion, a so-called ‘legacy effect’ from ‘metabolic memory’ that underscores the long-term benefits of glycaemic control.

Glycaemic control can be achieved through nonpharmacologic and pharmacologic means. It is recommended that all patients with diabetes adhere to weight reduction, diet and exercise management strategies. Dietary modification can assist with weight reduction, hypertension, insulin release and responsiveness.[64] Despite these benefits, however, only a minority of patients are able to attain and maintain significant weight loss with dietary modification alone.[65] Weight loss medications may be effective though are limited by side effect profiles. [66] Surgical treatment of obese patients with diabetes is a promising strategy that results in substantial and sustained weight loss (20-30% at 1-2 years) and resultant improvements in glycaemic control.[67] However, further long-term follow-up data is required before this can be recommended routinely. Regular exercise can assist with obesity and also results in improvements in glycaemic control and insulin responsiveness independent of weight reduction.[68] Like dietary modification, however, sustaining regular exercise programs is challenging for the majority of patients.

Despite the benefits of nonpharmacologic strategies, the majority of patients with diabetes will require hypoglycaemic medications over the course of their disease. [66] While patients with type 1 diabetes require insulin therapy from diagnosis, there is an increasing range of pharmacologic options for patients with type 2 diabetes. There is a lack of strong evidence supporting any agent over another with regards to cardiovascular benefits, however; while some have suggested metformin may reduce the risk of macrovascular complications, this has yet to be conclusively established.[69]

1.3.5 Multifactorial risk reduction

There is some evidence that intervening on multiple risk factors may have cardiovascular benefits. In the relatively small Steno-2 study, investigators randomised 160 individuals with diabetes to conventional or intensive therapy, the latter consisting of reduced dietary fat, light-to-moderate exercise, smoking cessation, tight glycaemic control, tight blood pressure control, angiotensin converting enzyme inhibitor therapy, lipid-lowering and aspirin.[70] In addition to microvascular benefits, there were significant reductions in coronary events, stroke, peripheral vascular events and cardiovascular death. In contrast, the larger Look AHEAD study, which randomised 5145 overweight or obese individuals with diabetes, was unable to show a reduction in cardiovascular events with intensive lifestyle intervention alone despite significant other benefits, suggesting that reducing multiple risk factors with both nonpharmacologic and pharmacologic means is required to reduce macrovascular disease.[71]

1.4 Conclusion

Diabetes mellitus is a major public health concern that appears destined to increase significantly in the coming decades. The relationship between diabetes and cardiovascular disease is clear, and given the sheer number of individuals with diabetes and thus at risk of cardiovascular disease, there is an urgent need to implement strategies to reduce this risk. Multiple treatment strategies are likely to be required to have maximum effect, and antiplatelet therapy may be one possible measure that would be widely applicable and cost-effective. Questions exist as to whether it has a definite net benefit, however, and thus the use of such antiplatelet therapy in people with diabetes is discussed further in the next chapter.

CHAPTER 2: ASPIRIN THERAPY IN PEOPLE WITH DIABETES

2.1 Antiplatelet drugs

2.1.1 Aspirin – the first antiplatelet drug

The medicinal value of salicylates has been appreciated since ancient Egyptian times when willow bark was used as an antipyretic, analgesic and general tonic.[72] Despite centuries of use, however, it was not until 1971 that the mechanisms of salicylates – by this point in time synthesised in the pure and stable form of acetylsalicylic acid – were elucidated. In his seminal report, Vane described the dose-dependent inhibition of prostaglandin synthesis by aspirin and other non-steroidal anti-inflammatory drugs.[73] Prostaglandins had earlier been recognised to be linked closely with the regulation of fever, inflammation and pain. Aspirin targets cyclooxygenase or prostaglandin endoperoxidase synthase and causes irreversible inhibition by acetylation, preventing arachidonic acid access to its active binding site.[74] It was later discovered that thromboxane A2, derived from prostaglandins, is a potent vasoconstrictor and stimulator of platelet aggregation.[75] Hence, aspirin became also recognised for its antithrombotic effects and this has led to it still being used by more people today than any other drug.

Oral aspirin is rapidly absorbed from the upper gastrointestinal tract and platelet inhibition can be measured within one hour. [76] While the plasma half-life of aspirin is approximately 20 minutes, platelets cannot generate new cyclooxygenase and the antiplatelet effects of aspirin therefore last for the life of the platelet (10 days). The antiplatelet effect of aspirin can be detected by prolonged bleeding times and

thromboxane A2-dependent platelet aggregation; it has been shown that a single dose of 75-100mg of aspirin is effective in abolishing platelet production of thromboxane A2 in most individuals.[77, 78]

2.1.2 Bleeding hazards with aspirin

The efficacy of all antiplatelet agents requires careful balancing against their bleeding hazards. The most worrisome risks are bleeding from the gastrointestinal tract and intracranial vessels. It should be noted that gastrointestinal tract bleeding is of particular relevance to aspirin compared to other antiplatelets given prostaglandins have a physiologically important role in protecting the gastric mucosa from acid damage. Overall, analyses from randomised trials suggest that major extracranial bleeds (fatal or requiring hospitalisation or transfusion) are significantly increased by about one half and that haemorrhagic strokes (both non-fatal and fatal) are significantly increased by about one quarter.[53] Aspirin has also been studied at differing doses and the evidence suggests that bleeding hazards increase with doses greater than 100mg.[79] The presence of diabetes has been recognized to be an independent risk factor for major bleeding, conferring an additional 50% increased risk.[80, 81]

2.1.3 Impact of diabetes on the antiplatelet effects of aspirin

There continues to be controversy as to whether the presence of diabetes modifies the antiplatelet effects of aspirin. Clinical data that have led to this suggestion include observations that many people with diabetes continue to experience vascular events despite aspirin therapy, and that bleeding with aspirin therapy

compared to no aspirin therapy is only minimally increased in people with diabetes.[81] Other data supporting this theory is the higher platelet reactivity and lower-than-expected inhibition of platelet function while on treatment in people with diabetes, often referred to as 'aspirin resistance'.[82] A number of mechanistic explanations have been proffered for these observations. One is the accelerated turnover of platelets that has been described in people with diabetes compared to people without diabetes.[83, 84] This hypothesis is supported by experimental data showing faster recovery of platelet cyclooxygenase activity and increased mean platelet volume in people with diabetes.[82] Another possibility is that glycosylation of platelets membranes in the presence of hyperglycaemia may reduce aspirin permeability.[84, 85] A number of experimental studies have also suggested that more frequent dosing may counteract inadequate platelet inhibition in people with diabetes.[82, 83] These data raise the possibility that people with diabetes may represent a different population in terms of both expected risks and benefits associated with aspirin therapy and highlight the need for further study into this area.

2.1.4 Other effects of aspirin

In recent years, evidence has emerged that aspirin and other non-steroidal anti-inflammatory drugs may inhibit carcinogenesis, metastasis and associated mortality.[86-89] As a result, some have suggested – including one major guideline – that preventative effects on carcinogenesis be incorporated into clinical decision-making when balancing the benefits and risks of aspirin.[90] This may be particularly important when considering the use of aspirin in primary prevention, where the

vascular benefits and bleeding hazards may be well balanced, as discussed later. Others, however, are concerned that key analyses[86] describing preventative effects of aspirin on cancer excluded data from two large trials, the Physician's Health Study[91] and the Women's Health Study,[92] which did not find significant effects of aspirin on cancer incidence and mortality based on their alternate day dosing of aspirin (as opposed to daily aspirin use). As a result, this continues to be an area of intense controversy.

2.1.5 Alternative antiplatelet drugs

The development of antiplatelet drugs continues to be actively pursued. Common other antiplatelet drugs that are currently in clinical use include dipyridamole, P2Y12 inhibitors (such as clopidogrel, prasugrel and ticagrelor) and glycoprotein IIb-IIIa inhibitors (such as abciximab, eptifibatide and tirofiban). Despite the development of these, however, aspirin remains the most widely used antiplatelet drug. The above agents are often used in combination with aspirin for defined periods of time where more intensive antiplatelet inhibition is required, for example following acute coronary syndromes or during vascular intervention. While some agents such as clopidogrel have been successfully trialled as long-term alternatives to aspirin, as opposed to in combination with aspirin, aspirin is often still chosen based on only moderate improvements in efficacy with alternative agents and significantly higher costs.[53, 93] A more in depth discussion of other antiplatelet agents is beyond the scope of this thesis.

2.2 Aspirin in secondary prevention

Meta-analyses of randomised trials have conclusively demonstrated that aspirin is of substantial net benefit in the secondary prevention of cardiovascular disease. In the Antithrombotic Trialists' Collaboration overview, aspirin was associated with a 22% reduction in serious vascular events (myocardial infarction, stroke and vascular death) in a wide range of individuals at high risk of occlusive vascular events.[53] Doses of 75-100mg were at least as effective as higher daily doses. As a result, all major guidelines recommend that aspirin be used in people requiring secondary prevention, including those with diabetes.[90, 94]

2.3 Aspirin in primary prevention

2.3.1 Primary prevention in the general population

Given that aspirin is of definite and substantial benefit in the secondary prevention of cardiovascular disease, the potential utility of aspirin in those who do not have manifest occlusive arterial disease is of interest. A number of meta-analyses have assessed the efficacy and safety of aspirin on vascular outcomes in this primary prevention setting.[80, 95] The 2009 Antithrombotic Trialists' Collaboration overview included individual participant data from six primary prevention trials of aspirin.[80] These analyses suggested that aspirin is associated with a significant 12% proportional reduction in all serious vascular events (myocardial infarction, stroke and death from a vascular cause). Given the low vascular risk of these individuals, however, this only translates into a small absolute reduction in serious vascular events of 0.07% per year from aspirin. Of the separate outcomes, aspirin produced

an 18% proportional reduction in major coronary events (RR 0.82, 95% CI 0.75-0.90), mostly driven by a 23% proportional reduction in non-fatal myocardial infarction (RR 0.77, 95% CI 0.69-0.86) with no clear reduction in coronary heart disease mortality (RR 0.95, 95% CI 0.82-1.10). Again, this resulted in only small absolute reductions in major coronary events (0.28% vs 0.34% per year). Aspirin also seemed to reduce ischaemic strokes (RR 0.86, 95% CI 0.74-1.00) and increase haemorrhagic strokes (RR 1.32, 95% CI 1.00-1.75); as a result there was no effect on the aggregate of all strokes (RR 0.95, 95% CI 0.95 0.85-1.06). There was no significant reduction in overall vascular mortality (RR 0.97, 95% CI 0.87-1.09) or on total mortality (RR 0.95, 95% CI 0.88-1.02). Calculations of the absolute effects of aspirin in primary prevention on 5-year outcomes suggest that the absolute reduction in occlusive vascular events would be only about twice as large as the absolute increase in bleeding. Given the individuals in these trials were mainly not taking statin therapy, which may approximately half the risk of occlusive vascular events, any net benefit of aspirin in primary prevention seemed uncertain as the benefits and hazards might be balanced.

2.3.2 Primary prevention in people with diabetes

While the utility of aspirin in the primary prevention of occlusive vascular events in general thus remains uncertain, there is the possibility that particular categories of individuals may eventually be identified in which there is a net benefit. One particularly important category is people with diabetes. The vast majority of people with diabetes do not yet have manifest occlusive arterial disease and, as discussed

above, there are therefore millions of individuals with diabetes worldwide who are at risk of occlusive events. If aspirin was of net benefit in this large population of people, its routine use would be a cheap strategy to prevent a large number of occlusive events worldwide.

The 2002 Antithrombotic Trialists' Collaboration overview of antiplatelet therapy included data from about 5000 patients with diabetes from 9 trials.[53] In the subset of individuals with diabetes, there was a non-significant 7% reduction in vascular events; this estimate was associated with wide confidence intervals ranging from a 23% risk reduction to an 8% hazard. Though there was no significant heterogeneity of effect between those with and without diabetes in the later 2009 Antithrombotic Trialists' Collaboration primary prevention overview (χ^2_1 =0.0, p=0.9), three other trials of aspirin for primary prevention in diabetes have individually been unpromising.[96-98] Three subsequent meta-analyses have included tabular data from some of these trials. [95, 99, 100] The first included tabular data from nine trials assessing aspirin in primary prevention in general, finding significant proportional reductions in total cardiovascular events (OR 0.90, 95% CI 0.85-0.96) and significant proportional increases in nontrivial bleeding (OR 1.31, 95% CI 1.14-1.50); sensitivity analyses suggested these effects were comparable when people with diabetes were included or excluded. [81] The second analysis included tabular data from the same nine trials and came to similar conclusions. [85] The third analysis included tabular data from seven aspirin trials enrolling patients with diabetes.[100] These investigators reported nonsignificant effects of aspirin on major cardiovascular events or major bleeding. An earlier tabular meta-analysis, also published in 2009, including data from trials in

people with diabetes found nonsignificant proportional reductions in major cardiovascular events (RR 0.90, 95% CI 0.81-1.00) and nonsignificant proportional increases in gastrointestinal bleeding (RR 2.50, 95% CI 0.76-8.21). [101] None of these other meta-analyses demonstrated any significant reductions in cardiovascular or total mortality. Taking the evidence in totality, it is clear that existing analyses do not clearly support the routine use of aspirin in the primary prevention setting, including those with diabetes, and firm recommendations for or against its use cannot be made at present.

As a result of such uncertainty, there have been varying guideline recommendations for the use of aspirin in people with diabetes and no history of occlusive vascular disease in recent years. Based on the clear net benefit of aspirin in high-risk settings (i.e. secondary prevention), the American Diabetes Association (ADA) had, since 1997, recommended the use of aspirin in people with type 2 diabetes and at least one additional cardiovascular risk factor, such as hypertension or hypercholesterolaemia; this was in contrast to more circumspect recommendations from UK and European guidelines in 1998.[102-104] Subsequent UK guidelines in 2005, however, suggested that aspirin be used in people with diabetes and either atherosclerotic disease (but not necessarily a previous occlusive event), over 50 years of age, disease duration greater than 10 years or who are receiving treatment for hypertension.[105] National Institute of Health and Clinical Excellence (NICE) guidelines in 2008 also recommended aspirin in people with diabetes who are over 50 years of age and with a blood pressure below 145/90, and to those under 50 years of age with significant other cardiovascular risk factors (features of metabolic

syndrome, strong early family history of cardiovascular disease, smoking, hypertension, extant cardiovascular disease and microalbuminuria).[106] In 2007, revised ADA guidelines suggested that those with diabetes above 40 years of age received aspirin.[107] In recent years, guidelines have become increasingly circumspect. The ADA recommended in 2010 that aspirin is reasonable in people with diabetes and a 10 year risk of cardiovascular events greater than 10%.[108] In 2012, European guidelines recommended against aspirin in people with diabetes without clinical evidence of atherosclerotic disease.[109]

2.4 Need for an updated individual participant data meta-analysis

It is clear that uncertainty continues to exist as to whether aspirin is of net benefit in the primary prevention setting, and particularly in the many individuals who have diabetes. Tabular meta-analyses have methodological shortcomings that limit their reliability. For example, by using aggregated (summary) data from each trial, a tabular meta-analysis does not allow accurate assessment of whether the proportional effects of treatment differ among prognostic subgroups of individuals, and the effects of age, gender, baseline risk and diabetes cannot be reliably assessed. Hence, an updated meta-analysis with more detail (by collecting data on each individual participant themselves in the trial) would be substantially more informative.

CHAPTER 3: STUDY PROTOCOL AND STATISTICAL METHODS

3.1 Trial eligibility

The present analyses were undertaken using the Antithrombotic Trialists' Collaboration database. Eligible trials were all published and unpublished unconfounded trials which involved a randomised comparison of aspirin versus no aspirin (with no other antiplatelet drug in either group). Trials could be either in the primary or secondary prevention setting.

3.1.1 Primary prevention trials

Primary prevention trials excluded individuals with any history of occlusive disease at entry. Primary prevention trials were sought only if they recruited at least 1000 participants with at least 2 years of scheduled treatment. Individual participant data were provided from all ten published trials. Subsequent enquiry showed that 2% of individuals in primary prevention trials did in fact have some evidence of previous vascular disease but they remain in all analyses apart from those estimating the absolute effects of aspirin. Unpublished trials were sought through electronic searches and discussions, but none were identified.

3.1.2 Secondary prevention trials

Secondary prevention trials were included in analyses if they involved individuals with previous myocardial infarction (six trials) or stroke or transient cerebral ischaemia (ten trials), and had contributed individual participant data to the 2002

Antithrombotic Trialists' Collaboration report. Electronic searches established that no similar trials of aspirin had been reported since 2002.

3.2 Data collection

We asked the coordinators of all potentially eligible trials for details about method of randomisation, blinding of treatment allocation, scheduled duration of treatment, and, if different, scheduled duration of follow up. Investigators for trials were asked to contribute, for each patient originally randomised, data on baseline characteristics (age, sex, blood pressure, and medical history) and dates of randomisation, follow up, and any vascular events that had occurred. In addition, we asked them for a tabular summary of the numbers of patients originally allocated to each treatment group (that is, without any post-randomisation exclusions) and the numbers of patients experiencing particular outcomes during the scheduled follow up period. These outcomes were non-fatal myocardial infarction, non-fatal stroke (ischaemic, haemorrhagic or unknown), non-fatal or fatal pulmonary embolism, death from a vascular or unknown cause, death from a definitely non-vascular cause, and major extracranial bleeding. We checked data both for internal consistency and for consistency with relevant published reports and referred queries back to trial coordinators.

3.3 Outcome measures

The main outcome measures were serious vascular events, defined as non-fatal myocardial infarction, non-fatal stroke or death from a vascular cause (including sudden death, pulmonary embolism, haemorrhage, and, for secondary prevention

trials only, death from an unknown cause); major coronary event (myocardial infarction, coronary death, or sudden death); any stroke (haemorrhagic or probably ischaemic [ie, definitely ischaemic or of unknown type]); death from any cause; and major extracranial bleed (mainly gastrointestinal and usually defined as a bleed requiring transfusion or resulting in death). In primary prevention trials, myocardial infarctions and strokes were classified as fatal or non-fatal in accordance with each trial's definition. In the secondary prevention trials, these outcomes were regarded as non-fatal only if the patient was alive at the end of the trial or died of a non-vascular cause. Strokes were subdivided into intracranial haemorrhages (including intracerebral, subdural, subarachnoid, and extradural haemorrhages), ischaemic strokes and strokes of unknown aetiology. If during the trial a patient experienced more than one type of non-fatal outcome – for example, a myocardial infarction followed by a stroke – both events were recorded, but such patients contributed only once to the composite outcome of serious vascular event. If during the trial a patient experienced more than one non-fatal event of the same type (for example, two myocardial infarctions) or more than one pathological type of stroke (for example, a haemorrhagic stroke and an ischaemic stroke), only the first event was to be recorded.

3.4 Statistical methods

3.4.1 Calculation of event rate ratios

The log-rank "observed minus expected" statistic o – e (and its variance v) was estimated for each trial, where o is the number of observed events in the aspirin

group and e the number of events that would be expected in the aspirin group if treatment had no effect. This process involves estimation of separate o-e and statistics at every point in time at which an event occurs, made possible by the availability of individual participant rather than tabular data. The summation of all separate o – e's yields the overall log-rank o – e statistic for the trial, and the summation of all separate v's provides its overall variance.

To calculate the overall event rate ratio across all trials, the log-rank o – e values from each trial were summed to produce a grand total (G) with variance (V) equal to the sum of their separate variances. The one-step estimate of the log event rate ratio across all trials is G/V, its 95% confidence interval is given by the formula $G/V \pm 1.96 / \sqrt{V}$, and its associated 2-sided p-value is provided by comparing the statistic G^2/V against a chi-squared distribution with 1 degree of freedom. The χ^2 test statistic (χ^2_{n-1}) for heterogeneity between n trials is $S-(G^2/V)$, where S is the sum over all the trials of $(o – e)^2 /v$. Rate ratios in different subgroups were compared by standard χ^2 tests for heterogeneity. For trials that randomised unequally (ie, 2:1), we multiplied the control group by two when displaying adjusted control totals and describing the total amount of information available, but not in other calculations.

3.4.2 Forest plots

Forest plots were employed to graphically convey the proportional effects of aspirin across multiple trials. These illustrated measures of effect (rate ratios) for each result from each of the relevant studies (represented by a square) and incorporated confidence intervals (represented by horizontal lines). The area of each square is

proportional to the variance of the sum of the o – e statistics for the trials represented in each row (i.e. it is proportional to the amount of 'statistical information' provided by each trial). In the present analyses, 99% confidence intervals have been used for individual subgroups whilst 95% confidence intervals have been used for subtotals and totals. The measure of overall effect is plotted as a diamond, the lateral points of which indicating confidence intervals for this estimate. A vertical line representing the null hypothesis of no effect is also plotted (in this case a rate ratio for 1.0). If confidence intervals overlap with this, there is no evidence to reject the null hypothesis of no true treatment effect at the given level of significance. Absolute rate differences were estimated from the difference in annual event rates in the events/person-years columns and are also presented.

3.4.4 Proportional and absolute effects of treatment

Calculated rate ratios are described in the results as both proportional and absolute reductions. Proportional reductions may be more widely generalisable to different circumstances, while absolute reductions may be more directly relevant for decision making in a specific circumstance, hence both are presented.

3.4.5 Effects in specific subgroup categories

In addition to the primary and secondary outcomes, subgroup tests were conducted using the available information. It is important to note, however, that findings from multiple subgroup analyses may be misleading. False negative and false positive significance tests increase in likelihood rapidly as more subgroup analyses are performed. Given multiple testing, especially where very small numbers of patients

in a subgroup have been assessed (increasing the role of random error), it is important that ‘lack of evidence of an effect’ is not misinterpreted as ‘evidence of lack of an effect’. The relevant question in each subgroup is whether there is convincing evidence that there is any material difference in the subgroup from the overall effect. If the subgroup findings are presented as definitive conclusions there is clearly a risk of patients being denied effective intervention or treatment with an ineffective (or even harmful) intervention. Nevertheless, even though the low power of heterogeneity tests means that individual subgroup results needs to be interpreted cautiously on their own, homogeneity of multiple subgroups suggests that the proportional effects are more reliable, especially when assessing absolute effects.

3.4.6 Identifying risk factors and risk modelling

To identify risk factors for various outcomes in people in the primary prevention trials, we used Poisson regression, stratified by trial, to estimate the common linear dependence of the log of the event rate on age, sex, diabetes, current cigarette smoking, total cholesterol, mean (of systolic and diastolic) blood pressure, body-mass index, and allocation to aspirin or control. Additionally, the results of this model for major coronary events in the controls of each trial were used to classify the baseline risks of all participants (including those allocated aspirin) as low (predicted 5-year risk of coronary heart disease without aspirin <5%), moderate (5-10%) or high (≥10%).

CHAPTER 4: CHARACTERISTICS OF STUDY POPULATION

Individual participant data from a total of twenty-six[96-98, 110-131] trials were eligible for inclusion (123,361 individuals and 7,801 serious vascular events; Table 4.1 and 4.2). Ten[96-98, 110-116] of these (n=106,332) were undertaken in the primary prevention setting and 16[117-132] of these (n=17,029) in the secondary prevention setting.

Individuals were mostly middle-aged (mean 57±9 years of age, Table 4.3). While primary prevention trials were mostly gender-balanced (46.2% men), secondary prevention trials randomised a majority of men (82.9% men). Individuals were followed-up for an average of 6.2±3.0 years. Details of other risk factors, including hypertension, hypercholesterolaemia, smoking and body mass index were available from the majority of primary prevention trials but only a minority of secondary prevention trials (Table 4.3). Within these limitations, mean blood pressure was 133±18/81±10mmHg, mean total cholesterol 5.6±1.1mmol/L, mean body mass index 26.3±4.6kg/m^2 and 17% of individuals were current smokers. As mentioned above, subsequent enquiry showed that 2% of individuals in primary prevention trials did in fact have some evidence of previous vascular disease but they remain in all analyses apart from those estimating the absolute effects of aspirin.

Twenty-three of these trials contributed individual participant data from people with (n=13,101) and without diabetes (n=106,886) to these analyses; information on diabetes was not available for participants in the remaining three trials (Table 4.4).[117, 122, 126] Three trials[96-98] (7526 individuals) were conducted exclusively in individuals with diabetes and the remainder (20 trials with 112,461 individuals) included a range

of 1.3% to 23.1% of individuals with diabetes. Individuals with diabetes were more often male, current smokers, hypertensive, overweight and had some evidence of previous vascular disease (Table 4.4).

Table 4.1: Characteristics of included randomised aspirin trials in primary and secondary prevention settings

Study	Dates of Recruitment	Participating Countries	Year of Main Publication	Aspirin regimen	Randomised factorial comparison	Placebo control	Eligible age range at entry (years)	Target population
Primary prevention trials								
British Doctors	Nov 1978-Nov 1979	UK	1988	500mg daily	None	No	19-90	Male doctors
US Physicians	Aug 1981-Aug 1984	USA	1988	325 mg e.o.d	Beta carotene vs placebo	Yes	45-73	Male doctors
ETDRS	Apr 1980—Jul 1985	USA	1992	650mg daily	None	Yes	18-70	DM with diabetic retinopathy
TPT	Feb 1989-1984	UK	1998	75mg daily	Warfarin vs placebo	Yes	45-69	Men with risk factors for CHD
HOT	Oct 1992-May 1994	Europe, N & S America, Asia	1998	75mg daily	Three blood pressure regimens	Yes	50-80	Men and women with DBP 100-115mmHg
PPP	Jun 1993-Apr 1998	Italy	2001	100mg daily	Vitamin E vs open control	No	45-94	Men and women with >1 risk factor for CHD
WHS	Sep 1992-May 1995	USA	2005	100mg e.o.d.	Vitamin E vs placebo	Yes	≥45	Female health professionals
JPAD	Dec 2002-May 2005	Japan	2008	81 to 100mg daily	None	Yes	30-85	Pts with T2DM with no atherosclerotic disease
POPADAD	Nov 1997-July 2001	Scotland	2008	100mg daily	Antioxidant vs placebo	Yes	≥40	DM with asymptomatic PAD (ABI≤0.99)
AAA	Apr 1998-Dec 2001	Scotland	2010	100mg daily	None	Yes	50-75	Pts with low ABI, free from clinical cardiovascular disease
Secondary prevention trials								
Cardiff-I	Feb 1971-Sep 1973	UK	1974	300mg daily	None	Yes	<65	Men with prior myocardial infarction
AITIA	Oct 1972-1975	USA	1977	500mg t.d.s.	None	Yes	Any age	Men and women with recent transient ischaemic attack
Reuther	Apr 1972-Jun 1976	Germany	1978	500mg t.d.s.	None	Yes	Any age	Men and women with recent transient ischaemic attack
CA Co-op	Nov 1971-Jun 1976	Canada	1978	325mg daily	Sulfinpyrazone vs placebo	Yes	Any age	Men and women with recent transient ischaemic attack
Cardiff-II	Not specified	UK	1979	300mg t.d.s.	None	Yes	Any age	Men and women with prior myocardial infarction
Paris-I	May 1975-Jul 1979	USA	1980	324mg t.d.s.	None (Third arm of Persantine plus Aspirin)	Yes	30-74	Men and women with prior myocardial infarction
AMIS	Jan 1975-Aug 1979	USA	1980	500mg b.d.	None	Yes	30-69	Men and women with prior myocardial infarction
CDP-A	Nov 1972-Feb 1975	USA	1980	324mg t.d.s.	None	Yes	30-64	Men with prior myocardial infarction
Gamis	1970-1977	Germany	1980	500mg t.d.s.	None (Third arm of Phenoprocoumon)	Yes	45-70	Men and women with prior myocardial infarction
Toulouse TIA	Jun 1973-Aug1976	France	1981	300mg t.d.s.	None (three arms, all received Dihydroergocornine, one arm both Dipyridamole and Aspirin)	No	Any age	Men and women with recent transient ischaemic attack or minor ischaemic stroke
AICLA	Oct 1975-Dec 1978	France	1983	330mg daily	None (third arm of Dipyridamole plus Aspirin)	Yes	Ay age for men, >50 for women	Men and women with prior transient ischaemic attack or ischaemic stroke
Danish Co-op	Jun 1976-Oct 1979	Denmark	1983	1000mg daily	None	Yes	<75	Men and women with recent transient ischaemic attack
Britton	Oct 1978-Aug 1982	Sweden	1987	1500mg daily	None	Yes	Any age	Men and women with recent ischaemic stroke
UK TIA	Jul 1979-Oct 1985	UK	1988	600mg b.d. or 300mg daily	None (three arm study)	Yes	Any age	Men and women with recent transient ischaemic attack or minor ischaemic stroke
Danish Low Dose	Jan 1982-Dec 1986	Denmark	1988	50-100mg daily	None	Yes	Any age	Men and women with prior endarterectomy
SALT	Dec 1984-Jan 1989	Sweden	1991	75mg daily	None	Yes	50-79	Men and women with prior transient ischaemic attack or ischaemic stroke

Table 4.2: Number of events generated from included randomised aspirin trials in primary and secondary prevention settings

Study	Number of patients	Non-fatal MI	Major coronary events	Haemorrhagic stroke	Ischaemic stroke	Unknown stroke	Any stroke	Serious vascular events	Major extracranial bleed	CHD death	Stroke death	Bleed death	Other vascular death	Any vascular death	Any non-vascular death	Unknown death	Any death
Primary prevention trials																	
British Doctors	5139	149	267	20	26	87	133	434	30	136	42	4	42	224	194	3	421
US Physicians	22071	342	459	36	173	10	219	686	78	127	22	2	26	177	205	62	444
ETDRS	3711	119	524	0	0	170	170	759	NR	397	50	0	82	529	30	22	706
TPT	5085	233	353	20	58	22	100	468	33	141	25	5	23	194	197	48	439
HOT	18790	182	345	26	0	291	317	712	176	170	51	10	53	284	0	0	589
PPP	4495	36	46	4	29	6	39	112	9	10	7	4	31	52	0	12	140
WHS	39876	365	493	92	391	4	487	999	218	134	58	1	54	247	587	154	1251
JPAD	2539	21	26	15	47	0	62	90	4	5	6	0	2	13	34	11	72
POPADAD	1276	78	127	4	65	12	81	201	19	61	17	3	19	100	56	37	195
AAA	3350	137	186	20	74	23	117	320	50	56	34	0	29	119	168	2	362
Subtotal (10 trials)	106332	1662	2826	237	863	625	1725	4781	617	1237	312	29	361	1939	1344	351	4619
Secondary Prevention Trials																	
Cardiff-I	1239	25	129	1	0	0	1	133	0	104	1	0	2	107	6	1	114
AITIA	319	6	17	1	0	39	40	61	3	7	6	0	10	23	3	0	26
Reuther	60	0	1	1	1	4	6	7	1	1	2	0	0	3	0	0	3
CA Co-op	283	4	16	0	0	43	43	63	0	12	9	0	5	26	5	0	31
Cardiff-II	1725	96	306	2	1	7	10	316	0	206	10	0	4	220	10	0	230
Paris-I	1216	84	195	0	2	18	20	212	0	110	5	0	3	118	19	0	137
AMIS	4524	317	707	1	3	97	101	795	0	388	10	0	10	408	52	5	465
CDP-A	1529	59	146	1	0	24	25	178	0	85	5	0	14	104	6	0	110
Gamis	626	26	61	2	0	0	2	78	0	35	2	0	7	44	7	8	59
Toulouse TIA	303	2	7	0	0	16	16	27	0	5	5	0	4	14	11	0	25
AICLA	402	11	15	4	0	49	53	79	0	4	6	0	5	15	12	10	37
Danish Co-op	203	10	20	2	1	29	32	50	0	10	4	0	1	15	5	1	21
Britton	505	21	42	6	42	15	63	114	5	15	20	0	22	57	14	0	71
UK TIA	2435	77	245	16	80	224	320	558	15	163	55	2	33	253	77	13	343
Danish Low Dose	301	2	16	1	0	20	21	42	0	14	1	0	3	18	4	2	24
SALT	1359	53	119	15	154	11	180	307	4	54	32	0	34	120	35	5	160
Subtotal (16 trials)	17029	793	2042	53	284	596	933	3020	28	1213	173	2	157	1545	266	45	1856
Total (26 trials)	123361	2455	4868	290	596	1221	2658	7801	645	2450	485	31	518	3484	2595	396	6475

Table 4.3: Baseline characteristics of individuals enrolled in included randomised aspirin trials in primary and secondary prevention settings

Study	Number of patients	Age (years)	SBP (mmHg)	DBP (mmHg)	BMI (kg/m^2)	Total-C (mmol/L)	Follow-up (years)	Diabetes (%)	Men (%)	Current smokers (%)	Hypertension (%)	Vascular disease (%)
Primary prevention trials												
British Doctors	5139	61 (7)	136 (17)	83 (10)	24.4 (2.5)	-	5.6 (0.9)	101 (2.0)	5139 (100.0)	1597 (31.1)	508 (9.9)	396 (7.7)
US Physicians	22071	53 (10)	126 (12)	79 (8)	24.9 (3.0)	5.5 (1.2)	5.0 (0.5)	533 (2.4)	22071 (100.0)	2438 (11.1)	5213 (23.8)	286 (1.3)
ETDRS	3711	47 (14)	139 (23)	83 (10)	30.0 (5.8)	-	6.1 (1.4)	3711 (100.0)	2096 (56.5)	869 (23.4)	1646 (44.4)	585 (15.8)
TPT	5085	57 (7)	139 (18)	83 (10)	27.4 (3.6)	6.4 (1.0)	6.7 (1.6)	68 (1.8)	5085 (100.0)	2096 (41.2)	791 (23.8)	45 (0.9)
HOT	18790	61 (7)	144 (15)	86 (8)	28.4 (4.7)	6.0 (1.1)	3.8 (0.7)	1501 (8.0)	9907 (100.0)	2983 (15.9)	18790 (100.0)	497 (2.6)
PPP	4495	64 (8)	145 (16)	85 (8)	27.6 (4.7)	6.1 (1.2)	3.7 (1.0)	742 (16.5)	1912 (42.5)	667 (14.8)	3065 (68.2)	170 (3.8)
WHS	39876	54 (7)	124 (13)	77 (8)	26.0 (5.1)	5.2 (1.0)	10.0 (1.0)	1027 (2.6)	0 (0.0)	5235 (13.1)	10317 (25.9)	144 (0.4)
JPAD	2539	65 (10)	135 (15)	77 (9)	-	5.2 (0.9)	4.0 (1.1)	2539 (100.0)	1387 (54.6)	537 (21.2)	1473 (58.0)	0 (0.0)
POPADAD	1276	60 (10)	145 (21)	79 (10)	24.4 (3.6)	5.6 (1.1)	6.4 (1.5)	1276 (100.0)	563 (44.1)	397 (31.1)	619 (48.5)	0 (0.0)
AAA	3350	62 (7)	148 (22)	84 (11)	26.0 (5.1)	6.2 (1.1)	8.2 (1.6)	88 (2.6)	954 (28.5)	1085 (32.4)	764 (22.8)	15 (0.4)
Subtotal (10 trials)	106332	56 (9)	132 (17)	80 (9)	-	5.6 (1.10)	6.8 (2.8)	11586 (11.0)	49114 (46.2)	17904 (16.8)	43186 (40.7)	2138 (2.0)
Secondary Prevention Trials												
Cardiff-I	1239	55 (8)	-	-	-	-	1.0 (0.6)	-	1239 (100.0)	-	-	1239 (100.0)
AITIA	319	58 (14)	-	-	-	-	1.4 (0.8)	-	211 (69.6)	-	-	319 (100.0)
Reuther	60	58 (10)	-	-	-	-	2.0 (0.1)	10 (16.7)	39 (65.0)	-	30 (50.0)	60 (100.0)
CA Co-op	283	61 (9)	146 (23)	85 (11)	-	-	2.7 (1.3)	23 (8.1)	189 (66.8)	-	104 (36.7)	283 (100.0)
Cardiff-II	1725	56 (10)	143 (29)	90 (18)	-	-	0.9 (0.3)	66 (4.5)	1468 (85.1)	-	-	1725 (100.0)
Paris-I	1216	56 (8)	132 (18)	83 (9)	-	-	3.2 (0.7)	123 (10.1)	1056 (86.8)	-	-	1216 (100.0)
AMIS	4524	55 (8)	128 (16)	80 (9)	-	-	3.0 (0.6)	480 (10.6)	4021 (88.9)	-	0 (0.0)	4524 (100.0)
CDP-A	1529	56 (7)	132 (18)	81 (10)	-	-	1.8 (0.6)	217 (14.2)	1529 (100.0)	-	-	1529 (100.0)
Gamis	626	59 (7)	-	-	-	-	1.3 (0.8)	124 (19.8)	486 (77.6)	-	122 (19.5)	626 (100.0)
Toulouse TIA	303	63 (9)	-	-	-	-	3.0 (1.3)	-	260 (85.8)	-	-	303 (100.0)
AICLA	402	64 (10)	150 (21)	90 (12)	-	-	2.9 (0.4)	93 (23.1)	274 (68.2)	-	258 (64.2)	402 (100.0)
Danish Co-op	203	59 (9)	138 (22)	84 (12)	-	-	2.6 (1.0)	12 (5.9)	148 (72.9)	-	-	203 (100.0)
Britton	505	68 (10)	-	-	-	-	1.8 (0.5)	85 (16.9)	314 (62.2)	-	232 (46.1)	505 (100.0)
UK TIA	2435	60 (9)	151 (25)	88 (12)	-	-	4.0 (1.8)	90 (3.7)	1779 (73.1)	-	660 (27.1)	2435 (100.0)
Danish Low Dose	301	59 (8)	149 (23)	85 (12)	-	-	1.9 (0.6)	22 (7.3)	195 (64.8)	-	-	301 (100.0)
SALT	1359	57 (7)	-	-	-	-	2.9 (1.2)	170 (12.5)	892 (65.6)	367 (27.0)	640 (47.1)	1359 (100.0)
Subtotal (16 trials)	17029	58 (9)	137 (23)	84 (12)	-	-	2.5 (1.4)	1515 (10.2)	14100 (82.9)	367 (27.0)	2046 (20.1)	17029 (100.0)
Total (26 trials)	123361	57 (9)	133 (18)	81 (1)	26.3 (4.6)	5.6 (1.1)	6.2 (3.0)	13101 (10.9)	64213 (51.2)	18271 (17.0)	45232 (38.9)	19167 (15.5)

Table 4.4: Baseline characteristics of individuals with and without diabetes enrolled in included randomised aspirin trials

	No Diabetes		Diabetes		All patients
	Primary Prevention	Secondary Prevention	Primary Prevention	Secondary Prevention	
Number of people	93498	13388	11586	1515	119987
Age (years)	56.3 (8.6)	57.3 (13.1)	57.3 (13.1)	60.0 (8.6)	56.6 (9.2)
Men	41956 (45%)	10976 (82%)	5910 (51%)	1194 (79%)	60036 (50%)
Smokers	14935 (16%)	334 (2.5%)	11586 (21%)	33 (2%)	17729 (15%)
Vascular disease					
History of MI	254 (0%)	8478 (63%)	255 (2%)	1037 (68%)	10034 (8%)
History of angina	522 (0%)	0 (0%)	58 (0%)	0 (0%)	580 (0%)
History of PAD	243 (0%)	93 (0%)	373 (3%)	16	725 (1%) (1%)
History of atrial fibrillation	44 (0%)	0 (0%)	9 (0%)	0 (0%)	53 (0%)
History of CVD	1295 (1%)	13388 (100%)	749 (6%)	1515 (100%)	6034 (5%)
Heart failure at trial entry	76 (0%)	55 (0%)	23 (0%)		173 (0%)
Blood pressure					
History of hypertension	36284 (39%)	1764 (13%)	6703 (58%)	282 (19%)	45033 (38%)
Systolic BP (mmHg)	131.0 (16.5)	137.0 (23.1)	140.1 (19.3)	136.5 (21.5)	132.6 (17.9)
Diastolic BP (mmHg)	80.1 (9.0)	83.9 (12.3)	81.3 (9.9)	82.7 (11.6)	80.6 (9.6)
Physical measurements					
Body mass index (kg/m^2)	26.2 (4.5)	NR	27.8 (5.5)	NR	26.3 (4.6)
Total cholesterol(mmol/L)	5.6 (1.1)	NR	5.5 (1.1)	NR	5.6 (1.1)

CHAPTER 5: EFFICACY OF ASPIRIN IN PEOPLE WITH DIABETES

5.2 Aspirin in people with and without diabetes

5.2.1 Serious vascular events

Across both primary and secondary prevention trials, there were a total of 3857 serious vascular events during 380,000 person-years (1.0% per year) among individuals allocated aspirin compared to a total of 4373 during 380,000 person-years (1.1% per year) among those allocated control. Thus, aspirin therapy resulted in a 13% proportional reduction in serious vascular events (RR 0.87 [95% CI 0.83-0.91], p<0.0001; Figure 5.1). This effect seemed similar in people with and without diabetes (χ^2_1 =0.74, p=0.39).

5.2.2 Major coronary events

Given the proportional effects from aspirin may differ between major coronary events and strokes, and because these outcomes account for a large proportion of serious vascular events, the effects of aspirin on each separate outcome contributing to the composite of serious vascular events were assessed separately.

Considering both primary and secondary prevention trials together, allocation to aspirin yielded a 17% proportional reduction in major coronary events (RR 0.83 [95% CI 0.79-0.88], p<0.0001; Figure 5.2). There was no evidence of heterogeneity of relative effect between individuals with and without diabetes on non-fatal MI (χ^2_1 =2.10, p=0.15; Figure 5.3) or the composite of major coronary events (χ^2_1 =0.32, p=0.57; Figure 5.2).

5.2.3 Ischaemic and all strokes

Considering both primary and secondary prevention trials together, aspirin decreased the incidence of ischaemic strokes (RR 0.82 [95% CI 0.73-0.93], p=0.001; Figure 5.4). Overall, aspirin significantly reduced the aggregate of all strokes (RR 0.91 [95% CI 0.84-0.98], p=0.012; Figure 5.5). There was no evidence that the relative effects of aspirin on ischaemic or the outcome of all strokes were modified by the presence of diabetes (χ^2_1 =0.16, p=0.69 or χ^2_1 =0.01, p=0.90 respectively).

5.2.4 Cause specific mortality

Since allocation to aspirin seemed to decrease vascular mortality (RR 0.94 [95% CI 0.88-1.01, p=0.07; Figure 5.6] and non-vascular mortality (RR 0.91 [95% CI 0.84-0.99, p=0.021; Figure 5.7), there was a consequent significant reduction in total mortality (RR 0.93 [95 CI 0.89-0.98, p=0.004; Figure 5.8). The proportional reduction in total mortality from allocation to aspirin was similar for diabetics and non-diabetics (χ^2_1 =0.05, p=0.82; Figure 5.8).

5.3 Aspirin for primary prevention in people with and without diabetes

While aspirin is of definite net benefit in people with diabetes and previous occlusive vascular disease, whether the absolute benefits outweigh bleeding hazards in people with diabetes and no previous occlusive vascular disease is not certain. Thus, the following sections comprise an assessment of the effect of aspirin in this primary prevention setting.

5.3.1 Serious vascular events

In primary prevention trials, there was a 10% proportional reduction in serious vascular events from aspirin (RR 0.90 [95% CI 0.85-0.96], p=0.0006; Figure 5.9). In the subgroup of individuals with diabetes, aspirin therapy resulted in a 7% proportional reduction (RR 0.93 [99% CI 0.81-1.06], p=0.16), an effect consistent with that seen in those without diabetes (RR 0.89 [99% CI 0.81-0.98]); χ^2_1 =0.44, p=0.51; Figure 5.9).

Because the absolute reduction in serious vascular events depends on baseline risk, we analysed effects of aspirin in primary prevention trials across predicted 5-year risk of coronary heart disease categories. Proportional reductions in serious vascular events were comparable across varying categories of coronary heart disease risk (predicted 5-year risk less than 5%, 5-10% or 10% or more in primary prevention trials) in those with and without diabetes (χ^2_1 =0.65, p=0.72 and χ^2_1 =1.96, p=0.37 respectively; Figure 5.10)

5.3.2 Major coronary events

In primary prevention trials, there was a 14% proportional reduction in major coronary events from aspirin (RR 0.86 [95% CI 0.80-0.92, p=0.0001; Figure 5.9). In the subgroup with diabetes, aspirin therapy resulted in a 10% proportional reduction (RR 0.90 [99%CI 0.76-1.07], p=0.11), an effect similar to that seen in those without diabetes (χ^2_1 =0.76, p=0.38). This was driven mainly by non-fatal myocardial infarction, for which there was a 19% proportional reduction from aspirin in primary prevention trials (RR 0.81 [95% CI 0.73-0.89], p<0.0001; Figure 5.9). Proportional

reductions in major coronary events were similar across categories of predicted 5-year risk of coronary heart disease in people with and without diabetes (χ^2_1 =1.33, p=0.51 and χ^2_1 =1.40, p=0.50 respectively; Figure 5.11).

5.3.3 Ischaemic and all strokes

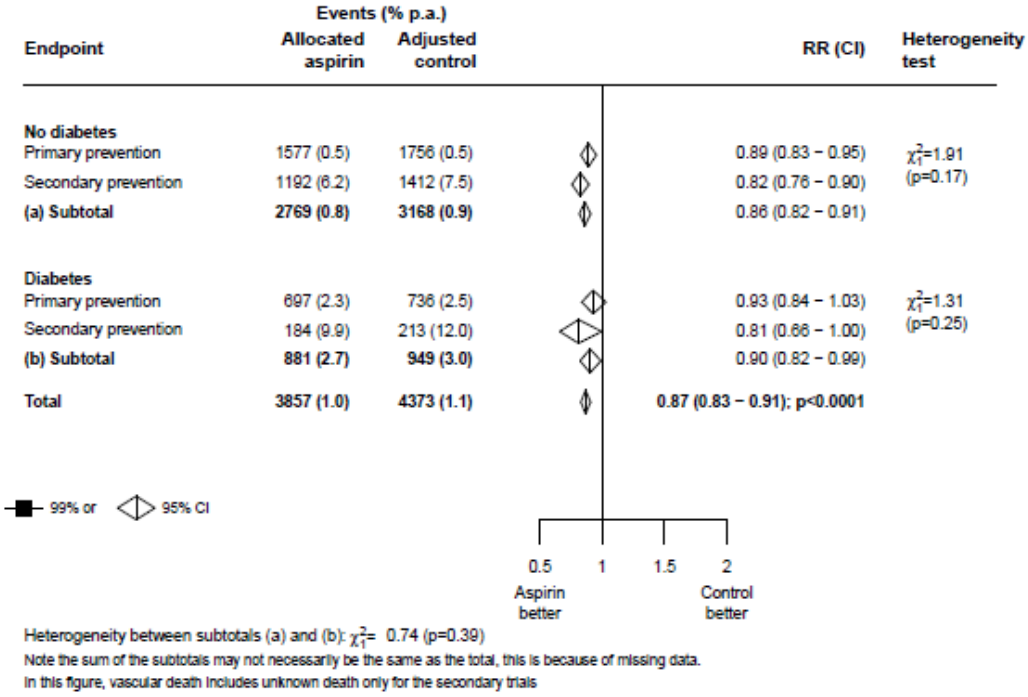
In primary prevention trials, there was a 16% proportional reduction in ischaemic strokes (RR 0.84 [95% CI 0.73-0.96], p=0.01; Figure 5.9). In the subgroup of patients with diabetes, the proportional effects on ischaemic (RR 0.76 [99% CI 0.52-1.10], p=0.05) were similar to those observed in people without diabetes (χ^2_1 =0.58, p=0.45). As there was no effect on unknown strokes in all primary prevention trials (RR 1.03 [95% CI 0.88-1.21], p=0.70), there was no significant effect on the composite outcome of any stroke (RR 0.96 [95% CI 0.87-1.05], p=0.39; Figure 5.9); this again seemed similar (χ^2_1 =0.17, p=0.68) in both the subgroup with diabetes (RR 0.92 [99% CI 0.72-1.18], p=0.40) and without diabetes (RR 0.97 [99% CI 0.83-1.12], p=0.55). The proportional reduction in any stroke was similar across categories of predicted 5-year risk of coronary heart disease in people with and without diabetes (χ^2_1 =4.28, p=0.12 and χ^2_1 =2.86, p=0.24 respectively; Figure 5.12).

5.3.4 Cause specific mortality

In primary prevention trials, aspirin therapy resulted in a 3% proportional reduction in any vascular mortality (RR 0.97 [95% CI 0.88-1.06], p=0.46); this reduction seemed similar (χ^2_1 =1.57, p=0.21) in both the subgroup with (RR 0.90 [99% CI 0.75-1.08], p=0.13) and without diabetes (RR 1.01 [99% CI 0.86-1.18], p=0.87; Figure 5.13). Since allocation to aspirin in primary prevention trials seemed to also decrease non-

vascular mortality (RR 0.92 [95% 0.85-1.00], p=0.05), there was a subsequent reduction in total mortality with aspirin (RR 0.94 [95% CI 0.89-1.00], p=0.05; Figure 5.13). This proportional reduction seemed similar in both people with and without diabetes (χ^2_1 =0.03, p=0.87) and across categories of predicted 5-year risk of coronary heart disease (χ^2_1 =1.60, p=0.45 and χ^2_1 =0.15, p=0.93 respectively; Figure 5.14).

Figure 5.1: Effects of aspirin allocation on any serious vascular events in patients with and without diabetes

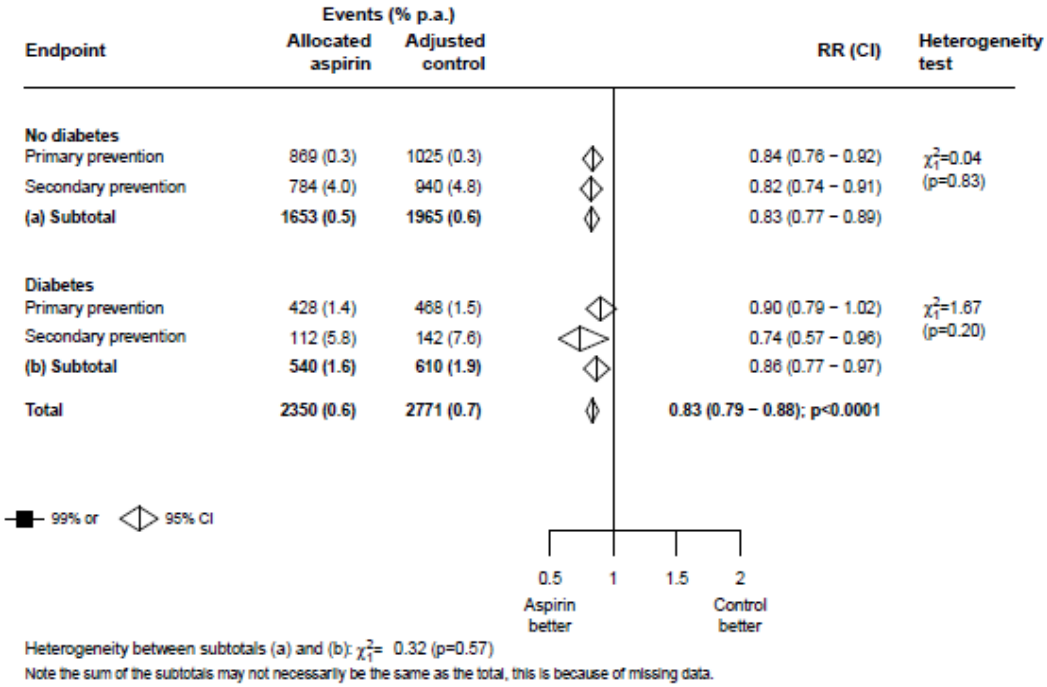


Heterogeneity between subtotals (a) and (b): χ^2_1= 0.74 (p=0.39)

Note the sum of the subtotals may not necessarily be the same as the total, this is because of missing data.

In this figure, vascular death includes unknown death only for the secondary trials

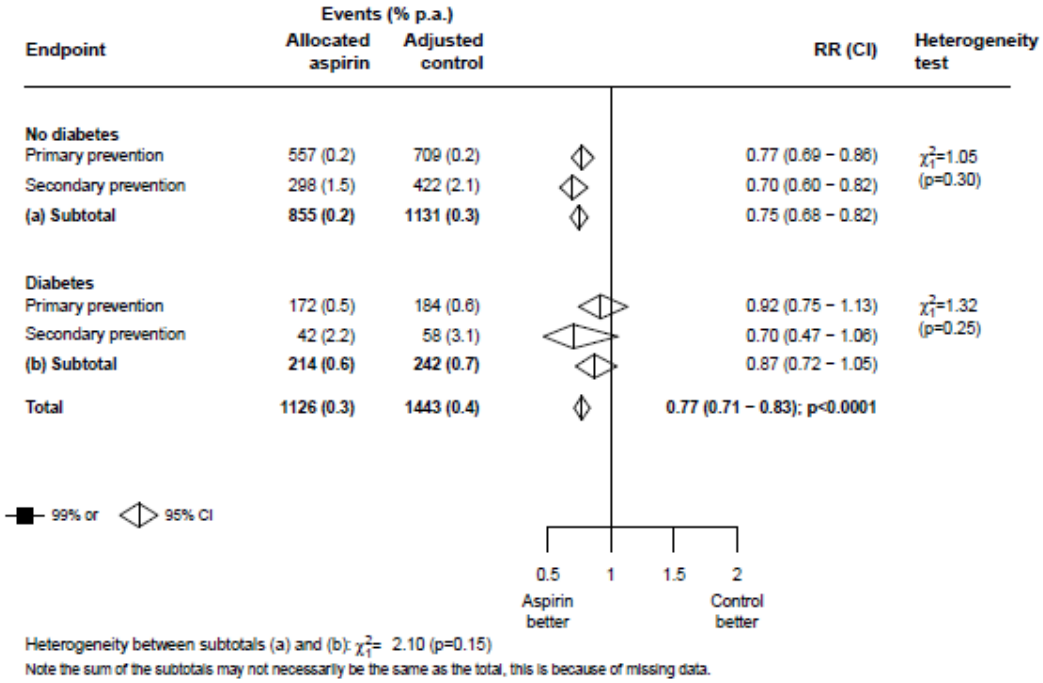
Figure 5.2: Effects of aspirin allocation on major coronary events in patients with and without diabetes



Heterogeneity between subtotals (a) and (b): χ^2_1= 0.32 (p=0.57)

Note the sum of the subtotals may not necessarily be the same as the total, this is because of missing data.

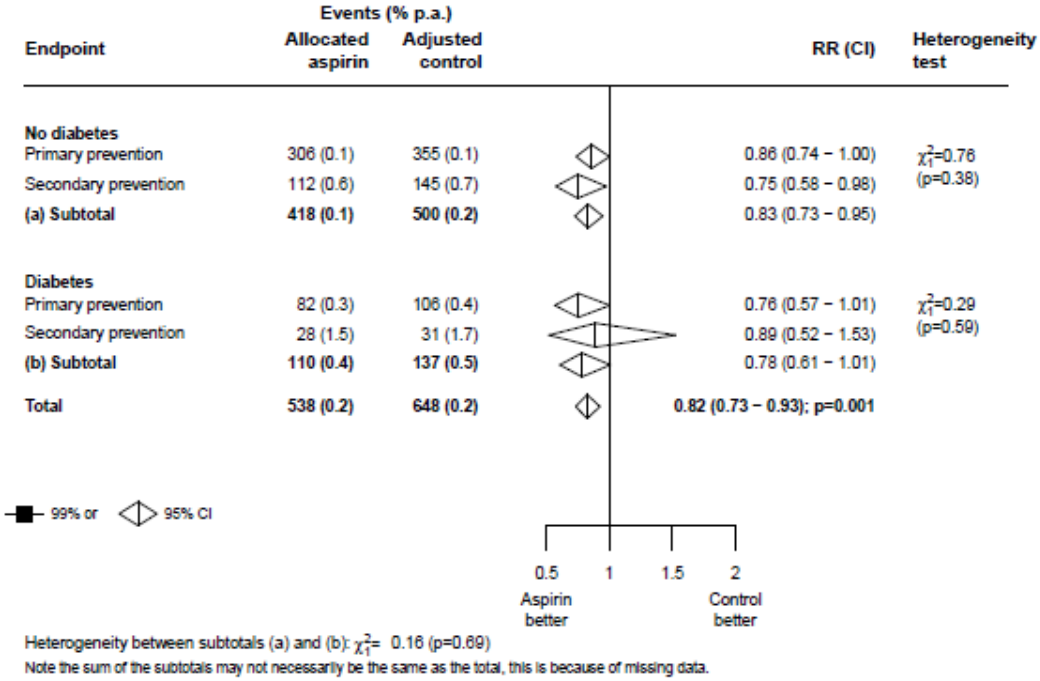
Figure 5.3: Effects of aspirin allocation on non-fatal myocardial infarction in patients with and without diabetes



Heterogeneity between subtotals (a) and (b): χ^2_1= 2.10 (p=0.15)

Note the sum of the subtotals may not necessarily be the same as the total, this is because of missing data.

Figure 5.4: Effect of aspirin allocation on ischaemic stroke in patients with and without diabetes



Heterogeneity between subtotals (a) and (b): χ^2_1= 0.16 (p=0.69)

Note the sum of the subtotals may not necessarily be the same as the total, this is because of missing data.

Figure 5.5: Effect of aspirin allocation on any stroke in patients with and without diabetes

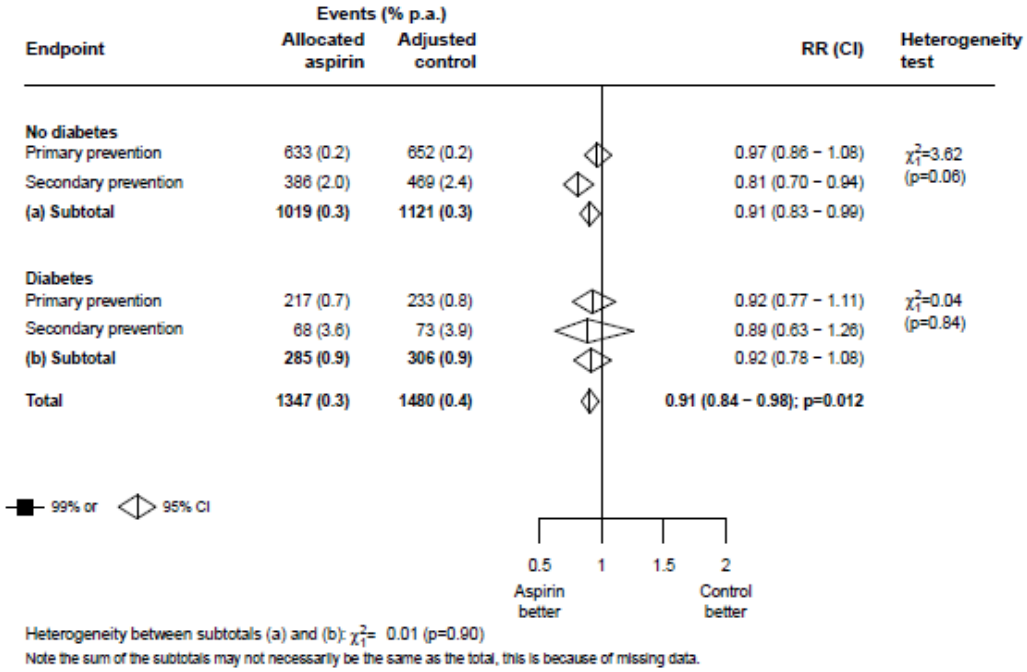
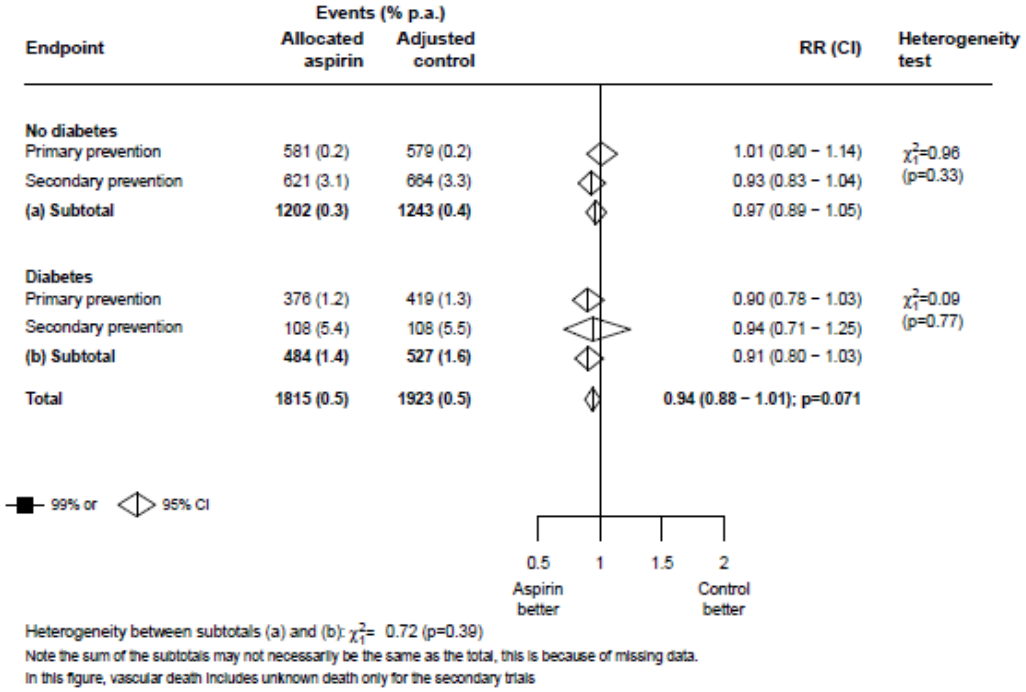


Figure 5.6: Effect of aspirin allocation on any vascular death in patients with and without diabetes

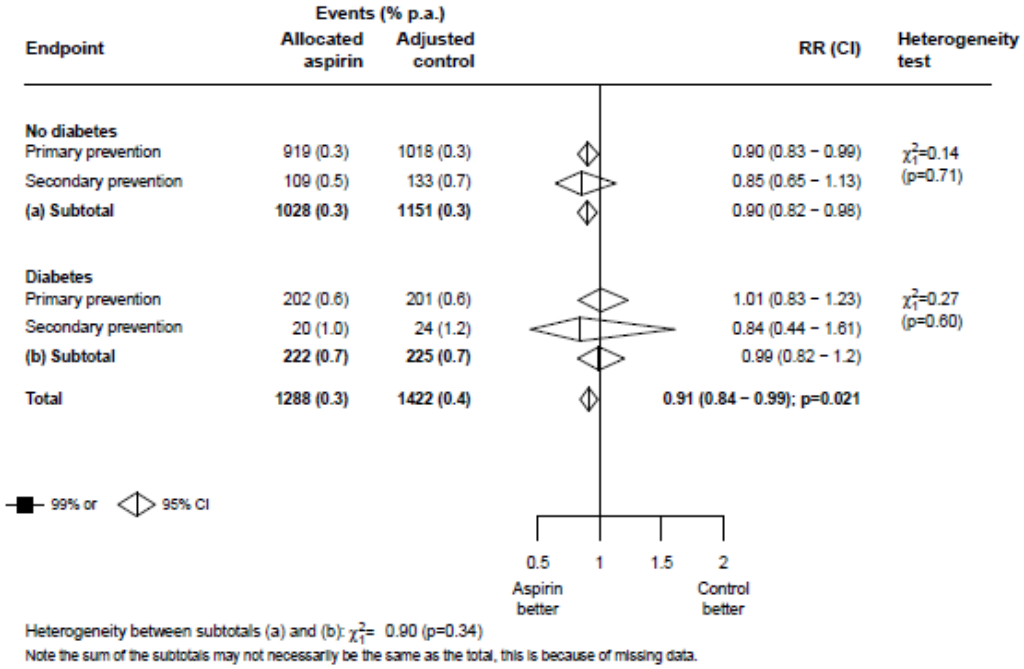


Heterogeneity between subtotals (a) and (b): χ^2_1= 0.72 (p=0.39)

Note the sum of the subtotals may not necessarily be the same as the total, this is because of missing data.

In this figure, vascular death includes unknown death only for the secondary trials

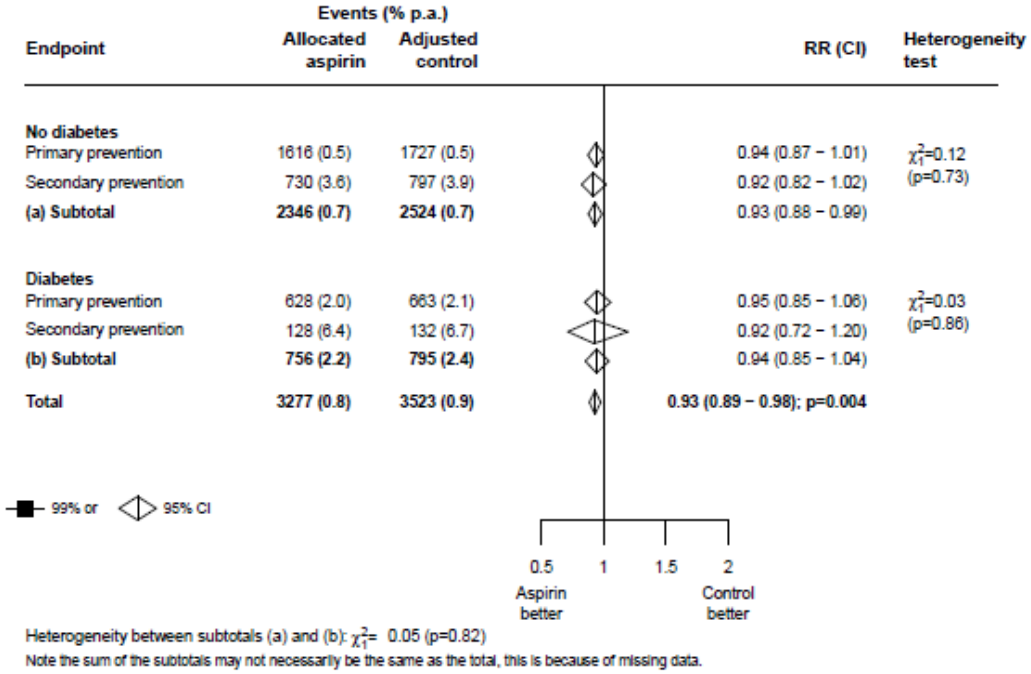
Figure 5.7: Effect of aspirin allocation on non-vascular death in patients with and without diabetes



Heterogeneity between subtotals (a) and (b): χ^2_1= 0.90 (p=0.34)

Note the sum of the subtotals may not necessarily be the same as the total, this is because of missing data.

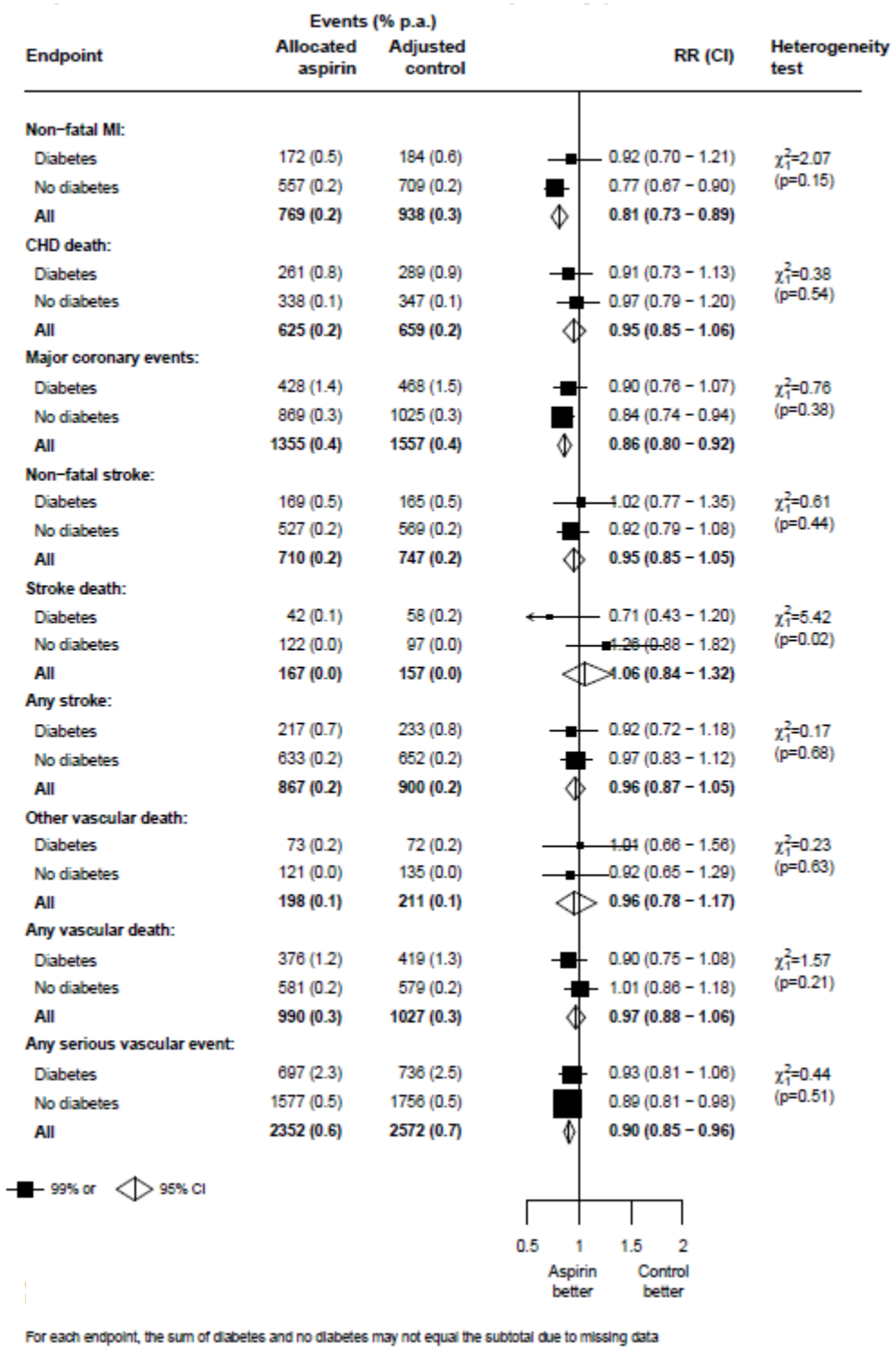
Figure 5.8: Effect of aspirin allocation on any death in patients with and without diabetes



Heterogeneity between subtotals (a) and (b): χ^2_1= 0.05 (p=0.82)

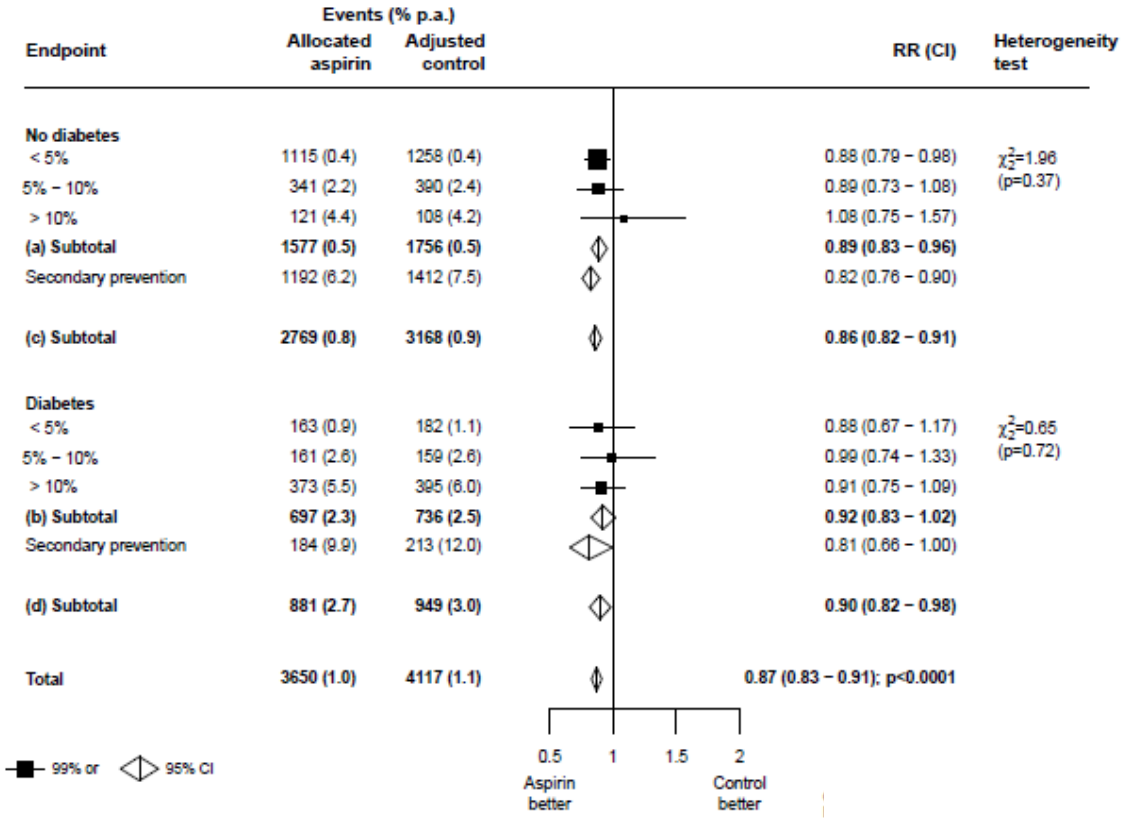
Note the sum of the subtotals may not necessarily be the same as the total, this is because of missing data.

Figure 5.9: Effect of aspirin allocation on serious vascular events in patients with and without diabetes in primary prevention trials



For each endpoint, the sum of diabetes and no diabetes may not equal the subtotal due to missing data

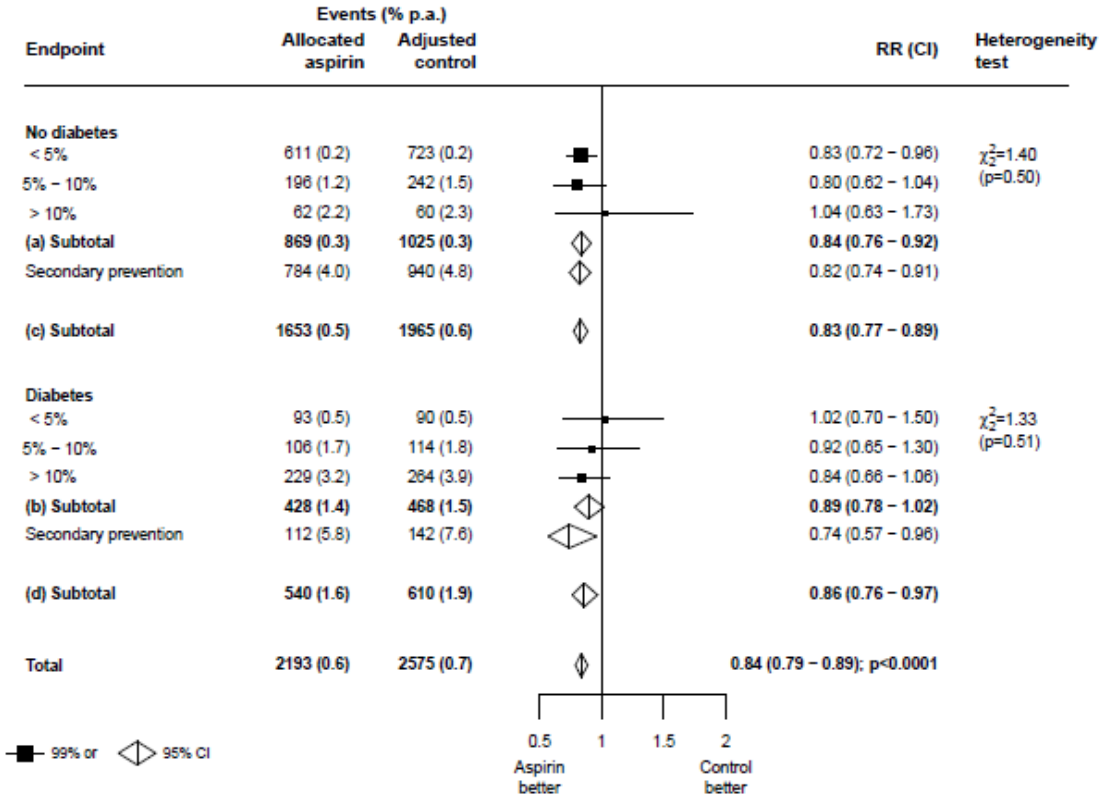
Figure 5.10: Effect of aspirin allocation on any serious vascular events in patients with and without diabetes in primary prevention trials, subdivided by vascular risk, and secondary prevention trials



Heterogeneity between subtotals (a) and (b): χ^2_1= 0.26 (p=0.61)
Heterogeneity between subtotals (c) and (d): χ^2_1= 0.51 (p=0.48)

MCE risk calculated among the primary prevention trials
Heterogeneity test in only calculated between the 3 levels of MCE risk in the primary prevention trials only

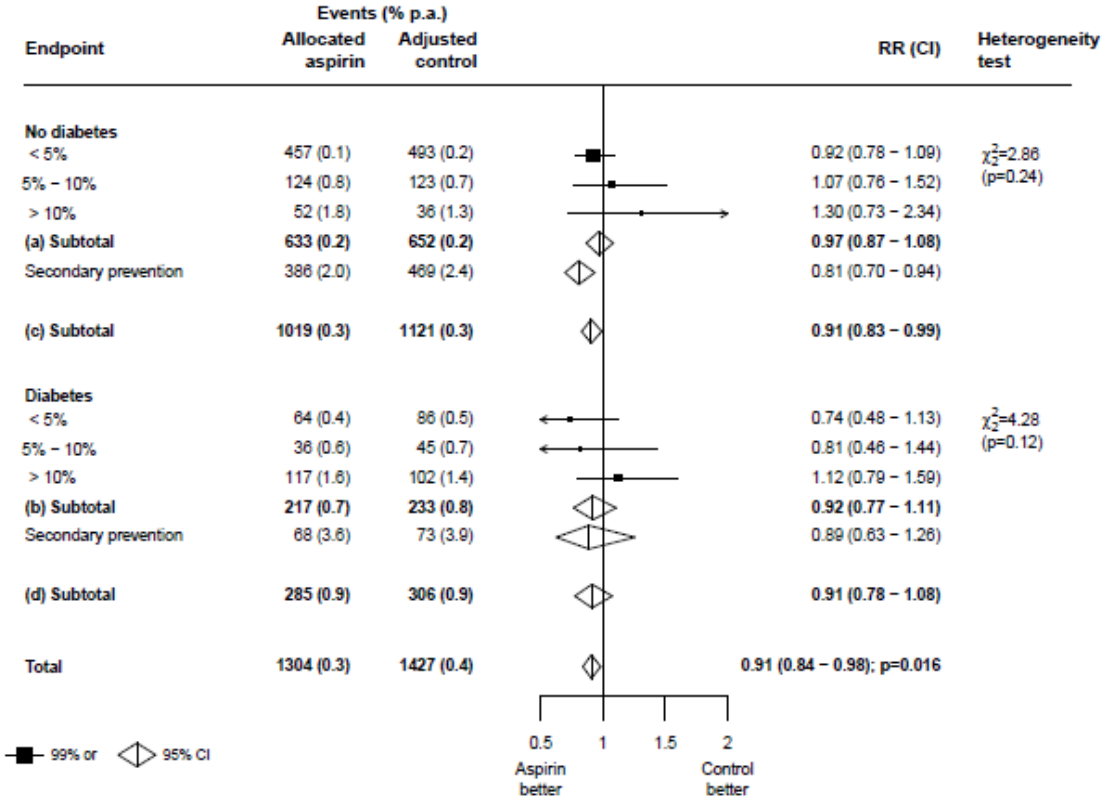
Figure 5.11: Effect of aspirin allocation on major coronary events in patients with and without diabetes in primary prevention trials, subdivided by vascular risk, and secondary prevention trials



Heterogeneity between subtotals (a) and (b): χ^2_1= 0.67 (p=0.41)
Heterogeneity between subtotals (c) and (d): χ^2_1= 0.27 (p=0.61)

MCE risk calculated among the primary prevention trials
Heterogeneity test in only calculated between the 3 levels of MCE risk in the primary prevention trials only

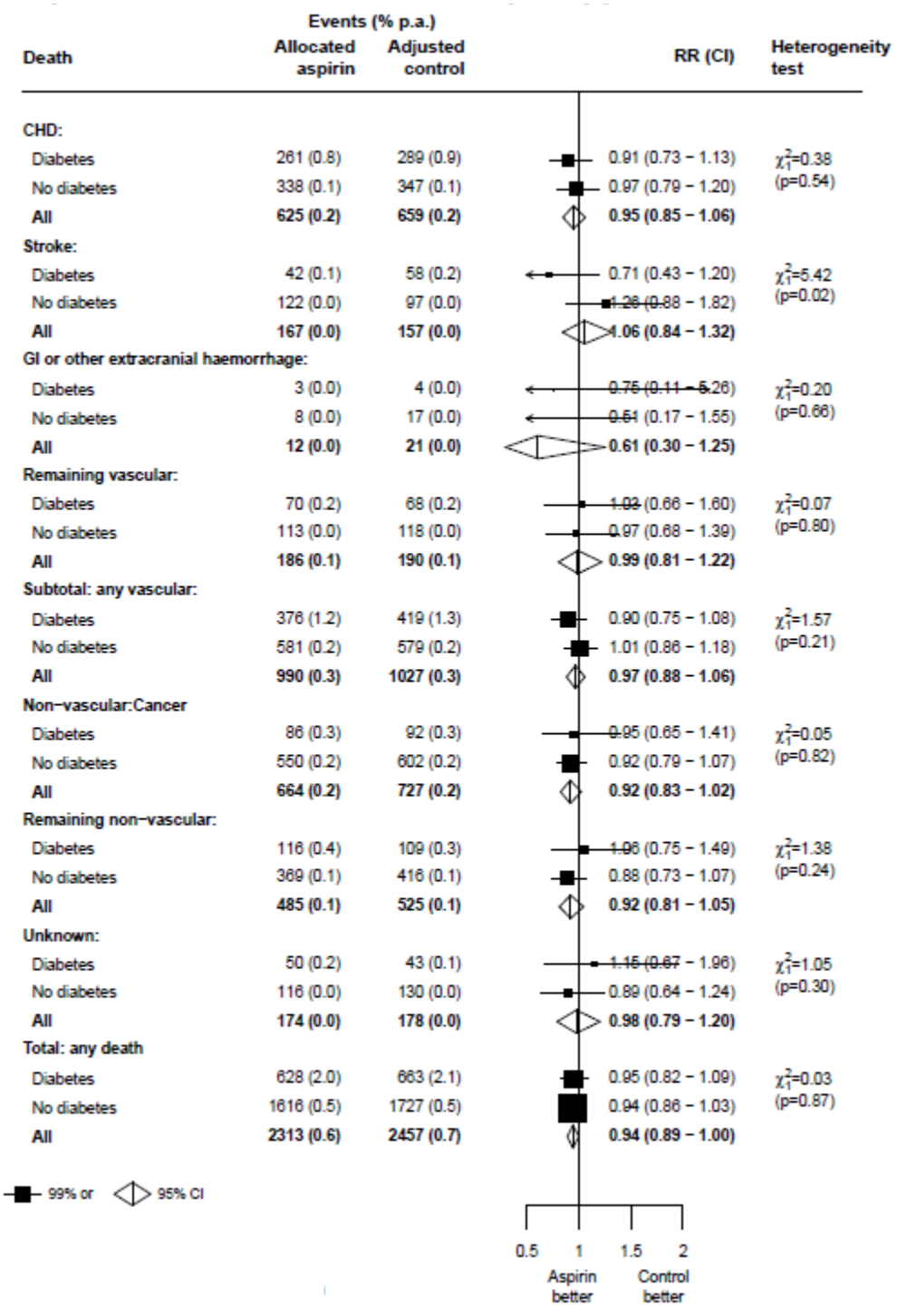
Figure 5.12: Effect of aspirin allocation on any stroke in patients with and without diabetes in primary prevention trials, subdivided by vascular risk, and secondary prevention trials



Heterogeneity between subtotals (a) and (b): χ^2_1= 0.22 (p=0.64)
Heterogeneity between subtotals (c) and (d): χ^2_1= 0.01 (p=0.94)

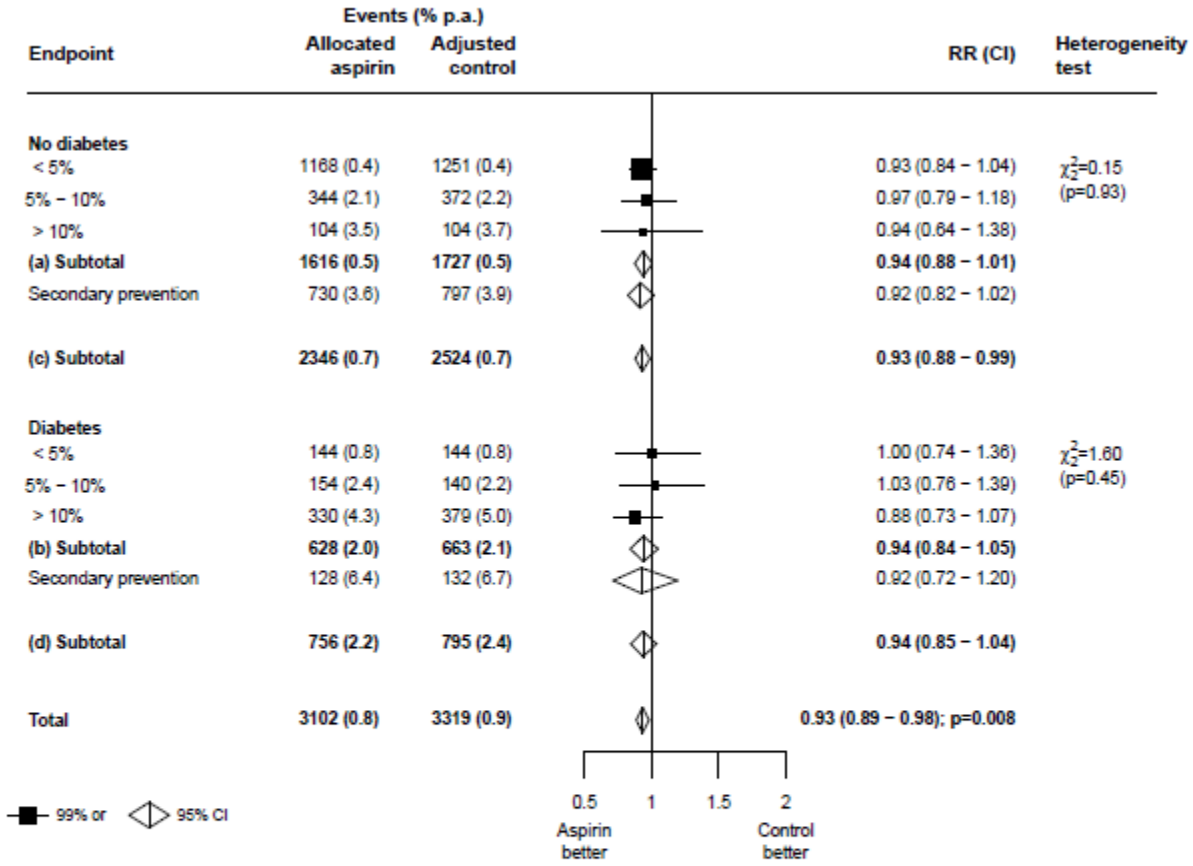
MCE risk calculated among the primary prevention trials
Heterogeneity test in only calculated between the 3 levels of MCE risk in the primary prevention trials only

Figure 5.13: Effects of aspirin allocation on cause-specific mortality in patients with and without diabetes in primary prevention trials



For each endpoint, the sum of diabetes and no diabetes may not equal the subtotal due to missing data

Figure 5.14: Effect of aspirin allocation on any death in patients with and without diabetes in primary prevention trials, subdivided by vascular risk, and secondary prevention trials



Heterogeneity between subtotals (a) and (b): χ^2_1= 0.00 (p=0.99)
Heterogeneity between subtotals (c) and (d): χ^2_1= 0.01 (p=0.92)

MCE risk calculated among the primary prevention trials
Heterogeneity test in only calculated between the 3 levels of MCE risk in the primary prevention trials only

CHAPTER 6: SAFETY OF ASPIRIN IN PEOPLE WITH DIABETES

6.1 Aspirin in people with and without diabetes

6.1.1 Intracranial bleeding

Considering both primary and secondary prevention trials together, aspirin increased the incidence of haemorrhagic strokes (RR 1.36 [95% CI 1.07-1.71), p=0.01; Figure 6.1). There was no evidence that the relative effects of aspirin on haemorrhagic strokes modified by the presence of diabetes (χ^2_1 =0.76, p=0.38)

6.1.2 Extracranial bleeding

Considering both primary and secondary prevention trials together, allocation to aspirin increased the rate of major gastrointestinal and other extracranial bleeding by about a half (RR 1.56 [95% CI 1.33-1.82], p<0.0001; Figure 6.2). There was no suggestion that the presence or absence of diabetes modified this overall risk (χ^2_1 =1.00, p=0.32).

6.2 Aspirin for primary prevention in people with and without diabetes

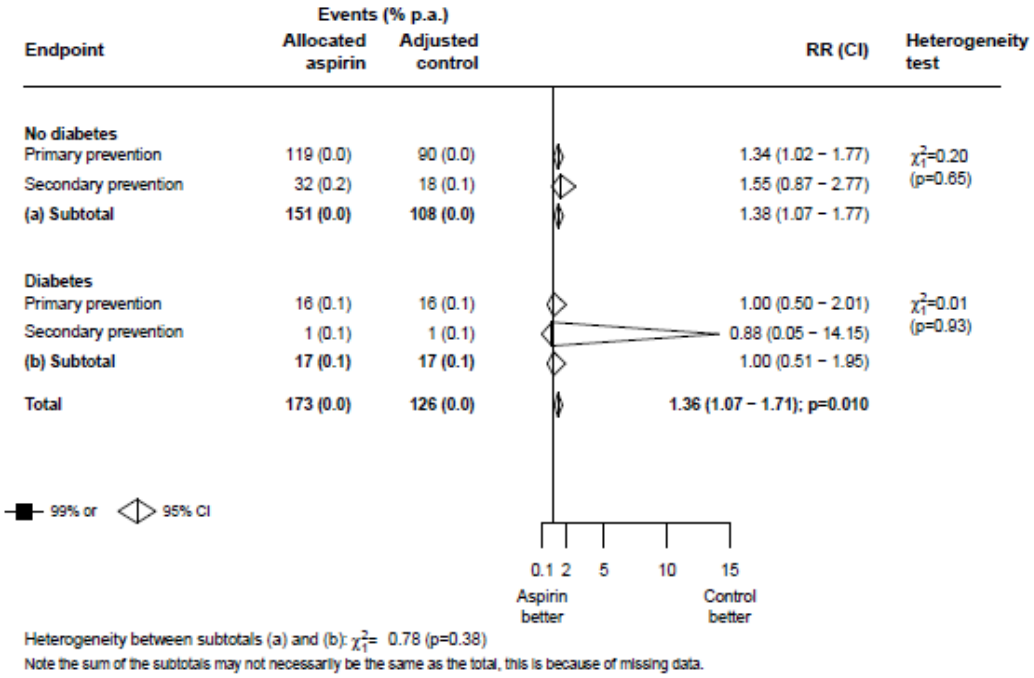
6.1.1 Intracranial bleeding

In primary prevention trials, there was a 29% proportional increase in haemorrhagic strokes (RR 1.29 [95% CI 1.00-1.67], p=0.05; Figure 5.9). In the subgroup of patients with diabetes, the proportional effects on haemorrhagic strokes (RR 1.00 [99% CI 0.40-2.50], p=0.99) were similar to those observed in people without diabetes (χ^2_1 =0.61, p=0.43).

6.1.2 Extracranial bleeding

In primary prevention trials, aspirin increased the rate of major gastrointestinal and other extracranial bleeds by about a half (RR 1.52 [95% CI 1.30-1.78], p<0.001; Figure 6.3). This effect seemed similar (χ^2_1 =0.99, p=0.32) in both people with (RR 1.23 [99% CI 0.67-2.26], p=0.45) and without diabetes (RR 1.58 [99% CI 1.26-1.97], p<0.0001). This effect also seemed similar across categories of predicted 5-year risk of coronary heart disease (χ^2_1 =1.62, p=0.45 and χ^2_1 =3.03, p=0.22 respectively; Figure 6.4).

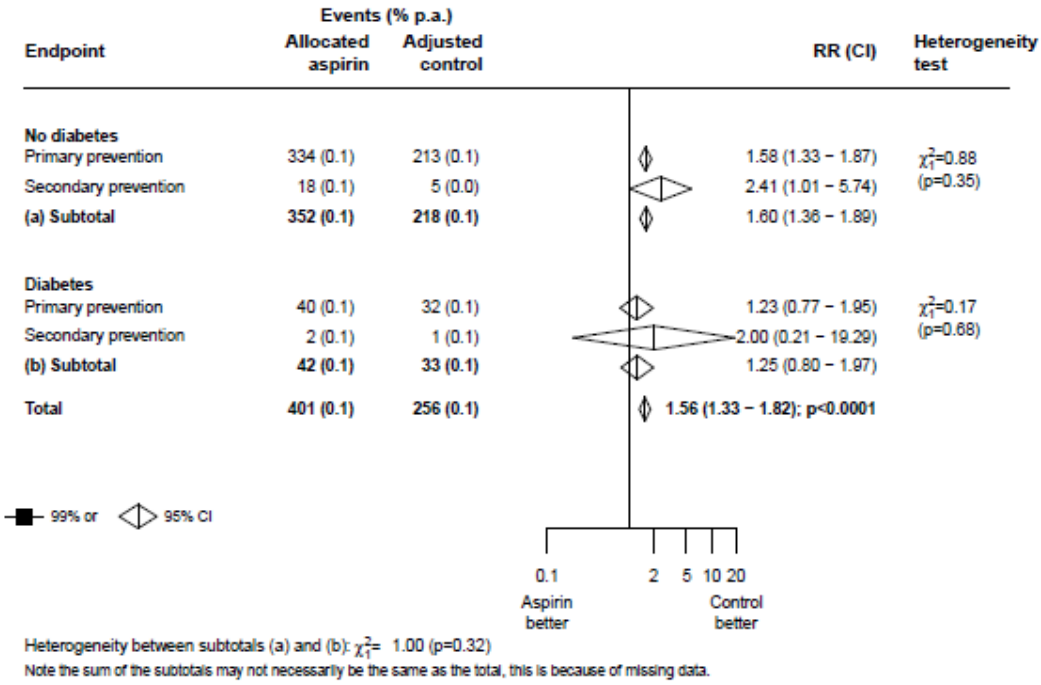
Figure 6.1: Effects of aspirin allocation on haemorrhagic stroke in patients with and without diabetes



Heterogeneity between subtotals (a) and (b): χ^2_1= 0.78 (p=0.38)

Note the sum of the subtotals may not necessarily be the same as the total, this is because of missing data.

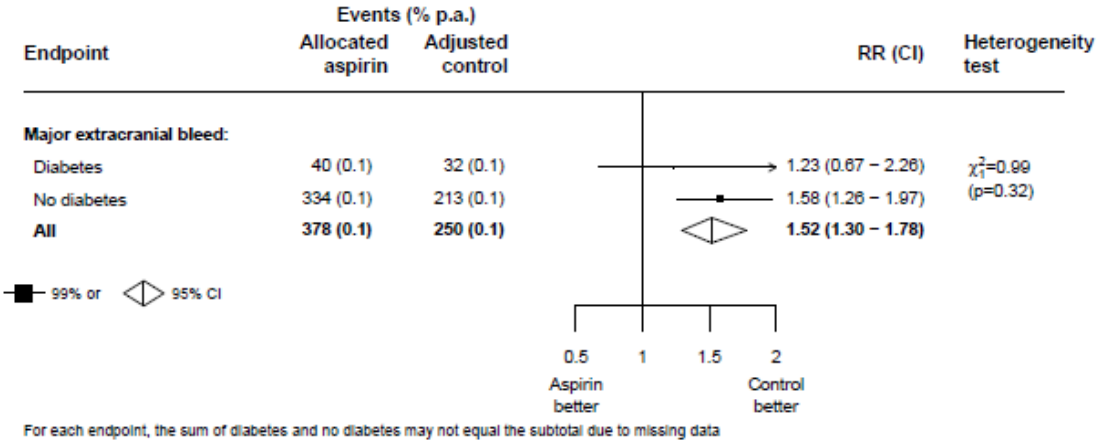
Figure 6.2: Effect of aspirin allocation on major extracranial bleeding in patients with and without diabetes



Heterogeneity between subtotals (a) and (b): χ^2_1= 1.00 (p=0.32)

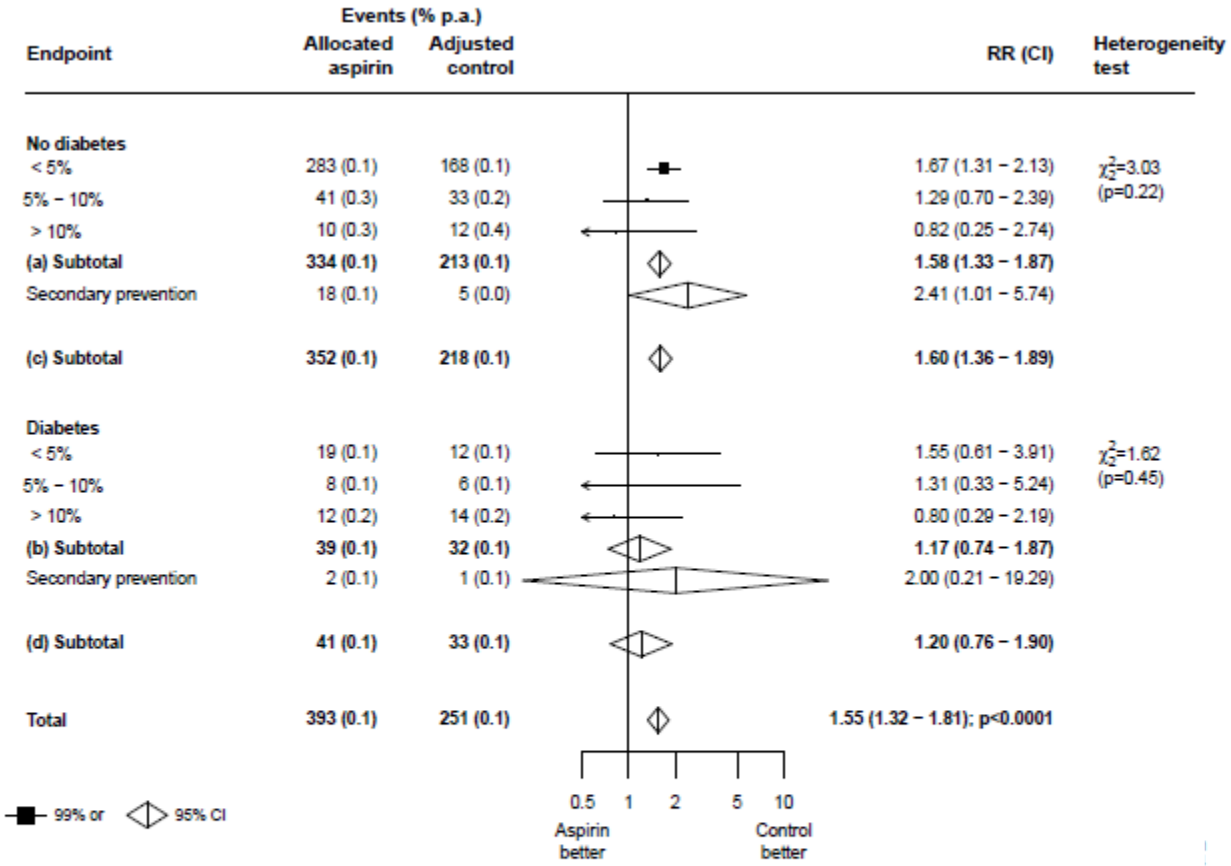
Note the sum of the subtotals may not necessarily be the same as the total, this is because of missing data.

Figure 6.3: Effect of aspirin allocation on major extracranial bleeding in patients with and without diabetes in primary prevention



For each endpoint, the sum of diabetes and no diabetes may not equal the subtotal due to missing data

Figure 6.4: Effect of aspirin allocation on major extracranial bleeding in patients with and without diabetes in primary prevention trials, subdivided by vascular risk, and secondary prevention trials



Heterogeneity between subtotals (a) and (b): χ^2_1= 1.36 (p=0.24)
Heterogeneity between subtotals (c) and (d): χ^2_1= 1.36 (p=0.24)

MCE risk calculated among the primary prevention trials
Heterogeneity test in only calculated between the 3 levels of MCE risk in the primary prevention trials only

CHAPTER 7: NET EFFECTS OF ASPIRIN IN PEOPLE WITH DIABETES

7.1 Risk factor model

Major baseline predictors for major coronary events were older age per decade (RR 1.81 [95% CI 1.73-1.89]), male gender (RR 1.68 [95% CI 1.50-1.88]), diabetes (RR 2.67 [95% CI 2.31-3.09]), smoking (RR 1.85 [95% CI 1.70-2.01]), increasing blood pressure per 20mmHg (RR 1.45 [95% CI 1.36-1.55]), increasing cholesterol per 1mmol/L (RR 1.18 [95% CI 1.13-1.23]) and increasing body mass index per 5kg/m^2 (RR 1.10 [95% CI 1.05-1.16]; Table 7.1). With the exception of increasing cholesterol, all of these baseline characteristics were also predictors of major extracranial bleeding: age (RR 2.10 [95% CI 1.90-2.32]), male gender (RR 1.99 [95% CI 1.54-2.58]), diabetes (RR 1.56 [95% CI 1.15-2.11]), smoking (RR 1.49 [95% CI 1.22-1.81]), increasing blood pressure (RR 1.31 [95% CI 1.12-1.53]) and increasing body mass index (RR 1.23 [95% CI 1.13-1.34]). In similar fashion, predictors of ischaemic stroke (age, male gender, diabetes, smoking and increasing blood pressure) were often also predictors of intracerebral haemorrhage (age, smoking, increasing blood pressure).

7.2 Hypothetical calculations of absolute effects of aspirin

The proportional effects of aspirin in the primary prevention setting appeared similar regardless of diabetes status and across varying categories of coronary heart disease risk (5%, 5-10% or 10% or more over 5 years). Given the evidence that the proportional effects did not depend on diabetes status or baseline risk, as assessed by tests for heterogeneity, homogeneity of proportional effects is a reasonable

assumption when estimating absolute effects. The absolute excess risk of aspirin will therefore depend ultimately on the participant's baseline absolute risk at the point at which aspirin is initiated, rather than any individual participant characteristic. Based on this assumption, we modelled the absolute effects of aspirin according to diabetes status and varying levels of baseline risk. This is based on constant relative risks for serious vascular events and major extracranial bleeding based on each of the predicted levels of baseline risk in the absence of treatment.

We first estimated the absolute effects of aspirin allocation in primary prevention on 5-year outcomes with regards to serious vascular events (vascular death, non-fatal MI or stroke) and non-fatal major extracranial bleeding in both those with and without diabetes. In those without diabetes, there was a 2.81% 5-year risk of serious vascular events that was reduced by 0.40% with aspirin therapy (Figure 7.1). In the same population, this was balanced against a 0.32% 5-year risk of non-fatal major extracranial bleeding that increased by 0.18% with aspirin therapy. Thus, for people without diabetes, the absolute benefit of taking aspirin was of approximately similar magnitude to the absolute increase in bleeding hazards. Furthermore, aspirin trials were mainly in people not taking statins, which would have further reduced baseline risk in the absence of aspirin therapy and thus the potential absolute reduction in serious vascular events from aspirin in this context.

In people with diabetes, however, there was a substantially higher 5-year risk of serious vascular events (12.23%) that was reduced by 1.41% with aspirin therapy (Figure 7.1). In the same population, there was a corresponding 0.51% 5-year risk of

non-fatal major extracranial bleeding that would be increased by 0.28% with aspirin therapy. Thus, the absolute primary prevention benefit in people with diabetes seems to be many times larger than the absolute increase in bleeding. This suggests that above a threshold of baseline vascular risk, such as some people with diabetes, the benefits of aspirin might outweigh the bleeding hazards.

We therefore estimated the absolute effects of aspirin allocation in primary prevention on 5-year outcomes across categories of baseline vascular risk. For those at low, moderate and high baseline coronary heart disease risk, the predicted 5-year rate of serious vascular events was 2.22, 11.67, and 24.00% respectively (Figure 7.2). In each of these categories, aspirin therapy would seem to reduce this 5-year rate by 0.21, 1.11 and 2.28% respectively. This was balanced against an increase in non-fatal major extracranial bleeding from aspirin therapy of 0.16, 0.34 and 0.60% respectively. Thus, consistent with the potential net benefit of aspirin in people with diabetes seen above, people with higher vascular risk may be increasingly more likely to derive net benefit with aspirin. Even if baseline vascular risk was halved by statins or other measures, these calculations suggest there might still be a net benefit from aspirin in those at high, and perhaps moderate, baseline vascular risk. We also estimated similar absolute effects according to both diabetes status and categories of baseline vascular risk (Figure 7.3). These estimations are also consistent with the above discussion, showing that there may be a potential net benefit for aspirin in people with higher vascular risk, including some people with diabetes.

Table 7.1: Rate ratios associated with risk factors for selected outcomes in primary prevention trials

Variable	Major coronary events	Ischaemic stroke	Haemorrhagic stroke	Major extracranial bleeding
Age (per decade)	1.81 (1.73-1.89)	2.24 (2.10-2.39)	1.61 (1.37-1.89)	2.10 (1.90-2.32)
Male gender	1.68 (1.50-1.88)	1.49 (1.28-1.73)	0.79 (0.48-1.30)	1.99 (1.54-2.58)
Diabetes	2.67 (2.31-3.09)	2.16 (1.78-2.62)	1.62 (0.91-2.87)	1.56 (1.15-2.11)
Current smoker	1.85 (1.70-2.01)	1.90 (1.69-2.14)	2.07 (1.54-2.77)	1.49 (1.22-1.81)
Mean blood pressure (per 20mmHg)	1.45 (1.36-1.55)	1.77 (1.62-1.94)	1.82 (1.44-2.31)	1.31 (1.12-1.53)
Cholesterol (per 1mmol/L)	1.18 (1.13-1.23)	1.05 (0.99-1.11)	0.87 (0.75-1.01)	0.98 (0.90-1.06)
Body mass index (per 5kg/m^2)	1.10 (1.05-1.16)	1.05 (0.99-1.12)	0.89 (0.75-1.05)	1.23 (1.13-1.34)

Figure 7.1: Estimated 5-year absolute effects of aspirin allocation in patients with and without diabetes in primary prevention

95% confidence intervals provided for estimated 5-year absolute effects of aspirin allocation (A) on major extracranial bleeding, vascular death and composite of serious vascular events, compared to control (C).

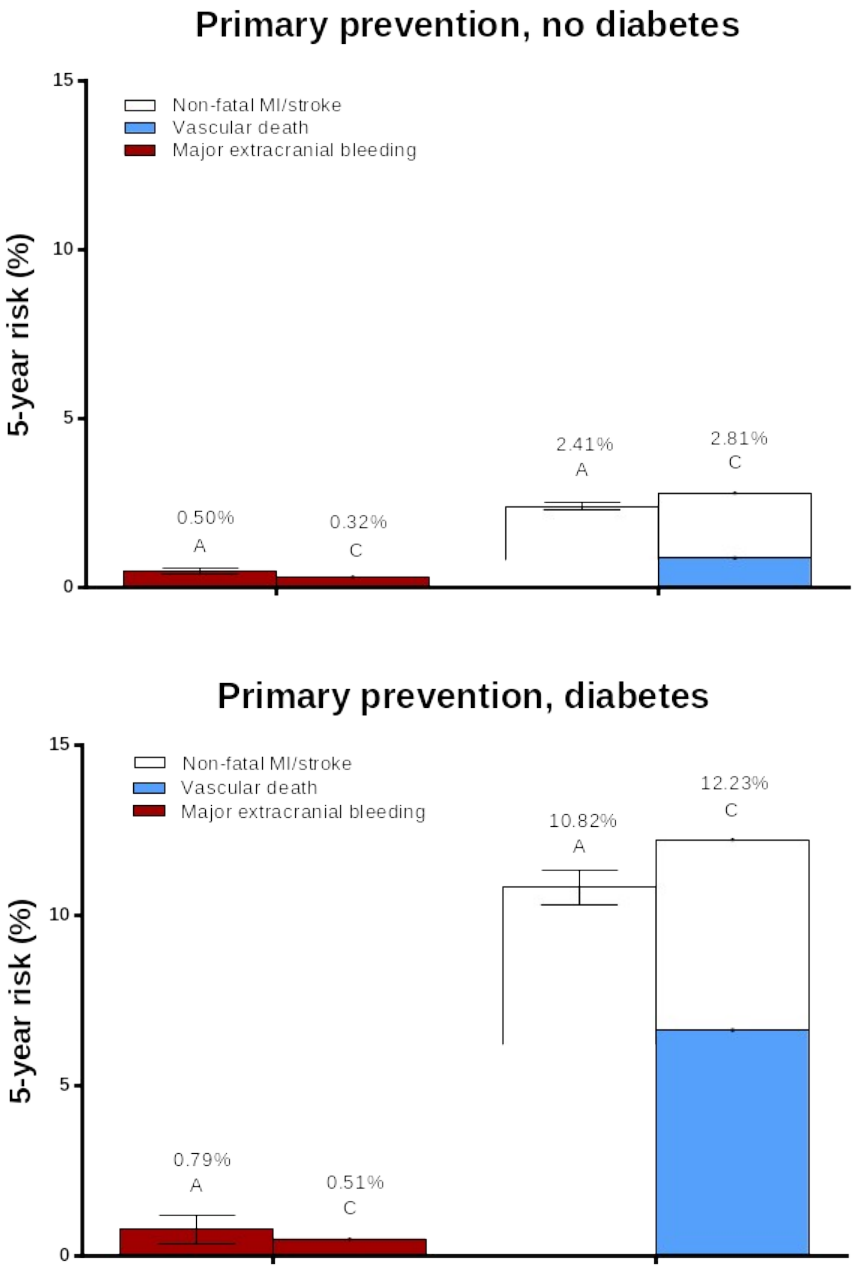


Figure 7.2: Estimated 5-year absolute effects of aspirin allocation in patients in primary prevention subdivided by vascular risk

95% confidence intervals provided for estimated 5-year absolute effects of aspirin allocation (A) on major extracranial bleeding, vascular death and composite of serious vascular events, compared to control (C).

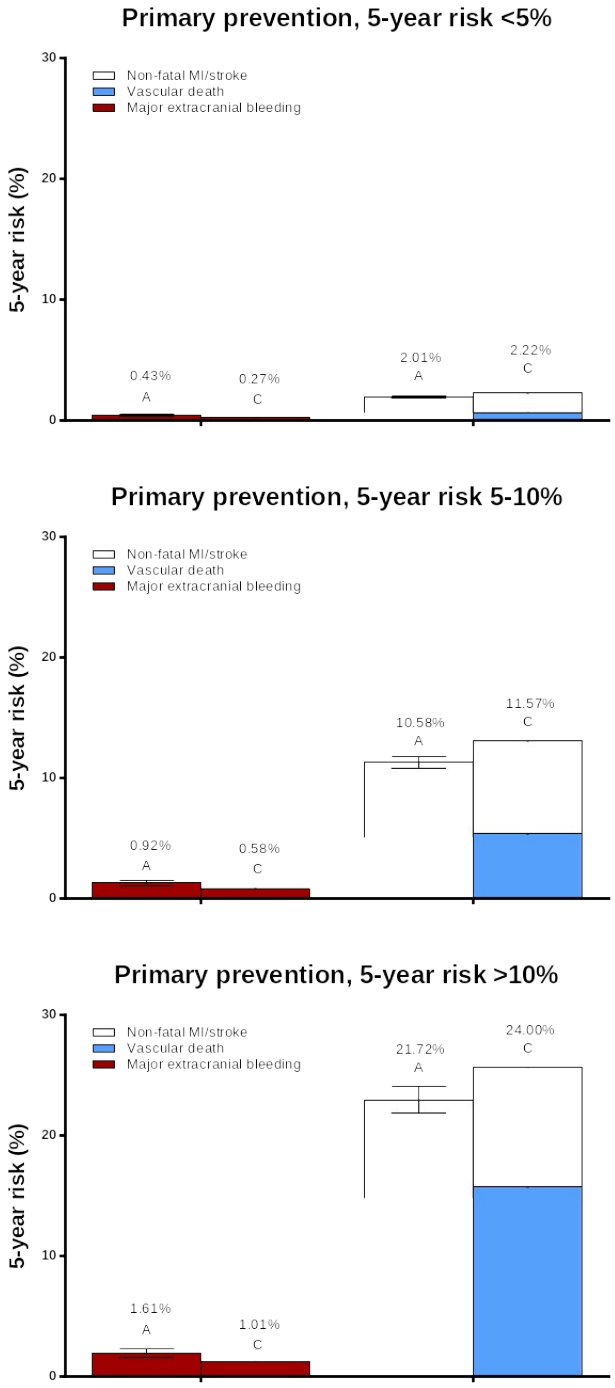
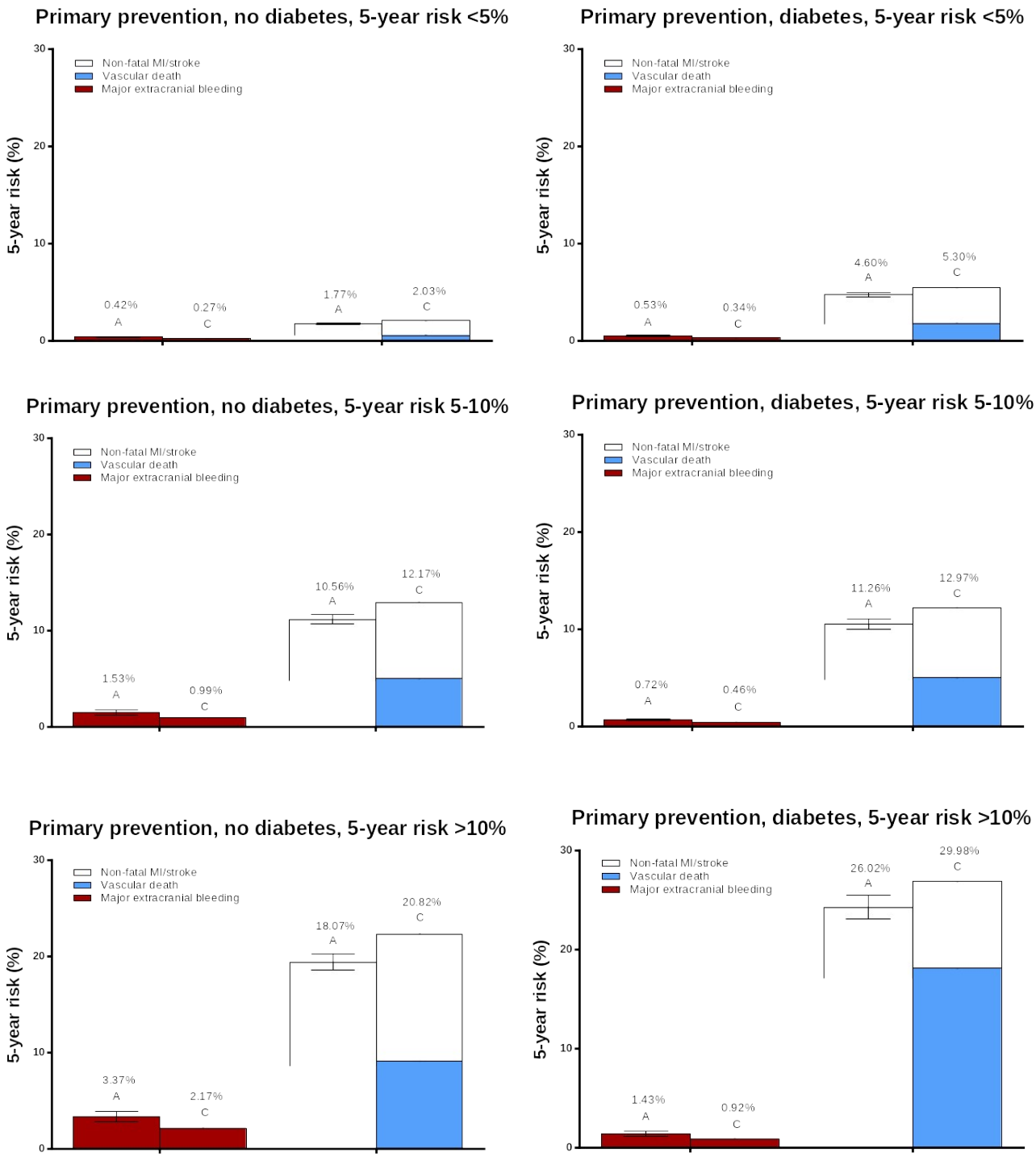


Figure 7.3: Estimated 5-year absolute effects of aspirin allocation in patients with and without diabetes in primary prevention subdivided by vascular risk

95% confidence intervals provided for estimated 5-year absolute effects of aspirin allocation (A) on major extracranial bleeding, vascular death and composite of serious vascular events, compared to control (C). Note that increasingly small subgroup numbers should be taken into account when interpreting specific estimates of control event rates.



CHAPTER 8: DISCUSSION

8.1 Main findings

The present analyses provide the most reliable evidence to date regarding the effects of aspirin according to diabetes status and, importantly, in those without occlusive vascular disease, in who any vascular benefits from long-term aspirin therapy must be carefully balanced against bleeding hazards of potentially comparable magnitude.

Previous meta-analyses have shown that aspirin is of substantial net benefit in the secondary prevention of cardiovascular disease.[53] The balance of benefits and hazards of aspirin in the primary prevention setting, however, is less clear. It is in this context that the use of individual participant data for the present meta-analysis, and the availability of additional information from further aspirin trials enrolling more people with diabetes, has allowed for a more reliable evaluation of aspirin than was previously possible.[80]

In the primary prevention setting, long-term aspirin therapy produced clear reductions in serious vascular events, an effect driven particularly by reducing non-fatal myocardial infarction and ischaemic stroke. These proportional benefits did not seem to depend significantly on diabetes status, suggesting similar proportional effects in people with and without diabetes. Because the absolute reductions in these outcomes are of an order of magnitude smaller than in secondary prevention trials, however, any increase in bleeding hazards requires careful consideration.

From the present analyses, long-term aspirin therapy increases both intracerebral and major extracranial bleeding, with proportional effects again similar in both people with and without diabetes. Furthermore, there seemed to be a reduction in total mortality from aspirin in this primary prevention setting. Hypothetical calculations based on these proportional effects suggest that, for primary prevention in those with diabetes and at sufficiently high baseline vascular risk, the benefits of aspirin therapy might outweigh any bleeding hazards. However, confidence intervals surrounding estimates remain inadequately wide in the primary prevention subgroup. Before firm recommendations on the clinical utility of aspirin in this setting are made, the arrival of further randomised evidence that would increase the precision of these estimates is eagerly awaited.

8.2 Comparison with other studies

This meta-analysis of individual participant data confirms many of the previous findings from tabular meta-analyses of randomised trials. However, the present report contains data from a number of additional trials and participants. Furthermore, incorporation of the individual participant data allowed detailed and more reliable subgroup analyses to be conducted, particularly to assess risk factors and to separate participants into different risk categories. As the proportional effects of aspirin do not differ substantially by other characteristics, we could put the absolute risks in context across different subgroups, in particular those people with diabetes.

The two most recent meta-analyses of randomised trials, published in 2011 and 2012 respectively, included tabular data from nine aspirin trials in the primary

prevention setting.[95, 99] Given the lack of individual participant data, they were not able to compare the proportional effects of aspirin in people with and without diabetes, but both did undertake sensitivity analyses excluding trials that recruited people with diabetes only. Their conclusion from such sensitivity analyses was that the results without these trials remained comparable results to the main analysis. Another meta-analysis, published in 2010, included tabular data from seven aspirin trials enrolling patients with diabetes.[100] Investigators from all three of these analyses reported non-significant effects of aspirin on major cardiovascular events or major bleeding. An earlier meta-analysis of randomised trials, published in 2009, contained tabular data from six aspirin trials, including both those conducted only in people with diabetes and also those where data on the subset of participants with diabetes was separately reported.[101] These investigators similarly concluded that a clear benefit for aspirin in primary prevention in people with diabetes could not be identified based on included data.

Crucial calculations that these previous reports were unable to undertake were estimations of the absolute benefits and hazards in different subgroups of people possible only with the benefit of individual participant data. Despite evidence for a definite net benefit of aspirin in the general primary prevention setting remaining uncertain, there is an emerging possibility that particular categories of individuals may exist in which primary prevention with aspirin is of definite net benefit. Those people with diabetes and at particularly high vascular risk, but no previous occlusive vascular disease, may represent such a category. Hypothetical calculations

suggested that, in such individuals, aspirin was potentially of benefit though these analyses are limited by wide confidence intervals of estimates.

Since the present analyses were conducted, the results from the Japanese Primary Prevention Project have been published.[133] In this trial, investigators tested aspirin in 14 454 Japanese individuals aged 60 to 85 years with hypertension, dyslipidaemia or diabetes, and no diagnosed atherosclerotic disease. After a median follow-up of 5.02 years, the study was terminated due to futility after only reaching 400 primary endpoint events (target 624) due to a lower than originally estimated event rate. There was no significant difference in the primary endpoint (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) between the groups (2.77% [95% CI, 2.40-3.20%] for aspirin vs 2.96% [95% CI 2.58-3.40%] for no aspirin; hazard ratio 0.94 [95% CI 0.77-1.15], p=0.54). Proportional effects on individual outcomes were consistent with those from the present meta-analysis. In subgroup analyses, there was no significant difference in the effect of aspirin observed in people with and without diabetes. While their data was not available for inclusion, it is unlikely that they would materially change the conclusions of the present analyses.

While they may be subject to biases and confounders, observational studies can generate large numbers of non-randomised participants in databases and thus provide useful insights. A recent, large observational study identified 186 425 individuals treated with low-dose aspirin and compared them with 186 425 controls.[81] These investigators reported that, similar to the present results, diabetes was independently associated with an increased risk of major bleeding. Intriguingly,

however, aspirin use was not associated with increased bleeding in the subgroup of people with diabetes. The possible explanation speculated for this – that there may be a reduced antiplatelet effect of aspirin in the presence of diabetes – is supported by plausible effects of diabetes on platelet function, as discussed earlier in this thesis. While the proportional increase in bleeding with aspirin for primary prevention in people with diabetes did not reach statistical significance in the present analyses, we found no evidence of heterogeneity to the effect in those without diabetes in whom a definite increase was seen.

8.3 Clinical and public health implications

It is clear that diabetes represents a major public health challenge and, if aspirin was of definite net benefit to the vast majority without pre-existing vascular disease, it would represent a cheap, widely-available and simple treatment. While the present analyses suggest that aspirin may be of benefit in some categories of people with diabetes, this requires further confirmation before its widespread use can be advocated. Thus, the trend to more circumspect guideline recommendations regarding aspirin in this population seems justified at present.

8.4 Uncertainties and future directions

Despite centuries of use in the form of salicylates, and now years of established use in secondary prevention, we are still learning about the effects of aspirin therapy. This thesis raises the possibility that aspirin may be of net benefit for primary prevention in some people with diabetes, and potentially other high-risk, but still primary prevention, populations. A number of limitations warrant consideration,

however, and support the need for further evidence to increase our confidence in the balance of vascular benefits and bleeding hazards. First, included trials were mainly in people who were not taking statin therapy. Statins are now increasingly given routinely because of their proven safety and efficacy in this primary prevention setting, though hypothetical calculations did consider the decrease in the probable absolute benefit of aspirin if people were taking statin therapy.[134] Second, the rates of diabetes-related complications have declined substantially in recent years, a trend likely attributable to both improvements in diabetes management and changing diagnostic practices.[135] This may contribute similarly to a decrease in baseline vascular risk before the addition of aspirin is considered. Third, though our findings suggest there may be a worthwhile benefit of aspirin for primary prevention in people with diabetes – as suggested by the results as a whole and the hypothetical calculations – the proportional effects in this subgroup did not reach statistical significance and further direct randomised evidence would thus be helpful in confirming these potential benefits.

Thankfully, a number of appropriately large, randomised trials of aspirin are currently in progress, in addition to the recently published JPPP study (Table 8.1). The ASCEND (A Study of Cardiovascular Events in Diabetes) study has completed recruitment and results are anticipated in 2017.[136] This trial randomised more than 15,000 individuals with diabetes in the United Kingdom to determine the effect of aspirin and omega-3 fatty acids in a 2 x 2 factorial design. The ACCEPT-D (Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes) study is aiming to randomise 5,000 individuals and is anticipated to end in

2015.[137] This trial is testing aspirin and simvastatin versus simvastatin alone in individuals with diabetes in Italy. A number of other aspirin trials, though not exclusively in people with diabetes, will also add to our understanding of the effects of aspirin in primary prevention. The ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events) study is aiming to enroll approximately 12,000 individuals at moderate risk (10-20% 10-year coronary heart disease risk) across multiple countries.[138] Notably, treated diabetes is an exclusion criterion for this trial. Finally, the ASPREE (Aspirin in Reducing Events in Elderly) study also aims to test aspirin in 19,000 elderly individuals in Australia and the United States, with the results expected in 2018.[139] It is anticipated that when the results of these contemporary trials become available, these analyses will be eventually updated with further individual participant data and will clarify the balance of risks and benefits.

Table 8.1: Large, ongoing randomised trials of aspirin in primary prevention

Trial	Study Population	Aspirin regimen	Randomised factorial comparison	Expected Number of Participants	Expected Number of Events	Expected Date of Completion
ACCEPT-D	Individuals ≥ 50 years with diabetes and n	100 mg daily	None	2,100	515	2015

	previous major vascular event.					
ARRIVE	Men ≥ 55 years with 2-4 risk factors and women ≥ 60 years with ≥3 risk factors. No treated diabetes or previous vascular disease.	100mg daily	None	12,551	1488	2016

ASCEND	Individuals ≥ 40 years with diabetes and no diagnosed occlusive vascular disease.	100mg daily		Omega-3 fatty acids vs placebo	15,000	1,250	2017
ASPREE	Individuals ≥ 70 years with no diagnosed cardiovascular event.	100mg daily		None	19,000	3,787	2018

CHAPTER 9: CONCLUSION

People with diabetes are at an increased risk of occlusive vascular events compared to people without diabetes. While aspirin is of definite net benefit in those with pre-existing vascular disease, the present analyses suggest that aspirin may also be of net benefit in people with diabetes, and potentially other high-risk populations, who do not yet have manifest vascular disease. Furthermore, we found no evidence to support speculated differences in the proportional effects of aspirin in the presence of diabetes. Given the millions of people with diabetes worldwide who might benefit from this cheap and widely available therapy, the completion of further randomised trials that may definitively allow for a conclusion as to a net benefit or not of aspirin in this setting is eagerly awaited.

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