Role of aspirin in primary prevention of cardiovascular disease

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Abstract |The benefits of aspirin therapy for the secondary prevention of cardiovascular disease clearly outweigh the risks of bleeding, and low-dose aspirin is uniformly recommended in this setting. However, no clear consensus exists about whether, and if so, in whom, aspirin therapy is appropriate for the primary prevention of cardiovascular disease . Three trials of low-dose aspirin versus placebo in three populations at increased risk of myocardial infarction or ischaemic stroke in the absence of established cardiovascular disease were reported in 2018. The ASPREE trial in elderly people was terminated early for futility because aspirin had no effect on disability-free survival, but significantly increased the risk of major haemorrhage and, unexpectedly, all-cause mortality. In the ASCEND trial in patients with diabetes mellitus and no evidence of vascular disease, aspirin significantly reduced serious vascular events, but increased major bleeding. In the ARRIVE trial in people with multiple risk factors for cardiovascular disease, aspirin had no effect on major cardiovascular events, but increased gastrointestinal bleeding. The aim of this Review is to place these new results in the context of previous evidence on aspirin for the primary prevention of cardiovascular disease, and to appraise whether the new evidence is likely to enable a more targeted use of aspirin in particular individuals for whom the net benefit is both clinically worthwhile and statistically definite.

[H1] Introduction

When used for the secondary prevention of cardiovascular disease, the benefits of a prolonged course of aspirin (acetylsalicylic acid) therapy at low doses (75–100 mg daily) clearly outweigh the risks of bleeding[1], but whether to recommend aspirin for the primary prevention of cardiovascular disease has long been debated[2,3]. The evidence from randomized clinical trials of aspirin therapy versus placebo (or control therapy) has accumulated steadily since the first trials were reported 30 years ago[4,5]. However, no clear consensus exists about whether, and if so, in whom, aspirin therapy is appropriate for the primary prevention of cardiovascular disease, and the heterogeneity in advice from treatment guidelines committees[6-11] perhaps reflects the underlying observation that, in the vast majority of apparently healthy people, aspirin therapy has small absolute benefits (of the order of 1-2 serious vascular events avoided per 1,000 treated per year) that are offset by bleeding hazards of a similar magnitude. As shown in Table 1, some guidelines groups have suggested, for example, that aspirin should not be used for primary prevention of cardiovascular disease,[9] while others have suggested that aspirin is offered to individuals in a certain age range and/or above some given level of predicted risk of cardiovascular disease[10,11].

Two major populations at increased predicted risk of myocardial infarction (MI) or ischaemic stroke in the absence of established atherosclerotic cardiovascular disease (ASCVD) are elderly individuals and patients with diabetes mellitus. In 2018, two new trials assessing low-dose aspirin therapy (100 mg daily) versus placebo for the primary prevention of ASCVD in these groups were reported: the ASPREE trial[12-14] in elderly individuals and the ASCEND trial[15] in patients with diabetes. The results of the ARRIVE trial[16] in people with multiple risk factors for cardiovascular disease (with the exclusion of patients with diabetes) were also reported in 2018. Given this newly available information, reviewing the existing evidence and appraising whether the new trial evidence is likely to help determine whom to offer long-term aspirin therapy for the primary prevention of ASCVD is timely. In this Review, we discuss the mechanism of action of aspirin and its pharmacology and summarize the previous evidence from clinical trials of aspirin therapy for the primary prevention of cardiovascular disease (particularly meta-analyses of such evidence) and the new randomized, clinical trials. Given that the evidence on the effects of aspirin therapy on cancer prevention is less definite (and the effects only accrue in the long term)[17], we focus on the effects of aspirin on ASCVD prevention. The overall aim of this Review is to appraise whether the new trial evidence is likely to allow a more targeted use of aspirin in particular groups for whom the 'net' benefit (that is, the

reduction in vascular events versus the increase in the risk of bleeding) is both clinically worthwhile and statistically definite.

[H1] Mechanism of action of aspirin

Aspirin has been reported to modulate several metabolic pathways, at least in part through acetylation of proteins involved in inflammation, haemostasis, thrombosis and cell proliferation[18]. The best characterized target of aspirin is the enzyme cyclooxygenase (COX), which has two isoforms, COX1 and COX2 (also known as prostaglandin G/H synthase 1 and 2, respectively), endowed with both COX and hydroperoxidase activities. COX1 and COX2 catalyse the conversion of arachidonic acid to the cyclic endoperoxides prostaglandin G_2 and prostaglandin H_2, which are biosynthetic intermediates in the formation of biologically active prostanoids, including thromboxane A_2 (TXA_2), the major arachidonic acid derivative in human platelets. Covalent acetylation of critical serine residues in COX1 and COX2 by aspirin permanently inactivates the COX activity of these enzymes and blocks to a variable extent this pathway of arachidonic acid metabolism, thereby reducing prostanoid production[18] (Figure 1).

In contrast to the acetylation of other proteins by aspirin, which has been described based on in vitro experiments often using millimolar concentrations of aspirin, acetylation of COX isozymes has the following distinctive characteristics that make this pathway the most plausible mechanism of action explaining the multifaceted, pharmacological effects of aspirin[18] (Figure 2). First, the COX1 enzyme and aspirin have been co-crystallized and the 3D model shows that the acetylation site within the COX channel, just below the COX catalytic site, can explain the irreversible inactivation of COX activity[19] (Figure 2a). Second, acetylation of platelet COX1 by aspirin is a saturable process that has been characterized in vitro and ex vivo[20] (Figure 2b). Third, this effect is necessary and sufficient to account for saturable suppression of the platelet production of thromboxane B_2 (TXB_2), an inactive metabolite of TXA_2, at low (micromolar) drug concentrations in vitro and following oral administration of low-dose aspirin (50–100 mg daily), as assessed both ex vivo and in vivo[2,21] (Figure 2c). In turn, virtually complete suppression by low-dose aspirin of the platelet biosynthesis of TXA_2, a potent inducer of platelet aggregation, can account for the saturability of the clinical effects of aspirin in preventing atherothrombosis in the same dose range[1]. The same mechanism of action can also explain the increase in gastrointestinal bleeding complications associated with the use of low-dose aspirin, because of the role of TXA_2-dependent platelet function in primary haemostasis[1].

Moreover, it has been suggested that platelet COX1 inhibition at sites of colorectal mucosal injury may contribute to the chemopreventive effect of low-dose aspirin therapy against sporadic adenoma recurrence and its neoplastic transformation in humans[17].

[H1] Pharmacology of aspirin

The bioavailability of plain oral aspirin tablets is approximately 40– 50% over a wide range of doses[22]. However, a considerably lower bioavailability has been reported for some aspirin preparations designed to delay absorption until the drug reaches the small intestine, such as enteric-coated aspirin tablets and sustained-release, microencapsulated aspirin preparations[23]. Lower systemic bioavailability of enteric-coated aspirin than plain aspirin tablets and poor absorption in the small intestine owing to the higher pH environment than in the stomach can result in inadequate platelet inhibition, particularly in individuals with high body weight[24]. Given the short half-life of aspirin in the human circulation (approximately 20 min)[20,22], the long-lasting duration of its antiplatelet effect is a result of the acetylation of COX1 in platelet progenitors (megakaryocytes) in the bone marrow and the limited de novo protein synthesis in blood platelets[25]. These factors enable the use of a once-daily aspirin regimen when aspirin is used as an antiplatelet agent. However, the changes in systemic bioavailability of aspirin that have been reported with delayed absorptionformulations and in association with obesity[23], or a faster renewal of the drug target, as might occur in conditions of accelerated megakaryopoiesis[26], can shorten the duration of the antiplatelet effect of aspirin.

A substantial interindividual variability in the recovery rate of platelet COX1 activity during the 24-h dosing interval of 100-mg enteric-coated aspirin has been described in both patients with diabetes and in individuals without diabetes[27]. In patients without diabetes, a higher body weight was the only independent predictor of a faster recovery of platelet COX1 activity, assessed on the basis of repeated measurements of serum TXB_2[27]. Under extreme conditions of increased platelet regeneration, such as in essential thrombocythaemia, in which accelerated renewal of platelet COX1 underlies the aspirin-insensitive TXA_2 biosynthesis in most patients with this condition[26], a twice daily regimen of low-dose aspirin is currently being recommended in both primary and secondary prevention settings[28]. The efficacy and safety of an optimized, twice-daily, low-dose aspirin regimen is currently being investigated (see below).

As a result of its unique pharmacokinetic and pharmacodynamic features, aspirin has a lower inhibitory effect on prostaglandin (PG)I_2 biosynthesis in vascular cells than on platelet TXA_2 biosynthesis at all doses, reaching a ceiling effect on inhibition of PGI_2 biosynthesis at a dose of 650–1,300 mg daily (reviewed previously[23]). Substantial inhibition of PGI_2 biosynthesis at high aspirin doses is likely to reflect dose-dependent acetylation of COX2 in vascular cells (both endothelial and smooth muscle cell)[23]. Whether more profound suppression of PGI_2 biosynthesis by high-dose aspirin is sufficient to initiate or predispose to atherothrombosis is unknown. However, two independent lines of evidence suggest that PGI_2 is important for endothelial thromboresistance: first, mice lacking the PGI_2 receptor have increased susceptibility to experimental thrombosis[29], and second, use of COX2 inhibitors is associated with increased risk of coronary atherothrombosis[30].

Aspirin has effects on haemostasis that are unrelated to the inactivation of platelet COX1 (reviewed previously[23]). These effects include dose-dependent inhibition of platelet function, increase of fibrinolysis and suppression of plasma coagulation[23]. In contrast to the saturable and well-characterized inhibition of COX1 by aspirin, the putative mechanisms underlying the COX1-independent effects of aspirin on haemostasis are dose dependent and less clearly defined[23]. To test the clinical relevance of the dose-dependent effects of aspirin, the ongoing ADAPTABLE trial was designed to compare the efficacy of two different, once-daily doses of aspirin for secondary prevention of cardiovascular disease in patients with ASCVD. The trial is aimed to recruit 15,000 patients at high risk of ischaemic events, who will be randomly assigned (1:1) to receive aspirin 81 mg daily or 325 mg daily, with a follow-up of 30 months to assess the incidence of cardiovascular and bleeding events[31].

[H1] Randomized trials in primary prevention

Evidence for the efficacy and safety of aspirin for the primary prevention of ASCVD has been accumulating since 1988, when the findings of the BDS trial[4] were reported. This study showed that aspirin 500 mg daily did not reduce the primary endpoint of vascular mortality as compared with no aspirin among 5,139 apparently healthy male doctors. Moreover, there was no significant difference in the incidence of non-fatal MI or stroke--indeed, disabling strokes were somewhat commoner among those allocated aspirin[4]. This report was followed shortly after by the publication of the US PHS trial[5] including 22,071 male doctors, in which an aspirin therapy of 325

mg on alternate days did not influence the primary endpoint of vascular mortality, but significantly reduced the risk of MI by 44% as compared with placebo. However, given that the risk of ASCVD is typically low in middle age, subsequent primary prevention trials of low-dose aspirin have generally (but not always, such as the WHS trial[32]) sought to identify study populations at above average risk by selecting groups with risk factors for ASCVD, including hypertension (HOT trial[33]), diabetes mellitus (ETDRS[34], POPADAD[35], JPAD[36] and ASCEND[15] trials), reduced ankle–brachial index (AAA trial[37]), old age (ASPREE trial[12-14]) or a combination of risk factors (PPP[38], TPT[39], JPPP[40] and ARRIVE[16] trials). In total, 14 completed trials to compare aspirin versus placebo (or no aspirin) for the primary prevention of cardiovascular disease have included a total of almost 168,000 individuals (Table 2). During the 3 decades of research into aspirin as a possible means of primary prevention of cardiovascular disease, a large number of meta-analyses have summarized the available evidence, and multiple guidelines have been based on such summaries, without any clear consensus emerging (Table 1). Before providing a reappraisal that includes the three trials reported in 2018 (ASPREE, ARRIVE and ASCEND), we summarize what had been established before this new evidence was reported.

[H2] ATT Collaboration meta-analysis. In 2009, the ATT Collaboration published analyses of individual participant data from six trials (BDS[4], PHS[5], TPT[39], HOT[33], PPP[38] and WHS[32] trials) that included 95,000 individuals[41]. These analyses demonstrated that allocation to aspirin therapy yielded a 12% reduction in serious vascular events (MI, stroke or vascular death) compared with no aspirin (absolute rates 0.51% versus 0.57% per year), which was mainly attributable to a one-fifth reduction in nonfatal MI in the aspirin group (0.18% versus 0.23% per year). A non-significant reduction in ischaemic (or other) stroke events (0.16% versus 0.18% per year) and a non-significant increase in haemorrhagic stroke events (0.04% versus 0.03% per year) were observed in the aspirin group compared with the control group and, in aggregate, aspirin therapy had no net effect on total stroke rates (0.20% versus 0.21% per year)[41]. Aspirin therapy had a small and non-significant effect on vascular mortality and all-cause mortality. However, balanced against this small reduction of about 6 per 10,000 per year fewer serious vascular events with aspirin therapy was a significant increase in major gastrointestinal bleeding and other extracranial bleedings compared with no aspirin (0.10% versus 0.07%, or 3 per 10,000 events per year)[41].

The availability of individual participant data enabled the ATT Collaboration to establish a number of important aspects of the effects of aspirin[41]. First, the 12% reduction in serious vascular events with aspirin in the overall study population was similar in each of the prognostic subgroups studied, which included age (<65 and ≥65 years); sex; history of vascular disease, diabetes or hypertension; smoking status; systolic and diastolic blood pressure; total cholesterol level; BMI and predicted risk of coronary heart disease (CHD)[41]. This observation suggested that the absolute benefits of aspirin could be reliably determined for particular individuals simply by applying the 12% reduction to their predicted annual rate of serious vascular events. Secondly, the development of risk scores both for vascular outcomes (major coronary events (non-fatal MI or CHD death), ischaemic (or other) stroke and haemorrhagic stroke) and for major extracranial bleeds allowed to demonstrate that those individuals at the highest absolute risk of vascular outcomes are also at the highest risk of bleeding (which, of course, is not surprising given that the risks of both outcomes are strongly correlated with age)[41]. As discussed in more detail below, this finding has major implications for any future strategy for selecting individuals who might derive net benefit from aspirin therapy.

The ATT meta-analysis included only six of the 14 trials now available[41]. More recent meta-analyses have included a larger number of trials, albeit without analysis of individual participant data. For example, the US Preventive Services Task Force (USPSTF) published a systematic review in 2016 analyzing 11 primary prevention trials of aspirin, including a total of 118,445 individuals[42,43]. Because the five additional trials involved few additional events, the study findings were quantitatively similar to those of the ATT meta-analysis (a 22% relative reduction in non-fatal MI, no significant effect on stroke or vascular death rates and a 58% increase in gastrointestinal bleeding events with aspirin therapy), and reached broadly similar conclusions. In contrast to the interpretation offered by the ATT [41], however, the USPSTF recommended aspirin for individuals aged 50–59 years who were at increased risk of ASCVD (≥10% 10-year risk) but who were not at increased risk of bleeding[10]. However, as pointed out by an editorial accompanying the USPSTF guideline[44], and explained in more detail below, this target population is small.

[H2] ASPREE, ARRIVE and ASCEND trials. In 2018, three more trials of aspirin 100 mg daily versus placebo added to the evidence reviewed by the USPSTF in 2016: the ASPREE trial[12-14] including 19,114 elderly people (aged ≥70 years) without clinically significant morbidity, the ARRIVE trial[16] including 12,546 people aged ≥55 years with elevated predicted risk of cardiovascular disease and

the ASCEND trial[15] including 15,540 patients with diabetes mellitus and no prior history of ASCVD. The design and primary results of each trial are briefly summarized below.

In the ASPREE trial[12-14], participants were eligible to be enrolled if they were community-dwelling, aged ≥70 years (or ≥65 years among black or Hispanic individuals in the US) and did not have cardiovascular disease, dementia or disability. The primary end point was a composite of death, dementia or persistent physical disability. The trial was terminated for futility at a median of 4.7 years, at which time aspirin had no significant effect on disability-free survival (HR 1.01, 95% CI 0.92–1.11)[12]. Aspirin also had no significant effects on secondary end points, which included cardiovascular disease (non-fatal MI or CHD-related death, non-fatal stroke or stroke-related death, and heart failure hospitalization; HR 0.95, 95% CI 0.83–1.08)[13], but significantly increased major haemorrhage events (haemorrhagic stroke, symptomatic intracranial bleeding or extracranial bleeding; HR 1.38, 95% CI 1.18–1.62; *P* <0.001) compared with placebo[13]. All-cause mortality was higher in the aspirin group than in the placebo group (HR 1.14, 95% CI 1.01–1.29), but not to an extent that reached significance if the P value was corrected for multiple comparisons[14].

In the ARRIVE trial[16], participants had no previous history of ASCVD, were aged ≥55 years if male or ≥60 years if female, and had a predicted 10-year risk of cardiovascular disease (on the basis of age, dyslipidaemia, smoking status, blood pressure and family history) of 20–30%. The primary end point was a composite of MI, stroke, cardiovascular death, unstable angina or transient ischaemic attack (TIA). Median follow-up was 5 years. Aspirin had no significant effect on the primary end point (HR 0.96, 95% CI 0.81–1.13), but significantly increased gastrointestinal bleeding events (HR 2.11, 95% CI 1.36–3.28, *P* = 0.0007)[16].

In the ASCEND study[15], participants had diabetes mellitus but no evidence of ASCVD, and were aged ≥40 years. The primary end point was serious vascular events, a composite of MI, stroke or TIA, or vascular death (excluding death from intracranial haemorrhage). Mean follow-up was 7.4 years. Despite treatment of a high proportion of participants with cardioprotective medications (for example, about 75% were taking a statin at baseline), allocation to aspirin produced a significant 12% reduction in the primary outcome compared with placebo (HR 0.88, 95% CI 0.79–0.97, *P* = 0.01), while increasing major bleeding events by 29% (HR 1.29, 1.09–1.52, *P* = 0.003). This finding suggests that aspirin adds to the benefits of statin therapy in a clinical setting where TXA_2-dependent platelet activation contributes to atherothrombotic vascular events[45].

[H2] Summary of findings As reported in the supplementary appendix of a 2019 meta-analysis of tabular data from 13 of the 14 trials of aspirin for primary prevention of cardiovascular disease that are now available (the ETDRS[34] trial was not included), with the exception of MI, no heterogeneity was observed in the risk ratios for the major efficacy and safety outcomes among the trials[46]. In particular, the unexpected increase in mortality observed in the ASPREE trial was largely attributable to an increase in cancer mortality (HR 1.31, 95% CI 1.10–1.56), and among all trials no significant heterogeneity was observed in the risk ratios for cancer mortality or in the risk ratios for cardiovascular or all-cause mortality[46]. Therefore, to conclude that the relative effects of aspirin differ in elderly individuals is premature.

Contemporary drug therapies (such as statin therapy) have reduced the absolute risk of ischaemic events for apparently healthy people compared with equivalent individuals included in earlier trials of aspirin, whereas the relative effects of aspirin seem to be similar when aggregated across all the populations studied; therefore, the overall absolute benefits of aspirin in the most recent trials are smaller than reported previously[41]. It should be noted, however, that accurate estimates of treatment efficacy (in terms of ischaemic events) and risk of bleeding for particular individuals at risk, and specifically those with diabetes and elderly people, will require further study through meta-analysis of individual participant data from all available trials because, to date, the variation in treatment effects has only been assessed at trial level.

[H1] Safety of aspirin in primary prevention

[H2] Risk of bleeding. The main hazard of low-dose aspirin therapy is haemorrhage, which is due to inhibition of TXA_2-dependent platelet function, an important component of primary haemostasis[1]. Observational studies[47] and a meta-analysis of randomized trials in patients at high-risk of cardiovascular disease [48] have demonstrated that long-term, low-dose aspirin therapy approximately doubles the risk of major extracranial bleeding, mostly upper gastrointestinal bleeding. The risk of these bleeding complications increases sharply in individuals aged ≥70 years[1], a population that was largely excluded from trials of aspirin (or of other antithrombotic drugs). This risk is further increased by a history of gastrointestinal disturbances and by concomitant use of NSAIDs[1]. In middle-aged patients, this increased risk corresponds to an estimated absolute excess of approximately 1–2 major bleeding complications per 1,000 patients treated with low-dose

aspirin for 1 year, but the excess is smaller in young people and substantially higher in elderly individuals and in those with a history of ulcer bleeding[1].

As mentioned above, aspirin use increased the risk of major gastrointestinal and other extracranial bleeding events by about half compared with no aspirin in the six primary prevention trials analyzed by the ATT Collaboration in 2009 (0.10% versus 0.07% per year; RR 1.54, 95% CI 1.30–1.82, *P* <0.0001)[41]. The excess risk was mainly due to non-fatal bleeding events (probably by chance there were fewer fatal bleeding events in participants allocated to aspirin therapy than in the control group [9 versus 20 events])[41].

In the primary prevention trials reported in 2018, therapy with 100 mg enteric-coated aspirin once daily increased gastrointestinal bleeding events to a similar proportional extent as in the earlier trials. In the ARRIVE study[16], where the mean age was 64, gastrointestinal bleeding events occurred in 61 (0.97%) subjects in the aspirin group and 29 (0.46%) subjects in the placebo group over a mean of 5 years (HR 2.11, 95% CI 1.36–3.28, *P* = 0.0007). Haemorrhagic stroke occurred in 8 (0.13%) and 11 (0.18%) subjects in the aspirin and placebo groups, respectively[16]. In the ASPREE study[13] , where the median age was 74 years, the rate of major haemorrhage in the aspirin group was 8.6 events per 1,000 person-years compared with 6.2 events per 1,000 person-years in the placebo group (HR 1.38, 95% CI 1.18–1.62, *P* <0.001). The increased risk of bleeding with aspirin persisted throughout the course of therapy. The rate of fatal haemorrhage was <1 event per 1,000 person-years in each group. Upper gastrointestinal bleeding accounted for >40% of the absolute excess of major haemorrhage events. The relative risk of upper gastrointestinal bleeding with aspirin compared with placebo in the ASPREE trial appeared particularly large (HR 1.87, 95% CI 1.32–2.66) [13], although, as shown in a 2019 systematic review and meta-analysis[46], the results of the primary prevention trials of aspirin are broadly consistent. The risk of intracranial bleeding in the ASPREE trial was also higher with aspirin than with placebo (HR 1.50, 95% CI 1.11–2.02)[13]. Given the age of the participants in the ASPREE trial, it is not surprising that the rate of major extracranial bleeding in the control group was approximately 9-fold higher than in the control groups in earlier primary prevention trials on aspirin, which resulted in a larger absolute excess risk associated with aspirin therapy in ASPREE[13]. In the ASCEND trial,where the mean age was 63 years, major bleeding events occurred in 314 (4.1%) participants in the aspirin group compared with 245 (3.2%) participants in the placebo group (RR 1.29, 95% CI 1.09–1.52, *P* = 0.003) during a mean follow-up of

7.4 years[15]. The incidence of fatal bleeding events (19 (0.2%) participants versus 16 (0.2%) participants) and haemorrhagic stroke (25 (0.3%) participants versus 26 (0.3%) participants) was similar in the aspirin and placebo groups. No apparent attenuation of the effect of aspirin on the risk of bleeding occurred over time[15].

[H2] Co-therapy with gastroprotectant drugs. Although the general consensus among gastroenterologists is that proton-pump inhibitors (PPIs) should be prescribed to patients at high-risk of bleeding who are taking low-dose aspirin[49], such a strategy has not been widely adopted because of a lack of definitive supporting evidence. In the ASCEND trial[15], approximately half the excess risk of bleeding was gastrointestinal, with about one-third occurring in the upper gastrointestinal tract. However, only approximately 25% of participants were receiving PPIs at the end of the trial. A similar proportion of patients receiving PPIs was reported at trial entry in the ARRIVE[16] and ASPREE[13] studies. Bleeding rates in individuals taking low-dose aspirin might be lower if PPIs were routinely used, as suggested by the 3-year findings from the COMPASS trial[50] of co-therapy with the PPI pantoprazole. The trial showed a substantial reduction in the incidence of bleeding in the upper gastrointestinal tract with pantoprazole compared with placebo in patients with ASCVD receiving an antithrombotic regimen consisting of low-dose aspirin, rivaroxaban or both, which confirms the observations reported in short-term studies of PPIs[51] (Figure 3).

PPIs are metabolized by hepatic cytochrome P450 enzymes and, therefore, might interfere with the elimination of other drugs that are cleared by this route (such as cyclosporine, diazepam and warfarin). Moreover, PPIs can interfere with the conversion of clopidogrel to its $P2Y_{12}$-inhibiting metabolite, although the clinical relevance of this pharmacokinetic interaction has not been established[52]. In addition, chronic use of PPIs has been associated with an increased risk of osteoporosis-related bone fractures[53] and with increased susceptibility to certain infections (such as community-acquired *Clostridium difficile* infection)[54]. The findings from the COMPASS study[50] indicate that long-term use of pantoprazole with antithrombotic therapy seems to be safe except for a potential increase in enteric infections compared with placebo.

[H2] Interactions with other cardiovascular drugs. A concern has been expressed that aspirin might reduce the benefits of angiotensin-converting-enzyme (ACE) inhibitors on cardiovascular morbidity and mortality in a secondary prevention setting[3]. It has been suggested that a large part of the cardiovascular benefit of ACE-inhibitors is attributable to their positive effect on vascular

prostaglandin synthesis and that this effect is inhibited by aspirin[3]. Similarly, concerns have been raised that aspirin might impair the therapeutic benefits of agents that improve outcomes in heart failure, including ACE-inhibitors and β-blockers, most probably by blocking prostaglandin production in the kidney, which results in impaired vasodilatation, decreased renal function, sodium and water retention and circulatory volume expansion[3]. However, low-dose aspirin does not inhibit renal prostaglandin synthesis, which in humans is largely driven by constitutively expressed COX2[21,23]. In a largely female, middle-aged patient population with osteoarthritic disorders, the risk of hospitalization owing to heart failure was roughly doubled by all NSAID regimens studied compared with placebo, consistent with this outcome being a COX2-dependent hazard unrelated to variable platelet inhibition[30]. In the elderly patient population recruited in the ASPREE trial[13], 75% of whom had hypertension at baseline, the risk of hospitalization for heart failure was not modified by low-dose aspirin therapy compared with placebo (2.1% versus 1.9%; HR 1.07, 95% CI 0.79–1.44). Similarly, in the population with diabetes included in the ASCEND trial[15], with approximately 60% reported use of ACE-inhibitors or angiotensin-II-receptor blockers at baseline, the rate of fatal or non-fatal heart failure did not differ between the low-dose aspirin and placebo groups (1.2% versus 1.5%; RR 0.84, 95% CI 0.64–1.10).

[H1] Balance of benefits and risks

The uncertainty about the balance of benefits and risks of taking low-dose aspirin for primary prevention of cardiovascular disease is reflected by contradictory recommendations by US and European organizations (Table 1) as well as by a heterogeneous regulatory framework[2]

However, there are a number of difficulties involved in the identification of individuals in whom the net benefit of aspirin therapy is clearly favourable. Given that the relative effects of aspirin use seem to be consistent in a wide range of individuals, the basic task is to delineate groups of people in whom the predicted absolute risk of CHD is high whereas the predicted risk of bleeding is low. This goal raises a number of practical considerations, as described below.

[H2] Poor performance of current multivariate risk scores. In healthy populations, cardiovascular disease risk scores comprising multiple risk factors of only moderate strength (for example, high cholesterol level and/or high blood pressure) yield a distribution of predicted risk in which the majority of individuals have a predicted risk of CHD <1% and only a small proportion have a

predicted risk exceeding 1.5% per year (Figure 4)[41]. This poor performance is an intrinsic and unavoidable characteristic of such multivariate scores, however sophisticated and however well calibrated. In principle, a risk score developed by performing angiographic assessment of coronary arteries in the whole general population would be more sensitive and specific than current risk scores, enabling a clear distinction between those individuals without CHD (who are the majority of people in the general population and who, indeed, would be at very low risk of CHD) and those with subclinical CHD (who are a minority of people in the general population, and who would probably have an annual risk of CHD >3%). Such a method of directly visualizing those individuals with occult CHD would enable preventive measures to focus the aspirin treatment on just those at elevated risk. However, notwithstanding the efforts to develop the assessment of coronary artery calcium (CAC) scores for such a purpose[55], as discussed below, currently no technology permits such an approach. Consequently, all efforts to improve the utilization of low-dose aspirin in primary prevention must work within the constraints inherent to multivariate risk scores that incorporate variables that have individually moderate associations with the risk of CHD.

[H2] A very low proportion of individuals are at high risk of CHD and low risk of bleeding . Figure 4 shows the distribution of predicted risk of CHD and risk of extracranial bleeding in the six trials included in the 2009 ATT meta-analysis[41]. Each point in the graph represents an individual, organized according to the predicted risk of CHD. The analysis shows that 75% of individuals in the 2009 ATT meta-analysis had a risk of <0.5% per year, 15% had a risk of ≥0.5 and <1.0% per year, 5% had a risk of ≥1.0% and <1.5% per year and 5% had a risk of >1.5% per year. In each CHD risk group, the distribution of predicted risk of major extracranial bleeding is shown in the box (interquartile range) and whisker (95% percentile range). For example, if it is determined that only those individuals with absolute annual risk of CHD of ≥1.0% per year (among whom the expected benefit per 1,000 people per year, assuming a rate ratio of 0.88[41], would be about 1.2 serious vascular events prevented) and a predicted risk of major extracranial bleeding <0.1% per year (among whom the excess risk, assuming a rate ratio of 1.5, would be 0.5 bleeding events per 1000 people per year) would derive clear net benefit, then only about 3% of the population in the 2009 ATT meta-analysis would satisfy these criteria. The criteria for determining a 'margin of safety' for an excess of benefit over hazard that minimizes the risk of harm for healthy people is, of course, subjective, but the statistical problem of identifying eligible patients might be inherent irrespective of where this margin is set.

[H2] Potential for increasing the proportion of individuals with net benefit from aspirin therapy Data from a meta-analysis of studies on gastroprotectant agents[51] (Figure 3) suggest that reducing the risk of bleeding through the use of such drugs in individuals with elevated risk of CHD is a potential means for increasing the proportion of individuals that might gain net benefit from aspirin therapy. However, the effects of different gastroprotectant agents on the risk of bleeding are unclear: this meta-analysis suggests that PPIs reduce the risk of serious gastrointestinal bleeding by as much as two-thirds but, as discussed by the authors of the meta-analysis, this estimate might be inflated by bias arising from the inclusion only of small studies[51]. The results on long-term use of pantoprazole in the COMPASS trial[50] are consistent with a more modest reduction in the risk of bleeding with the use of PPIs. Although whether PPIs reduce the risk of bleeding uniformly at all levels of risk of CHD is currently unclear, if PPIs are assumed to reduce the risk by half in all individuals, then the proportion of individuals who might derive 'net benefit' from aspirin treatment under the criteria outlined in the previous section would more than double (from 3% to about 7%). The largely reassuring safety results of the COMPASS trial[50] suggest that more detailed consideration should be given to a strategy of combination treatment of aspirin and PPIs for selected individuals at elevated risk of CHD.

[H2] Comparing the disutility of vascular and bleeding events A variety of approaches have been used to calculate the net effects of aspirin in primary prevention. For example, the USPSTF conducted a decision analysis to estimate the net quality-adjusted life-years in men and women at different ages with the use of data from their own systematic evidence reviews and population data from the US National Health and Nutrition Examination Survey on cardiovascular disease and cancer rates, as well as data on bleeding events from an Italian population-based study and disutility values drawn from the literature[56]. Two separate analyses of the WHS assessed more specifically the net benefit of aspirin on different outcomes over 10 years with the use of the 'number-willing-to-treat' (the ratio of the severity of a benefit compared with a harm) among women assigned to various risk-based categories[57,58]. These different approaches yielded variable findings, with the conclusions depending strongly on the time horizon for calculating the net effects. Within the obvious limitations of assessing the balance of benefits and risks on the basis of absolute benefits and harms, a ratio of benefit to hazard close to 1.0, as can be calculated in the ASCEND trial[15], is also observed in secondary prevention with other antithrombotic interventions aimed at reducing the residual risk of cardiovascular disease by adding either ticagrelor[59] or

rivaroxaban[60] to existing antithrombotic therapies. Therefore, further research is needed to develop algorithms that incorporate a formal assessment of the relative disutility of major ischaemic and bleeding events according to age, prior clinical history and other prognostic characteristics of the patient.

[H2] Are there additional long-term benefits of long-term antiplatelet therapy that are not related to ASCVD? In 2016, the USPSTF issued guidelines stating that the USPSTF recommended initiating low-dose aspirin use for the primary prevention of cardiovascular disease and colorectal cancer in adults aged 50–59 years who have a ≥10% 10-year risk of cardiovascular disease, are not at increased risk for bleeding, have a life expectancy of ≥10 years and are willing to take low-dose aspirin daily for ≥10 years[10]. This recommendation was based on the accumulated evidence for a chemopreventive effect of low-dose aspirin therapy against colorectal and other types of cancer that seemed to emerge after about a decade of aspirin therapy. Nevertheless, the evidence on the effects of aspirin therapy on cancer prevention is less definite than that on the prevention of cardiovascular disease.

[H1] Research gaps

[H2] Improved risk stratification scores. Future research is needed to explore improved methods of risk stratification in order to increase the balance of expected benefit to risk for specific identifiable groups of apparently healthy people. The identification of novel biomarkers that are only moderately associated with risk of ASCVD (comparable, for example, to a risk factor like cholesterol) is unlikely to be sufficient, especially given the decreasing rates of ASCVD in many regions of the world. Instead, we need methods that will enable the identification of those individuals with existing (but clinically silent) disease. For example, CAC is a highly specific feature of coronary atherosclerosis. CAC scoring has emerged as a means of assessing the risk for major cardiovascular outcomes, especially useful in asymptomatic people for planning primary prevention interventions such as statin and aspirin therapy[55]. However, according to an assessment by the USPSTF published in 2018[61] , evidence from adequately powered clinical trials evaluating the incremental effect of the CAC score (or other nontraditional risk factors, such as the ankle–brachial

index or high-sensitivity C-reactive protein level) in the assessment of the risk of ASCVD and the initiation of preventive therapy is insufficient. In addition, an elevated CAC score is of little prognostic value in people who are taking statin therapy, which is a limitation in clinical practice.

[H2] Safer antithrombotic drugs. Besides the need for more efficient risk scores and treatment algorithms, development of safer antithrombotic agents through a better understanding of the molecular mechanisms contributing to atherothrombosis versus haemostasis is clearly needed[62].

[H2] Tailored aspirin dosing. A 24-hour dosing interval of aspirin administration is generally assumed to be adequate to maintain virtually complete and persistent suppression of TXA_2-dependent platelet activation, because of the irreversible nature of platelet COX1 inactivation by the drug and trivial de novo protein synthesis in anucleate platelets[23]. However, accelerated renewal of the drug target because of abnormal megakaryopoiesis (such as in essential thrombocythaemia[25,26]) and/or reduced acetylation of COX1 in the platelet progenitors because of impaired systemic bioavailability of aspirin (such as in obesity[25,27]) can substantially reduce the duration of the antiplatelet effect of aspirin, requiring a shorter dosing interval (for example, 12 h). The efficacy and safety of an optimized, twice-daily, low-dose aspirin regimen is currently being explored in a phase II trial on essential thrombocythemia[63] and in a phase III trial on type 2 diabetes mellitus (ANDAMAN trial[64])
In addition, as mentioned above, the clinical relevance of the dose-dependent effects of aspirin will be assessed in the ongoing ADAPTABLE trial[31].

[H2] Role of aspirin in cancer prevention. Further investigation is needed on the mechanism of action of aspirin therapy in the setting of prevention of colorectal and other types of cancer[17] as well as longer-term follow-up of cancer incidence and mortality in the primary prevention trials reported in 2018. The findings from these studies might provide the necessary prospective evidence on the role of aspirin in chemoprevention to enable a reliable assessment of the benefit–risk balance of aspirin therapy in this setting.

[H1] Conclusions

In conclusion, the results of 3 new randomized trials of aspirin versus placebo in people with diabetes, the elderly, and people at increased risk of ASCVD, are statistically consistent with the

results of previously reported trial findings in the primary prevention setting. They reinforce the point that, when used in primary prevention, aspirin yields small absolute benefits and small hazards. Given the wide range of people now studied in such trials there is a need for an updated assessment, using meta-analysis of individual participant data, of whether some people derive clear net benefit. The main challenge when assessing whether aspirin use would be of net benefit to particular individuals is that the expected benefits and risks are strongly correlated, so identifying large numbers of people at high risk of ASCVD but low risk of bleeding is likely to be difficult. Future work to explore this dilemma requires a new approach, perhaps combining the use of coronary imaging, to identify a group of apparently healthy people at substantially increased risk of vascular events, with the use of gastroprotectant therapy to reduce the risk of bleeding. Tailoring the aspirin regimen according to body weight and platelet turnover is an additional strategy worth investigating to optimize effectiveness[25,65].

References

1. Patrono, C., García Rodríguez, L.A., Landolfi, R. & Baigent, C. Low-dose aspirin for the prevention of atherothrombosis. N. Engl. J. Med. 353, 2373-2383 (2005).
2. Patrono, C. Low-dose aspirin in primary prevention: cardioprotection, chemoprevention, both or neither? Eur. Heart J**.** 34, 2403-2411 (2013).
3. Cleland, J.G. Is aspirin useful in primary prevention? Eur. Heart J. 34, 3412-3418 (2013).
4. Peto, R. et al. Randomised trial of prophylactic daily aspirin in British male doctors. BMJ 296, 313-316 (1988)
5. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N. Engl. J. Med. 321, 129-135 (1989).
6. Vandvik, P.O. et al. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141, e637S–668S (2012).
7. Rydén, L. et al. ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, prediabetes, and cardiovascular diseases of the European

Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur. Heart J. 34, 3035–3087 (2013).
8. American Diabetes Association. 10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes. Diabetes Care 42 (Suppl. 1), S103–S123 (2019).
9. Piepoli, M.F. et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur. Heart J. 37, 2315-2381 (2016).
10. Bibbins-Domingo, K. on behalf of the U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann. Intern. Med. 164, 836-845 (2016).
11. Arnet, D.K. et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. J. Am. Coll. Cardiol. doi.org/10.1016/j.jacc.2019.03.010 (2019).
12. McNeil, J.J.et al. Effect of aspirin on disability-free survival in the healthy elderly. N. Engl. J. Med. 379, 1499-1508 (2018).
13. McNeil, J.J. et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N. Engl. J. Med. 379, 1509-1518 (2018).
14. McNeil, J.J. et al. Effect of aspirin on all-cause mortality in the healthy elderly. N. Engl. J. Med. 379, 1519-1528 (2018).
15. The ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N. Engl. J. Med. 379, 1529-1539 (2018).
16. Gaziano, J.M. et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet 392,1036-1046 (2018).
17. Patrignani, P. & Patrono, C. Aspirin and cancer. J. Am. Coll. Cardiol. 68, 967-976 (2016).
18. Patrono, C. The multifaceted clinical read-outs of platelet inhibition by low-dose aspirin. J. Am. Coll. Cardiol. 66, 74-85 (2015).
19. Loll, P.J., Picot, D. & Garavito, R.M. The structural basis of aspirin activity inferred from the crystal structure of inactivated prostaglandin H2 synthase. Nat. Struct. Biol. 2, 637-643 (1995).

20. Patrignani, P. et al. Reappraisal of the clinical pharmacology of low-dose aspirin by comparing novel direct and traditional indirect biomarkers of drug action. J. Thromb. Haemost. 12, 1320-1330 (2014).
21. Patrignani, P., Filabozzi, P. & Patrono, C. Selective cumulative inhibition of platelet thromboxane production by low-dose aspirin in healthy subjects. J. Clin. Invest. 69,1366-1372 (1982).
22. Pedersen, A.K. & FitzGerald, G.A. Dose-related kinetics of aspirin: presystemic acetylation of platelet cyclooxygenase. N. Engl. J. Med. 311,1206-1211 (1984).
23. Patrono, C., Baigent, C., Hirsh, J. & Roth, G. Antiplatelet drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133,199S-233S (2008).
24. Rocca, B. et al. Antithrombotic therapy and body mass: an expert position paper of the ESC Working Group on Thrombosis. Eur. Heart J. 39, 1672-1686f (2018).
25. Giaretta, A., Rocca, B., Di Camillo, B., Toffolo, G.M. & Patrono, C. In silico modeling of the antiplatelet pharmacodynamics of low-dose aspirin in health and disease. Clin. Pharmacol. Ther. 102, 823-831 (2017).
26. Pascale, S. et al. Aspirin-insensitive thromboxane biosynthesis in essential thrombocythemia is explained by accelerated renewal of the drug target. Blood 119, 3595-3603 (2012).
27. Rocca, B. et al. The recovery of platelet cyclooxygenase activity explains interindividual variability in responsiveness to low-dose aspirin in patients with and without diabetes. J. Thromb. Haemost. 10, 1220-1230 (2012).
28. Tefferi, A., Vannucchi, A.M. & Barbui, T. Essential thrombocythemia treatment algorithm 2018. Blood Cancer Journal 8, 1-6 (2018).
29. Murata, T. et al. Altered pain perception and inflammatory response in mice lacking prostacyclin receptor. Nature 388,678-682 (1997)
30. Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 382, 769-779 (2013).
31. US National Library of Medicine. ClinicalTrials.gov http://www.clinicaltrials.gov/ct2/show/NCT004433589?term=NCT00433589&rank=1 (2009).
32. Ridker, P.M. et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N. Engl. J. Med. 352,1293-1304 (2005).

33. Hansson, L.et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 351, 1755-1762 (1998).
34. Early Treatment Diabetic Retinopathy Study report 14. ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. JAMA 268, 1292-1300 (1992).
35. Belch, J. et al; Prevention of Progression of Arterial Disease and Diabetes Study Group. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 337, a1840 (2008).
36. Ogawa, H. et al; Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 300,2134-2141 (2008).
37. Fowkes, F.G. et al; Aspirin for Asymptomatic Atherosclerosis Trialists. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA 303, 841-848 (2010).
38. De Gaetano G. et al. Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Lancet 357,89-95 (2001).
39. The Medical Research Council's General Practice Research Framework. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. Lancet 351, 233–241 (1998).
40. Ikeda, Y. et al. Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial. JAMA 312, 2510-2520 (2014).
41. Baigent, C. et al; Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 373,1849-1860 (2009).
42. Guirguis-Blake, J.M., Evans, C.V., Senger, C.A., O'Connor, E.A. & Whitlock, E.P. Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Ann. Intern. Med. 164, 804-813 (2016).

43. Whitlock, E.P., Burda, B.U., Williams, S.B., Guirguis-Blake, J.M. & Evans, C.V. Bleeding Risks With Aspirin Use for Primary Prevention in Adults: A Systematic Review for the U.S. Preventive Services Task Force. Ann. Intern. Med.164, 826-835 (2016).
44. Baigent, C. Aspirin for Disease Prevention: Public Policy or Personal Choice? Ann Intern Med.164, 846-847 (2016).
45. Davì, G. et al. Thromboxane biosynthesis and platelet function in type-II diabetes mellitus. N. Engl. J. Med. 322,1769-1774 (1990).
46. Zheng, S.L. & Roddick, A.J. Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events. A Systematic Review and Meta-analysis. JAMA 321, 277-287 (2019)
47. García Rodríguez, L.A., Hernández-Díaz, S. & de Abajo, F.J. Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. Br. J. Clin. Pharmacol. 52,563-571 (2001).
48. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients. BMJ 324, 71-86 (2002).
49. Lanas, A. & Chan, F.K.L. Peptic ulcer disease. Lancet 390,613–624 (2017).
50. Moayyedi, P. et al. for the COMPASS Investigators. A randomized trial of proton pump inhibitors versus placebo to prevent upper gastrointestinal bleeding in patients receiving rivaroxaban or aspirin. United European Gastroenterology (UEG) week, October 20-24, 2018, Vienna, Austria (abstracts LB15 and LB16).
51. Scally, B. et al. Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomised trials. Lancet Gastroenterol. Hepatol. 3, 231-241 (2018).
52. Focks, J.J., Brouwer, M.A., van Oijen, M.G., Lanas, A., Bhatt, D.L. & Verheugt, F.W. Concomitant use of clopidogrel and proton pump inhibitors: impact on platelet function and clinical outcome- a systematic review. Heart 99,520-527 (2013).
53. Yu, E.W., Bauer, S.R., Bain, P.A. & Bauer, D.C. Proton pump inhibitors and risk of fractures: a meta analysis of 11 international studies. Am. J. Med. 124,519–526 (2011).
54. Janarthanan, S., Ditah, I., Adler, D.G. & Ehrinpreis, M.N. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. Am. J. Gastroenterol. 107,1001–1010 (2012).

55. Greenland, P., Blaha, M.J., Budoff, M.J., Erbel, R. & Watson, K.E. Coronary calcium score and cardiovascular risk. J. Am. Coll. Cardiol. 72, 434-447 (2018).
56. Dehmer, S.P, Maciosek, M.V, Flottemesch, T.J, LaFrance, A.B, Whitlock, E.P. Aspirin for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: A Decision Analysis for the US Preventive Services Task Force. Ann Intern Med 164, 777-786 (2016)
57. Dorresteijn, J.A.N, et al. Aspirin for primary prevention of vascular events in women: individualized prediction of treatment effects. Eur Heart J 32, 2962-2969 (2011)
58. van Kruijsdijk, R.C.M, et al. Individualized prediction of alternate-day aspirin treatment on the combined risk of cancer, cardiovascular disease and gastro-intestinal bleeding in healthy women. Heart 101, 369-376 (2015)
59. Bonaca, M.P. et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N. Engl. J. Med. 372, 1791-1800 (2015).
60. Eikelboom, J.W. et al. for the COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. N. Engl. J. Med. 377, 1319-1330 (2017).
61. Lin, J.S. et al. Nontraditional risk factors in cardiovascular disease risk assessment: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 320, 281-297 (2018).
62. Gachet, C. Antiplatelet drugs: which targets for which treatments? J. Thromb. Haemost. 13 Suppl 1, S313-S322 (2015).
63. De Stefano, V. et al. The Aspirin Regimens in Essential Thrombocythemia (ARES) phase II randomized trial design - implementation of the serum thromboxane B2 assay as an evaluation tool of different dosing regimens in the clinical setting. Blood Cancer J. 8, 49 (2018).
64. US National Library of Medicine. ClinicalTrials.gov http://www.clinicaltrials.gov/ct2/show/NCT004433589?term=NCT00433589&rank=1 (2009).
65. Rocca, B. & Patrono, C. Determinants of the interindividual variability in response to antiplatelet drugs. J. Thromb. Haemost. 8,1597-1602 (2005).

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Author contributions

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Further information

ADAPTABLE trial: https://theaspirinstudy.org

Key points The benefits of aspirin therapy for the secondary prevention of cardiovascular disease (CVD) clearly outweigh the risks of bleeding, but whether to recommend low-dose aspirin for primary prevention of CVD is controversial.

- Use of risk scores for vascular events and major extracranial bleeds to classify individual participant data from a meta-analysis shows that individuals at the highest risk of vascular events are also at the highest risk of bleeding.
- In 2018, results from three trials on low-dose aspirin in three populations at increased risk of myocardial infarction or ischaemic stroke in the absence of established CVD added to the evidence base.
- Overall, other than for myocardial infarction, the relative effects of aspirin on the other major efficacy and safety outcomes appear similar in all of the primary prevention trials, including the 3 (ASPREE, ASCEND and ARRIVE) completed in 2018 .
- The main challenge when assessing the net benefit of aspirin is that benefits and risks are strongly correlated; therefore, identifying large numbers of people at high risk of vascular ischaemia but low risk of bleeding is difficult.

- New approaches are required to overcome this challenge, perhaps combining coronary imaging to identify apparently healthy people at substantially increased risk of vascular events, with gastroprotective therapy to reduce the risk of bleeding.

Figure 1 | **Mechanism of action of aspirin.** Arachidonic acid, a 20-carbon fatty acid containing four double bonds, is liberated from the *sn*-2 position of cell membrane phospholipids by several phospholipases, which are activated by diverse stimuli. Arachidonic acid is then converted by prostaglandin (PG)G/H synthases, which have both cyclooxygenase (COX) and hydroperoxidase (HOX) activity, to the unstable intermediates PGG2 and PGH2, respectively. The synthases are colloquially termed cyclooxygenases and exist in two isoforms, COX-1 and COX-2. PGH_2 is converted by tissue-specific isomerases to multiple prostanoids, including thromboxane A_2 (TXA_2). These bioactive lipids activate specific cell-membrane receptors of the superfamily of G-protein-coupled receptors, such as the TXA_2 receptor (TP), the PGD_2 receptors (DPs), the PGE_2 receptors (EPs), the $PGF_{2\alpha}$ receptors (FPs) and the prostacyclin I_2 (PGI_2) receptor (IP)[1]. Aspirin inactivates the COX activity of COX1 and COX2. In humans, low-dose aspirin is a relatively selective inhibitor of platelet COX1, whereas high-dose aspirin and other NSAIDs inhibit both COX1 and COX2.

Figure 2 | **Molecular basis of the antiplatelet pharmacodynamics of aspirin. a** | Crystal structure of the cyclooxygenase catalytic site of the ovine prostaglandin G/H-synthase 1 (also known as cyclooxygenase 1) acetylated by acetylsalicylic acid (aspirin). The carboxylic moiety of the salicylic acid (shown in yellow) interacts reversibly with Arg120 (shown in pink), a common docking site for all NSAIDs. This interaction creates a local pool of acetylating moiety just beneath Ser530 (Ser529 in the human enzyme)(shown in orange), thereby explaining the selective acetylation of this particular serine residue by aspirin. The acetylated Ser530 occupies a strategic position within the cyclooxygenase channel, directly below Tyr385 (shown in pink), a crucial residue for initiating cyclooxygenase catalysis. Any arachidonic acid diffusing up the channel would be prevented from interacting with Tyr385 by steric hindrance introduced by this adduct. The haem moiety of the enzyme is shown in red **b** | Graph showing the hyperbolic relationship between the percentage of acetylated platelet COX1 (AceCOX1) and inhibition of platelet COX1 activity, as reflected by serum levels of thromboxane B_2 (TXB_2), a stable metabolite of thromboxane A_2. **c** | Graph depicting the log-linear relationship between oral aspirin dose and inhibition of platelet TXB_2 production in healthy individuals, as reflected by serum TXB_2 measurements performed before and 24 h after

aspirin dosing, with each individual serving as their own control. Panel **a** adapted from REF.[19]. Panel **b** adapted from REF.[20]. Panel **c** adapted from REF.[21].

Figure 3 | **Effects of gastroprotectant drugs on the risk of gastrointestinal bleeding** Results of meta-analyses of randomized trials, with each line comparing a particular class of gastroprotectant agents vs placebo or open control, and odds ratios calculated using inverse-variance weighted methods for combining 2x2 contingency tables. Data obtained from Ref.[51]. GPT, gastroprotectant; H2RA, histamine 2 receptor antagonists; PA, prostaglandin analogues; PPI, proton-pump inhibitors.

Figure 4 | **Risk of major coronary events versus risk of bleeding**. Box and whisker plot showing the proportion of people at given levels of predicted risk of major extracranial bleeding (MEB) and predicted risk of major coronary events (MCE), indicating that those individuals at the highest absolute risk of MCE are also at the highest risk of bleeding. Data are from the 2009 ATT Collaboration meta-analysis of 95,000 individuals in six trials of primary prevention of cardiovascular disease [41]. The estimated risk of MCE (nonfatal myocardial infarction or death related to coronary heart disease) and of MEB are plotted for each individual (methods described in REF.[41]) before being organized into four categories of annual risk of MCE (<0.5%; ≥0.5 and <1.0%; ≥1.0 and <1.5%; and ≥1.5%). The box corresponds to the interquartile range and the whisker to the 95% percentile of predicted risk of MEB.

Table 1 | **Guidelines on the use of aspirin in primary prevention of cardiovascular disease**

Organization (year)	**Recommendation**	**Class (level of evidence)**	**REF.**
ACCP (2012)	Suggests the use of low-dose aspirin (75–100 mg daily) in patients aged >50 years over no-aspirin therapy	II (B)	6
ESC/EASD (2013)	Antiplatelet therapy with aspirin in patients with diabetes mellitus at low risk of CVD is not recommended	III (A)	7
	Antiplatelet therapy for primary prevention may be considered in high risk patients with diabetes mellitus on an individual basis	IIb (C)	
ADA (2019)	Aspirin therapy (75–162mg daily) may be considered as a primary prevention strategy in those with diabetes who are at increased risk of CVD, after a discussion with the patient on the benefits versus increased risk of bleeding	C	8
ESC (2016)	Aspirin is not recommended in individuals without CVD owing to the increased risk of major bleeding	III (B)	9
USPSTF (2016)	Recommends initiating low-dose aspirin for the primary prevention of CVD and CRC in adults aged 50–59 years who have a ≥10% 10-year risk of CVD, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years	B	10
	The decision to initiate low-dose aspirin for primary prevention of CVD and CRC in adults aged 60–69 years who have a ≥10% 10-year risk of CVD should be made in an individual basis. People who are not at increased risk of bleeding, have a life expectancy of ≥10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. People who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin therapy	C	
ACC/AHA (2019)	Low-dose aspirin (75–100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults aged 40–70 years who are at higher risk of ASCVD but not at increased risk of bleeding	IIb (A)	11
	Low-dose aspirin (75–100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults aged >70 years	III (B–R)	
	Low-dose aspirin (75–100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding	III (C–LD)	

ACCP, American College of Chest Physicians; ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; CRC, colorectal cancer; CVD, cardiovascular disease; EASD, European Association for the Study of Diabetes; USPSTF, United States Preventive Services Task Force.

Table 2 | **Randomized trials on aspirin versus control in primary prevention of cardiovascular disease**

Trial (publication year)	Comparison	Factorial comparison	Type of participants	Number of participants	Mean follow-up (years)	Primary efficacy outcome	Main bleeding outcome	REF.
British Doctors' Study (1988)	ASA 500 mg versus usual care	Not applicable	Male doctors from the UK	5,139	6	All-cause death: RR 0.88, 95% CI 0.71–1.09, P=NS	Major extracranial bleed: 20/3429 [0.6%] vs 10/1710 [0.6%]; RR 1.00, 99% CI 0.37-2.70	4,41
US PHS (1989)	ASA 325 mg on alternate days versus placebo	β-carotene 50mg alternate days versus placebo	Male doctors aged 40–84 years from the USA	22,071	5	Cardiovascular-related death: RR 0.96, 95% CI 0.60–1.54, P=NS	Major extracranial bleed: 48/11037 [0.4%] vs 30/11,034 [0.3%]; RR 1.59, 99% CI (0.89-2.84)	5,41
ETDRS (1992)	ASA 650 mg versus placebo	Not applicable	Patients with diabetic retinopathy aged 18–70 years	3,711	5	All-cause death: RR 0.91, 99%CI 0.75–1.11; P=0.24	NA	33
HOT (1998)	ASA 75 mg versus placebo	Three blood-pressure lowering regimens	Patients with hypertension aged 50–80 years	18,790	3.8	Major cardiovascular events[a]: RR 0.85; 95% CI 0.73–0.99, P = 0.03	Fatal bleeding events: 7/9,399 [0.1%] vs 8/9,391[0.1 %]; P=NS	32
TPT (1998)	ASA 75mg versus placebo	Warfarin versus placebo	Men aged 45–69 years at high risk of ischaemic heart disease	5,085	6.8 (median)	All ischaemic heart disease (IHD)[b]: proportional reduction 20%, 95% CI 1–35, P = 0.04	Major bleeding events: 20/2,545 [0.8%] vs 13/2,540 [0.5%]; P=NS	38
PPP (2001)	ASA 100 mg versus	Vitamin E versus open	Individuals aged ≥50 years with	4,495	3.6	Serious vascular events[a]: HR	Severe bleeding: 1.1% vs.	37

	open control	control	risk factors for CVD			0.71, 95% CI 0.48–1.04, P=NS	0.3%, P < 0.0008	
Women's Health Study (2005)	ASA 100 mg on alternate days versus placebo	Vitamin E versus placebo	Healthy female health professionals aged ≥45 years	39,876	10.1	Major cardiovascular events[a]: RR 0.91, 95% CI 0.80–1.03, P = 0.13	Gastrointestinal bleeding requiring transfusion: 127/19,934 vs 91/19,942; RR 1.40, 95% CI 1.07-1.83; P=0.02	31
POPADAD (2008)	ASA versus placebo	Antioxidant versus placebo	Patients with diabetes mellitus and low ABI aged ≥40 years	1,276	6.7 (median)	Vascular event or amputation[c]: HR 0.98, 95% CI 0.76–1.26, P = 0.86	Gastrointestinal bleeding: 28/638 [4.4%] aspirin vs 31/638 [4.9%]; P=NS	34
JPAD (2008)	ASA 81 or 100mg versus usual care	Not applicable	Patients with diabetes mellitus aged 30–85 years	2,539	4.4	Atherosclerotic events[d]: HR 0.80, 95% CI 0.58–1.10, P = 0.16	Gastrointestinal bleeding: 12/1262 [1.0%] vs 4/1277 [0.3%]; P=NS	35
AAA (2010)	ASA 100 mg versus placebo	Not applicable	Participants aged 56–75 years with low ABI and no evidence of CVD	3,350	8.2	Major cardiovascular or cerebrovascular events[e]: HR 1.03, 95% CI 0.84–1.27, P=NS	Major haemorrhage requiring hospital admission: HR 1.71, 95% CI 0.99–2.97 P=NS	36
JPPP (2010)	ASA 100 mg versus usual care	Not applicable	Patients with diabetes mellitus, high blood pressure and dyslipidaemia, aged 60–85	14,464	5	Serious vascular events[f]: HR 0.94, 95% CI 0.77–1.15, P = 0.54	Extracranial haemorrhage[g]: HR 1.85, 95% CI 1.22–2.81, P = 0.004	39

			years					
ARRIVE (2018)	ASA 100 mg versus placebo	Not applicable	Individuals aged ≥55 years with CVD risk factors	12, 546	5	Serious vascular events[h]: HR 0.96, 95% CI 0.81–1.13, P = 0.6038	Gastrointestinal bleeding: HR 2.11, 95% CI 1.36–3.28, P = 0.0007	16
ASPREE (2018)	ASA 100 mg versus placebo	Not applicable	Individuals aged ≥70 years without significant morbidity	19,114	4.7	Disability-free survival[i]: HR 1.01, 95% CI 0.92–1.11, P = 0.79	Major haemorrhage: HR 1.38, 95% CI 1.18–1.62, P<0.001	12-14
ASCEND (2018)	ASA 100 mg versus placebo	Fish oil supplementation versus placebo	Patients with diabetes mellitus aged ≥40 years	15,480	7.4	Serious vascular events[j]: rate ratio 0.88, 95% CI 0.79–0.97, P = 0.01	Major bleeding events: rate ratio 1.29, 95% CI 1.09–1.52, P = 0.003	15

The ACCEPT-D trial, which was designed to compare aspirin 100 mg versus usual care among people with diabetes and no evidence of vascular disease who were receiving statin therapy (target *n* = 5,170), has been abandoned and the data are not expected to be available. [a]Nonfatal myocardial infarction (MI), nonfatal stroke or death from cardiovascular cause. [b]Fatal and nonfatal MI and coronary-related death. [c]Death from coronary heart disease or stroke, nonfatal MI or stroke, or above-ankle amputation for critical limb ischaemia. [d]Fatal or nonfatal ischaemic heart disease, fatal or nonfatal stroke, and peripheral artery disease. [e]Fatal or nonfatal coronary event or stroke or revascularization. [f]MI, stroke or transient ischaemic attack (TIA), or vascular-related death excluding any confirmed intracranial haemorrhage.[g] Extracranial haemorrhage requiring hospitalisation or transfusion. [h]MI, stroke, cardiovascular-related death, unstable angina, or TIA. [i]Death from any cause, dementia or persistent physical disability. [j]MI, stroke or TIA, or vascular-related death excluding any confirmed intracranial haemorrhage. ABI, ankle–brachial index; ASA, acetylsalicylic acid; CVD, cardiovascular disease; NA, not available; NS, not significant; RR, relative risk.

Figure 1

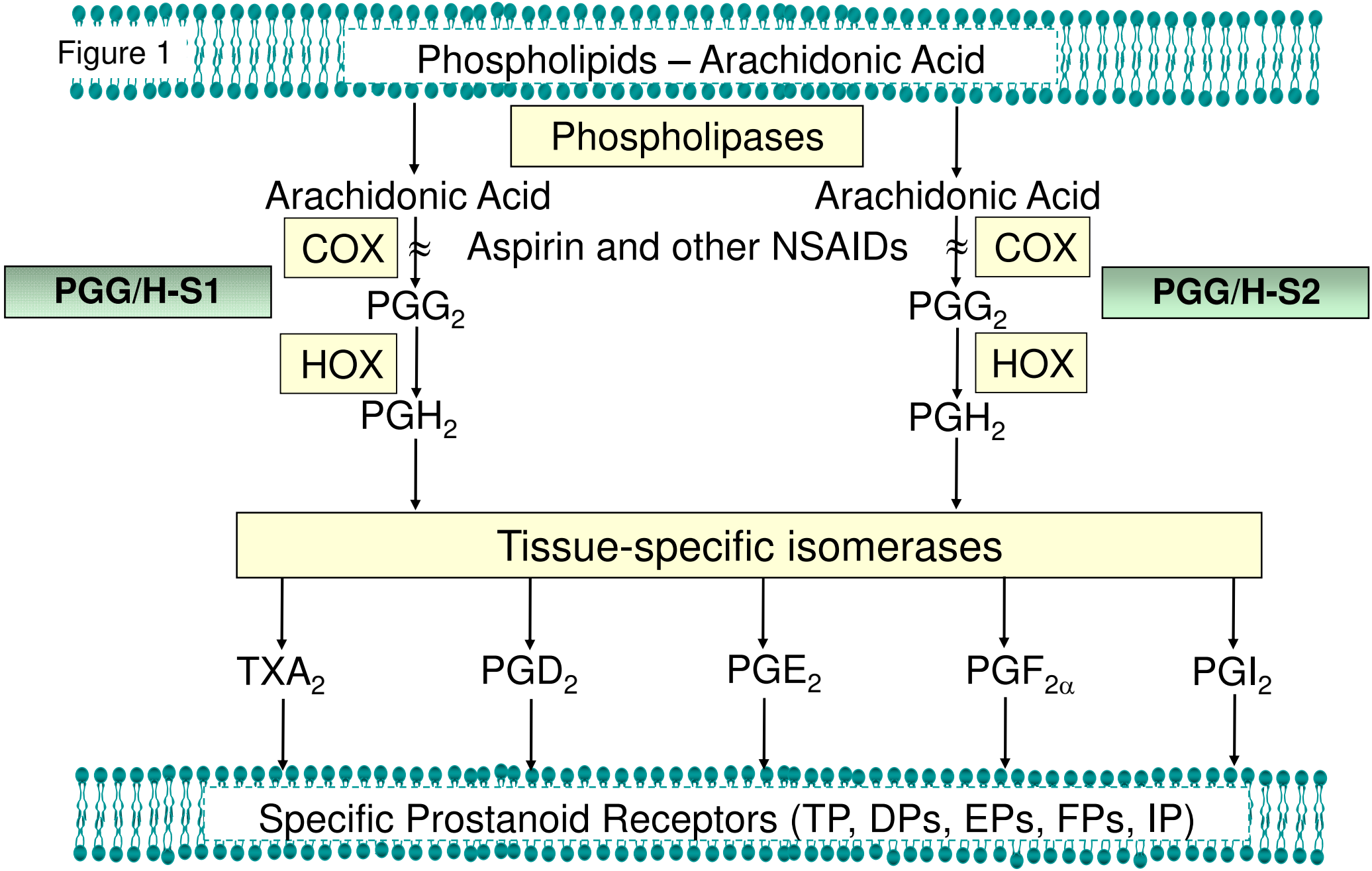
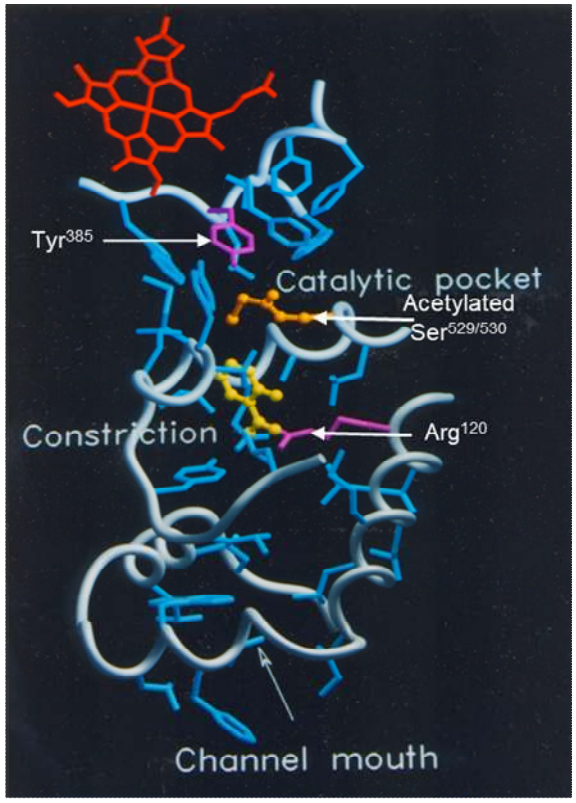
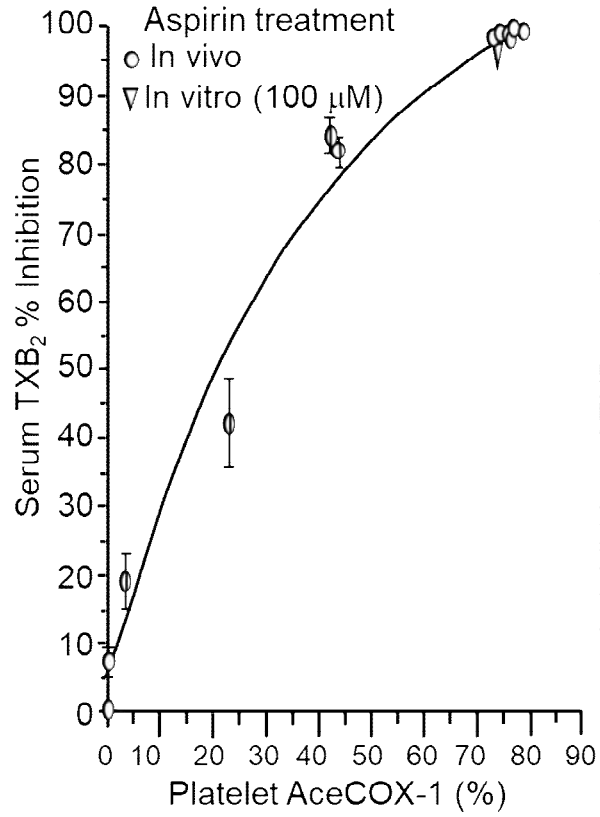

Phospholipids – Arachidonic Acid
Phospholipases
Arachidonic Acid
Arachidonic Acid
COX
≈
Aspirin and other NSAIDs
≈
COX
PGG/H-S1
PGG/H-S2
PGG2
PGG2
HOX
HOX
PGH2
PGH2
Tissue-specific isomerases
TXA2
PGD2
PGE2
PGF2α
PGI2
Specific Prostanoid Receptors (TP, DPs, EPs, FPs, IP)

Figure 2


Tyr385
Catalytic pocket
Acetylated
Ser529/530
Constriction
Arg120
Channel mouth


Aspirin treatment
In vivo
In vitro (100 μM)
Serum TXB2 % Inhibition
Platelet AceCOX-1 (%)
0
10
20
30
40
50
60
70
80
90
100

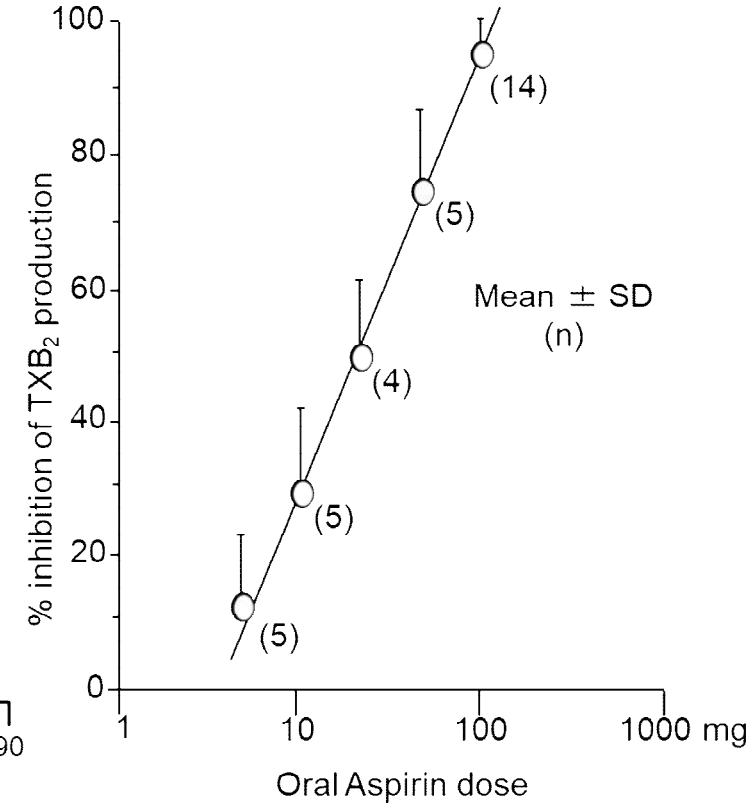

% inhibition of TXB2 production
Oral Aspirin dose
Mean ± SD
(n)
(5)
(5)
(4)
(5)
(14)
1
10
100
1000 mg
0
20
40
60
80
100

Figure 3

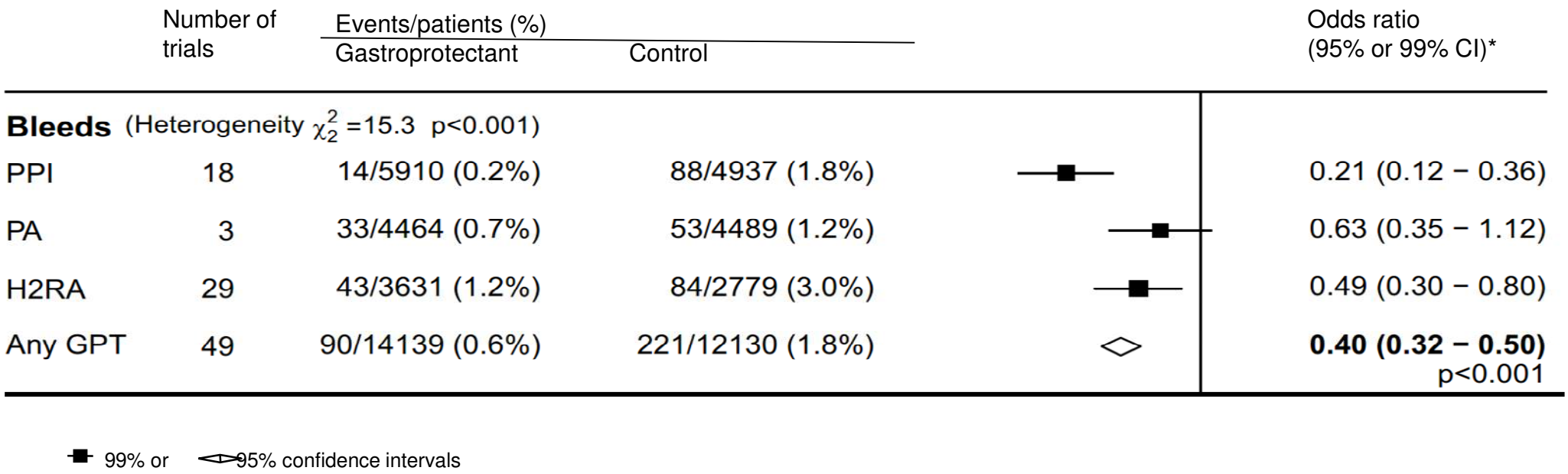
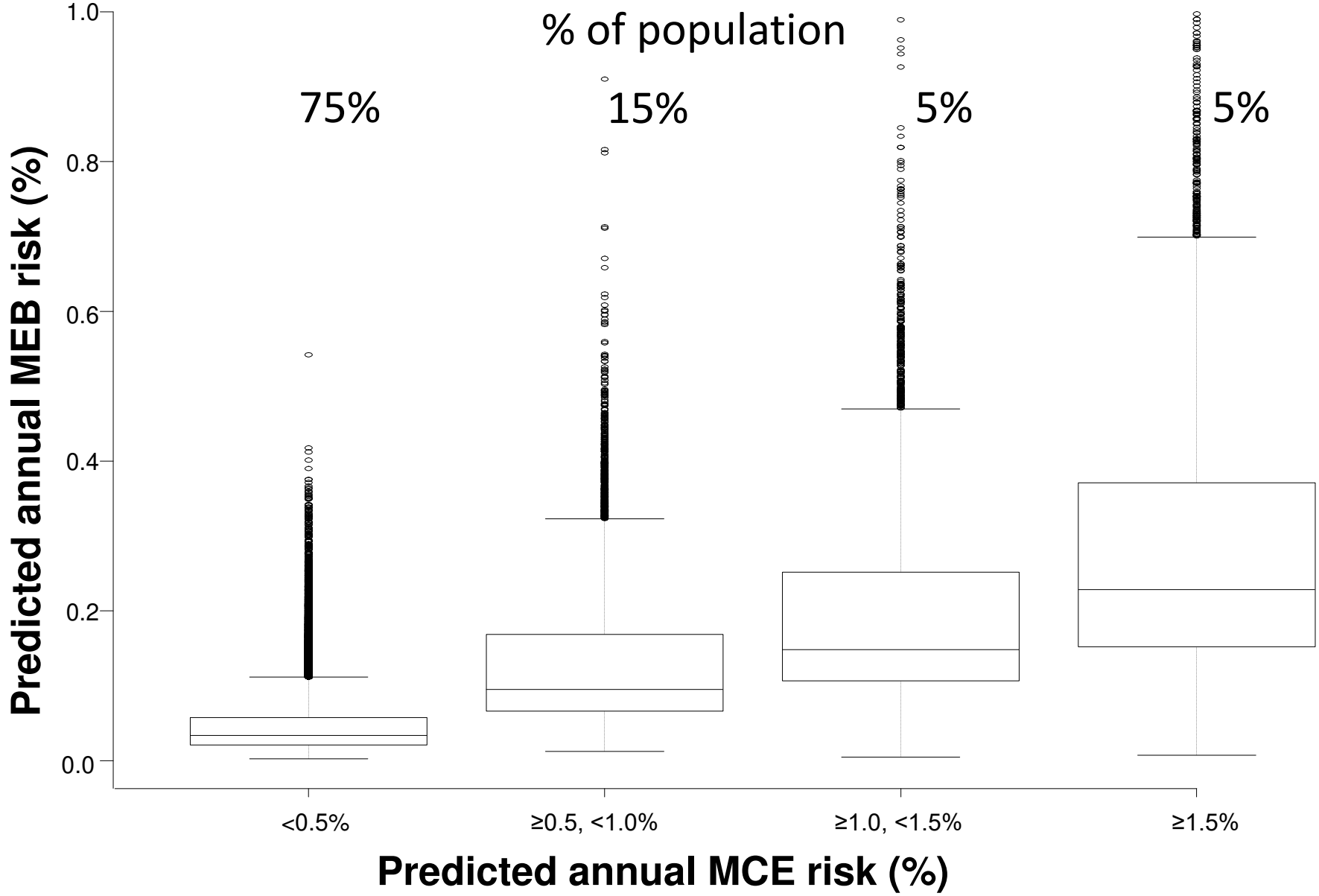

Number of trials
Events/patients (%)
Gastroprotectant
Control
Odds ratio (95% or 99% CI)*
Bleeds (Heterogeneity χ^2_2 =15.3 p<0.001)
PPI 18 14/5910 (0.2%) 88/4937 (1.8%) 0.21 (0.12 − 0.36)
PA 3 33/4464 (0.7%) 53/4489 (1.2%) 0.63 (0.35 − 1.12)
H2RA 29 43/3631 (1.2%) 84/2779 (3.0%) 0.49 (0.30 − 0.80)
Any GPT 49 90/14139 (0.6%) 221/12130 (1.8%) 0.40 (0.32 − 0.50) p<0.001
99% or
95% confidence intervals

Figure 4


% of population
75%
15%
5%
5%
Predicted annual MEB risk (%)
1.0
0.8
0.6
0.4
0.2
0.0
<0.5%
≥0.5, <1.0%
≥1.0, <1.5%
≥1.5%
Predicted annual MCE risk (%)