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IM - REVIEW

# Aspirin in primary prevention: the triumph of clinical judgement over complex equations

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## Abstract

Aspirin, in 2017, has celebrated its 120th birthday. The efficacy and safety of low-dose aspirin in secondary prevention of cardiovascular disease is well supported by many studies, instead in primary prevention it remains controversial, especially in the aftermath of the publication in 2018 of three novel primary prevention randomized clinical trials, showing that the benefit of low-dose aspirin, although additive to that of statin, is counterbalanced by an excess of (mainly gastrointestinal) bleeding events. The signal for a net benefit seems to be even more controversial in the elderly starting aspirin after the age of 70 years. While international guidelines have promptly downgraded their recommendations to more conservative indications, the practicing clinician is called to make the effort to individualize the treatment, after careful evaluation of the haemorrhagic risk vis-a-vis the risk to develop, in the mid-term and long-term follow-up, major cardiovascular events or cancer. This is a particularly complex task, given the different immediate and long-term impact of diverse outcomes on health, the dynamic nature over time of the benefit/risk balance, prompting periodic re-assessments of its indication, and the interindividual variability in aspirin response. The chemopreventive properties of aspirin, anticipated by a large body of epidemiological and mechanistic evidence, are awaiting their final confirmation by the long-term follow-up of the latest trials specifically designed to assess this endpoint, with the expectation to subvert the delicate benefit/risk balance of aspirin in primary prevention. This review is intended to provide an interpretation of past and current evidence to guide clinical decision making on the contemporary patient.

**Keywords** Aspirin · Primary prevention · Clinical trials · Cancer · Aspirin responsiveness

## Abbreviations

| | |
|---|---|
| COX-1 | Cyclooxygenase |
| $TXA_2$ | Thromboxane $A_2$ |
| MI | Myocardial infarction |
| $PGI_2$ | Prostacyclin |
| NNT | Number needed to treat |
| NNH | Number needed to harm |
| ASCVD | Atherosclerotic cardiovascular disease |
| CRC | Colon-rectal cancer |
| DM | Diabetes mellitus |
| NSAIDs | Nonsteroidal antiinflammatory drugs |
| ACS | Acute coronary syndrome |
| GI | Gastrointestinal |
| RCT | Randomized controlled trial |
| EMT | Epithelial mesenchymal transition |

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## Introduction

Aspirin, in 2017, has celebrated its 120th birthday. Aspirin, used in preventing cardiovascular and cerebrovascular diseases, is the most widely prescribed drug all over the world [1].

Historians of medicine have traced its birth in 1897, but the fascinating history of aspirin actually dates back more than 3500 years, when willow bark was used as a painkiller and antipyretic by Sumerians and Egyptians, and then by great physicians from ancient Greece and Rome [1]. Bayer chemist Felix Hoffmann synthesized aspirin in 1897, and 70 years later, the pharmacologist John Vane elucidated its mechanism of action in inhibiting prostaglandin production [1].

In the late 1960s and early 1970s, scientists became more and more interested in the mechanisms of thrombosis, a final common pathway for most acute coronary syndromes. It became apparent that aspirin prolonged the bleeding time, an overall test for primary hemostasis, mostly affected by the status of blood platelets [2].

Low-dose aspirin selectively acetylates the hydroxyl group of a serine residue at position 529 of the cyclooxygenase (COX-1) enzyme, thereby blocking platelet formation of thromboxane $A_2$ ($TXA_2$) [3]. This effect is irreversible because platelets are anucleate and, therefore, unable to resynthesize COX-1. Aspirin's maximal antithrombotic efficacy with the lowest bleeding risk has been recorded at 75–100 mg daily [3].

After ingestion, immediate-release aspirin is completely and rapidly absorbed by passive diffusion across the membranes of the stomach and upper small intestine. The absorption rate depends on dosage form, presence or absence of food, and gastric pH. At variance with the uncoated form, enteric-coated aspirin is erratically absorbed by the gastrointestinal mucosa, resulting in lower bioavailability [3].

Plasma levels peak within 30–40 min of (uncoated formulation) or 3–4 h after (enteric-coated formulation) oral intake. The half-life of aspirin is only 15–20 min, but the antiplatelet effect lasts longer because of the irreversible mechanism of action, which blocks the exposed platelet for its entire lifespan (i.e., 7–10 days) and, therefore, can only be reversed through generation of new platelets. These estimates indicate that aspirin has a rapid onset of effect but a narrow window of opportunity to inhibit circulating platelets.

Along the $TXA_2$ pathway, aspirin inhibits platelet activation and aggregation, two essential steps in the pathophysiology of thrombosis and myocardial infarction (MI). Platelet activation represents a central moment in the process that leads to thrombus formation. When endothelial damage occurs, platelets come into contact with exposed collagen and von Willebrand factor by the receptor complex glycoprotein Ib/V/IX, becoming activated. After the initial adhesion of platelets to the extracellular matrix, the repair process requires a rapid response to autocrine and paracrine mediators, including adenosine diphosphate (ADP), thrombin, epinephrine, and $TXA_2$. These mediators amplify and sustain the initial platelet response, and they recruit circulating platelets from the flowing blood to form a growing hemostatic plug [4].

However, permanent COX-1 inactivation may increase the risk of upper gastrointestinal bleeding through two distinct mechanisms: inhibition of $TXA_2$-mediated platelet aggregation and dose-dependent impairment of prostacyclin ($PGI_2$)-mediated cytoprotection in the gastrointestinal mucosa. The latter increases the risk of bleeding and perforation by promoting new mucosal lesions and worsening existing ones four- to tenfold when aspirin is used at analgesic doses [3].

Antisecretory therapy (i.e., use of proton pump inhibitors) reduces the risk of upper gastrointestinal bleeding [5–7].

Overall, the benefit of low-dose aspirin in patients with acute coronary syndromes or previous MI, stroke, or transient ischaemic attacks is supported by more than 200 studies involving more than 200,000 patients [8]. In patients who are at high risk because they already have occlusive vascular disease, long-term antiplatelet therapy (e.g., with aspirin) reduces the yearly risk of serious vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death) by about a quarter [9, 10]. This decrease typically corresponds to an absolute reduction of about 10–20 per 1000 in the yearly incidence of non-fatal events, and to a smaller, but still definite, reduction in vascular death. Against this benefit, the absolute increase in major gastrointestinal or other major extracranial bleeds is an order of magnitude smaller. Hence, for secondary prevention, the benefits of antiplatelet therapy substantially exceed the risks [9, 10].

Numerous professional societies and governmental agencies recommend the use of 75–100 mg of aspirin in patient subgroups with overt cardiovascular disease with a 10-year risk of myocardial infarction or stroke that exceeds 20% [11, 12]. While consensus exists as to secondary prevention, the benefit–risk ratio is quite more controversial and guidelines less uniform with regard to primary prevention. Moving to clinical practice, a recent report [13] obtained from the prospective REPOSI register held in Italian and Spanish internal medicine and geriatric wards in 2012 and 2014 showed that Italian internists are inappropriately prescribing aspirin in primary prevention in their older multimorbid patients, and that conversely they use this drug sparingly in the frame of secondary prevention, despite the latter being a more appropriate indication.

Given this area of uncertainty and difficulty to draw scientific evidence into clinical practice, our review is intended to provide an interpretation of past and current evidence to guide clinical decision making on the contemporary patient.

## Aspirin in primary prevention of atherothrombosis

The role of aspirin in the primary prevention of myocardial infarction and stroke in groups with a moderate estimated risk of a first cardiovascular event has been controversial, despite 30 years of randomized trials (Table 1) [14].

Six large randomized studies published from 1988 to 2005, included 100,000 participants who contributed 700,000 person-years of follow-up [15–20]. Most of these patients had a 10-year risk of less than 10%. The results of these studies were generally supportive of the use of

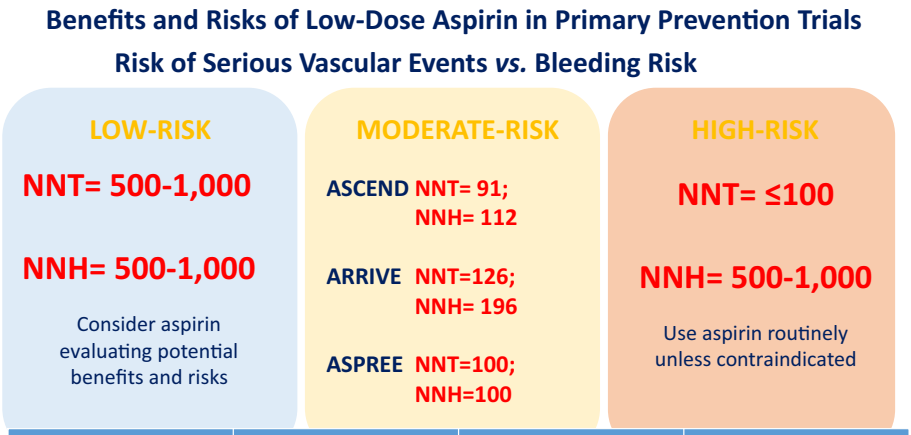
**Table 1** Primary prevention trials of aspirin in diabetes

| Study (years) | Aspirin dose | Follow-up (years) | Number of DM participants | Age range (years) | CHD endpoint | Endpoint event rate (control vs. aspirin) | RR (95% CI) |
|---|---|---|---|---|---|---|---|
| British Medical Doctors (1988) [15] | 500 mg daily | 5.6 | 101 | > 50 | CHD death + nonfatal MI + sudden death | 18.8% vs. 18.8% | 1.00 (0.42–2.40) |
| Physicians' Health Study (1989) [16] | 325 mg alternate days | 5.0 | 533ss | > 40 | Fatal + nonfatal MI | 10.5% vs. 6.2% | 0.59 (0.33–1.06) |
| ETDRS (1992) [83] | 650 mg daily | 5.0 | 3711 | > 18 | Fatal + nonfatal MI | 15.3% vs. 13.0% | 0.85 (0.73–1.00) |
| Thrombosis Prevention Trial (1998) [17] | 75 mg daily | 6.7 | 68 | > 45 | CHD death + nonfatal MI + sudden death | 15.4% vs. 13.8% | 0.90 (0.28–2.89) |
| Hypertension Optimal Treatment Trial (1998) [18] | 75 mg daily | 3.8 | 1501 | > 50 | CHD death + nonfatal MI + sudden death | 3.6% vs. 2.8% | 0.77 (0.44–1.36) |
| Primary Prevention Project (2003) [84] | 100 mg daily | 3.7 | 1031 | > 50 | Fatal + nonfatal MI | 2.0% vs. 1.0% | 0.49 (0.17–1.43) |
| Women's Health Study (2005) [20] | 100 mg alternate days | 10.1 | 1027 | ≥ 45 | Fatal + nonfatal MI | 5.9% vs. 7.9% | 1.34 (0.85–2.12) |
| JPAD (2008) [21] | 81–100 mg daily | 4.4 | 2539 | > 30 | Fatal + nonfatal MI | 1.1% vs. 1.0% | 0.87 (0.40–1.87) |
| POPADAD (2008) [22] | 100 mg daily | 6.7 | 1276 | > 40 | CHD death + nonfatal MI | 12.9% vs. 13.9% | 1.09 (0.82–1.44) |
| JPPP (2014) [24] | 100 mg daily | 5.02 | 4903 | 60–85 | CHD death + Nonfatal MI + nonfatal stroke, | 2.96% vs. 2.72% | 0.95 (0.74–1.23) |
| ASCEND (2018) [29] | 100 mg daily | 7.4 | 15.480 | 63.2 ± 9.2 | MI + stroke or TIA or death from any vascular cause, excluding any confirmed intracranial hemorrhage | 12.1% vs. 10.8% | 0.88 (0.80–0.97) |

*CHD* coronary heart disease, *ETDRS* Early Treatment of Diabetic Retinopathy Study, *JPAD* Japanese primary prevention of atherosclerosis with aspirin for diabetes, *POPADAD* prevention of progression of arterial disease and diabetes, *JPPP* Japanese Primary Prevention Project

75–150 mg aspirin per day to prevent incident myocardial infarction and stroke.

Since 2005, there have been six additional studies of aspirin (81–100 mg daily) in the primary prevention setting; four have been published [21–24]. These studies had less consistent results. In the Antithrombotic Trialists' Collaboration individual-participant meta-analysis of aspirin in primary prevention (95,000 individuals) without previous disease, aspirin was associated with a 12% reduction in major vascular events and a 54% excess of major extracranial bleedings, suggesting an uncertain net value as the reduction in occlusive events needs to be weighed against the increase in major bleeds [8]. This would translate into a similar number needed to treat (NNT) (the number of patients you need to treat to prevent one additional bad outcome) and number needed to harm (NNH) (indicating how many persons on average need to be exposed to the drug over a specific period to cause harm in a person who would not otherwise have been harmed), ranging between 500 and 1000 (Fig. 1). These "magic" numbers and particularly their ratio are powerful and potentially helpful tools in the interpretation of trial results, since they provide us with a rapid estimation of the benefit/risk ratio of a given strategy. In general, treatment should only be considered if NNT < NNH. The large heterogeneity of primary prevention studies included in the meta-analysis, addressing widely different populations of




| TRIAL | NNT | NNH | NNH/NNT |
|---|---|---|---|
| COMPASS | 77 | 83 | 1.07 |
| PEGASUS TIMI 54 | 79 | 106 | 1.34 |
| ASCEND | 91 | 112 | 1.38 |
| ARRIVE | 126 | 196 | 1.55 |
| ASPREE | 100 | 100 | 1 |

**Fig. 1** Benefits and risks of low-dose aspirin in primary prevention trials. Upper panel. Numbers of vascular events avoided and episodes of major bleeding caused per 1000 patients treated with aspirin per year. Number needed to treat (NNT) and number needed to harm (NNH) values are given for subjects in three categories of risk on the basis of randomized controlled trials. Both in modern trials such as ASCEND, and in the recent secondary prevention trials, such as COMPASS and PEGASUS-TIMI 54 (exploring the efficacy and safety of adding rivaroxaban or ticagrelor to aspirin), the magnitude of NNT and NNH and the NNH/NNT ratio is close to one, indicating individual-basis assessment of the benefit/risk ratio. Modified from Patrono C (2017) Cardiovasc Res 113:e61–e63

at-risk subjects, giving different aspirin regimens, with low event rates, should be acknowledged. Moreover, these trials presented a high rate of aspirin discontinuation during the follow-up, were performed before statin era or statin treatment prevalence was not reported, and had different primary endpoints (from as hard as mortality to as soft as a mix of atherosclerotic events). With these limitations in mind, this was the best available evidence until recently, and has been variably interpreted by US and European guidelines, the first recommending low-dose aspirin in primary prevention patients at increased 10-year cardiovascular risk (at least 10%), and without an increased risk of bleeding [25, 26], the second not recommending aspirin in individuals without cardiovascular disease due to the increased risk of major bleeding [12]

Gap of knowledge included assessing the efficacy and safety of aspirin: (1) in the contemporary patient, more extensively treated with antithrombotic strategies other than antiplatelets, such as statins, anti-hypertensives, etc., all significantly reducing the absolute risk of vascular events; (2) in the intermediate risk patient, including patients with diabetes, the elderly, and individuals with an estimated 10-year of cardiovascular disease of 20–30%. The trials A Study of Cardiovascular Events in Diabetes (ASCEND), ASpirin in Reducing Events in the Elderly (ASPREE) and use of Aspirin to Reduce Risk of Initial Vascular Events in patients at moderate risk of cardiovascular disease (ARRIVE) were designed and performed to fill this gap of knowledge (Fig. 1).

## What do new trials add (or do not add)?

The ARRIVE [27] is a randomized, double-blind, placebo-controlled, multicenter trial to assess the efficacy and safety of aspirin among 12,546 subjects at moderate estimated risk of a cardiovascular event. The subjects had no known history of CVD or diabetes and were considered at moderate risk (estimated 10-year risk of major CHD events of 10–20% corresponding to a 10-year CVD risk of 20–30%): men > 55 years with two or more CV risk factors and women > 60 years with three or more CV risk factors. The intervention consisted of 100 mg enteric-coated aspirin daily versus placebo. Median follow-up was 5 years. In the original sample size calculation, it was estimated that 1488 events would provide 91% power to detect a relative risk reduction of 15%, assuming a placebo event rate of 13.4%. Due to lower-than-expected event rates, the protocol was amended from the original event-driven to a time-driven design. Against the expectations based on the anticipated event rate, and cardiovascular disease risk assessment algorithms, the actually observed rate of vascular events was only one-third

of the expected (550 vs. 1488 events) with an observed atherosclerotic cardiovascular disease (ASCVD) event rate normalized to 10 years by 8.43% in the placebo arm and 8.80% in the aspirin arm. In the intention-to-treat analysis, the primary endpoint occurred in 269 (4.3%) patients in the aspirin group versus 281 (4.5%) patients in the placebo group (hazard ratio [HR] 0.96; 95% confidence interval [CI] 0.81–1.13; $p=0.6038$). Gastrointestinal bleeding events occurred in 61 (1.0%) patients in the aspirin group versus 29 (0.5%) in the placebo group (HR 2.11; 95% CI 1.36–3.28; $p=0.0007$). NNT was 126 and NNH was 196 (Fig. 1). When looking at the proportion of the individual components of the primary endpoint in the two treatment arms, findings from ARRIVE are generally consistent with previous primary prevention studies that tended to show aspirin's ability to lower the risk of a first non-fatal myocardial infarction without affecting the risk of total stroke or vascular mortality. Notable is the high number of participants who prematurely terminated the study (approximately a third in both groups). Since crossovers were not tracked and non-compliance to the study allocation (60% of the baseline sample) was only patient-reported, the results of both the intention-to-treat and per-protocol analyses should be interpreted with caution, particularly in the context of their diverging results and lower than anticipated statistical power [28]. Finally, the ARRIVE trial failed to address the primary question for which it was designed, i.e., efficacy and safety of low-dose aspirin in moderate risk patients. This highlights the weakness and over-estimation of current methods to define the 10-year risk of cardiovascular disease, which are still based on historical data, underscoring the need for more reliable and contemporary estimates of cardiovascular risk, based on changes in demographic, lifestyle factors, and management strategies.

ASCEND [29] was performed to assess the efficacy and safety of enteric-coated aspirin 100 mg daily, as compared to placebo, in 15,480 adults who had diabetes mellitus (94% of whom type 2 diabetes, median disease duration, 7 years) without clinically apparent cardiovascular disease. The primary efficacy outcome was the first serious vascular event, i.e., nonfatal myocardial infarction, nonfatal stroke or transient ischaemic attack, or death from any vascular cause (excluding confirmed intracranial hemorrhage). During a mean follow-up of 7.4 years, serious vascular events occurred in a significantly lower percentage of participants in the aspirin group than in the placebo group (658 participants [8.5%] vs. 743 [9.6%]; rate ratio 0.88; 95% CI 0.79–0.97; $p=0.01$), translating into a 12% reduction, the same relative risk reduction as in the Antithrombotic Trialist's Meta-analysis. In contrast, major bleeding events occurred in 314 participants (4.1%) in the aspirin group, as compared with 245 (3.2%) in the placebo group (rate ratio 1.29; 95% CI 1.09–1.52; $p=0.003$), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. This benefit/risk balance was replicated across 5-year estimated and observed vascular risk groups, suggesting that the benefit and hazards of aspirin was largely independent on baseline vascular risk. Incidence of major bleeding events increased with vascular risk. It should be emphasized that the majority of diabetic patients had near-target cardiometabolic control, as reflected by a baseline glycated hemoglobin of 55 mmol/mol. In addition, and in contrast to previous primary prevention trials, there were high rates of use of other preventive strategies, with the majority of ASCEND participants taking statins (75%) and blood-pressure lowering drugs. At variance, near the end of the trial, only about one quarter of participants were receiving proton-pump inhibitors. In such contemporary context, 91 subjects with diabetes would need to be treated to avoid a serious vascular event over a period of 7.4 years (NNT), and 112 to cause a major bleeding event (NNH) (Fig. 1). Thus, low-dose aspirin is effective in the prevention of first cardiovascular events in patients with diabetes, when added on top of currently available cardioprotective strategies. These results also provided high-quality evidence on the efficacy and safety of low-dose aspirin to support or revise current treatment recommendations in this setting [30].

The ASPREE [31–33] trial enrolled 19,114 community-dwelling men and women in Australia and the United States who were 70 years of age or older (or $\geq 65$ years of age among blacks and Hispanics in the United States) and who did not have cardiovascular disease, dementia, or disability at study entry. Participants were randomly assigned to receive 100 mg of enteric-coated aspirin or placebo. The primary endpoint was a composite of death, dementia, or persistent physical disability; secondary end points included major hemorrhage and cardiovascular disease (defined as fatal coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalization for heart failure).

After a median of 4.7 years of follow-up, the rate of the composite of death, dementia, or persistent physical disability was 21.5 events per 1000 person-years in the aspirin group and 21.2 per 1000 person-years in the placebo group (hazard ratio 1.01; 95% confidence interval [CI] 0.92–1.11; $p=0.79$). When dissecting the primary endpoint into the secondary individual endpoints, differences between the aspirin group and the placebo group were significant with regard to death from any cause (12.7 events per 1000 person-years in the aspirin group and 11.1 events per 1000 person-years in the placebo group, hazard ratio 1.14; 95% confidence interval [CI] 1.01–1.29).

Even more surprisingly, cancer was the major contributor to the higher mortality in the aspirin group, accounting for 1.6 excess deaths per 1000 person-years. Cancer-related death occurred in 3.1% of the participants in the aspirin group and in 2.3% of those in the placebo group (hazard

ratio 1.31; 95% CI 1.10–1.56). The increased mortality was observed across cancer types, including CRC, breast, lung, stomach, and esophageal cancers. Notably, "on-treatment" effect of aspirin on cancer mortality, if any, may largely be due to worsened survival among participants with undiagnosed cancers (tumors prevalent at the time of enrollment or early incident tumors) rather than an effect of aspirin on cancer incidence and subsequent mortality.

The rate of cardiovascular disease was 10.7 events per 1000 person-years in the aspirin group and 11.3 events per 1000 person-years in the placebo group (hazard ratio 0.95; 95% CI 0.83–1.08). The rate of major hemorrhage was 8.6 events per 1000 person-years and 6.2 events per 1000 person-years, respectively (hazard ratio 1.38; 95% CI 1.18–1.62; $p < 0.001$). This translated into an NNT and NNH both equal to 100 (Fig. 1).

Overall, the use of low-dose aspirin as a primary prevention strategy in older adults did not prolong disability-free survival over a period of 5 years, and resulted in a significantly higher risk of major hemorrhage and did not result in a significantly lower risk of cardiovascular disease than placebo. Higher all-cause mortality was observed more frequently among apparently healthy older adults who received daily aspirin than placebo and was attributed primarily to cancer-related death.

As stated by the trialists, this result was unexpected in the context of previous studies, and should be interpreted with caution. Indeed, this is the first trial of low-dose aspirin in primary prevention indicating a significant increase in the risk of death in the active group, with the remaining 13 trials indicating a consistent, although non-significant, decrease in all-cause-mortality with aspirin [34].

A number of considerations need to be undertaken.

First, the ASPREE trial has the merit to have enrolled older subjects, usually neglected by the majority of clinical trials. On the other hand, the choice of the primary endpoint is equally inedited, comprising death (an endpoint that low-dose aspirin has never proved to successfully reduce in primary prevention), and dementia, an endpoint which is hardly modulated over a 4.5-year follow-up), and disability, a novel outcome measure during aspirin trials.

Second, at the time of randomization only 11% of the participants in each group had previous regular aspirin use, thus suggesting that the majority of recruited patients were perceived at particularly low risk by the practicing physician. Thus, the trial results do not rule out a favorable effect of aspirin if its administration had been commenced at an earlier age or continued for a longer period of time. Of note, the increase in death was primarily observed among individuals without a prior history of aspirin use and among the Australian cohort, in which the background prevalence of aspirin use was much lower than in the United States. In contrast, among the US cohort (HR 0.79; 95% 0.57–1.11) and among those with a prior history of aspirin use, there was a nonsignificant decrease in deaths (HR 0.86; 95% CI 0.62–1.19).

Third, the rate of adherence to the assigned intervention was 62.1% in the aspirin group and 64.1% in the placebo group in the final year of trial participation.

Fourth and most importantly, no plan for adjustment for multiple comparisons of secondary end points has been performed, seriously flawing the statistical power of the present findings, and raising the risk of false positive results.

The evidence derived from the three recent trials needs to be incorporated into the whole body of evidence accumulated over the last 40 years in the setting of primary prevention.

In a recent meta-analysis [35], including a total of 13 trials randomizing 164,225 participants with 1,050,511 participant-years of follow-up, aspirin use was associated with a significant reduction in the composite cardiovascular outcome compared with no aspirin (HR 0.89, [95% CI 0.84–0.95]; absolute risk reduction 0.38%, [95% CI 0.20–0.55%]; NNT 265), at the cost of an increased risk of major bleeding events (HR 1.43, [95% CI 1.30–1.56]; absolute risk increase 0.47% [95% CI 0.34–0.62%]; NNH 210).

Another recent meta-analysis and trial sequential analysis of randomized controlled trials, in 157,248 subjects from 11 trials without established atherosclerotic disease, examined all-cause mortality as the primary efficacy outcome and major bleeding as the primary safety outcome. After a mean follow-up of 6.6 years, aspirin was not associated with a lower incidence of all-cause mortality [risk ratio (RR) 0.98, 95% CI 0.93–1.02; $p = 0.30$]; however, aspirin was associated with an increased incidence of major bleeding (RR 1.47, 95% CI 1.31–1.65; $p < 0.0001$) and intracranial haemorrhage (RR 1.33, 95% CI 1.13–1.58; $p = 0.001$) [36].

Again, a number of inherent limitations of meta-analyses exists, including the availability and quality of reported data [37], particularly in the diabetes subgroup, endpoint definitions between trials differing depending on contemporary consensus definitions (including definition of myocardial infarction), the total daily doses of aspirin varying in studies from 50 to 500 mg, the short duration of the trials. More importantly, eight trials began randomizing study participants over 20 years ago, with three trials initiating recruitment in the 1970s and 1980s [38, 39]. Thus, the long time frame encompassed by trials in this study, with diagnostic advances and increasing adoption of additional primary prevention strategies, may impair the applicability of the findings from earlier studies to current practice.

The last systematic review published until now [40], including 15 trials, confirmed that aspirin reduced the risk of non-fatal myocardial infarction and stroke, while not reducing significantly the risk of death, and at the cost of increased gastrointestinal and intracranial bleeding. Again,

the short intervention period (median 6.4 years) did not allow to detect any effect on cancer.

Hopefully, a meta-analysis of individual participant data may answer the question whether a statistically significant interaction exists between age and the effect of aspirin on mortality.

## The interindividual variability in the response to aspirin: implications for the optimal dose and dosing regimen

Patients may experience recurrent events while on aspirin as with any other antithrombotic drug. The clinical evidence of treatment failure, which simply reflects the complexity of atherothrombosis, has increasingly feeded the concept of aspirin resistance, further corroborated by the laboratory evidence of less-than-expected inhibition of platelet function [41].

In diabetes, this concept was favored by the pathophysiological evidence of enhanced platelet hyperreactivity/activation in this setting, coupled with the epidemiological evidence of suboptimal response to aspirin in this patients, as emerged in metanalyses of clinical trials over the last years [38].

The vast majority of studies reporting the occurrence of suboptimal response to aspirin in different clinical settings, including DM, have relied on a single measurement of platelet function ex vivo using classic light transmittance aggregation or bedside, whole blood assays, all exhibiting less than ideal intrasubject and intersubject variability and limited sensitivity to the effect of aspirin, not reflecting directly its mechanism of action [39].

In general, the variability of the TX-independent component of the different aggregation signals and the instability of the "resistant" phenotype on repeated measurements, due to large intrasubject coefficient of variation, make platelet function assays unsuitable markers of aspirin responsiveness, reflecting to the best residual platelet reactivity.

In contrast, platelet COX-1, as reflected by serum $TXB_2$ levels, is uniformly and persistently suppressed by aspirin treatment [38].

However, several lines of evidence suggest that an interindividual variability in the response to antiplatelet agents, including aspirin, may exist. The most frequent causes of suboptimal response to aspirin include poor compliance, pharmacodynamic interaction with nonsteroidal antiinflammatory drugs (NSAIDs), pharmacokinetic issues such as prescription of enteric-coated formulations of aspirin or excess fat, due to a larger distribution volume. Adequate bioavailability may be restored by weight loss and/or avoidance of enteric-coated formulations [42].

Mechanisms associated with lower response to aspirin may include: (a) impaired inhibition of COX-1, mainly related to oxidative stress-induced lipid hydroperoxide and peroxynitrite generation; (b) increase in aspirin-insensitive agonists, related to low-grade inflammation, with increased $TXA_2$ formation by platelet or extraplatelet COX-2, cellular COX-1 and/or COX-2, or to oxidative stress, with enhanced TX receptor activation by eicosanoids, such as 8-iso-$PGF_{2\alpha}$; and (c) accelerated recovery of COX-1, due to enhanced platelet turnover [43] (Fig. 2).

In a fraction of both diabetic and non-diabetic patients, accelerated platelet turnover may accelerate platelet COX-1 recovery, allowing $TXA_2$ biosynthesis that escapes aspirin inhibition during the usual 24-h dosing interval [42, 43]. Our and several other groups have suggested that inadequate TX inhibition can be easily measured and corrected by a twice-daily low-dose aspirin regimen [44].

An ongoing clinical trial, Aspirin Twice a Day in Patients with Diabetes and Acute Coronary Syndrome (ANDAMAN) is currently assessing the efficacy and safety of a twice-daily regimen of enteric-coated low-dose aspirin on the occurrence of new ischemic events and bleeding in patients with diabetes and ACS.

Despite a plethora of studies and metanalyses showing that higher doses do not afford greater benefit than doses as low as 75 mg [9], debate remains regarding the optimal dose.

While mechanistic [44] and retrospective observational [46] evidence suggests that obese subjects have lower-than-expected response to aspirin and that higher doses are more effective in these individuals [45–47], this has not been confirmed by prospective, randomized controlled trials during prespecified, subgroup analyses according to body weight (ASCEND) [29], where patients with a body weight less than 75 kg seem to afford less protection from serious vascular events than subjects with body weight above that threshold.

A clinical trial, called Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE) [48], will randomly assign 20,000 subjects with established coronary heart disease to either low dose (81 mg) or high dose (325 mg) [48], screening and enrollment should commence in March 2016; with long-term ascertainment of cardiovascular endpoints and major bleeding, ADAPTABLE is expected to answer the question which dosage of aspirin is best for patients with established cardiovascular disease [48], although, to finally address this issue, a clinical trial should ideally tailor the aspirin dosage based on the bioavailability of the drug, which is strictly dependent on body weight [47].

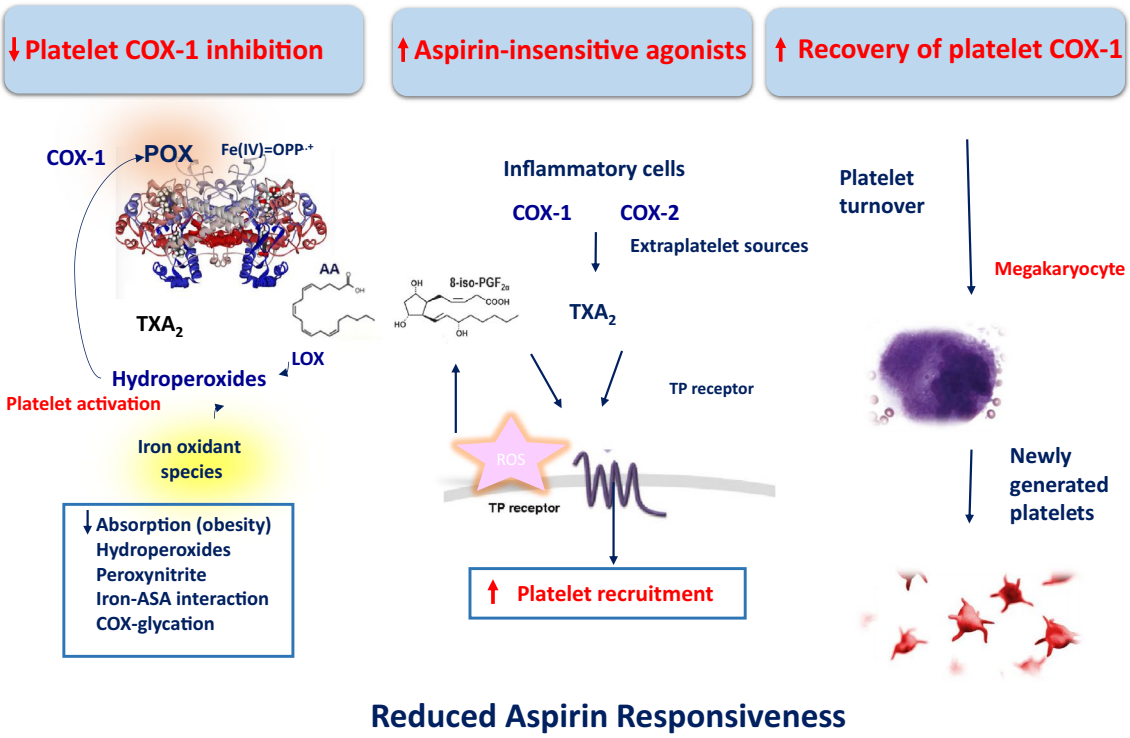



**Fig. 2** The interindividual variability in the response to aspirin. Mechanisms associated with lower response to aspirin include: **a** impaired inhibition of COX-1, mainly related to decreased absorption of the drug (i.e., in the setting of obesity), and to oxidative stress-induced lipid hydroperoxide and peroxynitrite generation, impairing acetylation of COX-1 (reviewed elsewhere, reference 42); **b** increase in aspirin-insensitive agonists, related to low-grade inflammation, with increased $TXA_2$ formation by platelet or extraplatelet COX-2, cellular COX-1 and/or COX-2, or to oxidative stress, with enhanced TX receptor activation by eicosanoids, such as 8-iso-$PGF_{2\alpha}$; and **c** accelerated recovery of COX-1, due to enhanced platelet turnover, allowing $TXA_2$ biosynthesis that escapes aspirin inhibition during the usual 24-h dosing interval. Interaction of hydroperoxides with COX-1 heme-containing peroxidase (POX) at the catalytic site leads to the oxidation of critical COX aminoacid residues resulting in impaired acetylating effects of aspirin

## Recalculating the benefit/risk balance in light of the chemopreventive benefit

At least 4 independent lines of evidence suggest the chemopreventive effect of aspirin against the development of colorectal cancer: numerous observational studies and their meta-analysis [49, 50]; 4 randomized controlled trials (RCTs) in subjects with sporadic colorectal adenomas and a meta-analysis [51]; an RCT of Lynch syndrome with post-trial follow-up [52, 53]; an individual patient data (IPD) meta-analysis of 51 RCTs in the prevention of vascular events [54].

In case–control studies, regular use of aspirin was associated with reduced risk for colorectal cancer (pooled odds ratio [OR] 0.62; 95% confidence interval [CI] 0.58–0.67; $p < 0.0001$; 17 studies), with little heterogeneity in the effect among studies [50]. Similarly, consistent reductions were observed in risks for esophageal, gastric, biliary, and breast cancer. Overall, the largest effects seen in case–control studies were on the risk for gastrointestinal (GI) cancers (OR 0.62; 95% CI 0.55–0.70; $p < 0.0001$; 41 studies) [50].

An important role of COX isozymes, particularly COX-2, in GI carcinogenesis has been hypothesized both from mechanistic studies [55–58] and from epidemiological data [59].

An enhanced biosynthesis of $PGE_2$ plays an important role in tumorigenesis; this prostanoid binds to and activates G protein-coupled EP1-4 receptors, whose signaling can influence the adhesive, migratory, and invasive behavior of cells during the development and progression of cancer [55] and generate a microenvironment that facilitates tumor formation and progression through successful evasion of type I interferon and/or T cell-dependent tumor elimination [56]. In addition, COX-2 expression is markedly elevated in most human colorectal cancer [57]. Consistently, observational and prospective randomized studies suggest an association between the regular use of COX inhibitors (both aspirin, other traditional nonsteroidal antiinflammatory drugs and selective COX-2 inhibitors) and reduced risk for GI (particularly colorectal) cancer [59].

An individual patient data meta-analysis of the 4 aspirin RCTs in approximately 3000 participants with recent histories of sporadic colorectal adenoma (three RCTs) or

large-bowel cancer (1 RCT) demonstrated a 17% relative risk reduction in any adenoma recurrence, and a 28% relative risk reduction in the recurrence of advanced lesions [51], with no apparent dose dependence of the chemopreventive effect within the fourfold range of daily doses used in these trials. In fact, a direct comparison of higher dose (300 or 325 mg/day) versus lower dose (81 or 160 mg/day) aspirin showed significantly greater risk reduction for any adenoma recurrence (the primary endpoint of these analyses) with lower dose aspirin.

Flossmann and Rothwell [60] reported longer-term effects of aspirin on the incidence of cancer among British subjects in two early trials of aspirin for the prevention of CVD and cerebrovascular disease. A post hoc analyses of RCTs for CV prevention revealed that daily aspirin for about 5 years reduced incidence and mortality due to CRC by 30–40% after 20 years of follow-up and reduced the 20-year risk for all-cause cancer mortality by about 20% [61].

Benefit increased with duration of treatment and was consistent across different study populations [61], suggesting a potential effect in reducing the progression of pre-existing cancer and/or metastasis [7].

The results of these studies [54, 60, 61] indicate that the detectable benefits were seen at daily doses as low as 75 mg; the apparent chemopreventive effect of aspirin was saturable at low doses and chemoprevention was apparent in men at high CV risk treated with a 75-mg controlled-release aspirin formulation specifically developed to maximize cumulative inhibition of platelet COX-1 in the pre-hepatic circulation and minimize inhibition of COX-2 in the systemic compartment [62]. Furthermore, in the long-term observational follow-up of the Women's Health Study, the benefit of aspirin on the risk of CRC was observed after 10 years of follow-up with an alternate day 100 mg aspirin. None of these features are compatible with a direct inhibitory effect of low-dose aspirin on COX-2 or with various COX-independent mechanisms that have been proposed. Given aspirin's pharmacokinetics (very short half-life) and pharmacodynamics (relatively selective inhibition of platelet COX-1), any putative effect exerted on a nucleated cellular target would have translated into transient, short acting effects. In fact, a direct inhibitory effect on COX-1-independent pathways of aspirin would explain anticancer effects, but would require supratherapeutic concentrations of the drug, not achievable at low doses. Moreover, transient acetylation of COX-2 can be rapidly reversed by new protein synthesis in proliferating, nucleated cells. Instead, the main characteristics of the chemopreventive effect of aspirin appear to resemble the features of its antiplatelet effect, that is, its long-lasting duration and its saturability at low doses.

Recently, low-dose aspirin has also been shown to acetylate COX-1 in nucleated cells of the intestinal mucosa, thereby reducing local $PGE_2$ production [63].

Overall, one of the main mechanistic hypotheses to explain the efficacy of low-dose aspirin in this setting, is the one that considers platelet activation one of the earlier events of tumorigenesis [64]. The platelet, activated by mucosal injury, may secrete a number of lipid mediators, including the prostanoids thromboxane $A_2$ ($TXA_2$) and prostaglandin $E_2$ ($PGE_2$), angiogenic and antiangiogenic factors, growth factors, proteases and extracellular vesicles containing microRNAs, through which may influence and activate, in turn, the stromal environment inducing a phenotypic switch. For instance, inhibition of COX-1 in platelets by low-dose aspirin may suppress the induction of COX-2 in adjacent nucleated cells of the intestinal mucosa in early-stage neoplasia. Platelet activation at sites of intestinal mucosal injury might trigger downstream signaling events leading to reduced apoptosis, enhanced cellular proliferation and angiogenesis [65].

Platelet inhibition might also be important in later stages of carcinogenesis, as extensive experimental evidence shows that platelets are important, if not essential, in the development of tumor metastases from the bloodstream [66, 67]. The crosstalk between platelets and cancer cells induces a mesenchymal-like phenotype, conferring a high metastatic capacity and the capacity to form aggregates surrounding tumor cells, thus facilitating escape from immune response [68] (Fig. 3).

While the evidence derived from observational studies and retrospective RCT is mounting and continues to produce data in other cancer types, such as hepatocarcinoma or ovary cancer [69, 70], prospective, randomized trials specifically designed to assess aspirin's role in chemoprevention will definitely provide the most robust line of evidence. A randomized factorial trial "Esomeprazole and aspirin in Barrett's oesophagus (AspECT)" [71] has recently reported a reduced incidence of all-cause mortality, esophageal adenocarcinoma or high-grade dysplasia in the arm assigned to both aspirin and esomeprazole.

In ASCEND, ARRIVE, and ASPREE, cancer incidence was a prespecified endpoint, but given the short follow-up, no signal of efficacy has appeared until the end of the trial. The efficacy observed in the WHS after 10 years of follow-up suggests that ongoing, longer follow-up is needed to observe the anticipated effect on cancer. Indeed, in the three trials, the prespecified focus for assessing the effects on cancer is 5 and 10 years after the end of the scheduled intervention phase.

It has been estimated that, even assuming a hypothetical 10% reduction in overall cancer incidence with aspirin, then the absolute benefit of cancer prevention would be at least as large as the CV benefit both in younger and older men and women, and the combined beneficial effects would outnumber the potential harm by a factor of 3–5 [65].

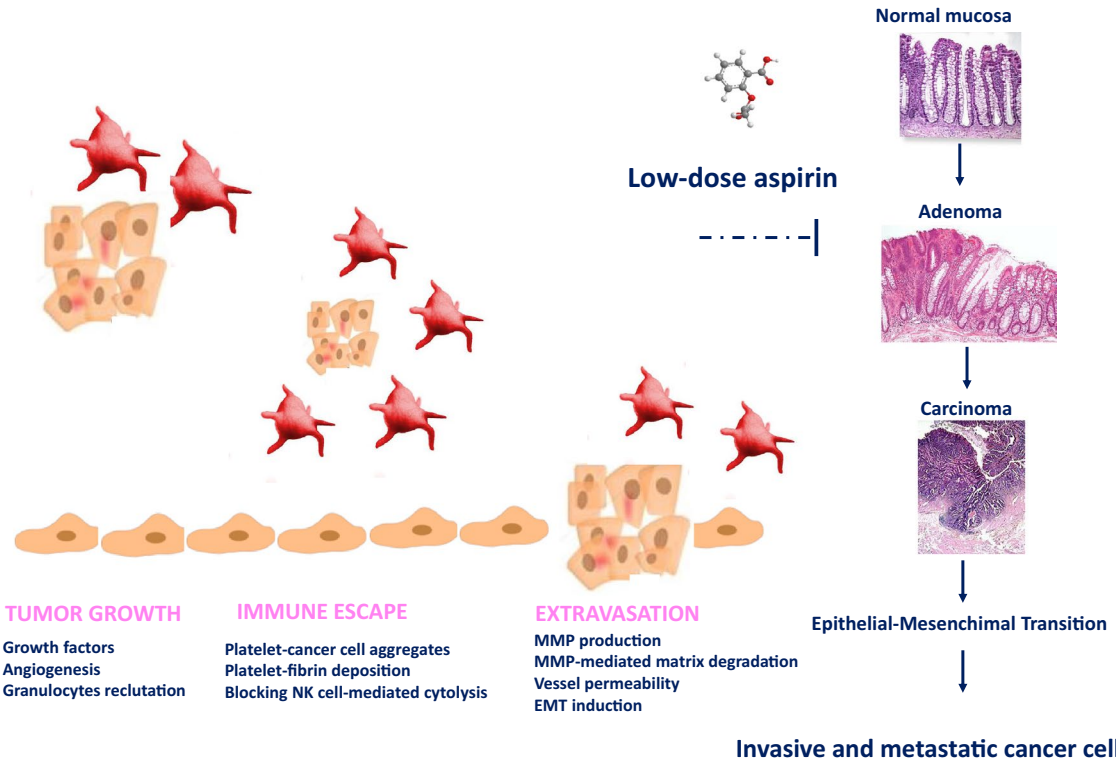



**Fig. 3** The crosstalk between platelets and cancer cells. Platelets have been involved in the mechanisms leading to carcinogenesis, tumor growth, tumor angiogenesis, and tumor metastasis. Platelets can attach to cancer cells, leading to platelet-cancer cell congregates generation, and fibrin stratification around cancer cells, whereby improving tumor cells to avoid immune response. Cell binding to endothelial cells is increased by platelets through selectin-dependent tethering/rolling and integrin-dependent adhesion. Platelets are implicated in basement membrane exposure and metastatization, by increasing matrix metalloproteinases (MMP)-mediated degradation of extracellular matrix. In the end, platelet may foster an endothelial–mesenchymal transition (EMT), thus leading to transformation of cancer cells toward an invasive mesenchymal-like phenotype, with enhanced expression of mesenchymal makers, transcription factors and MMPs, conferring a high metastatic capacity. Inhibition of COX-1 in platelets by low-dose aspirin may suppress the induction of COX-2 in adjacent nucleated cells of the intestinal mucosa in early stage neoplasia, as well as the detrimental effects of platelets on tumor growth, immune escape, EMT and extravasation

## Current guidelines

Guidelines recommendations have progressively been downgraded over the past 20 years (Table 2). In 2016, the US Preventive Services Task Force (USPSTF) issued updated recommendations for the use of low-dose aspirin for primary prevention of CVD and colorectal cancer (CRC) [72–74].

These guidelines incorporated findings from meta-analyses of primary prevention trials, suggesting that the CV benefits of aspirin began within the first 5 years of therapy, whereas the decrease in CRC mortality rates was not seen until after 10 years of therapy [25].

After performing a decision analysis with use of a microsimulation model, the USPSTF made a class B recommendation for adults aged 50–59 years who have a 10% or greater 10-year CVD risk, 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.[25].

The CVD prevention guidelines from the European Society of Cardiology already included in 2016 a class III recommendation, stating that "antiplatelet therapy is not recommended in individuals without CVD due to increased risk of major bleeding" [12].

After the publication of the three novel trials, both American and British guidelines have been updated. The 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease provided a weak Class IIb recommendations for adults 40–70 years of age who are at higher ASCVD risk but not at increased bleeding risk, advising against aspirin among adults > 70 years of age [75].

The 2019 British NICE guidelines remind readers that aspirin is not licensed for the primary prevention of CVD and that people can reduce their CVD risk by other means such as smoking cessation or taking at statin. The guidelines emphasize "if aspirin is being considered, discuss the likely benefits and risks with the person" [41].

**Table 2** Summary of current guidelines on aspirin in primary cardiovascular prevention

| | Guideline | Recommendation |
|---|---|---|
| 2016 | USPSTF | Recommend low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, 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 (grade B) |
| 2016 | ESC | Recommend against initiating aspirin in individuals without overt cardiovascular disease (class III) |
| 2016 | EASD | Antiplatelet therapy (e.g., with aspirin) is not recommended for people with DM who do not have CVD (class IIIA) |
| 2019 | AHA/ACC | Recommend against aspirin in individuals older than 70 years and provide a weak recommendation (class IIb) that aspirin might be considered among adults aged 40–70 years |
| 2019 | NICE | Recommend against aspirin for the primary prevention of CVD. Consider prescribing aspirin in people with a high risk of stroke or myocardial infarction |
| 2019 | ADA | Recommend aspirin therapy (75–162 mg/day) for primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a discussion with the patient on the benefits versus increased risk of bleeding. Aspirin is not recommended for those at low risk of ASCVD (such as men and women aged ≤ 50 years with diabetes with no other major ASCVD risk factors) as the low benefit is likely to be outweighed by the risks of bleeding |

*USPSTF* US Preventive Services Task Force, *AHA* American Heart Association, *ESC* European Society of Cardiology, *ADA* American Diabetes Association, *ACC* American College of Cardiology, *NICE* National Institute for Health and Care Excellence, *CVD* cardiovascular disease, *CRC* colo-rectal cancer, *ASCVD* atherosclerotic vascular disease

Similarly, the ADA guidelines in Diabetes downgraded their recommendations to more conservative indications based on ASCVD risk [30] (Table 2).

In the EASD, European Guidelines on cardiovascular disease prevention in clinical practice antiplatelet therapy (e.g., with aspirin) is not recommended for people with DM who do not have CVD (Class IIIA) [12].

Thus, for primary prevention, according to the majority of guidelines, the use of aspirin needs to be carefully considered and may generally not be recommended. Aspirin may be considered in the context of high cardiovascular risk with low bleeding risk, but generally not in older adults.

## Conclusions

Given its long and outstanding career, aspirin has been widely prescribed in the past, and physicians tend to feel very confident with its use. In this scenario of great enthusiasm, the message conveyed by the recently published trials risks to be misinterpreted on the opposite side, and demonize the prescription of a drug that, despite being a centenarian, continues to be the object of intensive research interest. On the other hand, clinical practice needs to be strictly evidence-based. Similarly to what observed in recent secondary prevention trials, such as COMPASS [76] and PEGASUS-TIMI-54 [77] where the clinical question is to add a second strategy (rivaroxaban or ticagrelor) on top of aspirin, modern primary prevention trials such as ASCEND show relatively low NNT and NNH, with NNH to NNT ratio close to 1 (Fig. 1). While low values suggest that treatment is worthwhile, the ratio close to 1 makes this choice a challenging one, prompting individual-basis assessment also considering the patient preference. Thus, using aspirin in primary prevention settings requires the effort to individualize the treatment, after careful evaluation of the hemorrhagic risk vis-a-vis the risk to develop, in the mid-term and long-term follow-up, major cardiovascular events or cancer. Since this is a delicate and dynamic balance, the practicing physician should periodically reassess the risk through a careful examination of the patient's history, both on the cardiovascular, bleeding and cancer side [78].

To facilitate this task, a new app for mobile phones has been developed (Aspirin-Guide decision support tool), which calculates the ischaemic risk and the hemorrhagic risk according to diagnostic algorithms which consider the 'number needed to treat and to harm' derived from the literature, and then provides the 10 years risk of cardiovascular events according to age and gender of the patient, and also considering the potential benefit in prevention of colorectal cancer [79]. Unfortunately, this would result in excessive simplification, given the different immediate and long-term impact of diverse outcomes on health. In addition, the single patient may prefer to avoid a thrombotic vs. a bleeding event, or vice versa.

Overall, the recent contribution of the ARRIVE, ASCEND and ASPREE trials provides useful insight into the role of aspirin use for primary prevention in the modern era (Table 3). At least in diabetes, the use of aspirin is associated with a 12% decrease in the rate of serious vascular events; this benefit, however, came at the cost of a 29% increase in the rate of major bleeding events. Notably, aspirin did reduce vascular events in diabetic patients, three quarters of whom already on statin treatment, suggesting that the benefit of aspirin is additive to that of statins, and, therefore, the rationale for its use remains solid in these populations [34, 80].

**Table 3** Tips for the practicing physician

| Tips for the practicing physician |
|---|
| **What I learned about aspirin from newer evidence** |
| Overall, in primary prevention aspirin reduces serious vascular events by about 12% |
| CV risk calculators are not adequate to estimate CV risk and need to be updated |
| Contemporary primary prevention population has an absolute risk lower than the past |
| We should consider preventing optimally the bleeding risk as we are optimally fighting the thrombotic risk |
| The chemopreventive effect can shift the balance towards a net clinical benefit. Longer follow-up of prospective studies is warranted |
| Aspirin poor response may occur in a fraction of both diabetic and non-diabetic individuals |
| **What will I do tomorrow morning with my primary prevention patient?** |
| I will optimize GI bleed prevention, in addition to aggressive thrombotic risk prevention |
| I will periodically reassess history of GI bleeding or use of drugs affecting hemostasis |
| I will revise history and risk factors for cancer |
| I will not discontinue ongoing aspirin treatment on a routine basis |
| I will prefer to start treatment in the younger person over the elderly |
| I will discuss with the patient potential benefits and risks of antiplatelet therapy |

Interestingly, the extent of the efficacy of aspirin was independent of the estimated event risk of the diabetic population, based on CV risk algorithms. However, in the calculation of the absolute thrombotic risk, even the ASCEND trial made no mention to organ damage, such as microalbuminuria, left ventricular hypertrophy, ankle–brachial index, intimal media thickness, which enhance per se the risk of cardiovascular events, regardless of risk scores, and should be accounted for when computing the thrombotic risk of our individual patient. Tools for more accurate risk assessment could be used to identify the subjects at the highest risk to guide the deployment of preventive measures such as aspirin. Novel imaging modalities for the estimation of coronary inflammation and the residual inflammatory risk, such as perivascular fat attenuation index by standard coronary computed tomography angiography, may have a role in the risk stratification for coronary events, as recently suggested by the CRISP CT study [81].

Based on the ASPREE, the elderly subject over 70 who has never taken antiplatelet agents until now (over 90% of subjects in the trial), should not routinely been initiated to aspirin prophylaxis. No information can be derived on the typical patient with long-standing ongoing aspirin use, asking the physician: "Should I keep taking an aspirin a day?". In a Swedish Nationwide, Population-Based Cohort Study [82], collecting 62,690 cardiovascular events during a median of 3.0 years of follow-up, discontinuation of low-dose aspirin in the absence of major surgery or bleeding was associated with a > 30% increased risk of cardiovascular events. Moreover, the potential benefit associated with long-term aspirin use in the setting of chemoprevention should be weighted against the increase bleeding risk.

In patients receiving aspirin-based antiplatelet treatment without routine PPI use, the long-term risk of major bleeding was higher and more sustained in older patients in practice than in the younger patients in previous trials, with a substantial risk of disabling or fatal upper gastrointestinal bleeding. Given that half of the major bleeds in patients aged 75 years or older are upper gastrointestinal, the estimated NNT for routine PPI use to prevent such bleeds is low, and co-prescription should be encouraged especially in this age group [7]. *Helicobacter pylori* eradication may be an additional strategy to mitigate bleeding in patients at risk.

Thus, until clarifying whether the unexpected result of the ASPREE is reliable or the consequence of the play of chance, we should cautiously consider the initiation of aspirin in the elderly, and re-evaluate its indication in the long-standing user over 70 years of age, considering and reassessing over time his/her individual benefit-risk balance, including the chemopreventive effect in this equation. Individual participant meta-analysis including the most recent trials is also expected to solve the question whether an interaction exists between age and the benefit of aspirin.

Furthermore, long-term observational follow-up of populations enrolled in trials, regardless of maintaining or withdrawing aspirin treatment after the end of the trial, may unveil whether the reduced relative risk of serious vascular events may translate into benefits on mortality or disability over the long run.

Finally, an interindividual variability in the response to aspirin exists, leading to a suboptimal response to aspirin at least in a fraction of patients. This may account for a dilution effect in the efficacy (and safety?) of low-dose aspirin. Strategies to overcome this issue are under investigation and may in the future, further subvert our current knowledge on the efficacy of aspirin in primary prevention.

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## Compliance with ethical standards

**Conflict of interest** FS has received lecture fees from Bayer.

**Statements on human and animal rights** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** For this study, formal consent was not required.

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