REVIEW ARTICLE

Aspirin for primary cardiovascular prevention: why the wonder drug should not be precipitously dismissed

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ABSTRACT

Primary cardiovascular prevention is the combined set of actions aimed at reducing the likelihood of symptomatic atherosclerotic disease or major adverse cardiovascular events (MACEs) in currently asymptomatic individuals. Older studies on aspirin for primary prevention were positive or neutral as to the primary ischemic endpoint (often represented by MACE), but the reduction in nonfatal ischemic events seemed largely counterbalanced by an increase in bleeding events. The 3 latest large randomized controlled trials on aspirin in primary prevention, all published in 2018, reached basically similar conclusions, leading to an intense debate on whether aspirin therapy is warranted in asymptomatic patients and whether there are subgroups that may benefit. In the present review, we provide an overview of the available evidence on aspirin for primary cardiovascular prevention, focusing on the results of meta-analyses and on strengths and pitfalls of meta-analytic assessments. Based on a meta-regression of the benefits and harm of aspirin therapy in primary prevention as a function of the 10-year risk of MACE, which is an alternative type of pooled analysis of available evidence, we propose a treatment algorithm acknowledging differences among patients and emphasizing the need for an individualized assessment of benefits and risks. Following general preventive measures (physical exercise, smoking cessation, treatment of hypertension and hypercholesterolemia, etc), a tailored approach to aspirin prescription is warranted. When patients are younger than 70 years of age, clinicians should assess the 10-year cardiovascular risk: when such risk is high and bleeding risk is low, aspirin treatment should still be considered, also taking patients' preferences into account.

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Introduction Cardiovascular disease is the leading cause of morbidity and mortality worldwide. This justifies the continuing search for optimal strategies in primary and secondary cardiovascular prevention. Primary cardiovascular prevention is the combined set of actions aimed at reducing the likelihood of symptomatic atherosclerotic disease or major adverse cardiovascular events (MACEs), while secondary prevention consists in limiting the probability of new events in patients with symptoms or prior MACE. Aspirin inhibits platelet activation elicited by acute plaque complications, thus blocking the very first step of the thrombogenic cascade. The drawback of aspirin therapy, as for any antithrombotic drug, is the increased risk of bleeding, ranging from trivial to potentially life-threatening. Assessing the balance between the reduction of MACE and the increase in bleeding is then crucial to establish whether aspirin should be prescribed for primary and secondary cardiovascular prevention.

It is reasonable to assume that the higher the likelihood of cardiovascular events, the greater the expected absolute benefit from aspirin. We may also speculate that the benefit of aspirin therapy would have been more evident in the past decades when the risk for MACE was higher than now due to a much less intensive control of cardiovascular risk factors and less effective antithrombotic strategies. Yet, it is worth remembering that

6 trials on aspirin for secondary prevention carried out back in the 1970s provided at that time limited and conflicting information on benefit from aspirin when taken individually.[1-6] The benefit from aspirin therapy indeed became clear only when these trials were pooled together in the first meta-analysis in the cardiovascular field. In detail, among over 10 000 patients with previous myocardial infarction (MI), those randomized to aspirin had a lower risk of all-cause and cardiovascular death, less frequent stroke, and a 21% lower risk of reinfarction compared with placebo. Aspirin also increased the risk of bleeding, although very high doses (up to 1000 mg/d), increasing the risk of gastrointestinal (GI) bleeding more than lower doses, were frequently used in older trials.[7,8] In a more recent meta-analysis including 16 trials and 17 000 patients, aspirin allocation was associated with a reduction of about one-fifth in the total number of strokes ($P = 0.002$) and coronary events ($P < 0.001$), and a nonsignificant increase in hemorrhagic stroke, with similar effects in men and women.[9]

In the setting of primary prevention, however, the balance between benefit and risk is expected to be less favorable because the background risk of events, and hence the absolute benefit expected from aspirin, is generally 1 order of magnitude lower than in secondary prevention.[9] Indeed, the studies carried out since the early 1990s yielded either positive or neutral results as to ischemic end points, but this seemed largely counterbalanced by an increase in bleeds. The 3 latest trials on aspirin for primary prevention published in 2018 reached basically similar conclusions,[10-14] leading to a widespread broad negation of the role of aspirin in asymptomatic patients, and also shedding doubts as to whether some patient subgroups may benefit from its use.

In the present review, we provide an overview of the available evidence on aspirin in primary cardiovascular prevention, focusing on the results from meta-analyses and on their strengths and potential pitfalls. We will then propose an algorithm for clinical decision making based on a different type of pooled analysis of the available evidence. We will then explain the rationale for the assessment based on the "weighed net clinical benefit." Such approaches should prove more useful than the classic meta-analytic evaluations performed so far and help in clinical decisions in individual patients.

The Antithrombotic Trialists' Collaboration In 2009, the results of a meta-analysis of individual participant data from 6 large trials of aspirin in primary prevention (together with the already mentioned 16 available trials in secondary prevention) were published.[9] Trials in primary prevention included a total of 95 000 patients, 3554 MACEs, and over 660 000 person-years exposure to the drug. Allocation to aspirin yielded a 12% relative reduction in MACE (0.51% aspirin vs 0.57% control per year; $P < 0.001$), mainly due to a 20% relative reduction in the risk of nonfatal MI (0.18% vs 0.23% per year; $P < 0.001$). Men and women seemed to achieve similar benefit. Aspirin did not reduce the incidence of ischemic stroke (0.16% vs 0.18% per year; $P = 0.08$) or cardiovascular mortality (0.19% vs 0.19% per year; $P = 0.7$). Allocation to aspirin was associated with slightly higher rates of hemorrhagic stroke (0.04% vs 0.03%; $P = 0.05$), and definitely higher rates of major extracranial bleeds (0.10% vs 0.07% per year; $P < 0.001$).

While this meta-analysis is certainly to be praised for its attempt to assess efficacy and safety of aspirin with a patient-level approach, several methodological issues should be pointed out in drawing firm conclusions. First, the primary prevention setting was defined as the absence of "any history of occlusive disease,"[9] instead of the absence of symptoms of atherosclerotic disease or prior cardiovascular events. Second, the studies included (British Doctors' Study,[15] United States Physicians' Health Study,[16] Thrombosis Prevention Trial,[17] Hypertension Optimal Treatment Trial,[18] Women's Health Study)[19] differed widely with respect to the number of participants, target populations, aspirin regimens, the presence of a placebo arm, follow-up durations, and dates of recruitment and follow-up, which ranged from 1978 to 2005.[9] This reflects the extreme degree of heterogeneity of the primary prevention setting, which is matched by an equally large variability of cardiovascular risk, in turn possibly affecting the possibility of demonstrating benefit from aspirin therapy. Third, the Antithrombotic Trialists' Collaboration selected studies with "at least 1000 nondiabetic participants with at least 2 years of scheduled treatment."[9] Although this was probably due to the fact that individual participants' data were available only from the trials there included, it differs from the exclusion criteria of other meta-analyses,[20,21] which reflects the different perception of what primary prevention really is or attempts at limiting the heterogeneity among studies. Nonetheless, such exclusions limited the total population size, possibly reducing the likelihood that a small prognostic benefit from aspirin attained a statistical significance. Similarly, assessment of benefits and risks in subgroups (men vs women, diabetic vs nondiabetic patients, different aspirin doses, etc) may have been affected by even smaller sample sizes.

Influence of weight on aspirin benefit: the minefield of subgroup analyses Just before the publication of the 3 latest megatrials on aspirin for primary prevention in 2018,[10-14] a new meta-analysis of data so far available in primary cardiovascular prevention sparked additional interest in this issue. Rothwell et al[22] used individual patient data from 10 trials (including 117 279 participants) to assess the effects of low-dose aspirin (75–100 mg daily or 100 g on alternate days) and higher dose aspirin (300–325 mg or ≥500 mg daily) across categories of body weight and height, after stratification by

age, sex, and cardiovascular risk factors. The authors found that low-dose aspirin reduced cardiovascular events in patients weighing 50 to 69 kg (hazard ratio [HR], 0.75; 95% CI, 0.65–0.85), but not in those weighing 70 kg or more (HR, 0.95; 95% CI, 0.86–1.04). Low-dose aspirin apparently also reduced all-cause death and the composite of all-cause death or cardiovascular events in the 50 to 69 kg category, but not in patients weighing more. By contrast, daily aspirin doses of 300 mg or more reduced cardiovascular events only in patients weighing more than 90 kg. Based on these findings alone, one may postulate that no benefit from aspirin therapy had emerged so far because of aspirin underdosing in most cases. This conclusion is at odds with the prevailing notion that higher aspirin doses do not achieve greater antiplatelet inhibition than lower doses, but simply increase the risk of adverse effects, such as GI bleeding. Additionally, the risk of bleeding on low-dose aspirin in patients weighing 70 kg or more tended to be higher than in those weighing 70 to 79 kg and 80 to 89 kg, which is unexpected if aspirin was underdosed in heavier patients. For patients on high-dose aspirin, those weighing less should be expected to have higher rates of bleeding, and vice versa; on the contrary, patients weighing 90 to 99 kg had the highest bleeding risk and those weighing 60 to 69 kg had a risk similar to placebo. For this analysis, studies on primary prevention were pooled together with those on secondary prevention of stroke, and the primary prevention setting was not considered separately. Additionally, while epidemiologic evidence indicates that regular and long-term use of aspirin is associated with a lower incidence of colorectal cancer,[23] in this meta-analysis, an increase in cancer risk emerged in some patient subgroups, most notably those aged 70 years or older and weighing less than 70 kg. The risk of cancer was apparently particularly high in diabetic women younger than 50 years at baseline, partially due to an increased incidence of breast cancer.[22]

The influence of weight on aspirin efficacy, the increased risk of cancer, and other unexpected findings all derive from subgroup analyses. One should exert great caution when interpreting such results, which have the limits of meta-analyses involving disparate patient subgroups, increasing the likelihood of chance findings.

Older trials pooled with the ARRIVE, ASCEND, and ASPREE studies The ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events),[10] ASCEND (A Study of Cardiovascular Events in Diabetes),[11] and ASPREE (Aspirin in Reducing Events in the Elderly)[12-14] trials have been discussed in detail in recent authoritative reviews, to which the reader is referred.[24,25] The results of these studies, summarized in TABLE 1, have been pooled together with previous studies. In commenting the overall evidence in primary cardiovascular prevention, Ridker[26] observed that no trial has ever shown a mortality benefit, and a net benefit on hard clinical endpoint is unlikely to emerge in an era when the approach to primary cardiovascular prevention is increasingly aggressive. A subsequent meta-analysis yet evaluated 11 trials with 157 248 individuals, excluding studies that enrolled subjects with evidence of subclinical vascular disease, such as a reduced ankle brachial index.[20] At a mean follow-up of 6.6 years, aspirin was indeed not associated with a lower incidence of all-cause death (relative risk [RR], 0.98; 95% CI, 0.93–1.02; $P = 0.30$), but was associated with a higher incidence of major bleeding (RR, 1.47; 95% CI, 1.31–1.65; $P < 0.001$) and intracranial hemorrhage (RR, 1.33; 95% CI, 1.13–1.58; $P = 0.001$). A similar effect on all-cause mortality and major bleeding was demonstrated in patients with diabetes and those deemed at high cardiovascular risk (here defined as those with a 10-year risk >7.5%). Aspirin was associated, however, with a lower incidence of MI (RR, 0.82; 95% CI, 0.71–0.94; $P = 0.006$), although this effect had not been found to a significant extent in the most recent trials.[20]

A broader definition of primary prevention ("participants without known preexisting cardiovascular disease") was used in another meta-analysis,[27] which led to the inclusion of trials with asymptomatic peripheral or aortic atherosclerotic disease, such as the POPADAD (Prevention of Progression of Arterial Disease and Diabetes)[28] and AAA (Aspirin for Asymptomatic Atherosclerosis) trials.[29] A total of 13 trials randomizing 164 225 participants with a median baseline 10-year risk of the primary cardiovascular outcome of 9.2% (range, 2.6%–15.9%) were included. Aspirin use was associated with significant reductions in the primary cardiovascular outcome (a composite of cardiovascular death, nonfatal MI, and nonfatal stroke) compared with no aspirin (hazard ratio [HR], 0.89; 95% CI, 0.84–0.95), with a number needed to treat of 265. The use of aspirin was not associated with a lower all-cause mortality rate (HR, 0.94; 95% CI, 0.88–1.01) or cardiovascular mortality rate (HR, 0.94; 95% CI, 0.83–1.05) compared with no aspirin. Furthermore, the use of aspirin was associated with reduction in MI (HR, 0.85; 95% CI, 0.73–0.99) and ischemic stroke (HR, 0.81; 95% CI, 0.76–0.87). Aspirin use was, however, also associated with an increased risk of major bleeding (HR, 1.43; 95% CI, 1.30–1.56), with a number needed to harm of 210.[27]

The efficacy and safety of aspirin in patients with diabetes were evaluated in a dedicated meta-analysis, considering data from 10 trials and 33 679 patients.[30] Aspirin did not significantly reduce the risk of MACEs (RR, 0.93; 95% CI, 0.87–1.00; $P = 0.06$), cardiovascular death (RR, 0.95; 95% CI, 0.83–1.09; $P = 0.49$), MI (RR, 0.91; 95% CI, 0.75–1.11; $P = 0.36$), or stroke (RR, 0.91; 95% CI, 0.76–1.10; $P = 0.33$), and there was a small but significant increase in the risk of all bleeding events (RR, 1.29; 95% CI, 1.07–1.55; $P = 0.01$).[30] Given the P value of 0.06 for MACE prevention

TABLE 1 The 3 latest trials on aspirin for primary cardiovascular prevention

Study	Study design	Patient population	No. of patients; follow-up	Results: efficacy	Results: safety
ARRIVE[10]	Randomized, double-blind, placebo-controlled, multicenter study (Germany, Italy, Ireland, Poland, Spain, United Kingdom, United States)	Patients ≥55 years (M) or ≥60 years (W), estimated moderate cardiovascular risk	12 546; 5 y	No significant differences in: • composite of time to first MI, stroke, cardiovascular death, unstable angina, or transient ischemic attack (HR, 0.96; 95% CI, 0.81–1.13; $P = 0.604$) • fatal or nonfatal MI (HR, 0.85; 95% CI, 0.64–1.11; $P = 0.233$)	GI bleeding (usually mild) more frequent in the aspirin group (HR, 2.11, 95% CI 1.36–3.28; $P < 0.001$); similar incidence of serious adverse events in both arms
ASCEND[11]	Randomized, double-blind, placebo-controlled, multicenter study (United Kingdom)	Patients ≥40 years diagnosed with diabetes mellitus (any type), no known cardiovascular disease, no clear indication for antiplatelet therapy	15 480; 7.4 y	Serious vascular events less frequent in the aspirin group than in the placebo group (RR, 0.88; 95% CI, 0.79–0.97; $P = 0.01$). Similar incidence of GI cancer (RR, 0.99; 95% CI, 0.80–1.24) or any cancer (RR, 1.01; 95% CI, 0.92–1.11)	Major bleeding more frequent in the aspirin group (RR, 1.29; 95% CI, 1.09–1.52; $P = 0.003$), more GI and other extracranial bleedings
	Randomized, double-blind, placebo-controlled, multicenter study (Australia, United States)	Subjects aged ≥70 years (or ≥65 years if blacks or Hispanics in the United States), no cardiovascular disease, dementia, or physical disability	19 114; 4.7 y	No significant differences in: • composite of death, dementia, or persistent physical disability (HR, 1.01; 95% CI, 0.92–1.11; $P = 0.79$) • cardiovascular disease (HR, 0.95; 95% CI, 0.83–1.08) Higher risk of death from any cause (but formal comparison not possible)	Higher rate of major hemorrhage in the aspirin group (HR, 1.38; 95% CI, 1.18–1.62; $P < 0.001$)

Abbreviations: ARRIVE, Aspirin to Reduce Risk of Initial Vascular Events; ASCEND, A Study of Cardiovascular Events in Diabetes; ASPREE, Aspirin in Reducing Events in the Elderly; GI, gastrointestinal; HR, hazard ratio; RR, relative risk

by aspirin, this meta-analysis basically confirms a substantial equivalence between the prevention of ischemic events and the increase in bleeding events, as reported in the ASCEND trial.[11]

A further meta-analysis, with a particular focus on subgroups, has been published very recently, and has evaluated whether sex, concomitant statin treatment, diabetes, and smoking affected the benefit from aspirin.[31] The risk of MACEs seemed to be significantly reduced in men (RR, 0.89; 95% CI, 0.83–0.95), but not in women, possibly because of the greater cardiovascular risk among men. Nonetheless, aspirin was reported to reduce the risk of MACEs in patients treated with statins (RR, 0.88; 95% CI, 0.80–0.96) or nonsmokers (RR, 0.90; 95% CI, 0.82–0.99), while it was not associated with significant benefit in patients not receiving statins or smokers.[31] Therefore, aspirin apparently conferred a greater benefit in patients at a lower cardiovascular risk, which is counterintuitive and has no plausible background. These results cast many shadows over the feasibility of subgroup analyses in this field. Reappraising all available data from another perspective, such as the baseline cardiovascular risk, might prove a more fruitful approach.

Meta-regression: another approach to assess aspirin benefit In 2014, an international panel of experts published a consensus document advocating a tailored strategy to aspirin prescription in primary cardiovascular prevention.[32] The authors proposed a pooled analysis of prior trials, which differed from the standard meta-analytic approach because it evaluated the reduction in thromboembolic events and the increased bleeding as a function of cardiovascular risk in the control group. Here, we plotted the relative benefit or harm from aspirin versus placebo as a function of the 10-year risk of MACEs in the control group. The analysis suggested that the relative benefit from aspirin (in terms of reduced ischemic events) increases progressively in parallel with the 10-year risk of MACEs, whereas the relative risk of major bleeding is much less affected by the level of cardiovascular risk. A substantial proportion of major bleeds occurred in the GI tract, which is worth noting as such risk can be substantially reduced with proton pump inhibitors (PPIs).[33] We concluded that the reduction in the number of thromboembolic events was balanced by an increased risk of bleeding in patients at low risk of MACEs, while patients at higher risk seemed to derive a net benefit from aspirin. The 10% and 20% values of 10-year risk of MACEs were selected as cutoff points useful for clinical decisions.[34] In this proposal, aspirin for primary cardiovascular prevention was not to be prescribed when the estimated 10-year risk of MACEs was less than 10%, might be considered when the risk was 10% to 20%, and was largely advised when the 10-year risk was greater than 20%.[32]

We have now updated the same analysis following the publication of the latest trials on

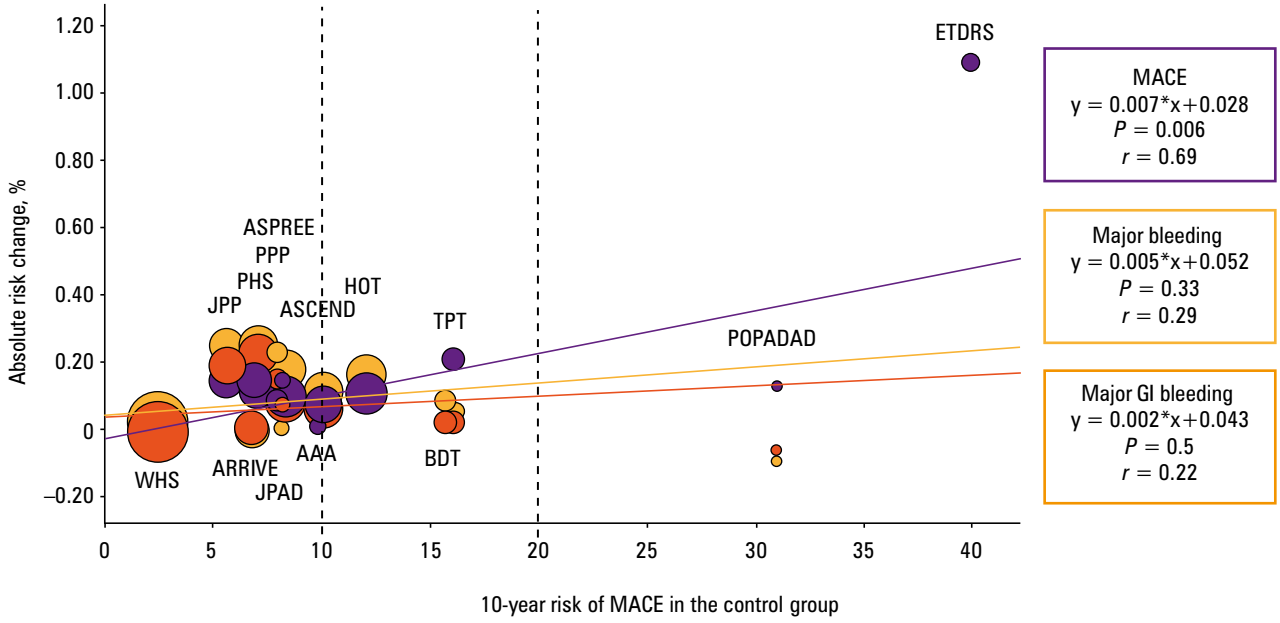

FIGURE 1 The magnitude of antithrombotic benefit and bleeding risk as a function of the cardiovascular risk in trials of aspirin for primary prevention. Modified from De Caterina et al[34]

This univariate linear regression reports the aspirin effect as a function of the baseline cardiovascular risk. The regression lines correspond to major cardiovascular events (vascular death, nonfatal myocardial infarction, nonfatal stroke, excluding transient ischemic attacks or need for revascularization), major bleeding, and major gastrointestinal (GI) bleeding. The independent variable is the risk of major cardiovascular events per 10 patient-years in the control group of each trial. On the y-axis, the percent absolute risk change is provided; for major cardiovascular events, this is calculated as risk/follow-up years in the control group minus risk/years in the aspirin group, while for major bleeding and major GI bleeding, it is calculated as risk/follow-up years in the aspirin group minus the risk/years in the control group. Study weight is proportional to study size (number of patients recruited). Each study is represented by 3 circles, 1 for each endpoint, the size of which is proportional to patient number. Only 1 circle is reported for the ETDRS[35] and 2 for the United States PHS,[16] since the data reported do not allow a complete evaluation of the bleeding risk. Abbreviations: AAA, Aspirin for Asymptomatic Atherosclerosis;[29] BDT, British Doctors Trial;[15] HOT, Hypertension Optimal Treatment;[18] JPAD, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes;[46] JPPP, Japanese Primary Prevention Project;[47] MACE, major adverse cardiovascular event; PHS, Physician Health Study;[16] POPADAD, Prevention of Progression of Arterial Disease and Diabetes;[28] PPP, Primary Prevention Project;[48] TPT, Thrombosis Prevention Trial;[17] WHS, Women's Health Study;[19] others, see **TABLE 1**

aspirin for primary prevention[10-14,34] (**FIGURE 1**). The correlation between the 10-year risk of MACEs and the relative reduction in ischemic events is weaker than in the 2014 diagram (r = 0.691 vs r = 0.729, P <0.001 vs P = 0.006, respectively). Furthermore, the slope of the line depicting the relative reduction in ischemic events appears largely driven by the ETDRS (Early Treatment Diabetic Retinopathy Study),[35] an old trial that included patients either in primary or secondary prevention, and statistical significance is lost when this trial is excluded (P = 0.085).[34] We also note, however, that only 2 trials—ETDRS[35] and POPADAD[28]—included patients beyond the 20% risk threshold, and that the reduction in ischemic events appears much more prominent in the former[35] than in the latter,[28] with basically no bleeding events reported in ETDRS.[35] Other possible limitations of this analysis are the high degree of heterogeneity of trials on aspirin for primary prevention, including the much more intensive control of cardiovascular risk factors in most recent trials, and the assessment of MACE instead of the harder endpoint of total or cardiovascular death. Despite these cautions, the diverging slopes of the lines representing the relative benefit and risk of aspirin therapy seem to corroborate the conclusions of the 2014 consensus document.

A practical algorithm to guide decision regarding aspirin therapy for primary prevention A revised version of the decisional algorithm is reported in **FIGURE 2**. Patients in primary cardiovascular prevention should achieve optimal control of cardiovascular risk factors, primarily targeting recommended levels of low-density lipoprotein cholesterol (with extensive use of statins) and blood pressure.[36-38] Afterwards, provided that they are younger than 70 years of age and free from physical disability or dementia, they should undergo an evaluation of their cardiovascular risk, with attention to evidence of subclinical atherosclerotic disease or diabetes. When the 10-year risk of MACE is greater than 20% or with evidence of subclinical atherosclerosis (carotid, coronary, or peripheral artery disease), there is still currently a reasonably strong rationale for starting a therapy with aspirin, particularly if there are no conditions of increased bleeding risk and in any case following discussion with the patient about the potential risks and benefit. Aspirin should be most often prescribed together with a PPI to reduce the risk of GI bleeding. Aspirin therapy should be more

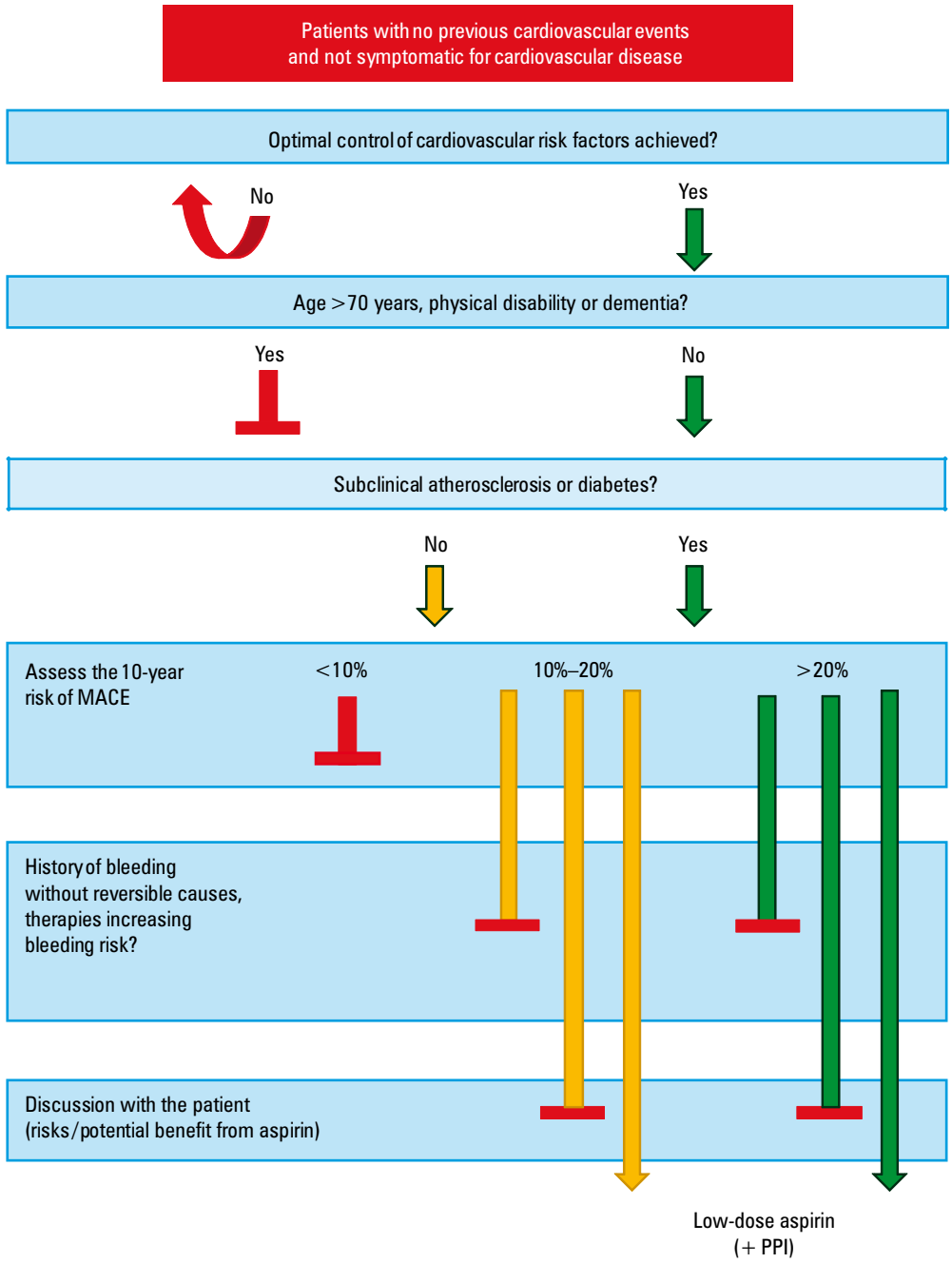

FIGURE 2 Proposed stepwise approach to aspirin prescription for primary cardiovascular prevention. Modified from De Caterina et al[34]

Patients in primary cardiovascular prevention should achieve optimal control of cardiovascular risk factors. Afterwards, when they are aged <70 years and free from physical disability or dementia, they should undergo a stratification of their cardiovascular risk, with attention to evidence of subclinical atherosclerosis or diabetes. When the 10-year risk of major adverse cardiovascular evets (MACEs) is >20% or there is already evidence of subclinical atherosclerosis, there is a rationale for starting a therapy with aspirin, particularly if there are no conditions of increased bleeding risk and following discussion with the patient about potential risks and benefit. Aspirin should be prescribed together with a proton pump inhibitor (PPI) to reduce the risk of gastrointestinal bleeding. Starting of aspirin therapy should be carefully evaluated when the 10-year risk is between 10% and 20%; and aspirin should not be prescribed when the 10-year risk is <10%.

carefully evaluated when the 10-year risk is between 10% and 20%, and should not be prescribed when the 10-year risk is less than 10%. Importantly, all patients must be thoroughly informed about the risks and potential benefits from this therapy.[34] Based on population studies pointing to a reduction in GI, particularly colorectal, cancer,[23] a family history of these types of cancer should be regarded as a further encouragement to start aspirin.

A similar stepwise approach based on risk stratification has been recently proposed by Chiang et al.[39] The decision to start, continue, or stop aspirin in primary prevention must be

preceded by a discussion with the patient, in which the clinician is asked first to assess the patient's understanding and eagerness to engage in discussion regarding aspirin therapy (step 1), review potential benefits and harms from aspirin (step 2), ascertain patient's preferences with questions exploring familiarity with issues on conditions prevented by aspirin and about its adverse effects, and patient's willingness to take this medication long-term (step 3). When these steps are taken, aspirin should be started or continued when there is a combination of high cardiovascular risk, a low bleeding risk, and patient's preference to avoid cardiovascular events. As general indications, the authors here suggest considering therapy initiation when the 10-year risk of MACEs is greater than 15%; and therapy continuation when the risk is greater than 10% and the patient has been on aspirin from more than 10 years. Risk thresholds for treatment could be lower when the bleeding risk is low and there is a strong patient preference for reducing the risk of cardiovascular events. The relative benefit and risk of aspirin therapy should be carefully weighted in oldest patients (for example, those >75 years). Finally, aspirin should not be prescribed or should be actually discontinued when the 10-year risk is less than 5%, there is a high risk of bleeding, or the patient expresses a clear preference to avoid bleeding. Also these authors recommend optimal control of cardiovascular risk factors as a necessary prerequisite to risk estimation and decision about aspirin therapy.[39] Such recommendations, apart from different decision level thresholds, are substantially similar to ours.

Guideline recommendations The notion that aspirin therapy should be decided based on an individualized assessment of ischemic and bleeding risks is corroborated by the most recent guidelines published in 2019. While the 2016 European Society of Cardiology guideline on cardiovascular disease prevention had adopted the extreme position of tout-court advising against aspirin therapy in every patient ("[a]ntiplatelet therapy is not recommended in individuals without cardiovascular disease due to the increased risk of major bleeding" [class III, level of evidence (LOE) B] and "[a]ntiplatelet therapy [e.g. with aspirin] is not recommended for people with diabetes mellitus who do not have cardiovascular disease" [class III, LOE A])[38], the 2019 European Society of Cardiology Guidelines on diabetes now recommend that "[i]n patients with DM at high/very high risk, aspirin (75-100 mg/day) may be considered in primary prevention in the absence of clear contraindications" (class IIb, LOE A), whereas "[i]n patients with diabetes at moderate cardiovascular risk, aspirin for primary prevention is not recommended" (class III, LOE B). It is also specified that "[w]hen low-dose aspirin is used, PPI should be considered to prevent GI bleeding" (class IIa, LOE A).[40] In the broader setting of primary prevention, the 2019 American College of Cardiology / American Heart Association Guidelines recommend that "[l]ow-dose aspirin (75–100 mg orally daily) [...] be considered for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) among select adults 40 to 70 years of age who are at higher cardiovascular risk but not at increased bleeding risk" (class IIb, LOE A), whereas "...it should not be administered on a routine basis in individuals aged >70 years" (class III, LOE B), and "...should be avoided in individuals of any age at increased risk of bleeding" (class III, LOE C).[41]

Possible developments: quantifying the net clinical benefit and weighting the ischemic and bleeding risks In the diagram reported in FIGURE 1, the relative decrease of MACEs is compared with the relative increase in major bleeding as a function of the 10-year risk of MACEs, and equal weights are attributed to MACEs and major bleeding events. This is clearly an over-simplification, because all MACEs are irreversible, and usually more severe than mostly reversible bleeding events. Several possible developments of this type of analysis can be envisaged. First, the qualitative assessment of the risks of MACEs and bleeding events could be replaced by a more appropriate quantification of the different risks. Here, analyses of the "net clinical benefit" are now regarded with interest as tools to better quantify the risk-to-benefit ratio from antithrombotic therapies in different settings,[42-44] and have also been attempted in the setting of aspirin therapy for primary prevention, although as a cumulative evaluation over the entire population.[31] Calculations of the net clinical benefit from aspirin across the spectrum of MACE risk, possibly in the setting of an individual patient-level analysis, would be probably more informative. Second, a more sophisticated approach to the assessment of the net clinical benefit would attribute different weights to the single ischemic and bleeding endpoints according to their impact on morbidity and mortality. This approach may be considered for studies on contemporary cohorts of subjects, managed with a state-of-the-art control of risk factors and with a larger use of PPIs to reduce the risk of GI bleeding.

Conclusions A great research effort spanning several decades has attempted to define whether aspirin should be prescribed or not for the primary prevention of cardiovascular events. The most clear-cut conclusion that can be derived is that aspirin is not beneficial for all patients without symptoms or prior cardiovascular events and may be actually harmful. It is still reasonable, however, to assume that a subgroup of patients may benefit from aspirin. Subgroup analyses have given limited and often counterintuitive results and, moreover, had a large number of limitations. In the absence of clear conclusive evidence, the latest guideline recommendations rely mostly on common sense, suggesting to consider aspirin therapy when the individual risk of thromboembolic

events is higher than the bleeding risk. This has been interpreted as "the triumph of clinical judgment over complex equations,"[45] but the proposed dichotomy between decisional algorithms and clinical reasoning is likely an over-simplification of the problem. Although a reasoned approach to each individual case is mandatory, clinicians can greatly benefit from a general theoretical framework, such as the one here proposed, including the need for a combined assessment of thromboembolic and bleeding risk; the identification of some decisional nodes, for example, an evaluation of patient's age and general health status; and the use of risk scores with reasonable cutoff points.

Following a critical appraise of the available evidence, and the consideration that the net benefit from aspirin tends to increase in parallel with the risk of MACEs, we propose a rather "simple equation," meant to help clinicians and not to belittle their clinical skills. Following general preventive measures (physical exercise, smoking cessation, treatment of hypertension and hypercholesterolemia, etc)—the benefits of which are undisputed and which entail remarkably low risk—a tailored approach to aspirin prescription in primary cardiovascular prevention is now warranted. When patients are less than 70 years of age, clinicians should assess the 10-year cardiovascular risk. When that risk is very high and bleeding risk is low, aspirin treatment should still be strongly considered, also taking into account patient preferences.

ARTICLE INFORMATION

CONFLICT OF INTEREST AA has no conflicts to disclose. RDC declares having received fees and honoraria from Bayer related to the topic.

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