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Aspirin for Primary Prevention of Cardiovascular Diseases: "WALTZ" with the Evidence

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Abstract

Purpose of Review In this review article, a detailed analysis of the current literature is provided, along with a "glimpse" into what the future holds for aspirin in the context of primary prevention.

Recent Findings The role of aspirin in primary prevention of cardiovascular diseases (CVD) has been extensively evaluated; however, the results provided over the years have been controversial. Identification of individual subgroups who may benefit from aspirin administration at an acceptable risk of bleeding complications is of paramount importance. Additionally, questions emerge at everyday clinical practice regarding the optimal use of aspirin in different phenotypes of patients due to age, sex, obesity status, frailty and diabetes mellitus.

Summary Until further data become available, the effective management of the well-established CV risk factors constitutes the milestone in the primary prevention of CVD. Moreover, based on the available evidence, the beneficial addition of aspirin in the modern era of lifestyle and pharmacological interventions for primary CVD prevention remains largely undetermined and further research is needed.

Keywords Aspirin · Primary cardiovascular disease prevention · Bleeding risk

Introduction

Aspirin's roots go back to 1500 B.C., when ancient Sumerians used salicin, a product of willow trees, as a way to alleviate joint pains and other inflammatory rheumatic diseases. [1] A millennia later, Hippocrates expanded the use of willow bark to mitigate labor pain, and through the centuries, salicin's analgesic and antipyretic properties were discovered. The active component of willow bark, salicin, was extracted in 1824 by two Italian pharmacists, but it was not until August 10th, 1897, when Bayer chemist Felix Hoffmann synthesized acetylsalicylic acid by acetylating the phenol group from salicylic acid refluxed with acetic anhydride [2]. In the early 1970s, scientists became aware of aspirin's antiplatelet and antithrombotic effects, and in 1980, a meta-analysis showed that patients with prior myocardial infarction, had a 21% risk reduction of re-infarction if under aspirin. This breakthrough discovery marked a milestone in cardiology that made aspirin the undeniable gold standard in secondary cardiovascular (CVD) prevention [3, 4]. Years later, the role of aspirin in primary prevention was to be examined and is still under debate. Indeed, up until 2016, guidelines were not against recommending aspirin for primary prevention for specific groups of people, even with a limited set of evidence available at the time [5]. Aspirin has long been associated with increased major bleeding risk, primarily from the upper gastrointestinal tract, and, thus, the principle of "do not harm" has been in the center stage when it came to using aspirin as a means of primary prevention of CVD.

In this review article, we aim to provide a detailed analysis of the current literature, while giving a glimpse into what the future holds for aspirin in the context of primary prevention, as well as pinpointing questions that emerge and may be of particular interest for future research.

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The Long History of Large Randomized Clinical Controlled Trials

The role of aspirin in primary prevention of CVD has been extensively evaluated; however, the results provided over the years have been controversial. Numerous randomized controlled trials (RCTs) have been published since the 1980s, with evidence either favoring or questioning the medication's protective effect in specific populations. [6] The first 2 major studies addressing the drug's benefit in individuals without history of CVD—British Male doctors and Physicians Health Study—involved apparently healthy male physicians [7, 8]. Concerning total CVD mortality, although the benefit was not proven in both studies, the Physicians showed a significant reduction in the incidence of fatal and nonfatal myocardial infarction (MI) [8]. The discrepancy of results between trials involving population with similar baseline characteristics could be interpreted by the different drug dosing (500 mg daily vs 325 mg every other day, both using mostly plain aspirin), and study design (single- vs double-blind).

In the following decade, studies focusing on populations with CV comorbidities have assessed the administration of aspirin when combined with treatments targeting specific risk factors The findings, now, depicted a beneficial role of aspirin for primary CVD prevention [9, 10]. More specifically, in the setting of hypertension, the Hypertension Optimal Treatment (HOT) trial revealed reduced risk for major adverse cardiovascular events (MACE) with aspirin [9], while the Primary Prevention Project (PPP) trial, including individuals with more than one CVD risk factors, found that aspirin significantly reduced the risk of both MACE and CV mortality [11]. However, this benefit was limited to the non-diabetic participants of the study, supporting the already existing hypothesis that aspirin is less effective in patients with diabetes [10].

Proceeding to the last two decades, the major double-blind RCTs are summarized in Table 1. In specific, Women's Health Study, in 2005, examining the efficacy of aspirin administration among apparently healthy women, depicted a significantly lower risk of stroke without an effect in other CV events, and a higher rate of gastrointestinal (GI) bleeding [12], with the highest benefit being observed in the subgroup of older women [12]. A few years later, 2 large randomized trials focusing on individuals with diabetes were published (JPAD, POPADAD); no evidence of reduction in total CV events was observed confirming the results of PPP study, while the difference in bleeding risk was not significant either [13, 14]. However, in the case of JPAD trial, fatal CV events were significantly lower in the aspirin arm, especially in the population ≥ 65 years [14]. Both studies used plain aspirin. In the AAA trial, the effect of aspirin was tested according to the ankle-branchial index (ABI) values with the results showing that individuals with lower ABI (≤ 0.95) did not have a significant reduction in CV events, regardless of age and sex [15]. Finally, a Japanese study (JPPP), including elderly individuals with multiple risk factors stopped due to futility reasons, after a median of 5 years, as it was unable to prove any beneficial effect of aspirin administration in all subgroups [16].

After 2018, the most up-to-date evidence is available from four large high-quality RCTs. To begin with, the ARRIVE trial included males ≥ 55 years with 2–4 CVD risk factors and women ≥ 60 years with ≥ 3 risk factors, excluding diabetic subjects. Although no significant effect on CV mortality and MACE was observed, the major benefit of aspirin therapy for CVD events was referred to the subgroup with CVD risk less than 10.5%. However, this favorable effect is counterbalanced by a higher hemorrhagic risk [17]. In the same year, the ASCEND trial in diabetics [18], despite exhibiting a significant reduction in any MACE (12% lower risk), it also presented a higher risk of major bleeding [19]. The ASPREE trial investigated the effect of aspirin on the primary CVD prevention in the elderly [20] showing not a significantly lower risk of disability-free survival [20], CV events [21] and all-cause mortality [22] in subjects older than 70 years of age.; that, along with the higher risk of major hemorrhage made aspirin a not favorable preventive medication for the elderly without prior CVD. In the TIPS-3 trial, the effect of aspirin alone and in combination with a polypill containing a statin, a beta-blocker, a thiazide diuretic and an angiotensin-converting enzyme inhibitor was assessed in individuals at intermediate or high CVD risk; the results showed that, only the combination of aspirin with polypill was beneficial in terms of MACE and stroke (fatal and nonfatal) and not the administration of aspirin alone [23]. A common limitation in the aforementioned trials is the poor compliance of the enrolled individuals, due to multiple drug intake as well as the concurrence of COVID-19 pandemic, especially in the case of TIPS-3 trial.

In the AASER chronic renal disease study, a lower risk of MI was reported, with no effect in CV mortality though [24]. However, due to the limitations of small sample size and open-label study design, further RCTs are required to support these findings in this particular subgroup.

Some "Help" from the Meta-Analyses

The "tool" of meta-analyses can be used in order to elucidate the numerous controversies on the field emerging from biases in the methodological design as well as construction of the different trials. A careful interpretation of the information provided and summarized in this paragraph is required.

Table 1 CVD and hemorrhagic outcomes of the major RCTs conducted in the last two decades

	WHS (2005)[12]	POPADAD (2008)[13]	JPAD (2008)[14]	AAA (2010)[15]	JPPP (2014)[16]	ARRIVE (2018)[17]	ASCEND (2018)[19]	ASPREE (2018)[21]	AASER (2018)[24]	TIPS3 (2020)[23]
Population*	Women aged≥45 years	Individuals aged≥40 years with diabetes and ABI≤0.99	Individuals aged 30-85 years with diabetes	Individuals aged 50-75 years	Individuals aged 60-85 years with hypertension, dyslipidemia or diabetes	Men aged≥55 years with 2-4 CVD risk factors, women aged≥60 years with ≥3 CVD risk factors, excluding diabetes	Individuals aged≥40 years with diabetes	Individuals aged≥70 years, without dementia or significant physical disability	Individuals with eGFR=15–60 ml/min/1.73m^2	Men aged≥50 and women aged≥55 years with intermediate/high CVD risk
Men (%)	0	44	55	29	42	70	63	44	68	47
Mean Age (years)	55	60	65	62	71	64	63	74	67	64
Formulation and Dosage	100mg on alternate days	100mg once daily	81 or 100mg once daily	100mg EC once daily	100mg EC once daily	100mg EC once daily	100mg EC once daily	100mg EC once daily	100mg EC once daily	75mg EC once daily
MI	RR 1.02 (0.84-1.25)	HR 0.98 (0.68-1.43) [Nonfatal]	HR 0.81 (0.49-1.33)	RR 1.05 (0.79-1.40)	HR 0.53 (0.31-0.91)	HR 0.90 (0.67-1.20)	HR 0.98 (0.80-1.19)	HR 0.93 (0.76-1.15)	0 vs 8 (P=0.014)	HR=0.69 (0.31-1.56) [Polypill + Aspirin vs double placebo]
Stroke	RR 0.83 (0.69-0.99)	HR 0.71 (0.44-1.14) [Nonfatal]	HR 0.84 (0.53-1.32)	RR 0.88 (0.59-1.31)	HR 1.04 (0.80-1.34) [Nonfatal]	HR 1.12 (0.80-1.55)	HR 0.88 (0.73-1.06)	HR 0.93 (0.76-1.15)	4 vs 2 (Statistically non-significant)	HR 0.42 (0.20-0.89) [Polypill + Aspirin vs double placebo]
CVD Mortality	RR 0.95 (0.74-1.22)	HR 1.23 (0.79-1.93)	HR 0.10 (0.01-0.79)	RR 1.17 (0.72-1.90t)	HR 1.03 (0.71-1.48) [Nonfatal]	HR 0.97 (0.62-1.52)	HR 0.91 (0.75-1.10)	HR 0.97 (0.71-1.33)	0 vs 1 (Statistically non-significant)	HR 0.69 (0.46-1.05) [Polypill + Aspirin vs double placebo]
Any MACE	RR 0.91 (0.80-1.03)	HR 0.98 (0.76-1.26)	HR 0.80 (0.58-1.10)	HR 1.03 (0.84-1.27)	HR 0.94 (0.77-1.15)	HR 0.95 (0.79-1.15)	HR 0.88 (0.79-0.97)	HR 0.89 (0.77-1.03)	HR 0.40 (0.15-1.08)	HR 0.69 (0.50-0.97) [Polypill + Aspirin vs double placebo]
Bleeding	RR 1.22 (1.10-1.34) [Any GI Bleeding]	HR 0.90 (0.53-1.52) [Any GI Bleeding]	RR 1.44 (0.55-3.77) [Major Bleeding]	HR 1.71 (0.99-2.97) [Major hemorrhage]	HR 1.85 (1.22-2.81) [Major extracranial hemorrhage]	HR 2.11 (1.36-3.28) [Any GI Bleeding]	HR 1.29 (1.09-1.52) [Major hemorrhage]]	HR 1.38 (1.18-1.62) [Major hemorrhage]	3 vs 2 (Statistically non-significant)	RR 0.75 (0.32-1.77) [Major Bleeding- Polypill + Aspirin vs double placebo]

*All trials enrolled individuals without history of CVD

Results favoring aspirin are highlighted with green color. Results favoring placebo are highlighted with red color. Results at white font are statistically nonsignificant

WHS Women's Health Study, *POPADAD* Prevention Of Progression of Arterial Disease And Diabetes, *JPAD* Japanese Primary Prevention Project, *AAA* Aspirin for Asymptomatic Atherosclerosis, *JPPP* Japanese Primary Prevention Project, *ARRIVE* Aspirin to Reduce Risk of Initial Vascular Events, *ASCEND* A Study of CV Events in Diabetes *ASPREE* ASPirin in Reducing Events in the Elderly, *AASER* Aspirin for Primary Prevention of Cardiovascular Disease and Renal Disease Progression in Chronic Kidney Disease Patients, *TIPS-3* The International Polycap Study-3, *CVD* Cardiovascular Disease, *MACE* major adverse cardiovascular event, *RR* risk ratio, *HR* hazard ratio, *GI* gastrointestinal, *MI* myocardial infarction, *eGFR* estimated glomerular filtration rate

To begin with, a meta-analysis of 13 randomized clinical trials including more than 160,000 patients without known CVD showed that aspirin use for primary prevention was associated to a substantial reduction in the risk of CV events (HR 0.89, 95% CI, 0.84–0.95) and an increase in the risk of major bleedings (HR 1.43, 95% CI 1.30–1.56) compared to no-aspirin use [21]. In particular, aspirin reduced the risk of a composite of CV death, myocardial infarction or nonfatal stroke by 13% (HR, 0.87, 95% CI, 0.79–0.95) in patients with low 10-year CVD risk, by 8% (HR, 0.92, 95% CI, 0.84–1.00)

in those with high 10-year CVD risk, and by 11% (HR, 0.89 95% CI 0.80–1.00) in patients with diabetes, without affecting all-cause or CV mortality in any of these groups. Comparing to no aspirin use, no significant difference in incident cancer or cancer mortality was found, either [25].

Proceeding to another meta-analysis including, again, 13 trials all in respect to the same criteria, namely: randomized clinical trials comparing aspirin use versus no aspirin, with more than 1,000 participants free of CVD followed for at least 12 months demonstrated no difference in the risk of all-cause and CV mortality between the aspirin and control groups. Aspirin treatment, though, induced a reduction in the risk of myocardial infarction by 14% (RR 0.86; 95% CI, 0.77–0.95), in the risk of stroke by 10% (RR 0.90; 95% CI, 0.82–0.99) along with a reduction in the risk of major adverse cardiovascular events (MACE) by 9% (RR 0.91; 95% CI, 0.86–0.95), which was more pronounced in patients under statin treatment, non-smokers and males. Nevertheless, yet one more time the beneficial effect of aspirin is outweighed by an increased risk of major bleedings, calculated at 46% (RR 1.46; 95% CI, 1.30–1.64) compared to controls, with the study subsequently reporting no net clinical benefit of aspirin use for primary CVD prevention [26•].

Focusing mainly on stroke, a pooled analysis of 11 clinical trials including, approximately, 157,000 patients demonstrated no significant benefit of aspirin on primary ischemic stroke prevention, whereas a substantial increase in the risk of hemorrhagic stroke was observed (odds ratio, 1.29; 95% CI, 1.06 to 1.56) in the aspirin group compared to controls. There was no improvement in overall survival rate with the use of aspirin, while the reduction in myocardial infarction rates was counterbalanced by an increase in hemorrhagic events [27]. On the contrary, a meta-analysis of 11 primary prevention trials demonstrated a 22% reduction in the risk of nonfatal MI, an effect that was found to begin within the first 5 years of aspirin use and to be relatively higher in older adults. Notably, this benefit persisted with aspirin doses of 100 mg or less in parallel with an emerging 14% benefit for nonfatal stroke reduction, which was not seen with higher doses of aspirin. However, in line with the other similar meta-analyses, no significant effect on cardiovascular or all-cause mortality was found [28].

Owing to the sparsity of relevant data, the identification of any subpopulations with higher likelihoods of benefit from aspirin use for primary prevention remains an open matter. Given this fact, data from 10 clinical trials involving a total of 34,000 diabetic patients without apparent CVD were pooled in order to evaluate the use of low-dose aspirin (75–100 mg/day) for primary prevention in diabetes mellitus. A stratified analysis was performed, based on the estimated CV risk (low, moderate, high) of the studied population in each of the included trials. In this analysis, low-dose aspirin was associated with a 12% lower risk for MACE in the moderate/high CV risk group in contrast to the low-risk group, where no significant benefit was observed. In addition to this, low-dose aspirin was associated with more bleeding events in the low-risk group, but not in the moderate/high-risk group, although there is no given explanation for this. Once again, even in this population, no reduction in CV mortality was shown [29].

Fixed-dose combination treatments, widely known as polypills, have gained increasing interest, due to evidence supporting that they improve treatment adherence and risk factor control. However, their role in CVD primary prevention has been extensively debated A meta-analysis of 3 trials with 18,000 participants evaluating a fixed-dose combination strategy of at least two blood pressure lowering agents plus a statin (with or without aspirin) compared to a control strategy, demonstrated significant reductions in the primary outcome of a composite of CV death, MI, stroke or revascularization. This effect was greater for combination strategies including aspirin where the analysis of pooled data of about 9,000 participants showed a reduction in the risk for primary outcome by half (HR 0·53, 95% CI 0.41–0.67, $p < 0.0001$) compared to the control group, over the course of a 5-year follow-up period. In respect of bleeding events, the analysis of trials showed a trend toward higher risk for gastrointestinal bleedings in the aspirin group compared to controls, which did not reach statistical significance. Despite these favorable results supporting the use of fixed-dose combination treatments including both statin and aspirin in diabetic patients, no difference in all-cause mortality between the two strategies was found [30].

In conclusion, based on the meta-analyses, aspirin use for primary prevention results in lower risk of ischemic CV events in the general population, but this benefit is outweighed by an increase in hemorrhagic events, mainly gastrointestinal bleedings. [21–25, 26•] Elderly patients and diabetics at moderate or high CV risk are more likely to benefit from treatment with low doses of aspirin (75–100 mg/day) [21–25, 26•] but what shall be underlined is that the outcomes of these meta-analyses may have several limitations, namely: clinical heterogeneity of the included populations, lack of data about specific subpopulations (i.e., chronic kidney disease patients, subjects with family history of CVD), different follow-up practice and duration in the included trials, various definitions given for both ischemic and bleeding events that should, therefore, be interpreted more accurately.

Guidelines

The aforementioned studies as well as their meta-analyses give an interesting perspective of the role of aspirin in primary prevention of CVD events, same as the guidelines

available, which, one can also consult. Toward this end, all major recommendations in favor of aspirin use are presented in Table 2. The 2011 Canadian guidelines [31], which were issued before the course-changing clinical trials, suggest that aspirin (75–162 mg daily) may be considered for patients whose vascular risk is high and bleeding risk is low. The more recent 2019 ACC/AHA primary prevention guidelines [32] recommend the infrequent usage of low-dose aspirin in routine prevention, with a limited scope to selected adults aged 40 to 70 years who are at higher CVD risk and not at increased bleeding risk [IIb, A]. In regard to diabetic patients, the joint ESC/EASD 2019 [33] and the ESC 2021 guidelines [34••] suggest that those at high/very high CV risk may be considered for daily aspirin (75–100 mg) administration. The 2020 ADA [35] guidelines corroborate these recommendations, by suggesting aspirin therapy (75–162 mg/day) as a primary prevention strategy for both men and women aged > = 50 years with diabetes and at least one additional major risk factor, but who are not at increased risk of bleeding.

Concerning stroke prevention, the 2014 AHA/ASA guidelines [36] suggest that aspirin (81 mg daily or 100 mg every other day) can be useful in preventing a first stroke in women, including those with diabetes mellitus whose CVD risk is sufficiently high compared to the risk of treatment. For both men and women regardless of age, AHA/ASA suggests that aspirin might be considered in patients with chronic kidney disease (30 < GFR < 45). Apart from the AHA/ASA guidelines, only the 2011 American Heart Association Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women [37] provided recommendations strictly for females, despite outdated. More specifically, they are in line with the rest of the guidelines concerning the use of aspirin in diabetic women without known CV disease, albeit at even higher doses (75–325 mg); they also suggest that aspirin therapy can be useful in women aged over 65 years at low doses (81 mg/d or 100 mg every other day) if blood pressure is carefully controlled and the ischemic stroke/MI risk is higher than the gastrointestinal bleeding or hemorrhagic stroke risk, while for younger (< 65 years) women without known CVD, low-dose

Table 2 Recent recommendations from the major scientific societies regarding use of aspirin in primary CVD prevention

Guidelines	Recommendations	Class of recommendation	Level of evidence
ACC/AHA 2019	Low-dose aspirin might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk	IIb	A
AHA/ASA 2014	Aspirin (81 mg daily or 100 mg every other day) can be useful for the prevention of a first stroke among women, including those with diabetes mellitus, whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment	IIa	B
	Aspirin might be considered for the prevention of first stroke in people with chronic kidney disease (GFR < 45). This recommendation does not apply to severe kidney disease (GFR < 30)	IIb	C
Canadian 2011	In special circumstances in men and women without evidence of manifest vascular disease in whom the vascular risk is considered high and bleeding risk is low, ASA 75–162 mg daily may be considered	IIb	C
ESC/ESD 2019 on Diabetes	In patients with diabetes mellitus at high/very high risk, aspirin (75–100 mg/day) may be considered in primary prevention in the absence of clear contraindications	IIb	A
	When low-dose aspirin is used, proton pump inhibitors should be considered to prevent gastrointestinal bleeding	IIa	A
	Missing knowledge: assess the effect of body mass, especially moderate-to-sever obesity on antiplatelet drug responsiveness and effectiveness in patients with DM, and to investigate higher dose strategies		
ESC 2021 on CVD prevention	Concomitant use of a proton pump inhibitor is recommended in patients receiving antiplatelet therapy who are at high risk of gastrointestinal bleeding	I	A
	In patients with DM at high or very high CVD risk, low-dose aspirin may be considered for primary prevention in the absence of clear contraindications	IIb	A
USPSTF 2021	Adults aged 40 to 59 years with a 10% or greater 10-year cardiovascular disease (CVD) risk The decision to initiate low-dose aspirin use for the primary prevention of CVD in adults ages 40 to 59 years who have a 10% or greater 10-year CVD risk should be an individual one. Evidence indicates that the net benefit of aspirin use in this group is small. Persons who are not at increased risk for bleeding and are willing to take low-dose aspirin daily are more likely to benefit	Grade C	

aspirin may be reasonable for ischemic stroke prevention. Finally, the US Preventive Services Task Force has issued a draft statement in 2021 [38], which suggests tailoring the decision to initiate low-dose aspirin for the primary prevention of CVD in adults aged 40 to 59 who have a 10% or greater 10-year CVD risk, since the net benefit of aspirin use in this group is small. People who are not at increased risk for bleeding and are willing to take low-dose aspirin daily are more likely to benefit [34••].

Of note, the European Society of Cardiology also recommends the concomitant use of a proton pump inhibitor for those receiving antiplatelet therapy and are at high risk of gastrointestinal bleeding [30].

Clinical Gaps and Future Perspectives

Aspirin, in the last decades, is strongly recommended for the treatment of patients with established CVD [39]. As implied from the RCTs and their meta-analyses, there are ongoing debates and clinical gaps in knowledge for aspirin in primary prevention. [36] This weakens the recommendations in guidelines that can easily puzzle the treating physician when a therapeutic decision on the administration of aspirin should be made. (Fig. 1) In the current literature, the role of obesity, sex, aspirin formulation, dosage and risk scores re-adjustment are emerging points to be further examined. Starting from sex analysis, in the Women's Health Study, a reduction of ischemic strokes was shown, with no significant effect on mortality [12]. This finding was confirmed by a sex-specific meta-analysis, with the limitation that out of the 6 studies, solely 1 was involving only women in contrast with 3 involving only men [40]. Concerning the recent 4 major RCTs, no result variations were found between sex. Regarding body mass index interaction, a contemporary meta-analysis concluded that low-dose aspirin was less effective as body-weight was increasing [41], a finding not observed in the large RCTs published at the same year. Conversely, in the ASCEND trial, the opposite effect was found [19]. However, in neither of these studies participants were stratified by sex and body mass index, underscoring the reason for more research in this setting [42].

Another issue that needs further clarification is the appropriate dosing and formulation of aspirin when administered for primary CVD prevention [42]. The recent major trials reported in this review evaluated the effects of low-dose enteric coated aspirin administration once daily. Nevertheless, in a previous study evaluating the pharmacodynamic effects of different dosing regimens in the secondary CVD prevention in diabetics, a twice-daily low-dose aspirin administration was proved superior to the once daily dose scheme [43]. Regarding the relationship of formulation type with efficacy and bleeding risk, an RCT recruiting obese individuals with diabetes free of CVD examined aspirin bioavailability when administered in 3 forms: plain, modified-release lipid-based and delayed-release EC. This study revealed an incomplete drug absorption in the EC arm [44]. Interestingly, lower bleeding risk with EC formulation has been questioned by an earlier large case–control study, which showed that treatment with EC aspirin provided a higher relative risk of bleeding

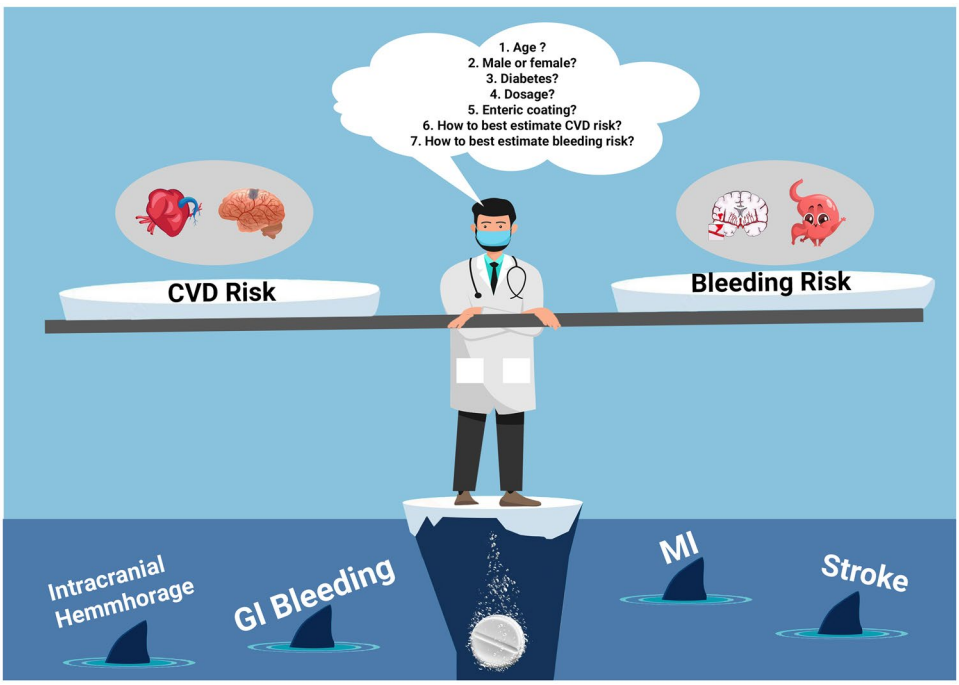

Fig. 1 The treating physician when a therapeutic decision on the administration of aspirin should be made for primary CVD prevention. CVD: cardiovascular disease; GI: gastrointestinal; MI: myocardial infarction

compared to plain aspirin [45]. It should be emphasized that there is not a standard way of estimating the bleeding risk in primary prevention, since existing risk scores, such as HAS-BLED, focus on patients with atrial fibrillation. As the ESC guidelines suggest, bleeding risk may be partially mitigated by the simultaneous use of a proton pump inhibitor since its effect on reducing gastrointestinal bleedings is clearly demonstrated in various trials, albeit with some reservations regarding their prolonged use as osteoporosis, B12 deficiency and increased susceptibility to enteric infections are known associated risks [38].

Last but not least, a limitation affecting most recent RCTs is the lower than expected risk of CV events, according to the estimation of the available risk scores [17, 19]. This finding could be interpreted by the improved medical care and more effective management of CV risk factors in the current era [46]. The inclusion of coronary artery calcium score in risk stratification may be helpful in distinguishing individuals at whom aspirin provides higher benefit/risk ratio [47•, 48]. Using a subpopulation (asymptomatic people < 70 years old with not high bleeding risk) from the multi-ethnic study of atherosclerosis [47•] subgroups where the detection of calcium artery score ≥ 100 and particularly ≥ 400 might be used to identify those who would likely see more benefit than harm. For primary prevention, the authors found that aspirin does not benefit patients with high estimated CVD risk but with zero coronary artery calcium. Similar results were exhibited in another study [48], in which a correlation was found between higher coronary artery calcium, and both CVD and bleeding events, in favor of CVD. The more updated recommendations are provided by a recent consensus paper [49], where aspirin is probably recommended for women with low risk of bleeding and at least one of the following: current smokers, elevated coronary artery calcium score ≥ 100 or carotid plaque, strong family history of premature CVD, suboptimal controlled lipids or blood pressure, high CV risk.

Conclusions

In summary, the beneficial effect of aspirin in primary CVD prevention remains uncertain for the totality of the general population. Identification of individual subgroups who may benefit from aspirin administration at an acceptable risk of complications is of paramount importance [42]. Until further data become available, the effective management of the well-established CV risk factors constitutes the milestone in the primary prevention of CVD [50]. The beneficial addition of aspirin in the modern era of lifestyle and pharmacological interventions for primary prevention remains largely undetermined and further research is needed. Until more robust data are provided in this setting the up-to-date treating physicians should "hear" their patients' CVD and bleeding risk and "WALTZ" with the evidence.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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