Review Article

Aspirin for Primary Prevention of Cardiovascular Diseases: Current Concepts, Unanswered Questions and Future Directions

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Cardiovascular diseases (CVD) represent the leading cause of morbidity and mortality worldwide. Prevention of CVD is an essential strategy for reducing the incidence of these conditions. Recent years have seen a decrease in heart disease mortality that was associated with changes in risk factors and improved treatment.[1] Aspirin was considered the drug most widely used in the last century.[2] It has been demonstrated to be useful for secondary prevention of coronary artery disease[3] and stroke.[4] Currently there is growing evidence in favor of the administration of aspirin for primary prevention of CVD. Although there are many articles suggesting the possible efficacy and safety of aspirin for this purpose, there is no international consensus concerning its definite use and numerous questions need to be answered to allow the drawing of definitive conclusions. This article will review the main investigations of the use of aspirin for primary prevention of CVD. It will also provide suggestions for further studies in order to clarify unanswered questions and future directions.

Brief aspirin pharmacology

Aspirin is a drug derived from salicylic acid.[5] It was discovered at the end of the 19th century and has been used widely over the years as an analgesic, anti-inflammatory, and antipyretic agent. However, its mechanism of action was discovered only four decades ago.[6,7]

Aspirin is rapidly absorbed by the stomach and small intestine after ingestion. The highest plasma levels are reached about 40 minutes after an oral dose. Aspirin has a short plasma half-life of 15 to 20 minutes.[8] Aspirin irreversibly inhibits both cyclooxygenase enzymes (COX-1 and COX-2). These enzymes catalyse the conversion of arachidonic acid to prostaglandin G_2 and subsequently to prostaglandin H_2. Tissue-specific isomerases then produce thromboxane A_2 (TXA_2) and prostaglandin I_2. TXA_2 is produced in platelets by COX-1 enzyme. At low doses, aspirin irreversibly acetylates COX-1 enzyme. Inhibition of COX-1 enzyme persists for the life of the platelet and reduces the synthesis of TXA_2. The main physiological actions of TXA_2 are vasoconstriction, proliferation of vascular smooth cells and platelet aggregation. Prostaglandin I_2 is produced by COX-2 in endothelial cells. The actions of prostaglandin I_2 are opposite to those of TXA_2. They are vasodilatation, decreased vascu-

lar smooth cell proliferation and atherosclerosis. Low doses of aspirin inhibit the COX-1 enzyme; however, higher doses are needed for the same effect on COX-2 enzyme. These differences explain why low doses of aspirin have been useful for reducing thrombogenic mechanisms, while higher doses have predominantly anti-inflammatory effects.[9-11]

Primary prevention of cardiovascular diseases

Primary prevention represents a leading world strategy for reducing the incidence of CVD. It is well recognized that modification of lifestyle, environmental changes, and reduction of related risk factors decrease the incidence of these conditions and this approach is recommended by most medical societies.[1,12] Nevertheless, other approaches have been suggested. In this regard, the use of aspirin has been widely studied, based on its mechanism of action and prior medical benefits in secondary prevention. However, there is no consensus on its use in primary prevention because of the variety of results.[1] In the 1970s the first investigations were published reporting the efficacy of aspirin for primary prevention of CVD.[13,14] Since those results, a great number of studies have been designed with the aim of demonstrating the efficacy of this therapy (Table 1).[15-22] The US Physicians' Health Study, a randomized trial, studied 22,071 United States male physicians divided into 2 groups. The group that received 325 mg aspirin every other day had a 44% lower incidence of myocardial infarction compared with the placebo group.[16] Hansson et al[17] studied 18,790 hypertensive patients followed for 3.8 years. Male patients who received 75 mg aspirin daily had a significantly lower incidence of myocardial infarction by 42% compared with placebo. There was a non-significant reduction by 19% in women. Another research group studied the effects of low doses aspirin on the risk of developing CVD in female patients. They assigned 39,876 women to receive 100 mg aspirin on alternate days or placebo. Patients were followed for 10 years and monitored for the first major cardiovascular event. There was a non-significant reduction in the risk of major cardiovascular events in the aspirin group compared with placebo (RR 0.91; 95% CI 0.80-1.03; p=0.13). When individual endpoints were compared, there was a 17% reduction in the risk of stroke (p=0.04), while there was no significant effect on the risk of fatal or non-fatal myocardial infarction (p=0.83), or death from cardiovascular causes (p=0.68). The beneficial effects of aspirin on major cardiovascular events were greater among women 65 years old or older. Regarding side effects, there was a non-significant increase in the risk of hemorrhagic stroke in the aspirin group and significant gastrointestinal bleeding requiring transfusion.[20] When these data were analyzed by age groups, it was observed that women over 65 years old had better results with aspirin administration for primary prevention. This is of major importance, because is well demonstrated that there is an increased risk of developing CVD in female patients aged over 50 years. The use of aspirin after this age may significantly reduce adverse clinical outcomes.

Raju et al[23] designed a meta-analysis with the aim of obtaining best estimates of the usefulness of aspirin in the primary prevention of CVD. This study included 9 randomized controlled trials with 100,076 patients. Aspirin was found to be useful in reducing the risk of all-cause mortality, but did not reduce cardiovascular mortality. The relative risk reduction was 17% for myocardial infarction (RR 0.83; 95% CI 0.69-1.00, p=0.0006) and 14% for ischemic stroke (RR 0.86; 95% CI 0.75-0.98, p=0.48). There was an increase in the risk of hemorrhagic stroke (RR 1.36; 95% CI 1.01-1.82), major bleeding (RR 1.66; 95% CI 1.41-1.95), and gastrointestinal bleeding (RR 1.37; 95% CI 1.15-1.62). This meta-analysis supports previous outcomes concerning the beneficial effects of aspirin in the primary prevention of CVD. Although there was a reduction in the risk of myocardial infarction and ischemic stroke, there was not a reduction in cardiovascular mortality. These results may be explained by the aspirin doses, which ranged from 75 to 500 mg/day, concomitant use of other drugs, and associated risk factors. Another interesting finding was a reduction in all-cause mortality, which may be attributed to the efficacy of aspirin in reducing cancer mortality[24] and other medical conditions.[25,26] This study also found hemorrhagic strokes, major and gastrointestinal bleedings as adverse clinical outcomes. These side effects represent the main reason there is caution about recommending aspirin administration for primary prevention.

Recently, another meta-analysis of 107,686 participants from 14 prospective randomized controlled trials was published. The objective was to evaluate the benefit of aspirin for the primary prevention of CVD. Aspirin was found to reduce major cardiovascular events. Myocardial infarction had a risk reduction of 14% (RR 0.86; 95% CI 0.75-0.98; p=0.02); however, there was no reduction in the risk of overall stroke

Table 1. Randomized trials of aspirin use for primary prevention of CVD.

Reference	Trial design	Participants and interventions	Main clinical outcomes
BDS[15]	Randomized, non-blinded	5139 healthy male doctors, aged 19-90 years, follow up 6 years. Aspirin group received 500 mg daily vs. control group.	No significant difference in the incidence of non-fatal MI or stroke.
PHS[16]	Randomized, double-blind, placebo-controlled	22,071 healthy male physicians aged 40-84 years, follow up 5 years. Aspirin group received 325 mg every other day vs. control group.	Aspirin reduces the risk of MI, but there is inconclusive evidence concerning stroke and cardiovascular death.
H OT[17]	Randomized, double-blind	18,790 hypertensive patients, aged 50-80 years, mean follow up 3.8 years. Aspirin group was assigned to 75 mg/day vs. control group.	Aspirin significantly reduced major cardiovascular events with the greatest benefit seen in all MI. There was no effect on the incidence of stroke.
TPT[18]	Randomized, factorial, double-blind	5499 men at high risk of IHD, aged 45–69 years, mean follow up 6.8 years. Four factorial treatment groups were studied: active warfarin and active aspirin, active warfarin and placebo aspirin, placebo warfarin and active aspirin and placebo warfarin and placebo aspirin. Aspirin was given as 75 mg a day.	Aspirin reduces non-fatal IHD. Combined treatment with warfarin and aspirin is more effective in the reduction of IHD than only one drug.
PPP[19]	Randomized, open-label, 2×2 factorial	4495 patients, mean age 64.4 years, with one or more of the following conditions: hypertension, hypercholesterolemia, DM, obesity, family history of premature MI, or elderly, mean follow up 3.6 years. Aspirin was given as 100 mg/day.	Low-dose aspirin given in addition to treatment of specific risk factors contributes an additional preventive effect, with an acceptable safety profile.
WHS[20]	Randomized, double-blind, placebo-controlled, 2×2 factorial	39,876 healthy women, aged 45 years or older, mean follow up 10.1 years. Aspirin group received 100 mg on alternate days vs. control group.	Aspirin lowered the risk of stroke without affecting the risk of MI or death from cardiovascular causes.
AAAT[21]	Randomized, double-blind, controlled	3350 women and men free from CVD with a low ankle–brachial index, aged 50-75 years, mean follow up 10 years. Aspirin group received once daily 100 mg vs. placebo group.	Administration of aspirin did not result in a significant reduction in vascular events.
JPPP[22]	Randomized, open-label, parallel, multicenter	14,464 patients with hypertension, dyslipidemia or DM, aged 60-85 years, mean follow up 5.02 years. Aspirin group received 100 mg/day vs. placebo group.	Low-dose aspirin did not significantly reduce the risk of the composite outcome of cardiovascular death, nonfatal stroke, and nonfatal MI.

BDS – British Doctors' Study; PHS – Physicians' Health Study; TPT – Thrombosis Prevention Trial; HOT – Hypertension Optimal Treatment study; PPP – Primary Prevention Project; WHS – Women's Health Study; AAAT – Aspirin for Asymptomatic Atherosclerosis Trial; JPPP – Japanese Primary Prevention Project; MI – myocardial infarction; IHD – ischemic heart disease; DM – diabetes mellitus; CVD – cardiovascular disease.

(RR 0.95; 95% CI 0.87-1.05; p=0.34). When the sample was divided by sex, a reduction in major cardiovascular events of 12% among women (p=0.01) and 12% in men (p<0.01) was seen. Hemorrhagic strokes and major bleeding were increased with aspirin administration. For hemorrhagic strokes there was not a significant increase among women, but a 69% increase among men. Major bleeding events were significantly augmented, irrespectively of sex.[27] This work supports the efficacy of aspirin for primary prevention of CVD and suggests other interesting aspects. First, it seems there are differences between the efficacy of aspirin for myocardial infarction and stroke. This point should be analyzed individually, because if we can identify which patients would benefit from aspirin use it would be possible to obtain better results and reduce side effects. There are risk factors that predispose for the development of these con-

ditions, and their interpretation associated with an evaluation of global cardiovascular risk could represent a better approach to patient management. Second, hemorrhagic strokes were significantly increased among men. This medical condition is less common than ischemic stroke, but has a significantly higher mortality. Thus, it should be further studied why men appear to have a greater predisposition and which related risk factors are more important for evaluating individual vulnerability. As male patients suffer from CVD with a higher incidence than female patients, aspirin is more likely to be considered in men, but should be carefully evaluated from a benefit/risk point of view.

In 2009, the U.S. Preventive Services Task Force[28] published an update of previous guidelines[29] for the use of aspirin in the primary prevention of CVD. This consensus recommended the use of aspirin for men age 45 to 79 years old when there was a potential benefit in reducing the incidence of myocardial infarction that outweighed the risk of gastrointestinal hemorrhage. The use of aspirin was recommended for females aged 55 to 79 years old when the potential benefits of a reduction in ischemic strokes outweighed the risks of gastrointestinal hemorrhage. The expert panel did not recommend the use of aspirin in patients over 80 years old, or younger than 45 and 55 years old in men and women, respectively. Based on earlier trials, the dose of 75 mg/day was suggested as effective for preventing CVD with a low incidence of bleeding. Thus, one of the most interesting points of these 2009 guidelines was the recommendation of aspirin administration according to sex. Although a patient's sex is a recognized risk factor for developing CVD, other factors that have a greater influence on a patient's prognosis were not considered.

Another guideline was published three years later. The recommendation was to use 75 to 100 mg/day of aspirin for persons aged 50 years or older without symptomatic CVD.[30] These authors used the Framingham risk score, which predicts the 10-year risk of experiencing a cardiovascular event. This score evaluates the risk as low (<10%), moderate (10-20%), or high (>20%), based on several risk factors.[31] If the value of preventing myocardial infarction is higher than that of avoiding a gastrointestinal bleed, those people who are at moderate or high risk of CVD should take aspirin for primary prevention. It was remarked that there is evidence that aspirin reduces total mortality slightly if taken over 10 years.

Recently, the European Society of Cardiology's Working Group on Thrombosis released a position statement on aspirin use for the primary prevention of CVD.[32] They proposed a more conservative guide for aspirin administration than earlier recommendations (Figure 1). The first step should be to evaluate the patient's risk of major cardiovascular events using the Framingham risk score. Those patients with high risk (>20%) are eligible. Patients with a moderate risk (10-20%) are considered as potentially eligible. The second step should be to identify patients with a prior history of bleeding or current use of drugs that increase the bleeding risk. Finally, patients with a high risk and without medical conditions that increase the probability of bleeding can receive low-dose aspirin for primary prevention. Those with moderate risk should be individually discussed to evaluate the benefits/risks. Thus, this consensus is more conservative, because it only recommends the use of aspirin in patients with high cardiovascular risk. It evaluates the use of aspirin, taking into account individual cardiovascular risk and bleeding hazard. Patients with a high cardiovascular risk may benefit most. In these cases, the use of aspirin may represent a potential alternative for reducing CVD. The guide excluded those individuals with a low or moderate risk. In these patients, the benefit of aspirin administration is less likely, with reduced positive results and a balance of benefits/risks that is not well defined. Further studies should be designed to validate these recommendations in clinical practice. Although this guide suggests an individual evaluation of each patient before beginning aspirin therapy, there are many factors that can influence aspirin efficacy which do not depend on personal risk factors. Some of those factors include aspirin doses, duration of therapy, concomitant use of other drugs, and aspirin resistance.

At the same time, the Guidelines for Primary Prevention of Stroke were published by the American Heart Association and American Stroke Association.[33] This committee supports the above statements on aspirin use in primary prevention and adds new suggestions. They recommend the use of aspirin in people with a high cardiovascular risk when the benefits outweigh the treatment risk. Additionally, this guideline recommends the use of low-dose aspirin for prevention of a first stroke among women either with or without diabetes mellitus, and in patients with chronic kidney disease stages one to three.

This paper supports the use of low-dose aspirin for the primary prevention of CVD in patients with high cardiovascular risk. The main handicap for wide

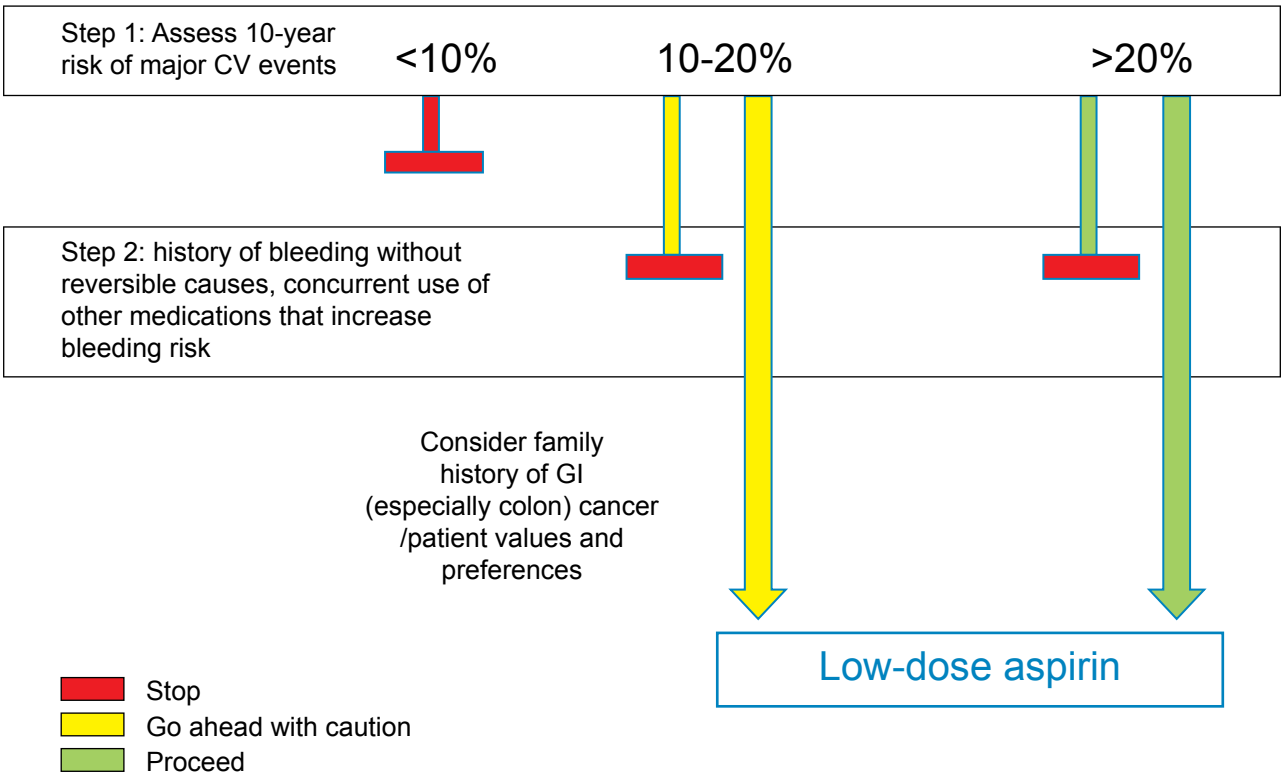

Figure 1. Proposed practical stepwise approach to the use of aspirin in primary prevention of cardiovascular disease (CVD). Patients eligible to receive aspirin for the primary prevention of CVD will be those with an estimated 10-year risk >20% based on the Framingham score. Patients with a 10-year risk between 10% and 20% will be deemed as "potentially eligible", and those with a risk <10% will be considered ineligible. The second step will be assessing safety in eligible and potentially-eligible patients, through a history of bleeding without reversible causes, and concurrent use of other medications that increase bleeding risk. In the absence of such conditions, patients with a risk >20% should be given low-dose aspirin, and those with a risk 10% to 20% should be engaged in a case-by-case discussion. Reprinted with permission from Halvorsen S, Andreotti F, ten Berg JM, et al. Aspirin therapy in primary cardiovascular disease prevention. A Position Paper of the European Society of Cardiology working group on thrombosis. J Am Coll Cardiol. 2014; 64: 319-327.

aspirin use in clinical practice is bleeding risk. So far, the general consensus is to use aspirin in patients with high cardiovascular risk when the benefits outweigh the risk of bleeding.

Further studies are needed to determine the benefit of aspirin in patients with low or moderate cardiovascular risk, and to find ways of reducing the bleeding risk in these patients so as to increase the benefits of aspirin use.

Primary prevention of cardiovascular diseases in patients with diabetes mellitus

Diabetes mellitus (DM) is a condition commonly associated with CVD. It has been reported that diabetic patients have a 2-3 fold higher risk of cardiovascular events.[34,35] The use of aspirin for the primary prevention of CVD in diabetic patients has been widely studied, but there are contradictory results (Table 2).[36-41] Diabetic patients have a predisposition for thrombogenic reactions and atherothrombosis.[42] The mechanism of action of aspirin may reduce both processes, which could explain some encouraging results from the use of aspirin for the primary prevention of CVD in these patients. At the end of the last century, the first reports were published concerning the benefits of aspirin use for preventing CVD in patients with DM.[36,43] Based on these investigations, the American Diabetes Association released a position statement a few years later, which recommended aspirin therapy for primary prevention of cardiovascular events in all diabetic patients over 30 years old with one additional risk factor for CVD.[44] Since then, other studies have demonstrated beneficial outcomes from low-dose aspirin use in primary prevention. The Japanese primary prevention of atherosclerosis with aspirin for

Table 2. Randomized trials of aspirin use for primary prevention of CVD in diabetic patients.

Reference	Trial design	Participants and interventions	Main clinical outcomes
ETDRS[35]	Randomized, double blind, placebo controlled, multicenter	3711 diabetic patients, aged 18-70 years, mean follow up 5 years. Aspirin group received 325 mg once per day vs. placebo group.	Aspirin use reduced the occurrence of fatal and non-fatal MI.
POPADAD[36]	Randomized, multicenter, double blind, 2×2 factorial, placebo controlled	1276 adults, aged 40 years or more, with type 1 or type 2 DM and an ABP index of 0.99 or less but no symptomatic CVD, mean follow up 6.7 years. Patients were divided into 4 groups. First, received daily 100 mg aspirin tablet plus antioxidant capsule. Second, aspirin tablet plus placebo capsule, Third, placebo tablet plus antioxidant capsule. Fourth, placebo tablet plus placebo capsule.	No evidence to support the use of aspirin in primary prevention of cardiovascular events and mortality.
JPAD[37]	Randomized, prospective, multicenter, open-label, blinded	2539 diabetic patients without a history of atherosclerotic disease, aged 30-85 years, median follow up of 4.37 years. Aspirin group 81 or 100 mg/day vs. placebo group.	Low-dose aspirin did not reduce the risk of cardiovascular events.
Sub-analysis of JPAD[38]	Randomized, prospective, multicenter, open-label, blinded	2523 diabetic patients who had serum creatinine measured without a history of atherosclerotic disease, aged 30-85 years, median follow up of 4.37 years. Aspirin and non aspirin patients divided into 3 groups: eGFR ≥90 mL/min/1.73 m^2, eGFR 60–89 mL/min/1.73 m^2, eGFR <60 mL/min/1.73 m^2.	The incidence of atherosclerotic events of fatal and nonfatal IHD, stroke, and peripheral arterial disease was significantly lower in the aspirin group.
Sub-analysis of JPAD[39]	Randomized, prospective, multicenter, open-label, blinded	2539 diabetic patients without a history of atherosclerotic disease, aged 30-85 years, median follow up of 4.37 years. Patients were divided into 2 groups: SBP≥140 mmHg and/or DBP≥90 mmHg: unattained group, SBP<140 mmHg and DBP<90 mmHg: attained group.	Aspirin therapy may reduce cerebrovascular events in diabetic patients with higher blood pressure.
Sub-analysis of JPAD[40]	Randomized, prospective, multicenter, open-label, blinded	2539 diabetic patients without a history of atherosclerotic disease, aged 30-85 years, median follow up of 4.37 years. Patients were divided into 2 groups CRP≥0.1 mg/dL: high CRP group, CRP<0.1 mg/dL: low CRP group.	Aspirin therapy may reduce cerebrovascular events in diabetic patients with higher CRP.

ETDRS – Early Treatment Diabetic Retinopathy Study; POPADAD – The Prevention of Progression of Arterial Disease and Diabetes; JPAD – Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; MI – myocardial infarction; DM – diabetes mellitus; CVD – cardiovascular diseases; ABP – ankle–brachial pressure; IHD – ischemic heart disease; CRP – C-reactive protein; SBP – systolic blood pressure; DBP – diastolic blood pressure.

diabetes (JPAD) trial, a multicenter, prospective and blinded study, enrolled 2539 patients with type 2 DM, but no history of atherosclerotic disease. They divided the patients into two groups (unattained group: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg; attained group: systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg:). The incidence of cerebrovascular events was significantly higher in the unattained group (5.2%) than in the attained group (1.9%) (HR 2.84; 95% CI 1.52-5.52; p=0.0008) in patients whose did not receive aspirin therapy. However, the incidence of cerebrovascular events in the unattained group (3.3%) was as low as the incidence in the attained group (2.1%) (HR 1.64; 95% CI 0.83-3.29; p=0.15) in patients receiving aspirin therapy.[40]

A subanalysis from the JPAD trial revealed that aspirin therapy may reduce the incidence of cerebro-

vascular events in diabetic patients with high levels of C-reactive protein.[41] C-reactive protein has been associated with inflammation and advanced atherosclerosis.[45] The thrombus inhibition by aspirin may explain the results of this investigation, supporting the hypothesis that diabetic patients with a higher risk of thrombosis, analyzed in terms of C-reactive protein and other inflammation markers, could receive greater benefits from aspirin use. If it can be demonstrated that the levels of inflammation markers are factors that may modify the benefits of aspirin use in primary prevention for reducing cardiovascular events in diabetic patients, they may be included in future recommendations for aspirin therapy in addition to the classic risk factors. On the other hand, there is a growing evidence of the lack of benefit from the use of aspirin for the primary prevention of CVD in diabetic patients. In a meta-analysis of randomized controlled trials, 10,117 patients were studied to evaluate the benefits and risks of low-dose aspirin in patients with diabetes and no CVD. There was no statically significant reduction in the risk of cardiovascular events (RR 0.90; 95% CI 0.8-1.00) or cardiovascular mortality (RR 0.94; 95% CI 0.72-1.23). When patients were analyzed by sex, it was observed that aspirin use significantly reduced the risk of myocardial infarction in men (RR 0.57; 0.34-0.94), but not in women (RR 1.08; 0.71-1.65).[46] Based on these results, the authors concluded that there is no evidence of a benefit from aspirin administration for the primary prevention of CVD in diabetic patients. Similar outcomes were shown in another meta-analysis:[47] there was no significant association between aspirin use and the reduction of CVD. Thus, there are contradictory results concerning the use of aspirin for the primary prevention of CVD in diabetic patients.

Future studies should analyze factors that may modify the benefits of aspirin use. It has been found that concomitant risk factors worsen the prognosis of diabetic patients.[48] Other factors to investigate are age of onset, metabolic control, and drugs simultaneously used. There is evidence that children and young adults with recent onset diabetes are at relatively low risk of CVD.[49] In these patients the use of aspirin could not show great benefit. It has been demonstrated that glibenclamide, a second generation of sulfonylurea, has antiarrhythmic properties due to the blockage of cardiomyocyte ATP-dependent potassium channels during myocardial ischemia. The blockage of these channels increases the refractory period in the heart and reduces the risk of malignant cardiac arrhythmias. Patients who receive glibenclamide for the treatment of DM could obtain additional protection and this may explain the diversity of results.[50-52] Statins and carvedilol have also demonstrated beneficial effects in reducing complications and improving the prognosis of patients with DM. Both drugs simultaneously administrated with aspirin in diabetics could increase the benefits as regards the primary prevention of CVD. The use of statins for primary prevention in diabetic patients has demonstrated a significant reduction in the first-time occurrence of major cardiovascular events (RR 0.75; 95% CI 0.67-0.85), fatal/non-fatal stroke (RR 0.69; 95% CI 0.51-0.92), and fatal/non-fatal myocardial infarction (RR 0.70; 95% CI 0.54-0.90).[53] Carvedilol, a third-generation, nonselective beta-blocker that possesses alpha-1 adrenergic blocking, antioxidant, and calcium antagonist properties, has shown an improvement in glycemic control, insulin resistance, and triglyceride levels, and less development of microalbuminuria in hypertensive diabetic patients.[54-56] This may reduce the progression to CVD and the concomitant use of aspirin therapy could show better benefits in terms of primary prevention.

Multiple factors may be related with aspirin's usefulness in the primary prevention of CVD. They should be evaluated in each patient. Further studies and guidelines that have the objective to evaluate the benefits of aspirin in these patients should take into account the abovementioned information.

Ongoing studies

Although studies of aspirin use for the primary prevention of CVD began some decades ago, there are clinical settings where aspirin administration needs further investigation. New investigations have been designed and are currently ongoing to clarify key points such as the use of aspirin in older people and the concomitant administration of aspirin and simvastatin in diabetic patients. Atherosclerotic disease has a higher prevalence in older people. In these patients, there is a dearth of evidence concerning the use of aspirin for the primary prevention of CVD; however, it is a population group that could receive high benefits. ASPREE[57] and ENVIS-ion[58] enrolled older patients without CVD. Both randomized studies administer daily oral 100 mg aspirin in the study group compared with a matching placebo group. The primary endpoint includes total mortality, onset of dementia, or persistent disability. The results of these studies could

help us to extend our knowledge regarding aspirin use in this patient population. Also, they should establish a balance of risk and benefits in order to guide physicians who are considering using aspirin for primary prevention in these patients.

Recent published data reveal that low-dose aspirin does not reduce the risk of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke in older Japanese patients.[22]

It should be taken into account that the pharmacodynamic and pharmacokinetic characteristics of aspirin are different in older patients, which could influence aspirin's efficacy and increase side effects. This and other points should be further evaluated to achieve definitive conclusions.

Another current study aims to evaluate the efficacy of aspirin plus simvastatin for the primary prevention of major cardiovascular events in diabetic patients.[59] This study is based on the positive effects of aspirin and simvastatin in the prevention of cardiovascular events in diabetic patients and the importance of using multiple preventive strategies for reducing cardiovascular risk. The association of aspirin and simvastatin may reduce the elevated thrombogenic condition observed in diabetic patients.

Hemorrhagic complications with aspirin use

Hemorrhagic complications are the most severe side effects with aspirin use. It has been observed that the relative risk of bleeding events with low-dose aspirin is higher when it is used for primary prevention compared to secondary prevention.[60] The risk of intracranial hemorrhage is increased by about 40%[61] and the prevalence of ulcer and erosion in aspirin-treated patients is 10.7% and 63.1%, respectively.[62] These complications result in increased rates of hospitalization and mortality. However, these percentages may vary depending on factors that have been demonstrated to influence the risk of bleeding associated with aspirin use. Factors associated with an increased risk for major bleedings (gastrointestinal and cerebral bleedings) are diverse and include 1) prior history of bleeding, 2) associated risk factors, 3) aspirin doses and treatment duration, and 4) simultaneous use of other drugs. Although these factors have been widely studied, there are inconsistent results and only a few have been well established as risk factors for bleeding events.

A prior history of gastrointestinal bleeding has been demonstrated to be a risk factor for a new hemorrhagic event in patients using aspirin. The use of low-dose aspirin has been associated with an increase in the risk of hospitalization with upper gastrointestinal bleeding in patients with a previous history of gastrointestinal bleeding (OR 6.5; 95% CI 2.0-21.2). There was also an increase in the risk of bleeding with a prior history of ulcer (OR 2.0; 95% CI 1.0-4.1).[63] Another study showed that patients with a history of uncomplicated ulcer disease had a relative risk of 4.2 (95% CI 2.4-7.2) and patients with a history of complicated peptic ulcer disease a relative risk of 5.7 (95% CI 2.7-12.0) compared to patients without a previous episode of peptic ulcer disease.[64] The predisposition of patients with a prior history of gastrointestinal bleeding to develop a new hemorrhagic event is related to some pathogenic mechanisms associated with aspirin use. Suppression of prostaglandin synthesis with aspirin is the most important factor associated with gastric ulcers. However, this is not the only mechanism. It has been established that topical irritant effects on the epithelium and interference with the healing of pre-existing lesions are mechanisms that can explain gastrointestinal damage with aspirin use and the risk of bleeding.[65,66] Recently, an investigation group found that patients with a prior history of ulcer bleeding using low-dose aspirin have an increased risk for recurrent bleeding. They suggest the use of proton-pump inhibitors added to the therapy with aspirin for reducing the incidence of hemorrhagic complications.[67] These results were supported by another study that reported a reduced risk of upper gastrointestinal bleeding with concomitant use of these drugs.[68] Proton-pump inhibitors could be an alternative for patients with a high risk of CVD who are using aspirin. Recently, the use of aspirin plus proton-pump inhibitors in a single pill has been proposed in order to reduce upper gastrointestinal complications and increase patients' adherence to the treatment.[69,70] This reflects the application of our knowledge of the pharmacokinetic characteristics of both drugs to achieve high levels of efficacy and safety with this combination.

The most studied risk factors for developing hemorrhagic complications in patients receiving aspirin therapy are age, male sex, diabetes, current smoking, mean blood pressure, and body mass index. They have been studied in multiple clinical investigations with large samples and diverse study designs. The Antithrombotic Trialists' Collaboration indicated that age, male sex, diabetes, current smoking, and mean blood pressure (per 20 mmHg) were each associated with about a twofold increased risk for hemorrhagic events. These same risk factors were also related with an in-

creased risk for coronary events.[71] Recently 501,946 individuals aged 30-95 years old were studied to examine the effects of low-dose aspirin use on major hemorrhagic events. The risk of bleeding events associated with aspirin use was 1.35 (95% CI 1.10-1.65; p=0.0029) for gastrointestinal hemorrhage and 1.28 (95% CI 0.99-1.66; p=0.0623) for cerebral hemorrhage. The hemorrhagic events occurred in 63.9% of men and 36.1% of women. There was also an increased risk for major bleeding in hypertensive and diabetic patients, but with a lower incidences than in patients without these conditions.[72] Similar results were found by De Berardis et al,[73] who reported that the risk of major bleeding events with the use of aspirin was significantly lower in non-diabetic and non-hypertensive patients than in those with these conditions. Additionally, female patients had a significantly higher incidence of major bleeding events than males. Other studies have demonstrated that alcohol use[64] and increased body mass index[74] are linked with an increased risk for gastrointestinal bleedings in patients taking aspirin, but the results were inconsistent. As can be seen, there is no clear consensus about the influence of these risk factors in the development of hemorrhagic complications in patients using aspirin. These conditions should be evaluated overall, in association with other factors that have been demonstrated to be associated with an elevated risk for bleeding with aspirin use. It should be necessary to make an individual risk assessment of each patient for better medical outcomes.

Aspirin doses and treatment duration are often related with a raised risk for bleedings. Kelly et al[75] demonstrated that patients receiving >325 mg/day of aspirin had a higher risk for hemorrhagic complications than those receiving ≤325 mg/day. Aspirin dose was shown to increase the risk of major gastrointestinal bleeding in patients enrolled in the Nurses' Health Study. In this investigation, 87,680 women were studied over a 24-year follow up. The relative risk of gastrointestinal bleeding was 1.03 (95% CI 0.85-1.24) in those individuals who used 0.5 to 1.5 standard aspirin tablets/week, 1.30 (95% CI 1.07-1.58), in those taking 2 to 5 tablets/week, 1.77 (95% CI 1.44-2.18) for 6-14 tablets/week, and 2.24 (95% CI 1.66-3.03) for >14 tablets/week, all compared with those who denied any aspirin use.[76] Further, when the sample was adjusted for doses, increased duration of treatment did not confer greater risk. Other investigators have failed to find a direct association between aspirin dose and the risk of bleeding events. In the Antithrombotic Trialists Collaboration the risk of a major extracranial bleed did not show significant differences in patients receiving <75 mg of aspirin versus those receiving 160 to 325 mg per day.[77] Similar outcomes were found by Serebruany et al.[78] They found no significant differences in major bleeding between patients treated with <100 mg/day and those treated with 100 mg to 325 mg/day. Regarding aspirin treatment duration, it has been found that patients have an almost fivefold risk of gastrointestinal bleeding in the first week of treatment, while the risk is reduced to threefold after three months. It appears that there is an adaptation process to aspirin use that reduces the risk of gastrointestinal bleeding. There are contradictions in the risk of bleeding events related to aspirin doses and treatment duration. Other factors, such as aspirin preparation, treatment regimen, associated risk factors, and concomitant use of other drugs, are likely have an influence on the risk of bleeding. Thus, it appears that the aspirin dose and treatment duration for a reduced risk of bleeding should be the lower dose. The duration of treatment should be carefully considered, taking into account the risk of major cardiovascular events.

Simultaneous administration of non-steroidal anti-inflammatory drugs, platelet aggregation inhibitors, and anticoagulants has been associated with an elevated risk of bleeding. A combination of low-dose aspirin and non-aspirin antiplatelet medications increases the risk of bleeding for gastroduodenal ulcers (OR 6.70; 95% CI, 1.83-24.50; p=0.002)[79] and the recommendation is to use a single drug whenever possible.[80] The use of a vitamin K antagonist plus low-dose aspirin also increases the risk of gastrointestinal bleeding (OR 5.3; 95% CI 2.9-9.5). The concomitant administration of non-steroidal anti-inflammatory drugs in low-dose aspirin patients has been found to increase the risk for developing gastrointestinal bleeding. It has been demonstrated that odds ratios rose by eightfold[81] to twelvefold[82] in those patients who took both aspirin and non-steroidal anti-inflammatory drugs, with the risk being higher than for users of aspirin alone and non-users.

The risk of bleeding in patients using aspirin should be carefully evaluated before and after the start of treatment. Physicians should estimate the balance of risks and benefits in each patient, which constitutes the key aspect in aspirin use for the primary prevention of CVD. This is of major importance, because the risk of bleeding events is the main reason for the non-use of aspirin for primary prevention of CVD and

for abandoning treatment. As mentioned above, most proposed risk factors for hemorrhagic events in patients using low-dose aspirin need further investigation. From accumulated data, Valkhoff et al[83] established that a prior history of peptic ulcer disease or gastrointestinal bleeding, concomitant use of non-steroidal anti-inflammatory drugs including coxibs, *Helicobacter pylori* infection, and short aspirin therapy duration are definitive risk factors for gastrointestinal bleeding. For intracerebral hemorrhage, the risk factors that have been most widely studied and that appear to have the greatest link with bleeding risk are: prior history of stroke or cerebral bleeding, hypertension, older age, and cerebral amyloid angiopathy.[84-86] For both gastrointestinal and intracerebral bleeding, the related risk factors are diverse and heterogeneous. Table 3 summarizes the most studied risk factors. It can be seen that there are common conditions for both gastrointestinal and intracerebral bleeding. Many of them can be eliminated, or at least controlled, which could reduce the probability of bleeding events. The challenge is how to integrate this knowledge in order to reduce the incidence of hemorrhagic events. To achieve this aim, it will be necessary to understand the mechanisms associated with each risk factor, in order to allow the planning of better medical strategies. Future guidelines should take into account the presence of these conditions, which could help us to make better risk/benefits evaluations.

Unanswered questions and future directions

Several issues should be further clarified in order to reach an accurate aspirin indication. First, the guidelines for aspirin administration for the primary prevention of CVD are based on the Framingham score. However, other scores have been demonstrated to be effective for evaluating the risk of cardiovascular events.[87-91] Second, there is no consensus on the ranges to be used internationally for aspirin treatment. It seems that lower doses determine the best benefits and a reduction in hemorrhagic complications,[92] but factors such as duration of therapy, aspirin preparation, treatment regimen, and concomitant administration of other medications warrant further study. Third, a prior history of peptic ulcer disease or gastrointestinal bleeding, concomitant use of non-steroidal anti-inflammatory drugs, *Helicobacter pylori* infection and high aspirin dose have been proposed as risk factors for gastrointestinal bleeding,[83] but there is no consensus regarding factors affecting intracerebral bleeding linked to aspirin use. Fourth, DM is a metabolic condition with complex pathophysiological mechanisms that has received multiple therapeutic interventions and further studies should be addressed to obtain definitive conclusions.

Finally, aspirin resistance may play an important role in clinical outcomes in the prevention of CVD and could explain, in part, the diversity of results. This is defined as the failure of aspirin to prevent an acute vascular thrombotic event, despite regular intake of adequate doses. The prevalence of this condition ranges from 5% to 70% in patients with CVD and it has been demonstrated that aspirin resistance increases the risk of cardiovascular events.[93,94] Aspi-

Table 3. Main risk factors associated with gastrointestinal and intracerebral hemorrhage.

Gastrointestinal hemorrhage	Intracerebral hemorrhage
Prior history of peptic ulcer disease or GI bleeding	Prior history of stroke or cerebral bleeding
Concomitant use of non-steroidal anti-inflammatory drugs	Hypertension
Helicobacter pylori infection	Older age
Short-duration aspirin therapy	Cerebral amyloid angiopathy
Anticoagulants and other platelet aggregation inhibitors	History of heavy alcohol use
History of heavy alcohol use	Neoplasm
High body mass	Vasculitis
Corticosteroid use	Diabetes mellitus
Calcium channel blocker use	Smoking
History of dyspepsia	Bleeding disorders
High aspirin dose	Vascular malformations
Regular aspirin use	Aneurysms
Older age	Trauma
Presence of severe comorbidities	Anticoagulant use
	Diet risk

rin resistance has been seen with greater frequency in female patients.[95] This epidemiologic element could explain the diversity of results among men and women when aspirin is administrated for the primary prevention of CVD. Other risk factors for aspirin resistance include DM, obesity, post-acute coronary syndrome, a history of stent thrombosis, and coronary artery bypass grafting.[96] The mechanisms of aspirin resistance are poorly understood. They include low bioavailability, an increased aspirin turnover, use of nonsteroidal anti-inflammatory drugs, genetic modification of platelet COX-1, and platelet hyperreactivity.[97] In all likelihood, aspirin resistance is a multifactorial condition. A large number of platelet function assays have been designed in order to identify aspirin resistance. Some of the most studied are Flow Cytometric Markers of Platelet Activation, Soluble P-Selectin, Urine or Serum Thromboxane B2, Light Transmission Aggregometry, and VerifyNow. These assays have wide values of sensitivity and specificity with no consensus about which are most useful in clinical practice.[96] The heterogeneity of platelet function assays has been an adverse factor for evaluating the prevalence of aspirin resistance and determining patients who are at high risk of cardiovascular diseases.

Conclusions

Current guidelines propose the use of aspirin for the primary prevention of CVD in patients at moderate or high risk based on the Framingham risk score. The balance of benefits and risks should be carefully evaluated in each patient before and after starting aspirin treatment. Bleeding episodes represent the main adverse event with aspirin use. Physicians need to estimate a patient's risk, taking into account those factors that predispose to hemorrhagic complications. The use of aspirin in diabetic patients needs further study before a global implementation in clinical practice, because of the lack of evidence of clear benefits. Future prospective studies are needed to examine aspirin benefits using other risk scores, the dose of aspirin associated with a better risk/benefit ratio, the influence of risk factors on aspirin efficacy and safety, and the role of aspirin resistance.

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