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Aspirin and the primary prevention of cardiovascular diseases: An approach based on individualized, integrated estimation of risk

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Abstract:	While the use of aspirin in the secondary prevention of cardiovascular (CVD) is well established, aspirin in primary prevention is not systematically recommended because the absolute CV event reduction is similar to the absolute excess in major bleedings. Recently, emerging evidence suggest the possibility that the assumption of aspirin, may also be effective in the prevention of cancer. By adding to the CV prevention benefits, the potential beneficial effect of aspirin in reducing the incidence of mortality and cancer could tip the balance between risks and benefits of aspirin therapy in the primary prevention in favour of the latter and broaden the indication for treatment with in populations at average risk. While prospective and randomized study are currently investigating the effect of aspirin in prevention of both cancer and CVD, clinical efforts at the individual level to promote the use of aspirin in global (or total) primary prevention could be already based on a balanced evaluation of the benefit/risk ratio.
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Author Comments:	Dear Editor, Enclosed please find our manuscript, entitled "Aspirin and the primary prevention of cardiovascular diseases: an approach based on individualized, integrated estimation of risk.", that we wish to submit for evaluation and potential publication on High Blood Pressure and Cardiovascular Prevention. As you will see, this manuscript addresses in a critical way evidence published so far about the favourable effect of the treatment with aspirin in subjects without previous known cardiovascular diseases. In our opinion, this is a topic of growing importance and interest, as recent data, derived from longer follow up of previous randomized controlled trial and from meta-analysis, may account for an enlarged indication for

	therapy with aspirin in primary prevention. In particular, Authors decided to propose a global estimation of individual risk, by focusing on the comparative evaluation of the anti atherotrombotic, antineoplastic actions of aspirin and the consequent increased risk of bleeding. We strongly believe that this "state of the art" paper could be helpful to clinicians in everyday practice. Please consider that the paper in the present version is not under consideration elsewhere. A recent Italian consensus document of the Italian Society of Cardiovascular Prevention (SIPREC) reports many of the concepts reported in the present position article. Therefore, we acknowledge the contribution of Prof. Carlo Patrono and Prof. Bruno Trimarco to have critically gone through the Italian version of this manuscript. All of the authors have read and approved the manuscript. I sincerely hope you will find our manuscript of interest for the Readers of High Blood Pressure and Cardiovascular Prevention and I wish to thank you in advance for the consideration you will give to our work. With my best regards, Massimo Volpe
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Aspirin and the primary prevention of cardiovascular diseases:

An approach based on individualized, integrated estimation of risk

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Abstract (161 words)

While the use of aspirin in the secondary prevention of cardiovascular (CVD) is well established, aspirin in primary prevention is not systematically recommended because the absolute CV event reduction is similar to the absolute excess in major bleedings. Recently, emerging evidence suggest the possibility that the assumption of aspirin, may also be effective in the prevention of cancer. By adding to the CV prevention benefits, the potential beneficial effect of aspirin in reducing the incidence of mortality and cancer could tip the balance between risks and benefits of aspirin therapy in the primary prevention in favour of the latter and broaden the indication for treatment with in populations at average risk.

While prospective and randomized study are currently investigating the effect of aspirin in prevention of both cancer and CVD, clinical efforts at the individual level to promote the use of aspirin in global (or total) primary prevention could be already based on a balanced evaluation of the benefit/risk ratio.

Introduction

The twentieth Century may be characterized, from the standpoint of Medicine, as the "Century of Aspirin", since acetylsalicylic acid, aspirin, has been one of the most outstanding medical innovations, which has improved, without any doubt, the expectancy and the quality of life for many people across the world. In "The Revolt of the Masses", J. O. Gasset wrote: "*The life of the average man today is easier, more convenient and safer than that of the most powerful man from a different era. He does not care to be richer than his neighbour if the world around him provides him with magnificent roads, railways, telegraphs, hotels, personal safety and aspirin*" [1].

Since its discovery in 1899, aspirin has become the most popular drug worldwide. The clinical use of aspirin, initially restricted to a successful treatment of rheumatic diseases, has been revolutionized by the development of low-dose formulations for the treatment and the prevention of cardiovascular diseases (CVD). In patients affected by coronary artery and cerebrovascular disease, the chronic assumption of aspirin has been associated with a consistent and significant reduction of mortality and recurrence of major atherothrombotic events. In this population, the increase in bleeding turns out to be acceptable in the end [2-3]. On the other hand, the role of antithrombotic drugs in primary prevention, for patients without previous CVD, is still unclear, because of their low risk of developing atherothrombotic events at baseline. More recently, many randomized trials and meta-analyses have suggested a beneficial role of aspirin even in the setting of primary prevention of CVDs.

Indeed, the favorable effects of a preventive therapy with aspirin are not likely to disappear when moving from the setting of secondary prevention to primary prevention in high-risk patients, as the CV risk develops as a continuum rather than following a switch on/off pattern.

Data from both experimental and observational studies have demonstrated that aspirin might play a role in preventing colorectal cancer (CRC) and other types of cancer. This possible additional beneficial effect is very appealing, and may therefore strengthen and broaden the indications of the treatment with aspirin in populations at average risk. Prospective and randomized studies are currently investigating the effect of aspirin for the prevention of both cancer and CVD [4-6].

To assess the expected magnitude of the reduction of CV events with aspirin therapy, it is essential to estimate the baseline CV risk for everyone. For this purpose, the Framingham coronary heart disease (CHD) risk score [7], the American College of Cardiology/American Heart Association (AHA/ACC) Task Force risk equations [8] and the Systematic Coronary Risk Evaluation (SCORE) system, recommended by the European Society of Cardiology [9], are now widely used in clinical practice. The Framingham CHD risk score predicts the 10-year risk of developing a coronary event (a composite of myocardial infarction-MI and coronary death), so that individuals are categorized as low (<10%), moderate (10% to 20%), or high (>20%) risk. The SCORE system estimates the 10-year risk of a fatal atherosclerotic event: individuals should be considered at low risk with a SCORE <1%, at moderate risk with a SCORE >1% and <5%; at high risk with a SCORE >5% and <10%; and at very high risk with a SCORE 10%. [9] The combined risk of fatal and nonfatal CV events is three-fold higher than of fatal events alone. [9]

Similarly, to assess the individual likelihood of CRC, several risk-prediction models have been designed. Freedman et al. have proposed a chart that estimates the chance of developing CRC given a specific age, risk-factor profile (including colonoscopy and adenoma history in the last 10 years, number of relatives with CRC, leisure and physical activity time, regular use of aspirin/NSAIDs, smoking, vegetable intake, body mass index, and, for white women aged ≥50 years, estrogen status within the last 2 years). [10]

In this view, the development of a composite or combined prediction model for CV and CRC risk may be extremely helpful and appealing, and it would allow the assessment of the global risk/benefit odd of aspirin therapy in primary prevention.

Even before the scientific community will be able to assess the specific role of aspirin in primary prevention with conclusive results derived from ongoing trials, it appears reasonable to anticipate this recommendation in selected individuals at high CV risk, because this strategy might possibly contribute to avoid many CV events and their dangerous consequences for patients, national health services and national economies.

Aspirin for the primary prevention of cardiovascular disease: PROS

Since 1980s, 9 large-scale prospective randomized controlled trials (RCT) have analyzed the role of aspirin in primary prevention: the British Doctors' Trial (BMD) [11], the Women's Health Study (WHS) [12], the Primary Prevention Project (PPP) [13], the Physicians' Health Study (PHS) [14], the Thrombosis Prevention Trial (TPT) [15], the Hypertension Optimal Treatment (HOT) study [16], the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) [17] trial, the Aspirin for Asymptomatic Atherosclerosis Trial (AAAT) [18] and the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial [19], including altogether more than 100,000 participants [20], with a 1:1 ratio between ASA and non on ASA patients.

The Physicians' Health Study (PHS) [14] enrolled men aged ≥40 years, randomized to aspirin 325 mg every other day or placebo. With regards to the secondary endpoint of myocardial infarction (MI), there was a 44% reduction in the group treated with aspirin versus placebo. Similar results were obtained in the Thrombosis Prevention Trial (TPT), which enrolled high-risk patients [15]. The Hypertension Optimal Treatment (HOT) trial [16], including almost 20,000 patients aged 50-80 years old and randomized to aspirin 75

mg or placebo, and the Primary Prevention Project (PPP) [13], including 4,495 individuals aged >65 years randomized to aspirin or placebo for three years, demonstrated a significant reduction of MIs (36% and 25% respectively) when taking aspirin.

However, in the British Doctors Trial (BDT) [11], that enrolled about 5,000 healthy men aged <80 years old, randomized to aspirin 500 or 300 mg for six years, the investigators failed to report a reduction of MIs and CVD mortality.

Individuals with a higher baseline CV risk have been enrolled in 3 recent RCTs. The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) [19] trial randomized more than 1,000 individuals affected by type 1 or 2 diabetes mellitus and an ankle brachial index <0,99 to ASA 100 mg or placebo. It did not show any significant difference in CV endpoints between the two groups. On the other hand, in the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial [17], which included about 2,000 diabetic patients randomized to aspirin 81 mg or placebo, the primary endpoint, a composite of CV and cerebrovascular fatal and nonfatal events, showed fewer events in the aspirin arm. In contrast, significant differences in the number of fatal and nonfatal coronary artery events, ischemic stroke and peripheral artery thrombotic events were not demonstrated in the Aspirin for Asymptomatic Atherosclerosis Trialists study (AAAT) [18], which included more than 3,000 patients with an ankle brachial index <0,95 randomized to aspirin 100 mg or placebo.

Data on female subjects were obtained in the Women's' Health Study (WHS) [12], which enrolled more than 40,000 women >45 years old, did not show a significant reduction in the primary endpoint of MI, fatal and non-fatal, and death, CV or not. On the other hand, aspirin assumption was associated with a 22% reduction of ischemic stroke. Instead, currently data show a consistent benefit of aspirin in women aged >65 years, leading to a 26% reduction of CV events and 30% of ischemic stroke.

Following the publication of these trials, new meta-analyses have revisited pooled data on the role of aspirin in CV prevention. The Anti-Thrombotic Trialists Collaboration has carried one of the most important one. [21] The endpoints were fatal and non-fatal MI, non-fatal hemorrhagic and ischemic stroke; all cause death and a composite of MI, stroke and atherotrombotic death. Reductions by aspirin were reported for MI and non-fatal stroke, especially ischemic ones, with an increase in bleeding events. No difference was reported in the number of CV deaths.

A different meta-analysis of 10 trials, including 118,445 individuals aged 55-65 years, was carried out by the US Preventive Society Task Force (USPSTF) [22], and demonstrated a consistent efficacy of aspirin therapy in the prevention of nonfatal MI (relative risk [RR] 0.83 [95% CI, 0.74 to 0.94]) and stroke (RR, 0.86 [CI, 0.76 to 0.98]), but not CV death (RR, 0.94 [CI, 0.86 to 1.03]). A low-dose formulation <100 mg was administered in 8 studies; the follow-up lasted a mean of 3-10 years. A significant reduction of all-cause mortality (RR, 0.94 [CI, 0.89 to 0.99]) was demonstrated with aspirin at any dose, not only with low dose therapy. [22]

Special attention should be reserved to diabetic patients whose CV risk is 2-4 times greater than non-diabetic patients. [23-24-25] Univocal results about the efficacy of aspirin in primary prevention in diabetic patients are not yet available. Inconclusive data derive from three randomized trials that enrolled only diabetic individuals [17; 19; 26] and from six trials including a diabetic subgroup (1%-22% of cumulative number) [11-16]. A non-significant reduction of coronary artery (9%) and cerebrovascular (11%) events resulted from four meta-analyses. [23; 27-29] On the contrary, a recent meta-analysis of the USPSTF described a similar effect of aspirin therapy in patients either affected by type 2 diabetes mellitus or not. [22]

THE WHS reported that in women aspirin did not seem to influence coronary artery events, CV and all-cause mortality. However, aspirin was associated with a 22% reduction of the number of transient ischemic attacks. [12] Currently available data show a consistent benefit of aspirin in women aged >65 years, leading to a 26% reduction of CV events and 30% of ischemic stroke. In this group of subjects, aspirin reduced risk of MI as well. The 2009 meta-analysis from the Antithrombotic Trialists' Collaboration showed that ASA plays a similar protective effect on CV in males and females. [21]

Aspirin for the primary prevention of cardiovascular disease: CONS

Therapy with aspirin is associated with an increased risk of major bleeding, especially gastrointestinal (GI) and intracranial bleeding events, defined as “a bleed requiring transfusion or resulting in death”. (30) Moreover, there is no evidence that enteric-coated aspirin may reduce gastric bleeding. [30-31-32]

A meta-analysis of six placebo-controlled RCTs showed that treatment with aspirin was associated with an increase in the relative risk of hemorrhagic stroke of 32% [21]. The bleeding risk increases with concurrent anticoagulation or NSAID use, smoking, uncontrolled hypertension, male sex, older age, history of GI ulcers or upper GI pain, bleeding disorders, renal failure, severe liver disease and thrombocytopenia. [33-34]

Therefore, the bleeding risk appears to be higher in individuals at higher CV risk, who might have the greatest benefit from aspirin therapy. In low-risk population treated with aspirin, 4 more bleeds per 1,000 persons have been calculated, versus 22 more bleeds per 1,000 persons in high-risk individuals. [7]

Aspirin for the primary prevention of colorectal cancer

CVDs and cancer are the leading causes of mortality and morbidity worldwide, as they together account for almost 2/3 of global mortality. It is now well known that they both share many risk factors, such as cigarette smoking, high-calorie diet, alcohol abuse, a sedentary lifestyle, a low socio-economic status and environmental pollution. [35-42] Therefore, targeted interventions on lifestyle were effective, although not univocally, in preventing both diseases. [43-44]

On the other hand, many studies, especially in animals, have shown that CV drugs such as ACE inhibitors and angiotensin receptor blockers [45-46], beta-blockers [47] and statins [48-49] may play a role in cancer prevention. It seems that ASA, through the irreversible inhibition of cyclooxygenase-1 (COX 1) (low dose) and COX-2 (high dose), may be able to inhibit specific pathways of carcinogenesis. Cohort studies have also shown a reduction in mortality from all causes and from cancer in patients with non-metastatic colorectal cancer who had started to regularly aspirin intake after diagnosis. [50-51] Some RCTs have also highlighted that aspirin decrease the recurrence of colorectal adenomas in patients undergoing endoscopic polypectomy. [52-53]

These data are supported by large meta-analyses that [6-54-55] have demonstrated that aspirin, when assumed for more than 5 years at a daily dose of 75 to 300 mg, can reduce the incidence of CRC by 40% [56], 20 years-mortality (10.2% versus 11.1% in placebo groups) and the risk of metastasis after a latency period of 8-10 years. This benefit seems to increase further with duration of the treatment. [57] However, these results derive from post-hoc analysis of RCTs designed and conducted to evaluate CV outcomes. Moreover, the exclusion of the WHS and PHS, which previously failed to show the protective effect of aspirin on cancer genesis, should be considered. [58] Thus, recently, the 15 years' follow-up of the WHS showed a net benefit of alternate-day regimen with aspirin when

considering CV events, the development of cancer and gastrointestinal bleeding in women ≥65 years. [59-60]

Data on the benefit of aspirin in the prevention of different types of cancer such as prostate [61], breast [62], oesophagus [63], and head-and-neck [64] are much less robust. [65-67] As mentioned above, the effects of the aspirin in the prevention of CRC seem to achieve a significance after at least 5-10 years of therapy. [68-69] Therefore, we believe that the greatest benefit might be achieved by initiating treatment in patients aged between 40 and 59 years. [70] However, more “ad hoc” studies will be required to clarify the effect of aspirin per different genders, age, race and genetics. It remains to be univocally determine the best dosage of aspirin to be used and its possible effects in the long term, about the duration of its beneficial effects after discontinuation of therapy.

Looking at the evidence collected so far, now, the use of aspirin for primary prevention is not recommended in patients at intermediate risk for CRC (adults of 50-70 years with a family history, but in the absence of hereditary diseases, such as Lynch syndrome and familial adenomatous polyposis and inflammatory bowel disease). The American Cancer Society has not made recommendations for or against the administration of aspirin, while the American Gastroenterological Association recommend the use only in patients with high risk for CRC. [71]

Recommendations of International Scientific Societies about the use of aspirin in primary prevention.

Inappropriate and "off-label", often based on patients’ preference, prescription of aspirin for primary prevention is a usual finding in clinical practice, because there is not a clear and unambiguous indication on whom might benefit more from this treatment. [72] The Food

and Drug Administration has denied the indication of aspirin for the CV primary prevention in the USA. In Italy, on the other hand, personal choices of every patient often take over. Generally, the scientific community shares the belief that the decision to begin the therapy with aspirin for primary CV prevention, should be evaluated on an individualized basis, and be tailored on the CV risk profile and the risk of haemorrhage. The individual characteristics of patients, the expected benefits, the potential risks and preferences of subjects should be considered to characterize, as far as possible, the role of aspirin with a view for an integrated primary prevention (Figure 1).

Per the latest guidelines of the European Society of Cardiology (ESC), ASA (or clopidogrel) is not recommended for individuals without CV or cerebrovascular disease because of the increase in the risk of bleeding (9). However, aspirin may be indicated for hypertensive patients with renal insufficiency or at high CV risk and should be considered in diabetes mellitus. [9]

The American College of Chest Physicians guidelines [7], if aspirin, when taken for more than 10 years, might reduce mortality from CV causes regardless of the starting risk profile, suggest low-dose use in all subjects aged >50 years in the absence of contraindications. The American Heart Association and the American Stroke Association [73] recommend the use of low-dose aspirin in patients with a risk of CV events high enough to offset the potential adverse effects of the treatment, i.e., 6-10% in 10 years.

The American Diabetes Association and the American Cardiology Collaboration [23] currently suggest aspirin for CV primary prevention for patients with diabetes mellitus and a CV risk >10% at 10 years (men >50 years old and women >60 years old with at least one more risk factor, as smoking, hypertension, dyslipidemia, albuminuria, family history of CVD), who are not at increased risk for bleeding (history of gastroduodenal ulcer,

gastrointestinal bleeding, use of medications which increase the risk of bleeding). aspirin is not recommended in males aged <50 years and women aged <60 years with low CV risk, because the risk of bleeding would exceed the potential benefits. Finally, aspirin could be considered in middle CV risk diabetic patients (young patients with at least one risk factor, elderly patients with no additional risk factors, patients with 5-10% risk of events in 10 years). [23]

The most recent recommendations have been issued by the USPSTF Guidelines. [22]. This document takes into account very accurately major thromboembolic risk factors (such as male gender, older age, race, dyslipidemia, hypertension, diabetes and cigarette smoking) and hemorrhagic risk factors (longer use of higher dosage of aspirin or other anti-inflammatory, history of ulcer disease or gastrointestinal disorders, blood coagulation disorders, renal insufficiency or severe hepatic, thrombocytopenia) when assessing the indication for therapy with aspirin. In addition, the analysis focuses on estimating the years of net life (DALYs) and the years of quality of life (QALYs) gained by administration of aspirin.

The USPSTF recommends the initiation of therapy with low-dose aspirin (average 81 mg) for the prevention of CV events and CRC in adults aged 50-59 years with 10-year CV risk >10% and a life expectancy of 10 years, who are willing to take on a long-term treatment (at least for 10 years) and who do not feature increased bleeding risk (grade B recommendation, reasonable assurance of a net benefit). It is reasonable that, in these individuals, the benefit in the prevention for MI, stroke and CRC outweighs the risk associated with gastrointestinal and cerebral bleeding, and that the higher gain can be achieved in terms DALYs (219-463 in women, in men 333-605) and QALYs (621-833 in women, in men 588-834).

In subjects aged between 60 and 69 years old, aspirin is not recommended, as the increase in life expectancy and life quality seems to not overcome the increase in haemorrhagic risk and the potential benefits in the prevention of CRC would appear after at least 10 years of continuous intake. [74] The decision to start treatment should therefore be evaluated case-by-case based upon individual characteristics. Now, evidence about the indication to start the treatment with aspirin for individuals aged <50 and >70 years, at increased CV risk and average risk of CRC are scarce. In individuals aged <50 years, the potential benefits are likely to be lower, as only a small percentage of patients have a CV risk estimated at 10 years >10%. [22] For different reasons, in adults aged >70 years, even though not yet stated clearly, the benefits of therapy with aspirin in primary prevention could be substantial, because of the given high CV risk frequently related to older age.

All these recommendations, often divergent, may be confusing in daily clinical practice. For this reason, a recent paper published by the European Society of Cardiology Working Group on Thrombosis [75] suggests to refer to a CV risk threshold above which the benefits of taking aspirin certainly outweighs the bleeding risks. This level has been identified as the 2% chance of major CV events/year, which corresponds to a CV risk assessed with the SCORE scale of 7-10% of death at 10 years. All subjects with a CV risk greater than or equal to that cut-off should consider treatment with aspirin. In subjects with CV risk between 1% and 2% the decision to start therapy with aspirin depends on the doctor's assessment of other comorbidities of the patient, especially regarding the risk of bleeding, and on the preferences of each patient. (Figure 2)

In this regard, the search for additional indexes of vascular organ damage is crucial. Indeed, even though they are generally not included in clinical studies, they might conversely be informative indicators of susceptibility and prediction of atherothrombotic

events, such as documented atherosclerosis of the carotid-vertebral axis, peripheral vascular disease, the ankle-brachial index, calcium score assessed with CT, and atrial fibrillation as well.

Clues from individualized integrated risk estimation to prospective studies

The struggle to define the net clinical benefit of a therapy with aspirin in patients without pre-existing CV disease is therefore all about finding the best possible estimation of the risk of atherothrombotic events and bleeding. [76-78] The clinician plays a crucial role, he/she should recommend therapy with aspirin to patients at high atherothrombotic risk with a low risk of bleeding and vice versa.

However, it must be stressed, that the analytical models proposed so far about the risk/benefit ratio usually have given the same importance to non-fatal ischemic events and bleeding events. Excluding the hemorrhagic stroke, which has often dramatic consequences in terms of disability and mortality, but only accounts for 1/5 of major bleedings [77], and major gastrointestinal bleedings, which are otherwise not frequent and usually easily manageable, probably many patients may still choose to accept a moderate increase in the bleeding risk consequent to treatment with aspirin in order to prevent CV and cerebrovascular ischemic events. According to the USPSTF, it is therefore crucial to take opinions and preferences of the informed patient into account. [22]

In this context, the reduction in cancer incidence and mortality could be of great importance to extend the indication of treatment with aspirin. [78] A score for the calculation of an integrated CV and oncological benefit/risk would be highly desirable, and could be a crucial tool for the clinician while awaiting for prospective studies able to clarify the dual combined role for aspirin in preventing CV and neoplastic diseases further.

As mentioned earlier, prospective studies are currently undergoing to analyze the role of aspirin in primary prevention; these could help to address the lack of data at our knowledge today, and obviously may represent the best possible evidence to propose on not aspirin in primary prevention and drive future medical choices. However, they may provide a relatively short snapshot of 5-6 years, which is hard to translate to a strategy that may prevent CV or neoplastic events that may occur 10-30 years later. In addition, reliable conclusion of a sufficient number of prospective studies in heterogeneous populations may take a few more years to become available.

The ACCEPT-D (Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes) study [79] will evaluate benefits of the addition of low-dose aspirin therapy in diabetic patients already taking simvastatin. The primary composite endpoint includes death from CV causes, nonfatal Mi, nonfatal stroke and hospitalization for CV causes (acute coronary syndrome, transient ischemic attack, peripheral arterial disease). It is expected to enroll approximately 5170 patients and reach a total of 515 events. Too little? Too specific? Too late?

The purpose of the ASCEND (A Study of Cardiovascular Events iN Diabetes Study) [80] is to evaluate, in diabetic patients without previous atherothrombotic events, if therapy with 100 mg of aspirin is able to significantly reduce the number of CV events compared to placebo and/or one gram of polyunsaturated omega-3 fatty acids. Adverse events, particularly the hemorrhagic ones, will be assessed. The primary composite endpoint will consist of death from CV causes (not hemorrhagic stroke), nonfatal MI, nonfatal stroke and transient ischemic attack. Again a very specific approach difficult to extend to the general population.

The ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events) [81] is an international randomized, double-blind placebo study, which aims to evaluate the effectiveness and

safety of a therapy with 100 mg enteric coated aspirin in in primary prevention for patients with an estimated risk of CVD >15% at 10 years (male patients aged ≥50 years with 2-3 and CV risk factors and female patients aged ≥60 years with 3 or more risk factors). The study will enroll about 12,000 patients, with an estimated duration of approximately five years, and reaching a total of 1488 events. The primary composite endpoint will be of death from CV causes, nonfatal MI and nonfatal stroke. This appears a more promising and meaningful approach.

The ASPREE trial (Aspirin in Reducing Events in the Elderly) [82] will examine the benefits of aspirin in the reduction of MI, stroke, dementia and some types of cancer in subjects older than 65 years (70 years for Caucasian) over the potential risks, particularly bleeding. The study will also determine the amount of years of life free from disability. The primary endpoint will consist of all-cause death, dementia and persistent physical disabilities. The secondary endpoint is a composed of fatal and non-fatal CV and cerebrovascular events, hospitalization for heart failure, fatal and nonfatal cancers, major bleeding events, depression.

Altogether these studies may add important information on the appropriateness of using aspirin in primary prevention. However, by the time being, they will be all completed, the population candidate for ASA in primary prevention, particularly in the middle age (50-65 years) may be left at risk, unless a programmatic clinical approach is considered in the meanwhile.

The purpose of the present document is to help physicians in unraveling a complex and controversial prevention topic. This will most likely represent in the coming years one of the main themes of CV prevention.

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Figure legends

Figure 1. Clinical evaluation of risk profile for prescription of aspirin in primary prevention to be taken into account on an individualized basis.

Figure 2. Suggested algorithm to be adopted in everyday clinical practice to prescribe aspirin in primary prevention. (modified from Ref 77)

Compliance with Ethical Standard:

Conflict of interest: All authors declare that they have no conflicts of interest

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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Figure

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Figure 1

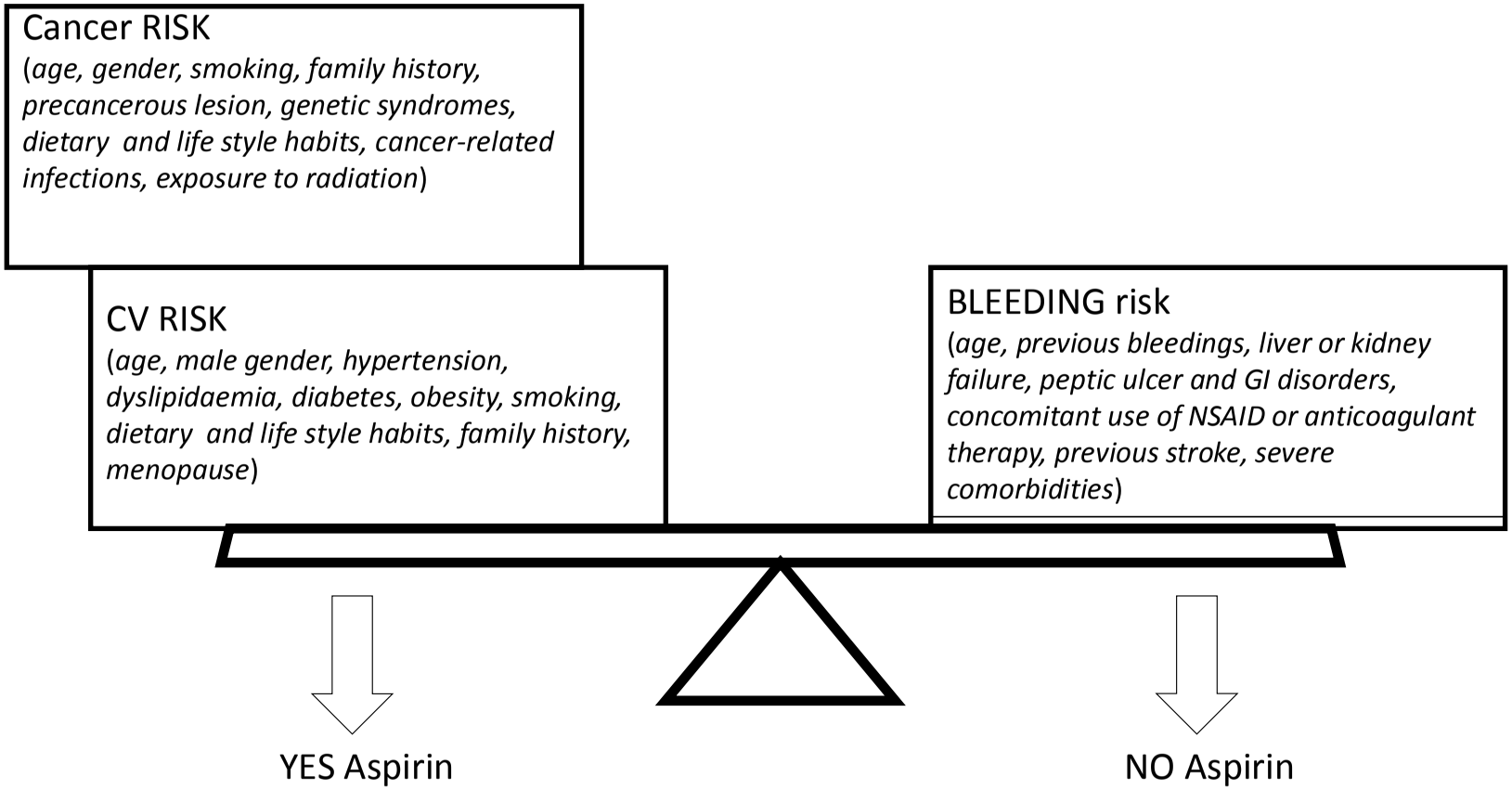
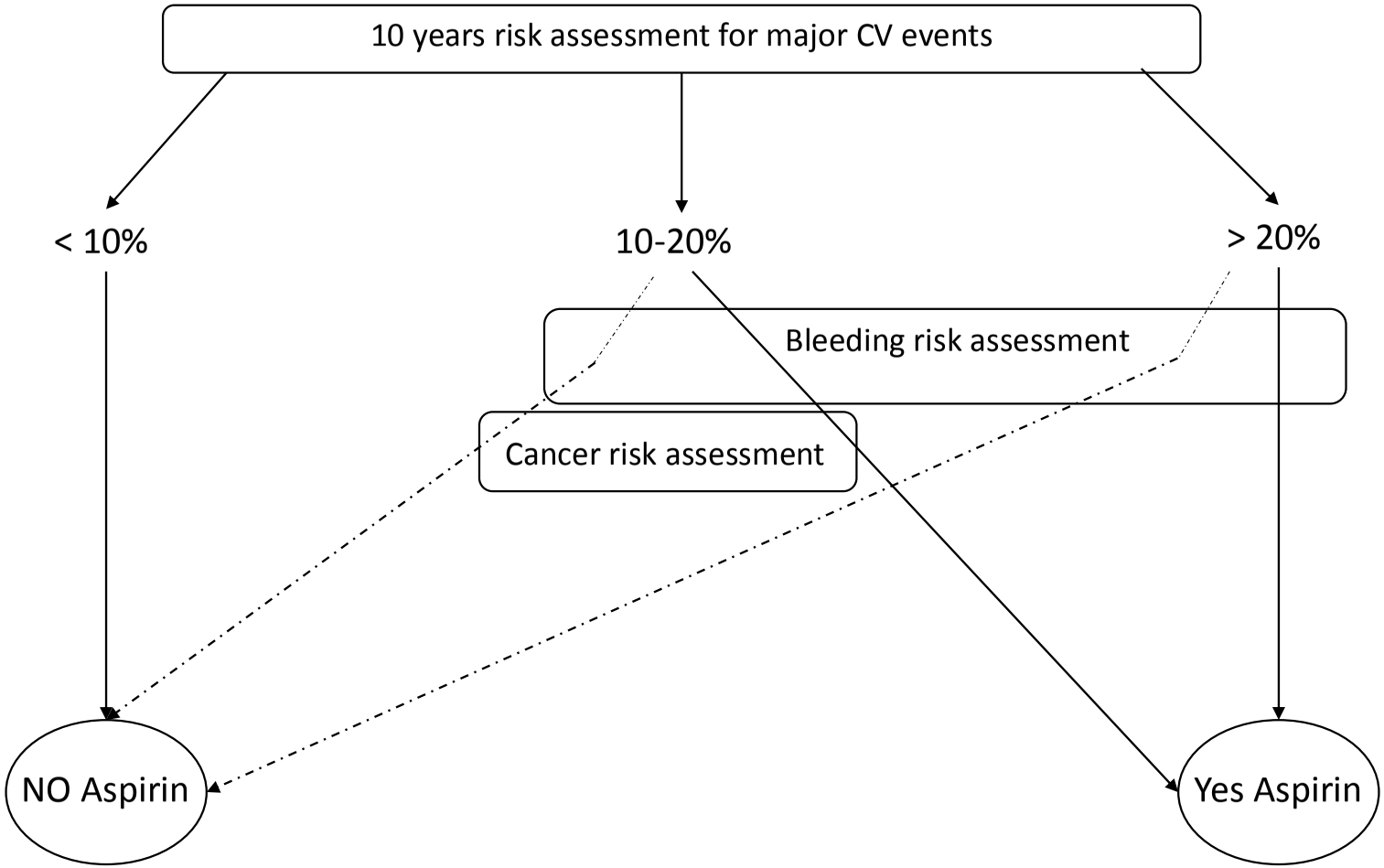


Figure 2


10 years risk assessment for major CV events
< 10%
10-20%
> 20%
Bleeding risk assessment
Cancer risk assessment
NO Aspirin
Yes Aspirin