# Acetylsalicylic acid in primary prevention: a review

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## ABSTRACT

The role of acetylsalicylic acid in secondary cardiovascular prevention is established. However, its role in primary prevention is much more controversial. In this review, we analyzed meta-analyses and trials regarding aspirin in primary prevention and, consequently, hemorrhagic risk related to anti-platelet therapy. Several factors have been considered (*e.g.*, sex, comorbidities, bleeding risk factors, concomitant drugs, weight, age), aspirin's pharmacokinetics included. In the end, we tried to individualize anti-aggregation therapy based on the risk/benefit ratio of every single subject. In conclusion, high-cardiovascular-risk subjects must be treated with acetylsalicylic acid in primary prevention according to their bleeding risk. For better cardiovascular stratification, other tools to detect risk modifier factors should be used (*e.g.*, instrumental evaluations).

## Introduction

The role of acetylsalicylic acid (ASA) in secondary cardiovascular (CV) prevention is well-established and consolidated in everyday clinical practice. On the contrary, its role in primary prevention is much more controversial. The 2021 and 2023 European Society of Cardiology (ESC) guidelines recommend low-dose ASA only in high-CV-risk patients,[1,2] *e.g.*, patients affected by diabetes with high or very high CV risk without contraindications (class of recommendation II b A). This therapy should not be administered to low- or moderate-CV-risk patients due to an increased hemorrhagic risk (III A). The 2019 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines also changed their recommendations on this subject.[3] They recommend against ASA in primary prevention in patients over 70 and adults with elevated bleeding risk (*e.g.*, previous bleeding, thrombocytopenia, chronic renal impairment, concomitant use of drugs that may increase the hemorrhagic risk) (II b).

Until now, the use of ASA as primary prevention remains controversial, with areas of uncertainty mainly due to increased bleeding risk despite the reduction, often not statistically significant, in CV events obtained in studies and meta-analyses.

There are several factors that may play a role in the use of low-dose ASA in primary prevention. Firstly, both older and more recent studies enrolled patients with different CV risks (from low-moderate to high), and secondly, the study design and the median follow-up time were different, making a comparison really challenging.

Altogether, it can be concluded that risk reduction in low- to moderate-CV-risk patients may not be significant when counterbalanced by an increase in hemorrhagic events.

Moreover, a careful evaluation is needed when talking about primary and secondary CV prevention as two separate entities. This distinction may be useful in common practice when estimating CV risk, but not when it comes to single patients. In fact, the atherosclerosis process is a *continuum* (Figure 1) as a result of a pathway that leads, after different exposures to several risk factors (*e.g.*, tobacco use, hypertension, diabetes, and dyslipidemia), to a reduction in endothelial-dependent vasodilatation in the early stages and ultimately to modifications of the vascular structure causing CV events.

All considered, it appears that CV prevention, and anti-

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aggregation therapy in particular, should be tailored to the single patient by balancing CV and hemorrhagic risks at that very moment.

In addition, when not well defined, the CV risk has to be completed with an instrumental evaluation such as coronary computed tomography, epiaortic, or arterial Doppler ultrasound, which can be useful in stratifying the CV risk profile of the single subject.

## Cardiovascular primary prevention studies regarding acetylsalicylic acid

From 1980 to 2010, ten randomized controlled trials (RCTs) on primary prevention have been published.[4] Of these ten, only the Hypertension Optimal Treatment (HOT) study showed a significant reduction in fatal myocardial infarction rate, while the others showed a reduction in non-fatal myocardial infarction despite a significant increase in bleeding.[5]

In 2018, three RCTs on primary CV prevention using ASA were published: the study of Cardiovascular Events in Diabetes (ASCEND),[6] the Aspirin to Reduce Risk of Initial Vascular Events study (ARRIVE),[7] and the Aspirin in Reducing Events in the Elderly study (ASPREE).[8]

The ASCEND study enrolled 15,480 diabetic patients and showed a significant reduction of 12% in CV events in the ASA group *versus* placebo, along with an increased major bleeding risk of 29%.[6] During the median follow-up time of 7.4 years, the ASA group underwent fewer CV events than the placebo group [658 (8.5%) *versus* 743 (9.6%); rate ratio 0.88; 95% confidence interval (CI), 0.79-0.97; p=0.01]. Major bleeding, mostly gastrointestinal and extracranial, occurred in 314 ASA patients (4.1%) *versus* 245 (3.2%) in placebo (rate ratio, 1.29; 95% CI, 1.09-1.52; p=0.003). To be noticed, in the ASCEND study, an elevated proportion of patients was undergoing therapy with statin and antihypertensive drugs.

The ARRIVE study design planned the enrollment of moderate CV-risk patients (risk lower than 10%) with a follow-up time of 5 years.[7] ASA therapy did not reduce CV events [hazard ratio (HR) 0.96; 95% CI, 0.81-1.13) but a non-significant trend in the reduction of myocardial infarction was found (HR 0.85; 95% CI 0.69-1-11). Later on, unstable angina and transient ischemic attacks (TIAs) were added as endpoints but only the pre-protocol analysis showed a reduction of 45% in non-fatal myocardial infarction (HR, 0.55; 95% CI, 0.36-0.84).

Both the ASCEND and ARRIVE trials failed to prove a significant impact on mortality in the 5-7-year follow-up.

The ASPREE trial enrolled elderly, healthy people (mean age 74 years). The study did not show a significant reduction in CV events using ASA, but, on the contrary, an increasing overall mortality ratio from all causes in the ASA group *versus* placebo emerged (HR 1.14; 95% CI, 1.01-1.29).[8]

All three studies demonstrated a significant increase in both major and minor bleedings in the ASA group *versus* placebo and a non-significant increase in fatal ones.

A few considerations are needed. Firstly, during the protocol design, the number of expected CV events in the follow-up time was often overestimated, making it difficult to reach endpoints and leading to non-significant results.

Moreover, in all three trials, the ASA therapy compliance was non-optimal, from 60% to 70%.[6-8] It is clear that in every RCT, reaching the endpoints is strictly correlated with elevated therapeutic adherence.[9] The ASA effect on CV risk is indeed acute, and platelets' half-time is 8 days, so non-adherence to antiaggregation exposes patients to the same risk as the placebo group after only a week.

Furthermore, when evaluating the hemorrhagic risk, other predisposing factors are often not precisely specified, *e.g.*, alcohol consumption and nonsteroidal anti-inflammatory drug use.

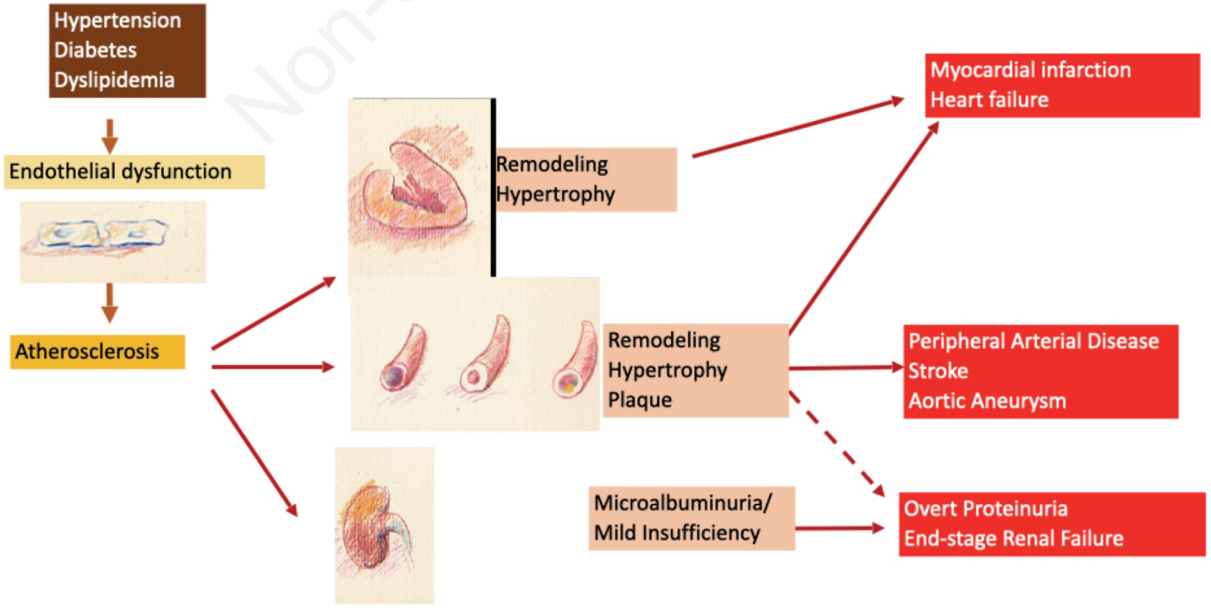


**Figure 1.** The atherosclerosis process pathway.

Of some relevance is the follow-up length, which is frequently too short to prove the favorable ASA effect on CV risk. The atherosclerosis process is in fact, as previously said, a *continuum* over many years.

## Meta-analyses regarding acetylsalicylic acid in primary prevention

The 2019 Zheng *et al*. meta-analysis listed only studies from 1988 to 2018, showing a reduction in major CV events (MACE) [HR 0.89; absolute risk reduction (ARR) 0.38%, 95% CI 0.20-0.55%] and a number needed to treat (NNT) of 265.[10] ASA was associated with an increased risk of major bleeding (HR 1.43, ARR 0.47%), number needed to harm (NNH) of 210, and a reduction in myocardial infarction [HR 0.85, credible interval (CrI), 0.73-0.99) and ischemic stroke (HR 0.81; CrI 0.76-0.87).

In the 2019 Mahmoud *et al.* meta-analysis, no significant differences between ASA and placebo were detected regarding overall mortality [relative risk (RR) 0.98; 95% CI 0.93-1.02]; only a reduction in non-fatal myocardial infarction was registered in the ASA group (RR 0.82; 95% CI 0.71-0.94; NNT=333).[11] However, additional analysis showed a lack of benefit even in the reduction of the non-fatal myocardial infarction rate when considering more recent studies (RR 0.90; 95% CI 0.79-1.02).

The 2019 Abdelaziz *et al.* meta-analysis demonstrated no effect of ASA therapy on mortality by all causes, but a lower incidence of non-fatal myocardial infarction (RR 0.82; 95% CI 0.72-0.94; NNT=357), a reduction in TIA risk (RR 0.79; 95% CI 0.71-0.89; NNT=370) and in ischemic stroke (RR 0.87; 95% CI 0.79-0.95; NNT=263) were detected.[12] This meta-analysis showed, on the other hand, a higher risk of major bleeding (NNH=222), cerebral hemorrhage (NNH=1000), and gastrointestinal major bleeding (NNH=385), but not fatal bleeding. A prespecified analysis proved that ASA was associated with reduced myocardial infarction, TIA, ischemic stroke, and MACE risk in three cohorts of patients: subjects assuming ASA at a very low dose (<100 mg); CV 10 years risk >7.5%; outcomes evaluated after a >5 years follow-up.

Examining the meta-analysis data, it appears clear how studies with very different characteristics in casuistry, unequal CV profile risk, various gender proportions, hypertension prevalence, 10-year CV risk, and median follow-up time were considered. Regarding gender ratio, women presented a lower pharmacologic effect of ASA than men, having a high resistance to antiaggregant action, resulting in a reduced benefit in CV prevention.

The Women Health study analyzed ASA effects on CV primary prevention in women.[13] The study enrolled women >45 years old and randomized to ASA 100 mg/die or placebo. A reduction in myocardial infarction rate and CV deaths was not proved; only a 10-year reduction in ischemic stroke was demonstrated. Conversely, the subgroup analysis showed a decrease in ASA therapy in myocardial infarction, MACE, and ischemic stroke in women >65 years old.

In the 2006 Berger *et al.* meta-analysis, a reduction in myocardial infarction risk in men (RR 0.77; 95% CI 0.67-0.89) was present but not in women (RR 0.95; 95% CI 0.77-1.17).[14] On the other hand, the meta-analysis also showed a lower ischemic stroke risk in women (RR 0.75; 95% CI 0.60-0.94) but not in men (RR 1.06; 95% CI 0.85-1.32).

It should also be considered that the first prevention ASA trials were conducted at a time when tobacco use was more prevalent, blood pressure control was suboptimal, and hypolipidemic therapy was less aggressive.[15] In more recent studies, risk factor control has deeply changed. In recent RCTs, statin therapy prevalence rose from 0-16% before 2001,[16] to 75%,[6] and tobacco use rates varied from 11-41% in older studies,[14-17] to 4-8%.[7,8] The difference in risk factor prevalence modifies, in recent trials, the CV profile risk, reducing the possibility of favorable ASA effects as well. By contrast, for overweight patients, the obesity and diabetes ratios have also increased, with a substantial impact on CV risk.[18] In particular, obesity modifies ASA pharmacokinetic, a hydrosoluble drug, due to an expanded volume of distribution. Luckily this impact is quite limited because platelet exposition to augmented ASA concentration occurs in portal circulation.[19]

The 2018 Rothwell *et al.* meta-analysis evaluated the impact of body weight and body mass index (BMI) in patients assuming low-dose ASA therapy (<100 mg/die) on CV event reduction.[20] A significant reduction was highlighted only in subjects <70 kg (HR 0.77; 95% CI 0.68-0.87; p<0.0001). The protective effect of ASA decreased with increasing body weight; however, a body weight >90 kg appeared to protect from bleeding.

A *post-hoc* analysis from recent RCTs based on body weight suggested that it does not modify ASA effects on CV risk and major bleeding but, instead, increases the risk of ASA-related bleeding in men.[21]

Analyzing a secondary study of the ASCEND trial, a significant interaction between low-dose ASA (100 mg/die) and body weight was found, which was not in accordance with the results displayed before.[6] Low-dose ASA was in fact effective only in patients with BMI>30 kg/mq (p=0.01) or body weight >70 kg (p=0.02).

A recent expert consensus statement,[22] although based on limited data, suggests a twice-a-day ASA administration in patients with BMI>40 kg/mq due to a possible drug resistance in this particular population.

Finally, it is worth considering that all primary prevention trials with ASA did not account for dose adjustment for body weight in the study design.

## Acetylsalicylic acid in primary prevention and diabetes

Patients affected by diabetes have a 2-4-time increased CV risk, and more than two-thirds of diabetic subjects die of cardiac causes. In fact, diabetes has a primary role in calculating the 10-year CV risk.[23] A high platelet activity has been demonstrated in diabetic patients due to early endothelial dysfunction caused by nitroxide (NO) synthesis downregulation. NO is a powerful inhibitor of arachidonic acid and thromboxane A2. Diabetic subjects, moreover, show increased adrenergic activity leading to platelet hyperactivity, mostly through the thromboxane A2 pathway.[24] An upregulation of glycoprotein IIb/IIIa and P2Y12 receptor expression is also present, causing an enhanced response to collagen and adenosine diphosphate.[25]

Furthermore, the hyperglycemic state determines a structural alteration of the cyclooxygenase 1 (COX-1) enzyme, leading to reduced ASA-binding activity and therefore lower antiaggregation. In diabetic patients, ASA pharmacokinetics may also be altered due to gastropathy which causes impaired ASA absorption.[26]

The 2019 Seidu *et al*. meta-analysis considered 12 RCTs with 34,227 patients and a median therapy duration of 5 years.[27] ASA was effective in reducing the MACE risk (RR 0.89, 95% CI 0.83-0.95), with NNT=95, (95% CI 61-208) in preventing MACE during the 5-years follow-up. However, the quality of the evidence was moderate due to the heterogeneity and MACE bias of the publications considered. A significant stroke reduction was reported with low-dose ASA (<100 mg/die) (RR 0.75, 95% CI 0.59-0.95). ASA had no effect on other endpoints, such as all-cause mortality. No significance was obtained for major and minor bleeding, although the definition criteria for bleeding were not strict. The meta-analysis concluded that ASA presented potential benefits in CV prevention in diabetic patients, but its use at a low dosage in primary prevention should be individualized based on CV risk and hemorrhagic risk.

In the ASCEND trial, 15,450 diabetic patients were enrolled. ASA in primary prevention showed a 12% reduction in CV events *versus* placebo, facing a 29% incidence of major bleeding during the 7.5-year follow-up.[6] Secondary analysis proved a reduction in all-cause mortality after 5 years, a reduction trend of CV risk only in patients with expected high or very high CV risk during 10-year follow-up, and a significant decrease in non-fatal stroke rate only with low-dose ASA (<100 mg/die).

The 2021 ESC guidelines recommended considering the use of low-dose ASA in diabetic patients with high or very high CV risk when not contraindicated (IIb, level A).[1] Antiplatelet therapy instead is not recommended in subjects with low or moderate CV risk due to increasing major bleeding risk (III, level A).

The 2023 ESC guidelines extended the recommendation, suggesting that primary prevention with ASA should be considered in all diabetic patients in the absence of contraindications.[2]

Diabetic patients with target organ damage or those affected by long-lasting type 1 diabetes (>30 years) are considered to be at very high risk. Patients affected by 10-year diabetes without target organ damage but with other risk factors such as tobacco use, hypertension, and hypercholesterolemia should be regarded as high-risk subjects.

A population study enrolling 373,185 patients with type 2 diabetes (mean age 70.1±12.3 years, 45.2% female sex) considering their CV risk was conducted in Catalonia.[28] Risk factors prevalence in this population included: hypertension (72%), obesity (45%), dyslipidemia (60%), and active tobacco use (14%). 53.4% (95% CI 53.1-53.6) of patients were at very high CV risk. It was more prominent in men (55.6%, 95% CI 55.3-55.9) than in women (50.7%, 95% CI 50.3-51.0). Moreover, 50% of very high-risk patients did not present previous CV events (*e.g.*, coronary artery disease, stroke, heart failure, peripheral artery disease). Both high- and very high-risk patients affected by type 2 diabetes represented 92.95% (95% CI 92.87-93.04) of the total population. One-third of type 2 diabetic patients without verified CV disease present in fact very high CV risk, so these subjects should be considered regarding therapy as if the CV disease is already established.

## Formulation and dosage

Enteric-coated (EC) aspirin is the most common drug formulation used in primary prevention studies and can be less effective when compared to regular formulations. EC absorption is in fact very variable due to incomplete coating degradation in the stomach, leading to a different exposition to small intestine esterase and consequently to fluctuant drug bioavailability.[17,29] It is clear how these elements can be crucial in determining reduced ASA efficacy. Less recent studies (*e.g.*, HOT study) did not use such formulation, and they reported significant ASA effect on myocardial fatal and non-fatal infarction rate.[30]

Moreover, buffered or EC formulations did not improve ASA safety: gastrointestinal bleeding and peptic ulcers rely on prostaglandin synthesis reduction mediated by COX-1 inhibition.[31] ASA 75 mg/die is more effective compared to a high dosage precisely because it has no impact on prostacyclin, leading to fewer gastrointestinal bleedings.[32] A meta-analysis of RCTs which compared ASA<75 mg/die *versus* ASA>75 mg/die showed no difference in CV events prevention in high-risk patients.[33] When considering ASA *versus* placebo, gastrointestinal bleedings were similar with all drug doses: <75 mg [odds ratio (OR) 1.7%; 95% CI 0.8-3.3), 75-150 mg (OR 1.5%; 95% CI 1.03-2.0), 160-325 mg (OR 1.4%; 95% CI 1.0-2.0).

## Age

The AHC/ACC task force guidelines limited the use of ASA in primary prevention to <70-year-old patients.[3] The US Preventive Service task force guidelines instead limit its use to subjects <60 years old. The Antithrombotic Trialists Collaboration published a meta-analysis where ASA was significantly effective in reducing CV events (p=0.0001) but not in patients >60 years or >70 years.[31] The absolute benefit overcomes the absolute risk when the first CV event at 10-year risk is higher than 10%.

A subgroup analysis of the Women Health study proved that women over 65 years old, assuming low-dose ASA, showed a reduction in myocardial infarction, MACE, and ischemic stroke.[13]

All considered, ASA should be prescribed and individualized after a careful evaluation of the risk/benefit ratio, not on an age basis only.

## Acetylsalicylic acid and hemorrhagic risk

The ASA hemorrhagic gastrointestinal risk is determined through inhibition of prostaglandin synthesis mediated by COX-1 inhibition. The protective effect of vasodilatation on intestinal mucosa is therefore lacking. The main bleeding risk factors are included in Table 1.[34,35]

The 2016 US Preventive Services task force synthesis showed an increased gastrointestinal bleeding risk by 58% of low-dose ASA in primary prevention.[36]

In meta-analyses, the risk ratio for major bleeding was

1.4-1.5.[10-12] The primary prevention trials are, however, very heterogeneous, especially in reporting and classifying bleeding outcomes.

It is clear that ASA determines mostly gastrointestinal, non-fatal bleeding, generally requiring only medical therapy and not surgical treatment.

Gastrointestinal bleeding, even when caused by ASA, must require further investigations on the source of hemorrhage, often leading to other diagnoses such as cancer and affecting overall mortality.

## Can the hemorrhagic risk be modified?

The 2007 ESC guidelines suggested considering ASA in asymptomatic patients with elevated 10-year CV risk as long as hypertension was well controlled.[37]

The 2023 ESC guidelines stated recommendations on gastric protection in diabetic patients using anti-platelet therapy. These guidelines suggest proton-pump inhibitors (PPIs) use for gastrointestinal bleeding prevention based on individual hemorrhagic risk.[2] Unfortunately, PPI use is only sporadically reported in studies and meta-analyses.

*Helicobacter pylori* eradication is effective in reducing gastrointestinal bleeding risk as well. A recent double-blind randomized study (Helicobacter Eradication Aspirin trial) enrolled 1208 patients >60 years old, receiving ASA 325 mg/die or less for at least 28 days in a year.[38] All subjects had $^{13}$C breath test for *Helicobacter pylori* positive. Patients were randomized to clarithromycin 500 mg + metronidazole 400 mg + lansoprazole 30 mg per os (active eradication) or placebo. The primary outcomes were hospitalization or death caused by gastrointestinal bleeding. A significant reduction in primary outcomes incidence was demonstrated in the active eradication group during the first 2.5 years of follow-up *versus* the placebo group (6 episodes per 1000 person-year, rate 0.92, 95% CI 0.41-2.04 *versus* 17 episodes per 1000 person-year, rate 2.61, 95% CI 1.62-4.19; HR 0.92, 95% CI 0.14-0.89, p=0.0028). However, this positive effect was not confirmed by extending the follow-up period after 2.5 years.

## Conclusions

Recent evidence recommends ASA for primary prevention in selected patients after a careful evaluation of the risk/benefit ratio between hemorrhagic and thrombotic risk. This evaluation is often challenging, as it can be hard to compare the severity of expected vascular events with drug-related hemorrhagic events, *e.g.*, TIA, which is a minor vascular event, is associated with increased stroke risk and cognitive impairment.

Half of all bleedings are of gastrointestinal origin, one-third of which come from the upper tract, and they can be treated with medical therapy or endoscopic procedures.

The absolute risk of fatal bleeding or cerebral hemorrhage with ASA is lower than the absolute risk of CV event.[39] Preventing first myocardial infarction or stroke is more relevant in a single patient than possible gastrointestinal bleeding. Moreover, the incidence of gastrointestinal hemorrhages in high-risk patients can be lowered through PPI treatment and *Helicobacter pylori* eradication.

In conclusion, high-CV-risk subjects must be treated with ASA in primary prevention, according to the risk chart matrix.[40] Furthermore, for better CV stratification, since the atherosclerotic process is a *continuum* that leads to organ damage before and clinical events after, other risk modifier



**Table 1.** Main bleeding risk factors.

| Bleeding risk factors | |
|---|---|
| Age | Risk is 1.5 to 2 times enhanced every decade after 50 years of age |
| Male sex | |
| Previous gastrointestinal bleeding | |
| Diabetes | |
| Tobacco use | |
| NSAIDs | |
| Anticoagulant | |
| *Helicobacter Pylori* infection | |
| Alcohol use | |
| Previous ulcer | |
| Uncontrolled hypertension | For cerebral hemorrhage |

NSAIDs, nonsteroidal anti-inflammatory drugs.

**Table 2.** Risk modifiers and additional risk factors.

| Modifier risk factors | Additional risk factors |
|---|---|
| Carotid and femoral artery Doppler ultrasound (to detect plaques) | Family history |
| CT angiography (coronary disease screening) | Glucose, cholesterol and pressure targets not reached |
| Calcium score index | |
| Ankle brachial index | |

CT, computed tomography.

factors should be considered, such as the ones displayed in Table 2.[41]

Finally, during a proper CV risk evaluation, family history and not reaching target levels of glucose, cholesterol, and pressure must also be considered (Table 2).

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