Overview of Aspirin and Platelet Biology

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Aspirin (ASA) has historically been one of the most important drugs in cardiology and has long been the cornerstone of antiplatelet therapy. Although its role in acute coronary syndrome remains undisputed, emerging data suggest that reappraisal of the efficacy of long-term ASA in some primary and secondary prevention may be warranted. The aim of this review is to place these new results in the context of previous evidence on aspirin by appraising the current body of evidence on its use of for cardiovascular diseases. This overview first summarizes the history of the discovery of aspirin, as well as its pharmacology and the concept of ASA resistance. We subsequently recapitulate the evidence of ASA on primary prevention and secondary prevention starting from the classical studies in order to serve as an introductory background to the examination of the most recent clinical trials that will be performed in the rest of the articles of this Supplement. Although the benefit of ASA in acute coronary syndrome remains incontrovertible, emerging evidence challenge the universal need for primary prevention, or for lifelong treatment in secondary prevention or all adults with stable coronary disease who are at highest risk for ASA-induced bleeding. The role of aspirin is quickly changing in recent times and this review provides a review for the clinician about the current role of this drug in cardiovascular care. **(Am J Cardiol 2021;144:S2−S9)**

History

According to the Ebers papyrus, the first use of salicylates extracted from the willow cortex can be traced to ancient Egyptians. The Ebers papyrus is considered the most comprehensive medical papyrus ever recovered and it dates back to 1534 BC. It covers more than 700 herbal remedies, but the most important plant species mentioned is *tjeret* or *salix*, known today as willows, which can be used as a general-purpose tonic or an anti-inflammatory and/or pain reliever for nonspecific aches and pains.[1] Hippocrates referred to the use of salicylic tea to reduce fevers around 400 BC. The first application of salicylates in "modern" medicine was recorded in 1758 when Reverend Edward Stone administered the ground-up dried bark of an English willow tree to patients with "agues" (malaria) and noticed clear improvement in symptoms.[2]

In 1828, Joseph Buchner at Munich University refined willow into yellow crystals and labeled it salicin[2] (after *salix*, Latin for *willow*). Although side effects (e.g., gastric irritation) limited its usefulness, salicin was tested for the first time in a "clinical trial" in 1876; John Maclagan, from Dundee Royal Infirmary, published in *Lancet* that the administration of salicin to patients with rheumatism resulted in remission of fever and joint inflammation.[3]

In 1863, the Bayer company was created to obtain chemical dyes and in 1890, Carl Duisberg created a pharmaceutical group within Bayer, which was led by the chemist Arthur Eichengrun. In 1894, a young chemist named Felix Hoffman joined the pharmaceutical group. In 1897, Hoffmann started working to find a less irritating substitute for salicylic acid; it is generally accepted that he pursued this idea because his father was suffering the side effects of taking sodium salicylate for rheumatism. On August 10, 1897 (according to his laboratory notebooks), Hoffman managed to acetylate the phenol group by refluxing salicylic acid with acetic anhydride and obtained acetylsalicylic acid (ASA) in its purest form.[1] Acetylsalicylic acid was found very effective at reducing pain, inflammation, or fever, and produced no unpleasant side effects. On 1899, this compound was registered under the "Aspirin" name: "A-" from "acetylation", "-spir-" from "spirsaure" (*Spirea umaria* is the meadowplant, from which salicylates can also be obtained, and is the German namesake for salicylic acid), and "-in" as a typical drug name ending. Currently aspirin is one of the most widely used medications globally, with an estimated 44,000 tons (50-120 billion pills) consumed each year, and it is on the WHO's *List of Essential Medicines.*[4]

Pharmacology

Pharmacokinetics

Aspirin is most commonly available as immediate-release or enteric-coated formulations.[5, 6] After oral intake, immediate-release ASA is rapidly and completely absorbed in the acidic conditions of the stomach and upper small intestine through a passive diffusion mechanism, which typically results in a quick (15 to 20 min) concentration peak, though gastric pH and presence of food can limit the absorption rate.[6] The enteric-coated form is absorbed by the gastrointestinal mucosa, which results in a lower

AtheroThrombosis Research Unit. Icahn School of Medicine at Mount Sinai Mount Sinai Heart. Mount Sinai Hospital, New York, New York. Manuscript received November 22, 2020; revised manuscript received and accepted December 11, 2020.

Disclosures: This Supplement is made possible thanks to the financial support of educational grant funding form AstraZeneca Pharmaceuticals to Academic CME.

This article is published as part of a supplement supported by an educational grant from AstraZeneca.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2020.12.018

bioavailability and slower peak (3 to 4 h) because of the increased pH in the small intestine.[7]

Around 60% to 80% of salicylate in the blood is bound to albumin. The volume of distribution is 0.1 to 0.2 L/kg. Acidosis increases the volume of distribution as it increases penetration of salicylate in the tissues.[5, 7]

Given that as much as 80% of therapeutic doses of aspirin are metabolized (de-activated) in the liver, aspirin acts on its targets in the portal circulation, where platelets are exposed to a higher drug level compared with the systemic circulation. Although the half-life is only 15 to 20 min, aspirin irreversibly inhibits cyclooxygenase (COX), so its pharmacodynamic effects persist for the lifespan of the platelet (7 to 10 days). Therefore, production of new platelets is the only way to overcome this effect,[8] though inhibitory effects of ASA on blood marrow megakaryocytes have also been proposed.[6]

Salicylates are excreted mainly by the kidneys as salicyluric acid (75%). Renal excretion of salicylic acid is extremely sensitive to changes in urinary pH; a 10-fold increase in renal clearance occurs when urine pH is increased from 5 to 8, hence the use of urinary alkalinization to improve salicylate elimination in ASA overdose.[7]

Mechanism of action

Aspirin acts by irreversibly blocking the cyclooxygenase (COX) activity of the prostaglandin H synthases 1 and 2, also known as cyclooxygenase (COX) -1 and -2, respectively. This effect is achieved by acetylating a serine residue (serine 529 in COX-1 and serine 516 in COX-2) in the substrate pocket of COX, which prevents arachidonic acid from reaching the COX catalytic site of the enzyme.[2, 5]This causes the upstream block of prostanoid biosynthesis and, ultimately, inhibition of thromboxane A_2 (TXA_2) and prostacyclin (PGI_2) generation. Mature platelets express only COX-1 and produce TXA_2 in response to a variety of stimuli. Vascular endothelial cells, which express both COX-1 and COX-2, represent the main site of PGI_2 generation. Low-dose ASA selectively inhibits COX-1 activity, whereas higher doses inhibit both COX-1 and COX-2.[7] As a result of this interaction, TXA_2 production is blunted for the lifetime of the platelet (approximately 10 days) so new platelets must be generated *de novo* to re-establish COX1 activity. This mechanism of action was specifically discovered by John Vane, who shared the Nobel Prize for Medicine in 1982 with Sune Bengström and Bengt Samuelsson (for their work on prostaglandins and TXA2).

These molecules underlie two opposed biological effects. The TXA_2 pathway is related to platelet activation and aggregation. On the other side, PGI_2 has an important role in anti-atherogenic effects and vascular thrombo-resistance, and exerts a crucial effect in protecting the gastrointestinal mucosa through the production of PGI_2. Prostaglandins are key in epithelial mucus production, microvascular mucosal perfusion, and wound healing in the gastrointestinal tract. Inhibition of the latter, in addition to the antiplatelet effect and to physical disruption of the protective gastric phospholipid barrier thereby allowing direct acid injury, explains why ASA increases the risk of bleeding and gastric perforation (e.g., by promoting new mucosal lesions and worsening of existing lesions by a factor of 4 to 10 when used at analgesic doses).[5] Because low-dose ASA has no measurable effects on COX-2- and PGI_2-mediated vascular functions, it does not increase blood pressure, impair renal function, or interfere with the antihypertensive effects of diuretics and angiotensin converting enzyme (ACE) inhibitors. Use of proton pump inhibitors reduces the risk of upper gastrointestinal bleeding

Importantly, a single low dose (75-100 mg) of ASA exceeds the minimum dose required for platelet inhibition and addresses interindividual variability in platelet response.[8]

Although COX-1 inhibition is the main effect of aspirin, additional mechanism(s) have also been discovered. Aspirin has been described to inhibit the proliferation of vascular smooth muscle cells,[9] thus mitigating the earlier phases of atherogenesis. This effect is mediated via TGF-β because these antiproliferative actions of ASA are abrogated in the presence of antibodies against TGF-β.[9] These findings are confirmed because TGF-β itself and also other drugs that release TGF-β (such as pioglitazone) also inhibit vascular smooth muscle cell proliferation.[10, 11]

Drug interactions

Concomitant use of reversible COX-1 inhibitors (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs] such as ibuprofen and naproxen) exert a competitive effect on the irreversible acetylation of platelets by ASA[12] and thus will decrease the antiplatelet actions of aspirin. Furthermore, non-selective NSAIDS increase the risk of both bleeding and thrombotic events when coadministered with ASA.[13] This interaction is not found with selective COX-2 inhibitors (‘coxibs’), but these drugs nonetheless increase the risk of thrombotic complications.[14]

Aspirin resistance

Aspirin resistance is a quite rare phenomenon defined as the failure of ASA to fully inactivate the platelet COX-1.[12, 15] Both pharmacological and pharmacokinetic mechanisms are involved in variability in responsiveness to antiplatelet agents, and include drug bioavailability, medication non-compliance, drug−drug interactions, cytochrome P450 activity, and genetic polymorphisms. As stated before, a single low dose of ASA exceeds the minimum dose required for platelet inhibition and addresses interindividual variability in platelet response.[8] Therefore, the use of tests that do not specifically measure the COX-1 activity is probably the main reason for the ambiguity on this topic.[15] The most egregious example[16] shows that platelet COX-1 activity (as reflected by serum TXB_2 levels) is uniformly and persistently suppressed (99%) by low-dose ASA in healthy subjects; however, other tests such as urinary 11-dehydro-TXB_2, arachidonic acid-induced aggregation, and VerifyNow® Aspirin show stable, incomplete inhibition (65%, 80%, and 35%), respectively. Therefore, the use of less sensitive, functional assays leads to misclassification of ’’responder’’ as ’’resistant’’ phenotypes. When COX-1-specific tests are used, ASA resistance is rarely observed and is almost always due to drug interactions (e.g.,

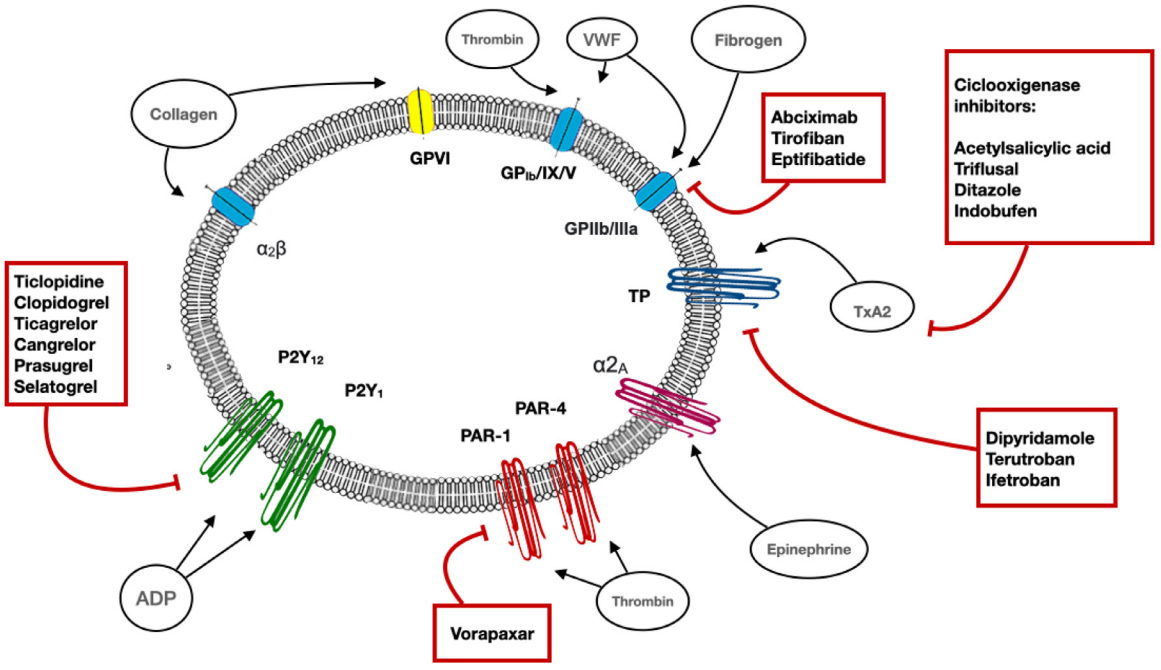

Figure 1. Major platelet receptors and pharmacological interactions. Black arrows show activation, red arrows show inhibition. ADP = adenosine triphosphate; GP = glycoprotein receptor. PAR = protease-activated receptor. TP = thromboxane receptor; TxA2 = thromboxane A2; VWF = Von Willebrand Factor.

naproxen, ibuprofen), noncompliance, or impaired absorption of enteric-coated formulation,[5, 8, 15] termed "pseudoresistance".

Another mechanism causing pseudoresistance is increased platelet turnover, specifically through two mechanisms. First, ASA, given its half-life of only 20 minutes, can only inactivate the platelets that are present in the circulation at that moment. The accelerated thrombopoiesis that characterizes diabetic patients does not allow newly generated platelets entering the circulation to be sufficiently exposed to aspirin. A potential strategy would be to administer aspirin twice daily,[17] but the clinical implications of this approach remain uncertain. Second, immature or reticulated platelets comprise the youngest component of the circulating platelet pool, contain cytosolic mRNA that is translationally active, and are more thrombogenic than platelets.[18] Even if ASA is able to irreversibly inhibit the COX-1 already present in the reticulated platelet, the cytosolic mRNA may produce new, fresh, unhibited molecules of COX-1 that are active and not acetylated. This explains that reticulated platelets show more "aspirin resistance" than mature platelets,[18] and that elevated immature platelet counts, a measure of platelet turnover, are associated with adverse cardiovascular outcomes.[19]

Platelet Biology

Platelets are anucleated 2−5 μm disk-shaped cellular components, with a mean volume of 6−10 femtoliters (approximately 6 orders of magnitude lower than a eukaryotic cell).[20] Platelets circulate in blood plasma and play a role in hemostasis maintenance, thrombosis formation, innate and active immunity, and inflammation responses.[21] Platelets are produced in bone marrow by megakaryocytes and circulate in the blood plasma for 7-10 days before they are removed by the spleen.

The basic sequence of platelet aggregation occurs in three steps: initiation, extension, and stabilization[20-23] (see Figure):

1) Initiation stage: collagen-mediated platelet thrombus formation occurs when subendothelial collagen becomes exposed to the circulation. Platelets, through their glycoproteins (GP), interact with collagen and collagen-deposited von Willebrand Factor (vWF), change their shape, and adhere to the site of injury. The attachment leads to secretion of adenosine diphosphate (ADP), serotonin, and TXA_2, leading to more platelet recruitment and activation. The extant rheological conditions largely influence these adhesive interactions. At low shear rate (e.g., veins and larger arteries), platelet adhesion to the vessel wall primarily involves binding to fibrilar collagen, fibronectin, and laminin, while under conditions of elevated shear stress (e.g., microvasculature or in stenotic arteries), platelet tethering to the damaged subendothelium depends on subendothelial vWF. Type-I and type-III collagens are considered the most important in supporting platelet adhesion to the damaged vasculature. Although soluble vWF does not bind to platelets to prevent aggregation in the normal circulation, immobilized vWF onto collagen (mainly type I, III, or VI) is highly reactive toward flowing platelets.

The GP Ib/IX/V complex is the major platelet receptor mediating interaction with vWF, and its dysfunction causes

Bernard Soulier syndrome (a congenital bleeding disorder). Two receptors have been demonstrated on the platelet surface that bind directly to collagen, the GP VI immunoglobulin superfamily member and the integrin $\alpha_2\beta_1$ (also termed GP Ia/IIa).

2) Extension phase: Amplification is characterized by a second wave of secretion and aggregation and is further enhanced by platelet-mediated release of thrombin, ADP, and TXA_2. The second wave also marks the extension phase, in which newly arriving platelets adhere to the initial platelet monolayer.

ADP is stored in δ-granules, secreted upon platelet activation, and binds two classes of purinergic receptors: $P2Y_1$ and $P2Y_{12}$. $P2Y_{12}$ is the major receptor to amplify and sustain ADP-mediated platelet activation initiated via $P2Y_1$. Indeed, $P2Y_{12}$ is the target of thienopyridine and related drugs (ticlopidine, clopidogrel, prasugrel).

Thromboxane A_2 is a labile prostanoid synthesized by activated platelets through the sequential actions of COX and TXA_2 synthase enzymes. TXA_2 is a vasoconstrictor and a potent platelet agonist causing conformational change. Once synthesized, it diffuses across the platelet membrane and activates other recruited platelets. Overproduction of TXA_2 has been implicated in the pathogenesis of cardiovascular disease, including myocardial infarction and unstable angina. Indeed, as discussed above, ASA exerts its antiaggregant effect by blockade of TXA_2 synthesis through COX inhibition. However, the role of TXA_2 in thrombus formation under pathological conditions of high shear remains unclear, with studies showing that ASA has no inhibitory effect either on *in vitro* thrombus formation at high shear and disturbed laminar flow in a parallel-plate perfusion chamber device,[24] or on *in vivo* high-degree coronary artery stenosis in a dog animal model.[25]

The TXA_2 receptor (TP) mediates the effects of TXA2. TP antagonists were investigated in the past as antiplatelet agents but their development was halted.

Thrombin is the most effective platelet activator even at very low concentrations, and no other platelet agonist seems to be as efficiently coupled to PLCβ activation. Thrombin-induced platelet responses are mediated partially by the GP Ib/IX/V complex and mainly by two protease activated receptors (PAR), namely PAR-1 and PAR-4 in humans (PAR-3 and PAR-4 in mice). PAR4 inhibitors (e.g., vorapaxar) were developed as antithrombotics, but their developments has also been halted.

3) Stabilization phase: Following protein receptor-effector interaction, activated platelets continue to aggregate forming bridges between surface glycoproteins, fibrinogen, fibrin, and vWF to activated glycoproteins. This stabilization phase includes subsequent signaling events in the platelet plug formation that allows consolidation of the platelet aggregate to prevent its dispersal by shear forces in the circulating blood.

The most relevant signaling events during this stabilization phase are outside-in signaling when integrins, particularly $\alpha_{IIb}\beta_3$ (GPIIb/IIIa), bind fibrinogen. This triggers essential events for thrombus growth and stabilization, such as cytoskeletal reorganization, formation and stabilization of large platelet aggregates, development of a procoagulant surface, and a clot retraction that helps to narrow the gaps between platelets and to increase the local concentration of soluble platelet agonists. The GPIIb/IIIa receptor is a therapeutic target for antithrombotic therapy in patients undergoing percutaneous coronary interventions with high thrombotic burden.

Depending on the vessel in which the clot forms, the thrombus can be platelet-rich (white clots, which form in arteries) or rich in fibrin and erythrocytes (red clots, which form in veins).[20, 22] Importantly, other triggers different from endothelial damage can activate platelets, such as inflammation; for instance, infections such as community-acquired pneumonia also induce platelet activation and platelet aggregation, which may explains the high rates of cardiovascular events after pneumonia.[26]

Acute Coronary Syndrome

Acute coronary syndromes (ACS) are caused by a superimposed thrombus over plaque rupture.[20, 22] Based on this mechanism of action, ASA, as both an antiplatelet and antithrombotic agent, has become a cornerstone in the treatment of ACS.[2]

The landmark Second International Study of Infarct Survival (ISIS-2) study conclusively showed the efficacy of administering ASA within 24 hours to patients presenting with acute myocardial infarction (MI).[27, 28] Aspirin 162 mg, either alone or in combination with a fibrinolytic agent, provided a 15-month absolute risk reduction of nonfatal reinfarction of 2.4% (relative risk reduction, 23%) and 5.2% (relative risk reduction, 42%), respectively. This study supports the current ACC/AHA Class I recommendation for all patients with suspected MI to receive aspirin.[2]

We want to highlight that the role of aspirin in treatment of ACS is not questioned.

Primary Prevention

Studies before 2018

The most famous study of primary prevention was the United States Physicians' Health Study (USPHS),[29] including 22,071 male doctors, in which ASA therapy of 325mg on alternate days significantly reduced the risk of MI by 44%. In 2009, the Antithrombotic Trialists' (ATT) Collaboration published analyses of patient participant data from six trials (British Doctors' Study [BDS], PHS, Thrombosis Prevention Trial [TPT], Hypertension Optimal Treatment [HOT] Trial, Primary Prevention Project [PPP] trial, and Women's Health Study [WHS] trial) that included 95,000 patients and 3554 cardiovascular events.[30] This meta-analysis demonstrated that ASA reduced by 12% serious vascular events (MI, stroke, or vascular death), which was mainly attributable to a one-fifth reduction in nonfatal MI in the ASA group[30]; in aggregate, ASA therapy had no net effect on total stroke, vascular mortality, and all-cause mortality. However, balanced against this small reduction of about 6

per 10,000 per year fewer serious vascular events with aspirin therapy was a significant increase in major gastrointestinal bleeding and other extracranial bleeding compared with no ASA[30] (0.10% versus 0.07%, or 3 per 10,000 events per year). The relative risk reduction of ASA was slightly smaller than that observed in secondary prevention studies (12% vs 19%). The subsequent United States Preventive Services Task Force (USPSTF) meta-analysis included 11 primary prevention trials of ASA comprising 118,445 patients[31]; however, given that the additional trials involved few additional events, the study findings were quantitatively similar to those of the ATT meta-analysis (a 22% relative reduction in nonfatal MI, no significant effect on stroke or vascular death rates and a 58% increase in gastrointestinal bleeding events with ASA therapy).[31]

Studies after 2018

In 2018, three new primary prevention randomized trials of aspirin 100mg daily versus placebo were published that changed our perception about the role of aspirin in primary prevention: ASPREE[32] (in the elderly), ASCEND[33] (in diabetics), and ARRIVE[34] (in high cardiovascular risk). These studies are addressed in detail in the article in this Supplement by Drs. Angiolillo and Capodanno.[35]

A new metaanlysis[36] including 162502 subjects and 15 trials (updated with ASPREE, ASCEND and ARRIVE) reported a reduced risk of nonfatal MI (RR 0.82, 95% CI 0.72 to 0.94, number needed to treat 357) and ischemic stroke (RR 0.87, 95% CI 0.79 to 0.95, number needed to treat 500), but similar risks of mortality and cardiovascular mortality in the ASA arm compared with controls.[36] Major bleeding was increased by 50% (RR 1.50, 05% CI 1.33 to 1.69, number needed to harm 222), with parallel increases in intracranial bleeding (RR 1.32, 95% CI 1.12 to 1.55, number needed to harm 1000) and gastrointestinal bleeding (RR 1.52, 95% CI 1.34 to 1.73, number needed to harm 385).[36]

Collectively, these findings confirm the lack of, or at best modest benefit from, routine ASA use in the setting of primary prevention, and suggest the potential for harm in the contemporary era.[37, 38] Contemporary drug therapies (such as statin therapy) have reduced the absolute risk of ischemic events compared with earlier trials of ASA, whereas the bleeding side effects of aspirin are still maintained. Therefore, the overall absolute benefits of ASA in the latest trials are smaller than reported previously.[38] In summary, the "blanket" use of ASA in primary prevention is being reconsidered, although its use in some specific subpopulations (e.g., patients with diabetes) could still be an option in individualized cases.

Secondary Prevention

Classic data on aspirin in secondary prevention

The evidence supporting aspirin for secondary prevention is primarily based on studies performed in the 1970s and 1980s, which are collectively summarized in the Anti-Thrombotic Trialists' (ATT) Collaboration meta-analyses.

Most of the early trials examining ASA use in secondary prevention reported trends toward a benefit, but when considering each trial in isolation, none of the six post-MI trials (Cardiff 1, Cardiff 2, Coronary Drug Project Aspirin Study [CDPA], Persantine-Aspirin Reinfarction Study [PARIS], Aspirin Myocardial Infarction Study [AMIS], German −Austrian Aspirin [GAMIS] Trial) consistently demonstrated a statistically significant reduction in the primary end point; this in fact prompted the creation of the ATT Collaboration, to perform meta-analysis of all these trials. The first ATT meta-analysis in 1988 included 25 randomized trials on antiplatelet treatment, with a collective 29000 patients in secondary prevention[39]; antiplatelet treatment significantly decreased risk of vascular death by 15%[39] (we mention "antiplatelet" because, although most trials investigated aspirin, a few trials used sulphinpyrazone or aspirin plus dipyridamole). The second ATT meta-analysis was published in 1994 and included 145 studies and 70000 patients[40]; in patients with previous MI, there was a 4% absolute risk reduction in vascular events over 2 years with antiplatelet therapy.[40] The third ATT study (2002) assessed lower doses of ASA and comprised 11 trials; aspirin was concluded to be protective in most patients at risk of vascular events that low-dose ASA is an effective antiplatelet regimen for long-term prevention.[41]

Finally, the most recent ATT metanalysis[30] involves 16 secondary prevention trials and 17,000 individuals at high average risk (43,000 person-years, 3306 serious vascular events). This fourth ATT metanalysis showed that allocation to ASA yielded a greater absolute reduction in serious vascular events (6.7%vs 8.2% per year, $p<0.0001$), with a non-significant increase in hemorrhagic stroke, but reductions of about a fifth in total stroke (2.08%vs 2.54% per year, $p=0.002$) and in coronary events (4.3%vs 5.3% per year, $p<0.0001$).

Modern reappraisal of aspirin

Although the role of aspirin in the treatment of ACS is well-established, whether the historical benefit seen for ASA in secondary prevention in the ATT metanalysis can be assumed to hold true in modern has not been determined. In fact, recent trials of ASA in primary prevention suggest that such a broad assumption may be unjustified.

As discussed earlier, the role of TXA_2 in thrombus formation under pathological conditions of high shear (e.g., stenotic arteries) remains unclear. In fact, some preclinical studies have suggested that ASA has no inhibitory effect either on thrombus formation either *in vitro* (at high shear rate in a perfusion chamber device),[24] *ex vivo* (using light transmission aggregometry[42] or *in vivo* in animal studies (high-degree coronary artery stenosis in a dog model).[25] These preclinical models suggest lack of effect of ASA on stenotic coronary arteries, and therefore would suggest that ASA is not needed in *all* secondary prevention patients and could be *potentially* dropped in certain subsets of patients, with the added benefit of reducing bleeding.

This approach was confirmed *in vivo* in human patients in a mechanistic substudy of the Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT) trial.[43] The Badimon chamber is the gold-

standard method to evaluate blood thrombogenicity,[44] and offers several advantages: it investigates thrombus formation directly from the whole blood (instead of plasma) of the patient, at different shear rates, and without addition of any anticoagulant. Patients in secondary prevention treated with both ticagrelor monotherapy and ticagrelor plus aspirin exhibited similar overall thrombus formation under dynamic flow conditions. The only difference between the groups was that DAPT patients showed reduced platelet activity in response to arachidonic acid versus ticagrelor monotherapy, as expected by the use of aspirin.[43] This mechanistic study suggests that ASA does not enhance the global antithrombotic effect of ticagrelor (which explains the lack of difference in ischemic end points of cardiovascular death, MI or stroke between both arms in the main TWILIGHT trial[45]) and only adds to the bleeding risk (which explains the reduced major bleeding events in the ticagrelor monotherapy arm in TWILIGHT [45].

Therefore, an alternative strategy to year-long DAPT after PCI is the early introduction of single antiplatelet therapy (SAPT) with more potent $P2Y_{12}$ inhibitors, i.e., halting aspirin early (usually 3 months) after PCI. We want to highlight three points in this regard. First, this strategy has not been studied for all patients in secondary prevention but only for the stable patients; secondary prevention patients at high risk should maintain DAPT. Second, replacing ASA with an alternative, more expensive antithrombotic has economic implications that have to be studied. Third, despite ASA being discontinued, an alternative antithrombotic (ie. a P2Y12 inhibitor) was always provided in these trials; in fact, there is a clear increase in cardiovascular events in patients who reported discontinuation of aspirin monotherapy.[46, 47]

Stable chronic CAD patients and PCI

The first potential area of clinical application of this strategy of halting ASA involves patients after PCI and stent implantation. These patients are conventionally treated with 12 months of DAPT and then $P2Y_{12}$ inhibition is stopped and only ASA is maintained. Trials hitherto investigating duration of DAPT studies were dropping the $P2Y_{12}$ inhibitor after some months and maintaining *aspirin monotherapy* for life. Based on the aforementioned thrombus formation studies, an alternative strategy to year-long DAPT after PCI is the early introduction of single antiplatelet therapy with more potent $P2Y_{12}$ inhibitors[37] (e.g., stopping aspirin 1-3 months after PCI). Studies evaluating these and other "de-escalation" strategies are discussed in detail in the article by Drs. Sinnaeve and Adriaenssens[48] in this Supplement.

Stable CAD patients and atrial fibrillation

The second potential area of clinical application is the patient with concomitant stable CAD, atrial fibrillation, and *recent PCI*. In these patients, the strategy of stopping ASA and maintaining dual antithrombotic therapy with an anticoagulant and single antiplatelet $P2Y_{12}$ agent decreased the risk of TIMI minor or major bleeds compared with triple therapy without any difference in major adverse cardiovascular events. This has been demonstrated in the What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing (WOEST) trial, A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI) and in the Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL) trial, and also in a metanalysis.[49] A recent meta-analysis including the Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention (AUGUSTUS) trial reported less bleeding in aspirin-less strategies without significant differences in cardiovascular events.[50] These studies are covered in detail in the article in this Supplement by Dr. Cannon[51].

In the subgroup of atrial fibrillation and concomitant CAD *without recent PCI*, the Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease Study (AFIRE) of 2,236 Asian patients compared rivaroxaban monotherapy vs rivaroxaban plus antiplatelet agent (at the discretion of the physician; specifically, 71% with ASA). The trial was stopped early because of increased mortality in the combination group.[52] Rivaroxaban monotherapy was noninferior to combination therapy for the primary efficacy end point.[52]

Conclusion

Given the central mechanistic role of platelet aggregation on atherosclerotic disease, aspirin has classically the cornerstone of antiplatelet therapy in acute coronary syndrome, primary prevention and secondary prevention. In fact, all new, more potent antiplatelet drugs were studied on top of aspirin in CAD patients. The key role of aspirin in acute coronary syndrome remains unquestionable in current times, but modern data are leading to reconsideration of its usefulness in *some* patients at primary and secondary prevention. In primary prevention, the benefit of aspirin has been reduced with modern more effective treatment (e.g., statins) that reduce ischemic risk, so the benefits of aspirin are currently more modest than in the classic studies. Moreover, its side effects (mainly bleeding episodes) could indeed offset those modest benefits. This leads to a current reconsideration of the "blanket" use of ASA in primary prevention. In secondary prevention, the limited additive antithrombotic effect of aspirin on top of more potent P2Y12 inhibitors suggest that aspirin could be halted in certain subset of stable patients (e.g., 3 months after PCI, stable patients with concomitant atrial fibrillation and CAD) without compromising efficacy with the added benefit of reducing bleeding. The fascinating role of aspirin in the current treatment paradigm of cardiovascular medicine deserves to be reevaluated.

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