Evolution of Clinical Thinking and Practice Regarding Aspirin: What Has Changed and Why?

Charles V. Pollack, Jr., MA, MD[a,*], and Tracy Y. Wang, MD, MHS, MSc[b]

Aspirin (ASA) is the original antiplatelet agent. Its routine use, long unquestioned for both primary and secondary prevention in cardiovascular disease, is under increasing scrutiny as the risk:benefit balance for ASA becomes less clear and other disease- and risk-modifying approaches are validated. It can be viewed as a significant advance in evidence-based medicine that the use of an inexpensive, readily available, long-validated therapy is being questioned in large, rigorous trials. In this overview we present the important questions surrounding a more informed approach to ASA therapy: duration of therapy, assessment of net clinical benefit, and timing of start and stop strategies. We also consider potential explanations for "breakthrough" thrombosis when patients are on ASA therapy. Other manuscripts in this Supplement address the specifics of primary prevention, secondary prevention, triple oral antithrombotic therapy, and the future of ASA in cardiovascular medicine. **(Am J Cardiol 2021;144:S10−S14)**

Aspirin (ASA) was the first pharmacologic agent found to selectively inhibit platelet activity successfully.[1] That this activity was discovered as a result of an accumulation of anecdotal accounts of bleeding associated with ASA use[2] presaged the risk:benefit debates and trials of the past decade. The history of ASA use and research (Table 1) typifies the tendency of seemingly effective treatments to become so ingrained in our therapeutic approaches, that new and potentially effective pharmaceuticals are often studied only as add-on agents instead of replacement therapy. Such intellectual inertia explains the resistance, until quite recently, to evaluate platelet $P2Y_{12}$ receptor antagonists as monotherapy instead of as part of enduring dual antiplatelet therapy (DAPT) grounded in ASA. Evolution in practice can occur quickly, but often brings along remnants of the tried-and-true without sufficient healthy skepticism. The large reductions in thrombotic risk seen when ASA was compared with placebo came from historical studies that were conducted in settings that bear little resemblance to contemporary clinical management of cardiovascular disease. Until recently, though, ASA has been a virtually immutable foundation of the evidence base promulgated through practice guidelines and recommendations for the past 40 years. Placebo was considered an infeasible control in the name of patient safety.

The availability of advanced antithrombotic agents has now brought us into a new era, in which clinicians and scientists are contemplating withdrawal of those previously established agents to minimize bleeding risk while maintaining efficacy. Instead of add-on therapy, it may well be that subtraction leads to the next advance in the treatment of acute and chronic ischemic cardiovascular disease. Including ASA, no antiplatelet agent has been shown to provide a wholly satisfactory risk:benefit balance in the primary prevention of cardiovascular disease; the previous benefits attributable to ASA may now be more safely achieved with tighter blood pressure and glycemic control, use of lipid-lowering agents, and successful lifestyle modification.[3] That shift in thinking about primary prevention with ASA is the subject of Dr. article by Drs. Angiolillo and Capodanno in this Supplement.

The challenge to ASA's foundational status in secondary prevention, where its utility until recently was unquestioned, derives from 3 major concerns, the first of which is the risk of bleeding that may outweigh antithrombotic/anti-ischemic benefit, especially when taking into account the duration of treatment. Although intracranial hemorrhage is rare, extracranial (particularly gastrointestinal and urinary tract) bleeding events are not uncommon in patients taking ASA, and are especially frequent in the elderly, in patients on long-term ASA therapy, and in patients on DAPT or who receive concomitant anticoagulation. Second, as with primary prevention, other disease-modifying therapies that are now readily available may provide similar protection against secondary events without that bleeding risk.[3] Third, there has been a growing realization that ASA is a "blunt instrument." As science has progressed and potent, advanced, and more targeted antithrombotic agents such as direct oral anticoagulants and platelet $P2Y_{12}$ receptor antagonists have come to dominate the array of treatment and secondary prevention options,[4,5] and the less precisely targeted option of ASA becomes less attractive.

This Supplement has been produced in recognition of this ongoing evolution in care and reconsideration of the risk:benefit balance of routine use of ASA. Any potential "subtraction" of ASA from cardiovascular treatment plans should be supported by rigorous trial evidence, which is in fact gradually accumulating. Nonetheless, it must be recognized that the mere questioning of the ASA dogma is a tremendous step forward in advancement of care.

Although most current research into "subtracting" ASA from cardiovascular treatment plans is driven by concerns

[a]Department of Emergency Medicine, University of Mississippi Medical Center, Jackson, Mississippi; and [b]Duke Clinical Research Institute, Duke University, Durham, North Carolina. Manuscript received November 19, 2020; revised manuscript received and accepted December 11, 2020.

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*Corresponding author: Tel: +1 (610) 329-2986, fax: +1 (888) 959-8345.

E-mail address: cvpollack@gmail.com (C.V. Pollack).

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Table 1
Evolution of use and research on aspirin in cardiovascular medicine (modeled after reference[45])

Era	Specialty	ASA Positioning	ASA Evolution
1899−1960	Internal Medicine and Rheumatology	Analgesic Anti-inflammatory Antipyretic	Prototype of new NSAIDs
1960−1980	Gastroenterology	ASA is gastrotoxic and can be replaced with safer drugs	NSAIDs not necessarily safer
1980−2010	Cardiology and Neurology	Low-dose ASA is effective antithrombotic and saves lives	ASA unquestioned as primary prevention; DAPT is essential for secondary prevention
2010−2021	Interventional Cardiology	ASA can cause serious bleeding complications	Risk:benefit balance is not favorable for primary prevention; Can we drop ASA from long term secondary prevention therapy?

ASA = aspirin; DAPT = dual antiplatelet therapy; NSAID = nonsteroidal anti-inflammatory drug.

over bleeding risk, consideration should also be given to the limited data on ASA efficacy. The Antithrombotic Trialists Collaboration meta-analysis in 2002 showed a reduction in cardiovascular event rates of around 25% in high-risk patients treated with ASA.[6] Residual risk remains, however, raising the consideration of a number of causative factors, including potential ASA resistance. In fact, a meta-analysis in 2014 identified 622 of 1,889 coronary heart disease (CHD) patients (33.0%) who were classified as being ASA resistant with confirmed ASA adherence.[7] And perhaps not surprisingly, patients identified in that analysis as having laboratory ASA resistance exhibited a 2.4-fold increased risk of major adverse cardiovascular events (MACE) compared with ASA-sensitive patients.

When tests that specifically assess cyclooxygenase 1 (COX1) activity (through which, in addition to inhibition of thromboxane A2 generation, ASA exerts its antithrombotic and vascular protective properties) are used, ASA resistance is not frequently observed, and when it is present,[8] it is often attributed to poor treatment adherence.[3] Nonadherence is in fact likely the primary cause of "clinical" ASA resistance—that is, the occurrence of a cardiovascular event in a patient who claims compliance with medication. This in turn could result from any of a number of potential contributing factors, including confusion caused by polypharmacy, patient-perceived non-importance of compliance due to the OTC availability of ASA, or attribution of gastric upset to ASA. Ischemic events in patients in whom reduced platelet inhibition by ASA is confirmed in the absence of non-compliance, is likely mediated by either platelet−independent (such as coronary artery spasm) or COX−independent platelet-mediated mechanisms. An example of the latter might be platelet activation through phospholipase C−mediated cleavage of inositol triphosphate and diacylglycerol from the cell membrane.[2] The inositol triphosphate then binds to an intracellular Ca^{2+} channel, increasing intracellular Ca^{2+} levels through release from the endoplasmic reticulum, whereas diacylglycerol ultimately activates protein kinase C, resulting in platelet activation without activation of COX. ASA will not interfere with this pathway to activation.[2]

There are both pharmacodynamic and pharmacokinetic potential explanations for "breakthrough" cardiovascular events while on ASA therapy. Polymorphisms in COX and other platelet receptors could account for pharmacodynamic-mediated resistance,[9−11] but the incidence of these is quite low.[11,12] Resistance attributable to pharmacokinetic likely results from underdosing, patient obesity, reduced bioavailability of ASA due to enteric coating,[11] and drug-drug interactions with nonsteroidal anti-inflammatory drugs (which bind reversibly to the same COX target and have longer half-lives)[13,14] or statins.[15]

The risk:benefit balance—and therefore overall clinical utility—of ASA therapy in secondary prevention may also vary with time. For example, the currently studied potential benefit of withdrawal of ASA from DAPT after percutaneous coronary intervention, discussed in this Supplement by Drs. Sinnaeve and Adriaenssens, follows 3 months[16,17] of DAPT, when the risk of acute and subacute stent thrombosis is highest[18] and during which time the added bleeding risk of DAPT may be more acceptable. In fact, the neutral findings of the GLOBAL LEADERS trial, in which the switch from DAPT to ticagrelor monotherapy occurred after just 1 month,[19] may have resulted from discontinuing ASA too soon. Similarly, the risk of recurrent cerebrovascular insult after stroke or transient ischemic attack (TIA) is highest in the first few days to weeks after the index event.

A striking reduction in the risk of early secondary stroke has been consistently attributed to ASA.[20,21] Most stroke guidelines, however, do not distinguish between the early and later phases of secondary prevention, and some recommend clopidogrel monotherapy as an equal alternative to ASA.[22,23] Multiple trials do seem to suggest that the longer the period of secondary prevention without ASA, the less severe the bleeding accompanying the reduction in ischemic event occurrence.[24]

A meta-analytic time-course analysis of randomized trials found, however, that treatment in the first few days and weeks after event should include ASA unless or until some other antithrombotic agent is shown to be superior.[25] That analysis indicated that dipyridamole monotherapy is inferior to ASA in prevention of early recurrent stroke, and that dual therapy of ASA with dipyridamole does not add to the beneficial effects of ASA on either the risk or the severity of early recurrent ischemic stroke. Further, clopidogrel plus ASA does appear to be more effective than ASA monotherapy in prevention of early recurrent stroke after TIA and minor ischemic stroke,[26,27] but the combination appears to have no effect on severity of secondary stroke.[28] The only trial of clopidogrel monotherapy versus ASA plus

dipyridamole (Prevention Regimen for Effectively Avoiding Second Strokes, PRoFESS) showed no statistically significant differences between the 2 treatments in either the primary outcome (first recurrence of stroke) or the secondary outcome of the composite of stroke, myocardial infarction, or death from vascular causes.[29]

Although PRoFESS showed no difference in overall severity of recurrent stroke on ASA plus dipyridamole compared with clopidogrel in secondary prevention,[29] Rothwell et al[25] make a convincing case that risk and severity of early recurrent stroke might have been reduced if randomization had occurred sooner after the initial TIA or stroke. As subjects could be enrolled up to 120 days later, the early protective effects of ASA could have been lost to the analysis after prolonged prerandomization use. In the Management of ATherothrombosis with Clopidogrel in High-risk patients (MATCH) trial, the benefit of ASA plus clopidogrel over clopidogrel monotherapy was seen only in patients randomized early after TIA or stroke.[30] These small but significant differences suggest that early ASA after stroke may be beneficial, with similar findings applied to cilostazol, ticagrelor, and direct oral anticoagulants. For example, survival curves in trials comparing ASA with cilostazol suggest that ASA is superior for the first 3 months, but that cilostazol is more effective thereafter.[31,32]

On the other hand, in the Acute Stroke or Transient Ischaemic Attack Treated with ASA or Ticagrelor and Patient Outcomes (SOCRATES) trial, patients with ischemic stroke or TIA were randomly assigned *within 24 hours* after symptom onset, in a 1:1 ratio, to receive either ticagrelor (180 mg loading dose on day 1 followed by 90 mg twice daily for days 2 through 90) alone without ASA or ASA (300 mg on day 1 followed by 100 mg daily for days 2 through 90). Overall, the study showed ticagrelor was not superior to ASA in reducing the rate of stroke, myocardial infarction (MI), or death at 90 days, though it was superior to ASA in reducing ischemic stroke, and there was no significant difference in the rate of major bleeding.[33]

The importance of SA during the vulnerable period of the first 30 days after stroke was acknowledged in the design of the Acute Stroke or Transient Ischaemic Attack Treated with Ticagrelor and ASA for Prevention of Stroke and Death (THALES) trial.[34] In THALES, patients were randomized within 24 hours of a qualifying event (mild-to-moderate acute noncardioembolic ischemic stroke as determined according to the clinical judgment of the investigators, with a National Institutes of Health Stroke Scale score ≤ 5, or a high-risk TIA as determined according to a score of 6 or higher on the ABCD^2 scale or symptomatic intracranial or extracranial arterial stenosis [$\geq$50% narrowing in the diameter of the lumen of an artery that could account for the TIA]). Patients received either ticagrelor (180 mg then 90 mg twice daily) plus ASA (300 to 325 mg) or matching placebo plus ASA, for 30 days. Thereafter, ASA 75 to 100 mg daily was recommended.[34]

A total of 11,016 patients were randomized, and a primary-outcome event (composite of stroke or death within 30 days) occurred in 5.5% in the ticagrelor−ASA group and in 6.6% in the ASA-only group (hazard ratio, 0.83; 95% confidence interval, 0.71 to 0.96; p = 0.02). Specifically, ischemic stroke occurred in 5.0% in the ticagrelor−ASA group and in 6.3% in the ASA group (hazard ratio, 0.79; 95% confidence interval , 0.68 to 0.93; p = 0.004), but the incidence of disability did not differ significantly between the 2 groups. Severe bleeding occurred in 0.5% of patients in the ticagrelor −ASA group and in 0.1% in the ASA group (p = 0.001).[34] On the basis of the THALES data, the FDA expanded the indications for ticagrelor to include secondary prevention in stroke and high-risk TIA, but the data also reinforced the importance of early ASA use in the after stroke period.

In summary, the role of ASA in secondary prevention of stroke and TIA is being aggressively challenged. Similar to evolving strategies in secondary prevention of acute coronary syndrome,[16,17] it may that an initial interval of ASA coverage is important, but thereafter, other approaches may provide stroke protection with a lower risk of bleeding.

Another scenario in which ASA is frequently considered for discontinuation is the perioperative setting. This is an area fraught with controversy given very limited rigorous evidence. The most often cited study, the PeriOperative Ischemia Evaluation-2 (POISE-2) trial, was a randomized, double-blind, multicenter controlled trial that evaluated the outcome of continuing or stopping ASA in 10,010 patients with either previous CAD or stroke who underwent noncardiac surgery, excluding patients with recent PCI (bare metal stent within 6 weeks, drug eluting stent within 12 months).[35] Previous ASA users were randomized to continued perioperative ASA or 7 days of perioperative placebo and then returning to ASA. No difference in 30-day perioperative death or MI was found between groups, but bleeding, mostly at the surgical site and not lethal, was higher with ASA use.[35,36] However, many of the POISE-2 trial patients had low vascular risk, with fewer than 5% of patients having previous coronary stent implantation. Furthermore, many patients were administered perioperative thromboprophylaxis with an anticoagulant in the trial. In the subgroup of patients with previous PCI, perioperative continuation of ASA had a net benefit on the primary outcome that persisted at 1 year.[37]

A 2018 Cochrane meta-analysis, based on very limited data from 5 randomized trials (total n = 666), found no significant differences in mortality, or in perioperative thrombotic or bleeding events, between patients who continued their single or dual antiplatelet regimen throughout the perioperative interval, and those who discontinued their regimen at least 5 days preoperatively.[38] Current practice guidelines state that for patients on ASA pre-operatively, continuing ASA is still reasonable when major noncardiac surgery is planned and the perceived risk of a MACE is greater than the risk of bleeding.[39] Although most procedures can be safely performed on ASA, a high bleeding risk associated with neurosurgery renders it probably the only procedural type that warrants serious consideration of perioperative cessation when a patient is on ASA for secondary prevention.[40,41] In patients naïve to ASA therapy, there is no indication for starting ASA therapy before surgery.[42]

European guidelines further state that when a patient is on $P2Y_{12}$ inhibitor monotherapy after stent implantation, it may be better to switch the $P2Y_{12}$ to ASA at least 7 days pre-operatively to permit $P2Y_{12}$ receptor function recovery.[43] This approach may, however, be less necessary with the availability of cangrelor, an intravenous, short acting $P2Y_{12}$ inhibitor replacement option. These "off-label"

strategies are poorly studied and the "replacement" of $P2Y_{12}$ inhibitor therapies with cangrelor, ASA, or glycoprotein IIb/IIIa inhibitors, or even the "bridging" of antiplatelet therapies (ASA or $P2Y_{12}$ inhibitors) with anticoagulants such as unfractionated or low molecular weight heparin, is not recommended by the ACC/AHA guidelines.

The challenges to the foundational position of ASA in cardiovascular medicine will continue. Newer antithrombotic agents with more predictable activity and lower risks of bleeding complications are available and still others are in development.[44] The use of other disease-modifying therapies is reducing the magnitude of the impact in thrombosis reduction formerly attributed to ASA. There will doubtless remain a role for ASA in this space—at this point we are reducing but not subtracting—but that role is evolving and being thoroughly dissected. It is indeed diminishing, largely in the name of patient safety.

Conflict of interest

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