The Future of Aspirin Therapy in Cardiovascular Disease

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Much has been written about the demise of aspirin (ASA) but reports of its death are premature. The drug remains one of the most widely prescribed by physicians worldwide. It is cheap, familiar, and effective for a variety of uses, including in patients with acute or prior myocardial infarction, ischemic stroke, peripheral artery disease, and percutaneous or surgical revascularization procedures, as well as for use for pain and fever relief. Beyond physician prescription or recommendation, over the counter use of ASA is common, including for primary cardiovascular prevention, though this decision really should involve a discussion of risks and benefits with a physician. ASA is an essential member of the duo that makes up dual antiplatelet therapy (a $P2Y_{12}$ inhibitor plus ASA) and also dual pathway inhibition (vascular dose rivaroxaban plus ASA), and data for both approaches are growing. Furthermore, research is ongoing as to the optimal dosing frequency (once vs twice daily), potentially safer gastrointestinal delivery, and possibly more effective formulations in terms of platelet inhibition. One goal of ASA research is to try to reduce bleeding complications that are a risk with all anti-thrombotic therapies. Although its exact roles will continue to evolve, the future for ASA remains bright. **(Am J Cardiol 2021;144:S40−S47)**

Aspirin (ASA) has been the cornerstone of cardiovascular medicine for the past several decades.[1,2] It has been studied extensively in the context of secondary and primary cardiovascular prevention. The data in secondary prevention are robust across disease states including acute myocardial infarction (MI), prior MI, ischemic stroke, peripheral artery disease, and percutaneous or surgical revascularization.[3−6] Even in primary prevention, in very high-risk individuals, ASA does appear to have a valuable role, particularly in patients with diabetes mellitus (Figure 1).[7−9] The risk-benefit window is narrow in an unselected primary prevention population, but with more careful triaging of patients, those with better net clinical benefit can likely be identified (Figure 2).[10] In the future, use of noninvasive coronary artery imaging to detect and quantify plaque burden may help further identify which patients under the broad primary prevention umbrella truly do benefit from ASA therapy.

Although the most feared bleeding complication is intracranial bleeding, this is a rare occurrence with ASA monotherapy. The most common major bleeding complication from ASA is gastrointestinal bleeding. Proton pump inhibitors are known to reduce the risk of recurrent gastrointestinal bleeding in patients who have already had previous gastrointestinal bleeding. They were also known to prevent endoscopic ulceration in patients receiving ASA therapy.

The Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT) was the first randomized trial to show that prophylactic proton pump inhibition lowered the risk of gastrointestinal (GI) bleeding in patients who were at relatively low gastrointestinal bleeding risk while receiving dual antiplatelet therapy (DAPT) with ASA plus clopidogrel.[11−14] Extrapolation of these results suggested in settings even other than DAPT that proton pump inhibitors may reduce GI bleeding - including in the setting of ASA monotherapy. Thus, use of proton pump inhibitors in patients at high GI bleeding risk, but possibly also in medium and low GI bleeding risk patients, could further alter the risk:benefit profile of ASA more favorably, including in the primary prevention setting. Of course, this does mean additional drug therapy and cost and potential side effects, but this strategy of prophylactic proton pump inhibition with ASA monotherapy does warrant much broader scale clinical trial investigation than has been performed to date.

An increased appreciation of the deleterious downstream effects of bleeding over the past decade has led to a reexamination of the value of ASA in various cardiovascular settings. For example, in the setting of atrial fibrillation and percutaneous coronary intervention, the data show that ASA has a much more limited role than previously believed. That is, triple antithrombotic therapy with ASA, a $P2Y_{12}$ inhibitor, and a full-dose oral anticoagulant is no longer routinely indicated. At most, it appears that a month of triple therapy may have a limited role, but certainly not durations beyond that time frame. However, for the hospitalized portion of care, at least a few initial doses of ASA remain warranted.

Recent data have suggested that de-escalation from DAPT to $P2Y_{12}$ inhibitor monotherapy after 3 months or even after 1 month may result in noninferior ischemic outcomes with significantly lower bleeding rates.[15] The strongest data for this strategy exist with the ticagrelor-based Ticagrelor with Aspirin or Alone in High-Risk Patients

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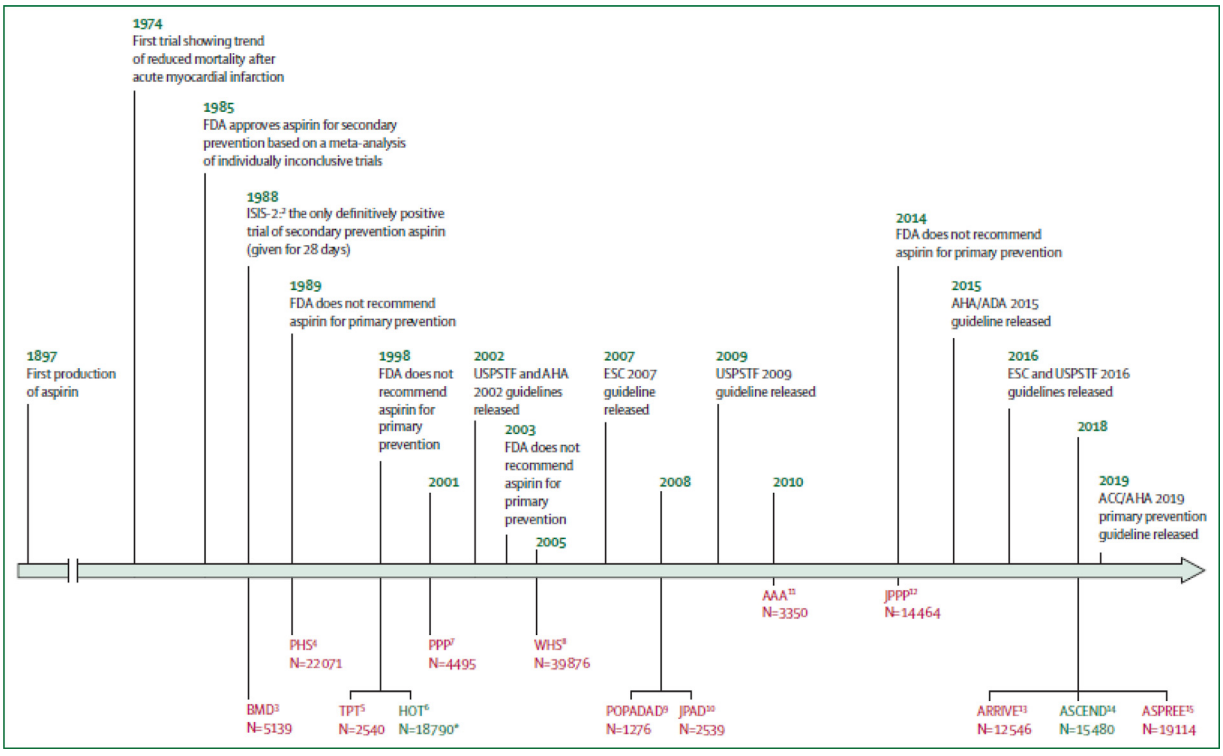

Figure 1. Timeline for aspirin studies in primary cardiovascular prevention. From Raber I et al. *Lancet.* 2019; 393:2155−67.[7]

after Coronary Intervention (TWILIGHT) study, though there are also trials of clopidogrel monotherapy as part of a secondary prevention de-escalation strategy.[16]

The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial had previously shown the modest superiority of clopidogrel 75 milligrams daily versus ASA 325 mg daily in high risk secondary cardiovascular prevention. Indeed, hospitalization for gastrointestinal bleeding was significantly lower with clopidogrel than with ASA in CAPRIE.[17] Thus, there was somewhat better efficacy and somewhat better safety with clopidogrel versus this dose of ASA. Presumably, a lower dose of ASA as is commonly used in secondary prevention now would have had a lower risk of GI bleeding, though there is no reason to think that the lower ASA dose would have had superior efficacy than clopidogrel. Therefore, it is likely the case that clopidogrel monotherapy and perhaps ticagrelor monotherapy may be superior to ASA in high ischemic risk secondary prevention. Multiple subgroup analyses from the CAPRIE trial found that high-risk subgroups within the high-risk secondary prevention patients enrolled in the trial derived even greater anti-ischemic benefits from clopidogrel versus ASA.[18−22] These data do provide a rationale for the de-escalation strategies discussed previously and do support that there may indeed be a growing role for $P2Y_{12}$ inhibitor monotherapy. This approach may accelerate with greater generic availability of ticagrelor worldwide. Of course, clopidogrel is already generic worldwide, and its use is anchored in global practice.

A phospholipid-coated formulation of ASA has been studied with respect to endoscopic evaluation. These analyses have suggested an early benefit consisting of decreased endoscopic ulceration with the phospholipid-coated ASA versus regular uncoated ASA.[23] Further study will be necessary to see if this translates into better adherence or less clinically important gastrointestinal bleeding. The antiplatelet effect of this new ASA formulation has also been evaluated, and the phospholipid formulation does appear to have faster antiplatelet effect than enteric-coated ASA (Figure 3).[24−26] Interestingly, the data supporting superior gastrointestinal bleeding profiles for enteric-coated ASA are rather weak.

Other novel formulations of ASA are also being evaluated. An inhaled nanoparticle ASA preparation, administered with a dry powder inhaler, was developed to enhance the speed of platelet inhibition induced by ASA. The inhaled ASA formulation bypasses GI and hepatic metabolism and has the potential to provide rapid drug exposure from the pulmonary circulation and to avoid gastrotoxicity. In a Phase 1 study, compared with chewing and swallowing ASA, inhaled ASA provided earlier and greater drug exposure and was a faster way to achieve greater platelet inhibition (as determined by arachidonic acid-induced platelet aggregation and serum thromboxane B_2 levels).[27] Another Phase 1 study, of an ASA-loaded solid lipid microparticle formulation, showed good sustained-release kinetics, increased anti-inflammatory properties, and provided protection from ASA-induced gastric ulcers.[28]

Much had been written about "aspirin resistance."[29−37] However, it appears that true biochemical ASA resistance is extremely infrequent, occurring in no more than a few percent of patients. Most purported ASA resistance is actually due to nonadherence. It is possible that nonsteroidal anti-inflammatory drugs might through steric hindrance

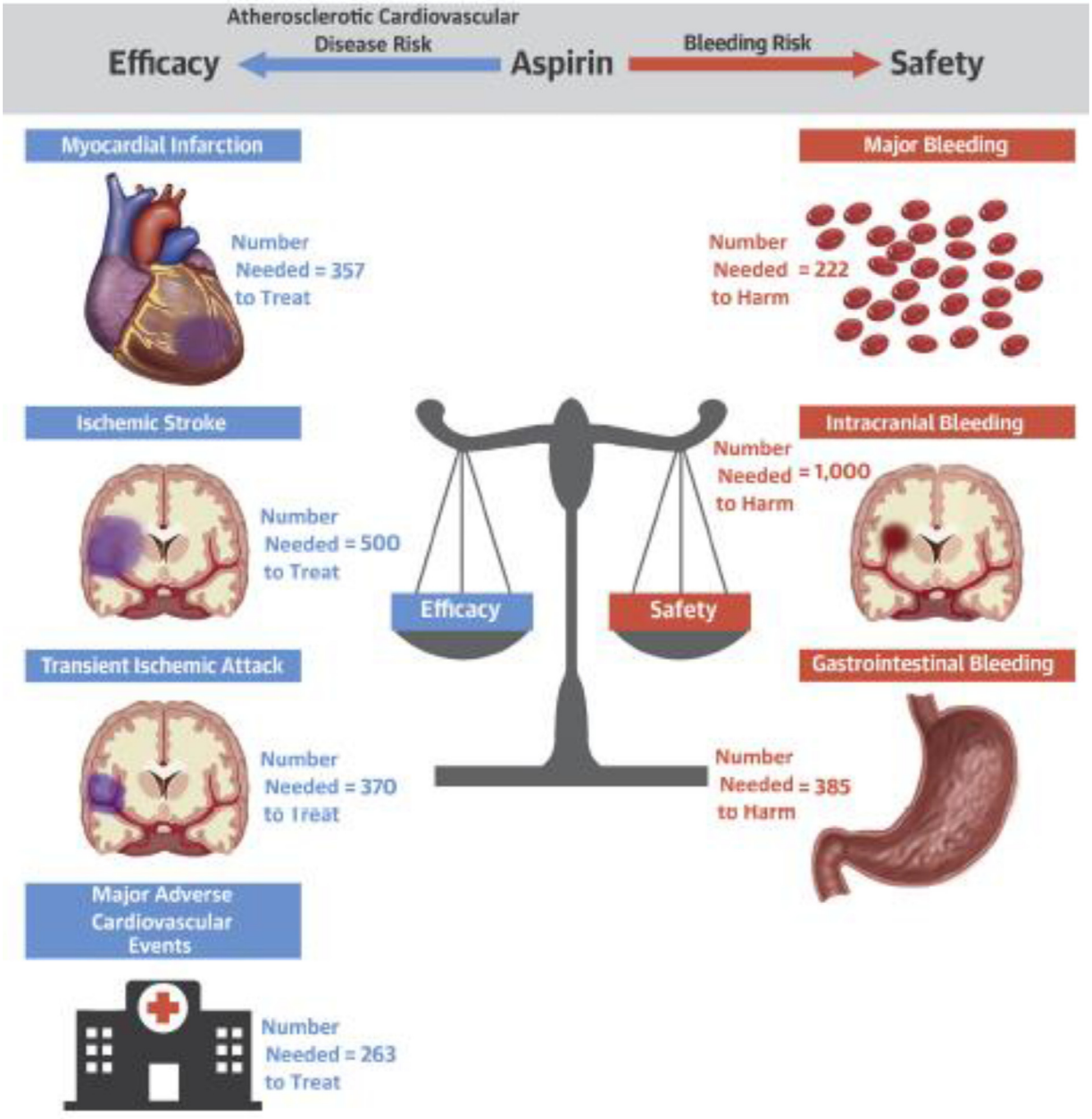

Figure 2. Net clinical benefit of aspirin in primary cardiovascular prevention in a broad population. There is a narrow window of benefit, though it can be improved with careful selection of patients. From Abdelaziz HK et al. *J Am Coll Cardiol*. 2019;73(23):2915−29.[10]

lead to some degree of lack of ASA antiplatelet effect when used around the clock. Interestingly, there was less ASA resistance with the above phospholipid-coated ASA than with enteric-coated ASA during a short-term assessment. If this pharmacokinetic and pharmacodynamic difference translates into a higher rate of ischemic events due to the enteric coating on many ASA formulations, that could be of great public health importance.

The Cardiovascular OutcoMes for People Using Anticoagulation StrategieS (COMPASS) trial evaluated a so-called vascular dose of rivaroxaban (2.5 mg twice daily) in conjunction with low dose ASA.[38−44] The trial found that this regimen significantly reduced ischemic events compared with ASA plus placebo. The results of the trial were so robust that the data safety monitoring board recommended early termination of the study. This curtailed the ability to have long follow up duration with this regimen, though even at the time of the trial's ending there was a lower rate of cardiovascular as well as all-cause mortality. Although one can debate the statistical significance of the mortality findings as it did not meet the prespecified p value, a prior trial of this regimen also found lower mortality. That trial was the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS 2−Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2−TIMI 51) trial of patients with stabilized acute coronary syndromes where this regimen also significantly reduced

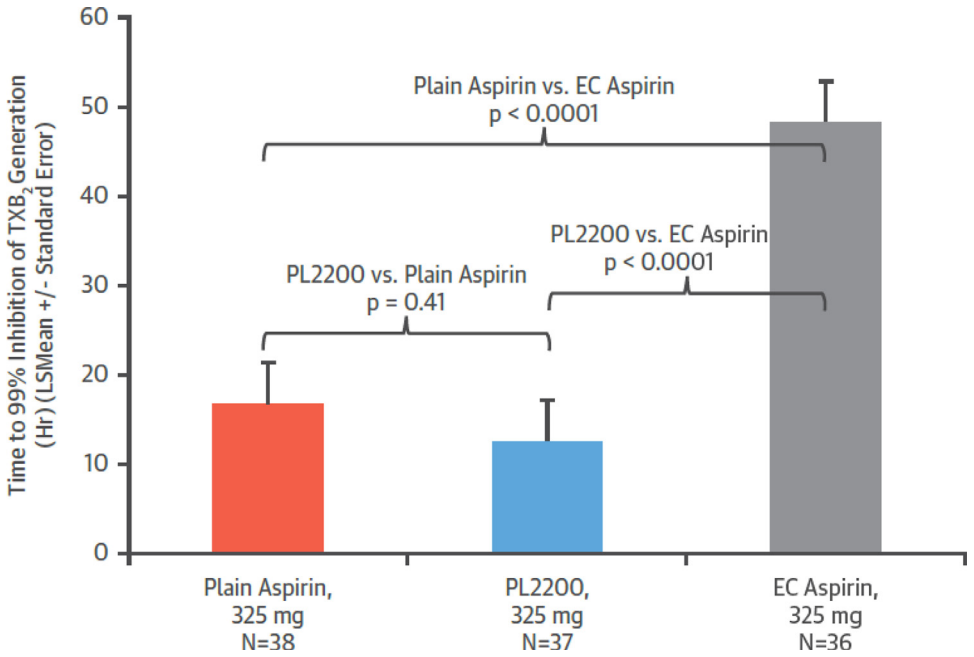

Figure 3. A phospholipid-coated aspirin provides faster antiplatelet effect than enteric-coated aspirin. From Bhatt DL et al. *J Am Coll Cardiol*. 2017;69 (6):603−12.[24]

ischemic events and significantly reduced cardiovascular and all-cause mortality.[45,46] Although the ATLAS ACS 2 −TIMI 51 trial did not lead to FDA approval of this regimen, the COMPASS trial did for high ischemic risk patients with coronary artery disease and/or peripheral artery disease at low risk of bleeding.[47] This regimen has also been studied in the Efficacy and Safety of Rivaroxaban in Reducing the Risk of Major Thrombotic Vascular Events in Subjects With Symptomatic Peripheral Artery Disease Undergoing Peripheral Revascularization Procedures of the Lower Extremities (VOYAGER PAD) trial, in which it was found to be superior to ASA plus placebo, including with background clopidogrel therapy in situations where the operator elected to use it.[48] Thus, use of this dual pathway inhibition with ASA and low dose rivaroxaban is likely to grow in popularity, especially in patients with peripheral artery disease and polyvascular disease (the presence of plaque in several arterial beds).[40,49]

High-risk patients may have increased production of activated platelets and platelet turnover. Thus, it is possible that once daily irreversible antiplatelet agents such as ASA may not provide protection against new activated platelets that are released from the bone marrow or later in the day. Therefore, there is a potentially logical reason that twice-daily ASA dosing may provide incremental benefit. This is being studied now in trials. Although adherence with a twice a day regimen does tend to be lower than a once a day regimen, for patients also using ticagrelor as part of DAPT, this may be less of a limitation because ticagrelor also needs to be given twice a day. Also, stated in another way, if the once a day ASA regimen leads to better adherence, the twice a day dosing may still provide the benefits that once a day ASA dosing does without losing that benefit even if the patient forgets to take their second dose. The exact dose of ASA if it were to be fractionated into two daily doses still needs further investigation, as higher doses of ASA do appear to be related to greater bleeding risk, in particular GI bleeding risk. In fact, ongoing research is trying to determine the optimal dose of ASA.[50−52]

Another potential approach to simulate twice-daily dosing in high-risk patients is being evaluated. An extended-release ASA (ER-ASA) formulation was developed to allow 24-hour antithrombotic coverage with dosing once per day. In an open-label, single-center study, 40 patients with diabetes, multiple cardiovascular risk factors, and high platelet turnover or high platelet reactivity received ER-ASA 162.5 mg/day for 2 weeks and then ER-ASA 325 mg/day for 14 ± 4 days. Indeed, all patients responded to ER-ASA 162.5 mg/day as assessed by arachidonic acid-induced platelet aggregation, and the antiplatelet effect persisted over 24 hours for all the platelet function measurements which were performed. The lower dose was also well tolerated and is being studied further.[53]

Use of DAPT may increase substantially based on recent trials, as well as recent regulatory approvals.[54] For example, the Ticagrelor Versus Placebo in Patients With Type 2 Diabetes Mellitus (THEMIS) and THEMIS-PCI trials found that ticagrelor used in diabetes with stable coronary artery disease significantly reduced ischemic events, albeit with increased major bleeding risk.[55−57] Based on these data, the US FDA has approved the use of ticagrelor with ASA for patients with coronary artery disease and high ischemic risk. Although THEMIS specifically studied diabetes patients, the label is not restricted to diabetes, as the FDA wisely acknowledges that patients without diabetes can also be at high ischemic risk and potentially benefit from DAPT. Health Canada also approved this regimen based on THEMIS and THEMIS-PCI, albeit for a slightly narrower indication than the US label. Regardless of the specifics around labeling, the availability of ticagrelor and these data will

likely lead to more use of DAPT in high ischemic, low bleeding risk patients.[58]

Indeed, trials such as COMPASS and THEMIS, as well as preceding trials such as Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) and Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared with Placebo on a Background of Aspirin Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) and others, support the concept that long-term antithrombotic therapy with more than ASA monotherapy is beneficial in a broad range of high ischemic risk and low bleeding risk patients.[59–65] It is essential when considering these regimens to only deploy them in those at low bleeding risk, as protracted double antithrombotic therapy in high bleeding risk patients almost always backfires. Still, there are many patients at high ischemic and low bleeding risk, and it does appear possible to identify them through various risk scores, such as the PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy (PRECISE-DAPT) score.[66] However, it is important to realize that these types of risk scores tend to be underused. Therefore, simple descriptors such as history of prior bleeding, anemia, or thrombocytopenia can identify patients at high bleeding risk who may not be good candidates for prolonged double antithrombotic therapy.

Thus, ASA as monotherapy, as part of DAPT, and as part of dual pathway inhibition lives on as it is being critically reappraised. Further refinement will occur in exactly how long ASA must be routinely continued in patients with atrial fibrillation undergoing percutaneous coronary intervention or in patients with or without acute coronary syndromes post stenting. Newer dosing regimens or novel formulations of ASA may further improve the already favorable profile of aspirin and enhance the utility of this remarkable drug.

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