



A critical reappraisal of aspirin for secondary prevention in patients with ischemic heart disease

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Aspirin was established more than a quarter century ago as an evidence-based therapy to reduce recurrent cardiovascular events in patients with coronary artery disease based on limited data by contemporary standards. Indeed it is unclear how regulatory agencies would define the optimal dose or duration of aspirin therapy if assessed in the current era. Subsequent clinical investigation has focused on the addition of antiplatelet agents on top of baseline aspirin therapy in the acute and chronic setting to reduce patient's risk of further ischemic events, at the cost of increased bleeding complications. The current armamentarium of potent and predictable antiplatelet and antithrombotic agents has ushered in a new era where clinicians and scientists are contemplating withdrawal of previously established agents to minimize bleeding risk while sustaining efficacy; indeed, subtraction may lead to the next advance in the treatment of acute and chronic ischemic vascular disease. (Am Heart J 2016;181:92-100.)

More than a quarter century ago, antithrombotic therapy, initially with vitamin K antagonists and subsequently aspirin, was shown to reduce recurrent cardiovascular events in patients with documented coronary artery disease.^{1,2} Because of aspirin's ease of administration, tolerable safety profile, and patients' acceptance, it became established as the first widely used evidence-based therapy for secondary prevention. Subsequent important milestones included the development of the adenosine diphosphate receptor antagonist antiplatelet agents (ticlopidine, clopidogrel, prasugrel, and ticagrelor), platelet thrombin receptor inhibitors (vorapaxar), and the non-vitamin K oral anticoagulants (dabigatran, apixaban, rivaroxaban, and endoxaban). Various combinations of the available antithrombotic therapies have been assessed

for secondary prevention for patients with documented coronary artery disease with dual antiplatelet therapy continued for 1 year established as the standard of care. Further research assessed the potential of triple antithrombotic therapy approaches including the non-vitamin K oral anticoagulants (apixaban and rivaroxaban) or with platelet thrombin inhibitor in addition to dual antiplatelet therapy.²⁻⁵ These latter trials have all had in common an increased frequency of bleeding suggesting that a "safety-ceiling" may have been reached, although efficacy has also been demonstrated with reduction in cardiovascular end points such as death and myocardial infarction (MI). The agents and combinations mentioned were typically subjected to a systematic stepwise approach, where a range of doses were assessed and the investigated dose(s) identified in a phase 2 program, which was followed by a large (or several) phase 3 trial(s) to properly determine the risk-to-benefit ratio and assess duration of therapy. However, for aspirin, no such approach has been used, to properly establish the right dose or duration and then test it in an appropriately powered phase 3 program. Indeed, most treatments used for secondary prevention after an acute coronary syndrome (ACS) were developed after a more stringent review and approval process defined by the US and European Union regulatory agencies.

This review will address the evidence supporting aspirin as the cornerstone therapy for secondary prevention in patients with established coronary artery disease as well as acknowledge the limitations of this historical work. We will further discuss strategies currently being

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investigated that are hypothesized to maintain or enhance the efficacy of standard antithrombotic secondary prevention while improving safety. Specifically, we will discuss the potential of replacing dual antiplatelet therapy with predictable mono-antiplatelet therapy as well as the dual-pathway strategy where a single antiplatelet agent is combined with low-dose anticoagulation therapy to inhibit both arms of thrombosis.

Historical aspirin research

The history of acetylsalicylic acid (ASA) dates back to antiquity with evidence for the use of Willow bark to treat pain and fevers from the second millennium BC in Egyptian papyri, Hippocrates around 400 BC, and in Western medicine through the middle ages and into the mid-18th century. A synthetic version was subsequently developed and marketed by Bayer in 1899 and used clinically for many years before the antiplatelet effect achieved through inhibition of the cyclooxygenase 1 activation pathway was identified and the first trial of aspirin for prevention of MI occurred in the early 1970s.

Two seminal studies supported previous work and established aspirin as a cornerstone therapy across the spectrum of ACS patients. The Second International Study of Infarct Survival (ISIS-2) trial demonstrated a reduction in vascular deaths from 11.8% to 9.4% ($P = .00001$) with daily aspirin (162.5 mg) for 1 month compared with placebo in patients with ST-elevation acute MI when randomized against placebo in a factorial design with streptokinase.⁶ Subsequently, the benefit of daily aspirin 75 mg after unstable angina was demonstrated in 1991 with a large treatment effect of aspirin, but by today's standard, it was a small study ($n = 796$) with limited representation of key patient populations (no female patients enrolled and all patient were <70 years old).⁷

The AntiThrombotic Trialist (ATT) collaborative published a combined analysis assessing antiplatelet's effect on vascular disease based on more than 100,000 patients in trials of primary and secondary prevention.⁸ The 16 trials of secondary prevention demonstrated a consistent benefit of aspirin compared with placebo with a 20% relative risk reduction in cardiovascular events for 2 years of antiplatelet therapy (4.3%-5.3% [0.80, 0.73-0.88]); however, at the time of that publication, there was limited attention or discussion of the risk profile of antiplatelet therapy and medical therapies in general. Within the full ATT collaborative analysis, the risks of both hemorrhagic stroke (1.39 [1.08-1.78]) and fatal hemorrhagic stroke (1.74 [1.20-2.53]) were increased with aspirin therapy. Furthermore, the risk of clinically relevant gastrointestinal bleeding was increased by 54% (1.54 [1.30-1.82]) with aspirin compared with placebo.

Current guidelines recommend 75 to 162 mg in all patients with documented coronary artery disease as indefinite therapy.⁹⁻¹² The historical evidence supporting

this recommendation is based on studies using <75 mg daily (3 trials), 75-150 mg daily (12 trials), 160-325 mg daily (19 trials), and 500-1500 mg daily (34 trials) with a broad range of durations of therapy.⁸

Contemporary antiplatelet therapy: establishing the benefits and discussing the risks

Accepting that aspirin was a proven therapy for secondary prevention and acknowledging its relatively weak antiplatelet effect—the advent of adenosine diphosphate (ADP)—receptor blocking agents led to the investigation of the capacity to improve patient's outcomes through increased platelet inhibition with more potent agents or with the addition of a second antiplatelet agent on top of baseline aspirin.

The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial enrolled 19,195 stable patients with prior stroke ($n = 12,083$), MI ($n = 11,630$), or peripheral arterial disease ($n = 11,592$) to ASA 325 mg or clopidogrel 75 mg daily for approximately 2 years.¹³ The aspirin arm had a 5.83%/y event rate for the combined end point of vascular death, MI, or ischemic stroke. Clopidogrel monotherapy was associated with a modest reduction in the combined end point (5.32%/y) with a relative risk reduction of 8.7% (95% CI 0.3-16.5, $P = .043$) with no major differences in terms of safety. Aspirin in fact had numerically increased rates of severe bleeding (1.55% vs 1.38%, not significant), severe intracranial hemorrhage (0.43% vs 0.31%, not significant), and gastrointestinal hemorrhage (any 2.66% vs 1.99% [$P < .05$] and severe 0.71% vs 0.49% [$P < .05$]) over a mean duration of follow-up of 1.9 years.^{13,14}

In patients with an acute stroke or transient ischemic attack ($n = 13,199$), ticagrelor monotherapy (180-mg loading dose followed by 90 mg twice daily) has recently been compared with aspirin monotherapy (300-mg loading dose followed by 100 mg daily) for 90 days.¹⁵ Ticagrelor was associated with a nonsignificant reduction in the combined end point of 90 day stroke, MI, or death (ticagrelor 6.7% vs clopidogrel 7.5%; hazard ratio [HR] 0.87, 95% CI 0.76-1.01). Major bleeding occurred in 0.5% of ticagrelor-treated patients and in 0.6% of aspirin-treated patients with intracranial hemorrhage in 0.2% and 0.3% and fatal bleeding in 0.1% and 0.1%. Although this study was not in patients with established coronary artery disease, it demonstrates a similar safety profile of ticagrelor monotherapy to aspirin monotherapy despite ticagrelor's enhanced potency.

The Clopidogrel in Unstable Angina to prevent Recurrent Events (CURE) study randomized patients with non-ST-elevation ACS at the time of presentation to clopidogrel and aspirin or aspirin monotherapy and solidified the theoretical concept demonstrating a 20% relative risk reduction in 1-year cardiovascular death (mean duration of treatment 9 months), recurrent MI, and

stroke at a modest increased risk of bleeding.¹⁶ The primary outcome of cardiovascular death, nonfatal MI, and stroke occurred in 11.4% in the ASA monotherapy group. Furthermore, in the ASA monotherapy group, major bleeding occurred in 2.7% with life-threatening bleeding in 1.8%, fatal bleeding in 0.2%, hemorrhagic stroke in 0.1%, and total bleeding complications of 5.0%.

The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) and the PLATElet inhibition and patient Outcomes (PLATO) studies furthered the concept demonstrating additional benefit on reduction of ischemic events with the combination of aspirin and the more potent and predictable antiplatelet agents prasugrel and ticagrelor, respectively, although this was achieved at the additional cost of further increased bleeding compared with aspirin and clopidogrel.^{7,17}

Assessing the contemporary status of prolonged (beyond the first year post-ACS) aspirin monotherapy for secondary prevention after ACS requires the review of trials where antiplatelet monotherapy was considered the standard of care in stable patients with a history of stent implantation or ACS.^{18,19} In the Dual Antiplatelet Therapy beyond one year after drug-eluting coronary stent procedure (DAPT) trial, stable patients 12 months post-percutaneous coronary intervention (PCI; approximately 25% post-ACS) were randomized to continued dual antiplatelet therapy with aspirin and clopidogrel 75 mg daily or aspirin alone.¹⁹ The aspirin monotherapy arm had a 5.9% risk of death, MI, or stroke for 18 months. The risk of GUSTO moderate or severe bleeding over the same period was 1.6% (moderate 1% and severe 0.6%) with hemorrhagic stroke in 0.2%. In the Prevention of Cardiovascular Events in Patients with Prior Heart Attack using Ticagrelor compared to Placebo on a Background of Aspirin (PEGASUS) study, patients greater than 1 year after a MI were randomized to low-dose aspirin and ticagrelor (60 or 90 mg BID) compared with aspirin alone and followed for a median of 33 months.¹⁸ The aspirin monotherapy arm had a 3-year rate of 9.04% for cardiovascular death, recurrent MI, or stroke. The risk of a TIMI major bleeding event was 1.06%; intracranial hemorrhage, 0.47%; and fatal bleeding, 0.26%.

In summary, secondary prevention with ASA monotherapy early after ACS is associated with a high residual ischemic risk for death, MI, or stroke of approximately 11% over the first year, which is improved with enhanced platelet inhibition achieved with addition of a second antiplatelet agent.^{16,17,20} In the setting of secondary prevention in stable patients, ASA monotherapy carries a residual risk of recurrent ischemic events of 5.83% to 9.04% over the subsequent 1 to 2 years which has a modest reduced with clopidogrel monotherapy or DAPT.^{13,18,19} In these same trials, ASA monotherapy was shown to have a clinically significant risk of adverse

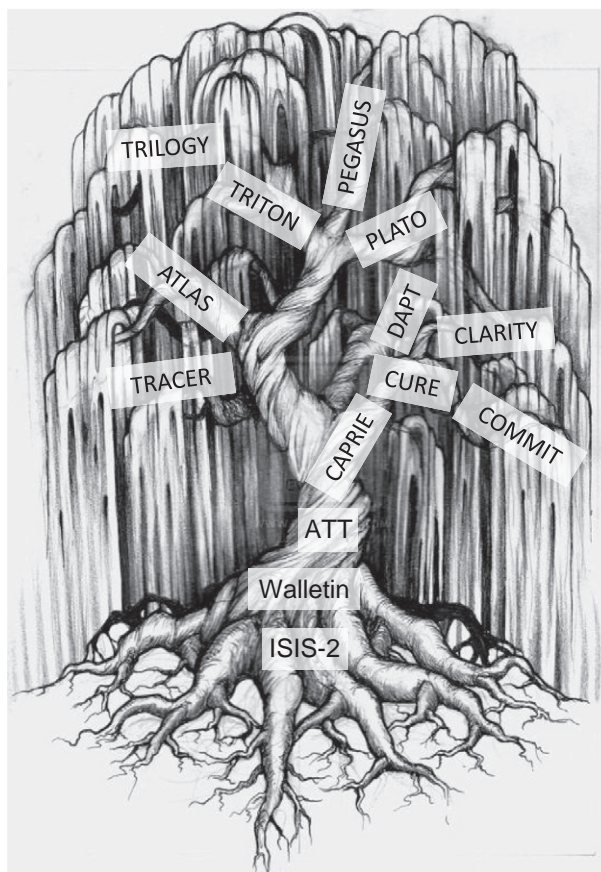
bleeding events of approximately 9%, including major bleeding (1.06%-2.7%), fatal bleeding (0.2%-0.26%), and hemorrhagic stroke (0.1%-0.47%) depending on the trial design. Although it is clear that aspirin was a true cornerstone therapy in the treatment of cardiovascular disease and an integral component of evidence-based therapy, aspirin's benefits were not achieved without significant risk of bleeding. In addition, the question of whether aspirin is still essential as an indefinite therapy with the clinical availability of more potent and predictable antithrombotic agents remains a critical question which has not been studied until the present age (Figure 1).

The dual-pathway strategy: combining antiplatelet and anticoagulant therapy for secondary prevention after ACS

Antithrombotic therapy in patients who have experienced an ACS is founded on decades of research into the pathophysiology of plaque rupture and thrombus formation. The heightened atherothrombotic risk associated with a MI has been shown to persist well beyond the original event, suggesting that continued inhibition in appropriately treated patients would be associated with significant improved outcome.²¹

Although there is strong physiological rationale to inhibit both the antiplatelet and anticoagulation pathways to prevent arterial thrombosis with combine oral antiplatelet and oral anticoagulant therapies for secondary prevention in ACS patients, this strategy has not been clinically applied because of challenges balancing efficacy and safety (Figure 2). With 25,000 patients enrolled in trials comparing warfarin plus aspirin to aspirin alone, there was no benefit of combination therapy (OR 0.96 [0.90-1.03]; follow-up ranged from 3 months to 5 years).²² When the combined analysis was limited to studies with tight anticoagulation targets for warfarin (equivalent to international normalized ratio 2.0-3.0), the combined end point of cardiovascular death, MI, and stroke was reduced (OR 0.73 [0.63-0.84]), although bleeding remained excessive (major bleeding: OR 2.32 [1.63-3.29]). The Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome (APPRAISE-2) study tested the atrial fibrillation dose of apixaban (5 mg twice daily) compared with placebo on top of standard antiplatelet therapy and was stopped early due to excessive bleeding risk (median follow-up 241 days).²³ A secondary analysis of apixaban plus aspirin (n = 1,202) vs apixaban, aspirin, and clopidogrel (n = 5,814) demonstrated no differential benefit on the composite end point of cardiovascular death, MI, and ischemic stroke, whereas the rates of TIMI major bleeding were increased with dual antiplatelet compared with aspirin alone with or without apixaban (apixaban and aspirin vs aspirin alone: 1.48% vs 0.25% [adjusted HR 6.62, 95% CI,

Figure 1



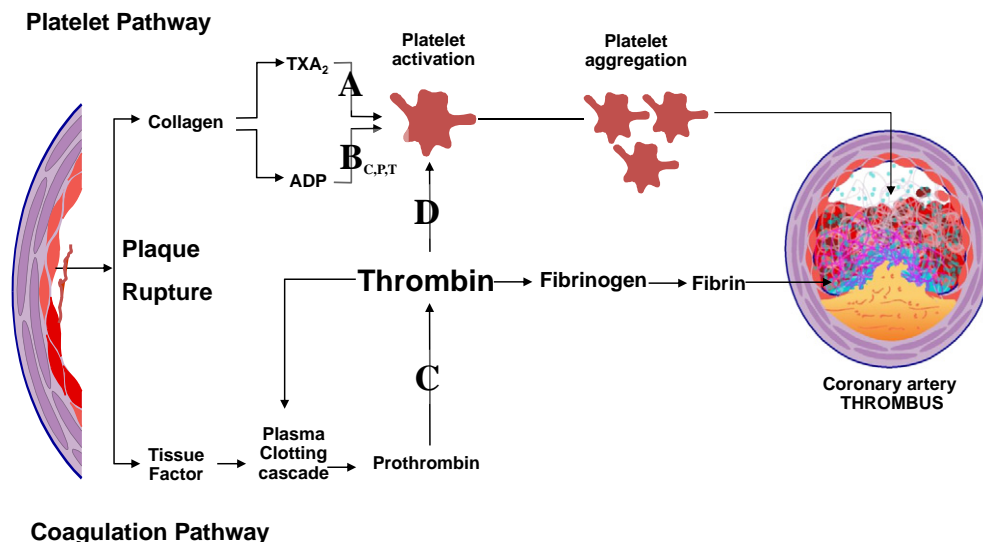
Key clinical trials of patients with ACSs overlying a willow tree signifying the origin of ASA. The base of the tree outlines the trials of antiplatelet monotherapy for secondary prevention (ISIS-2, Wallentin, ATT, and CAPRIE). Subsequent branches address various treatment strategies applied for secondary prevention after an ACS. Clopidogrel-based dual antiplatelet therapy (CURE, CLARITY, COMMIT, and DAPT). Ticagrelor-based DAPT studies compared with standard of care (PLATO and PEGASUS). Prasugrel-based DAPT studies compared with standard of care (TRITON and TRILOGY). Finally, studies that added agents on top of DAPT including low-dose rivaroxaban (ATLAS) and vorapaxar (TRACER) are identified.

0.75-51.73] and apixiban and DAPT vs DAPT alone: 2.58% vs 1.02% [adjusted HR 2.44, 95% CI 1.34-4.45].²⁴

The Anti-Xa Therapy to lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction (ATLAS ACS TIMI-51) trial assessed the dual-pathway strategy but, in contrast to previous investigations with warfarin or apixaban, used low-dose (rivaroxaban 5 mg twice daily) and ultra-low-dose (rivaroxaban 2.5 mg twice daily) anticoagulation (not atrial fibrillation doses) and stratified for antiplatelet usage specifically aspirin alone vs aspirin plus a thienopyridine.⁴ This trial achieved its primary efficacy end point with the addition of low-dose anticoagulation reducing cardiovascular death, MI, or stroke from 10.7% to 8.9% for 2 years (HR 0.84 [0.74-0.96]). Furthermore, the 2.5 mg twice daily dose of rivaroxaban provided sustained efficacy including reduction in cardiovascular death (4.1% vs 2.7%, $P =$

.002) and all-cause death (4.5% vs 2.9%, $P = .002$). The risk of non-coronary artery bypass grafting major TIMI bleeding was increased compared with placebo (0.6% vs 1.8%, $P < .001$), although there was no increase in fatal bleeding. Unfortunately, only 7% of the trial was randomized in the stratum of aspirin alone. Rivaroxaban 2.5 mg twice daily and aspirin alone ($n = 343$) compared with rivaroxaban 2.5 mg twice daily, aspirin, and clopidogrel ($n = 4772$) was associated with approximately half the risk of bleeding measured in various ways (non-Coronary artery bypass grafting TIMI major bleeding 0.6% vs 1.3%).

Taken together, these trials assessing the dual-pathway strategy with an oral anticoagulant and antiplatelet therapy consistently show an increase risk of bleeding with oral anticoagulation in addition to dual antiplatelet therapy. The question that remains unknown and worthy of significant consideration is the effect on efficacy and

Figure 2

A simplified schematic of the clotting cascade including the dual pathways of platelet and coagulation as well as sites of inhibition tested for secondary prevention after an ACS. Platelet inhibition has been achieved via thromboxane A₂ inhibition with aspirin (A), adenosine diphosphate inhibition with clopidogrel (B_C), prasugrel (B_P), and ticagrelor (B_T) and the platelet thrombin receptor antagonist vorapaxar (D). Inhibition of the coagulation cascade has included vitamin K antagonist agents which affect multiple points and the Xa inhibitors apixaban and rivaroxaban. Research to date has tested the impact of antiplatelet monotherapy (A + B_C), dual antiplatelet therapy (A + B_C and A + B_P and A + B_T), and triple antiplatelet therapy (A + B_C + D). In addition, a dual-pathway strategy has been tested historically with vitamin K antagonists and aspirin (A) and in the current era with dual antiplatelet therapy (A + B_C) and direct anti Xa inhibitors (C).

safety of a single predictable antiplatelet agent with oral anticoagulants at a low and safe level instead of triple therapy as studied in trials to date.

Contemporary trials in atrial fibrillation and atrial fibrillation plus stent implantation or recent ACS

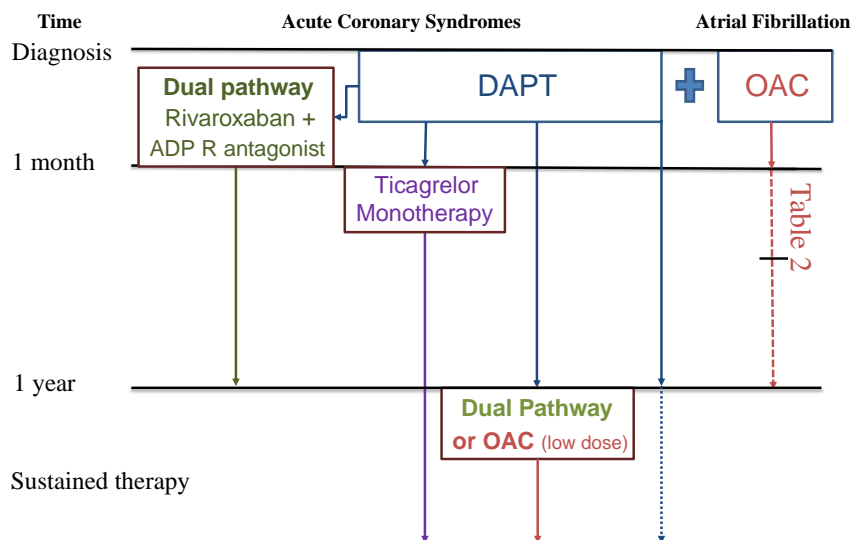
In contrast to coronary artery disease guidelines which recommend lifelong aspirin for secondary prevention after ACS, international atrial fibrillation guidelines for stroke prevention suggest oral anticoagulation alone without aspirin in the presence of stable coronary artery disease.²⁵⁻²⁷ The potential impact on the safety and efficacy of our current therapeutic antithrombotic armamentarium with antiplatelet down-titration post-ACS in the setting of a dual-pathway antithrombotic strategy can in part be surmised from research in patients with atrial fibrillation and those with atrial fibrillation plus stent implantation or recent ACS.

The Apixaban Versus Acetylsalicylic Acid (ASA) to prevent Stroke in Atrial Fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment (AVERROES) study assessed the relative efficacy and safety of apixaban 2.5 mg twice daily compared directly to aspirin in an atrial fibrillation population deemed to have contraindications for anticoagulant therapy.²⁸ In all

subgroups, apixaban had improved outcomes compared with aspirin with an overall reduction in stroke or systemic embolism from 3.7% to 1.6% (HR 0.45 [0.32-0.62], mean follow-up of 1.1 years). Overall major bleeding was not different (1.4%/y vs 1.2%/y, HR 1.13 [0.74-1.75]) with a trend to increased minor bleeding with apixaban (188 events vs 153 events, HR 1.24 [1.00-1.53], *P* = .05).

Acknowledging the limitations of registry data, the large Danish cohort (n = 82,000) has demonstrated that warfarin plus aspirin, clopidogrel, or both aspirin and clopidogrel were not associated with lower rates of fatal or nonfatal stroke compared with warfarin alone (mean [SD] follow-up of 3.3 [2.6] years).²⁹ In contrast, there was a striking higher rate of bleeding, which in the triple-therapy group is nearly 4 times higher than warfarin monotherapy (3.70 [2.89-4.76]). The What is the Optimal Antiplatelet and Anticoagulant Therapy in patients with Oral Anticoagulation and coronary stenting (WOEST) trial enrolled 573 patients with a clinical indication for chronic oral anticoagulation after stent implantation (approximately 27% post-ACS) to a strategy of oral anticoagulation in combination with a single antiplatelet agent (clopidogrel) compared with dual antiplatelet therapy (aspirin and clopidogrel).³⁰ The double-therapy group had a decreased risk of all TIMI bleeding by more than 60% for 1 year of therapy (HR 0.36 [0.26-0.50]).

Figure 3



Various timelines and the 4 different strategies being investigated describing the specific interventions as described in detail in the article (Unanswered questions and current research). In blue is current standard of care post-ACS—dual antiplatelet therapy (DAPT) for 12 months with potential extension beyond 1 year in selected patients (shown in dotted line). In purple, the strategy of ticagrelor monotherapy from 1 month and sustained for 2 years is outlined. Initiation of a dual-pathway strategy with low-dose oral anticoagulation and an ADP receptor antagonist and withdrawal of aspirin is outlined in green. Strategies for those patients with atrial fibrillation are outlined in Table 1 and shown in the figure in red.

Furthermore, there was no increased risk of ischemic events; in fact, the combined ischemic end point of death, repeat MI, stroke, target vessel revascularization, or stent thrombosis was less common in the double-therapy group (11.1% vs 17.6%, HR 0.60 [0.38-0.94]). The Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation (ISAR-TRIPLE) study further tested the concept of antiplatelet down titration in this complex patient population, comparing 6 weeks of aspirin, warfarin, and clopidogrel followed by warfarin and aspirin to 6 months of standard triple therapy.³¹ At 9 months, the combined end point of death, MI, stent thrombosis, stroke, or major bleeding was not different in the 2 strategies (HR 1.14 [0.68-1.91]) with no obvious increased risk of the ischemic end point from 6 weeks to 9 months of follow-up in a post hoc landmark analysis. There was no difference in TIMI major bleeding (5.3% vs 4.0%, $P = .44$) or any Bleeding Academic Research Consortium bleeding (37.6% vs 40.2%, $P = .63$).

The existing registry data and these modestly powered randomized trials support the concept that efficacy can be maintained and safety typically enhanced by reducing antiplatelet therapy in these selected patient populations.

Unanswered questions and current research

Ongoing research assessing the concept of antiplatelet down-titration through aspirin withdrawal can be cate-

gorized into 4 patient populations, accepting some overlap in the specific trial enrollment criteria (Figure 3).

The first group is those patients with perceived indication for oral anticoagulation for stroke prevention plus indication for antiplatelet therapy after an ACS or stent implantation. There are currently 3 trials addressing various combinations of oral anticoagulants and oral antiplatelet agents in this patient population (Table 1). The study exploring 2 strategies of rivaroxaban and 1 of oral vitamin K antagonist in patients with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI) has completed enrollment of more than 2,100 patients and will be reported in the near future. This trial assessed 3 arms: (1) standard of care arm with a vitamin K antagonist and dual antiplatelet therapy for 1, 6, or 12 months followed by low-dose aspirin and vitamin K antagonist alone; (2) low-dose rivaroxaban at 2.5 mg twice daily and dual antiplatelet therapy for a duration of 1, 6, or 12 months followed by rivaroxaban 15 mg once daily and aspirin; and (3) rivaroxaban 15 mg once daily and an ADP receptor blocker for 12 months. The Evaluation of dual therapy with dabigatran versus triple therapy with warfarin in patients with AF who undergo PCI (REDUAL-PCI) trial continues enrollment into 3 arms: standard of care or dabigatran at either the 110 mg BID dose of 150 mg BID dosing. In addition, the apixaban to vitamin K antagonist for the prevention of stroke or systemic embolism and bleeding in patients with non-valvular atrial fibrillation and acute coronary

Table 1. Atrial fibrillation and stent implantation or ACS trials

Study	Antithrombotic strategies	Specific details
RE-DUAL PCI	Dabigatran 150 + P2Y12 inhibitor Dabigatran 150 + P2Y12 inhibitor Warfarin + P2Y12 inhibitor + ASA	Complex patients ASA continued for 1 mo in dabigatran arms P2Y12 inhibitor = clopidogrel or ticagrelor
PIONEER AF-PCI	Rivaroxaban 15 mg + clopidogrel for 12 months Rivaroxaban 2.5 mg BID + DAPT for 1, 6, or 12 mo followed by rivaroxaban 15 mg and ASA Warfarin + DAPT for 1, 6, or 12 mo followed by warfarin and AS	Duration of DAPT left at discretion of site investigator
AUGUSTUS	Apixaban (afib dose) vs warfarin ASA vs placebo	2 × 2 factorial design All patients on a P2Y2 inhibitor for 6 mo

syndrome/percutaneous coronary intervention (AUGUSTUS) trial uses a 2 × 2 factorial randomization to apixaban or warfarin and aspirin or placebo on the background therapy of an ADP receptor inhibitor. These 3 trials assess different strategies of antithrombotic therapy and antiplatelet therapy and additionally have various approaches applied regarding the minimal duration of dual antiplatelet therapy. Although it is clear that each project will enhance our knowledge of the risk and benefits of various antithrombotic strategies, it appears unlikely that a single “optimal” clinical approach will arise and the complexity of various combinations and durations of therapy will require concise strategic communication for the practicing clinicians to apply these trials results.

The second population being studied with the concept of aspirin withdrawal is patients with stable chronic ischemic cardiovascular disease or peripheral arterial disease. The Randomized Controlled Trial of Rivaroxaban for the Prevention of Major Cardiovascular Events in Patients With Coronary or Peripheral Artery Disease (COMPASS—Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial is enrolling patients to long-term therapy with rivaroxaban 2.5 mg twice a day plus 150 mg of aspirin compared with rivaroxaban 5 mg twice a day as a solo therapy or aspirin 100 mg daily monotherapy, which would be considered standard of care in this stable patient secondary prevention population. This study has the potential to change the standard of care in stable patient populations from aspirin monotherapy to antithrombotic monotherapy or dual antithrombotic therapy. In addition, a study comparing cardiovascular effects of ticagrelor and clopidogrel in patients with peripheral arterial disease (EUCLID) is assessing antiplatelet monotherapy in stable symptomatic peripheral arterial disease (NCT 01732822).

The third population being addressed in ongoing research is based on patients undergoing PCI for ACS or stable coronary artery disease. The GLOBAL LEADERS trial has randomized 16,000 all-comer PCI patients to dual antiplatelet therapy with aspirin and ticagrelor or aspirin and clopidogrel for 12 months followed by aspirin alone for a total of 24 months of therapy compared with aspirin

plus ticagrelor for 1 month followed by ticagrelor alone for a total of 24 months. In essence, this trial is comparing ticagrelor monotherapy from 1 to 24 months to current evidence-based standard of care after a recent PCI. This concept is supported by a small study demonstrating a similar inhibition of the hemostatic system with dual antiplatelet therapy compared with P2Y12 monotherapy in healthy subjects but requires validation in patients with established coronary artery disease post-ACS.³²

Finally, the dual-pathway strategy with low-dose oral anticoagulation combined with antiplatelet therapy is being tested in the phase 2 GEMINI ACS-I trial. This trial randomizes patients after ACSs to the standard of care with dual antiplatelet therapy compared with rivaroxaban (2.5 mg BID) and sole antiplatelet therapy with clopidogrel or ticagrelor.³³ The dose of rivaroxaban was selected based on the observations made in the ATLAS program where bleeding was related to dose in a stepwise fashion, whereas rivaroxaban 2.5 mg BID maintained the ischemic benefit observed at higher doses. The trial has an enrollment window from 48 hours to 10 days with a requirement therefore of a loading dose of aspirin and at least an additional day aspirin maintenance dose. Acknowledging the lower risk of stent thrombosis with the current generation of drug-eluting stent and the benefit of rivaroxaban on stent thrombosis reduction in the ATLAS trial and accepting the irreversible action of aspirin on platelet inhibition where an antiplatelet effect will be sustained for 7 to 10 days, the strategies under comparison should manage early stent thrombosis risks, although a mature Data and Safety Monitoring Board will monitor this carefully. This important phase 2 trial has completed enrollment and will inform a phase 3 design to solidify the status of a dual-pathway strategy of predictable antiplatelet therapy with low-dose oral anticoagulation.

Conclusion

Aspirin was established more than a quarter century ago as one of the first evidence-based therapies to reduce

recurrent cardiovascular events in patients with established coronary artery disease. Despite limitations of this early research and limited discussion of the associated bleeding complications, aspirin has been clinically applied as a panacea across the spectrum of cardiovascular diseases as a foundation or cornerstone therapy. The current era of evidence-based medical care encourages researchers and clinicians to integrate efficacy and safety into therapeutic decisions, but historically, aspirin's safety was not held to the same scrutiny as agents in the current era of rigorous governmental regulation and medical oversight. Investigation has previously been focused on the addition of further antithrombotic agents in addition to baseline aspirin in the acute and chronic setting to reduce patient's risk of further ischemic events, at the cost of increased bleeding complications. The current armamentarium of potent and predictable antiplatelet and antithrombotic agents has ushered in a new era where clinicians and scientists are contemplating withdrawal of agents to minimize bleeding risk while sustaining efficacy; indeed, subtraction may lead to the next advance in the treatment of acute and chronic ischemic vascular disease.

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