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ISCHEMIC HEART DISEASE (D MUKHERJEE, SECTION EDITOR)

Secondary Prevention with Antithrombotic Therapies in Stable Ischemic Heart Disease Patients: a Review

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Abstract

Purpose of Review Stable and unstable ischemic heart disease are a growing component in all facets of healthcare, including ER visits, hospitalizations, and financial costs. With the changing emphasis of healthcare shifting towards the outpatient setting, the onus is on clinicians to appropriately manage such patients to avoid adverse effects and complications. Antithrombotic medications, including aspirin, $P2Y_{12}$ inhibitors, and rivaroxaban, are currently prescribed or have potential roles in the management of secondary cardiovascular prevention in ischemic heart disease patients. While the majority of studies and findings involve aspirin and clopidogrel, newer oral anticoagulation drugs are arriving, prompting new research to assess their impact on preventing mortality, myocardial infarction, and stroke in such patients.

Recent Findings Aspirin has a well-established history of safety and efficacy in management of secondary cardiovascular protection in ischemic heart disease patients. A dual-antiplatelet regimen, most commonly including aspirin plus clopidogrel, has been documented to be effective as well in achieving the same goals. Newer agents, such as rivaroxaban, are being analyzed to see if there is scope to include these agents for secondary prevention. One recent study, the COMPASS trial, revealed the major concern of these newer medications: while better cardiovascular outcomes were achieved in subjects on aspirin plus rivaroxaban, this was accomplished in the setting of a higher rate of major bleeding events.

Summary In conclusion, the evidence thus far has not been significant enough for the American College of Cardiology to recommend the incorporation of oral anticoagulants in the management of stable ischemic heart disease patients, in contrast to aspirin and clopidogrel. As the antithrombotic and antiischemic properties of these newer agents seem evident, so does their potential for increase in risk of bleeding events. Doctors have to individually tailor antithrombotic medication decisions based on the patient's risk-benefit profile.

Keywords Ischemic heart disease · Coronary artery disease · Acute coronary syndromes · Secondary cardiovascular prevention · Aspirin · Clopidogrel · Rivaroxaban

Abbreviations

ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CHD	Coronary heart disease
CVD	Cardiovascular disease
DAPT	Dual antiplatelet therapy
IHD	Ischemic heart disease
MI	Myocardial infarction
NSTEMI	Non-ST segment-elevation myocardial infarction
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention
SIHD	Stable ischemic heart disease
STEMI	ST segment-elevation myocardial infarction
TIMI	Thrombolysis in myocardial infarction

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Introduction

Ischemic heart disease (IHD) is present when a patient has one or more symptoms, signs, or complications from an inadequate supply of blood to the myocardium. This is most

commonly due to obstruction of the epicardial coronary arteries due to atherosclerosis. The term acute coronary syndrome (ACS) is applied to patients in whom there is a suspicion or confirmation of acute myocardial ischemia or infarction. The three types of ACS are ST segment-elevation myocardial infarction (STEMI), non-ST segment-elevation myocardial infarction (NSTEMI), and unstable angina.

The 2018 Heart Disease and Stroke Statistics Update of the American Heart Association reported that 16.5 million persons ≥ 20 years of age in the USA have coronary heart disease (CHD), with a slight male predominance (55%). The reported prevalence increases with age for both women and men. The Global Burden of Disease Study 2013 estimated that 17.3 million deaths worldwide in 2013 were attributed to cardiovascular diseases (CVD), a 41% increase since 1990 [1].

The prevalence of heart disease, including myocardial infarction (MI), chest pain, heart failure and stroke, is highest among Hawaiians and Pacific Islanders (19.1%) followed by American Indians and Alaska Natives (13.7%), non-Hispanic whites (11.1%), blacks (10.3%), Hispanics and Latinos (7.8%), and Asians (5.0%). Risk for cardiovascular disease is mostly attributed to modifiable risk factors, including dyslipidemia, smoking, diabetes mellitus, hypertension, obesity, inadequate exercise, and diet [1]. For persons aged 40 years (USA), the lifetime risk of developing CHD is 49% in men and 32% in women. For those reaching age 70 years, the lifetime risk is 35% in men and 24% in women [1].

Aspirin is recommended for secondary prevention in all patients with diabetes and CAD. Primary prevention is recommended for diabetic patients with a 10-year cardiovascular risk greater than 10% or one additional risk factor. Aspirin produces statistically significant and clinically important reductions in the risk of subsequent myocardial infarction (MI), stroke, and vascular death among a wide range of patients who have survived an occlusive cardiovascular disease event [2, 3].

The benefits of long-term aspirin therapy in secondary prevention were conclusively demonstrated by the Antithrombotic Trialists' Collaboration's meta-analyses. They included individual patient data from 195 randomized trials of antiplatelet therapy, principally with aspirin, among more than 135,000 high-risk patients with prior evidence of cardiovascular disease, including prior or acute MI, prior or acute stroke or transient ischemia attacks (TIA), and other high-risk groups such as unstable angina, stable angina, peripheral artery disease, coronary artery bypass graft surgery, percutaneous coronary intervention, atrial fibrillation, and valvular disease [2]. One of the most significant conclusions was that antiplatelet therapy, primarily with aspirin, significantly reduced the relative risk of subsequent vascular events (nonfatal MI, nonfatal stroke, and vascular death) by approximately 22% [2].

As for the role of clopidogrel in addition to aspirin in CAD patients, a landmark meta-analysis analyzed the results of five major trials that sought to assess the impact of this dual-antiplatelet regimen. The included trials were CURE, CREDO, CLARITY, COMMIT, and CHARISMA. The paper concluded that the addition of clopidogrel to aspirin showed a reduction in mortality, MI, and stroke, albeit with an increased incidence of major bleeding. With these findings, clopidogrel plus aspirin may be appropriate for secondary cardiovascular prevention in certain CAD patients [4, 5].

The bulk of evidence in this arena is comprised of studies on aspirin and clopidogrel. With newer antithrombotic agents becoming available, there is an impetus to analyze their potential benefits and risks on patients experiencing this very common pathology worldwide. This review article seeks to recap the major trials that have been performed thus far and what the current guidelines and future directions are for management of secondary prevention in stable ischemic heart disease patients.

Aspirin and $P2Y_{12}$ Inhibitors

Aspirin is probably the most famous therapy for patients with ACS and IHD. Aspirin functions by inhibiting the enzyme cyclooxygenase. This enzyme synthesizes eicosanoids including thromboxane A_2. Thromboxane A_2 has been identified as a platelet aggregation promoter. Thus, by inhibiting thromboxane A_2, aspirin prevents platelet aggregation. Upon administration of aspirin, platelet-inhibitory effects are witnessed within 60 minutes [6].

Thienopyridines are a class of drugs whose mechanism is inhibition of adenosine diphosphate (ADP) to its receptor. The ADP receptor plays a key role in the activation and aggregability of platelets along with fibrinogen binding. Examples of thienopyridines include clopidogrel, prasugrel, and ticagrelor. Onset of inhibition of platelet aggregation is 2 hous after administration of a 300 mg loading dose of clopidogrel [6].

One of the earliest landmark trials to evaluate the effects of aspirin on ACS patients was ISIS-2. In this study, 17,187 patients with suspected acute myocardial infarction were randomized and given either streptokinase, aspirin, both, or placebo. The aspirin dose was 162 mg daily for 1 month. In their results, subjects who received aspiring versus placebo demonstrated a prevention of approximately ~25% of early deaths. Additionally, the benefits of a 1-month course of aspirin were observed to be persistent at 15-month and 10-year follow-up encounters. One of the most salient findings was the 23% reduction in total vascular mortality for the aspirin patients [6, 7].

Researchers involved in the CURRENT-OASIS 7 trial sought to determine the optimal doses of aspirin and

clopidogrel for ACS patients who were referred for invasive intervention. The study involved 25,086 subjects. Results were analyzed based on four different dosing strategies: double-dose clopidogrel (600-mg loading dose, followed by 150 mg daily dose for 6 days, followed by 75 mg daily thereafter), standard-dose clopidogrel (300-mg loading dose, followed by 75 mg daily thereafter), higher-dose aspirin, (300 to 325 mg daily) and lower-dose aspirin 75 to 100 mg daily). The primary outcome was established as cardiovascular mortality, myocardial infarction, or stroke at 30 days. When the two clopidogrel groups were compared, the primary outcome occurred in 4.2% of the double-dose patients and in 4.4% of the standard-dose patients. Major bleeding was observed in 2.5% of the double-dose patients and in 2.0% of the standard-dose patients. Echoing a similar trend, when the aspirin groups were scrutinized, the primary outcome occurred in 4.2% of the higher-dose patients and in 4.4% of the lower-dose patients. No significant difference in major bleeding rates was noted between the two groups. Ultimately, the researchers found that there were no significant differences between the standard and augmented dosing regimens of aspirin and Plavix with regard to the primary outcome [8].

In the CURE trial, investigators wanted to ascertain whether the addition of clopidogrel to aspirin would reduce cardiovascular mortality, myocardial infarction, or stroke in ACS patients. A total of 12,562 patients were randomized into two groups. One group of subjects received dual-antiplatelet therapy (DAPT) with aspirin plus clopidogrel. The other group of subjects received aspirin plus placebo. At a mean follow-up of 9 months, a 20% reduction in the primary outcome (a composite of non-fatal myocardial infarction, stroke, and cardiovascular death) was observed in the DAPT group. A 14% reduction in the second primary outcome (a composite of non-fatal myocardial infarction, stroke, cardiovascular death, and refractory ischemia) was also noted. Across-the-board reductions in the incidence rates of severe ischemia, recurrent angina, revascularization procedures, and heart failure were documented in the DAPT group. However, the DAPT subjects were detected to have higher rates of major and minor bleeding. No increase was seen in life-threatening bleeding or intracranial hemorrhage [6, 9].

Similar findings were revealed in the COMMIT trial from China, in which 45,852 patients were randomized into either a DAPT group with clopidogrel plus aspirin or placebo plus aspirin. Two co-primary outcomes were established: the composite of mortality, reinfarction, or stroke; and all-cause mortality. Subjects in the DAPT group experienced a 9% proportional reduction in mortality, reinfarction, or stroke. They also showed a 7% reduction in all-cause mortality. With regard to bleeding, there was no appreciable significant increase in rates of fatal and major non-fatal bleeding events with the DAPT patients. However, a significant excess of minor bleeds was reported. Interestingly, no loading dose of clopidogrel was incorporated in this study design, partially due to concerns for bleeding [10]. While a loading dose can hasten the full impact of antiplatelet properties of clopidogrel, even starting with the standard dose of clopidogrel can result in partial antithrombotic effects within a few hours [11].

While clopidogrel is likely the most well-studied of the thienopyridines, other agents in the same class have also been investigated, including prasugrel and ticagrelor. Prasugrel, a newer thienopyridine, was compared to clopidogrel in ACS patients who were scheduled to undergo percutaneous coronary intervention in the TRITON–TIMI 38 trial. Patients were randomized into either the prasugrel or ticagrelor groups. Each subject received the loading dose and maintenance doses of their respective medications. The primary efficacy end point was a composite of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. The key safety end point was identified as major bleeding. A decrease in the primary end point (9.5% versus 12.1%) was seen in the prasugrel group. The researchers also appreciated significant reductions of myocardial infarction, urgent target-vessel revascularization, and stent thrombosis in the prasugrel subjects when compared to their clopidogrel counterparts. The prasugrel subjects also demonstrated higher rates of non-CABG-related TIMI major bleeding events, major or minor TIMI bleeding, bleeding requiring transfusions, and CABG-related TIMI major bleeding [12].

In the TRILOGY trial, researchers compared prasugrel versus clopidogrel in unstable angina or non-ST segment elevation myocardial infarction patients who did not undergo an invasive strategy. Unlike the TRITON–TIMI 38 findings, prasugrel was not found to significantly reduce the rates of cardiovascular death, myocardial infarction, or stroke when compared to clopidogrel upon median follow-up at 17 months. In another contrast to the TRITON-TIMI 38 trial, there was no increased rate of severe, major, or life-threatening bleeding in the prasugrel group when compared to the clopidogrel group in this study. Of note, the investigators purposefully adjusted the prasugrel dose in patients older than 75 years and patients weighing less than 60 kg, in order to attenuate the bleeding risk in those patients [13].

Ticagrelor is a $P2Y_{12}$ inhibitor with quicker onset of action and more efficacy of platelet inhibition compared to clopidogrel. The PLATO trial determined to compare ticagrelor with clopidogrel with regard to prevention of major cardiovascular events in ACS patients. Subjects were randomized into either a ticagrelor or clopidogrel group. Patients were administered the loading and maintenance doses of their respective antithrombotic medication. The primary endpoint, as has been the case for the majority of these trials, was a composite of cardiovascular mortality, myocardial infraction, or stroke. At 12-month follow-up, the primary end point occurred in 9.8% of the ticagrelor subjects, compared to 11.7%

of the clopidogrel subjects. Reductions in incidence of cardiovascular death, myocardial infarction, and all-cause mortality were appreciated in the prasugrel group. No reduction was noted in stroke alone in this group. In terms of safety, no major differences in the rates of major bleeding events were noted in the ticagrelor versus clopidogrel groups (11.6% versus 11.2%). However, a higher rate of major bleeding not associated with procedures was documented in the ticagrelor patients. In the end, the researchers found ticagrelor to be superior to clopidogrel due to these findings [14].

Rivaroxaban

Rivaroxaban is a direct factor Xa inhibitor, which prevents thrombosis by interfering in the conversion of prothrombin to thrombin. The drug has a high oral bioavailability, with a half-life of 5-9 hours. Because of its dose-dependent pharmacokinetics, rivaroxaban does not require routine monitoring or adjustment of doses [15].

In the randomized multinational double-blind ATLAS ACS-TIMI 46 trial, a phase II study analyzed rivaroxaban in comparison to placebo in ACS subjects who received either aspirin monotherapy or dual-antiplatelet therapy (DAPT). The goal was to determine the most appropriate dose and dosing regimen of rivaroxaban. The primary safety endpoint was clinically significant bleeding categorized by the thrombolysis in myocardial infarction (TIMI) bleeding criteria (major, minor, or requiring medical attention). The primary efficacy endpoints were mortality, myocardial infarction, stroke, or revascularization due to severe ischemia within 6 months. In their findings, the investigators found that bleeding events occurred at higher rates in subjects on rivaroxaban compared to placebo. In addition, this was a positive relationship that was dose-dependent. However, the aforementioned primary efficacy endpoints were significantly reduced in the rivaroxaban subjects compared to the placebo subjects (5.6% vs. 7%, HR 0.79, $P = 0.10$) [15].

The subsequent ATLAS ACS 2 trial sought to follow up on the role, efficacy, and safety of rivaroxaban in patients with recent ACS. Two dosing regimens of rivaroxaban were selected: 2.5 mg twice a day and 5 mg twice a day. The primary efficacy endpoint was the composite of mortality, myocardial infarction, or stroke. The primary safety endpoint was TIMI bleeding criteria events not linked with coronary artery bypass graft (CABG) surgery. The results showed that both dosing regimens, in comparison to placebo, decreased the rate of the primary composite consisting of mortality, myocardial infarction, or stroke (8.9% vs. 10.7% HR 0.84, $P = 0.008$). The 2.5 mg twice a day subjects demonstrated reduced cardiovascular mortality (2.7% vs. 4.1%, $P = 0.002$) and all-cause mortality (2.9% vs. 4.5%, $P = 0.002$). However, these findings were not observed in the higher 5 mg twice a day group. Furthermore, an increase in the rates of non-fatal bleeding events and intracranial hemorrhage was observed. The investigators found no significant increase in fatal bleeding. And expectedly, the rate of fatal bleeding events was lower among subjects on the lower dose of rivaroxaban compared to the higher dose (0.1% vs. 0.4%, $P = 0.04$) [16, 17].

Because of the increased bleeding seen in rivaroxaban, researchers sought to examine the safety profile of a dual pathway antithrombotic regimen consisting of a P2Y12 inhibitor (clopidogrel or ticagrelor) with either rivaroxaban or aspirin in patients following acute coronary syndromes. This was the context of the GEMIN-ACS-1 trial. Dosages were rivaroxaban 2.5 mg or aspirin 100 mg. Of all the subjects, 56% received ticagrelor while 44% received clopidogrel. The primary endpoint (TIMI-clinically significant bleeding unrelated to CABG) was similar between the subjects on rivaroxaban versus aspirin. The investigators believe this dual pathway antithrombotic therapy may be non-inferior to that of DAPT, but a larger powered trial would be necessary to confirm that [18•].

The COMPASS trial set out to evaluate whether rivaroxaban alone or in conjunction with aspirin was more effective than aspirin monotherapy in preventing recurrent cardiovascular events, including cardiovascular death, stroke, or myocardial infarction. A composite of these three events comprised the primary efficacy outcome of the study. Patients were distributed among three treatment arms: rivaroxaban plus aspirin, rivaroxaban alone, and aspirin alone. In their results, the investigators found that the group on the rivaroxaban plus aspirin combination had a 24% reduction in the composite rate of cardiovascular death, stroke, or myocardial infarction in comparison to aspirin alone. However, the rate of major bleeding was 70% higher in the rivaroxaban-aspirin subjects versus the aspirin monotherapy subjects. In terms of rivaroxaban monotherapy versus aspirin monotherapy, no significant difference in the primary efficacy outcome was noted, but a higher rate of major bleeding was observed with the rivaroxaban group [19••]. Chatterjee et al. performed a meta-analysis and trial sequential analysis of randomized clinical trials and reported that rivaroxaban was associated with a significantly lower risk of myocardial infraction in a broad spectrum of patients when tested against different controls [20].

Bleeding Risks of Antithrombotics

Antithrombotic therapy is a mainstay of management for patients with acute coronary syndromes and stable ischemic heart disease. The most commonly prescribed agents include aspirin, clopidogrel, vitamin K antagonists, and direct Factor

Xa inhibitors. Often times, patients are asked to take combinations of the aforementioned medications. By virtue of their mechanisms, bleeding is a commonly encountered side effect of antithrombotic agents. Thus, clinicians are faced with weighing the benefits of reducing ischemic events with antithrombotics versus the risk of these medications causing bleeding and associated complications [21]. While some researchers have found a relationship between bleeding and adverse effects, it has been difficult to consolidate findings on this topic due to the differences in definitions of bleeding [22]. To address this concern, one group of researchers devised the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) bleeding severity scale. Rao and his team created a scale that is stratified into three categories: severe or life-threatening, moderate, and mild bleeding. Events under the severe or life-threatening classification include intracranial hemorrhage or any event that causes hemodynamic instability necessitating interventional measures. Moderate bleeding was classified as events requiring transfusions but not causing hemodynamic instability in patients. Mild bleeding was defined by events that did not correspond to the first two categories described. In one project that compared and analyzed the results of multiple multicenter randomized trials, investigators found that there was a correlation between increased bleeding severity and short- and long-term mortality. One of the more interesting findings was that even mild bleeding events were linked with statistically significant increases in morbidity and mortality, signifying that bleeding of any severity is an important prognostic factor for these patients [22].

The study described above corroborated certain findings regarding predictors of major bleeding from the landmark Global Registry of Acute Coronary Events (GRACE) study. Mosucucci and his team reported that advanced age, female gender, renal insufficiency, anticoagulation agents, and procedures were associated with major bleeding. They noted a positive relationship between bleeding severity and MI or mortality rates. After analysis and adjustment of confounding variables, major bleeding was identified as "an independent predictor of hospital death." Of note, it is not possible to directly compare Rao's and Mosucucci's studies as the two projects utilize differing definitions of bleeding events. Indeed, that lack of standardization was a reason for the creation of the GUSTO bleeding severity scale [23].

A retrospective Danish study of patients using national registries studied the bleeding risks of patients with myocardial infarctions discharged on various antithrombotic therapies. These regimens included monotherapy with aspirin, clopidogrel, and Vitamin K antagonists, along with dual- or triple-therapy combinations consisting of these drugs. The two groupings of bleeding events utilized in this study were non-fatal and fatal bleeding. Again, this highlights the variability across the literature with regard to lack of a single standardized definition of bleeding events. The investigators opted to select hospital admission as a requisite for non-fatal and fatal bleeding events for their study, with the rationale being that bleeding which necessitates hospitalization is clinically significant and "therefore gives high specificity." Except for the monotherapy with vitamin K antagonists, every other regimen demonstrated an increase in rates of hospital admissions due to non-fatal or fatal bleeding. Additionally, a positive relationship was seen between bleeding risk and the number of antithrombotic agents that patient was taking [21]. When comparing antithrombotic agents, a meta-analysis reported that newer antithrombotics such as rivaroxaban may not be more effective than warfarin in the secondary prevention of ischemic stroke in patients with a prior history of cerebrovascular ischemia. However, these agents may possess a lower risk of intracranial bleeding [24].

Conclusions

According to the most recent guidelines on stable ischemic heart disease set forth by the American College of Cardiology, the only agents with a Class I recommendation with regard to preventing myocardial infarction and mortality are aspirin and clopidogrel. Aspirin as monotherapy is recommended in these patients, with clopidogrel proposed as an appropriate substitute in case the patient has a contraindication to aspirin. For certain high-risk patients, the organization suggests that dual-antiplatelet therapy with aspirin and clopidogrel may be considered (Class IIb recommendation). Other $P2Y_{12}$ inhibitors in the same class as clopidogrel, such as prasugrel and ticagrelor, have been studied for their antithrombotic effects on ACS patients. However, their roles in secondary cardiovascular prevention in SIHD patients have not been thoroughly investigated [4]. Table 1 lists the major findings from selected cardiology antithrombotic therapy trials.

The most promising development in the evolution of management of SIHD patients has been novel oral anticoagulation agents. With new medications such as rivaroxaban, the theoretical benefit of their antiischemic properties seems self-evident in promoting secondary prevention. However, major studies have not provided evidence of that as of yet [4]. One study demonstrated that a combination of moderate-intensity oral anticoagulation plus aspirin may be considered in high-risk SIHD patients who have failed on aspirin monotherapy. However, the benefit must be weighed against the risk of bleeding [25]. And at this juncture, that appears to be the current consensus. Of note, in October 2018, the FDA approved a new 2.5-mg formulation of the direct factor Xa inhibitor rivaroxaban for use in combination with low-dose aspirin to reduce the risk of major cardiovascular events in patients with chronic coronary artery disease (CAD) or peripheral artery disease

Table 1 Summary of major findings from selected cardiology antithrombotic therapy trials

Trial	Design	Endpoints	Outcomes
ATLAS ACS-TIMI 46	Double-blind, placebo-controlled, dose-escalation phase II study that stratified recent ACS patients to 1. Aspirin only (stratum 1) 2. Aspirin plus $P2Y_{12}$ inhibitor (stratum 2) Within each stratum, participants were then randomized using block randomization method at 1:1:1 into three possible groups 1. Rivaroxaban (either 5, 10, 15, or 20 mg) once daily 2. Rivaroxaban (either 2.5, 5, 7.5, or 10 mg) twice daily 3. Placebo	Primary safety endpoint: TIMI major bleeding, TIMI minor bleeding, bleeding requiring medical attention Primary efficacy endpoint: mortality, MI, stroke, or severe recurrent ischemia requiring revascularization within 6 months	Use of rivaroxaban in stabilized ACS patients increases bleeding in a dose-dependent manner and might reduce major ischemic outcomes [15]
ATLAS-ACS 2 TIMI 51	Double-blind, placebo-controlled phase III study that stratified recent ACS patients to 1. Aspirin only (stratum 1) 2. Aspirin plus $P2Y_{12}$ inhibitor (stratum 2) Within each stratum, participants were then randomized using block randomization method at 1:1:1 into three possible groups 1. Rivaroxaban 2.5 mg twice daily 2. Rivaroxaban 5 mg twice daily 3. Placebo	Primary efficacy endpoint: incidence of composite of cardiovascular death, MI, or stroke Primary safety endpoint: incidence of TIMI major bleeding events not associated with CABG	In recent ACS patients, rivaroxaban reduced the risk of composite endpoint of cardiovascular death, MI, or stroke. Rivaroxaban increased the risk of major bleeding and intracranial hemorrhage, but not of fatal bleeding [16]
GEMINI-ACS-1	Double-blind, multicenter randomized trial that randomized recent ACS patients to 1. Aspirin 100 mg once daily 2. Rivaroxaban 2. 5 twice daily All subjects received a $P2Y_{12}$ inhibitor (either ticagrelor or clopidogrel)	Primary endpoint: TIMI clinically significant bleeding not related by CABG	Dual pathway regimen of low-dose rivaroxaban plus $P2Y_{12}$ inhibitor had similar risk of clinically significant bleeding in recent ACS patients compared to aspirin plus $P2Y_{12}$ inhibitor [18•]
COMPASS	Double-blind trial that randomized SIHD patients to 1. Rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily 2. Rivaroxaban 50 mg twice daily 3. Aspirin 100 mg once daily	Primary outcome: composite of cardiovascular death, stroke, or MI	SIHD patients in the combination therapy group of rivaroxaban plus aspirin had better cardiovascular outcomes and more major bleeding events compared to aspirin monotherapy. Rivaroxaban monotherapy subjects had no better outcomes than aspirin monotherapy, but did have more major bleeding events
ISIS-2	Randomized "2 × 2 factorial" placebo-controlled trial where recent MI patients were randomized accordingly 1. Received 1.5 million units streptokinase infusion over 1 h or placebo infusion over 1 h 2. Received either receive aspirin 162 mg once daily or placebo	Primary outcome: all-cause mortality	Early survival advantage with short-term aspirin regimen persisted in the long-term [19••]
CURRENT-OASIS 7	Randomized 2-by-2 factorial design where ACS patients referred for invasive strategy were randomized to: four different dosing strategies 1. Double-dose clopidogrel (600-mg loading dose, followed by 150 mg daily dose for 6 days, followed by 75 mg daily thereafter)	Primary outcome was cardiovascular death, MI, or stroke at 30 days	There was no significant difference between double-dose and standard dose clopidogrel, or between higher-dose and lower-dose aspirin, with regard to primary outcome of cardiovascular death, MI, or stroke [8]

Table 1 (continued)

Trial	Design	Endpoints	Outcomes
	2. Standard-dose clopidogrel (300-mg loading dose, followed by 75 mg daily thereafter) 3. Higher-dose aspirin (300 to 325 mg daily) 4. Lower-dose aspirin 75 to 100 mg daily)		
CURE	Randomized, double-blind, placebo-controlled trial where ACS patients without ST segment elevation were randomized into 1. Clopidogrel (300 mg loading plus 75 mg once daily 2. Placebo All patients received aspirin (75–325 mg daily)	Primary outcome: composite of cardiovascular death, non-fatal MI, or stroke	Patients on DAPT with non-ST segment elevation ACS had reductions in the primary outcome and an increased risk of bleeding [9]
COMMIT	Randomized placebo-controlled trial with 2 × 2 factorial design where acute MI patients were randomly allocated to 1. Clopidogrel 75 mg daily plus aspirin 162 mg daily 1. 2. Placebo plus aspirin 162 mg daily	Co-primary outcomes: composite of death, reinfarction or stroke; and all-cause mortality	Patients receiving clopidogrel plus aspirin had a significant reduction in mortality and morbidity with no increase in life-threatening bleeds or major non-fatal bleeding. However, a significant excess of minor bleeds was reported [10]
TRITON-TIMI 38	Randomized double-blind trial where ACS patients with scheduled PCI were randomized to 1. Prasugrel (60 mg loading dose and 10 mg once daily maintenance dose) 2. Clopidogrel (300 mg loading dose and 75 mg once daily maintenance dose)	Primary efficacy endpoint: cardiovascular death, nonfatal MI, or nonfatal stroke	Prasugrel was associated with significantly reduced rates of ischemic events along with increased risk of major bleeding, including fatal bleeding [12]
TRILOGY	Double-blind randomized trial where ACS patients without ST segment-elevation not undergoing revascularization were randomized to 1. Prasugrel 10 mg once daily 2. Clopidogrel 75 mg once daily	Primary endpoint: cardiovascular death, MI, or stroke	Prasugrel did not significantly reduce the frequency of the endpoint compared to clopidogrel. Similar rates of bleeding were observed between the two groups [13]
PLATO	Multicenter, double-blind, randomized trial where ACS patients were randomized into: 1. Ticagrelor 180 mg loading dose, 90 mg twice daily thereafter 2. Clopidogrel 300 to 600 mg loading dose, 75 mg once daily afterwards	Primary endpoint: composite of death from vascular causes, MI, or stroke	Ticagrelor subjects had significant reductions of death from vascular causes, MI, and stroke without an increase in overall major bleeding when compared to clopidogrel. There was an increase in non-procedure-related bleeding [14]

(PAD) [26]. The role of oral anticoagulants secondary cardiovascular prevention in SIHD patients needs further assessment. For now, the clinician must carefully tailor decisions for each patient on a case-by-case basis to determine the appropriate risk-benefit profile for that individual.

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Compliance with Ethical Standards

Conflict of Interest Aaron Shanker and Vivek Bhupathi declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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