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Direct Oral Anticoagulants in Addition to Antiplatelet Therapy for Secondary Prevention after Acute Coronary Syndromes: a Review

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Abstract

Purpose of Review As the management of acute coronary syndrome (ACS) continues to evolve, many old practices proved to be of a little benefit and other approaches established the new pillars of modern medicine. Treating ACS patients with dual antiplatelet therapy (DAPT) for a year by combining aspirin and a P2Y12 inhibitor (clopidogrel, ticagrelor, or prasugrel) has resulted in better outcomes and is currently the standard of therapy. However, owing to the persistent activation of the coagulation cascade, patients may continue to experience recurrent ischemia and high mortality rates despite compliance with the dual antiplatelet therapy. Research is underway to establish new treatment modalities for secondary prevention post-ACS, including the use of the novel direct oral anticoagulants (DOACs).

Recent Findings Multiple trials have been conducted to evaluate the use of DOACs for the secondary prevention after ACS. Recent emerging data showed that the addition of rivaroxaban in a very low dose of 2.5 mg twice daily to the regular DAPT regimen after ACS is beneficial in the reduction of major cardiovascular events, including recurrent myocardial infarction (MI) and strokes. On the other hand, other DOACs, including apixaban, did not show similar efficacy and did not improve the cardiovascular outcomes.

Summary Patients who experience an ACS continue to suffer long-term consequences and thromboembolic complications. Many studies have shown that after the initial ACS event, patients remain in a hypercoagulable state and are more prone to recurrent ischemic attacks including stroke, recurrent MI, or unstable angina (UA). With the objective of seeking better outcomes, it is imperative to explore more aggressive anticoagulation strategies in ACS patients. In this article, we discuss the progress that was made and the limitations we face regarding the role of different anticoagulants in this setting.

Keywords Acute coronary events · Myocardial infarction · Unstable angina · Secondary prevention · Anticoagulation · Direct oral anticoagulants · Antiplatelet therapy · Vitamin K antagonist · Factor Xa inhibitor · Factor II inhibitor · Direct thrombin inhibitor · PAR-1 · Rivaroxaban · Apixaban · Warfarin · Vorapaxar

Abbreviations

ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
COX-1	Cyclooxygenase-1
DAPT	Dual antiplatelet therapy
DOACs	Direct oral anticoagulants
ECM	Extracellular matrix
F1 + 2	Prothrombin fragment 1 + 2
FDA	Food and Drug Administration
MACE	Major adverse cardiac events
MI	Myocardial infarction
NSTE-ACS	Non-ST-elevation ACS
PAR-1	Protease-activated receptor-1
PCI	Percutaneous coronary intervention
SIHD	Stable ischemic heart disease
STEMI	ST-elevation MI
TXA2	Thromboxane A2
UA	Unstable angina
VKAs	Vitamin K antagonists
VWF	Von Willebrand Factor

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Introduction

Acute coronary syndromes (ACS) remain a serious challenge to the US healthcare system; with a person expected to experience a coronary event every 40 s, there are more than 600,000 new and 200,000 recurrent myocardial infarctions (MI) each year [1]. Despite all the recent advances in ACS management and the improved survival rates, cardiovascular mortality remains relatively high [1, 2]. Patients who survive the initial event remain at risk for secondary thromboembolic and major adverse cardiac events (MACE) including—but not limited to—recurrence of ACS, premature cardiac death, and stroke [3–5]. Given the high morbidity and mortality of the disease, preventing recurrent attacks of ACS is of paramount importance.

The current treatment of ACS differs based on the type of the coronary event experienced; ST-elevation MI (STEMI) or non-ST-elevation ACS (NSTE-ACS). However, mechanical reperfusion with primary percutaneous coronary intervention (PCI) followed by dual antiplatelet therapy (DAPT) for 1 year is the mainstay of therapy in most situations [6–9]. Secondary prophylaxis of ACS can be achieved through many strategies including lifestyle modification, smoking cessation, beta blockage, aldosterone blockage, and antithrombotic therapy with DAPT, and in some cases, with anticoagulation [6, 9–11]. Before the PCI and DAPT era, vitamin K antagonists (VKAs)—such as warfarin—were frequently utilized after ACS to decrease ischemic complications and reduce the frequency of recurrent attacks [12]. However, the emerging use of DAPT and the higher risk of major bleeding with anticoagulation have limited this approach.

It has been suggested in various studies that a hypercoagulable state continues to exist past the acute phase of coronary syndromes [13–16] which may be contributing to the high rate of secondary complications in this patient population. The precise pathophysiologic changes that occur have been explored over the past two decades as a few clinical trials have attempted to elucidate the relationship between atherosclerosis, plaque rupture, the subsequent activation of the coagulation cascade, and the persistent pro-thrombotic state. This necessitates a continuous evaluation of other anticoagulation options after ACS for secondary prevention, including the direct oral anticoagulants (DOACs) [17].

Pathophysiology

The formation of the atherosclerotic plaque with its subsequent disruption (whether through erosion, hemorrhage, or rupture), activation of the coagulation cascade, and formation of the flow-limiting intracoronary thrombus constitute the basic underlying events in acute coronary syndromes. The concept of "vulnerable plaques" [18, 19] has been and still is heavily investigated and aims to identify plaques that are prone to rupture. It has been shown that rupture-prone plaques display the morphology of "thin-cap fibroatheromas" [18, 20, 21] with large necrotic cores rich in lipids and macrophages covered by thin fibrous caps. When these plaques rupture, the exposure of the extracellular matrix (ECM) products such as fibrillar collagen, Von Willebrand Factor (VWF), fibronectin, and laminin results in receptor-mediated activation of the circulating platelets and further recruitment of these anucleate cells in a process called platelet aggregation and ultimately the formation of a platelet plug [22]. One of the strongest chemical connections allowing platelet adherence to the vessel wall is that between the platelets and the endothelial VWF through an interaction between GPIb-a receptor on the former and the A1 domain of the latter [23].

There are several receptors on the surface of the platelet that play an important role in its activation, aggregation, and adherence to the vessel wall [22, 24]. The antiplatelet therapies, currently used, target these pathways to prevent clot formation and growth. Of the most clinically relevant platelet-activating receptors are Thromboxane A2 (TXA2) receptor, Protease-activated Receptor-1 (PAR-1), and Adenosine diphosphate (ADP) receptors P2Y1 and P2Y12. Aspirin is a well-known medication that works by inhibiting Cyclooxygenase-1 (COX-1), an enzyme necessary for the synthesis of TXA2, a potent platelet activator. It is used routinely for primary and secondary prevention of myocardial infarction [22]. Similarly, clopidogrel, prasugrel, and ticagrelor are examples of ADP-receptor antagonists that target the ADP-receptor P2Y12 at the platelet surface, resulting in reduced platelet activation. Vorapaxar is currently the only Food and Drug Administration (FDA)-approved PAR-1 antagonist.

The coagulation cascade, on the other hand, is a domino-like sequence of events, with one reaction resulting in the activation of a substrate that in turn serves as a mediator in a subsequent reaction. These sequential reactions serve as targets for the various anticoagulant medications. During platelet activation and aggregation, the coagulation cascade is concurrently activated via the extrinsic pathway as smooth muscle cells and macrophages in the ECM of the ruptured plaque secrete tissue factor (also known as factor III). Tissue factor then binds to factor VII activating it to factor VIIa which in turn activates factor X into factor Xa downstream in the cascade [25, 26], ultimately resulting in the formation of thrombin (factor IIa), and activation of fibrinogen into fibrin.

After the acute event, it has been shown that many patients continue to have high levels of serum prothrombin fragment 1 + 2 levels (F1 + 2) for several months [13, 16]. F1 + 2 are markers of the factor Xa-mediated prothrombin activation, and persistent elevation supports the idea that patients who experience ACS continue to have a hypercoagulable state for long periods after the index event.

Anticoagulation after ACS

Many anticoagulant drugs have been studied for secondary prevention after ACS to reduce mortality and recurrence of ischemic events. In this section, we will review multiple drugs evaluated for this purpose (Table 1).

Vitamin K Antagonists

VKAs, mainly warfarin, were extensively studied for the secondary prevention of thrombotic events; including MI and strokes. The ASPECT-2 study [27] randomized 999 patients with recent ACS to receive either aspirin 80 mg once daily, aspirin 80 mg plus warfarin with target INR of 2.0–2.5, or warfarin only with a target INR of 3.0–4.0. Primary efficacy endpoints of all-cause mortality, MI, or stroke were reduced in both warfarin-only and combination therapy groups; with event rates of 9% in the aspirin-only group, 5% in the warfarin-only group (HR 0.55, $P = 0.0479$), and 5% in the combination group (HR 0.5, $P = 0.03$). On the downside, major bleeding events were about two-fold higher with anticoagulation.

In the same year, the results of WARIS II [28] and CHAMP [29] trials were published. In the WARIS II study, 3630 patients with recent MI were randomized to warfarin with a target INR of 2.8–4.2, aspirin 75 mg daily plus warfarin with a target INR of 2.0–2.5, or aspirin 160 mg daily. Results were similar to the ASPECT-2 study; both the warfarin-only and the combination therapy groups were superior to aspirin alone in reducing the primary efficacy composite endpoint of ischemic events or death, but the risk of bleeding was significantly higher.

On the other hand, the CHAMP study randomized 5059 recent MI patients to either aspirin 162 mg or warfarin with target INR of 1.5–2.5 plus aspirin 81 mg. In contrast to the ASPECT-2 and WARIS II studies, the primary endpoint of mortality rates was not significantly different between both groups, but major bleeding events were almost doubled in the combination therapy group compared with the aspirin monotherapy group.

Direct Oral Anticoagulants (DOACs)

Direct Thrombin (Factor IIa) Inhibitors

Two oral direct thrombin inhibitors were studied for the secondary prophylaxis of ACS; ximelagatran and dabigatran. The Efficacy and Safety of the oral direct Thrombin inhibitor ximelagatran in patients with recent Myocardial damage (ESTEEM) [30] study was a phase II trial that investigated the use of ximelagatran versus placebo in patients with recent MI. The study assessed 1883 patients with recent STEMI or NSTE-ACS. All patients in the study received daily aspirin. There was a significant reduction of the primary composite endpoint of all-cause mortality, non-fatal MI, and recurrent ischemic attacks in the ximelagatran group compared to the placebo group (12.7 vs 16.3%, hazard ratio [31] 0.76, $P = 0.036$). Major bleeding events were relatively higher in the ximelagatran group, but overall rather low in both groups (1.8 vs 0.9%, HR 1.97). An observational study then demonstrated that the reduction of coagulation activity after MI, measured by D-dimer levels, was associated with less new ischemic events [32]. The drug, however, was later withdrawn from the market due to reports of severe hepatotoxicity related to its use [33, 34].

This was followed by the phase II RE-DEEM trial [35] which randomized 1861 patients with recent STEMI or NSTE-ACS to either dabigatran (in four different dosing groups) in addition to DAPT versus placebo. Similar to ximelagatran, dabigatran was associated with an increase of bleeding events by 2–4 folds compared to placebo in a dose-dependent manner. Dabigatran also showed a significant reduction in the systemic coagulation activity as measured by the D-dimer levels, which may correlate with less recurrent ischemic events [32]. However, the study failed to show any reduction in mortality rates, recurrent MI, or strokes among the dabigatran groups. A larger, more powered phase III study is warranted to further evaluate the role of dabigatran post-ACS events and its outcomes.

Direct Factor Xa Inhibitors

Factor Xa inhibitors directly inhibit factor X in the coagulation cascade, halting thrombin formation, and preventing thrombosis. Four factor Xa inhibitors were evaluated in the setting of ACS; rivaroxaban, apixaban, darexaban, and letaxaban.

Rivaroxaban was evaluated in the ATLAS-ACS trial [36] which enrolled 3491 patients with ACS in a dose-escalation (5–20 mg) phase II study to compare rivaroxaban versus placebo in addition to either aspirin alone or DAPT. Bleeding events were independently higher in patients receiving rivaroxaban compared to placebo, with a higher incidence occurring at higher doses of the drug. Primary efficacy endpoints of all-cause mortality, MI, stroke, or recurrent ACS requiring revascularization, on the other hand, were significantly reduced with rivaroxaban compared to placebo (5.6 vs 7%, HR 0.79, $P = 0.10$).

A phase III trial (ATLAS-ACS 2) [11–36, 37••] was then conducted to study the effect of low-dose rivaroxaban (2.5–5 mg twice daily) on 15,526 patients with recent ACS. Compared to placebo, the twice-daily 2.5-mg dose reduced the cardiovascular death rates (2.7 vs. 4.1%, $P = 0.002$) as well as all-cause mortality (2.9 vs. 4.5%, $P = 0.002$), but the higher dose of 5 mg twice daily did not demonstrate similar effects. The primary composite efficacy endpoints of cardiovascular

Table1 Summary of trials conducted to evaluate different anticoagulant drugs after ACS for the secondary prevention

Study	Design	Endpoints	Outcomes
ASPECT-2	Randomized, open-label study comparing: 1. Warfarin to a target INR of 3–4 2. Aspirin 80 mg once daily plus warfarin to a target INR of 2–2.5 3. Aspirin 80 mg once daily	*Primary efficacy endpoints: first occurrence of myocardial infarction, stroke, or death.	In patients with recent ACS, warfarin only or combined with aspirin is superior to aspirin only in reducing mortality and cardiovascular events. However, bleeding events are higher when warfarin is used.
WARIS II	Randomized, open-label study comparing: 1. Warfarin to a target INR of 2.8–4.2 2. Aspirin 75 mg once daily plus warfarin to a target INR of 2–2.5 3. Aspirin 160 mg once daily	*Primary efficacy endpoints: death, non-fatal reinfarction, or thromboembolic stroke.	After an acute MI, warfarin alone or in addition to aspirin is superior to aspirin alone in lowering the efficacy composite endpoint but associated with higher bleeding risk.
CHAMP	Randomized, open-label study comparing: 1. Warfarin to a target INR of 1.5–2.5 plus aspirin 81 mg once daily. 2. Aspirin 160 mg once daily.	*Primary efficacy endpoint: all-cause mortality.	In post-MI patients, receiving warfarin in addition to aspirin does not provide clinical benefit more than what can be achieved with aspirin monotherapy.
ESTEEM	Randomized, double-blind, placebo-controlled study comparing: 1. Ximelagatran (24, 36, 48, or 60 mg) plus aspirin 160 mg once daily. 2. Placebo plus aspirin 160 mg once daily.	*Primary efficacy endpoint: all-cause mortality, non-fatal MI, or severe recurrent ischemia.	In patients with recent MI, Ximelagatran in addition to aspirin is more effective than aspirin alone in reducing cardiovascular events and all-cause mortality.
RE-DEEM	Randomized, double-blind, placebo-controlled, dose-escalation study comparing: 1. Dabigatran (50, 75, 110, or 150 mg) twice daily. 2. Placebo twice daily	*Primary safety endpoint: major or clinically significant minor bleeding event.	After an ACS event, adding dabigatran to DAPT is associated with a dose-dependent increase in bleeding events and a significant reduction in the coagulation activity.
ATLAS-ACS-TIMI 46	Double-blind, placebo-controlled, dose-escalation, phase II study that stratified patients with recent ACS on the basis of investigator decision to: 1. Aspirin only (stratum 1) 2. Aspirin plus a thienopyridine (stratum 2). Participants within each stratum were then randomized with a block randomization method at 1:1:1 to receive either one of the following: 1. Rivaroxaban (at doses of 5, 10, 15, or 20 mg) given once daily. 2. Rivaroxaban (at doses of 2.5, 5, 7.5, or 10 mg) given twice daily. 3. Placebo-matching pill.	*Primary safety endpoint: clinically significant bleeding. *Primary efficacy endpoints: all-cause mortality, MI, stroke, or recurrent severe ischemia that requires revascularization	After stabilizing patients with ACS, the use of factor Xa inhibitor "rivaroxaban" increases bleeding risk in a dose-dependent manner but can reduce major ischemic outcomes.
ATLAS-ACS2-TIMI 51	Double-blind, placebo-controlled, phase III study that stratified patients with recent ACS event on the basis of national or local guidelines to: 1. Aspirin only (stratum 1) 2. Aspirin plus a thienopyridine (stratum 2). Participants within each stratum were then randomized with a block randomization method at 1:1:1 to receive either one of the following: 1. Rivaroxaban (at doses of 2.5 or 5 mg) given twice daily. 2. Placebo twice daily.	*Primary efficacy endpoint: a composite of cardiovascular death, MI, or stroke. *Primary safety endpoint: TIMI major bleeding not related to coronary artery bypass grafting (CABG).	In patients with a recent ACS event, rivaroxaban reduced the risk of cardiovascular death, MI, or stroke. However, rivaroxaban increased the risk of TIMI major bleeding not related to CABG and intracranial hemorrhage, but not the risk of fatal bleeding.
GEMINI-ACS-1	Double-blind, multi-center, randomized trial that assigned patients with recent ACS using a computer-generated	* Primary safety endpoint: TIMI clinically significant bleeding not related to CABG.	Combining a low-dose rivaroxaban with a P2Y12 inhibitor for the treatment of patients with ACS has a similar risk of

Table1 (continued)

Study	Design	Endpoints	Outcomes
	randomization scheme to receive either: 1. Aspirin 100 mg daily 2. Rivaroxaban 2.5 mg twice daily All patients were receiving a P2Y12 inhibitor (ticagrelor or clopidogrel stratum)		clinically significant bleeding as DAPT with aspirin and a P2Y12 inhibitor.
APPRAISE	Double-blind, placebo-controlled, dose-ranging phase II study that randomized patients with recent ACS to receive either: 1. Apixaban in doses of 2.5 mg twice daily, 10 mg once daily, 10 mg twice daily, or 20 mg once daily. 2. Placebo-matching pill. All patients were receiving aspirin. 76% of patients were receiving both aspirin and clopidogrel.	*Primary safety endpoint: International Society of Thrombosis and Hemostasis (ISTH) major or clinically relevant minor bleeding. *Secondary efficacy endpoint: cardiovascular mortality, ischemic stroke, MI, or recurrent severe ischemia	In patients with recent ACS, the addition of apixaban to standard medical therapy resulted in an increase in ISTH bleeding events in a dose-dependent manner and a trend towards the reduction of ischemic events.
APPRAISE-2	Double-blind, placebo-controlled, phase III study that randomized patients with recent ACS to receive either: 1. Apixaban 5 mg twice daily. 2. Placebo twice daily. All patients in the study were receiving either aspirin or aspirin plus a P2Y12 inhibitor.	*Primary efficacy endpoints: cardiovascular death, MI, or ischemic stroke. *Primary safety endpoint: major bleeding according to the TIMI definition.	Adding apixaban, at a dose of 5 mg twice daily, to mono or dual antiplatelet therapy in high-risk patients after an ACS event increased the number of major bleeding events without a significant reduction in recurrent ischemic events.
TRACER	Double-blind, placebo-controlled trial that randomized patients to either: 1. Vorapaxar at a loading dose of 40 mg then a maintenance dose of 2.5 mg once daily. 2. Matching placebo. Patients were stratified according to the intention to use a glycoprotein IIb/IIIa inhibitor (vs. none) and the intention to use a parenteral direct thrombin inhibitor (vs. other antithrombin agents).	*Primary efficacy endpoints: cardiovascular mortality, MI, stroke, or recurrent ischemia leading to rehospitalization or urgent coronary revascularization.	In patients with ACS, the addition of vorapaxar to standard medical therapy did not reduce the primary composite endpoint but significantly increased major bleeding risk, including intracranial hemorrhage.

death, MI, or stroke were reduced significantly with both doses, as compared to placebo (8.9 vs 10.7% HR 0.84, $P = 0.008$). Events of major bleeding were higher with rivaroxaban (2.1 vs. 0.6%, $P < 0.001$) as well as intracranial hemorrhage (0.6 vs. 0.2%, $P = 0.009$), but not fatal bleeding rates (0.3 vs. 0.2%, $P = 0.66$), and there were even fewer fatal bleeding events with the lower dose of 2.5 mg twice daily compared to 5 mg twice daily (0.1 vs. 0.4%, $P = 0.04$). Furthermore, a follow-up study [38] based on the ATLAS-2 trial showed that the risk of in-stent thrombosis was noted to be lower with rivaroxaban 2.5 mg twice daily compared with placebo (1.9 vs. 1.5%, HR 0.61, $P = 0.023$). The study also showed that patients who received rivaroxaban 2.5 mg in addition to DAPT after stent placement for ACS had significant mortality reduction (HR 0.56, $P = 0.014$).

The clear superiority of rivaroxaban in reducing ischemic events and mortality in ACS patients was compromised by a slight increase in bleeding risk. In an attempt for a better safety profile, the GEMINI-ACS-1 trial [39] was conducted. In this multi-center double-blinded phase II trial, 3037 patients with recent ACS were randomized to receive either aspirin 100 mg once daily or rivaroxaban 2.5 mg twice daily in addition to a P2Y12 inhibitor (ticagrelor stratum; 56% of patients, or clopidogrel stratum; 44% of patients). The primary endpoint of thrombolysis in myocardial infarction (TIMI) clinically significant bleeding events was similar in both groups; 5% of patients in both rivaroxaban and the aspirin groups; HR 1.09, $P = 0.584$. A more powered study for this treatment approach is warranted to evaluate the efficacy and safety profiles of Rivaroxaban in secondary prevention of ACS.

Notably, it has been shown that in patients with stable ischemic heart diseases (SIHD), adding low-dose rivaroxaban to aspirin was superior and had better outcomes compared with aspirin alone or rivaroxaban alone. In the phase III

COMPASS [40] trial, 27,395 patients with SIHD were randomized to receive either rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily, rivaroxaban 5 mg twice daily, or aspirin 100 mg once daily. The primary composite endpoint of cardiac death, stroke, or MI was significantly less in the rivaroxaban plus aspirin group compared with the aspirin-only group (4.1 vs 5.4%; HR 0.76; $P < 0.001$). Major bleeding events were higher among the rivaroxaban plus aspirin group compared to the aspirin-only group (HR 1.7; $P < 0.001$), but intracranial and fatal bleeding events were at comparable rates between both groups. A sequential analysis of randomized clinical trials including two in acute coronary syndrome reported that rivaroxaban is associated with a significantly lower risk of MI in a broad spectrum of patients when tested against different controls [41].

Adding apixaban (in doses of 2.5 mg twice daily, 10 mg once daily, 10 mg twice daily, or 20 mg once daily) to aspirin alone or a combination of aspirin and clopidogrel in 1715 patients with recent ACS was evaluated in the phase II APPRAISE trial [42]. The two higher-dose arms of apixaban (10 mg twice daily and 20 mg once daily) were prematurely discontinued from the study due to excessive bleeding events. Major and clinically relevant bleeding events were also noted to be higher in both lower-dose apixaban arms (HR of 1.78; $P = 0.09$ for the 2.5 mg twice daily group and HR of 2.45; $P = 0.005$ for the 10 mg once daily group) compared to placebo. Ischemic events including cardiovascular mortality, MI, or ischemic stroke were not significantly reduced with apixaban 2.5 mg twice daily (HR 0.73; $P = 0.21$) and apixaban 10 mg once daily (HR 0.61; $P = 0.07$).

Further testing of apixaban at a dose of 5 mg twice daily after ACS was done in the phase III APPRAISE-2 trial [43]. After recruiting 7392 patients, the study was prematurely terminated as major bleeding events were more pronounced (event rate 1.3% in apixaban group vs 0.5% in control group, HR 2.59; $P = 0.001$) without a clinically significant decrease in the primary outcome of cardiovascular death, MI, or ischemic stroke (primary outcome event rate of 7.5% in the apixaban group vs 7.9% in the placebo group, HR 0.95; $P = 0.51$).

Two other factor Xa inhibitors were evaluated in the setting of ACS; YM150 "darexaban" in the RUBY-1 trial [44] and TAK-442 "letaxaban" in the AXIOM trial [45]. Both medications showed no evidence of efficacy or a reduction in cardiovascular deaths, strokes, or MI when compared with placebo, but rather showed an increased risk of bleeding.

PAR-1 Inhibitors

The protease-activated receptor-1 (PAR-1) on the platelet surface plays a vital role in thrombosis as it undergoes activation by thrombin (factor IIa). Vorapaxar is the only FDA-approved PAR-1 antagonist that can interfere with platelet activation through blocking thrombin binding to the platelets.

Conflicting data exist regarding the efficacy of vorapaxar in the secondary prevention of atheroembolic diseases. The TRA2P trial [46] evaluated 26,449 patients with prior MI, stroke, or peripheral arterial disease (PAD) and randomized them to receive either vorapaxar 2.5 mg daily or placebo. Primary composite efficacy endpoint of cardiovascular death, MI, or stroke occurred in 9.3% of patients in the treatment group versus 10.5% in the placebo control group (HR 0.87, $P < 0.001$), therefore demonstrating better cardiovascular outcomes. However, when assessing the use of vorapaxar in 12,944 patients with recent ACS in the TRACER study [47], the drug failed to show a clinically significant reduction in the primary composite endpoint of cardiovascular death, MI, recurrent ACS with rehospitalization, strokes, or the need for urgent PCI and revascularization (HR 0.92, $P = 0.07$). Both studies, on the other hand, showed a clinically significant increase in bleeding risk with vorapaxar, including intracranial and fatal bleeding events.

Conclusions and Future Directions

Acute coronary syndromes are a major healthcare burden, not only due to their immediate life-threatening nature and their associated complications in the acute post-event phase but also because of the long-term increase in major adverse cardiac events. In many patients with ACS, a hypercoagulable state ensues and may persist for several months after the initial event.

Significant advances have been made in the field of secondary prevention of thrombotic events post-ACS, and even though the results of some trials have not been promising, other trials showed favorable outcomes. Standardizing the use of the dual-pathway approach with anticoagulation therapy in addition to the traditional antiplatelet therapy for secondary prevention of thrombotic events after an acute coronary event can be a double-edged sword. While available data suggest that this approach may reduce the high thrombotic burden and the recurrence of ischemic attacks, it appears that bleeding risk may outweigh the benefits in most clinical scenarios. A balanced risk-benefit profile of anticoagulation strategies remains a major target to achieve. Among the available anticoagulants in the market, only select DOACs showed consistent beneficial effects, which were counterbalanced by an increased bleeding risk; including fatal bleeding with certain drugs.

Most trials that were conducted to date showed that the liberal use of DOACs in ischemic heart disease could increase morbidity and mortality without a significant net clinical benefit. On the other hand, implementing an anticoagulation strategy with rivaroxaban—in a very low dose of 2.5 mg twice daily—seems to be a reasonable option for certain high-risk patients and results in a favorable outcome. Of note, the US Food and Drug Administration (FDA) approved rivaroxaban 2.5 mg twice daily to reduce the risk of major cardiovascular

(CV) events, such as CV death, myocardial infarction (MI), and stroke, in people with chronic coronary or peripheral artery disease (CAD/PAD) on October 11, 2018 [48]. In fact, applying this strategy in addition to a guideline-directed medical therapy appears to be protective against the high thrombotic load in patients with either ACS or SIHD.

Additionally, a recent meta-analysis study [49•] showed that the benefit of anticoagulation after ACS depends mainly on the type of ACS experienced; STEMI or NSTE-ACS. Data suggest greater benefit after a STEMI event compared with other types of acute coronary syndromes. This might be attributed to the different patient population and their comorbidity profiles as well as the different treatment approach utilized for each condition. Perhaps it would be appropriate to conduct further trials with stratification of patients based on their bleeding risk and ischemic status to better guide clinicians in choosing an optimal individualized regimen.

Ultimately, the decision to begin anticoagulation therapy post-ACS in each patient should be individualized, considering the patient's bleeding risk and pro-thrombotic vulnerability. The promising outcomes of using rivaroxaban for secondary prevention gives hope that one day dual-pathway antagonism might be standardized. However, reaching a fine equilibrium of a balanced risk-benefit profile of anticoagulation strategies remains a challenge to overcome at this time.

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Compliance with Ethical Standards

Conflict of Interest Peter Khalil and Ghazal Kabbach 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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49.• Chiarito M, Cao D, Cannata F, Godino C, Lodigiani C, Ferrante G, et al. Direct oral anticoagulants in addition to antiplatelet therapy for secondary prevention after acute coronary syndromes: a systematic review and meta-analysis. JAMA Cardiol. 2018;3(3):234–41 **This systematic review and meta-analysis study summarizes the results of six trials that included more than 29,000 patients post-ACS and studied the efficacy of adding DOACs in addition to DAPT for the secondary prevention.**