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More, More, More: Reducing Thrombosis in Acute Coronary Syndromes Beyond Dual Antiplatelet Therapy—Current Data and Future Directions

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Common to the pathogenesis of acute coronary syndromes (ACS) is the formation of arterial thrombus, which results from platelet activation and triggering of the coagulation cascade.[1] To attenuate the risk of future thrombotic events, patients with ACS are treated with dual antiplatelet therapy (DAPT), namely, the combination of aspirin with a $P2Y_{12}$ inhibitor, such as clopidogrel, ticagrelor, or prasugrel. Despite DAPT, some ≈10% of ACS patients experience recurrent major adverse cardiovascular events over the subsequent 30 days,[2] driving the quest for more effective inhibition of thrombotic pathways. In this review, we provide an overview of studies to date and those ongoing that aim to deliver more effective combinations of antithrombotic agents to patients with recent ACS. We have chosen to confine the review to ACS patients without atrial fibrillation because those with atrial fibrillation have a clear indication for combination therapy that includes oral anticoagulation and should, we feel, be treated as a separate cohort.

In this article, we discuss the limitations of the currently available clinical trial data and future directions, with suggestions for how practice might change to reduce the risk of coronary thrombosis in those at greatest risk, with minimal impact on bleeding.

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J Am Heart Assoc. 2018;7:e007754 DOI: 10.1161/JAHA.117.007754.

Beyond DAPT: Triple-Therapy Combinations in ACS

Cilostazol

Cilostazol, a selective phosphodiesterase type 3 inhibitor, reduces platelet aggregation induced by collagen, 5′-ADP, epinephrine, and arachidonic acid and improves endothelial cell function.[3] Studies comparing triple therapy (TT) comprising DAPT plus cilostazol versus DAPT alone have been generally small randomized trials with largely negative results.[4] The CILON-T (Influence of Cilostazol-Based Triple Antiplatelet Therapy on Ischemic Complications After Drug-Eluting Stent Implantation) trial randomized 960 patients undergoing percutaneous coronary intervention (PCI) to DAPT (aspirin and clopidogrel) or TT (DAPT and cilostazol). Despite reduction in platelet reactivity, addition of cilostazol did not significantly reduce the composite of cardiac death, nonfatal myocardial infarction (MI), ischemic stroke, or target lesion revascularization (8.5% versus 9.2%; 95% confidence interval [CI], 0.59–1.46; P=0.74).[5] The HOST-ASSURE (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis–Safety and Effectiveness of Drug-Eluting Stents and Antiplatelet Regimen) trial of 3755 patients undergoing PCI did not demonstrate the superiority of TT (conventional DAPT with cilostazol) over DAPT (double-dose clopidogrel and aspirin) with respect to 1-month composite clinical outcomes (1.2% versus 1.4%; 95% CI, 0.49–1.48; $P_{superiority}$=0.558).[6]

A meta-analysis of randomized and observational studies (n=11) of high-risk ACS patients undergoing PCI, using DerSimonian and Laird principles, showed that TT reduced all-cause mortality compared with DAPT (odds ratio [OR]: 0.72; 95% CI, 0.61–0.85; P<0.001) without an effect on MI (OR: 0.97; 95% CI, 0.63–1.51; P=0.901), target vessel revascularization (TVR; OR: 0.90; 95% CI 0.65–1.23; P=0.491), stroke (OR: 0.63; 95% CI, 0.32–1.21; P=0.163), or bleeding (OR: 1.07; 95% CI, 0.60–1.90; P=0.809).[7] However, a larger meta-analysis of 19 randomized trials and registries comparing aspirin and clopidogrel against TT with cilostazol in 7464 patients with ACS undergoing PCI[8] showed

that TT did not significantly reduce major adverse cardiovascular events or mortality (relative risk [RR]: 0.77; 95% CI, 0.55–1.09; P=0.15) but significantly reduced TVR (RR: 0.65; 95% CI, 0.55–0.77; P<0.00001). Cilostazol is restricted to use as a second-line agent in patients with claudication and is not currently recommended by the European Society of Cardiology (ESC)[9] or American College of Cardiology/American Heart Association (ACC/AHA) guidelines,[10,11] nor is it approved for ACS.

Warfarin

The addition of standard-dose warfarin to DAPT with clopidogrel after ACS has been assessed only in small registries that showed unacceptable increases in bleeding. Warfarin is the most commonly used vitamin K antagonist, which inhibits the production of vitamin K–dependent coagulation factors II, VII, IX, and X and, to a lesser extent, proteins C and S. This leads to a dose- and time-dependent anticoagulation effect that requires close monitoring.[12] A registry of 40 812 ACS patients treated with multiple different regimens revealed a 3-fold increase in bleeding with TT comprising warfarin, clopidogrel, and aspirin compared with DAPT.[13]

The WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) open-label randomized controlled trial compared dual antithrombotic therapy (warfarin and clopidogrel) with TT (warfarin, aspirin, and clopidogrel) in patients undergoing PCI with an indication for anticoagulation, mainly atrial fibrillation.[14] A third of patients had ACS. TT significantly increased bleeding compared with dual therapy (44.4% versus 19.4%; 95% CI, 0.26–0.50; P<0.0001) and increased the risk of the composite of all-cause death, MI, stroke, TVR, and stent thrombosis, driven by an increase in all-cause mortality (6.3% versus 2.5%, P=0.027). Consequently, the ESC guidelines on myocardial revascularization and the ACC/AHA guidelines recommend reserving TT with warfarin and DAPT to a short period after PCI in those with an indication for anticoagulation.[9,15]

Thrombin Receptor Antagonism

A key mediator of platelet activation is thrombin, which binds to protease-activated receptor 1 (PAR-1) and PAR-4 on the platelet surface in humans (Figure 1). Vorapaxar is the sole approved PAR-1 inhibitor.

The addition of vorapaxar to single antiplatelet therapy or DAPT with clopidogrel was assessed in 26 449 stable patients with a history of MI, stroke, or peripheral vascular disease in the TRA-2P (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events) trial, which was prematurely terminated because of excess bleeding in patients with prior stroke. The addition of vorapaxar affected the primary end point (a composite of cardiovascular death, MI, or stroke; 9.3% versus 10.5%, P<0.001) and reduced the major secondary end point (composite of cardiovascular death, MI, stroke, or recurrent ischemia leading to urgent coronary revascularization; 11.2% versus 12.4%, P=0.001), driven by a lower rate of MI (5.2% versus 6.1%, P=0.001; Figure 2). Vorapaxar increased major bleeding regardless of the classification used (GUSTO [Global Use of Strategies to Open Occluded Coronary Arteries]: 4.2% versus 2.5%, P=0.001; non–coronary artery bypass grafting–related TIMI [Thrombolysis in Myocardial Infarction], major: 2.8% versus 1.8%, P<0.001) as well as intracranial hemorrhage (1% versus 0.5%, P<0.001).[16] In the subgroup analysis of MI patients, vorapaxar significantly reduced the primary efficacy end point (8.1% versus 9.7%, P<0.0001), particularly in high-risk patients, albeit with a significant increase in GUSTO moderate or severe bleeding (3.4% versus 2.1%, P<0.0001[17]; Figure 2).

Vorapaxar was also assessed in 12 944 patients with recent ACS in the TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in ACS) trial, which was terminated prematurely because of excess bleeding.[19] Patients were randomized to vorapaxar or placebo in addition to DAPT (aspirin and clopidogrel; Table). Over a median follow-up of 30 months, moderate and severe GUSTO bleeding occurred more frequently with vorapaxar than placebo (7.2% versus 5.2%, P<0.001), most notably, intracranial hemorrhage (1.1% versus 0.2%, P<0.001), without significant reduction in the primary composite efficacy end point of cardiovascular death, MI, stroke, recurrent ischemia requiring rehospitalization or urgent coronary revascularization (18.5% versus 19.9%; 95% CI, 0.85–1.01; P=0.07). The “harder” secondary efficacy end point of the composite of cardiovascular death, MI, and stroke was lower with vorapaxar than placebo (14.7% versus 16.4%, P=0.02[19]; Figure 2). Although vorapaxar is not approved in patients with recent ACS, it is approved as add-on therapy to aspirin or DAPT including clopidogrel in high-risk patients without previous stroke and with prior MI, between 2 weeks and 12 months from the acute event, based on the prespecified MI stratum of TRA-2P.[17] Vorapaxar has never been tested in combination with ticagrelor or prasugrel and is contraindicated in conjunction with these agents. The 2015 ESC guidelines on non–ST-segment–elevation ACS state that although vorapaxar is approved “for reducing ischemic events in patients with a history of MI, the benefit of vorapaxar in addition to aspirin and clopidogrel is modest and must be carefully weighed against the increase in bleeding events, including intracranial hemorrhage.”[20] The ACC/AHA guideline for the management of patients with non–ST-segment–elevation ACS[10] makes no mention of vorapaxar, and the 2013 ACCF/AHA guideline for the management of ST-segment–elevation MI (STEMI) states that “more information

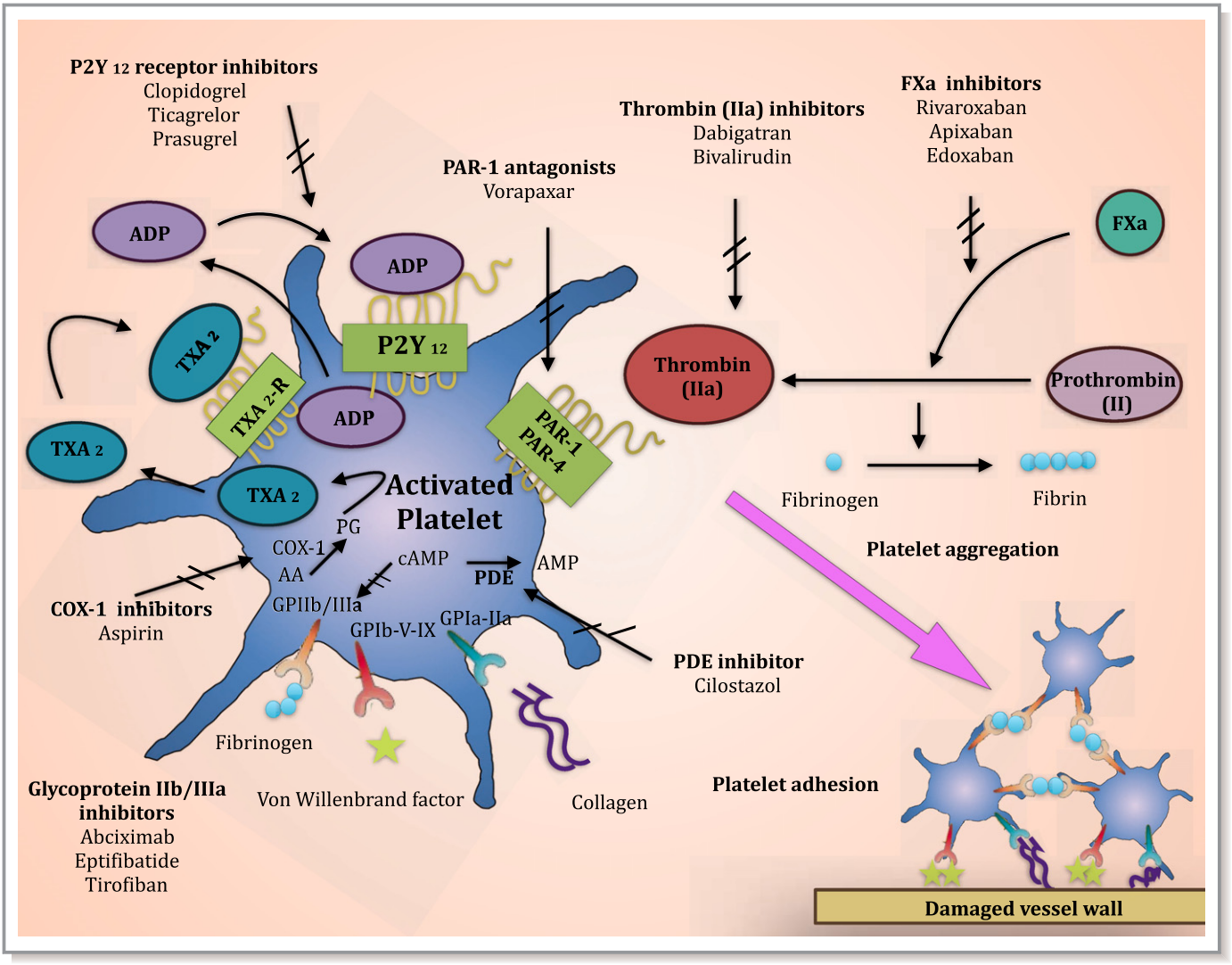

Figure 1. Platelet activation and aggregation and sites of action of antiplatelet drugs. Platelet activation can occur via multiple pathways that include, among others, von Willebrand factor, collagen, thromboxane A_2 (TxA_2), and ADP via $P2Y_{12}$ receptors and thrombin via protease activated receptors PAR-1 and PAR-4. Platelet activation results in conformational change, release of α and dense granule contents, and activation of glycoprotein (GP) IIb/IIIa leading to platelet aggregation. cAMP is an inhibitor of GPIIb/IIIa and therefore regulates platelet aggregation. Phosphodiesterase (PDE) converts cAMP to AMP, which is the inactive compound. Cilostazol is a selective PDE3 inhibitor reducing platelet aggregation. COX indicates cyclooxygenase; FXa, factor Xa.

specific to patients with STEMI is needed with regard to the use of prasugrel, ticagrelor, novel factor Xa (FXa) and factor IIa (FIIa) antagonists, and platelet protease–activated receptor 1 antagonists."[11]

Direct Oral FXa Inhibition

Direct FXa inhibitors are a class of anticoagulant drugs that act directly on factor X in the coagulation cascade and inhibit the action of FXa, namely, the conversion of prothrombin into thrombin (Figure 1).

The dose-finding, phase II, ATLAS ACS-TIMI 46 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 46)[23] study assessed the safety and efficacy of the direct oral FXa inhibitor rivaroxaban (5, 10, 15, or 20 mg once or twice daily) in addition to DAPT (with clopidogrel) or single antiplatelet therapy with low-dose aspirin in 3941 patients with recent ACS. Bleeding complications increased in a dose-dependent manner in all TT groups (P<0.0001). The subsequent ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51) study—a phase III, double-blind, randomized, placebo-controlled trial—compared the addition of 2.5 or 5 mg BID rivaroxaban to DAPT with clopidogrel in 15 526 patients with ACS.[21] The 1-year primary efficacy end point, a composite of

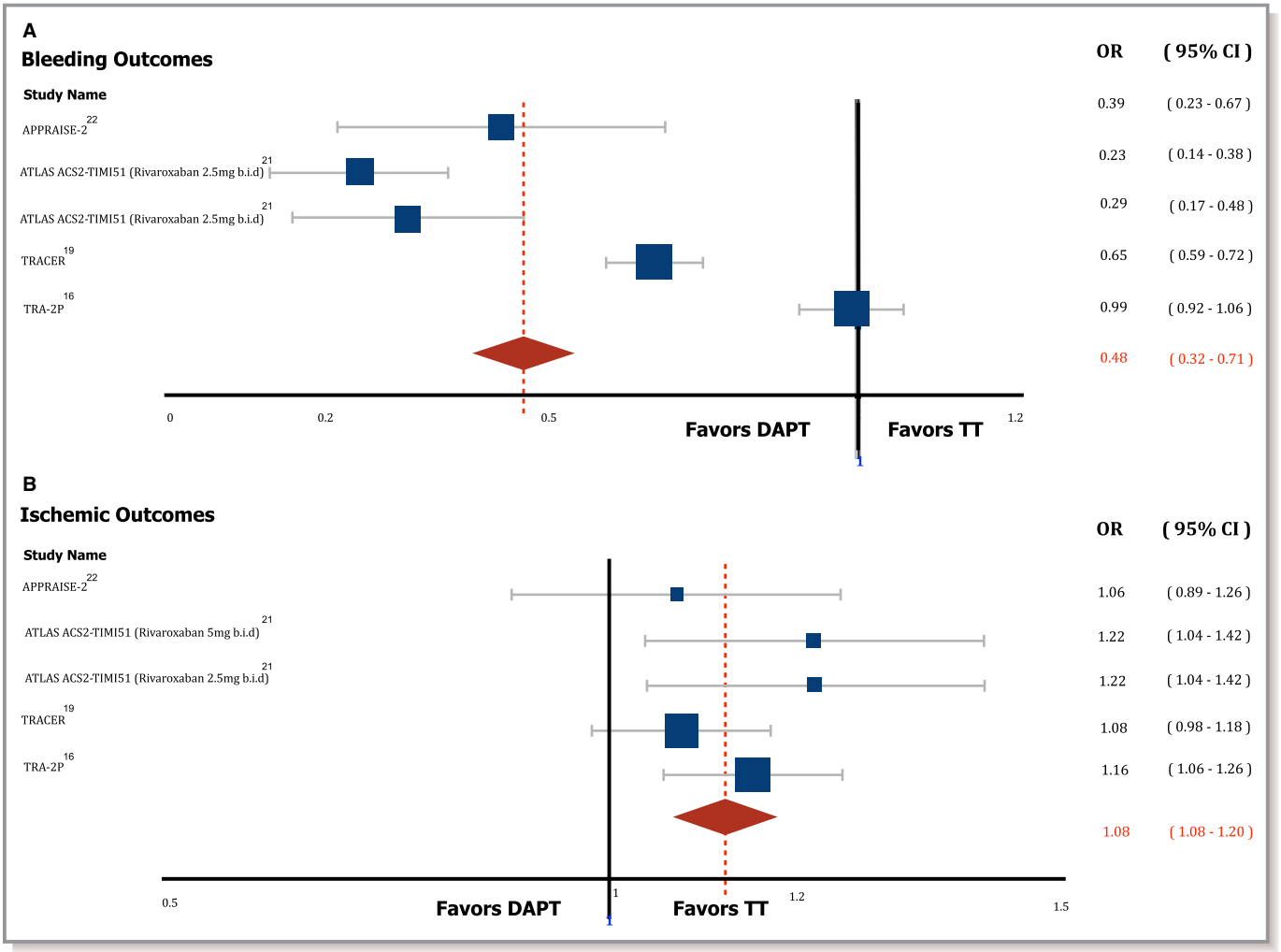

Figure 2. Forest plot of the major triple therapy (TT) studies. A, Primary safety outcomes reported on major TT studies. Bleeding results are reported as odds ratios (ORs) and 95% confidence intervals (CIs). B, Primary efficacy outcomes reported on major TT studies. Ischemic results are reported as ORs and 95% CIs. Pooled ORs were calculated for bleeding and ischemic outcomes using a random-effect model by the method of DerSimonian and Laird.[18] Forest plots are used to represent the meta-analysis graphically and to show the degree of heterogeneity between studies. DAPT indicates dual antiplatelet therapy.

cardiovascular death, MI, and stroke, was significantly reduced by the combined doses of rivaroxaban (8.9% versus 10.7%, *P*=0.008) and each dose alone (2.5 mg: 9.1% versus 10.7%, *P*=0.02; 5 mg: 8.8% versus 10.7%, *P*=0.03) compared with placebo (Figure 2).[18] Rivaroxaban at the 2.5-mg dose significantly reduced cardiovascular death compared with placebo (2.7% versus 4.1%, *P*=0.002). In contrast, this was not seen with the addition of 5 mg rivaroxaban compared with placebo (4% versus 4.1%, *P*=0.63). In the comparison of the 2 doses of rivaroxaban (2.5 versus 5 mg), the rates of cardiovascular death and all-cause mortality were significantly different for both comparisons (*P*=0.009). Subgroup analysis showed that rivaroxaban reduced the primary efficacy end point in STEMI patients (8.4% versus 10.6%, *P*=0.019)[24] and reduced stent thrombosis compared with placebo (1.9% versus 1.5%, *P*=0.017),[25] and the reduction in the primary efficacy end point in patients with STEMI appeared to become apparent as early as 30 days after the index event.[24] Rivaroxaban combined doses, compared with placebo, significantly increased the rate of non–coronary artery bypass grafting–related TIMI major bleeding (2.1% versus 0.6%, *P*<0.001) and intracranial bleeding (0.6% versus 0.2%, *P*=0.009) but not fatal bleeding (0.3% versus 0.2%, *P*=0.66),[21] and the rates of non–coronary artery bypass grafting–related TIMI major bleeding were similar with the 2.5- and 5-mg BID doses (1.8% versus 2.4%, *P*=0.12).

Rivaroxaban 2.5 mg BID received approval for the prevention of atherothrombotic events in patients after ACS with elevated cardiac biomarkers. The 2017 ESC guidelines for the management of acute MI in patients presenting with an ST-segment–elevation state that rivaroxaban 2.5 mg BID may be considered in selected patients who receive aspirin and

Table. Main Characteristics of Phase III Studies Assessing TT in Patients With ACS Without Atrial Fibrillation

Study	ATLAS ACS2-TIMI51[21]	APPRAISE-2[22]	TRACER[19]	TRA-2P[16]
Type	Double-blind placebo-controlled phase III	Double-blind placebo-controlled phase III	Double-blind placebo-controlled phase III	Double-blind placebo-controlled phase III
Antithrombotic agent	Rivaroxaban	Apixaban	Vorapaxar	Vorapaxar
Patients, n	15 526	7392	12 944	26 449
Clinical presentation, %				
STEMI	50	40	0	0
Non-STEMI	26	42	100	0
Unstable angina	24	18	0	0
PCI for index admission, %	60	44	57	0
DAPT use, %	93	81	92	62
$P2Y_{12}$ inhibitor use	Clopidogrel	Clopidogrel	Clopidogrel	Clopidogrel
Duration of treatment, mo	13	8	12	12
Dose	2.5 mg BID, 5 mg BID, or placebo	5 mg BID or placebo	2.5 mg once daily or placebo	2.5 mg once daily or placebo
Primary safety end point	TIMI major bleeding not related to CABG	TIMI major bleeding not related to CABG	TIMI clinically significant bleeding and moderate or severe bleeding GUSTO	TIMI clinically significant bleeding and moderate or severe bleeding GUSTO
Safety outcome, HR (95% CI); *P* value	2.5 mg BID: 3.46 (2.08–5.77); *P*<0.001 5 mg BID: 4.47 (2.71–7.36); *P*<0.001	5 mg BID: 2.59 (1.40–4.46); *P*=0.001	2.5 mg once daily: 1.35 (1.16–1.58); *P*<0.001	2.5 mg once daily: 1.66 (1.43–1.93); *P*<0.001
Primary efficacy end point	CV death, MI, stroke	CV death, MI, or ischemic stroke	CV death, MI, stroke, recurrent ischemia with rehospitalization or urgent revascularization	CV death, MI, or stroke
Efficacy outcome, HR (95% CI); *P* value	2.5 mg BID: 0.84 (0.72–0.97); *P*=0.007 5 mg BID: 0.85 (0.73–0.98); *P*=0.03	5 mg BID: 0.95 (0.80–1.11); *P*=0.510	2.5 mg once daily: 0.92 (0.85–1.01); *P*=0.07	2.5 mg once daily: 0.87 (0.80–0.94); *P*<0.001

ACS indicates acute coronary syndromes; CABG, coronary artery bypass grafting; CI, confidence interval; CV, cardiovascular; DAPT, dual antiplatelet therapy; GUSTO, Global Use of Strategies to Open Occluded Arteries; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; TT, triple therapy.

clopidogrel after STEMI and who are at low bleeding risk (class IIb, level of evidence B).[26] The 2015 ESC guideline for the management of non–ST-segment–elevation ACS states that "rivaroxaban 2.5 mg twice daily, while not recommended in those receiving ticagrelor or prasugrel, might be considered in combination with aspirin and clopidogrel if ticagrelor and prasugrel are not available for NSTEMI [non-STEMI] patients who have high ischemic and low bleeding risks" (class IIb, level of evidence B).[20] It is contraindicated in patients with prior ischemic stroke or transient ischemic attack and cautioned in those aged >75 years or weighing <60 kg because of high bleeding risk in older and/or underweight patients. The ACC/AHA guideline for the management of patients with non–ST-segment–elevation ACS[10] states, "Although there are some data on therapy with aspirin, clopidogrel, and warfarin, there is sparse information on the use of newer $P2Y_{12}$ inhibitors (prasugrel, ticagrelor), direct thrombin inhibitor (dabigatran), or factor-Xa inhibitors (rivaroxaban, apixaban) in patients receiving triple therapy."

The more recently published GEMINI ACS 1 (A Study to Compare the Safety of Rivaroxaban Versus Acetylsalicylic Acid in Addition to Either Clopidogrel or Ticagrelor Therapy in Participants With Acute Coronary Syndrome) study was a phase II randomized trial of 3037 patients with ACS comparing aspirin or rivaroxaban 2.5 mg BID in addition to clopidogrel or ticagrelor.[27] The primary end point was non–coronary artery bypass grafting–related TIMI clinically significant bleeding. There was no significant difference between rivaroxaban and aspirin with respect to the primary outcome (5% versus 5%; 95% CI, 0.80–1.50; *P*=0.584). Moreover, among patients receiving ticagrelor, there was no difference in bleeding whether they were assigned to receive concomitant aspirin or

rivaroxaban and no difference compared with clopidogrel (non– coronary artery bypass grafting–related TIMI clinically significant bleeding 7% versus 6% [95% CI, 0.79–1.68]; 3% versus 3% [95% CI, 0.53–1.171]; Pinteraction=0.588). Although phase II trials are not powered to assess efficacy, there was nevertheless no signal for reduction in ischemic end points with rivaroxaban (5% versus 5%; 95% CI, 0.77–1.46; *P*=0.731). Similarly, the study was not powered for assessing ischemic end points, so no definite conclusions about the safety of the combination of rivaroxaban with a $P2Y_{12}$ inhibitor versus standard DAPT therapy can be drawn.

The addition of apixaban, a direct oral FXa inhibitor, to single antiplatelet therapy or DAPT was evaluated in the phase II dose-finding APPRAISE (Apixaban for Prevention of Acute Ischemic and Safety Events) study.[28] Some 1700 patients with recent ACS were randomized to apixaban 2.5 mg BID, 10 mg once daily, 10 mg BID, 20 mg once daily, or placebo. Apixaban significantly increased major or clinically relevant nonmajor bleeding compared with placebo in a dose-dependent manner. This led to APPRAISE-2 (Apixaban for Prevention of Acute Ischemic and Safety Events 2), a phase III, randomized, double-blind, placebo-controlled trial assessing the safety and efficacy of adding apixaban 5 mg BID to DAPT in 7392 patients with recent ACS.[22] Apixaban did not significantly affect the primary efficacy end point of the composite of cardiovascular death, MI, and ischemic stroke (7.5% versus 7.9%; 95% CI, 0.80–1.11; *P*=0.51) but significantly increased TIMI major bleeding (1.3% versus 0.5%; 95% CI, 1.50–4.46; *P*=0.001), including fatal bleeding, leading to premature termination of the trial (Figure 2).

The addition of darexaban, another FXa inhibitor, to DAPT in ACS patients was examined in the phase II RUBY-1 (Study Evaluating Safety, Tolerability, and Efficacy of YM150 in Subjects With Acute Coronary Syndromes) trial.[29] Darexaban dose-dependently increased TIMI major bleeding compared with placebo (0.6% versus 0.3%; 95% CI, 1.13–4.60; *P*=0.022), and although not powered to assess efficacy outcomes, there was no observed difference between groups (5.6% versus 4.4%; *P* value not significant).

The phase II dose-finding AXIOM (Phase 2 Study of TAK-442, an Oral Factor Xa Inhibitor, in Patients Following Acute Coronary Syndrome) study assessed the addition of letaxaban or placebo to DAPT in 2753 patients with recent ACS.[30] There was no difference in major bleeding (0.9% versus 0.5%; 95% CI, 0.50–1.37; *P*=0.47), but letaxaban dose-dependently increased the rate of combined TIMI major and minor bleeding compared with placebo (2.1% versus 0.9%; 95% CI, 1.53–2.86, *P*=0.025).

Direct Oral Thrombin (FIIa) Inhibition

Direct oral thrombin (FIIa) inhibitors are a class of anticoagulants that act by directly inhibiting thrombin to delay clotting. The efficacy and safety of the direct thrombin inhibitor dabigatran was evaluated in RE-DEEM (Randomized Dabigatran Etexilate Dose Finding Study in Patients With Acute Coronary Syndromes Post Index Event With Additional Risk Factors for Cardiovascular Complications Also Receiving Aspirin and Clopidogrel: Multi-centre, Prospective, Placebo Controlled, Cohort Dose Escalation Study).[31] This phase II, randomized, double-blind, placebo-controlled trial of 1861 patients with recent ACS assessed the addition of different doses of dabigatran (50, 75, 110, and 150 mg BID) to DAPT that included clopidogrel.

Dabigatran dose-dependently increased major bleeding compared with placebo (*P*<0.001) but did not reduce the composite end point of cardiovascular death, nonfatal MI and nonhemorrhagic stroke compared with placebo (4% versus 3.8%; *P* value not significant). Dabigatran thus has no role in ACS and currently is not indicated for patients on DAPT because of a doubling of major bleeding risk noted in the ESC and ACC/AHA guidelines.[10,11,20,26]

Non–Vitamin K Oral Anticoagulant Meta-Analysis

A meta-analysis of 7 randomized, placebo-controlled, phase II and III studies of different non–vitamin K oral anticoagulants (FXa inhibitors apixaban, darexaban, rivaroxaban, and FIIa inhibitors dabigatran and ximelagatran) in ACS showed that addition of a non–vitamin K oral anticoagulant to DAPT for 6 months prevented 5 major adverse cardiovascular events and caused 42 additional clinically significant bleeding events per 1000 patients treated.[32] The authors followed the principles of DerSimonian and Laird, using a random effect model, and reported pooled hazard ratios of the studies. However, there was no access to patient-level data, and results should be interpreted with caution, given the limitations of a meta-analysis mixing phase II and III studies of drugs at different doses and with differing pharmacodynamics.

Discussion

TT combinations comprising the addition of an oral anticoagulant—in particular, low-dose rivaroxaban or PAR-1 antagonist to DAPT, predominantly aspirin and clopidogrel—generally increase bleeding with, at best, a modest effect reducing ischemic end points in ACS patients (Figure 2).

However, there was a lack of uniformity in the definition of bleeding among the reported trials, making indirect comparisons of relative bleeding with different agents challenging. The definition of bleeding events has variably included laboratory parameters, such as decrease in hemoglobin, and clinical events, including the need for transfusion, surgery, cardiac tamponade, and hematoma. Standardization of bleeding reports using the BARC (Bleeding Academic

Research Consortium) system would have been highly desirable but was not available at the time of some of these studies.[33] Although it remains clear, regardless of the definitions used, that TT significantly increases the risk of bleeding compared with DAPT, the lack of uniformity in bleeding definition coupled with the lack of direct head-to-head comparisons of TT combinations makes it impossible to compare bleeding risk with different strategies.

There has also been heterogeneity in the definition of primary efficacy outcomes. Although some studies included only "hard" clinical end points of major adverse cardiovascular events, others included more "soft" end points such as revascularization or hospitalization. Some included ischemic strokes only, and others included all strokes.

Overall, the risk–benefit ratio suggests that it may be reasonable to justify the use of rivaroxaban in TT combination for high-risk ACS patients who are at low bleeding risk, and vorapaxar could be considered for patients with prior MI but not in the acute or subacute phase of ACS, with some restrictions.[20] Rivaroxaban and vorapaxar should not be considered as add-on therapy in combination with $P2Y_{12}$ inhibitors other than clopidogrel because data are lacking and bleeding would be expected to increase disproportionately. However, adding warfarin to DAPT appears not to be justified, as the WOEST study not only demonstrated a higher risk of bleeding with TT but also ischemic end points occurred less frequently with oral anticoagulation combined with a single antiplatelet agent.[14]

Identifying the Right Patient

The trials assessing TT studied patients with recent ACS and $\geq$1 additional risk factor. Although several risk stratification scores are available to assess the risk of recurrent ischemic events in ACS patients, such as GRACE (Global Registry of Acute Coronary Events), PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) and TIMI scores, none of these were used to identify and target those patients with ACS who were truly at high risk. Platelet function tests can also identify patients on clopidogrel at increased risk of MI, stent thrombosis, and cardiovascular death.[34,35] However, altering pharmacotherapy based on the results of platelet-function testing failed to reduce recurrent ischemic events in patients undergoing PCI, including for ACS,[36,37] and current guidelines do not support platelet-function testing.[15,38] Finally, patients undergoing complex PCI (defined as the composite of at least 3 stents implanted, at least 3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, and chronic total occlusion as target lesion)[38,39] or prior stent thrombosis are clearly at increased risk of thrombosis,[38] and although consideration may be given to longer total duration of DAPT treatment in these patients, the option of TT has not been specifically evaluated. The increased risk of bleeding is a significant concern with more effective antithrombotic agent combinations. Some of this excess bleeding could perhaps potentially be mitigated, at least in part, by careful bleeding risk assessment and use of gastric protection. Because the predominant source of bleeding is gastrointestinal, mandating the use of gastric protection with a proton pump inhibitor would seem pragmatic[22] but was not routinely done in any study. The new 2017 ESC guidelines now clearly recommend the routine use of a proton pump inhibitor for patients taking DAPT, as level of evidence class I, level B,[38] whereas the ACC/AHA 2016 guidelines recommend that "in patients with increased risk of gastrointestinal bleeding, including those with advanced age and those with concomitant use of warfarin, steroids, or nonsteroidal anti-inflammatory drugs, use of PPIs [proton pump inhibitors] is reasonable (Class IIa)".[15]

In addition, avoiding more potent antiplatelet therapies in patients with prior gastrointestinal bleed or intracranial hemorrhage also seems prudent, and such patients were excluded from most recent trials. Risk scores are available and may be considered to identify patients at high bleeding risk.[38] The PRECISE-DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy)[40] or PARIS (Patterns of Nonadherence to Antiplatelet Regimen in Stented Patients)[41] scores in patients receiving coronary stents and treated with DAPT have been shown to be predictive of bleeding, but prospective validation in randomized controlled trials is lacking.[38] Other risk scores for bleeding can be helpful, including HASBLED (Hypertension, Abnormal liver/renal function, Stroke history, Bleeding predisposition, Labile international normalized ratio, Elderly, Drug/alcohol usage),[42] validated predominantly in patients with atrial fibrillation taking warfarin, or CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) scores in ACS patients undergoing coronary angiography.[43,44] There is clearly a need to identify circulating biomarkers that reflect platelet, inflammatory, coagulation, and endothelial function that identify patients at risk of bleeding and thrombosis and to incorporate those markers into trials for prospective validation.

Identifying the Right Drug Combination

The control arms in the reported trials, against which TT was compared, have mostly included patients receiving a combination of aspirin and clopidogrel,[21–23,28–31,45] but current guidelines recommend ticagrelor or prasugrel over clopidogrel in ACS.[15,20,26,38] Consequently, any new combination regimen should be compared with "current best." The combination of a non–vitamin K oral anticoagulant with DAPT that includes these more effective $P2Y_{12}$ inhibitors may increase bleeding

compared with clopidogrel, but this has never been tested. Furthermore, the efficacy and safety profile of DAPT including ticagrelor or prasugrel versus TT remains unknown.

Studies to date have shown modest absolute reduction in ischemic end points when DAPT was combined with oral anticoagulants, offset by increased bleeding. In the current era of combined antithrombotic and antiplatelet therapy, it remains unclear whether there is still a need for conventional treatment with aspirin and whether this can be replaced by more advanced combination therapy.[46] Two recent trials aiming to show the superiority of ticagrelor compared with aspirin or clopidogrel as single antiplatelet therapy in the setting of recent stroke (6.7% versus 7.5%; 95% CI, 0.78–1.01; P=0.07)[47] and peripheral arterial disease (10.8% versus 10.6%; 95% CI, 0.92–1.13; P=0.65),[48] respectively, did not show a statistical difference. Despite the clear superiority of ticagrelor over clopidogrel exhibited in PLATO (Platelet Inhibition and Patient Outcomes),[49] in the acute setting, results from the recent CHANGE DAPT (Change of Dual Antiplatelet Therapy in Patients With Acute Coronary Syndrome) trial have reinitiated the argument about the preferred antiplatelet therapy in the era of the new drug-eluting stents with thinner struts, mitigating against stent thrombosis.[50]

The duration of the preferred antithrombotic regimen is another important aspect of choosing the right regimen for the right patient, for whom prolonged treatment with DAPT reduces ischemic end points at the cost of increased bleeding, as exhibited in the PEGASUS TIMI-54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54)[51] study. The 2017 ESC guideline states that prolonged duration of DAPT may be considered for patients at high thrombotic risk, such as those undergoing complex PCI or those implanted with a bioresorbable vascular scaffold,[38] and particularly for those who have tolerated DAPT without a bleeding complication.[38]

The ongoing open-label trial GLOBAL LEADERS (Comparative Effectiveness of 1 Month of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy Versus a Current-Day Intensive Dual Antiplatelet Therapy in All-Comers Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and BioMatrix Family Drug-Eluting Stent Use) aims to assess the role of ticagrelor as a single antiplatelet agent for 2 years after a 1-month course of DAPT (comprising ticagrelor and aspirin) for the long-term prevention of cardiac adverse events. The study (n>16 000) recruited all-comers undergoing PCI, both for elective and ACS indications, who all received bivalirudin and a biomatrix stent.[52]

Patients were then randomized to ticagrelor 90 mg BID for 24 months plus aspirin for 1 month versus DAPT with either ticagrelor or clopidogrel for 12 months plus aspirin for 24 months. The primary outcome is a composite of all-cause mortality or nonfatal MI, and the safety end point is major bleeding.

Finally, edoxaban, another FXa inhibitor, is being evaluated in a phase II trial, together with aspirin and clopidogrel, in ACS.[53]

Conclusions and Future Directions

In patients with recent ACS for which DAPT is the current standard of care, the use instead of TT—with the addition of an oral anticoagulant, PAR-1 antagonist, or cilostazol—has been investigated with the aim of reducing future ischemic events. Except for cilostazol, which gave neutral results in terms of safety and efficacy, TT leads to a significant increase in bleeding, and this is unacceptably high with vorapaxar and with warfarin. Rivaroxaban 2.5 mg twice daily can be considered in combination with aspirin and clopidogrel for ACS patients who have high ischemic and low bleeding risk. There is a clear signal that TT can reduce ischemic events, but the excessive bleeding seems to offset the potential benefit.

There is an absolute necessity for improved, more accurate risk stratification of patients, for both future ischemic events and bleeding, to allow targeted individualized treatment.

Future trials should focus even more stringently on identifying patients at high ischemic and low bleeding risk who may gain the most from newer antithrombotic agent combinations. In addition to risk scores in ACS such as GRACE and TIMI, angiographic features associated with recurrent thrombosis, such as diameter and length of stented segment, stent underexpansion, and completeness of revascularization, as well as circulating (bio)markers could be incorporated into risk assessment to identify patients who would gain most.

Because clinically meaningful bleeding remains a concern with more effective antithrombotic agent combinations, accurate bleeding risk stratification and perhaps mandated prophylactic use of proton pump inhibitors should be applied universally. Unfortunately, most clinical risk factors included in several bleeding scores are also risk factors for thrombosis (eg, age, hypertension, prior thromboembolism). Further validation of circulating biomarkers would be relevant to better risk stratify patients and separate bleeding and thrombosis risk. Moving away from TT, we await the results of novel combination therapies involving direct oral FXa or FIIa inhibitors and a $P2Y_{12}$ inhibitor, not only in the setting of atrial fibrillation but also in patients with ACS at high ischemic and low bleeding risk.

Disclosures

None.

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Key Words: acute coronary syndrome • anticoagulation • dual antiplatelet therapy • thrombosis