Curr Atheroscler Rep (2013) 15:318
DOI 10.1007/s11883-013-0318-8

Acute Coronary Syndromes: Advances in Antithrombotics

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Published online: 2 March 2013
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Abstract Contemporary management of acute coronary syndromes (ACS) has evolved to include rapid revascularization, potent antithrombotic, and antiplatelets, all of which reduce the risk of ischemic complications. Despite these advances, recurrent ischemic and bleeding event rates are still substantial. This increased risk post-percutaneous coronary intervention (PCI) has been the seminal event leading to recent clinical trials evaluating more potent antiplatelet drugs (prasugrel, ticagrelor, and protease-activated receptor-1 [PAR-1] inhibitors) and novel oral anticoagulants (NOAC). Ideally, an effective anticoagulation regimen adequately reduces the incidence of recurrent ischemia and limits iatrogenic bleeding. In this review, we will discuss the advances in ACS pharmacotherapy, review the recent trials evaluating these drugs, and discuss the major dilemmas in interpreting and implementing their findings.

Keywords Antithrombotics · Antiplatelets · Acute coronary syndromes · Novel oral anticoagulants · Dual antiplatelet therapy · PAR-1 inhibitors

Abbreviations

ACS	Acute coronary syndromes
ACC/AHA	American College of Cardiology / American Heart Association
ATLAS-1 ACS-TIMI 46	Rivaroxaban in Combinations with Aspirin alone or with Aspirin and a Thienopyridine in Patients with Acute Coronary Syndromes—Thrombolysis In Myocardial Infarction 46
APPRAISE	Apixaban for Prevention of Acute Ischemic and Safety Events
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
CABG	Coronary artery bypass graft
CKD	Chronic kidney disease
DAPT	Dual-antiplatelet therapy
HORIZONS-AMI	Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction
NOAC	Novel oral anticoagulants
NSTEMI	Non-ST elevated myocardial infarction
PAR-1	Protease-activated receptor-1
PCI	Percutaneous coronary intervention
PLATO	PLATelet Inhibition and Patient Outcomes
RE-DEEM	Dose-finding study for Dabigatran Etexilate in Patients with Acute Coronary syndrome
SPS3	Small subcortical strokes trial
ST	Stent thrombosis
STEMI	ST elevated myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction
TRITON-TIMI 38	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—TIMI 38

This article is part of the Topical Collection on *Coronary Heart Disease*

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TRACER	Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome
TRA-2P	Thrombin receptor Antagonist in Secondary Prevention of atherothrombotic ischemic events
UFH	Unfractionated heparin

Introduction

Acute coronary syndromes are conditions characterized by the sudden onset of coronary insufficiency as a result of thrombotic occlusion of one or more coronary arteries. Depending on the extent of coronary occlusion, ACS include stent thrombosis (ST) segment elevations myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA). STEMI is a result of complete and sustained coronary occlusion, while NSTEMI and UA are due to a transient or partial occlusion of the coronary arteries. The problem of an atherosclerotic plaque rupture with subsequent coronary thrombosis, a predominant detrimental event in ACS, has led to the adoption of several therapeutic measures designed to limit thrombus formation using either antiplatelet (COX-1, P2Y12, and GPI Ib/IIIa inhibitors) or anticoagulant (heparin, bivalirudin, and fondaparinux) therapies, or to alleviate the obstruction through fibrinolytics and primary coronary intervention (PCI). Currently, clinicians choose between three parenteral anticoagulants for STEMI patients undergoing PCI namely unfractionated heparin (UFH), enoxaparin or bivalirudin, all of which have earned a Class I recommendation in the ACC/AHA guidelines [1]. Fondaparinux, a factor Xa inhibitor, must be coadministered with an additional anticoagulant with anti-factor IIa activity due to the risk of catheter thrombosis when fondaparinux is used alone [2] (Table 1).

Despite contemporary management, every year more than half of patients who have had an ACS event will experience either a recurrent ischemic or bleeding event [3]. This increased risk of ischemic complications post-PCI has led cardiovascular pharmacotherapy to evolve to include more potent antiplatelets such as prasugrel, ticagrelor, PAR-1 inhibitors, and NOAC.

Thrombin and Platelet Hemostasis

Acute coronary syndromes are usually the result of a cascade of events triggered by a vulnerable plaque rupture and thrombosis of a coronary plaque, rather than a slow atherosclerotic process that eventually leads to coronary artery obstruction and critical arterial stenosis [4]. Platelets and thrombin are key components of hemostasis and prevent blood loss after injury. However, they are also responsible for the formation of pathological thrombi, which cause atherothrombotic disease. Following a plaque rupture, which releases thrombogenic factors, the activation of clotting factors, predominantly thrombin, initiates a cascade of events resulting in platelet activation and the formation of a platelet-rich thrombus [5]. Thrombin plays a major role in the clot development pathway by converting fibrinogen to fibrin and forming a crosslinked fibrin-rich clot. It remains enzymatically active, generates its own growth through factors V, VIII, and XI, and activates platelets via thromboxane A2 independent pathways [6]. The current standard of care, aspirin, and P2Y12 inhibitors target the thromboxane A2 and the ADP P2Y12 platelet activation pathways minimally affect other pathways, while agonists such as thrombin, considered to be the most potent platelet activator, stimulate platelet activation and thrombosis (Fig. 1). The challenge remains to develop therapies that more effectively inhibit platelet activation without increasing bleeding complications. An array of new cardiovascular medicines include NOAC, which offer a novel mechanism of action and may provide more complete thrombin inhibition, and PAR-1 inhibitors that help mitigate thrombin-mediated platelet activation.

Antiplatelets: Out With the Old and In With the New

Since the randomized phase III Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial in 2009, clopidogrel in combination aspirin has been the mainstay treatment in ACS patients [7]. Not only did clopidogrel treatment result in reducing the primary composite endpoint of death, MI, and stroke (9.3 % vs. 11.4 %; RR 0.80 95 % CI 0.72 to 0.90; $P<0.001$), but the beneficial effects were apparent from 24 hours after drug administration and persisted throughout the 12 months of the study. Since then, several limitations of clopidogrel have been elucidated including a slow onset of action, suboptimal inhibition, and interpatient variability [8, 9]. A growing concern with the standard of care is the interpatient variability of clopidogrel regarding platelet inhibition, primarily due to genetic polymorphisms that alter the pharmacokinetics of clopidogrel metabolism. To address this issue, newer antiplatelet agents have been developed, namely prasugrel and ticagrelor, which are less affected by interpatient variability and have a more rapid and potent antiplatelet effect than clopidogrel [10] (Table 2).

Prasugrel is an oral, irreversible, P2Y12 inhibitor that rapidly and predictably inhibits platelets with low interpatient variability. The benefits over clopidogrel are

Table 1 Summary of clinical trials of novel or anticoagulants and newer antiplatelets in acute coronary syndrome (ACS)

	Study	Year	Trial Characteristics	Patients (*N*)	Drugs	Primary Efficacy Endpoint	Primary Safety Endpoint
Novel Anticoagulants (NOACs)	RE-DEEM	2011	Randomized double-blind, placebo-controlled dose escalating phase II	1,864	Dabigatran (50, 75, 110 and 150 mg BID) vs. placebo plus standard ACS therapy	Composite of cardiovascular death, non-fatal myocardial infarction, and non-hemorrhagic stroke 4.6 % (50 mg) 4.9 % (75 mg), 3.0 % (110 mg), 3.5 % (150 mg) vs. 3.8 % (placebo)	Composite of major or clinically relevant minor bleeding, 50 mg (3.5 %) vs. 75 mg (4.3 %) vs. 110 mg (7.9 %) vs. 150 mg (7.8 %) vs. placebo (2.2 %), $P<0.001$
	ATLAS ACS-TIMI 46	2009	Randomized double-blind dose-escalating placebo-controlled phase II	3,491	Rivaroxaban (5–20 mg) plus aspirin alone or both aspirin and thienopyridine	Death, myocardial infarction, stroke or severe recurrent ischemia requiring revascularization 5.6 % (rivaroxaban) vs. 7.0 % (placebo)	Clinically significant bleeding (TIMI major, TIMI minor or requiring medical attention)
	ATLAS ACS-TIMI 51	2012	Randomized double-blind placebo-controlled phase III	15,526	Rivaroxaban (2.5 or 5 mg BID) plus aspirin alone or both aspirin and thienopyridine	Composite of cardiovascular death, myocardial infarction or stroke (ischemic, hemorrhagic or stroke of uncertain cause), 8.9 (rivaroxaban) vs. 10.7 %, $P=0.008$	TIMI major bleeding not related to CABG, 2.5 mg (2.1 %) vs. 5 mg (0.6 %), $P<0.001$
	APPRAISE-2	2012	Randomized double-blind placebo-controlled phase III	7,392	Apixaban 5 mg BID vs. placebo plus standard ACS theraphy	Composite of cardiovascular death, myocardial infarction or stroke, 7.5 % apixaban vs. 7.9 % placebo, $P=0.51$	TIMI major bleeding, 5 mg (1.3 %) vs. placebo (0.5 %), $P<0.001$
Antiplatelets	TRITON	2007	Randomized double-blind placebo-controlled	13,608	Prasugrel 10 mg (60 mg loading dose) vs. clopidogrel 75 mg (300 mg loading)	Cardiac death, MI, CVA prasugrel 9.9 %, clopidogrel 12.1 %, $P<0.001$	Non-CABG-related major bleeding, prasugrel 2.4 % vs. clopidogrel 1.8 %, $P=0.03$
	PLATO	2009	Randomized double-blind placebo-controlled	18,624	Ticagrelor 90 mg bid (180 loading) vs. clopidogrel 75 mg (300–600 mg loading)	Vascular death, MI, CVA ticagrelor 9.8 % vs. clopidogrel 11.7 %, $P<0.001$	Major bleeding (PLATO criteria), ticagrelor 11.6 % vs. clopidogrel 11.2 %, $P=0.43$
	CURRENT-OASIS 7	2010	Randomized double-blind placebo-controlled	25,085	Clopidogrel double dose (600 mg loading 150 mg/day 2–7, then 75 mg) vs. standard dose 75 mg (150 mg loading)	Cardiac death, MI, CVA (at 30 days) double 4.2 % vs. standard 4.4 %, $P<0.30$	Major bleeding (CURRENT criteria), double 1.6 % vs. standard 1.1 %, $P=0.009$
PAR-1 Inhibitors	TRACER	2011	Randomized double-blind placebo-controlled	12,944	Vorapaxar (loading 40 mg, maintenance 2.5 mg daily) or placebo	Cardiac death, MI, stroke, and recurrent ischemic with hospitalization or urgent revascularization, vorapaxar 14.7 % vs. 16.4 %, $P=0.02$	Moderate to severe bleeding, vorapaxar 7.2 % vs. 5.2 %, Intracranial hemorrhage 1.1 % vs. 0.2 %, $P<0.001$
	TA-2P	2012	Randomized double-blind placebo-controlled	26,449	Vorapaxar (2.5 mg daily) or placebo	Cardiac death, recurrent MI, stroke or urgent revascularization, vorapaxar 11.2 % vs. 12.4 %, $P=0.001$	Moderate or severe bleeding, vorapaxar 4.2 % vs. 2.5 %, $P<0.001$

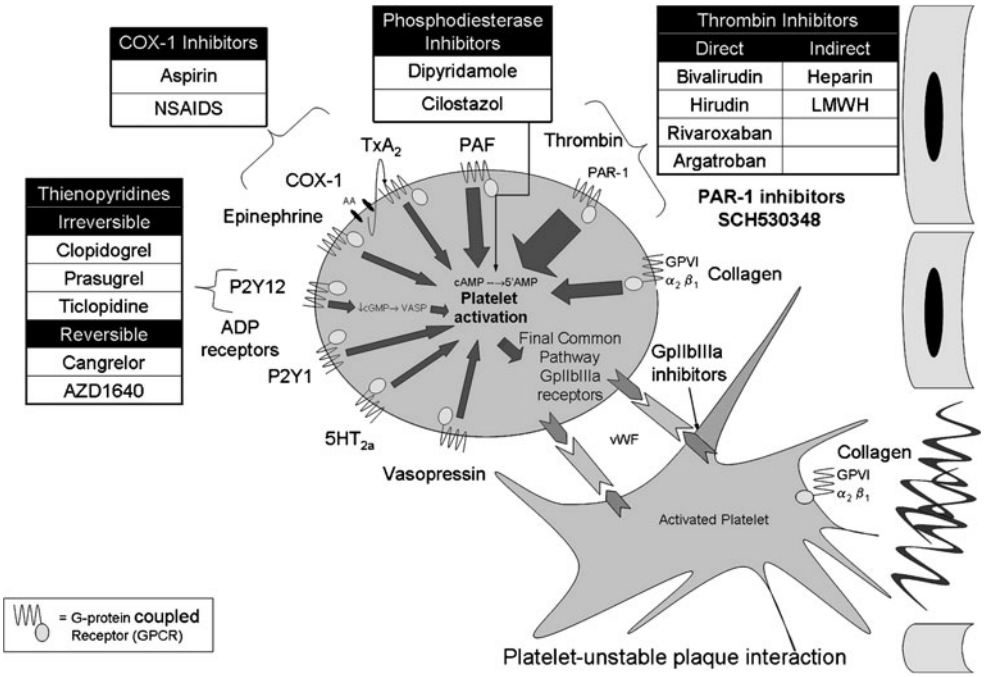

Fig. 1 Mechanisms of platelet activation. [38] Reprinted with permission from Gladding, P., et al., *Antiplatelet drug nonresponsiveness.* Am Heart J, 2008. 155(4): p. 591–9

thought to be due to its optimal bioavailability profile allowing the drug to be less affected by genetic polymorphisms that limit the function of clopidogrel [11•, 12]. The safety and efficacy of prasugrel (60 mg loading dose, 10 mg maintenance dose) versus clopidogrel (300 mg loading dose, 75 mg maintenance dose) in ACS patients undergoing PCI was evaluated in the phase III TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—TIMI 38) trial [13]. The primary endpoint of a composite of cardiovascular death, MI or stroke was decreased in patients pretreated with prasugrel (9.9 % vs. 12.1 %; $P<0.001$), mostly driven by the decrease in non-fatal MI (7.4 % vs. 9.7 %, $P<0.001$). However, these benefits came at the price of increased life threatening (1.4 % vs. 0.89 %, $P=0.01$) and fatal bleeding (0.4 % vs. 0.1 %, $P=0.02$). Further subanalysis demonstrated an increased benefit in patients with STEMI [14] and an excess risk of bleeding in patients with a history of stroke, transient ischemic attack or age ≥75 years or body weight < 60 kg which has earned prasugrel a "black box" warning [15].

Similarly, ticagrelor is a reversible P2Y12 receptor antagonist that is quickly absorbed and has a more pronounced inhibition on platelet aggregation than clopidogrel. Ticagrelor potency has also been shown to be less affected by interpatient variability, a major limitation of clopidogrel [11•]. In the double-blind phase III PLATO (PLATelet Inhibition and Patient Outcomes) trial, ticagrelor (180 mg loading dose, 90 mg twice daily maintenance dose) was compared to clopidogrel (300–600 mg loading dose, 75 mg maintenance dose) in 18,624 patients with ACS [16••]. The primary composite endpoint of death form vascular causes, MI or stroke at 12 months occurred in 9.8 % of ticagrelor patients compared with 11.7 % of those on clopidogrel (HR 0.84 95 % CI 0.77-0.92, $P<0.001$). There were no significant differences in the primary safety endpoint of major, fatal or life threatening bleeding. However, there was a significant increase in non-CABG-related (4.5 % vs. 3.8 %, $P=0.03$) and fatal intracranial bleeding (0.12 vs. 0.03, $P=0.02$) in patients treated with ticagrelor. Thus, this agent may not be appropriate for patients at high risk of bleeding. Conversely, ticagrelor demonstrated superiority over clopidogrel in subsets of patients with positive troponins [17], CKD [18], and patients undergoing CABG postrandomization [19].

The recurrence of ischemic events in ACS patients despite treatment with DAPT has led to the hypothesis that blocking PAR-1 may lead to greater platelet inhibition mediated by thrombin receptor inhibition. Vorapaxar, a novel PAR-1 antagonist, was evaluated in Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER), a multinational, double-blind, randomized trial. Vorapaxar was compared against placebo in 12,944 patients with NSTEMI receiving standard therapy. The primary endpoint was a composite of cardiovascular death, MI, stroke, and recurrent ischemia with hospitalization or urgent coronary revascularization [20]. While there was no significant reduction in the primary efficacy endpoint in patients randomized to vorapaxar plus standard therapy, rates of moderate and severe bleeding and intracranial hemorrhage were significantly greater in these patients. The study was prematurely terminated due to safety concerns. Similarly, in the phase III, placebo-controlled Thrombin receptor Antagonist in

Table 2 Current guidelines antithrombotics in acute coronary syndrome (ACS)

Source	2012 ACCF/AHA/SCAI	2011 ESC
Antiplatelet Recommendations	I. Aspirin as soon as possible after hospital presentation (early invasive or initial conservative [LOE=A])	I. Aspirin 150–300 mg initial dose, then 75–100 mg daily
	II. Before PCI: clopidogrel (LOE=B), ticagrelor (LOE=B) or GPI (LOE=B)	II. P2Y12 inhibitor in addition to aspirin as soon as possible and maintained over 12 months unless contraindicated
	III. At the time of PCI: clopidogrel (LOE=A), prasugrel (LOE=B), ticagrelor (LOE=B) or GPI ticagrelor (LOE=A)	III. Ticagrelor (180 mg loading dose, 90 mg BID) for all patients at moderate-to-high risk ischemic events (eg. elevated troponins), regardless of initial treatment strategy
	IV. Noninvasive: clopidogrelor ticagrelor added to aspirin and continued for up to 12 months (LOE=B). Longer duration of clopidogrel, ticagrelor prasugrel beyond 12 months can be considered in those with DES (LOE=C)	IV. Prasugrel (60 mg loading dose, 10 mg daily dose) for P2Y12 inhibitor naive patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI (unless high risk)
		V. Clopidogrel 600 mg loading dose (or supplemental 300 mg dose at time of PCI) for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option
Antithromotic Recommendations	I. An anticoagulant should be administered to patients undergoing PCI (LOE=C)	I. Discontinuation of anticoagulation should be considered after an invasive procedure unless otherwise indicated (LOE=C)
	II. Unfractionated heparin: dosing based on whether or not GPI was administered (LOE=C)	II. Fondaparinux is the most favorable (LOE=A)
	III. Bivalirudin: lower bleeding rates associated with bivalirudin are mitigated when used concomitantly with GPI (LOE=B)	III. Enoxaparin is recommended when fondaparinux is not available (LOE=B)
	IV. Enoxaparin: Administer IV at the time of PCI for those who have not received prior antithrombin therapy or who have received "upstream" SC enoxaparin (LOE=B)	IV. If fondaparinux or enoxaparin are not available, UFH with a target aPTT or other LMWHs are indicated (LOE=C)
	V. Fondaparinux: PCI should not be performed with fondaparinux as the sole antithrombin agent in patients treated with upstream fondaparinux. An additional anti II-a should be administered (LOE=C Harm)	V. Bivalirudin plus provisional GPI are recommended as an alternative to UFH plus GPI (LOE=B)

aPTT activated partial thromoboplastin time, *DES* drug-eluting stent, *GPI* glycoprotein inhibitor, *LMWH* low molecular weight heparin, *LOE* level of evidence, *PCI* percutaneous coronary intervention, *UFH* unfractionated heparin

Secondary Prevention of atherothrombotic ischemic events (TRA-2P) trial, 26,449 patients with established atherosclerotic disease were evaluated for the safety and efficacy of vorapaxar with standard therapy [21]. The primary endpoint of cardiovascular death, recurrent MI, stroke or urgent revascularization was not significantly reduced, but there was a significant increase in bleeding including intracranial hemorrhage among patients with a history of stroke who were treated with vorapaxar [22].

NOAC: New Players on the Frontline of Antithrombotic Therapy

Historically, heparin has dominated the intravenous antithrombotic therapy in ACS patients, due to superior results when compared to aspirin therapy alone. However, several drawbacks have hindered its use in the management of ACS patients' including dose-dependent platelet aggregation, increased coagulation factors, and decreased antithrombin levels through the rebound effect, and heparin-induced thrombocytopenia. In light of these disadvantages, bivalirudin, a direct thrombin inhibitor, has become a in the favored treatment for ACS management. Among bivalirudin therapy's many advantages, it also reduces platelet aggregation after PCI and decreases monocyte activation after PCI, which may reduce the proinflammatory cytokine release that occurs in STEMI, in contrast to UFH. However, one of the major limitations of bivalirudin is the higher rate of acute stent thrombosis (ST) that can occur within 24 hours, as shown in the HORIZONS-AMI trial.

Despite attempts to develop safer and more predictable drugs, the safety and efficacy of NOAC has only recently been evaluated in phase II and III trials, including RE-DEEM (Dose Finding study for Dabigatran Etexilate in Patients with Acute Coronary syndrome) [23], ATLAS-1 ACS-TIMI 4 (Rivaroxaban in Combinations with Aspirin alone or with Aspirin and a Thienopyridine in Patients with Acute Coronary Syndromes – Thrombolysis In Myocardial Infarction 46), [24] and APPRAISE (Apixaban for Prevention of Acute Ischemic and Safety Events) [25] (Table 1). These agents were greatly anticipated after positive phase III trial results were obtained that included data indicating

fewer food and drug interactions, a more rapid and predictable onset of anticoagulant effect, a wider therapeutic window, and most importantly, standardized daily dosing that abolished the need for routine monitoring.

Dabigatran is a reversible, direct inhibitor of free and fibrin bound thrombin and thrombin-induced platelet aggregation. It has a bioavailability of 6.5 % and a half-life of 12–14 hours, regardless of dose, making regular anticoagulant monitoring unnecessary [26]. Dabigatran has undergone phase II and III trials for the prevention of thromboembolism in patients undergoing hip or knee arthroplasty [27, 28] and phase II trials for the prevention of stroke in AF patients [29], and is now approved for all three indications . RE-DEEM was a phase II double-blind placebo-controlled trial that evaluated the safety and efficacy of dabigatran as an add-on therapy in patients with a recent ACS already receiving DAPT who were at high risk of recurrent cardiovasular events [23]. In this trial, 1,861 patients were randomized to four regimens of increasing doses of dabigatran (50, 75, 110, and 150 mg twice daily). Although underpowered for efficacy, the primary efficacy endpoint, a composite of cardiovascular death, non-fatal MI or non-hemorrhagic stroke were reduced in both higher dose groups compared to lower doses (4.6 % vs. 4.9 % vs. 3.0 % vs. 3.5 % with increasing doses of dabigatran and 3.8 % for placebo). There was a dose dependent increase in clinically relevant bleeding with either 110 mg or 150 mg twice daily when given with DAPT. Gastrointestinal bleeding and epistaxis were the most common bleeding events.

The most promising NOAC, is rivaroxaban, a reversible, direct inhibitor of both free and platelet-bound Xa, making it much more potent than the indirect Xa inhibitors. It has an oral bioavailability of 80-100 % and a half-life of 7–11 hours. Similar to dabigatran, rivaroxiaban is renally excreted and should be used with caution in patients with severe renal impairment [30]. Currently, rivaroxaban is approved for the use of thromboprophylaxsis in nonvaluvular AF. In the phase II double-blind trial, ATLAS ACS TIMI 46 randomized 3,491 patients with a recent ACS to increasing doses of rivaroxaban or placebo in patients taking either aspirin alone (n=761, stratum 1) or combined aspirin and a thienopyridine (n=2,730, stratum 2) [24]. The primary safety endpoint of clinically significant bleeding was increased with rivaroxaban compared with placebo in a dose-dependant manner (HR 2.21 vs. 3.35 vs. 13.6 vs. 5.06 with increasing doses of rivaroxaban, $P<0.0001$). Rates of the primary efficacy endpoints of death, myocardial infarction, stroke, or severe recurrent ischemia requiring revascularisation were lower with rivaroxaban versus placebo (5.6 % vs. 7.0 %, HR 0.79 [95 % CI0.60–1.05], $P=0.10$). Similarily, rivaroxaban reduced the main secondary efficacy endpoint of death, myocardial infarction, or stroke compared with placebo (3.9 % vs. 5.5 %; HR 0.69, [95 % CI 0.50–0.96], $P=0.0270$). While rivaroxaban treatment reduced major ischemic outcomes, an increased rate of bleeding was seen in a dose dependent manner. This led to a phase III study of low-dose rivaroxaban as adjunctive therapy in an ACS population, to determine whether rivaroxaban treatment may reduce ischemic outcomes in addition to standard of care.

In the phase III Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 50 (ATLAS ACS 2-TIMI 51) trial, 15,536 patients were randomized to three arms: placebo, rivaroxaban 2.5 mg or 5 mg twice daily in addition to standard care [31]. Similarly, as in the ATLAS ACS TIMI 46 trial, patients were stratified into either a rivaroxaban plus aspirin alone (stratum 1) or a theinopyridine and aspirin (stratum 2) group. Both doses of rivaroxaban decreased the primary efficacy endpoint of cardiovascular death, MI or stroke compared to placebo (9.1 % and 8.8 % for low and high dose of rivaroxaban, respectively versus 10.7 for placebo, $P=0.02$, 0.03) at 13 months post-PCI. The lower twice daily 2.5 mg dose decreased all-cause (2.9 % vs. 4.5 %, $P=0.002$) and cardiovascualar (2.7 % vs. 4.1 %, $P=0.002$) mortality, while the higher twice daily 5 mg dose reduced the rate of MI compared with placebo. However, rivaroxaban treated patients at either dose experienced more TIMI major bleeding (2.1 % vs. 0.6 %, $P<0.001$) and intracranial hemorrhage (0.6 % vs. 0.2 %, $P=0.009$) than controls but without a significant increase in fatal bleeding (0.3 % vs. 0.2 %, $P=0.66$).

Apixaban is an oral reversible factor Xa inhibitor that is rapidly absorbed and excreted by the hepatobilliary system. However, it does not induce or inhibit cytochrome P450 machinery. It has a bioavailabiltiy of 50 % and a half-life of 10–14 hours [32, 33]. In the phase II, double-blind APPRAISE trial, 1,715 patients were randomized to increasing doses of apixaban ranging from 2.5 mg twice daily to 20 mg once daily. The majority of the patient population (76 %) were on DAPT. The primary outcome of major or clinically relevant nonmajor bleeding was increased in apixaban 2.5 mg twice daily and 10 mg daily compared with placebo (HR 0.73, $P=0.21$). There was a nonsignificant trend towards a decrease in the main efficacy outcome, a composite of cardiovascular death, severe reccurent ischemia or ischemic stroke. This study suggested a potential beneficial effect in ACS patients, which resulted in the subsequent APPRAISE-2 trial. The trial evaluated 10 mg (5 mg bid) apixaban in high risk ACS patients with ≥ 2 risk factors. The primary safety outcome of major bleeding was increased in the apixaban group (1.3 % vs. 0.5 %, $P<0.001$), while there was no significant difference in the rates of cardiovascular death, MI or ischemic stroke between the two groups (7.5 vs. 7.9, $P=0.51$). Consequently, the study was prematurely terminated due to the apparent lack of benefits compared to an increasing bleeding risk.

Future Directions: What's Missing?

In a recent meta-analysis of 31,286 ACS patients from seven heterogeneous trials, Komocsi et al. showed NOAC therapy was associated with an astonishing three-fold increased risk for major bleeding [34••]. However, there was no difference in the net beneficial clinical outcomes, which was a composite of major ischemic events (MI, death, ischemic stroke, or severe recurrent ischemia) and TIMI defined major bleeding between NOAC and placebo (OR 0.98 95 % CI 0.90–1.06). Notably, there was a significant reduction in the risk for definite or probable stent thrombosis without a significant increase in overall mortality. Thus, it can be concluded that the moderate benefits of routine NOAC for ACS are superseded by the substantially increased bleeding risk. However, the most recent studies have focused on clopidogrel, while the P2Y12 inhibitors prasugrel and ticagrelor have not been tested with the NOAC, though they are increasingly used in place of clopidogrel as first line agents. Both P2Y12 inhibitors were associated with reduced ischemic events compared to clopidogrel, though associated with a minor increase in bleeding risk. Determining the optimal antithrombotic regimen for patients undergoing PCI requires factorial testing that addresses the increasing number of available antiplatelet option. Although clinical trials have aptly compared NOAC with warfarin, no studies inform the decision of which NOAC to select for a given patient. With the lack of comparative effectiveness studies, comparisons across trials are inherently flawed with varying degrees of population characteristics, trial design and definitions of efficacy and safety endpoints [35]. This makes it difficult to comprehensively evaluate the benefits of one drug regimen versus another (Table 1.)

The results of the APPRAISE-2 trial raised doubt about whether meaningful incremental efficacy can be achieved with an acceptable risk of bleeding by combining a long-term oral anticoagulant with both aspirin and a P2Y12-receptor antagonist in patients with coronary disease. However, in APPRAISE 2 of high-risk patients, patients with prior stoke or TIA were not excluded, and it is well known that these patients have an increased likelihood to bleed with DAPT therapy, let alone triple antithrombotic therapy. The current recommendations on the use of DAPT in patients with stroke are: Combination therapy of aspirin and clopidogrel is not routinely recommended for ischemic stroke or TIA patients unless they have a specific indication for this therapy. The results of the secondary prevention of small subcortical strokes trial (SPS3) demonstrated that patients assigned to combination treatment had more death from all causes, 5.8 % vs. 4.1 % (P=0.04), compared with those receiving aspirin alone [36]. These results support the current guidelines that recommend against the use of the combination of clopidogrel plus aspirin for secondary stroke prevention, and now extend this advice to those with recent small subcortical strokes or lacunar infarcts that have been confirmed by MRI. Moreover, the effects of NOAC in combination with modern DAPT therapy among certain types of ACS (STEMI, NSTEMI or UA) or ACS with indications for additional anticoagulation (e.g. atrial fibrillation (AF), mitral stenosis, cancer) is still unknown [37•]. Further trials should be conducted to evaluate the effects of NOAC in this subset of ACS patients

Conclusion

While clopidogrel and heparin have undoubtedly revolutionized the management of ACS, their inherent pharmacokinetic limitations have led to the development and testing of newer agents in several large randomized-controlled trials. These new agents have a more predictable pharmacological profile, a lower bleeding risk, lower rates of interpatient variability, and because routine monitoring is not necessary, may facilitate better patient adherence to clinical guidelines. Meta-analyses have only provided indirect comparisons; thus, direct comparative trials are required to comprehensively evaluate the benefits of one drug regimen versus another in ACS patients. Additional trials to evaluate the effects NOAC and newer P2Y12 inhibitors in ACS are essential to understand the components of an optimal antithrombotic regimen and further our collective goal as interventionalists to provide maximal reduction in recurrent ischemic complications while minimizing the risk of bleeding.

Acknowledgements The authors would like to thank Dr. Deb Aronson for editorial assistance.

Conflicts of Interest Nilusha Gukathasan declares no conflicts of interest.

Roxana Mehran has consulted for Abbott Vascular, Astra Zeneca, Janssen (J+J), Regado Biosciences, The Medicines Company, BMS/Sanofi, and Merck, and has grants/grants pending with The Medicines Company, BMS/Sanofi, and Lilly/DSI.

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