Pharmacotherapy in the cardiac catheterization laboratory: evolution and recent developments

Abstract: Many recent innovations have been made in developing new antiplatelet and anticoagulant drugs in the last few years, with a total of nine new antithrombotic drugs approved by the Food and Drug Administration after the year 2000. This has revolutionized the medical therapy given to manage acute coronary syndrome and support cardiac catheterization. The concept of dual antiplatelet therapy has been emphasized, and clopidogrel has emerged as the most-popular second antiplatelet drug after aspirin. Newer P2Y12 inhibitors like prasugrel and ticagrelor have been extensively studied and compared to clopidogrel. The role of glycoprotein (Gp) IIb/IIIa inhibitors is being redefined. Other alternatives to unfractionated heparin have become available, of which enoxaparin and bivalirudin have been studied the most. Apart from these, many more drugs with novel therapeutic targets are being studied and are currently under development. In this review, current evidence on these drugs is presented and analyzed in a way that would facilitate decision making for the clinician. For this analysis, various high-impact clinical trials, pharmacological studies, meta-analyses, and reviews were accessed through the MEDLINE database. Adopting a unique interdisciplinary approach, an attempt has been made to integrate pharmacological and clinical evidence to better understand and appreciate the pros and cons of each of these classes of drugs.

Keywords: acute coronary syndrome, anticoagulants, antiplatelets, percutaneous coronary intervention

Introduction

The pharmacology of hemostasis and thrombosis has been rapidly evolving, with six new drugs approved by the Food and Drug Administration (FDA) after 2009. The evolution of antithrombotic drugs has been gradual in the 20th century, with aspirin, unfractionated heparin (UFH), and warfarin being the only ones available for the most part of the century. The last decade of the century saw some brisk developments with the introduction of thienopyridines (ticlopidine in 1991 and clopidogrel in 1997) and low-molecular-weight heparins (LMWHs) (enoxaparin in 1993 and dalteparin in 1994). Toward the end of the decade, the glycoprotein (Gp) IIb/IIIa inhibitors were introduced. The dawn of the 21st century marked an explosion of new discoveries with drugs like synthetic pentasaccharides (fondaparinux), direct thrombin inhibitors, and direct Xa inhibitors. These drugs are listed in Table 1.

With this wide selection of therapeutic options at our disposal, it is only natural to expect that a lot of research has been done in defining and contrasting the safety and efficacy profiles of these drugs. This discussion focuses on analyzing the various therapeutic options currently available to support percutaneous coronary intervention (PCI) and for managing acute coronary syndrome (ACS). The latest American College of Cardiology Foundation/American Heart Association (ACC/AHA) guidelines have
been referred to for the purpose of the discussion (unless otherwise specified).2

Methods

The MEDLINE database was primarily explored via PubMed to search and access clinical trials, studies, meta-analyses, and reviews relevant to our discussion. The registry ClinicalTrials.gov was also referred to while analyzing the various clinical trials.

Since the discussion is broad-based, no uniform inclusion/exclusion criteria were defined in selecting the studies to be included in this review. An attempt has been made to select studies with the highest impact in terms of their reputation as well as their general influence on the trends in interventional pharmacology. A total of 30 clinical trials have been discussed and/or mentioned in this review. No original meta-analysis has been performed in this review. Any caveat, potential bias, or limitation, if present, has been mentioned along with the discussion of the individual studies.

Overview of the pharmacology of currently available drugs

Antiplatelets and anticoagulants affect the two main limbs of hemostasis: platelet reactivity and the coagulation cascade. Platelets and clotting factors form an interdependent, intricately interlinked, and almost sequential effector mechanism of hemostasis. Platelet adhesion, activation, and aggregation are the seminal steps of hemostasis. Although the coagulation cascade develops on a scaffolding of the platelet plug, platelet activation and aggregation are strongly facilitated by clotting factors: most prominently thrombin. Thrombin is a protein with multiple physiological roles involving various systems. This exemplifies the fact that multiple physiological pathways including the coagulation cascade, fibrinolytic pathway, kinin pathway, and the complement pathway are all interlinked.

Arterial and venous thrombi have traditionally been considered to be unique in terms of pathophysiology and clot content. Arterial thrombi are formed secondary to some form of endothelial dysfunction (eg, atherosclerotic plaque) in an environment where the shear stress is high. Such an environment leads to the formation of a platelet-rich clot with minimal activation of the coagulation cascade: sometimes referred to as the white thrombus. On the other hand, venous clots form in undamaged veins where the blood flow and shear stress are low. This allows adequate activation of the coagulation cascade that causes entrapment of red blood cells in the mesh, thereby forming a fibrin and red-cell rich red thrombus.3

Based on this background, it is easy to comprehend why antiplatelet therapy is predominantly used to prevent arterial thrombosis (eg, ACS) and not venous thrombosis (eg, deep venous thrombosis). However, these distinctions are not at all absolute, and experimental evidence supports the use of
adjunctive antiplatelet therapy for the management of venous thrombosis, thereby reinforcing the importance of undeniable crosstalk between the two systems.⁴

Each of these classes of drugs exploits a unique step in the normal hemostatic processes, which is illustrated in Figures 1 and 2. Other special characteristics of the pharmacology of individual drugs are discussed in the respective sections.

**Current literature on the new drugs**

Extensive research has been done to test the efficacy and safety profiles of the newer drugs and compare them with the current standard of treatment. The current understanding of the various characteristics of the available drugs and some of the pressing issues in interventional pharmacology is being discussed.

Although the role of aspirin in ACS is paramount and a class I indication as per the current guidelines, the choice of second antiplatelet drug after aspirin has been evolving. P2Y₁₂ inhibitors are a diverse class of drugs comprising thienopyridines (clopidogrel and prasugrel) and ticagrelor. A P2Y₁₂ inhibitor is given along with aspirin for the acute management of ACS as well as for maintenance therapy post-PCI, to provide a more complete antiplatelet effect.

**Clopidogrel: optimum loading dose**

Various trials have shown the benefit of adding clopidogrel to aspirin in ACS patients, and it has emerged as the most

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**Figure 1** An overview of the mechanism of action of antiplatelet drugs, showing their effects on various steps of platelet activation and aggregation. **Abbreviations:** AA, arachidonic acid; ADP, adenosine diphosphate; COX, cyclooxygenase; GPib, glycoprotein ib; GPib–IIia, glycoprotein iib/iiia; PAR-1, platelet-activated receptor 1; PGG₂, prostaglandin G2; PGH₂, prostaglandin H2; TXA₂, thromboxane A2.
common choice for the second antiplatelet agent after myocardial infarction (MI) or stroke at 30 days was similar. Many studies have been done to determine the optimum loading dose of clopidogrel for patients undergoing PCI. The most prominent among these was the CURRENT-OASIS trial enrolling ACS patients planned to undergo PCI. The incidence of primary outcomes (cardiovascular death, non-fatal MI, or stroke) at 30 days was lower with double-dose clopidogrel (3.9%) versus standard-dose groups (4.5%; hazard ratio [HR] = 0.86; 95% confidence interval [CI]: 0.73–1.02). Studies have shown that a loading dose of 600 mg of clopidogrel was significantly better than a loading dose of 300 mg in terms of antiplatelet efficacy.

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HR = 0.85; 95% CI: 0.74–0.99; \( P = 0.39 \). Post hoc analysis revealed a reduction in definite stent thrombosis (ST) in the double-dose group (1.6% versus 2.3%; HR = 0.68; 95% CI: 0.55–0.85; \( P < 0.001 \)). Incidence of major bleeding was slightly higher in the double-dose group (2.5% versus 2.0%; HR = 1.24; 95% CI: 1.05–1.46; \( P = 0.01 \)). Overall, the results were not entirely conclusive.

However, there have been other trials and meta-analyses done to address this issue, and double-dose regimen has invariably been proven to be superior.\(^5\)\(^9\) Siller-Matula et al performed a meta-analysis studying the efficacy of the two clopidogrel doses in patients undergoing PCI, at 1 month after start of therapy.\(^10\) It showed a 34% relative risk (RR) reduction of major adverse cardiac events (MACE) in the double-dose group (RR = 0.66; 95% CI: 0.52–0.84; \( P < 0.001 \)) with no increase in risk of major bleeding in the group (RR = 0.91; 95% CI: 0.73–1.15; \( P = 0.44 \)).

von Beckerath et al in their pharmacological study enrolling 60 patients studied three different doses of clopidogrel: 300 mg, 600 mg, and 900 mg.\(^11\) Compared to 300 mg, the 600 mg dose was shown to achieve a higher plasma concentration (\( P \leq 0.03 \)) and an enhanced inhibition of adenosine diphosphate (ADP)-induced platelet aggregation 4 hours after drug administration (\( P = 0.01 \) and \( P = 0.004 \) for 5 and 20 \( \mu \)mol/L ADP, respectively). However, intestinal absorption was proposed to act as a bottleneck in doses higher than 600 mg. The 900 mg dosing failed to increase plasma concentration (\( P \geq 0.38 \)) or inhibit ADP-induced platelet aggregation 4 hours after drug administration (\( P = 0.59 \) and \( P = 0.39 \) for 5 and 20 \( \mu \)mol/L ADP, respectively).

In a later study with a larger sample size (N = 103) called the ALBION trial, Montalescot et al studied the pharmacology of different clopidogrel doses up to 24 hours after administration.\(^12\) They noted a uniform increment in the efficacy of higher doses (600 mg and 900 mg) of clopidogrel compared to the standard dose (300 mg). Thus, when compared to 600 mg, the 900 mg dose was found to have a superior pharmacology. Higher doses had a faster onset as well as a greater maximal inhibition of platelet activity. The rates of hypo-responders were also decreased proportionately with higher doses (\( P = 0.20 \) and \( P = 0.007 \) for 5 and 20 \( \mu \)mol/L ADP, respectively).

### Clopidogrel versus newer P2Y\(_{12}\) inhibitors

Two new P2Y\(_{12}\) inhibitors have been approved by the FDA recently: prasugrel in 2009 and ticagrelor in 2011. The newer drugs offer definite benefits over clopidogrel.

#### Pitfalls of clopidogrel

When compared to the newer P2Y\(_{12}\) inhibitors, the antiplatelet action of clopidogrel has been described to be slow, modest, and variable. Pharmacological studies comparing these drugs have shown a delayed onset of activity and higher on-treatment platelet reactivity with clopidogrel. Another issue with clopidogrel is that of resistance and interpatient variability. Serebruany et al did an ex vivo platelet-function study recruiting both healthy volunteers and post-PCI, heart failure, and stroke patients.\(^13\) They demonstrated that the variability of response to clopidogrel follows a normal distribution, with the percentage of hypo-respondents and hyper-respondents (±2 standard deviations) in their study being 4.2% and 4.8%, respectively.

Various mechanisms have been proposed to explain clopidogrel resistance such as drug interactions, P2Y\(_{12}\) receptor variability, etc, but the one which has been studied the most is unfavorable metabolism. Both clopidogrel and prasugrel are prodrugs that have to be converted to their active metabolites. Hagihara et al in their study showed that 90% of clopidogrel was converted into an inactive acid metabolite.\(^14\) Interpatient variability also exists in the activity of microsomal enzymes responsible for the formation of its active metabolite, with CYP2C19 polymorphisms being studied the most.\(^15\) This explains the moderate efficiency and high variability of response to clopidogrel when compared to other drugs.

#### Clopidogrel versus prasugrel

The most prominent trial comparing these two drugs was the TRITON–TIMI 38 enrolling ACS patients undergoing PCI.\(^16\) The prasugrel group had a significantly reduced incidence of primary outcome (cardiovascular death, nonfatal MI, or nonfatal stroke): 4.7% versus 5.6% in clopidogrel group (HR = 0.82; 95% CI: 0.73–0.93; \( P = 0.002 \)).

The increased efficacy of prasugrel was at the expense of increased risk of bleeding. The incidence of non-coronary artery bypass grafting (CABG)-related TIMI (Thrombolysis In Myocardial Infarction) major bleed was 2.4% with prasugrel versus 1.8% with clopidogrel (HR = 1.32; 95% CI: 1.03–1.68; \( P = 0.03 \)). The prasugrel group had an increased incidence of both “life threatening” (1.4% versus 0.9%; HR = 1.52; 95% CI: 1.08–2.13; \( P = 0.01 \)) and “fatal” bleeding (0.4% versus 0.1%; HR = 4.19; 95% CI: 1.58–11.11; \( P = 0.002 \)). Even though few patients underwent CABG, the incidence of CABG-related bleeding was also found to be higher in the prasugrel group: (13.4% versus 3.2%; HR = 4.73; 95% CI: 1.90–11.82; \( P < 0.001 \)). Post hoc analysis revealed three high-risk groups: patients with a history of
stroke/transient ischemic attack had a net harm from prasugrel, while elderly (>75 years) and patients with body weight less than 60 kg had no net clinical benefit.

Many studies have shown the pharmacological superiority of prasugrel over clopidogrel. Brandt et al measured inhibition of platelet aggregation after administering prasugrel in healthy subjects, compared it to that of clopidogrel up to 24 hours, and found it to be significantly higher (P<0.1). The peak inhibition of platelet aggregation for prasugrel was also higher (P<0.001). The antiplatelet action of prasugrel was shown to be more rapid; time taken to reach ≥20% inhibition of platelet aggregation was 30 minutes for prasugrel and 1.5 hours for clopidogrel. This factor may have been responsible for a reduction in the rate of “early” MI (before day 3) in the TRITON–TIMI 38 trial (4.7% with prasugrel versus 5.6% with clopidogrel; P=0.01). The antiplatelet activity of prasugrel is also more consistent. Jernberg et al studying aspirin-treated patients with coronary artery disease documented no nonresponders with prasugrel as compared to 45% in the clopidogrel group (P=0.0007).

Clopidogrel versus ticagrelor

Ticagrelor is the latest addition to the group of P2Y₁₂ inhibitors. It is chemically unique and is the first member of a new class of drugs known as cyclopentyl-triazolo-pyrimidines. The major trial designed to analyze the safety and efficacy of ticagrelor and compare it with clopidogrel was the PLATO trial enrolling 18,624 ACS patients in 43 countries. The incidence of primary endpoint (death from vascular causes, MI, or stroke) at 12 months was significantly lower in the ticagrelor group (9.8% versus 11.7%; HR=0.84; 95% CI: 0.77–0.92; P<0.001).

On further statistical analysis, these benefits were found to be both short-term (0–30 days) and long-term (31–360 days), and in both ST segment elevation MI (STEMI) and unstable angina/non-STEMI (NSTEMI) patients; this was irrespective of whether PCI was done or not.

There was no statistically significant increase in the incidence of total major bleeding in the ticagrelor group by both study criteria (11.6% versus 11.2%; HR=1.04; 95% CI: 0.95–1.13; P=0.43) and TIMI criteria (7.9% versus 7.7%; HR=1.03; 95% CI: 0.93–1.15; P=0.57). On a subset analysis, no increase in CABG-related major bleeding was found in the ticagrelor group by either criterion. However, a statistically significant increase in the incidence of non-CABG-related major bleeding was found in the ticagrelor group (4.5% versus 3.8%; HR=1.19; 95% CI: 1.02–1.38; P=0.03 by study criteria; and 2.8% versus 2.2%; HR=1.25; 95% CI: 1.03–1.53; P=0.03 by TIMI criteria).

Treatment with ticagrelor, like aspirin, was associated with a statistically significant reduction in all-cause mortality (4.5% versus 5.9%; HR=0.78, 95% CI: 0.69–0.89; P<0.001). This observation can be attributed to better efficacy, backed up by a superior pharmacological profile, without a concomitant increase in the rate of overall major bleeding. This definite survival benefit with ticagrelor is in stark contrast to the absence of such benefit with the other antiplatelet drugs like prasugrel and Gp IIb/IIIa inhibitors.

The encouraging results in clinical trials have been backed up by favorable pharmacological data. As opposed to thienopyridines, ticagrelor is a reversible P2Y₁₂ inhibitor: a factor that may have contributed to its better safety profile. Gurbel et al studied the pharmacology of ticagrelor in their two studies. The ONSET/OFFSET study enrolled patients with stable coronary artery disease on aspirin therapy, and compared the pharmacology of ticagrelor with that of clopidogrel. The antiplatelet action of ticagrelor was found to be rapid (41% inhibition of platelet aggregation at 30 minutes versus 8% with clopidogrel; P<0.0001) and more potent (90% of patients had >70% inhibition of platelet aggregation at 2 hours versus 16% with clopidogrel; P<0.0001). Despite the greater antiplatelet effect, inhibition of platelet aggregation at 24 hours after the last dose was equal in both ticagrelor- and clopidogrel-treated patients, thereby implying faster offset of action. The RESPOND study, recruiting a similar patient population, compared the antiplatelet action of ticagrelor in clopidogrel responders and nonresponders. The antiplatelet effect of ticagrelor was found to be same in both these groups. Inhibition of platelet aggregation in nonresponders treated with ticagrelor was higher than those treated with clopidogrel, at all times (P<0.05).

Armstrong et al explored another aspect of ticagrelor pharmacology in which it was shown to inhibit cellular uptake of adenosine via equilibrative nucleoside transporter 1. This potentially increases the local concentration of adenosine, which is a known inhibitor of platelet aggregation. This multipronged effect of ticagrelor on adenosine and ADP pharmacology may have contributed to the superior efficacy observed in clinical trials.

Prasugrel versus ticagrelor

As discussed previously, both prasugrel and ticagrelor have been found to have superior clinical efficacy as compared to clopidogrel, with a significantly increased risk of bleeding events with prasugrel. However, till date, no head-to-head comparison has been made between these two newer P2Y₁₂ inhibitors. A multicenter, randomized trial, ISAR
REACT 5, is underway to compare prasugrel and ticagrelor in ACS patients with a planned invasive strategy and can help define the best option for P2Y₁₂ inhibition.²³

In a pharmacodynamic study by Alexopoulos et al enrolling clopidogrel hypo-responders 24 hours post-PCI, ticagrelor was found to be superior to prasugrel.²⁴ The primary endpoint of platelet reactivity was found to be significantly lower with ticagrelor (32.9 platelet reactivity units; 95% CI: 18.7–47.2) as compared to prasugrel (101.3 platelet reactivity units; 95% CI: 86.8–115.7).

**Timing of administering the second antiplatelet**

As mentioned before, dual antiplatelet therapy with aspirin and a P2Y₁₂ inhibitor has become the standard of care, with the 2013 ACC/AHA guidelines for STEMI recommending the use of a P2Y₁₂ inhibitor (clopidogrel, prasugrel, or ticagrelor) as a class I indication.²⁵ However, no explicit recommendations have been made with respect to the timing of the second antiplatelet drug after aspirin. Administration of a loading dose of a P2Y₁₂ inhibitor both before and during primary PCI has been approved. Administration of early dual antiplatelet therapy (which is commonly practiced) has a logistic drawback in patients where the coronary anatomy upon catheterization is found to be non-amenable to PCI, thereby requiring emergency CABG. Various studies have underlined the increased risk of postoperative bleeding with preoperative clopidogrel use.²⁶,²⁷ The previous guidelines recommended a minimum time period of 5 days after stopping the second antiplatelet drug (a P2Y₁₂ inhibitor) before considering emergency CABG.²⁸ The current guidelines have revised the minimum recommended time period to 24 hours.²⁵

Kapetanakis et al proposed withholding the administration of clopidogrel until an angiogram is performed (thereby revealing the coronary anatomy) and the need for CABG is assessed.²⁹ However, it has been argued that this strategy will deny optimum antiplatelet therapy in the majority of the patients who do not require surgery, especially in view of the slower onset of antiplatelet action of clopidogrel. In the CIPAMI trial, early clopidogrel administration in STEMI patients was found to have a lower incidence of composite endpoint (death, reinfarction, urgent target-vessel revascularization) as compared to clopidogrel administration after angiogram (3% versus 7%; P=0.09).³⁰ Another proposed strategy is to withhold the dual antiplatelet therapy before angiography, only in patients where the likelihood of CABG is high. A risk score to predict the need for CABG was designed by Sadanandan et al³¹ although its clinical applicability has been questioned.³²

As the newer P2Y₁₂ inhibitors prasugrel and ticagrelor have a superior pharmacological profile compared to clopidogrel, this property can be exploited to devise novel therapeutic strategies. Marchini et al presented an algorithm in which dual antiplatelet therapy was withheld in patients requiring emergent cardiac catheterization if the anticipated delay from presentation to catheterization was less than 6 hours.³³ Prasugrel was administered only after confirming the coronary anatomy during angiography and assessing the need for CABG. The underlying rationale is that, because of the faster and more-potent antiplatelet action of prasugrel, this strategy will achieve an enhanced platelet inhibition within a similar or potentially faster timeframe compared to preprocedural clopidogrel therapy. Ticagrelor can potentially fit in this treatment strategy as well.

**Gp IIb/IIa inhibitors**

Most of the earlier studies done on Gp IIb/IIa inhibitors were in the pre-dual antiplatelet-therapy era and demonstrated a clinical benefit at a somewhat increased risk of bleeding.³⁴,³⁵ The FINESSE (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events) study enrolled STEMI patients undergoing PCI and randomized them to receive abciximab plus reteplase (combination facilitated PCI), abciximab (facilitated PCI), or placebo (primary PCI) before the procedure.³⁶ There was no statistically significant clinical benefit with either facilitated or combination facilitated PCI, and each of these was associated with an increased risk of bleeding.

The results from the limited studies in which clopidogrel pretreatment was given showed questionable benefit and an increased bleeding risk.³⁷ Arguments have thus been made to restrict the use of Gp IIb/IIa inhibitors as a bailout strategy in face of intraprocedural complications during PCI (eg, distal embolization, no reflow phenomenon, etc). The same has been adopted in the European Society of Cardiology (ESC) guidelines.³⁸

Of special interest is the meta-analysis performed by De Luca et al evaluating STEMI patients undergoing primary PCI.³⁷ The analysis showed no mortality benefit after 30 days (2.8% versus 2.9%; P=0.75) and an increased risk of major bleeding (4.1% versus 2.7%; P=0.0004) with Gp IIb/IIa inhibitors. However, a significant relationship between patient risk profile and mortality benefit from Gp IIb/IIa inhibitors was observed (P=0.008), with higher-risk patients benefitting the most.

This notion is in line with the findings of the ISAR-REACT 2 trial in which clinical benefits of abciximab were observed in high-risk NSTEMI patients with elevated
troponin levels. In these patients, the primary endpoint (death, MI, or urgent target-vessel revascularization within 30 days) in the abciximab group was 13.1% compared with 18.3% in the placebo group (RR=0.71; 95% CI: 0.54–0.95; P=0.02). This benefit was not observed in patients without an elevated troponin level. This drives the rationale of restricting routine Gp IIb/IIIa inhibitor use to high-risk patients (eg, large anterior wall MI and/or large clot burden).

While some studies have shown benefit of intracoronary administration of abciximab, others have shown no benefit, and intracoronary Gp IIb/IIIa-inhibitor therapy remains a class IIb indication. A meta-analysis comparing the three Gp IIb/IIIa inhibitors in patients undergoing PCI for STEMI showed no difference in their efficacy and risk profiles. Although all three approved Gp IIb/IIIa inhibitors have been shown to have comparable benefits, abciximab has been studied the most and is hence commonly used.

**Protease-activated receptor 1 inhibitor: vorapaxar**

The most recent addition to antiplatelet drugs is vorapaxar, approved in May 2014. Protease-activated receptor 1 inhibition prevents thrombin-mediated platelet activation. It has been proposed that adding a platelet-activated receptor 1 inhibitor to the current standard of dual antiplatelet therapy may provide a more comprehensive platelet inhibition. This approval was based on the findings of the TRA 2°P-TIMI 50 trial, which enrolled patients with a history of ACS on maintenance antiplatelet therapy. As compared to dual antiplatelet therapy, maintenance therapy with vorapaxar resulted in some reduction in primary outcomes of cardiovascular death, MI, or stroke (8.1% versus 9.7%; HR=0.80; 95% CI: 0.72–0.89; P<0.0001) at the expense of an increased risk of bleeding (3.4% versus 2.1%; HR=1.61; 95% CI: 1.31–1.97; P<0.0001).

**LMWHs versus UFH**

LMWHs boast certain practical advantages over UFH. Because of its favorable pharmacology, weight-adjusted enoxaparin has been shown to provide more stable and reliable anticoagulation without the need of laboratory monitoring. Enoxaparin, the most widely used LMWH, has been compared to heparin in various studies. The most prominent amongst these was the SYNERGY trial, which enrolled high-risk NSTEMI patients. The incidence of primary composite endpoint of all-cause death or nonfatal MI during the first 30 days was comparable in enoxaparin and heparin groups (14.0% versus 14.5%; odds ratio =0.96; 95% CI: 0.86–1.06; P=0.40). Also, no differences in ischemic events during PCI were observed between the two groups. A statistically significant increase in TIMI major bleeding was observed with enoxaparin (9.1% versus 7.6%; P=0.008), but GUSTO (Global Utilization of Streptokinase and t-PA for Occluded Arteries) severe bleeding rates were comparable in the two groups (2.7% versus 2.2%; P=0.08).

Cohen et al in their study showed that prerandomization anticoagulant therapy or switching from one anticoagulant to another at the time of randomization could have potentially influenced the endpoint analysis of the SYNERGY trial. In the subgroup analysis, it was found that patients receiving “consistent enoxaparin therapy” experienced fewer deaths or MI when compared to “consistent heparin therapy” (13.3% versus 15.9%; HR=0.82; 95% CI: 0.72–0.94; P=0.004; adjusted P=0.041). However, an increased incidence of GUSTO severe bleeding was observed with consistent enoxaparin therapy (2.9% versus 2.1%; P=0.0465).

The more recently concluded ATOLL trial enrolling STEMI patients undergoing primary PCI showed encouraging results. Intravenous (IV) enoxaparin was found to reduce the primary endpoint (30-day incidence of death, complication of MI, procedure failure, or major bleeding) when compared to UFH (28% versus 34%; RR=0.83; 95% CI: 0.68–1.01; P=0.06), with no difference in the occurrence of major bleeding (5% versus 5%; P=0.79). Another salient trial that deserves mention is the STEEPLE trial enrolling patients undergoing elective PCI, which interestingly showed a decreased incidence of non-CABG related bleeding in the first 48 hours with enoxaparin therapy compared to heparin (5.9% versus 8.5%; 95% CI: −4.7 to −0.6; P=0.01).

Based on the current data, enoxaparin seems to be more effective than UFH at the expense of a modest and questionable increase in the risk of bleeding. The other FDA-approved LMWHs dalteparin and tinzaparin have not been studied extensively for ACS. In the limited evidence available, both have been found to be clinically comparable or inferior to enoxaparin. Although dalteparin has been approved for use in unstable angina/NSTEMI, the data on its efficacy profile is not substantial. Tinzaparin has no role in ACS currently.

**Bivalirudin versus UFH**

Bivalirudin has emerged as the third viable option for anticoagulation in ACS. However, arguments on its safety and efficacy profile have been marked by intense controversy and debate. The most prominent amongst the earlier trials analyzing bivalirudin was the ACUITY trial published in 2004.
In this trial, patients with STEMI were enrolled and randomized to receive UFH/enoxaparin plus a Gp IIb/IIIa inhibitor, bivalirudin plus a Gp IIb/IIIa inhibitor, or bivalirudin alone. Bivalirudin monotherapy was found to be clinically noninferior to heparin plus Gp IIb/IIIa-inhibitor therapy. Moreover, a strong evidence of significantly lower risk of major bleeding was observed in the bivalirudin group as compared to the heparin plus Gp IIb/IIIa group (4% versus 7%; RR=0.52; 95% CI: 0.40–0.66; P<0.0001). However, it is critical to note that when the bivalirudin plus Gp IIb/IIIa-inhibitor group was compared to the heparin plus Gp IIb/IIIa-inhibitor group, both these groups found to have similar rates of composite ischemic endpoint (9% versus 8%; P=0.16) and bleeding (8% versus 7%; P=0.32).

The findings of clinical noninferiority and reduced bleeding risk with bivalirudin therapy versus heparin plus Gp IIb/IIIa-inhibitor therapy in the ACUITY trial was in line with the results obtained from the subsequent trials: ISAR-REACT 4 (enrolling NSTEMI patients undergoing PCI) and HORIZONS-AMI. The HORIZONS-AMI trial enrolled high-risk STEMI patients undergoing PCI.54 Bivalirudin when compared with heparin plus Gp IIb/IIIa-inhibitor therapy showed similar rates of MACE (5.4% versus 5.5%; P=0.95) but a decreased risk of major bleeding (4.9% versus 8.3%; RR=0.60; 95% CI: 0.46–0.77; P<0.001). A reduction in death from cardiac causes at 30 days and all-cause mortality was also observed in the bivalirudin group owing to a significantly reduced risk of major bleeding. Of special note, however, was the finding of increased rate of acute ST in the bivalirudin group in the first 24 hours (1.3% versus 0.3%; P<0.001), but no significant increase in ST was shown to be present at 30 days (2.5% versus 1.9%; P=0.30).

It is imperative to note that in all clinical trials on bivalirudin discussed so far, the reduced bleeding risk was observed when it was compared to heparin plus routine Gp IIb/IIIa-inhibitor therapy. A series of trials with modified study design, all published after 2013, have introduced a whole new perspective on the current standing of bivalirudin. In the EUROMAX trial, STEMI patients undergoing PCI were enrolled and randomized to either test or control groups.55 The test group received bivalirudin, with Gp IIb/IIIa-inhibitor use restricted to bailout; and the control group received heparin/enoxaparin, with optional use of Gp IIb/IIIa inhibitors at the physician’s discretion. Overall, the rate of Gp IIb/IIIa-inhibitor use was differential: 11.5% in the bivalirudin group and 69.1% in the control group.

The incidence of primary composite outcome of death or non-CABG related major bleeding at 30 days was lower in the bivalirudin group (5.1% versus 8.5%; RR=0.60; 95% CI: 0.43–0.82; P=0.001), as was the risk of major bleeding (2.6% versus 6.0%; RR=0.43; 95% CI: 0.28–0.66; P<0.001). However, the incidence of MACE was similar in both bivalirudin and heparin groups (65% versus 61%; RR=1.09; 95% CI: 0.77–1.52; P=0.64). As noted in the HORIZONS-AMI trial, the risk of acute ST was significantly higher with bivalirudin (1.1% versus 0.2%; RR=6.11; 95% CI: 1.37–27.24; P=0.007). All three P2Y12 inhibitors were used alternatively in a similar proportion in both groups. Overall, the results of EUROMAX were positive and consistent with those of the previous trials.

In the BRAVE-4 trial, STEMI patients undergoing primary PCI were randomized to receive either prasugrel plus bivalirudin or clopidogrel plus heparin.56 Notably, the use of Gp IIb/IIIa inhibitors was reserved to bailout in both groups (3.0% in the prasugrel plus bivalirudin group versus 6.1% in the clopidogrel plus heparin group). The primary composite endpoint (death, MI, unplanned revascularization, ST, stroke, or bleeding at 30 days) was similar in both the groups (15.6% in the prasugrel plus bivalirudin group versus 14.5% in the clopidogrel plus heparin group; RR=1.09; one-sided 97.5% CI: 0–1.79; P=0.680). Bleeding according to HORIZONS-AMI definition was also similar (14.1% in the prasugrel plus bivalirudin group versus 12.0% in the clopidogrel plus heparin group; RR=1.18; 95% CI: 0.74–1.88; P=0.543). Thus, prasugrel plus bivalirudin therapy failed to show any safety or efficacy benefit in the BRAVE-4 trial. The trial was however stopped prematurely owing to slow recruitment, having enrolled only 548 of the 1,240 patients originally planned, and was thus underpowered to test its primary hypothesis.

The most recently published HEAT-PPCI trial recruited STEMI patients undergoing primary PCI randomized to receive either bivalirudin or heparin, with the use of Gp IIb/IIIa inhibitors restricted to bailout in both groups.57 It was the first major trial making a head-to-head comparison between bivalirudin and heparin with a nondifferential Gp IIb/IIIa-inhibitor use in the two groups (13% in the bivalirudin group versus 15% in the heparin group). Use of the various P2Y12 inhibitors was also proportional in both groups, with ticagrelor being used the most (61%). The incidence of primary composite outcome (all-cause mortality, cerebrovascular accident, reinfarction, or unplanned target lesion revascularization) was higher in the bivalirudin group compared to the heparin group (8.7% versus 5.7%; RR=1.52; 95% CI: 1.09–2.13; P=0.01). Notably, the incidence of major bleeding was similar in both groups (3.5% in the bivalirudin
group versus 3.1% in the heparin group; RR=1.15; 95% CI: 0.70–1.89; P=0.59). Similar to the HORIZONS-AMI and EUROMAX trials, the incidence of ST was found to be significantly higher with bivalirudin (3.4% versus 0.9%; RR=3.91; 95% CI: 1.6–9.5; P=0.001).

In light of this new information, the role of bivalirudin is being revisited. Although the earlier trials showed a decreased risk of bleeding with bivalirudin, the latest data argues that this finding may have been attributed to differential use of Gp IIb/IIIa inhibitors in the two trial groups. Furthermore, there is substantial evidence of increased risk of ST with bivalirudin as compared to heparin. An overview of the current evidence on bivalirudin is presented in Table 2.

**Fondaparinux: current status**

Although trials evaluating fondaparinux have shown clinical benefit, the major drawback has been the substantially increased risk of catheter-related thrombosis. Hence, the current guidelines recommend against using fondaparinux monotherapy to support PCI (class III indication). For instance, in the OASIS 6 trial enrolling patients with STEMI, the rate of guiding catheter-related thrombosis was significantly higher in patients receiving fondaparinux (0 versus 22; P<0.001).58

**The oral anticoagulants (rivaroxaban, apixaban, dabigatran)**

There is no role of long-term use of oral anticoagulants (like rivaroxaban, apixaban, dabigatran) as maintenance therapy for ACS as per the current guidelines, but their utility has been explored.59 Most promising has been the results of the ATLAS ACS 2-TIMI 51 trial enrolling stabilized ACS patients within 7 days of hospitalization.60 The patients were randomized to either rivaroxaban therapy (2.5 mg or 5.0 mg), or placebo. Incidence of composite primary endpoint of death from cardiovascular causes, MI, or stroke in these three groups was 9.1%, 8.8%, and 10.7%, respectively (HR for rivaroxaban combined =0.84; 95% CI: 0.75–0.96; P=0.008). The incidence of TIMI major bleeding not associated with CABG was 1.8%, 2.4%, and 0.6%, respectively (HR for rivaroxaban combined =3.96; 95% CI: 2.46–6.38; P=0.001). Thus, the better efficacy outcomes were at a cost of increased risk of bleeding. FDA approval was declined based on concerns over missing follow-up safety data and methodological issues with the trial.61

Results of the trials evaluating the other oral anticoagulants apixaban and dabigatran have not been encouraging. The APPRAISE-2 trial recruited patients with recent ACS

### Table 2. Summary of the findings from some of the salient trials on bivalirudin

<table>
<thead>
<tr>
<th>Sr no</th>
<th>Trial</th>
<th>Comparison</th>
<th>Safety endpoint</th>
<th>Efficacy endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>ACUITY trial14</td>
<td>Bivalirudin versus UFH/enoxaparin</td>
<td>Differential: bailout (7%) versus routine (100%)</td>
<td>9% versus 8%, P=0.45</td>
</tr>
<tr>
<td>1b</td>
<td>ACUITY trial14</td>
<td>Bivalirudin plus Gp IIb/IIIa inhibitor versus UFH/enoxaparin plus Gp IIb/IIIa inhibitor</td>
<td>Differential: bailout (7.2%) versus routine (100%)</td>
<td>9% versus 8%, P=0.16</td>
</tr>
<tr>
<td>2</td>
<td>HORIZONS-AMI trial15</td>
<td>Bivalirudin versus UFH/enoxaparin plus Gp IIb/IIIa inhibitor</td>
<td>Differential: bailout (11.5%) versus routine (100%)</td>
<td>6.5% versus 6.1%, P=0.54</td>
</tr>
<tr>
<td>3</td>
<td>EUROMAX trial16</td>
<td>Bivalirudin versus UFH/enoxaparin plus Gp IIb/IIIa inhibitor</td>
<td>Differential: bailout (11.5%) versus routine (100%)</td>
<td>6.5% versus 6.1%, P=0.54</td>
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<tr>
<td>4</td>
<td>BRAVE-4 trial17</td>
<td>Bivalirudin versus UFH/enoxaparin plus Gp IIb/IIIa inhibitor</td>
<td>Differential: bailout (11.5%) versus routine (100%)</td>
<td>6.5% versus 6.1%, P=0.54</td>
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<tr>
<td>5</td>
<td>HEAT-PPCi trial18</td>
<td>Bivalirudin versus UFH/enoxaparin plus Gp IIb/IIIa inhibitor</td>
<td>Differential: bailout (11.5%) versus routine (100%)</td>
<td>6.5% versus 6.1%, P=0.54</td>
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</tbody>
</table>

Notes: CI, confidence interval; Gp, glycoprotein; PCI, percutaneous coronary intervention; RR, relative risk; UFH, unfractionated heparin.

Abbreviations: CI, confidence interval; Gp, glycoprotein; PCI, percutaneous coronary intervention; RR, relative risk; UFH, unfractionated heparin.
(within the previous 7 days) who were randomized to receive either apixaban or placebo as maintenance therapy. The trial was terminated prematurely because of strong evidence of increased risk of TIMI major bleeding in the apixaban group (1.3% versus 0.5%; HR=2.59; 95% CI: 1.50–4.46; P=0.001) and no reduction in ischemic events (7.5% versus 7.9%; HR=0.95; 95% CI: 0.80–1.11; P=0.51).

The RE-DEEM trial also recruited patients with recent ACS and randomized them to receive various doses of dabigatran (50 mg, 75 mg, 110 mg, 150 mg) or placebo. A dose-dependent increase in major or minor bleeding was observed with dabigatran (HR for 150 mg group: 4.27; 95% CI: 1.86–9.81). There was no significant reduction in the rate of ischemic events with dabigatran (3.8% with placebo, 4.6% with 50 mg dose, 4.9% with 75 mg dose, 3.0% with 110 mg dose, and 3.5% with 150 mg dose).

Patients on long-term anticoagulation undergoing PCI: current status of the “triple therapy”

Antithrombotic therapy in patients on long-term anticoagulation undergoing PCI (eg, patients with atrial fibrillation) presents with a unique therapeutic challenge. Conventionally, patients are treated with dual antiplatelet therapy in addition to an oral anticoagulant as maintenance therapy after PCI (also known as triple oral antithrombotic therapy). This approach has been marked by the dilemma of increased bleeding risk with triple therapy versus ischemic risk without it, as reviewed by Reed and Cannon.

The first major trial addressing this issue was the WOEST trial completed recently, which enrolled patients on warfarin undergoing PCI and randomized them to receive either triple therapy or clopidogrel plus warfarin. The primary endpoint of bleeding within 1 year of PCI was significantly lower in the double therapy group compared to the triple therapy group (19.4% versus 44.4%; HR=0.36; 95% CI: 0.26–0.50; P<0.0001). The secondary endpoint of death, MI, stroke, systemic embolization, and target-vessel revascularization was somewhat lower in the double therapy group (11.3% versus 17.7%; HR=0.60; 95% CI: 0.38–0.94; P=0.025). In a subgroup analysis, uninterrupted oral anticoagulation therapy during PCI was not associated with an increase in bleeding or major adverse cardiac and cerebrovascular events compared to the conventional heparin-bridging therapy.

In spite of these new developments, more evidence is needed to form definite conclusions in this regard. Of note, the most recent ACC/AHA guidelines on atrial fibrillation has assigned a class IIb recommendation to the use of clopidogrel plus oral anticoagulants (without aspirin) for the maintenance therapy of atrial fibrillation patients who have undergone coronary revascularization. Conclusion of some of the ongoing trials will provide more evidence in this regard.

A decision tree depicting the current trends in interventional pharmacology is illustrated in Figure 3.

Future directions

The pharmacology of hemostasis and thrombosis is an ever-evolving field, and many more novel antiplatelet and anticoagulant drugs are being developed and tested. A brief overview of some of the important drugs under trial is presented below.

Upcoming antiplatelet drugs

IV P2Y12 inhibitors

Among the most important upcoming antiplatelet drugs are the reversible IV P2Y12 inhibitors: cangrelor and elinogrel. The earlier Phase III trials CHAMPION PLATFORM and CHAMPION PCI failed to show clinical benefit of cangrelor use during PCI. However, encouraging results were obtained in the most recent CHAMPION PHOENIX trial, which enrolled patients undergoing urgent or elective PCI randomized to receive cangrelor or clopidogrel before PCI. The cangrelor group then received clopidogrel after the infusion was complete. The rate of primary composite endpoint of death, MI, ischemia-driven revascularization, or ST at 48 hours was lower in the cangrelor group (4.7% versus 5.9%; RR=0.78; 95% CI: 0.66–0.93; P=0.005). There was no significant increase in severe bleeding with cangrelor (0.16% versus 0.11%; odds ratio =1.50; 95% CI: 0.53–4.22; P=0.44).

The contradictory findings of the CHAMPION trials have been attributed to different definitions of periprocedural MI. A reduction in the rate of periprocedural MI accounted for most of the benefits of cangrelor observed in the CHAMPION PHOENIX trial (3.8% versus 4.7%; RR=0.80; 95% CI: 0.67–0.97; P=0.02), whereas the same outcome was responsible for its failure in the previous trials. It has been argued that the definition of periprocedural MI in the previous studies did not allow for discrimination between reinfarction and biomarker-positive ACS: an issue that was supposedly addressed in the CHAMPION PHOENIX trial. The FDA however declined to approve cangrelor because of inconclusive evidence.

Elinogrel is the only P2Y12 inhibitor available for both oral and IV routes of administration. This gives it a unique
Management of ACS

Antithrombotic therapy

Antiplatelet therapy

"Routine" GPI: Aspirin: P2Y12 inhibitor: Options

• In high-risk cases

Aspirin: The "first" antiplatelet

P2Y12 inhibitor: The "second" antiplatelet

Options

Clopidogrel:

• Most commonly used P2Y12 inhibitor
• 600 mg dose preferred

Prasugrel:

• Better efficacy than clopidogrel
• Increased risk of bleeding

Ticagrelor:

• Similar "total" bleeding risk

If presentation to catheterization time is low

Coronary anatomy amenable to intervention

Intraprocedural complications: e.g., distal embolization, no-reflow phenomenon

PCI

Consider withholding prasugrel/ticagrelor until cardiac catheterization?

Prasugrel/ticagrelor administered

Emergency CABG

Coronary anatomy non-amenable to intervention

Bailout GPI use

Figure 3 A decision tree depicting the various therapeutic options available for the management of ACS, and highlighting their unique characteristics based on the current evidence.

Notes: A strategy for the timing of introducing the second antiplatelet drug (a newer P2Y12 inhibitor – prasugrel or ticagrelor): modified from the algorithm proposed by Marchini et al.33

Abbreviations: ACS, acute coronary syndrome; Addl, additional; CABG, coronary artery bypass grafting; GPI, glycoprotein IIb/IIIa inhibitor; NTG, nitroglycerine; O2, oxygen; PCI, percutaneous coronary intervention; ST, stent thrombosis.

pharmacological advantage over cangrelor, where an IV dose during PCI can be followed by an oral dose for a smooth transition of the antiplatelet effect. IV administration of cangrelor has to be followed by administration of another oral P2Y12 inhibitor (like clopidogrel). This in turn raises the issue of drug interaction, as studied by Steinhubl et al.73 However, the results of the Phase II trial INNOVATE-PCI were equivocal, with similar efficacy endpoints and no increase in TIMI major/minor bleeding observed with elinogrel.74 No Phase III trials have been planned as of now.

An important clinical benefit of these IV P2Y12 inhibitors is their quick onset of action and a short half-life. They can have a unique advantage for use in patients undergoing emergency CABG. Due to their quick offset of action, surgery can be safely performed within a few hours of stopping the drug. The BRIDGE trial enrolled patients undergoing planned CABG, and tested the use of cangrelor 1–6 hours before surgery.75 Platelet reactivity throughout the treatment period was lower with cangrelor than placebo (platelet reactivity units <240 throughout infusion in 98.8% versus 19.0% of patients; RR=5.2; 95% CI: 3.3–8.1; P<0.001). After discontinuation of cangrelor 1–6 hours before surgery, platelet reactivity was found to be similar in both groups (mean ±1 standard deviation platelet reactivity unit values: 279.7±106.5 in cangrelor group versus 297.8±67.3 in placebo group; P=0.212). Rates of CABG-related bleeding were similar with cangrelor and placebo groups (11.8% versus 10.4%; RR=1.1; 95% CI: 0.5–2.5; P=0.763). Thus, the findings of the trial supported this idea.

Upcoming anticoagulant drugs

Engineered LMWH

M118 (also referred to as “adomiparin sodium” in some texts) is a novel LMWH with the desirable attributes of both enoxaparin and UFH. It has shown potent activity against both factors Xa and IIa, and is thereby easily monitored by a
Table 3 List of clinical trials in order of their mention in the review

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<tr>
<th>Clinical Trial</th>
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<td>TRITON-TIMI 38 trial</td>
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<td>PLATO trial</td>
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<td>ISAR REACT 5 trial</td>
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<td>CIPAMI trial</td>
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<td>FINESSE trial</td>
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<tr>
<td>ISAR-REACT 2 trial</td>
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<td>TRA 2 P-TIMI 50 trial</td>
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<tr>
<td>REVERSAL-PCI trial</td>
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</table>

Conclusion

There should be no doubt in saying that these are the most exciting times in this part of the world of pharmacotherapeutics. With advances in the understanding of basic mechanisms of hemostasis and thrombosis, ingenious molecular targets are being exploited, and many of these theoretical hypotheses have been translated into success in clinical trials. It has become imperative for the clinician to be well versed with all the current evidence available and adapt that knowledge in making day-to-day decisions. The need for individualization of therapy is being stressed. A couple of decades ago, the clinician did not have much to choose from; now, there is a plethora of options available. A sound knowledge of the current evidence on these drugs can help make rational decisions.

The most-recently approved P2Y$_12$ inhibitor ticagrelor seems to be superior to other P2Y$_12$ inhibitors as it has been shown to be more effective than clopidogrel with no increase in total bleeding risk (although an increase in the risk of non-CABG-related bleeding was observed). However, we need to wait for the conclusion of the ongoing trial to make a more direct comparison between prasugrel and ticagrelor. Routine use of Gp IIb/IIIa inhibitors can be made in high-risk patients, while their use in other patients should be reserved for bailout. Enoxaparin has been found to be more efficacious but somewhat less safe than heparin, whereas the role of bivalirudin is being debated.

With this myriad of options available and more on their way, these innovations should be celebrated as an opportunity to practice better medicine.

Disclosure

The authors report no conflicts of interest in this work.

References


