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Emerging therapies for acute coronary syndromes

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In the majority of cases acute coronary syndromes (ACS) are caused by activation and aggregation of platelets and subsequent thrombus formation leading to a decrease in coronary artery blood flow. Recent focus on the treatment of ACS has centered on reducing the response of platelets to vascular injury as well as inhibiting fibrin deposition. Novel therapies include more effective P2Y12 receptor blockers thereby reducing inter-individual variability, targeting the platelet thrombin receptor (protease activated receptor 1) as well as directly inhibiting factor Xa or thrombin activity. In this review we discuss the clinical data evaluating the effectiveness of these various new ACS treatment options.

Keywords: prasugrel, ticagrelor, bivalirudin, fondaparinux, dabigatran, vorapaxar

INTRODUCTION

Over the past two decades improvements in detection and management have reduced the incidence, the morbidity and the mortality of acute coronary syndromes (ACS).Yet there are more than 1 million events yearly in the United States alone and ACS remains a leading cause of death in patients over 65 years of age (Yeh et al., 2010). The term ACS denotes unstable angina, non-ST-elevation myocardial infarction and ST-elevation myocardial infarction and ischemic sudden death with the exact diagnosis dependent on the extent and severity of myocardial damage. Necropsy studies have shown that 65% of sudden deaths resulting from ACS occur from thin-cap fibroatheromas; lesions characterized as possessing a thin fibrous cap ($<65\,\mu m$) overlying a necrotic core. The remaining events are precipitated by superficial erosion of the fibrous cap (Virmani et al., 2000). These processes lead to platelet activation and aggregation, the formation of fibrin rich thrombi, and the partial or total occlusion of the coronary artery resulting in an ACS. With plaque rupture or erosion there is release of tissue factor and exposure of subendothelial collagen and von Willebrand factor (vWF). Circulating platelets adhere to the exposed collagen and vWF and undergo cytoskeletal rearrangement, generation of cyclooxygenase I (COX-I) dependent thromboxane A_2 (TXA_2), and release the contents of stored granules including adenosine diphosphate (ADP). Interaction of TXA_2 with the TXA_2 receptor and ADP with its receptor (P2Y12) initiates positive feedback activating additional platelets in a regional manner and promoting the expression of the GpIIb–IIIa receptors. Coincident activation of factor X via tissue factor results in thrombin generation, which elicits additional platelet degranulation and TXA_2 release (Chackalamannil and Xia, 2006) and catalyzing the formation of fibrin, which serves as the cross-link between GpIIb–IIIa receptors on neighboring platelets (**Figure 1**).

Contemporary medical therapies are designed to promote plaque stability, reduce platelet activation and aggregation, prevent thrombus formation, and minimize myocardial oxygen demand. New pharmacotherapies for ACS reflect efforts to improve efficacy and minimize complications of anti-platelet and anti-thrombotic therapies by increasing target specificity and reducing inter-individual variation in therapeutic response. In this review we will describe recent advances in pharmacological therapy for ACS with particular attention to platelet aggregation and thrombus formation. Agents targeting glycoprotein IIb/IIIa (Gp IIb/IIIa) receptors will not be discussed.

ASPIRIN AND P2Y12 INHIBITORS

Aspirin irreversibly blocks COX-I, inhibiting generation of TXA_2 and consequent platelet activation. In an early study assessing the effect of aspirin in ACS, 1266 patients with unstable angina were randomized to 324 mg aspirin or placebo. Use of aspirin resulted in a 51% reduction of either death or MI at 12 weeks ($p = 0.0002$); without an increase in bleeding with sustained benefit at 1 year follow up (-43%, $p = 0.008$; Lewis et al., 1983). Subsequent smaller studies corroborated this benefit, and a meta-analysis of 15 randomized trials including 135,000 patients identified a reduction in the combined incidence of MI, stroke, or vascular death in ACS patients treated with aspirin ($-30 \pm 4\%$, $p < 0.0001$). Subsequently, virtually every trial assessing ACS pharmacotherapy has been performed on the background of aspirin therapy (Lewis et al., 1983; ISIS Collaborative Group, 1988; Antiplatelet Trialists' Collaboration, 1994; Antithrombotic Trialists' Collaboration, 2002).

Abbreviations: ACS, acute coronary syndrome; AT-III, anti-thrombin-III; CABG, coronary artery bypass grafting; COX-I, cyclooxygenase I; GpIIb–IIIa, glycoprotein IIb–IIIa; MI, myocardial infarction; NNT, number needed to treat; NS, non-significant; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TVR, target vessel revascularization; TXA_2, thromboxane A_2; UA, unstable angina; vWF, von Willebrand factor.

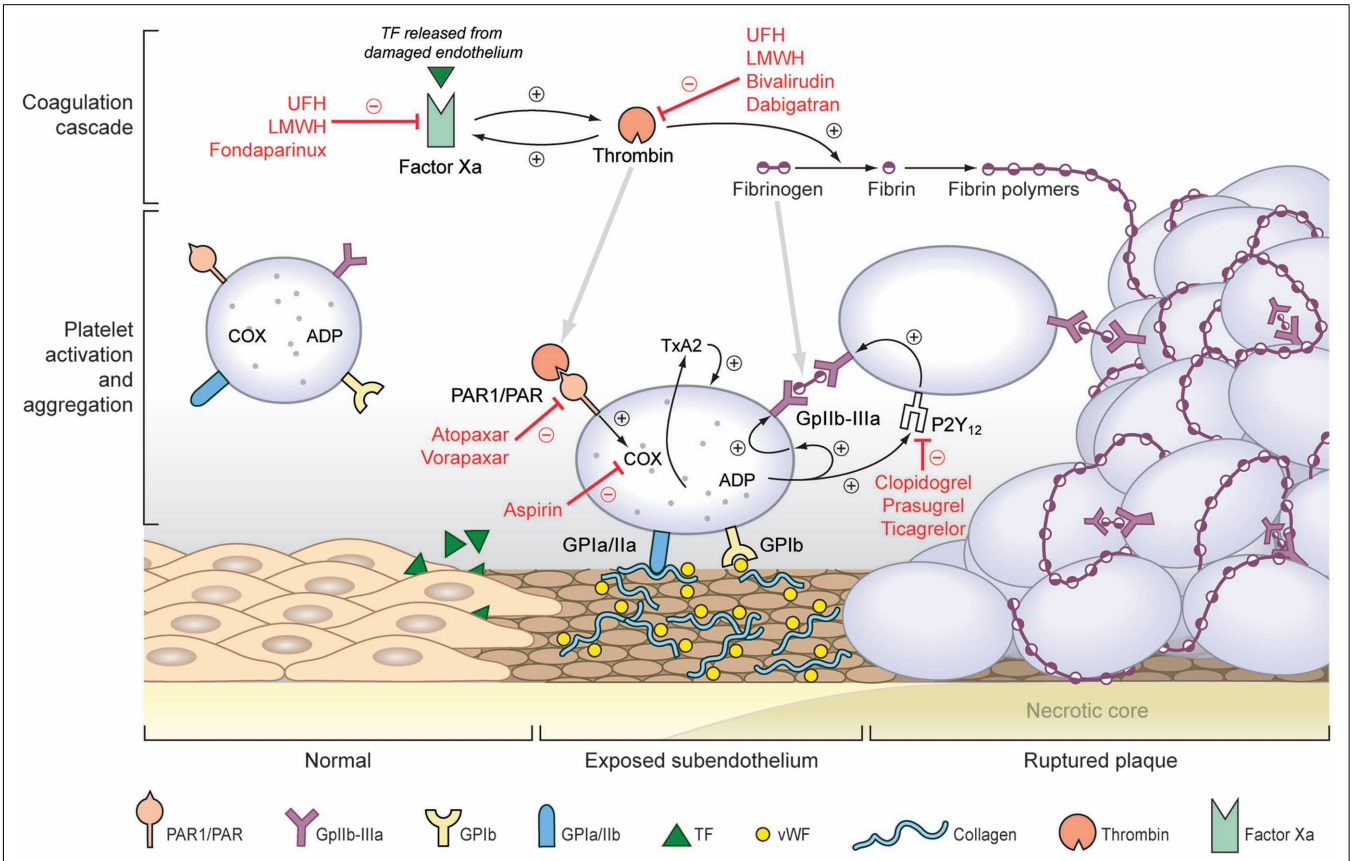

FIGURE 1 | Mechanism of acute coronary syndromes and targets of anti-platelet and anti-thrombotic agents.

The term "aspirin resistance" initially denoted patients who suffered a vascular event while on aspirin therapy, yet specifically refers to the inability of aspirin to sufficiently suppress TXA_2 production or platelet aggregation *in vitro* (Hennekens et al., 2004). The determination of aspirin resistance is complicated by the variable prevalence (6–26%) among studies depending on the laboratory assay employed (Gum et al., 2001; Gasparyan et al., 2008). Small prospective observational studies have identified increases in the risk of MI (OR 2.0, CI 1.2–3.4, $p = 0.006$), cardiovascular death (OR 3.5, CI 1.7–7.4, $p < 0.001$), and composite death, MI or CVA (OR 3.12, CI 1.1–8.9, $p = 0.03$) in patients with high platelet reactivity (HPR) on aspirin therapy (Eikelboom et al., 2002; Gum et al., 2003; Gasparyan et al., 2008). As a result, the concept of dual anti-platelet therapy (DAPT) emerged in order to reduce the rate of vascular events among those with HPR on aspirin therapy, and specifically to reduce the rate of reinfarction during and after percutaneous coronary intervention (PCI).

Clopidogrel is a thienopyridine pro-drug (**Table 1**; **Figure 2**) that requires cytochrome 2C19 (CYP2C19) biotransformation to the active metabolite, an irreversible P2Y12 receptor inhibitor. In a large prospective secondary prevention trial ($n = 19{,}185$), clopidogrel alone compared to aspirin did not significantly reduce recurrent vascular events (stroke, MI, or vascular death) among those with a history of myocardial infarction (-3.7%, $p = 0.66$), and was associated with similar rates of bleeding (9.27 vs. 9.28%; CAPRIE Steering Committee, 1996). However, when administered together, clopidogrel and aspirin provide more complete and uniform suppression of platelet activation via dual pathways for the lifespan of the platelet (average of 5–7 days; Moshfegh et al., 2000). The CURE trial randomized 12,562 patients with UA or NSTEMI to aspirin or DAPT with aspirin and clopidogrel. Patients randomized to DAPT had a reduced incidence of composite cardiovascular death, non-fatal MI, or stroke which was evident at 24 h (HR 0.66, CI 0.51–0.86, $p < 0.05$) and persisted for at least 12 months (HR 0.80, CI 0.72–0.90, $p < 0.001$). The event rate was driven primarily by a reduction in non-fatal MI. Not unexpectedly, the combination of clopidogrel and aspirin was associated with increased major bleeding rates (HR 1.38, CI 1.12–1.67, $p = 0.001$), although there was no difference in life threatening bleeding. Among the subgroup managed with a planned invasive strategy, the addition of clopidogrel was also associated with a significant reduction in composite cardiovascular death, non-fatal MI, or urgent target vessel revascularization at 30 days (HR 0.70, CI 0.50–0.97, $p = 0.03$), with no difference in major bleeding (HR 1.13, CI 0.61–2.1, $p = 0.69$; Mehta et al., 2001; Yusuf et al., 2001; Wright et al., 2011).

Despite these population level benefits, there is considerable inter-individual variability in response to clopidogrel that at least partially result from heterogeneity in CYP2C19 (Angiolillo et al., 2007). The most common CYP2C19 variant is CYP2C19(2,

Table 1 | Pharmacodynamics and pharmacokinetics of P2Y12 inhibitors in ACS.

Drug	Drug class	Half-life	Metabolism	Elimination	Onset*
Clopidogrel	Thienopyridine	6 h (pro-drug), 30 min (active metabolite)	Primarily CYP2C19	Renal and gastrointestinal	2 h
Prasugrel	Thienopyridine	2–15 h (active metabolite)	Serum esterase, CYP3A4, and CYP2B6	Renal and gastrointestinal	30 min
Ticagrelor	Cyclo-pentyl-triazolo-pyrimidine	8–9 h	Primarily CYP3A4	Hepatic and gastrointestinal	2–3 h

**Refers to loading dose administration.*

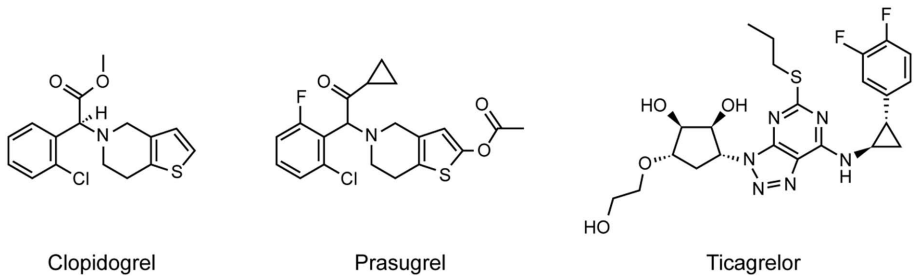

FIGURE 2 | Structure of P2Y12 inhibitors.

which has an allelic frequency between 25 and 55% depending on the ethnic population. Individuals with at least one copy of CYP2C19(2 have reduced plasma concentrations of the active clopidogrel metabolite and have reduced *in vitro* platelet responsiveness to clopidogrel (Kim et al., 2008; Kubica et al., 2011). Moreover, the CYP2C19(2 variant has been associated with significant increases in the risk of vascular events in a number of prospective studies and sub-studies of large ACS trials (reviewed elsewhere; Angiolillo et al., 2007; Kubica et al., 2011).

The concept of "tailored" anti-platelet therapy has emerged to describe an approach of providing stronger platelet inhibition to those patients with a lower risk of bleeding, in the early phases of ACS when ischemic complications are the highest, or in patients with residual HRP on DAPT (Wiviott et al., 2007; Antman et al., 2008). The latter have been identified as a high risk subset, with as much as a 6.7-fold increase in the 30-day risk of composite death, myocardial infarction, or revascularization in those undergoing PCI (Hochholzer et al., 2006). In patients with HPR, clopidogrel dose escalation can incrementally reduce platelet activity and decrease the incidence of HPR from 37 to 14% ($p = 0.002$; Gladding et al., 2008). However, whether HPR should dictate subsequent therapy is unclear. The GRAVITAS trial randomized patients that had undergone PCI with subsequent identification of HPR to placebo or an additional loading dose of clopidogrel (600 mg) and increased maintenance therapy (150 mg daily). There was no difference in the composite MI, cardiovascular death, or stent thrombosis rate at 6 months (HR 1.01, CI 0.58–1.76), despite a dose-associated reduction in HPR in those randomized to higher-dose clopidogrel (38 vs. 60%, $p < 0.001$; Price et al., 2011).

In order to overcome the impact of CYP2C19 heterogeneity on platelet responsiveness novel ADP receptor antagonists have been developed. Prasugrel is a thienopyridine structurally similar to clopidogrel (**Table 1**; **Figure 2**) but less dependent on CYP2C19 biotransformation, and provides faster and more pronounced platelet inhibition (**Table 1**; Mega et al., 2009b). In TRITON-TIMI 38, patients ($n = 13{,}608$) with ACS and planned PCI were randomized to prasugrel (60 mg loading dose followed by 10 mg daily) or clopidogrel (300 mg loading dose followed by 75 mg daily) for a median of 14.5 months. Prasugrel significantly reduced the incidence of non-fatal MI, (HR 0.76, CI 0.67–0.85, $p < 0.001$) driving a significant reduction in the composite cardiovascular outcome that also included cardiovascular death and stroke (HR 0.81, CI 0.73–0.90, $p < 0.001$). This benefit was associated with a significant increase in the risk of bleeding, including that classified as life threatening (HR 1.5, CI 1.1–2.1, $p = 0.01$) and fatal (HR 4.2, CI 1.6–11.1, $p = 0.002$; Wiviott et al., 2007).

TRIGGER-PCI, designed to evaluate the efficacy of prasugrel in patients undergoing PCI with HPR on clopidogrel therapy, was stopped after a preliminary analysis revealed low event rates and an unlikely benefit of prasugrel. The ongoing TRILOGY-ACS trial is evaluating prasugrel in patients with ACS undergoing medical management with HPR on clopidogrel therapy (Chin et al., 2010).

Unlike the thienopyridines, ticagrelor does not require conversion to its active metabolite and provides reversible inhibition of P2Y12 – features that theoretically confer less inter-individual variation (**Table 1**; **Figure 2**). In preclinical studies ticagrelor was not associated with greater bleeding than clopidogrel and provided more rapid and effective platelet inhibition (Husted et al., 2006; Storey et al., 2007). The PLATO trial compared ticagrelor to clopidogrel in ACS. In PLATO 18,624 patients admitted with ACS were randomized to ticagrelor (180 mg load, 90 mg twice daily) or clopidogrel (300 or 600 mg load, 75 mg daily). Ticagrelor was associated with a significant reduction in the composite endpoint

of vascular death, myocardial infarction, or stroke (RR 0.84, CI 0.77–0.92, $p = 0.0003$) as well as all cause mortality (HR 0.78, CI 0.69–0.89, $p < 0.001$) with no significant increase in the rate of composite major bleeding (HR 1.04, CI 0.95–1.13, $p = 0.43$). There was an increase in the intracranial bleeding rate (HR 1.87, CI 0.98–3.58, $p = 0.06$; Wallentin et al., 2009) although subgroup analyses demonstrated no increased bleeding rates in those identified as "high risk" from TRITON-TIMI 38 including those >75 years old (HR 1.04, CI 0.84–1.29, $p = 1.0$), <60 kg (HR 0.82, CI 0.60–1.12, $p = 0.12$) and with known cerebrovascular disease (HR 0.99, CI 0.71–1.37, $p = 0.77$; Wallentin et al., 2009).

Two novel anti-platelet agents have recently entered clinical trials for ACS: atopaxar and vorapaxar. Both are synthetic antagonists of the platelet thrombin receptor (protease activated receptor 1), and have the potential advantage of impeding platelet aggregation during rapid thrombin formation such as ACS (Morrow et al., 2009). In phase II trials with atopaxar, Japanese patients with ACS ($n = 241$) were randomized to 50–200 mg daily or placebo in addition to standard therapy (>96% aspirin, >89% clopidogrel) for 12 weeks. The bleeding rate was similar among all doses of atopaxar and placebo (5.0 vs. 6.6%, NS). However, there was an increased frequency of liver enzyme elevation among patients randomized to the 100 (6.2%) and 200 mg (14.8%) doses (Goto et al., 2010b). In phase II trial of vorapaxar, patients ($n = 1030$) with stable CAD undergoing non-urgent PCI receiving vorapaxar (10–40 mg load, with 0.5–2.5 mg daily) for 60 days had bleeding rates that were comparable to placebo (41% grouped vorapaxar vs. 35% placebo, NS). Moreover, those randomized to vorapaxar had non-significant reductions composite death or myocardial infarction (5% grouped vorapaxar vs. 7% placebo, NS; Becker et al., 2009). Phase III trials including more than 40,000 patients with ACS (TRACER) or a history of vascular disease (TrA2P-TIMI 50) are underway (Morrow et al., 2009; Van De Werf, 2010).

ANTI-THROMBOTIC AGENTS

HEPARINS

The heparins complex with anti-thrombin-III (AT-III) and accelerate AT-III mediated inhibition of factor Xa and thrombin (**Figure 1**). Unfractionated heparin (UFH) represents the cornerstone of anti-thrombotic therapy in ACS, but has a number of limitations. UFH poorly inhibits clot-associated thrombin activity resulting in persistent proaggregant and procoagulant thombin activity at the site of arterial thrombosis. Additional concerns with UFH include heparin-induced thrombocytopenia and thrombosis (HITT), the necessity of frequent monitoring, and platelet-activating effects at therapeutic doses (Xiao and Theroux, 1998).

Low molecular weight heparin (LMWH) provides greater factor Xa inhibition, a reduced incidence of HITT, and more predictable bioavailability and elimination characteristics than UFH. A number of trials comparing enoxaparin to UFH demonstrated comparable or superior efficacy with regard to ischemic ACS endpoints yet small increases in bleeding with enoxaparin, particularly when invasive strategies were employed (Antman et al., 1999, 2006; Goodman et al., 2000; Wallentin et al., 2003; Ferguson et al., 2004). A meta-analysis encompassing 12 randomized trials ($n = 49{,}088$) comparing enoxaparin to UFH in ACS concluded that there were significant reductions in the incidence of MI (HR 0.75, CI 0.65–0.86, $p < 0.001$) at 30 days, with an increase in major bleeding (HR 1.25, CI 1.04–1.50, $p = 0.02$). The net clinical benefit endpoint (death, MI, or major bleeding), approached significance at 30 days (HR 0.90, CI 0.76–1.00, $p = 0.051$; Murphy et al., 2007). Other LMWHs have also been evaluated in ACS but are in less frequent clinical use due to inferior clinical results (tinzaparin, dalteparin) or increased bleeding (nadroparin; Klein et al., 1997; Michalis et al., 2003; Katsouras et al., 2005; **Table 2**). As LMWHs are cleared renally and given that monitoring tests are less reliably available, UFH is preferable in those with advanced chronic kidney disease.

DIRECT FACTOR XA INHIBITORS

Direct factor Xa inhibitors block the coagulation cascade at an earlier step and are able to inhibit free and clot-associated factor Xa. Currently there is one direct factor Xa inhibitor FDA approved for use in ACS (fondaparinux) with three others in preclinical trials (apixaban, rivaroxaban, otamixaban). Fondaparinux is a synthetic pentasaccharide that mimics the AT-III binding portion of heparin and enhancing the anti-factor Xa activity >300-fold (**Table 3**; **Figure 3**). It is administered parenterally, eliminated

Table 2 | Low molecular weight heparins in ACS.

ESSENCE	In 3171 patients with UA or NSTEMI, enoxaparin reduced composite death, MI, recurrent angina at 30 days (19.8 vs. 23.3%, $p = 0.016$) and 12 months (32.0 vs. 35.7%, $p = 0.022$) with no change in major bleeding (6.5 vs. 7.0%; Goodman et al., 2000)
TIMI 11B	In 3910 patients with UA or non-Q wave MI, enoxaparin reduced composite death, MI, or urgent revascularization at 8 days (OR 0.83, CI 0.69–1.0, $p = 0.048$) with no increase in major bleeding (Antman et al., 1999)
SYNERGY	In 10 027 patients with NSTEMI and planned early invasive strategy, enoxaparin did not reduce composite death or non-fatal MI at 1 (14.0 vs. 14.5%, NS) or 6 months (17.6 vs. 17.8%, NS); increased major bleeding (9.1 vs. 7.6%; Ferguson et al., 2004)
FRISC	In 1506 patients with NSTEMI randomized to placebo or dalteparin. Dalteparin reduced composite death and MI at 6 days (HR 0.37, CI 0.20–0.68, $p = 0.001$), with no change in major or minor bleeding (FRISC Study Group, 1996)
FRIC	In 1482 patients with ACS dalteparin compared to UFH did not reduce composite death, MI, angina recurrence at 6 days (HR 1.18, CI 0.84–1.66, $p = 0.33$), there was no difference in major bleeding (1.0 vs. 1.1%; Klein et al., 1997)
FRAXIS	In 3468 patients with ACS nadroparin compared to UFH resulted in similar rates of composite cardiac death, MI, refractory angina, or recurrence of angina at day 14 (18.1 vs. 20.1%, NS) with increased major bleeding (3.5 vs. 1.6%, $p < 0.001$; FRAX. I. S. Study Group, 1999)
EVET	In 438 patients with ACS, enoxaparin compared to tinzaparin reduced composite recurrent angina, MI, or death at 30 days (17.7 vs. 28.0%, $p = 0.012$) with no difference in major bleeding (<2 patients per group, NS; Michalis et al., 2003)

Table 3 | Pharmacodynamics and pharmacokinetics of anti-coagulants in ACS.

Drug	Mechanism		Half-life	Metabolism	Elimination	Onset	Notes
UFH	AT-III mediated factor Xa and thrombin inhibitor	IV or SC	1–2 h	Hepatic	Extra-renal at therapeutic doses	Immediate (IV), 30 min (SC)	Inactive on clot-associated thrombin Unpredictable bioavailability
Enoxaparin	AT-III mediated factor Xa and thrombin inhibitor	SC	5–7 h	Hepatic	Renal	3–5 h	Inactive on clot-associated thrombin More factor Xa selectivity
Fondaparinux	Indirect factor Xa inhibitor	SC	17–21 h	Excreted largely as unchanged drug	Renal	2–3 h	Inactive on clot-associated thrombin Not for use in advanced CKD
Rivaroxaban	Direct factor Xa inhibitor	Oral	9–13 h	Hepatic	Renal and gastrointestinal	2–4 h	Phase III trials underway
Apixaban	(—) Factor Xa (direct)	Oral	12 h		Renal and biliary	3 h	Phase III trials underway
Otamixaban	(—) Factor Xa (direct)	IV	2–3 h		Biliary	Immediate	Phase III trials underway
Bivalirudin	Direct thrombin inhibitor, reversible	IV	25 min	Plasma proteases	Renal	Immediate	Inhibits clot-associated thrombin
Dabigatran	Direct thrombin inhibitor, reversible	Oral	12–17 h	Hepatic and plasma	Renal and gastrointestinal	1 h	Pro-drug, low bioavailability

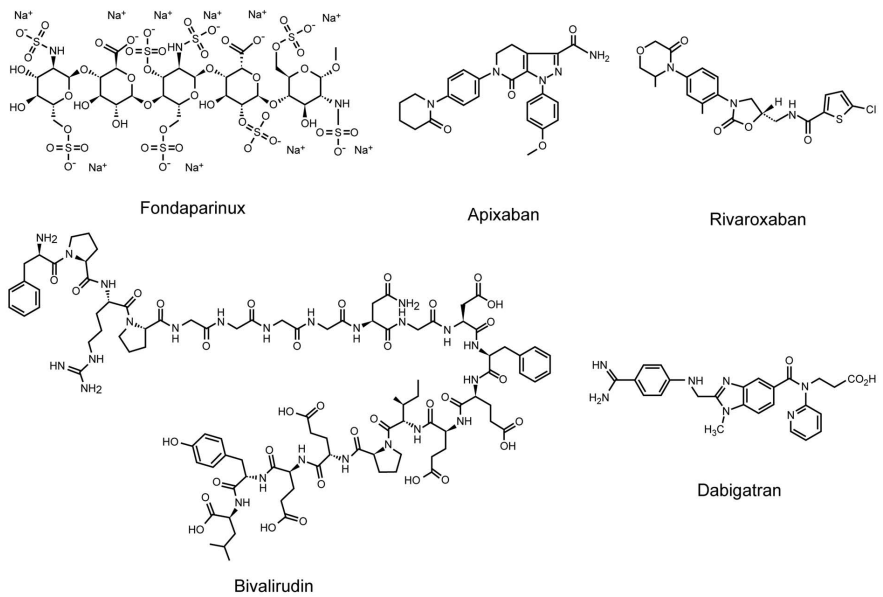

FIGURE 3 | Structure of factor Xa and direct thrombin inhibitors.

renally, with little inter-individual variability and no need for routine monitoring.

The utility of fondaparinux in ACS was first assessed in the dose finding PENTALYSE trial. STEMI patients ($n = 333$) undergoing thrombolysis were randomized to 48–72 h of UFH or one of five fondaparinux doses for 5–7 days. Patients receiving fondaparinux had lower 30 day revascularization rates (39 vs. 51%, $p = 0.054$) with a similar major bleeding risk (7.1 vs. 7.1%; Coussement et al., 2001). In the PENTUA trial patients with UA or NSTEMI were randomized to one of four doses of fondaparinux or enoxaparin for a period for 3–7 days after identification of ACS. Fondaparinux at the lowest dose (2.5 mg daily) provided a non-significant reduction in composite death, MI, or recurrent ischemia at 9 days (27.9 vs. 35.7% in the enoxaparin group, NS) with no major bleeding and comparable rates of minor bleeding (3.9 vs. 4.8%, NS; Simoons et al., 2004).

In the largest ACS trial to date (OASIS-5), over 20,000 patients with UA or NSTEMI were randomized to fondaparinux (2.5 mg daily) or enoxaparin (1 mg/kg twice daily) for a mean of 6 days. There was no difference in the incidence of composite death, non-fatal MI, or refractory ischemia (HR 1.01, CI 0.9–1.13) between fondaparinux and enoxaparin. However, major bleeding was

significantly decreased with fondaparinux at 9 days (HR 0.52, CI 0.44–0.61, $p < 0.001$) and all cause mortality was lower at 30 (HR 0.83, CI 0.71–0.91, $p = 0.02$) and 180 days (HR 0.89, CI 0.80–1.0, $p = 0.05$; Yusuf et al., 2006a). OASIS-6 was designed to determine whether fondaparinux was superior to UFH in STEMI patients who underwent mechanical revascularization or pharmacological thrombolysis (Yusuf et al., 2006b). Patients were randomized to fondaparinux (2.5 mg daily for 8 days or until discharge) or UFH (for 24–48 h); those in which UFH was deemed unnecessary (primarily following streptokinase administration) were randomized to fondaparinux or placebo. Fondaparinux was associated with a significant reduction in the incidence of the death or reinfarction at 30 days (HR 0.86, CI 0.77–0.96, $p = 0.008$); an effect that persisted to 6 months. There was no difference in bleeding rates.

The reductions in the composite cardiovascular outcomes with fondaparinux in the OASIS trials were restricted to those who underwent conservative management or thrombolysis, while the benefit of fondaparinux was not apparent in patients who underwent primary PCI. Furthermore, fondaparinux was associated with increased catheter related thrombi, prompting the subsequent use of procedural intravenous fondaparinux. In the event patients managed under a conservative strategy proceed to PCI on fondaparinux, current guidelines recommend a transition to an agent with anti-thrombin activity.

Otamixaban is a synthetic parenteral factor Xa inhibitor with a rapid onset of action and biliary clearance (**Table 3**; **Figure 3**). Phase II trials in patients undergoing planned PCI and those with high risk ACS are promising. Compared to UFH with eptifibatide, otamixaban has been associated with reductions in the rate of death or myocardial infarction at 7 days (HR 0.52, CI 0.28–0.98 with 0.105 mg/kg/h) with comparable rates of bleeding (3.1 vs. 2.7%; Cohen et al., 2007; Sabatine et al., 2009). The ongoing TAO trial is powered for ischemic endpoints and is evaluating otamixaban vs. UFH and eptifibatide in patients with ACS undergoing a planned invasive strategy.

Two orally administered synthetic factor Xa inhibitors are presently in phase III trials: rivaroxaban and apixaban (**Table 3**; **Figure 3**; Rothberg et al., 2005). Rivaroxaban is an orally administered factor Xa inhibitor, with high bioavailability and a rapid onset of action. ATLAS TIMI 46 was a phase II trial in which patients admitted with ACS and subsequently stabilized were randomized to placebo or escalating doses of rivaroxaban. Compared to placebo, rivaroxaban was associated with a non-significant decrease in the primary efficacy endpoint (death, MI, stroke, recurrent ischemia requiring revascularization) at the lowest dose (5 mg twice daily; HR 0.60, CI 0.29–1.25) with dose-dependent increases in bleeding (HR 1.71, CI 0.76–3.85 with 5 mg twice daily; Mega et al., 2009a). A phase III trial of 2.5 and 5 mg twice daily rivaroxaban is presently underway (ATLAS 2 TIMI 51).

Phase II trials with apixaban have yielded similar results (Alexander et al., 2009). The phase III APRAISE-2 trial, patients with ACS ($n = 7832$) were randomized to placebo or 5 mg twice daily of apixaban in addition to standard DAPT. At a mean follow up of 241 days, apixaban therapy was not associated with a reduction in composite cardiovascular death, MI, or stroke (HR 0.97, CI 0.8–1.1, $p = 0.51$) while resulting in increased major bleeding (HR 2.59, CI 1.5–4.5, $p = 0.001$; Alexander et al., 2011).

DIRECT THROMBIN INHIBITORS

Unlike the heparins, direct thrombin inhibitors are independent of AT-III, reduce the formation of fibrin monomers and abrogate the direct platelet-activating effects of thrombin on platelets. Direct thrombin inhibitors are also active on clot-bound thrombin, providing a regional specificity that heparins lack. Bivalirudin is approved for ACS, while dabigatran is currently in clinical trials.

Bivalirudin is a synthetic and reversible direct thrombin inhibitor (**Table 3**; **Figure 3**; Sibbing et al., 2008). Initially evaluated in patients with unstable or post-infarction angina undergoing planned angioplasty ($n = 4098$), bivalirudin therapy (1 mg/kg bolus then 2.5 mg/kg/h) reduced composite death, myocardial infarction, and repeat revascularization at 7 days (HR 0.78, CI 0.62–0.99, $p = 0.039$) with a reduced risk of bleeding (HR 0.34, CI 0.26–0.45, $p < 0.001$; Bittl et al., 2001). Subsequently REPLACE-2 was designed to compare the combination of UFH and GpIIb–IIIa inhibition to bivalirudin (0.75 mg/kg bolus, followed by 1.75 mg/kg/h for procedure duration) with provisional GpIIb–IIIa inhibition (if procedural complications dictated) in the setting of urgent or elective PCI ($n = 6010$). Bivalirudin was associated with a similar incidence in composite rate of death, myocardial infarction, and urgent revascularization (7.6 vs. 7.1%, $p = 0.40$), with a highly significant decrease in bleeding (2.4 vs. 4.1%, $p < 0.001$; Lincoff et al., 2003).

These trials, together with CACHET (Bittl et al., 2001; Lincoff et al., 2002) supported the use of bivalirudin during PCI, although patients with high risk ACS had been excluded. The ACUITY trial randomized nearly 14,000 patients with high risk UA or NSTEMI to (1) UFH or LMWH plus GpIIb–IIIa inhibitor, (2) bivalirudin plus GpIIb–IIIa inhibitor, or (3) bivalirudin alone. Bivalirudin alone conferred similar efficacy with respect to the primary cardiovascular endpoint (death, MI, urgent revascularization; HR 1.08, CI 0.93–1.24, $p < 0.001$ for non-inferiority) with significantly reduced major bleeding (HR 0.53, CI 0.43–0.65, $p < 0.001$) compared to the heparin group (Stone et al., 2006).

Finally, the HORIZONS-AMI trial was designed to specifically address whether or not bivalirudin offered a superior risk–benefit profile in patients with STEMI undergoing planned PCI. Patients with STEMI ($n = 3602$) within the preceding 12 h were randomized to heparin and GpIIb–IIIa or bivalirudin monotherapy (0.75 mg/kg bolus, then 1.75 mg/kg/h), with antithrombin therapies generally discontinued at PCI completion. Bivalirudin was associated with a reduced incidence of the composite outcome (death, reinfarction, revascularization, stroke, or major bleeding) at 30 days, driven primarily by decreased rates of major bleeding (HR 0.60, CI 0.46–0.77, $p < 0.001$), and death. All cause mortality at 30 days was significantly lower in the bivalirudin group (HR 0.66, CI 0.44–1.0, $p = 0.047$), an effect maintained at 3 year follow up. The bleeding and survival benefits of bivalirudin were evident in those that had received heparin therapy prior to randomization, and at all stages of renal disease – subgroups in where LMWH have proven less safe (Ferguson et al., 2004; Cohen et al., 2006), or are unadvised due to primary renal elimination and concern for bleeding risk (Robson, 2000; Sun et al., 2007). Whether or not early initiation of bivalirudin provides incremental benefit is the focus of the ongoing EUROMAX trial, in which patients with STEMI and

Table 4 | Recent trials of ACS therapies.

CLOPIDOGREL

GRAVITAS

Patients that underwent DES implantation with HPR on clopidogrel therapy were randomized to standard (75 mg daily) or high dose clopidogrel (150 mg daily). Primary endpoint was CV death, NFMI, definite, or probable stent thrombosis

High dose clopidogrel did not reduce composite primary outcome (Price et al., 2011)

PRASUGREL

TRITON-TIMI 38 sub-studies

Prasugrel conferred a reduction in primary endpoint in patients not undergoing stent implantation (HR 0.82, CI 0.53–1.25, p = 0.27), with an increase in non-CABG related major bleeding (0 vs. 5 events; Pride et al., 2009)

Prasugrel reduced incidence of primary endpoint in patients in patients that did (HR 0.76, CI 0.64–0.90) and did not (HR 0.78, CI 0.63–0.97) receive GpIIb–IIIa inhibitor therapy (O'donoghue et al., 2009)

Prasugrel resulted in greater platelet inhibition than clopidogrel in patients admitted with ACS both at 1–2 h and at 30 days (Michelson et al., 2009)

Prasugrel reduced incidence of primary endpoint at 30 days (HR 0.68, CI 0.54–0.87) and 15 months (HR 0.79, CI 0.65–0.97) in patients with STEMI; increased major post-CABG bleeding (HR 6.53, CI 1.78–23.94; Montalescot et al., 2009)

SWAP trial

Phase II trial in patients after ACS on clopidogrel 75 daily and then randomized to continued clopidogrel, prasugrel 10 mg daily, or prasugrel 60 mg once then 10 mg daily

Compared to maintenance clopidogrel, prasugrel therapy was associated with greater platelet inhibition as early as 2 h (60 mg load then 10 mg daily) and 6 days (10 mg daily) that persisted through 14 days (Angiolillo et al., 2010)

TICAGRELOR

PLATO sub-studies

Ticagrelor reduced primary endpoint (HR 0.84, CI 0.75–0.94), no difference in major bleeding (HR 0.99, CI 0.89–1.10) in those undergoing invasive strategy (Cannon et al., 2010)

In STEMI and planned reperfusion, ticagrelor reduced the incidence of primary endpoint (HR 0.87, CI 0.75–1.01), and all cause mortality (HR 0.82, CI 0.67–1.0), with no difference in major bleeding (Steg et al., 2010a)

In those with CKD ticagrelor reduced the incidence of primary endpoint (HR 0.77, CI 0.65–0.90), and all cause mortality (HR 0.72, CI 0.58–0.89; James et al., 2010)

BIVALRUDIN

HORIZONS-AMI

Acute stent thrombosis more frequent in patients randomized to bivalirudin (HR 4.43, CI 1.52–12.92; Dangas et al., 2011)

Bivalirudin provided comparable reductions in primary endpoints irrespective of the necessity for transfer to PCI-able facility (Wohrle et al., 2010)

In high risk patients bivalirudin use reduced 1 year mortality (8.4 vs. 15.9%, $p = 0.014$) and reinfarction (3.6 vs. 7.9%, $p = 0.042$; Parodi et al., 2010)

Bivalirudin provided comparable reductions in net adverse clinical events in those receiving 300 mg (12.3 vs. 15.2%, $p = 0.15$) and the 600 mg (7.3 vs. 10.4%, $p = 0.01$) clopidogrel prior to PCI (Dangas et al., 2009)

Bivalirudin monotherapy reduced net adverse cardiac events (HR 0.83, CI 0.71–0.97, $p = 0.02$), and all cause mortality (HR 0.71, CI 0.51–0.98) at 12 months (Mehran et al., 2009a)

ACUITY sub-studies

Patients ($n = 14{,}000$) with UA/NSTEMI randomized to heparin + GpIIb–IIIa inhibitor, bivalirudin + GpIIb–IIIa inhibitor, or bivalirudin alone. Primary endpoints: (1) death, NFMI, unplanned revascularization, (2) major bleeding, (3) ischemia and major bleeding

In those with CKD, bivalirudin reduced major bleeding (RR 0.64, CI 45–0.89, $p = 0.008$) with comparable composite ischemia effect (RR 1.18, CI 0.88–1.57, $p = 0.27$; Mehran et al., 2009b)

Bivalirudin was associated with reduced access-related major bleeding in patients that underwent femoral (3.0 vs. 5.8%, $p < 0.0001$), but not radial access (4.2 vs. 2.2%, $p = 0.19$; Hamon et al., 2009)

Among the elderly (>75 years old) bivalirudin resulted in comparable composite ischemia (11.7 vs. 9.6%, NS), with fewer major bleeds (5.8 vs. 10.1%, $p < 0.05$, NNT 16; Lopes et al., 2009)

Bivalirudin was associated with similar rates of early (<30 day) stent thrombosis (1.4 vs. 1.1%, $p = 0.37$; Aoki et al., 2009)

Bivalirudin was associated with less acquired thrombocytopenia (HR 0.75, CI 0.61–0.93; Caixeta et al., 2011)

No relationship between the time to anti-thrombin initiation and ischemic outcomes in patients admitted with ACS. Thirty-day bleeding risk increased as time to anti-thrombin initiation increased (OR 1.44, CI 1.15–1.80; Diercks et al., 2011)

Among patients undergoing PCI to vein grafts, there was a comparable incidence of major cardiac events and major bleeding with bivalirudin monotherapy (Kumar et al., 2010)

Among patients referred for medical therapy after angiography (32.4%), bivalirudin resulted in less major bleeding (4.4 vs. 2.5%, $p = 0.005$) with no difference in composite ischemia endpoint at 30 days (HR 0.87, CI 0.55–1.37) or 1 year (HR 1.01, CI 0.76–1.34; Goto et al., 2010a)

(Continued)

Table 4 | Continued

CLOPIDOGREL
Retrospective registry study of retroperitoneal hemorrhage after PCI in Michigan between 2002 and 2007
Bivalirudin use was associated with significantly fewer retroperitoneal hemorrhages (OR 0.51, CI 0.34–0.76, $p < 0.001$; Trimarchi et al., 2010)
ACTION registry sub-study
Retrospective study of anti-coagulant strategy from January to December 2007 in patients with NSTEMI undergoing PCI ($n = 11,085$)
Compared to reference heparin + GpIIb–IIIa (64%), bivalirudin alone (10.5%) was associated with less major bleeding (OR 0.48, CI 0.39–0.60) and lower in-hospital mortality (OR 0.39, CI 0.21–0.71; Lopes et al., 2010)
FONDAPARINUX
OASIS-6 sub-study
Patients ($n = 12,092$) with STEMI were randomized to fondaparinux (2.5 mg daily) or UFH. Primary endpoint was death, MI, or refractory ischemia at 30 days
There were comparable reductions in the incidence composite death or MI, as well as the incidence of major bleeding across age tertiles (Van Rees Vellinga et al., 2010)
FUTURE/OASIS-8
Standard (85 U/kg UFH bolus and ACT 300–350 or 60 U/kg and ACT 250–300 if GpIIb–IIIa) or low-dose (50 U/kg UFH bolus without ACT adjustment) heparin regimen during PCI in patients with NSTEMI that received initial fondaparinux
No difference between UFH regimens on composite major and minor bleeds (OR 0.80, CI 0.54–1.12, $p = 0.27$) but a trend toward increased composite death, MI, TVR (OR 1.58, CI 0.98–2.53, $p = 0.06$; Steg et al., 2010b)
French registry of anti-coagulant use in the setting of ACS between January and December 2007
Adjusted 30 day mortality rates were higher in patients treated with UFH compared to fondaparinux as the initial (HR 3.1, CI 1.3–7.4), and final anti-coagulant (HR 3.1, CI 1.3–7.3; Schiele et al., 2010)
OASIS-5
Fondaparinux reduced major bleeding in patients receiving discretionary GpIIb–IIIa inhibition (HR 0.60, CI 0.46–0.78) or pre-procedural thienopyridines (HR 0.62, CI 0.52–0.73; Jolly et al., 2009)
Fondaparinux was associated with a cost savings of $547 (CI $207–$924) per patient compared to enoxaparin therapy at 6 months (Sculpher et al., 2009)
Fondaparinux was associated with a similar incidence primary endpoint (NS at all strata), and significantly lower risk of major bleeding with in patients with low (HR 0.55, CI 0.39–0.77), medium (HR 0.53, CI 0.40–0.70), and high (HR 0.50, CI 0.38–0.64) risk of bleeding (Joyner et al., 2009)
RIVAROXABAN
ATLAS ACS TIMI 46
Patients with stabilized ACS ($n = 3,491$) randomized to rivaroxaban or placebo and treated for 6 months. Primary safety endpoint: clinically significant bleeding; Primary efficacy endpoint: death, NFMI, stroke, or recurrent ischemia
At 5 mg twice daily, rivaroxaban was associated with increased bleeding (HR 1.71, CI 0.76–3.85), and a non-significant reduction in primary efficacy endpoint (HR 0.60, CI 0.29–1.25; Mega et al., 2009a)
APIXABAN
APPRAISE
Patients with stabilized ACS ($n = 1,715$) randomized to one of four doses of apixaban or placebo. Primary outcome was major or clinically relevant bleeding. Secondary outcome was CV death, MI, severe recurrent ischemia, or ischemic stroke
At the lowest dose studied, apixaban (2.5 mg twice daily) was associated with non-significant increases in bleeding (HR 1.8, CI 0.91–2.48, $p = 0.09$), and non-significant decreases in composite CV death, MI, recurrent ischemia, and stroke (HR 0.73, CI 0.44–1.2, $p = 0.21$; Alexander et al., 2009)
OTAMIXABAN
SEPIA-ACS TIMI 42
Patients with NSTEMI ($n = 3,241$) were randomized to one of five otamixaban doses or UFH plus eptifibatide. Primary efficacy endpoint: death, MI, urgent revascularization, or bailout GpIIb–IIIa inhibitor use. Primary safety endpoint: CABG unrelated bleeding
Otamixaban at an intermediate dose (0.105 mg/kg/h) was associated with reduced incidence of primary efficacy endpoint (R 0.61, CI 0.36–1.02), with a non-significant increase in bleeding (3.1 vs. 2.7%; Sabatine et al., 2009)

planned PCI will be provided bivalirudin or UFH by emergency medical personnel.

Dabigatran is a synthetic, competitive, and reversible direct thrombin inhibitor with good oral bioavailability (**Table 3**; **Figure 3**). Recently approved for the prevention of stroke in patients with atrial fibrillation (Connolly et al., 2009), dabigatran is undergoing evaluation in ACS. In a phase II dose finding study, patients with ACS and at high risk for additional events were randomized to dabigatran twice daily or placebo a median of 7 days after the event and treated for 6 months. Preliminary findings demonstrated no difference in rate of composite cardiovascular death, non-fatal myocardial infarction, or stroke (3.8% on placebo, 4.6% 50 mg, 3.5% 150 mg) or the risk of bleeding (0.54% on placebo, 0.81% 50 mg, 1.73% 150 mg), although there was a

trend toward increased minor bleeding at every dose (Oldgren et al., 2009).

CONCLUSION

Platelet aggregation and thrombus formation comprise the intermediary events between plaque instability and MI, and pharmacological inhibition of these events has led to substantial reductions in ischemic complications and mortality. Newer agents are characterized by more predictable pharmacokinetics, reduced inter-individual response variability, and activity at the site of coronary occlusion. Recently approved agents (bivalirudin, fondaparinux, prasugrel, ticagrelor) have improved outcomes in clinical trials by more effectively balancing the anti-ischemic benefits and bleeding risks during ACS. Identifying the timing and setting of anti-platelet and anti-coagulant initiation, and the subgroups in which one agent provides a comparably favorable risk-benefit profile remains an area of active investigation (**Table 4**).

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