Drug Saf (2015) 38:481–491
DOI 10.1007/s40264-015-0286-8

REVIEW ARTICLE

Risks and Benefits of Triple Oral Anti-Thrombotic Therapies After Acute Coronary Syndromes and Percutaneous Coronary Intervention

Joakim Alfredsson[1,2] · Matthew T. Roe[2]

Published online: 1 April 2015

Abstract The key pathophysiological process underlying symptomatic coronary artery disease, including acute coronary syndromes (ACS), is usually a rupture or an erosion of an atherosclerotic plaque, followed by platelet activation and subsequent thrombus formation. Early clinical trials showed benefit with long-term aspirin treatment, and later—based on large clinical trials—dual anti-platelet therapy (DAPT), initially with clopidogrel, and more recently with prasugrel or ticagrelor, has become the established treatment in the post-ACS setting and after percutaneous coronary intervention (PCI). Treatment with DAPT is recommended for both ST-elevation myocardial infarction and non-ST-elevation ACS, as well as after PCI with stenting, in American and European clinical guidelines. Notwithstanding the benefits observed with DAPT, including third-generation $P2Y_{12}$ receptor inhibitors plus aspirin, ACS patients remain at high risk for a recurrent cardiovascular event, suggesting that other treatment strategies, including the addition of a third oral anti-platelet agent or a novel oral anticoagulant (NOAC) to standard DAPT regimens, may provide additional benefit for post-ACS patients and for patients undergoing PCI. Adding a third anti-thrombotic agent to DAPT after an ACS event or a PCI procedure has been shown to have modest benefit in terms of ischemic event reduction, but has consistently been associated with increased bleeding complications. Therefore, the quest to optimize anti-thrombotic therapies post-ACS and post-PCI continues unabated but is tempered by the historical experiences to date that indicate that careful patient and dose selection will be critical features of future randomized trials.

Key Points

Even with dual anti-platelet therapy (DAPT), including third-generation $P2Y_{12}$ receptor inhibitors plus aspirin, patients with acute coronary syndromes (ACS) remain at high risk for a recurrent cardiovascular event, suggesting that other treatment strategies added to standard DAPT regimens may provide additional benefit for post-ACS patients and for patients undergoing percutaneous coronary intervention (PCI).

Only one thrombin receptor antagonist (vorapaxar) and two novel oral anticoagulants (apixaban and rivaroxaban) have been tested in phase III clinical trials after an ACS.

Adding a third anti-thrombotic agent (protease-activated receptor [PAR]-1 antagonist or novel oral anticoagulant [NOAC]) to DAPT after an ACS event or a PCI procedure has been shown to have modest benefit in terms of ischemic event reduction, but has consistently been associated with increased bleeding complications.

✉ Joakim Alfredsson
joakim.alfredsson@liu.se

[1] Department of Cardiology and Department of Medical and Health Sciences, Linköping University, Linköping, Sweden

[2] Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA

1 Introduction

The key pathophysiological process that underlies symptomatic coronary artery disease (CAD), including acute coronary syndromes (ACS), is usually a rupture or an erosion of an atherosclerotic plaque, revealing sub-endothelial matter to the circulating blood components, followed by platelet activation and subsequent thrombus formation. Activated platelets trigger the coagulation system, leading to formation of thrombin, which converts soluble fibrinogen to fibrin, but, also, being one of the most potent platelet stimulators, further activates platelets. Collectively, activated platelets and the endogenous coagulation system mutually trigger thrombus formation [1].

Early clinical trials showed benefit with long-term aspirin treatment, which has long been standard of care after ACS [2, 3]. With the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial, the benefits of dual anti-platelet therapy (DAPT) with aspirin plus a $P2Y_{12}$ receptor inhibitor (in this case, clopidogrel) for the treatment of ACS (unstable angina [UA] and non-ST-elevation myocardial infarction [NSTEMI]) were established, with approximately 20 % reduction in composite ischemic events through 12 months, with aspirin plus clopidogrel vs. aspirin plus placebo. However, the majority of patients in the CURE trial were managed medically without revascularization [4].

The optimal anti-thrombotic regimen after percutaneous coronary intervention (PCI) with coronary stent placement was not clearly established for many years as stent thrombosis was initially a major clinical problem, with worse outcomes observed with aspirin plus a vitamin K antagonist (VKA) compared with DAPT (aspirin plus a $P2Y_{12}$ receptor inhibitor) [5]. Further studies showed similar findings and contributed to the establishment of DAPT as the standard of care following PCI, with the optimal duration of DAPT following either drug-eluting stent (DES) or bare-metal stent (BMS) still under debate [6–8].

Further advances have been observed with the development of more potent, third-generation $P2Y_{12}$ receptor inhibitors (prasugrel and ticagrelor) used together with aspirin for an intensified DAPT regimen after an ACS. TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) compared prasugrel with clopidogrel, in addition to aspirin, in a population with ACS and planned PCI; PLATO (Study of Platelet Inhibition and Patients Outcomes) compared ticagrelor with clopidogrel, in addition to aspirin, in a broad ACS population when administered upstream before angiography and revascularization. In both trials, the composite ischemic outcome of cardiovascular death (CVD), myocardial infarction (MI), or stroke was lowered by approximately 20 %, and the incidence of stent thrombosis decreased by 25–50 % with the more potent DAPT regimen, but with an increase in major bleeding of up to 25–30 % [9, 10]. Based on these data, treatment with DAPT is recommended for both ST-elevation MI (STEMI) and UA/NSTEMI as well as after PCI with stenting in American College of Cardiology (ACC)/American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines [11–16].

Long-term treatment with the oral VKA warfarin plus aspirin after an ACS has been studied in earlier trials. In a meta-analysis, warfarin (with international normalized ratio [INR] of 2–3) and aspirin lowered the incidence of recurrent ischemic events after ACS with about 25 %, compared with aspirin monotherapy, with no reduction in all-cause mortality and more than twice the frequency of major bleeding complications [17]. To date, no large-scale randomized trials have compared warfarin added to DAPT; however, observational data have demonstrated very high bleeding rates when combining warfarin and DAPT. Therefore, the combination is not recommended, except in patients with an indication for oral anticoagulation, such as atrial fibrillation, mechanical valve prosthesis, or venous thromboembolic disease, who have an ACS event or undergo PCI [18, 19]. The short-term use of subcutaneous anticoagulants following an ACS event has been associated with a lower risk of ischemic events, but these treatments have typically been administered for only 1–2 months. Given the lack of large-scale trials with an oral VKA plus DAPT following ACS or PCI and the limited treatment duration for subcutaneous anticoagulants with anti-platelet therapies following an ACS event in prior trials, these treatment strategies are not specifically addressed in this paper [20–23].

Notwithstanding the benefits observed with DAPT including third-generation $P2Y_{12}$ receptor inhibitors plus aspirin, ACS patients remain at high risk for a recurrent cardiovascular event (composite ischemic event rates in the prasugrel and ticagrelor treatment arms in the TRITON and PLATO trials were approximately 10 %) even with optimized DAPT regimens [9, 10]. The high residual risk of recurrent ischemic events following ACS suggest that other treatment strategies, including the addition of a third oral anti-platelet agent or a novel oral anticoagulant (NOAC) to standard DAPT regimens, may provide additional benefit for ACS patients and also potentially for patients undergoing PCI.

Therefore, the aim of this manuscript is to review the current evidence for long-term ‘triple’ oral anti-thrombotic therapies following an ACS event or a PCI procedure.

2 Additional Anti-Platelet Agents for Acute Coronary Syndromes (ACS) and Percutaneous Intervention (PCI)

2.1 Cilostazol

Cilostazol is a phosphodiesterase inhibitor that has been shown to decrease platelet aggregation [24]. Several randomized trials have compared triple anti-platelet therapy—including cilostazol, aspirin, and clopidogrel—vs. DAPT (aspirin and clopidogrel) after PCI with stent implantation [25–29]. A recent meta-analysis that included 19 trials and a total of 7464 patients treated with PCI and stent implantation observed a significantly lower rate of target vessel revascularization (risk ratio [RR] 0.65, 95 % confidence interval [CI] 0.55–0.77) and less angiographic restenosis (RR 0.54, 95 % CI 0.45–0.65, $p < 0.00001$), but no significant difference in the frequency of MI (RR 0.92, 95 % CI 0.63–1.34) or all-cause death (RR 0.77, 95 % CI 0.55–1.09) with the triple anti-platelet regimen including cilostazol compared with DAPT. However, no significant difference was observed in major/minor/minimal bleeding with this treatment strategy (RR 1.20, 95 % CI 0.92–1.57) [30]. Most of the trials included in this meta-analysis were conducted in East Asia, and cilostazol treatment is not recommended by the ACC/AHA or ESC guidelines for STEMI, UA/NSTEMI, or PCI. Nor is it approved for ACS or post-PCI in the USA and Europe [11–16].

2.2 Thrombin Receptor Inhibitors

Thrombin is the most important link between platelet activation and activation of the coagulation cascade in an atherothrombotic situation. Thrombin is also regarded as the most powerful platelet activator through interaction with the protease-activated receptors (PARs) on the platelet surface (Fig. 1) [31]. Two novel thrombin inhibitors, atopaxar and vorapaxar, are reversible inhibitors of the PAR-1 receptor that have been studied in recent clinical trials in an effort to further diminish platelet activation without excess bleeding based upon pre-clinical observations that suggested a favorable safety profile for these agents [32].

2.2.1 Atopaxar

The PAR-1 receptor antagonist atopaxar has been evaluated in two phase II trials. The LANCELOT-ACS (Lessons From Antagonizing the Cellular Effect of Thrombin-Acute Coronary Syndrome) trial randomized 603 patients with NSTE-ACS within 72 h of admission to receive atopaxar 50 mg, 100 mg, or 200 mg vs. placebo for 12 weeks in addition to standard care. The incidence of

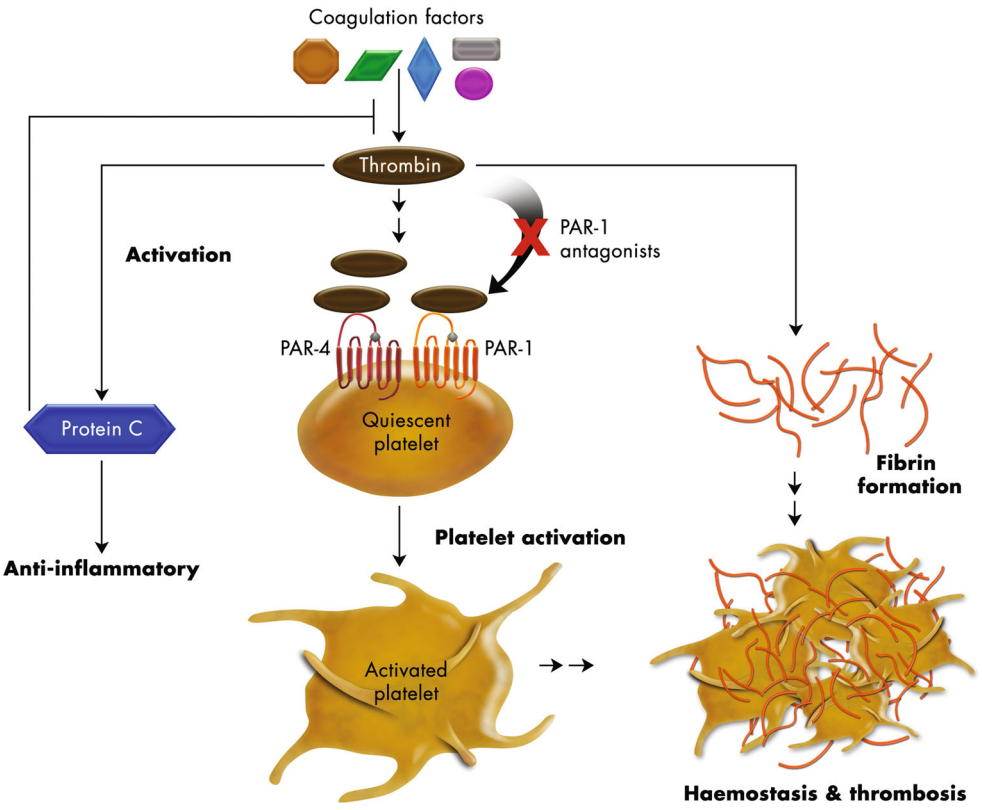

Fig. 1 Role of thrombin and protease-activated receptor (PAR)-1 antagonists in hemostasis and thrombosis. Reproduced from Angiolillo et al. [52] with permission from Oxford University Press and the author

CURE major or minor bleeding did not differ between the combined atopaxar groups and placebo (3.08 vs. 2.17 %, $p = 0.63$) and, although major bleeding was numerically higher with atopaxar, it did not reach statistical significance (1.80 vs. 0 %, $p = 0.12$). The incidence of composite ischemic outcomes (CVD, MI, stroke, or recurrent ischemia) was also similar with atopaxar vs. placebo (8.03 vs. 7.75 %, $p = 0.93$) [33]. Comparable results were obtained in the smaller Japanese-LANCELOT trial [34]. However, in both trials, a dose-dependent increase in liver enzymes and rate of QTc prolongation raised concerns and resulted in the development of atopaxar being suspended.

2.2.2 *Vorapaxar*

In preclinical trials, the oral PAR-1 receptor antagonist vorapaxar has been shown to inhibit thrombin-induced platelet aggregation without an increase in bleeding events [35], with similar findings observed with vorapaxar in a phase II trial when used in addition to standard treatment with aspirin and clopidogrel in ACS patients [36]. Based on these promising results, two large-scale randomized phase III trials have been conducted: the TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in ACS) and the TRA-2P (Thrombin Receptor Antagonist in Secondary Prevention of atherothrombotic ischemic events).

In the TRACER trial, 12,944 patients with NSTE-ACS were randomized to vorapaxar (maintenance dose of 2.5 mg daily for a minimum of 1 year) vs. placebo added to standard therapy including DAPT (99 % were treated with aspirin and 92 % were also treated with clopidogrel). The primary efficacy endpoint, a combination of CVD, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization through 2 years, was similar with vorapaxar compared with placebo (18.5 vs. 19.9 %; hazard ratio [HR] 0.92; 95 % CI 0.85–1.01). For the

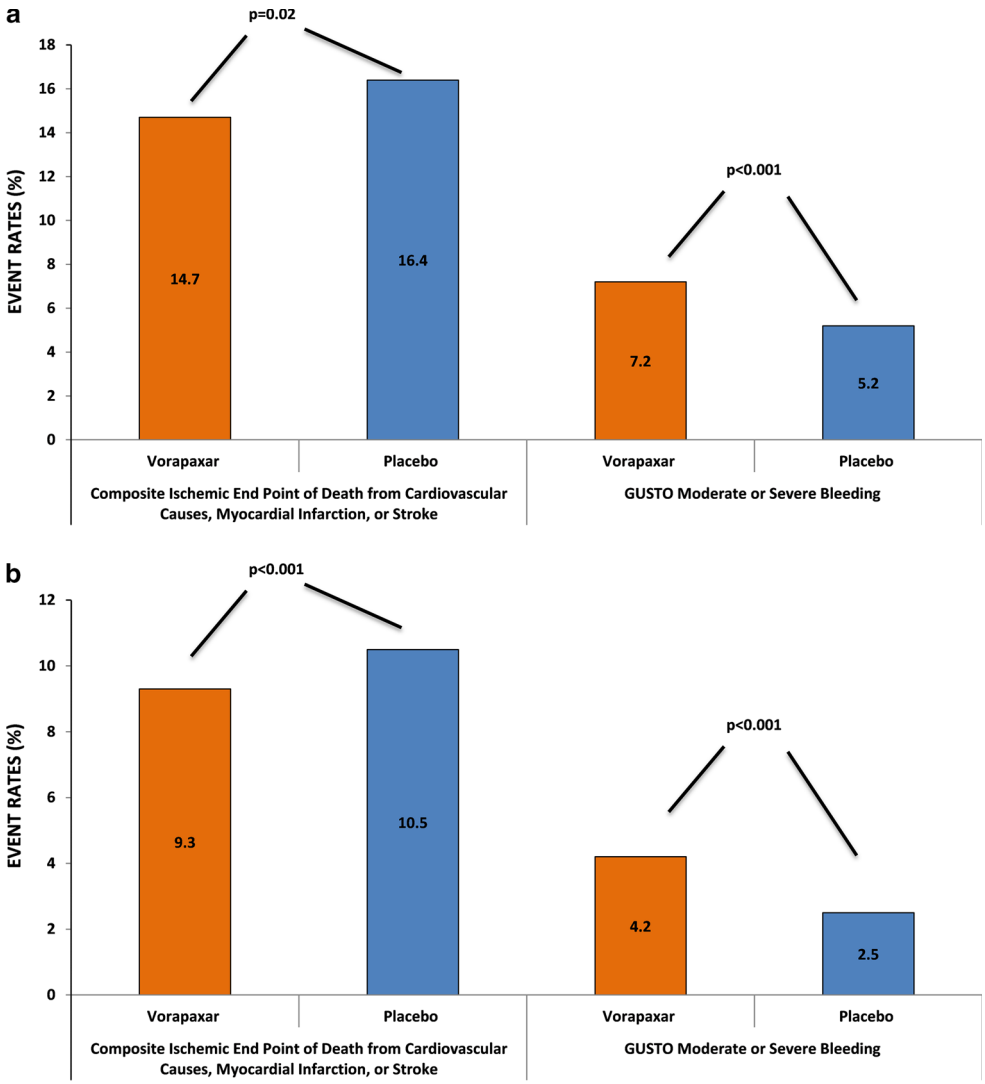

Fig. 2 **a** Kaplan–Meier estimates over 2 years of follow-up in the TRACER trial for the composite ischemic endpoint death from cardiovascular causes, myocardial infarction, or stroke, and GUSTO moderate or severe bleeding. **b** Kaplan–Meier estimates over 3 years of follow-up in the TRA-2P trial for the composite ischemic endpoint death from cardiovascular causes, myocardial infarction, or stroke, and GUSTO moderate or severe bleeding. *GUSTO* Global Use of Strategies to Open Occluded Arteries

secondary efficacy endpoint, CVD, MI, or stroke, there was a statistically significant difference, with a lower incidence in patients randomized to vorapaxar (14.7 vs. 16.4 %; HR 0.89; 95 % CI 0.81–0.98) (Fig. 2a). However, the frequency of GUSTO (Global Use of Strategies to Open Occluded Arteries) severe or moderate bleeding was significantly increased with vorapaxar (7.2 vs. 5.2 %; HR 1.35, 95 % CI 1.16–1.58) (Fig. 2a), with a threefold increase in the frequency of intracranial hemorrhage (ICH) (1.1 vs. 0.2 %; HR 3.39; 95 % CI 1.78–6.45) [37]. Findings were similar among key patient subgroups, including those managed medically and those treated with PCI. Based upon these results and the signal of increased ICH risk with vorapaxar that was amplified in patients with a history of stroke, the TRACER trial was stopped prematurely.

In the TRA-2P trial, 26,449 patients with a history of MI or ischemic stroke (within 2 weeks to 12 months) or peripheral artery disease (PAD) were randomized to vorapaxar (2.5 mg maintenance dose with background aspirin in 94 % of patients) vs. placebo with background aspirin therapy. The proportion of patients also treated with DAPT with a thienopyridine (almost exclusively clopidogrel) added to aspirin was 62 %, with large differences depending on whether MI, stroke, or PAD was the qualifying event. After completion of the enrollment and a median of 24 months of follow-up, the data and safety monitoring board reported an excess of ICH in patients with a history of stroke and recommended discontinuation of the study drug in these patients but that the trial be continued in the rest of the study population. After reporting of the TRACER trial results, the primary endpoint in the TRA-2P trial was changed to the more common composite endpoint of CVD, MI, or stroke. At 3 years of follow-up, the primary outcome occurred in 9.3 % of the vorapaxar group compared with 10.5 % in the placebo group (HR 0.87; 95 % CI 0.80–0.94) (Fig. 2b). The main secondary endpoint, a composite of CVD, MI, stroke, or recurrent ischemia leading to urgent revascularization, was also lower with vorapaxar (11.2 vs. 12.4 %; HR 0.88; 95 % CI 0.82–0.95). However, GUSTO severe or moderate bleeding occurred more frequently with vorapaxar (4.2 vs. 2.5 %; HR 1.66; 95 % CI 1.43–1.93) (Fig. 2b). The rate of ICH was also significantly higher with vorapaxar (1.0 vs. 0.5 %; HR 1.94; 95 % CI 1.39–2.70) [38]. In a later analysis in 14,042 patients with a history of stent implantation before randomization plus 449 patients receiving a stent during the trial, vorapaxar significantly reduced the incidence of late or very late ST (1.1 vs. 1.4 %; HR 0.71; 95 % CI 0.51–0.98) [39]. Based upon these results, vorapaxar has been approved in the USA for secondary prevention in patients with a history of MI or PAD and no history of prior transient ischemic attack or stroke.

3 Novel Oral Anticoagulants for ACS and PCI

Thrombin is not only the most powerful platelet activator but is also the most important link between the coagulation system and platelet activation. Elevated levels of thrombin have been detected after an ACS, and standard DAPT regimens have little effect on thrombin-mediated platelet activation. Inhibition of thrombin generation could therefore mitigate the risk of thrombotic events following ACS and PCI. Among the NOAC agents that inhibit steps in the coagulation system, two oral direct thrombin inhibitors, (ximelagatran and dabigatran) and three oral factor Xa antagonists (rivaroxaban, apixaban, and darexaban) have been evaluated in the post-ACS setting for patients without an indication for oral anticoagulation such as atrial fibrillation (Fig. 3).

3.1 Ximelagatran

In the effect of ximelagatran on ischemic events and death in patients with recent myocardial damage (ESTEEM) trial, the oral direct thrombin inhibitor ximelagatran (with background aspirin therapy) was found to be associated with a lower frequency of the composite endpoint of death, MI, or recurrent severe ischemia compared with placebo (12.7 vs. 16.3 %; HR 0.76; 95 % CI 0.59–0.98), without a significant increase in major bleeding (1.8 vs. 0.9 %; HR 1.97; 95 % CI 0.80–4.84) [40]. However, ximelagatran was subsequently found to be associated with hepatic toxicity, so development was suspended.

3.2 Dabigatran

Dabigatran, an oral direct thrombin inhibitor with a half-life of 12–17 h, was evaluated in the RE-DEEM (Randomized Dabigatran Etexilate Dose Finding Study In Patients With Acute Coronary Syndromes Post Index Event With Additional Risk Factors For Cardiovascular Complications Also Receiving Aspirin And Clopidogrel) phase II dose-escalation trial. A total of 1861 patients with an ACS within the last 14 days and planned treatment with DAPT were randomized to placebo or one of four dabigatran doses (50 mg twice daily [bid], 75 mg bid, 110 mg bid, or 150 mg bid). The rate of the primary outcome, a composite of International Society of Thrombosis and Hemostasis (ISTH) major or clinically relevant non-major bleeding through 6 months was 3.5, 4.3, 7.9, and 7.8 % across the dabigatran dosing groups, respectively, compared with 2.2 % in the placebo arm ($p < 0.001$ for the trend). The incidence of the ischemic composite endpoint of CV death, MI, or ischemic stroke was similar across the dabigatran dosing groups: 4.6, 4.9, 3.0, and 3.5 % compared with 3.8 % in the placebo arm

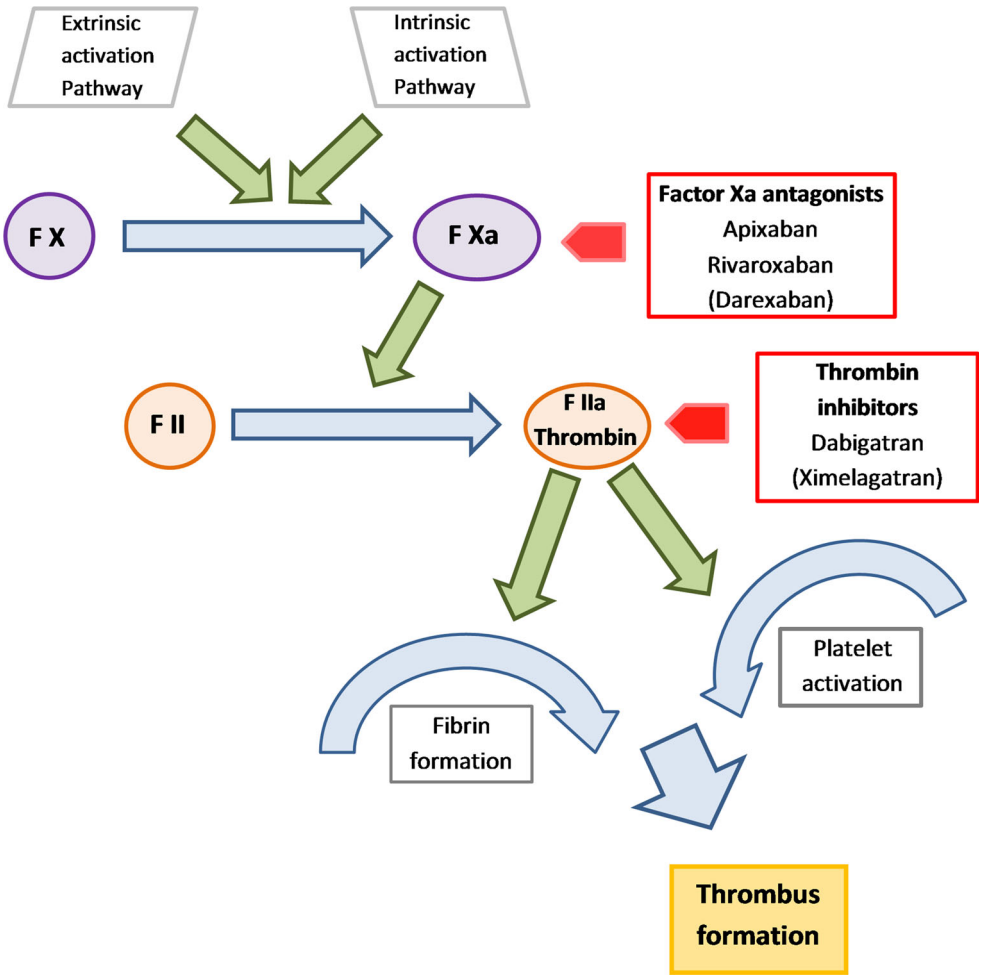

Fig. 3 Simplified model of coagulation activation, clot formation, and mode of action of novel oral anticoagulants. *F* factor

[41]. Further phase III trials with dabigatran in the post-ACS setting have not been performed.

3.3 Darexaban

Darexaban, an oral factor Xa inhibitor with a half-life of 14–18 h, was evaluated in a dose-escalation phase II trial RUBY-1 (Study Evaluation Safety, Tolerability and Efficacy of YM150 in Subjects with ACS). In this trial, 1279 patients with a recent ACS were randomized, within 7 days of presentation, to placebo or one of six darexaban doses (5 mg bid, 10 mg every day [qd], 15 mg bid, 30 mg qd, 30 mg bid, or 60 mg qd) with background DAPT treatment. The primary outcome, ISTH major or clinically relevant non-major bleeding, occurred in 3.1 % of patients treated with placebo and increased sequentially with higher darexaban doses (6.2, 6.5, and 9.3 % in 10 mg, 30 mg, and 60 mg qd regimens, respectively). The secondary ischemic composite endpoint of death, MI, stroke, or recurrent ischemia through 6 months was similar with darexaban (all doses combined) compared with placebo (6.5 vs. 5.2 %) [42]. Further phase III trials with darexaban in the post-ACS setting have not been performed.

3.4 Apixaban

Apixaban, a direct oral factor Xa inhibitor with a half-life of 12 h was evaluated in a dose-escalation phase II trial APPRAISE-1 (Apixaban for Prevention of Acute Ischemic Events 1). In this trial, 1715 patients with a recent ACS (within 7 days), and with at least one cardiovascular risk factor, were randomized to placebo or one of four doses of apixaban (2.5 mg bid, 10 mg qd, 10 mg bid, or 20 mg qd) for 6 months, with DAPT use in 81 % of patients. During the trial, as recommended by the data monitoring committee, the two higher doses of apixaban were discontinued because of a significant increase in bleeding. Compared with placebo, both of the lower doses of apixaban resulted in higher rates of ISTH major or clinically relevant non-major bleeding that appeared to be dose dependent, with the rates for 2.5 mg bid being 5.7 vs. 3.0 % (HR 1.78; 95 % CI 0.91–3.48) and those for 10 mg qd being 7.9 vs. 3.0 % (HR 2.45; 95 % CI 1.31–4.61), respectively. Lower numeric rates of the ischemic composite endpoint of death, MI, ischemic stroke, or recurrent severe ischemia were observed for apixaban 2.5 mg bid

(7.6 vs. 8.7 %; HR 0.73; 95 % CI 0.44–1.19) and 10 mg qd (6.0 vs. 8.7 %; HR 0.61; 95 % CI 0.35–1.04), respectively [43].

Based on the results from the APPRAISE-1 trial, an apixaban dose of 5 mg bid was chosen for the phase III trial (APPRAISE-2). After recruitment of 7392 ACS patients (of the 10,800 planned), the trial was prematurely stopped because of an increase in major bleeding that was not counterbalanced by a reduction in ischemic events. The final trial results demonstrated that, at a median follow-up of 241 days, the primary efficacy endpoint of CV death, MI, or ischemic stroke occurred in 7.5 % of patients randomized to apixaban compared with 7.9 % in patients randomized to placebo (HR 0.95; 95 % CI 0.80–1.11) (Fig. 4a), whereas TIMI (Thrombolysis in Myocardial Infarction) major bleeding (1.3 vs. 0.5 %; HR 2.59; 95 % CI 1.50–4.46) (Fig. 4a) and ICH (0.3 vs. 0.1 %; HR 4.06; 95 % CI 1.15–14.38) occurred more frequently with apixaban vs. placebo [44].

3.5 Rivaroxaban

Rivaroxaban, an oral, direct factor Xa inhibitor with a half-life of 5–7 h, was evaluated in the phase II ATLAS ACS-1 (Anti-Xa Therapy to lower cardiovascular events in addition to Aspirin with or without thienopyridine therapy in Subjects with ACS-Thrombolysis In Myocardial Infarction) trial. Rivaroxaban (tested in escalating total doses from 5 mg to 20 mg daily) was evaluated in 3491 patients with ACS that had been stabilized after their initial presentation. The risk of the primary safety endpoint, TIMI major/minor bleeding or bleeding requiring medical attention, increased with rivaroxaban in a dose-dependent manner: HR 2.21 (95 % CI 1.25–3.91) for 5 mg; HR 3.35 (95 % CI 2.31–4.87) for 10 mg; HR 3.60 (95 % CI 2.32–5.58) for 15 mg; and HR 5.06 (95 % CI 3.45–7.42) for 20 mg, respectively (trend $p < 0.0001$). No difference was observed in the primary ischemic endpoint of death, MI, stroke, or severe recurrent ischemia between the

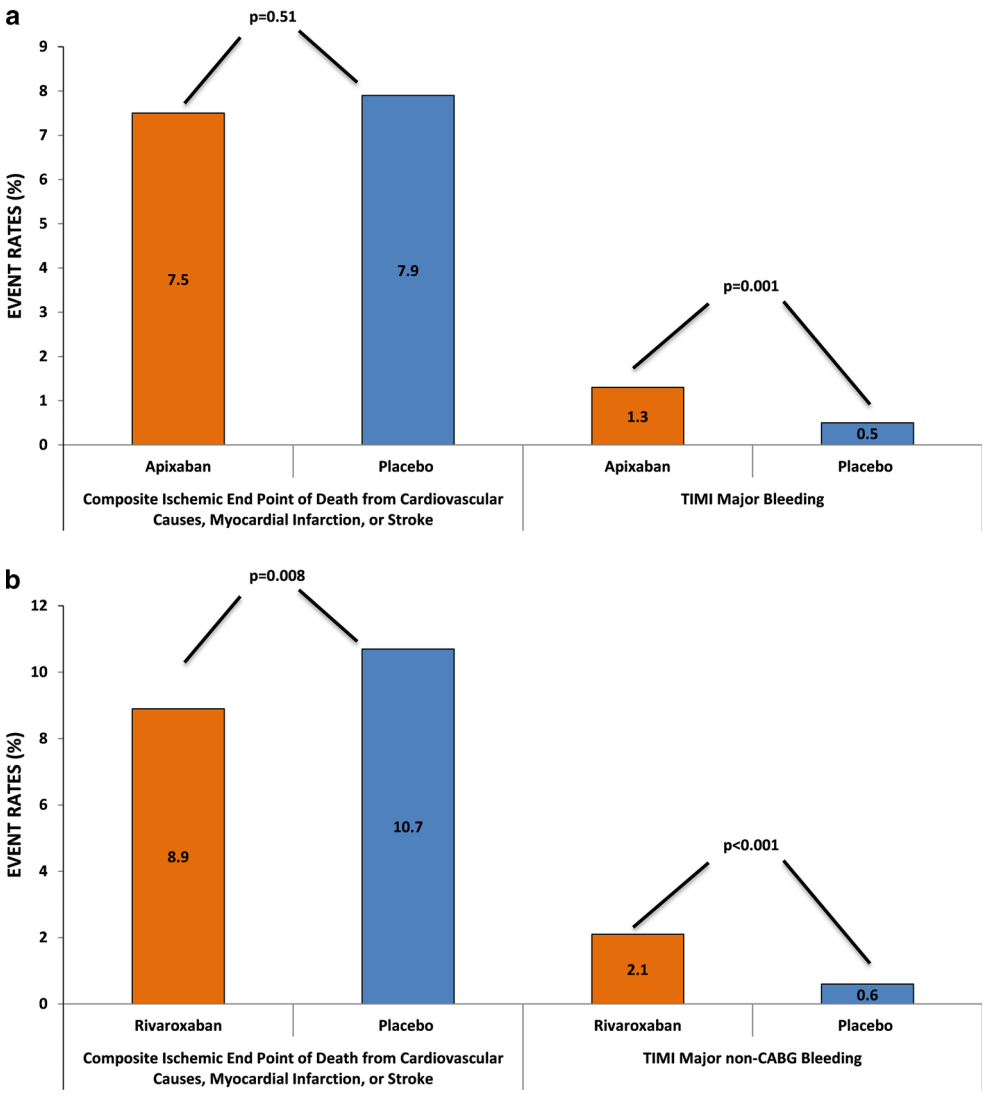

Fig. 4 **a** Event rates for the primary ischemic outcome death from cardiovascular causes, myocardial infarction, or stroke and TIMI major bleeding at a median follow-up of 241 days in the APPRAISE-2 trial. **b** Kaplan–Meier estimates over 2 years of follow-up in the ATLAS ACS 2 trial (both doses combined) for the composite ischemic endpoint death from cardiovascular causes, myocardial infarction, or stroke, and TIMI major non-CABG bleeding. *CABG* coronary artery bypass graft, *TIMI* Thrombolysis in Myocardial Infarction

combined rivaroxaban doses vs. placebo (5.6 vs. 7.0 %; HR 0.79; 95 % CI 0.60–1.05); but a signal of benefit in the secondary efficacy endpoint of death, MI, or stroke was observed with rivaroxaban (3.9 vs. 5.5 %; HR 0.69; 95 % CI 0.50–0.96) [45].

Based on the results of the ATLAS ACS-1 trial, two doses of rivaroxaban (2.5 mg bid and 5 mg bid) were chosen for the ATLAS ACS-2 phase III trial that randomized a total of 15,526 patients with a recent ACS event. After a mean duration of treatment of 13.1 months, which included DAPT therapy in 87 % of patients, the combined rivaroxaban doses were associated with a significant decrease in the frequency of the primary efficacy endpoint of CV death, MI, or stroke compared with placebo (8.9 vs. 10.7 %; HR 0.84; 95 % CI 0.74–0.96) (Fig. 4b). The benefits of rivaroxaban were consistent in both doses, with primary efficacy endpoint rates of 9.1 vs. 10.7 % (HR 0.84; 95 % CI 0.72–0.97) with the 2.5 mg dose and 8.8 vs. 10.7 % (HR 0.85; 95 % CI 0.73–0.98) with the 5 mg dose, respectively. An unexpected finding of a significant decrease in the frequency of cardiovascular death was observed only with the 2.5 mg bid rivaroxaban dose (2.7 vs. 4.1 %; HR 0.66; 95 % CI 0.51–0.86). Finally, the frequencies of TIMI major bleeding not related to coronary artery bypass grafting (2.1 vs. 0.6 %; HR 3.96; 95 % CI 2.46–6.38) (Fig. 4b) and ICH (0.6 vs. 0.2 %, $p = 0.009$) were increased with the combined rivaroxaban doses compared with placebo and also increased in a dose-dependent fashion from the 2.5 mg bid vs. 5 mg bid doses [46]. Subsequently, rivaroxaban was approved for use in the post-ACS setting in Europe, but not in the USA.

4 Discussion

4.1 Thrombin Receptor Inhibitors

Vorapaxar is the only PAR-1 receptor inhibitor that has been tested in phase III trials, but results from the two trials conducted have shown a similar directionality in the treatment effect with vorapaxar and a similar increased risk of major bleeding, but with different findings in terms of statistical significance. While the primary efficacy endpoint in the TRA-2P trial (a composite of cardiovascular death, MI, or stroke) was significantly lowered with vorapaxar compared with placebo, the primary efficacy endpoint in the TRACER trial (a composite of CVD, MI, stroke, or recurrent ischemia with rehospitalization/urgent revascularization) was not. However, when the triple composite efficacy endpoint (cardiovascular death, MI, or stroke) was assessed in the TRACER trial, results were similar to those of the TRA-2P, with almost identical point estimates for vorapaxar in the two trials. The addition of recurrent ischemia as a component of the primary composite endpoint in the TRACER trial appears to have diluted the treatment effect of vorapaxar that was apparent when the triple composite endpoint of cardiovascular death, MI, or stroke was analyzed. Nonetheless, bleeding rates were substantially increased and to a similar degree with vorapaxar in both trials, especially in patients with a history of stroke.

Both similarities and differences exist between the TRACER and TRA-2P trials. The time from hospital admission for ACS to randomization was <24 h in the TRACER trial, while the TRA- 2P trial protocol allowed for the inclusion of MI patients from 2 weeks to 12 months after an index MI event, with more than 55 % of MI patients included after more than 3 months, and 26 % of the patients after more than 6 months. Consequently, patients in the TRACER trial were more often treated with intravenous and subcutaneous anticoagulants and anti-platelets when randomization occurred, and those concomitant medications may have affected the initial delicate balance between ischemic benefits and bleeding risks. Furthermore, patients with a prior MI who were enrolled in the TRA-2P trial likely had a lower bleeding risk because of the time of randomization, since patients who experienced a major bleeding event between the time of the index MI event and the time of screening for the trial would likely not have been considered for randomization. The scenario was different in the TRACER trial, where randomization occurred early, before bleeding events may have occurred, but the point estimate for major bleeding with vorapaxar was actually higher in the TRA-2P trial than in the TRACER trial. Notwithstanding these differences between the TRACER and TRA-2P trials, vorapaxar has been approved in the USA, for patients with a history of MI or PAD, but without a history of prior ischemic stroke. Furthermore, the risks and benefits of vorapaxar with single (aspirin) vs. DAPT (aspirin + clopidogrel) have not been fully elucidated, and vorapaxar has not been tested in a setting using the more potent $P2Y_{12}$ receptor inhibitors (ticagrelor and prasugrel).

4.2 Novel Oral Anticoagulants

Of the many NOAC agents tested in the post-ACS setting, only apixaban and rivaroxaban were evaluated in large phase III trials with widespread background use of DAPT in both trials. The combined doses of rivaroxaban in the ATLAS ACS-2 trial were associated with a significant reduction in the ischemic composite endpoint of cardiovascular death, MI, or stroke, whereas no difference was seen with the single dose of apixaban in the APPRAISE-2 trial.

Two major differences between the two trials may explain the observed differences in the primary trial results.

First, the apixaban dose utilized was the same as the dose used for full systemic anticoagulation for atrial fibrillation in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, whereas the rivaroxaban doses tested were one-fourth to one-half of the total daily dose used for full systemic anticoagulation for atrial fibrillation in the ROCKET (Rivaroxaban Once-daily oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial [47, 48]. Higher doses of an NOAC in the post-ACS setting with frequent use of DAPT could indeed disturb the balance between mitigating the risk of ischemic events and increasing bleeding risks. Second, key differences existed in the inclusion criteria for these two trials, with two cardiovascular high-risk features in addition to a recent ACS required for inclusion in the APPRAISE-2 trial, while a recent ACS alone was sufficient for inclusion in the ATLASACS-2 trial. These differences in inclusion criteria likely explain the different trajectories of the ischemic composite event curves in the two trials as well as the relative differences in the bleeding complications with the NOAC vs. placebo. These findings may also indicate that patient clinical characteristics have a key influence on the delicate balance between ischemic benefits vs. bleeding risks when NOACs are added to anti-platelet therapies in the post-ACS setting.

A recent meta-analysis included all seven phase II and III trials that evaluated an NOAC in ACS, a total of 30,866 patients, 86.6 % of whom were treated with DAPT (aspirin plus clopidogrel). In this meta-analysis, the NOACs were associated with a slightly lower risk of all-cause mortality, MI, or stroke (HR 0.87; 95 % CI 0.80–0.95) at the cost of a substantially higher bleeding risk (HR 2.34; 95 % CI 2.06–2.66). DAPT appeared to be an important determinant for ischemic benefits with an NOAC, because an enhanced treatment effect was observed in the subgroup of patients treated with aspirin monotherapy (HR for the NOAC treatment effect for the ischemic composite endpoint = 0.70; 95 % CI 0.59–0.84), but a residual bleeding risk also persisted (HR 1.79; 95 % CI 1.54–2.09) [49]. Nonetheless, the NOACs have not been tested in settings using the more potent $P2Y_{12}$ receptor inhibitors (ticagrelor and prasugrel).

In the quest to delineate the optimal use of NOACs with anti-platelet agents, several ongoing trials are investigating NOACs with various combinations of anti-platelet agents (aspirin and/or $P2Y_{12}$ inhibitors) in patients with atrial fibrillation undergoing PCI given the intriguing exploratory findings from the WOEST (What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing) trial, which suggested that the combination of warfarin and $P2Y_{12}$ inhibitor (clopidogrel) monotherapy may have a favorable efficacy and safety profile following PCI compared with triple therapy with warfarin, aspirin, and clopidogrel [50]. These results have prompted consideration of this DAPT (without aspirin) following PCI for patients with atrial fibrillation with indications for an oral anticoagulant in recently published consensus recommendations from Europe [51]. Ongoing trials with rivaroxaban (PIONEER [NCT01830543]) and dabigatran (REDUAL-PCI [NCT02164864]), and a planned trial with apixaban (not yet named or registered on http://www.clinicaltrials.gov), will evaluate a variety of anti-platelet strategies with VKAs and a variety of doses of NOACs. These should provide further evidence regarding the safety and potential efficacy of dual-therapy and triple-therapy combinations for patients with atrial fibrillation (with an indication for an oral anticoagulant) who undergo PCI, and these results may inform treatment considerations as previously described.

5 Conclusions

Adding a third anti-thrombotic agent to DAPT after an ACS event or a PCI procedure has been shown to have modest benefit in terms of ischemic event reduction, but has consistently been associated with increased bleeding complications. Notwithstanding these consistent observations, both vorapaxar and rivaroxaban have been approved for use in the USA and Europe, respectively, for the indications previously detailed. Intriguing findings have been observed with the addition of a PAR-1 receptor inhibitor or an NOAC to aspirin monotherapy post-ACS, but $P2Y_{12}$ receptor inhibitors (especially the more potent agents, ticagrelor and prasugrel) have consistent benefits following ACS and PCI, so it is unlikely that these agents will be replaced in future studies. A promising path of future investigation appears to be comparing aspirin with a low dose of an NOAC (with background $P2Y_{12}$ receptor inhibition)—a strategy that will be tested in post-ACS patients with low-dose rivaroxaban in the upcoming GEMINI-1 trial (http://www.clinicaltrials.gov/ct2/show/NCT02293395). Therefore, the quest to optimize anti-thrombotic therapies post-ACS and post-PCI continues unabated, but it is tempered by historical experiences to date that indicate that careful patient and dose selection will be critical features of future randomized trials.

Acknowledgments This manuscript was co-written entirely by the authors with no external funding support. Dr. Joakim Alfredsson has consulted for Bristol-Meyers Squibb, Sanofi-Aventis, and Eli-Lilly and has received lecture fees from Astra-Zeneca, Novartis, Merck, Sharp & Dome, and Sanofi-Aventis. Dr. Matthew Roe has received research funding from Eli Lilly, Sanofi-Aventis, Amgen, Daiichi-Sanko, Janssen Pharmaceuticals, Ferring Pharmaceuticals, the ACC,

the AHA, and the Familial Hypercholesterolemia Foundation, and has consulted for or received honoraria from Astra Zeneca, Boehringer-Ingelheim, Merck, Amgen, and Elsevier Publishers. All conflicts of interest are listed online at https://www.dcri.org/about-us/conflict-of-interest.

References

1. Corti R, Farkouh ME, Badimon JJ. The vulnerable plaque and acute coronary syndromes. Am J Med. 2002;113(8):668–80.
2. Theroux P, Waters D, Qiu S, McCans J, de Guise P, Juneau M. Aspirin versus heparin to prevent myocardial infarction during the acute phase of unstable angina. Circulation. 1993;88(5 Pt 1):2045–8.
3. Baigent C, Collins R, Appleby P, Parish S, Sleight P, Peto R. ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. The ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. BMJ. 1998;316(7141):1337–43.
4. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345(7):494–502.
5. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med. 1998;339(23):1665–71.
6. Schomig A, Neumann FJ, Kastrati A, Schuhlen H, Blasini R, Hadamitzky M, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med. 1996;334(17):1084–9.
7. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. 2014;371(23):2155–2166.
8. Colombo A, Chieffo A. Dual antiplatelet therapy after drug-eluting stents—how long to treat? N Engl J Med. 2014;371(23):2225–6.
9. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045–57.
10. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357(20):2001–15.
11. Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). Eur Heart J. 2012;33(20):2569–619.
12. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(4):e362–425.
13. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011;32(23):2999–3054.
14. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. 2014 AHA/ACC Guideline for the management of patients with non-st-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130(25):2354–94.
15. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for percutaneous coronary intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011;124(23):2574–609.
16. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014;35(37):2541–619.
17. Andreotti F, Testa L, Biondi-Zoccai GG, Crea F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. Eur Heart J. 2006;27(5):519–26.
18. Hansen ML, Sorensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadsboll N, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Arch Intern Med. 2010;170(16):1433–41.
19. Task Force members, Lip GY, Windecker S, Huber K, Kirchhof P, Marin F, et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). Eur Heart J. 2014;35(45):3155–79.
20. No authors listed. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and fast revascularisation during instability in coronary artery disease. Investigators. Lancet 1999;354(9180):701–7.
21. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. JAMA. 2006;295(13):1519–30.
22. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med. 2006;354(14):1464–76.
23. Antman EM, McCabe CH, Gurfinkel EP, Turpie AG, Bernink PJ, Salein D, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. Circulation. 1999;100(15):1593–601.
24. Tamai Y, Takami H, Nakahata R, Ono F, Munakata A. Comparison of the effects of acetylsalicylic acid, ticlopidine and cilostazol on primary hemostasis using a quantitative bleeding time test apparatus. Haemostasis. 1999;29(5):269–76.
25. Gao W, Zhang Q, Ge H, Guo Y, Zhou Z. Efficacy and safety of triple antiplatelet therapy in obese patients undergoing stent implantation. Angiology. 2013;64(7):554–8.

26. Youn YJ, Lee JW, Ahn SG, Lee SH, Choi H, Yu CW, et al. Multicenter randomized trial of 3-month cilostazol use in addition to dual antiplatelet therapy after biolimus-eluting stent implantation for long or multivessel coronary artery disease. Am Heart J. 2014;167(2):241–8 e1.
27. Douglas JS Jr, Holmes DR Jr, Kereiakes DJ, Grines CL, Block E, Ghazzal ZM, et al. Coronary stent restenosis in patients treated with cilostazol. Circulation. 2005;112(18):2826–32.
28. Lee SW, Park SW, Kim YH, Yun SC, Park DW, Lee CW, et al. A randomized, double-blind, multicenter comparison study of triple antiplatelet therapy with dual antiplatelet therapy to reduce restenosis after drug-eluting stent implantation in long coronary lesions: results from the DECLARE-LONG II (Drug-Eluting Stenting Followed by Cilostazol Treatment Reduces Late Restenosis in Patients with Long Coronary Lesions) trial. J Am Coll Cardiol. 2011;57(11):1264–70.
29. Han Y, Li Y, Wang S, Jing Q, Wang Z, Wang D, et al. Cilostazol in addition to aspirin and clopidogrel improves long-term outcomes after percutaneous coronary intervention in patients with acute coronary syndromes: a randomized, controlled study. Am Heart J. 2009;157(4):733–9.
30. Chen J, Meng H, Xu L, Liu J, Kong D, Chen P, et al. Efficacy and safety of cilostazol based triple antiplatelet treatment versus dual antiplatelet treatment in patients undergoing coronary stent implantation: an updated meta-analysis of the randomized controlled trials. J Thromb Thrombolysis. 2015;39(1):23–34.
31. Leger AJ, Covic L, Kuliopulos A. Protease-activated receptors in cardiovascular diseases. Circulation. 2006;114(10):1070–7.
32. Major CD, Santulli RJ, Derian CK, Andrade-Gordon P. Extracellular mediators in atherosclerosis and thrombosis: lessons from thrombin receptor knockout mice. Arterioscler Thromb Vasc Biol. 2003;23(6):931–9.
33. O'Donoghue ML, Bhatt DL, Wiviott SD, Goodman SG, Fitzgerald DJ, Angiolillo DJ, et al. Safety and tolerability of atopaxar in the treatment of patients with acute coronary syndromes: the lessons from antagonizing the cellular effects of Thrombin-Acute Coronary Syndromes Trial. Circulation. 2011; 123(17):1843–53.
34. Goto S, Ogawa H, Takeuchi M, Flather MD, Bhatt DL, Investigators JL. Double-blind, placebo-controlled Phase II studies of the protease-activated receptor 1 antagonist E5555 (atopaxar) in Japanese patients with acute coronary syndrome or high-risk coronary artery disease. Eur Heart J. 2010;31(21):2601–13.
35. Ueno M, Ferreiro JL, Angiolillo DJ. Mechanism of action and clinical development of platelet thrombin receptor antagonists. Expert Rev Cardiovasc Ther. 2010;8(8):1191–200.
36. Becker RC, Moliterno DJ, Jennings LK, Pieper KS, Pei J, Niederman A, et al. Safety and tolerability of SCH 530348 in patients undergoing non-urgent percutaneous coronary intervention: a randomised, double-blind, placebo-controlled phase II study. Lancet. 2009;373(9667):919–28.
37. Tricoci P, Huang Z, Held C, Moliterno DJ, Armstrong PW, Van de Werf F, et al. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. N Engl J Med. 2012;366(1):20–33.
38. Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. N Engl J Med. 2012;366(15):1404–13.
39. Bonaca MP, Scirica BM, Braunwald E, Wiviott SD, O'Donoghue ML, Murphy SA, et al. Coronary stent thrombosis with vorapaxar versus placebo: results from the TRA 2 P-TIMI 50 trial. J Am Coll Cardiol. 2014;64(22):2309–17.
40. Wallentin L, Wilcox RG, Weaver WD, Emanuelsson H, Goodvin A, Nystrom P, et al. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial. Lancet. 2003;362(9386):789–97.
41. Oldgren J, Budaj A, Granger CB, Khder Y, Roberts J, Siegbahn A, et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J. 2011;32(22):2781–9.
42. Steg PG, Mehta SR, Jukema JW, Lip GY, Gibson CM, Kovar F, et al. RUBY-1: a randomized, double-blind, placebo-controlled trial of the safety and tolerability of the novel oral factor Xa inhibitor darexaban (YM150) following acute coronary syndrome. Eur Heart J. 2011;32(20):2541–54.
43. Committee AS, Investigators Alexander JH, Becker RC, Bhatt DL, Cools F, et al. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. Circulation. 2009;119(22):2877–85.
44. Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med. 2011;365(8):699–708.
45. Mega JL, Braunwald E, Mohanavelu S, Burton P, Poulter R, Misselwitz F, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet. 2009;374(9683): 29–38.
46. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012;366(1):9–19.
47. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–92.
48. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91.
49. Oldgren J, Wallentin L, Alexander JH, James S, Jonelid B, Steg G, et al. New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis. Eur Heart J. 2013;34(22): 1670–80.
50. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet. 2013;381(9872):1107–15.
51. Lip GY, Windecker S, Huber K, Kirchhof P, Marin F, Ten Berg JM, et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). Eur Heart J. 2014;35(45):3155–79.
52. Angiolillo DJ, Capodanno D, Goto S. Platelet thrombin receptor antagonism and atherothrombosis. Eur Heart J. 2010;31(1): 17–28.