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REVIEW ARTICLE

Oral Antiplatelet Therapy for Secondary Prevention of Acute Coronary Syndrome

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Abstract
Patients surviving an acute coronary syndrome (ACS) remain at increased risk of ischemic events long term. This paper reviews current evidence and guidelines for oral antiplatelet therapy for secondary prevention following ACS, with respect to decreased risk of ischemic events versus bleeding risk according to individual patient characteristics and risk factors. Specifically, data are reviewed from clinical studies of clopidogrel, prasugrel, ticagrelor and vorapaxar, as well as the results of systematic reviews and meta-analyses looking at the benefits and risks of oral antiplatelet therapy, and the relative merits of shorter versus longer duration of dual antiplatelet therapy, in different patient groups.

Key Points

Patients surviving an acute coronary syndrome (ACS) remain at increased risk of ischemic events long term.

The availability of new antiplatelet agents and extended or combination therapy has increased the options for secondary prevention among ACS patients.

1 Introduction

Patients with a history of acute coronary syndrome (ACS) remain at increased risk of ischemic events long term [1–3]. Data from the Global Registry of Acute Coronary Events (GRACE) showed that more than half (53.6%) of ACS patients were re-hospitalized at least once during the 5-year follow-up period after discharge [3]. During the immediate 2 years after ACS, 7.1% of patients died, 6.3% experienced heart failure, and 4.4% experienced reinfarction, despite treatment aimed at secondary prevention [4]. In another global registry, Reduction of Atherothrombosis for Continued Health (REACH), almost a fifth of patients with a prior myocardial infarction (MI) either died or experienced another MI or a stroke over the following 4 years, with the greatest risk in those who had had an event within the year prior to enrollment [1]. In recent years, the outlook for ACS patients has improved with the expansion of available options for antithrombotic treatment [5]. This narrative review provides a critical discussion based on the author's review of the medical literature concerning current oral antiplatelet therapy for secondary prevention following ACS with respect to individual patient characteristics and risk factors.

2 Platelet Activation

Platelets play a pivotal role in the pathogenesis of ACS. While activation of circulating platelets is essential for normal hemostasis in response to vascular injury, their activation and aggregation in the context of atherosclerotic plaque rupture or erosion promote pathological thrombus formation [6]. Atherosclerotic plaque and thrombi may occlude the blood vessels, thereby blocking the supply of oxygen to the tissues and resulting in an ischemic event. When the coronary arteries are affected, this can result in stable or unstable angina, depending on the degree and nature of the blockage; if the ischemia is severe, the outcome is MI and necrosis.

Multiple cellular pathways participate in the activation and aggregation of platelets at the site of endothelial

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disruption, and represent pharmacological targets for the acute and long-term treatment of atherothrombosis (Fig. 1) [5]. Secondary prevention strategies for ACS patients currently focus on the inhibition of three key platelet activation pathways: thromboxane A2 (TXA-2) generation via cyclooxygenase-1 (COX-1); adenosine diphosphate (ADP)-mediated activation of the $P2Y_{12}$ receptor; and thrombin-mediated activation of protease-activated receptor-1 (PAR-1).

3 Oral Antiplatelet Agents

Table 1 provides a summary of the key attributes of the oral antiplatelet agents described in this section.

3.1 Aspirin

The benefit of aspirin therapy for secondary prevention of ischemic events in patients at high risk for atherothrombosis is well established [7]. Aspirin irreversibly acetylates COX-1, inhibiting formation of the prothrombotic mediator TXA-2 from arachidonic acid. Its antiplatelet effects occur rapidly, and it takes 3–4 days for complete recovery of platelet aggregation after stopping treatment [8].

Aspirin remains a first-line, foundation treatment for prevention of ischemic events after ACS, and a daily maintenance dose of 75–100 mg is recommended indefinitely [9, 10]. Lower aspirin doses are preferred because higher doses (≥ 160 mg) are usually associated with increased bleeding risk without an improvement in ischemic outcomes [7, 11, 12]. As aspirin cannot prevent platelet activation via other pathways, combination therapy with another oral antiplatelet agent is usually recommended, and the combined use of aspirin and $P2Y_{12}$ inhibitors has been shown to provide additive inhibition of platelet activation [5, 13]. Aspirin resistance, i.e., a lower than normal platelet inhibitory effect, has been reported in some patient populations, and may be

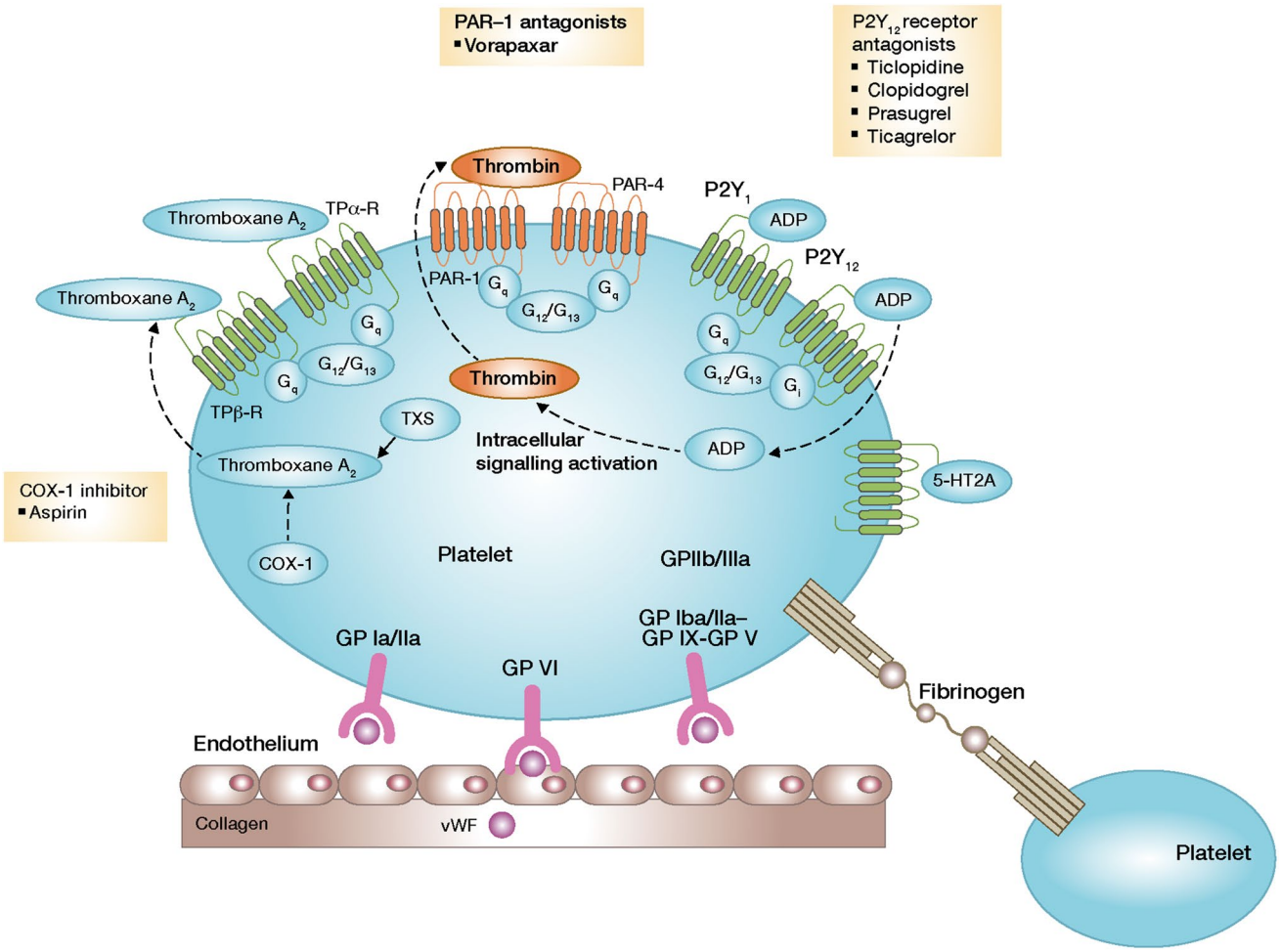

Fig. 1 Cellular targets for oral antiplatelet agents. *ADP* adenosine diphosphate, *COX* cyclooxygenase, *GP* glycoprotein, *PAR* protease-activated receptor, *vWF* von Willebrand factor

Table 1 Key pharmacological properties of oral antiplatelets. Adapted from Franchi and Angiolillo [5]. Aspirin onset/offset data added from Jimenez et al. [8]

Property	Aspirin	Clopidogrel	Prasugrel	Ticagrelor	Vorapaxar
Reversibility of binding to $P2Y_{12}$ receptor	Irreversible	Irreversible	Irreversible	Reversible	Reversible
Prodrug	No	Yes	Yes	No	No
Target	COX-1	$P2Y_{12}$	$P2Y_{12}$	$P2Y_{12}$	PAR-1
Onset of action	15 min[a]	2–8 h	30 min–4 h	30 min–4 h	1–2 h
Offset of action	3–4 days[a]	5–7 days	7–10 days	3–5 days	2–3 weeks
Maintenance dose	75–100 mg once daily	75 mg once daily	5–10 mg once daily	60–90 mg twice daily	2.5 mg once daily

COX-1 cyclooxygenase-1, *PAR-1* protease-activated receptor-1

[a]Enteric-coated aspirin in healthy subjects [8]

addressed by increasing the frequency of intake and/or combination with other antiplatelet agents [14].

3.2 Clopidogrel

Ticlopidine and clopidogrel represent the first and second generation of $P2Y_{12}$ inhibitors, respectively, and both belong to the thienopyridine class of antiplatelet drugs that selectively and irreversibly prevent binding of ADP to the $P2Y_{12}$ receptor. While effective as an antiplatelet agent, the use of ticlopidine is associated with potentially serious adverse effects, including bone marrow suppression [15]; therefore, clopidogrel is currently the most widely used $P2Y_{12}$ inhibitor.

Clopidogrel is a prodrug, requiring hepatic conversion via cytochrome (CYP) P450 enzymes to produce an active metabolite. This means it can take up to 8 h after a loading dose of clopidogrel to achieve significant platelet inhibitory effects [16]. Clopidogrel responsiveness may be diminished by concomitant administration of drugs that competitively inhibit its activation by CYP enzymes, such as proton pump inhibitors [17]. As binding of the clopidogrel metabolite to the $P2Y_{12}$ receptor is irreversible, restoration of platelet function is delayed until the body produces new platelets. Therefore, clopidogrel should be discontinued at least 5 days prior to elective surgery [9].

Dual antiplatelet therapy, predominantly with clopidogrel and aspirin, has been the backbone of secondary prevention of recurrent ischemic events in ACS patients for over a decade. The pivotal Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial demonstrated a 20% relative risk reduction in major adverse cardiovascular (CV) events (MACE) (death from CV causes, non-fatal MI, or stroke) in non-ST-elevation (NSTE)-ACS patients treated with clopidogrel plus aspirin versus aspirin alone for 12 months following ACS [18]. The benefit of clopidogrel was maintained from 2 h post-administration to the end of follow-up and was largely accounted for by a reduction in the risk of non-fatal MI. Subsequent studies confirmed the secondary prevention benefit of clopidogrel plus aspirin in patients with ST-elevation MI (STEMI) managed with fibrinolytics and in the setting of elective percutaneous coronary intervention (PCI) [19, 20].

However, it is well recognized that there is a considerable degree of inter-individual variability in response to clopidogrel as a result of multiple factors, including age, diabetes mellitus, drug–drug interactions, and genetic polymorphisms (particularly those affecting CYP2C19, the principal enzyme group involved in its metabolic activation) [21]. A review of 15 prospective studies noted that approximately 25% of patients were clopidogrel non-responders according to ADP aggregation testing; they exhibited high on-treatment platelet reactivity (HPR), which was associated with a 3.5-fold greater risk of recurrent ischemic events [22]. This review is supported by data from the National Institutes of Health (NIH)-funded Implementing GeNomics In pracTicE (IGNITE) network study, which found that in patients with a non-functional allele, the risk of MACE was significantly greater with clopidogrel compared with other antiplatelet therapies [23]. Consequently, the clopidogrel prescribing information contains a boxed warning about higher CV event rates in poor metabolizers [24]. The third-generation $P2Y_{12}$ inhibitors, prasugrel and ticagrelor, were developed with the aim of addressing the slow onset and heterogeneous platelet inhibiting properties of clopidogrel, and the Clinical Pharmacogenetics Implementation Consortium and the institutions involved in the IGNITE project collectively recommend that patients with poor or intermediate metabolizer phenotypes should be given treatment other than clopidogrel, such as prasugrel or ticagrelor [23]. It should be noted that a clinical study exploring CYP2C19 genotype-guided therapy after PCI is ongoing and these recommendations are based on clinical opinion and experience rather than clinical trial evidence.

3.3 Newer $P2Y_{12}$ Inhibitors

3.3.1 Prasugrel

Like clopidogrel, prasugrel is a thienopyridine and, therefore, blocks ADP binding to the $P2Y_{12}$ receptor irreversibly. It is also a prodrug, requiring metabolic activation, but has a faster onset of action than clopidogrel [25]. It is recommended that prasugrel is stopped at least 7 days prior to elective coronary artery bypass graft (CABG) surgery (class I recommendation), but shorter delays may be reasonable in patients referred for urgent CABG (class IIb recommendation) [9].

The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) established prasugrel as superior to clopidogrel for the secondary prevention of recurrent ischemic events following ACS, in patients managed with PCI [26]. Dual antiplatelet therapy with prasugrel and aspirin reduced the incidence of death from CV causes, non-fatal MI, or non-fatal stroke by 19% at 15 months, compared with clopidogrel and aspirin (hazard ratio [HR] 0.81, 95% confidence interval [CI] 0.73–0.90; $p < 0.001$) (Table 2). Rates of stent thrombosis were also lower for prasugrel plus aspirin compared with clopidogrel plus aspirin (1.1 vs. 2.4%; $p < 0.001$), but rates of TIMI-defined non–CABG-related major bleeding were significantly greater in the prasugrel-treated versus clopidogrel-treated group, including life-threatening and fatal bleeding (Table 2). However, considering both ischemic and bleeding events, the net clinical benefit was in favor of prasugrel (HR 0.87, 95% CI 0.79–0.95; $p = 0.004$). A subgroup analysis of TRITON-TIMI 38 identified an excess of intracranial bleeding with prasugrel treatment in patients with a prior stroke or transient ischemic attack (TIA), which resulted in net harm. There was also no net benefit of prasugrel in patients aged 75 years or older or those weighing less than 60 kg. As a result of these observations, the prasugrel prescribing information contains a boxed warning against its use in patients with active pathological bleeding or a history of TIA or stroke, and provisos concerning its use in older and lighter patients [27].

A subsequent analysis from TRITON-TIMI 38 confirmed a consistent net clinical benefit of prasugrel from randomization to day 3, and from day 3 until the end of the trial [28]. Also, among patients who experienced a non-fatal event during the trial, there was a significant reduction in both recurrent events and subsequent CV death with prasugrel versus clopidogrel (HR 0.65, 95% CI 0.46–0.92, $p = 0.016$, and HR 0.46, 95% CI 0.25–0.82, $p = 0.008$, respectively) [29]. It should be noted that these are landmark analyses and further studies are needed to confirm these findings.

In contrast to TRITON-TIMI 38, the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY-ACS) trial failed to show superiority of prasugrel over clopidogrel (both on top of aspirin) in NSTE-ACS patients managed with medical therapy alone [30]. At 17 months, the composite rate of CV death, MI, and stroke with prasugrel treatment was 13.9 versus 16.0% with clopidogrel treatment (HR 0.91, 95% CI 0.79–1.05; $p = 0.21$). Although there were higher rates of minor and moderate bleeding among patients receiving prasugrel, there was no significant increase in the rate of severe, major, or life-threatening bleeding, despite a treatment duration up to 30 months. In this study, patients > 75 years or < 60 kg body weight received a reduced dose of prasugrel (5 mg rather than 10 mg); all patients received the same dose of clopidogrel (75 mg).

3.3.2 Ticagrelor

Ticagrelor is the first in a new class of agents called cyclopentyltriazolopyrimidines that reversibly inhibits the $P2Y_{12}$ receptor by binding at a different site. It does not block ADP binding per se, but inhibits platelet activation by blocking ADP-induced signal transduction [5]. Unlike prasugrel, ticagrelor is a direct-acting agent with a faster onset of action than clopidogrel. Furthermore, it has a faster offset of action as a result of its reversible effects [16] (Table 1). It is recommended that ticagrelor is stopped at least 5 days prior to elective CABG surgery (class I recommendation), but shorter delays may be reasonable in patients referred for urgent CABG (class IIb recommendation) [9].

The pivotal ticagrelor trial was Platelet Inhibition and Patient Outcomes (PLATO), which evaluated the efficacy and safety of dual therapy with ticagrelor or clopidogrel plus aspirin for the reduction of CV events in patients hospitalized for either STEMI or moderate- to high-risk NSTE-ACS [25]. In contrast to TRITON-TIMI 38, patients were included whether or not an invasive strategy was planned. The study found that ticagrelor reduced the composite primary endpoint of CV death, MI, and stroke by 16% at 12 months compared with clopidogrel (HR 0.84, 95% CI 0.77–0.92; $p < 0.001$), but at the expense of an increase in the rate of PLATO- or TIMI-defined non–CABG-related major bleeding (TIMI-defined: 2.8 vs. 2.2%, $p = 0.03$) (Table 2). The individual endpoints of recurrent MI and CV death were also reduced in the ticagrelor group compared with clopidogrel (both $p < 0.01$) [25]. Moreover, ticagrelor treatment was associated with a significant reduction in the rate of death by any cause (4.5 vs. 5.9%; $p < 0.001$) [25], rates of both first and recurrent ischemic events [31], and rates of stent thrombosis (1.4 vs. 1.9%; $p = 0.0091$) [32]. A real-world evidence study conducted in Sweden (Swedish Web system for Enhancement and Development of Evidence-based care

Table 2 Major trials of oral antiplatelet agents for secondary prevention

	TRITON-TIMI 38	TRILOGY ACS	PLATO	TRA 2°P-TIMI 50	PEGASUS-TIMI 54
Population	ACS with scheduled PCI	Medically managed NSTE-ACS	Any ACS	History of MI, ischemic stroke, or PAD	History of MI (1–3 years prior)
No of patients	13,608	9326	18,624	26,449	21,162
Treatment	Aspirin + prasugrel (60 mg LD + 10 mg once daily) vs. Aspirin + clopidogrel (300 mg LD + 75 mg once daily)	Aspirin + prasugrel (30 mg LD + 5–10 mg once daily) vs. Aspirin + clopidogrel (300–600 mg LD + 75 mg once daily)	Aspirin + ticagrelor (180 mg LD + 90 mg twice daily) vs. Aspirin + clopidogrel (300 mg LD + 75 mg once daily)	Vorapaxar 2.5 mg daily vs. Placebo + Standard dual antiplatelet therapy	Aspirin + ticagrelor 90 mg twice daily vs. Aspirin + ticagrelor 60 mg twice daily vs. Placebo (aspirin alone)
Follow-up	14.5 months	30 months	12 months	3 years	3 years
Efficacy	CV death, MI, or stroke 9.9 vs. 12.1% (HR 0.81, 95% CI 0.73–0.90, $p < 0.001$)	CV death, MI, or stroke 13.9 vs. 16.0% [<75 years] (HR 0.91, 95% CI 0.79–1.05, $p = 0.21$)	CV death, MI, or stroke 9.8 vs. 11.7% (HR 0.84, 95% CI 0.77–0.92, $p < 0.001$)	CV death, MI, or stroke 9.3 vs. 10.5% (HR 0.87, 95% CI 0.80–0.94, $p < 0.001$)	CV death, MI, or stroke 7.85 vs. 9.04% [90 mg] (HR 0.85, 95% CI 0.75–0.96, $p = 0.008$) 7.77 vs. 9.04% [60 mg] (HR 0.84, 95% CI 0.74–0.95, $p = 0.004$)
Safety	TIMI major bleeding[a] 2.4 vs. 1.8% (HR 1.32, 95% CI 1.03–1.68, $p = 0.03$)	TIMI major bleeding[a] 2.1 vs. 1.5% [<75 years] (HR 1.31, 95% CI 0.81–2.11, $p = 0.27$)	TIMI major bleeding[a] 2.8 vs. 2.2% (HR 1.25, 95% CI 1.03–1.53, $p = 0.03$)	GUSTO moderate or severe bleeding 4.2 vs. 2.5% (HR 1.66, 95% CI 1.43–1.93, $p < 0.001$)	TIMI major bleeding[a] 2.60 vs. 1.06% [90 mg] (HR 2.69, 95% CI 1.96–3.70, $p < 0.001$) 2.30 vs. 1.06% [60 mg] (HR 2.32, 95% CI 1.68–3.21, $p < 0.001$)

ACS acute coronary syndrome, *CI* confidence interval, *CV* cardiovascular, *GUSTO* Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries, *HR* hazard ratio, *LD* loading dose, *MI* myocardial infarction, *NSTE-ACS* non-ST-elevation acute coronary syndrome, *PAD* peripheral artery disease, *PCI* percutaneous coronary intervention, *TIMI* thrombolysis in myocardial infarction

[a]TIMI major bleeding not related to coronary artery bypass grafting

in Heart Disease Evaluated According to Recommended Therapies [SWEDEHEART]) and including over 45,000 ACS patients, subsequently reported outcomes for ticagrelor versus clopidogrel that were consistent with those found in PLATO [33].

Outcomes with ticagrelor versus clopidogrel in PLATO were consistent across subgroups of patients with STEMI [34] or NSTE-ACS [35], and those managed with either PCI [36] or medical therapy alone [37]. Similarly, outcomes were consistent in older patients, those with low body weight, and those with prior TIA or non-hemorrhagic stroke [25]. However, ticagrelor efficacy was found to differ according to region, with a reduced benefit in terms of the primary endpoint in patients based in North America compared with the rest of the world [25, 38]. As a greater proportion of patients in North America were reported to take high-dose aspirin maintenance therapy (median ≥ 300 mg/day), a negative interaction between ticagrelor and high-dose aspirin was proposed as a possible explanation for this disparity, but no definitive explanation exists for these findings [38]. As a result, ticagrelor maintenance therapy is recommended to be taken with low aspirin doses of 75–100 mg/day [9, 10]. The ticagrelor prescribing information also warns against concomitant aspirin doses exceeding 100 mg, and contraindicates the use of ticagrelor in patients with active pathological bleeding or history of intracranial hemorrhage [39].

3.3.3 Prasugrel Versus Ticagrelor

There are currently limited data comparing the efficacy and safety of ticagrelor and prasugrel in ACS patients. The results of the first head-to-head randomized clinical trial (PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis-18 [PRAGUE-18]) were published recently [40, 41]. This open-label, phase IV study aimed to enroll 2500 patients with acute MI undergoing PCI in tertiary centers in the Czech Republic. However, early outcome analysis (up to 1 month post-event) of 1230 patients found no significant difference between prasugrel and ticagrelor (both plus aspirin) for the composite primary endpoint of death, re-infarction, urgent target vessel revascularization, stroke, serious bleeding requiring transfusion, or prolonging hospitalization at 7 days (4.0 and 4.1%, respectively; odds ratio [OR] 0.98, 95% CI 0.55–1.73; $p = 0.939$), nor in the key secondary endpoint of CV death, non-fatal MI, or stroke at 30 days (2.7 and 2.5%, respectively; OR 1.06, 95% CI 0.53–2.15; $p = 0.864$). Consequently, the trial was terminated early for 'lack of utility' [40]. The 1-year follow-up also found no significant differences between prasugrel and ticagrelor with regard to efficacy or bleeding. The primary endpoint (CV death, MI or stroke at 1 year) was 6.6% in the prasugrel group and 5.7% in the ticagrelor group (HR 1.167, 95% CI 0.742–1.835; $p = 0.503$). It should be noted that there are several limitations to this study, most notably that it was statistically underpowered to show superiority of one treatment over another. In addition, patients were allowed to switch to clopidogrel following discharge due to the high costs of prasugrel and ticagrelor in the Czech Republic. In fact, 34% of prasugrel patients and 44% of ticagrelor patients switched to clopidogrel for economic reasons; the mean time to switching was 8 days for both [41, 42].

An earlier meta-analysis of randomized trials of prasugrel and ticagrelor also showed no significant differences between treatments in the rates of CV death, MI or stroke, or non–CABG-related major bleeding [43]. This is an indirect comparative analysis. Recent pharmacodynamic studies suggest that there is little difference between prasugrel and ticagrelor in terms of timing and degree of platelet inhibition [44–46]. However, these studies have looked at only short-term pharmacodynamic effects after drug loading.

Other studies suggest that there may be a variable response with prasugrel when used long term or in patients with STEMI, influenced by older age and prior aspirin use [47, 48]. The open-label Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5 (ISAR-REACT 5) trial (NCT01944800) will compare the clinical effects of ticagrelor and prasugrel for up to 12 months in approximately 4000 ACS patients with a planned invasive strategy [49]. The estimated study completion date is January 2019.

In the absence of the contraindications referred to above, the most recent guidelines for maintenance treatment with dual antiplatelet therapy give a class IIa recommendation for the use of prasugrel or ticagrelor in preference to clopidogrel in ACS (NSTE-ACS or STEMI) patients who have undergone coronary stent implantation [50]. Ticagrelor (but not prasugrel) is recommended over clopidogrel in NSTE-ACS patients managed with medical therapy alone [50]. Other possible considerations in choice of agent include the dosing regimen and adverse event profile. Prasugrel is administered once daily and ticagrelor twice daily, which may have some bearing on patient compliance. In addition, ticagrelor is the only $P2Y_{12}$ inhibitor that is currently licensed (according to prescribing information) to be crushed and mixed with water, and either drunk or given by nasogastric tube, for patients with difficulty swallowing [39]. Finally, both drugs carry an increased risk of bleeding (including life-threatening or fatal bleeding in the case of prasugrel), and ticagrelor is associated with an increased risk of dyspnea [27, 39].

3.4 Vorapaxar

Vorapaxar is a novel oral PAR-1 antagonist that inhibits thrombin-mediated platelet activation, which is independent of the ADP- and TXA-2-mediated pathways.

Therefore, residual platelet activation is feasible despite dual inhibition of COX-1 and $P2Y_{12}$, raising the question of whether 'triple therapy' would be beneficial.

The phase III study Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) investigated the efficacy and safety of vorapaxar versus placebo in NSTE-ACS patients receiving aspirin and clopidogrel, but was terminated early due to increased major bleeding with vorapaxar, including more than a three-fold increase in the rate of intracranial bleeding (HR 3.39, 95% CI 1.78–6.48, $p < 0.05$) [51]. There was also no apparent benefit of vorapaxar in reducing CV events.

Another study, the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events-Thrombolysis in Myocardial Infarction 50 (TRA 2°P-TIMI 50) study evaluated vorapaxar versus placebo in patients with a history of prior MI, stroke, or peripheral artery disease (PAD) (Table 2) [52]. At 3 years, although there was a significant reduction in the rate of CV death, MI, stroke, or recurrent ischemia leading to revascularization with vorapaxar versus placebo (11.2 vs. 12.4%; HR 0.88, 95% CI 0.82–0.95; $p = 0.001$), there was a significantly increased risk of moderate or severe bleeding with vorapaxar (4.2 vs. 2.5%; HR 1.66, 95% CI 1.43–1.93; $p < 0.001$), including intracranial hemorrhage (1.0 vs. 0.5%; $p < 0.001$). A subsequent subgroup analysis of patients with prior MI, and excluding all those with a high propensity to bleed (e.g., those with prior stroke or TIA, those aged over 75 years or weighing less than 60 kg), found that there was a greater reduction in the primary endpoint with vorapaxar (6.8 vs. 8.6%; HR 0.75, 95% CI 0.66–0.85; $p < 0.0001$) [53], but moderate or severe bleeding rates were still higher with vorapaxar compared with placebo (2.7 vs. 1.8%; HR 1.52, 95% CI 1.20–1.93; $p = 0.0006$), although they were lower than in the overall study. These results suggest the potential utility of vorapaxar in a selected population [53]. Indeed, vorapaxar has been approved by the US Food and Drug Administration (FDA) for secondary prevention in patients with prior MI or PAD, in combination with aspirin and/or clopidogrel, but is contraindicated in patients with a history of stroke, TIA or intracranial hemorrhage, or with active pathological bleeding [54]. The prescribing information also warns that consideration should be given to factors that increase the risk of bleeding, including older age and low body weight. The European guidelines recommend that ischemic and bleeding risk should be thoroughly assessed before prescribing vorapaxar with aspirin and clopidogrel [55]. However, the current US guidelines for the management of patients with NSTE-ACS and STEMI, and duration of dual antiplatelet therapy in coronary artery disease (CAD), do not refer to vorapaxar [9, 10, 50].

4 Optimal Duration of Treatment

4.1 Guidelines

Current US guidelines for ACS broadly recommend that dual antiplatelet therapy be continued for 12 months after the index event, followed by aspirin monotherapy [9, 10]. An American College of Cardiology (ACC)/American Heart Association (AHA) guideline focused update on the duration of dual antiplatelet therapy in patients with CAD was published recently, taking into account existing guideline recommendations and the results of a systematic review of randomized clinical trials [50, 56]. This update gives a class I recommendation for 12 months of treatment with low-dose aspirin (81 mg, range 75–100 mg) and a $P2Y_{12}$ inhibitor in four specific groups of patients with an acute or recent coronary event (STEMI or NSTE-ACS), excluding those with specific contraindications to any of the drugs. These four ACS groups (with dual antiplatelet therapy recommendations) are (1) all medically managed patients (aspirin plus clopidogrel or ticagrelor); (2) STEMI patients treated with a fibrinolytic (aspirin plus clopidogrel); (3) patients who have undergone PCI with a drug-eluting stent (DES) or bare-metal stent (BMS) (clopidogrel, prasugrel, or ticagrelor); and (4) patients who have undergone CABG (resume treatment post-surgery and continue to 1 year). In the first three of these groups, the guidelines also give a class IIb recommendation that prolonging dual antiplatelet therapy beyond 12 months may be reasonable [50]. Conversely, dual antiplatelet therapy may be reasonable for just 6 months in patients with significant overt bleeding or at high bleeding risk (e.g., treatment with oral anticoagulant) or at increased risk of severe bleeding complication (e.g., major intracranial surgery). In patients with stable ischemic heart disease, the guidelines state that it may be reasonable to discontinue dual antiplatelet therapy sooner in PCI patients treated with 'newer-generation' DES (e.g., everolimus- or zotarolimus-eluting stents), as they are associated with a lower risk of stent thrombosis and MI compared with older DES types (e.g., sirolimus- and paclitaxel-eluting stents).

4.2 Evidence

Data from a number of clinical trials and recent meta-analyses indicating that extending dual antiplatelet therapy beyond 12 months may be beneficial in some patients are summarized below. Other studies have looked at shorter term dual antiplatelet therapy.

A subgroup analysis from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization,

Management, and Avoidance (CHARISMA) trial in patients with prior MI found that ~ 2 years of treatment with clopidogrel plus aspirin reduced the rate of ischemic events by almost a quarter compared with aspirin therapy alone (6.6 vs. 8.3%; HR 0.77, 95% CI 0.6–0.98; $p = 0.031$) [57]; however, the trial failed to meet its primary endpoint, showing no benefit in patients with clinically evident CV disease or multiple risk factors [58].

The Dual Antiplatelet Therapy (DAPT) study showed that 30 months of treatment with clopidogrel or prasugrel plus aspirin reduced major CV event rates following coronary stent placement, compared with 12 months of treatment, although with an increased risk of bleeding and a suggestion of increased all-cause mortality (2.0 vs. 1.5%; HR 1.36, 95% CI 1.00–1.85; $p = 0.05$) [59]. Among a subgroup of patients undergoing PCI and stent placement following an MI in this study (30.7% of the randomized cohort), major CV and cerebrovascular event rates were significantly reduced in those who continued on a thienopyridine for 30 months versus those who switched to placebo at 12 months (3.9 vs. 6.8%; HR 0.56, 95% CI 0.42–0.76; $p < 0.001$) [60], but this was at the expense of a higher rate of Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) moderate or severe bleeding (1.9 vs. 0.8%, $p = 0.005$). There was no difference in all-cause mortality in this subgroup analysis.

In the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial, treatment with ticagrelor (90 or 60 mg twice daily) plus aspirin was extended over a 3-year period in stable patients with a history of MI (1–3 years prior to enrollment) [61]. Patients who received extended ticagrelor treatment experienced a significant reduction in the composite endpoint of CV death, MI, or stroke at 3 years (ticagrelor 90 mg 7.9%, ticagrelor 60 mg 7.8%, and placebo [aspirin alone] 9.0%; HR 0.85 for ticagrelor 90 mg vs. placebo 0.85, 95% CI 0.75–0.96, $p = 0.008$; and HR 0.84 for ticagrelor 60 mg vs. placebo, 95% CI 0.74–0.95, $p = 0.004$). The risk of major bleeding was higher with both doses of ticagrelor compared with placebo (ticagrelor 90 mg 2.6%, ticagrelor 60 mg 2.3%, and placebo 1.1%; $p < 0.001$ for each dose vs. placebo), but less than 1% of patients in each group experienced non-fatal intracranial hemorrhage or fatal bleeding over the 3-year period. The authors estimated that, for every 10,000 patients who began treatment with ticagrelor, 41 TIMI major bleeding events per year would be caused with 90 mg twice daily and 31 TIMI major bleeding events per year would be caused with 60 mg twice daily. It should be noted though that patients with known bleeding disorders, prior ischemic stroke or intracranial bleed, or those with a need for oral anticoagulant therapy were excluded from this study. As a result of this study, the recommended ticagrelor maintenance dose was updated to 90 mg twice daily for the first year post-ACS, and 60 mg twice daily thereafter [39]. The US FDA conducted their own analysis based on the PEGASUS-TIMI data to assess the benefit–risk difference of ticagrelor in a lower-risk population [62]. Their study found that ticagrelor compared with placebo consistently reduced the risk of MACE by approximately 16%, with no difference with respect to fatal bleeding or intracranial hemorrhages over 1 year.

In a meta-analysis of five randomized trials in high-risk patients with prior MI, extending $P2Y_{12}$ inhibitor plus aspirin treatment beyond 1 year was shown to significantly decrease the risk of MACE (6.4 vs. 7.5%; risk ratio [RR] 0.78, 95% CI 0.67–0.90; $p = 0.001$) and CV death (2.3 vs. 2.6%; RR 0.85, 95% CI 0.74–0.98; $p = 0.03$) compared with aspirin alone [63]. Although there was an increase in major bleeding with extended dual antiplatelet therapy (1.85 vs. 1.09%; RR 1.73, 95% CI 1.19–2.50; $p = 0.004$), there was no significant increase in fatal bleeding or non-CV death. The authors of this meta-analysis did note that the studies they evaluated typically excluded patients with a high bleeding risk, such as those on long-term anticoagulant therapy, and/or with recent or active major bleeding, and history of prior stroke or TIA. Most of the patients were also biomarker-positive, indicating that they were at high risk of a recurrent event or CV death. As a result, the authors warned that the findings may not be generalizable to all ACS patients.

The duration of dual antiplatelet therapy following DES placement has been evaluated in a decision-analytic Markov model [64]. For the subgroup of patients with ACS, the authors found that only a 2% absolute reduction in MACE would be needed for 30 months of treatment with dual antiplatelet therapy to be preferable to 12 months followed by aspirin alone, including consideration of bleeding risk. However, a number of meta-analyses of randomized trials have generally shown that short-term (< 6 months) versus long-term (> 12 months) dual antiplatelet therapy after second-generation DES placement has similar rates of mortality and ischemic events, but with a lower rate of overall bleeding, particularly in low-risk patients [65–69]. The authors concluded that while shorter treatment may be safe and effective in some cases, high-risk patients may require a tailored approach. An analysis of 4190 patients from the Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients (PARIS) registry found that only around 10% of patients treated with DES have either a low thrombotic/high bleeding risk or a high thrombotic/low bleeding risk [70]. Thus, identification of a high thrombosis/low bleeding risk or low thrombosis/high bleeding risk population is challenging.

A large, randomized, multicenter, open-label trial is currently assessing the hypothesis that 6 months of dual antiplatelet therapy after DES implantation is not inferior to 12 month dual antiplatelet therapy with regard to clinical

outcomes. The final results of the study, known as the Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in ST-elevation Myocardial Infarction (DAPT-STEMI), are awaited, but should hopefully help answer the question of whether short- or long-term dual antiplatelet therapy is preferential in patients with DES implantation [71].

5 Risk Stratification

In order to identify patients most likely to benefit from more intensive antiplatelet therapy, identification of characteristics associated with increased mortality, CV event recurrence, and bleeding is crucial. Bleeding risk is the primary safety issue associated with antiplatelet treatment and must be balanced against the reduction in ischemic risk when selecting therapy [50, 72]. Analysis of a prospective, real-world, Italian registry found that the main reason for continuing dual antiplatelet therapy beyond 12 months in patients following an ACS was low bleeding risk, more so than high ischemic risk [73]. Major bleeding events during hospitalization for ACS are an independent predictor of adverse outcomes at 6 months and 1 year post–index event [74–76]. An analysis of the PLATO trial found that spontaneous major bleeding events were associated with similar mortality rates (short and long term) as spontaneous ischemic events in patients with ACS receiving dual antiplatelet therapy [77]. A further study evaluated the average daily ischemic rate and the average daily bleeding rate in 3602 patients with STEMI enrolled in the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) study [78]. The study found that while both rates decreased over time after the primary PCI, the daily risk of ischemia was greater than the daily risk of bleeding after 30 days. To complicate matters, many factors that increase ischemic risk also increase the risk of bleeding [50] (Table 3).

Post-discharge risk scores currently include GRACE and the more recent risk model using data from the long-tErm follow-up of antithrombotic management Patterns In acute CORonary (EPICOR) study, which predict mortality at 6 months and 1 year following ACS, respectively [79, 80]. Most recently, a 'DAPT score' has been developed [81], using data from the DAPT study [59] to assess the potential benefits and harms of continuing dual antiplatelet therapy beyond 1 year in patients undergoing PCI [81]. This risk score has the advantage of evaluating both thrombotic and bleeding risk, with positive or negative points assigned for each of the components (Table 3). Patients with scores ≥ 2 were found to have a reduced risk of ischemic events and smaller increases in bleeding during extended dual antiplatelet therapy, compared with those with scores < 2 [81]. In another analysis looking at subgroups of patients with or without prior MI before coronary stent implantation, among patients with DAPT scores ≥ 2, continued thienopyridine therapy versus aspirin alone was associated with significant reductions in MI/stent thrombosis: prior MI 2.7 versus 6.0%, $p < 0.001$; no MI 2.6 versus 5.2%, $p = 0.002$, with comparable bleeding rates [82]. Among patients with DAPT scores < 2, continued thienopyridine therapy versus aspirin alone was associated with significantly increased bleeding, but no ischemic benefit, in patients with or without prior MI. Therefore, while the DAPT score may still require further evaluation in other patient cohorts, it has thus far been shown to enhance the prediction of relative benefit and harm with dual antiplatelet therapy. Alfredsson et al. utilized data from the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) study to identify predictors of long-term bleeding risks in patients with NSTEMI [83]. The authors identified ten significant predictors of GUSTO severe/life-threatening/moderate bleeding (age, sex, weight, NSTEMI [vs. unstable angina], angiography performed at randomization, prior peptic ulcer disease, baseline creatinine, baseline systolic blood pressure, baseline hemoglobin and angiography before randomization) and five significant predictors of TIMI major/minor bleed (age, female sex, baseline creatinine, baseline hemoglobin and angiography before randomization), which could be used to reliably predict bleeding risk in patients receiving dual antiplatelet therapy after hospitalization for ACS.

A number of individual patient factors are also recognized to increase the risk of CV events and/or bleeding, which may also have an impact on the relative benefits of dual antiplatelet therapy, as summarized briefly below. The risk of adverse events following an ACS also progressively increases with multiple risk factors [84]. For these patients, more aggressive secondary prevention strategies, such as longer dual antiplatelet therapy, may be required.

5.1 Diabetes Mellitus

Patients with diabetes mellitus have an increased risk of mortality and ischemic events, and a generally poorer prognosis following ACS, compared with non-diabetic patients [1, 85–88]. Patients receiving insulin therapy appear to be at further risk than those who do not require insulin [88]. Moreover, diabetic patients have been shown to have hyperreactive platelets and reduced response to antiplatelet therapy compared with non-diabetic patients [89–91].

In PLATO, ticagrelor reduced the incidence of MACE in all ACS patients compared with clopidogrel, irrespective of diabetic status and glycemic control [25, 92]. In PEGASUS-TIMI 54, ticagrelor (pooled dose data) was again shown to reduce the relative risk of MACE consistently in both diabetic and non-diabetic patients over the 3-year follow-up period (p value for interaction = 0.99) [93]. However,

Table 3 Components of ischemic and bleeding risk scores

Ischemic risk scores		Bleeding risk scores		Ischemic AND bleeding risk score
GRACE[a]	TIMI[b]	CRUSADE[c]	ACUITY/HORIZONS-AMI[d]	DAPT[e]
Age per 10-year increase	Age ≥ 65 years		Age per 5-year increase	MI at presentation
Pulse per 30-min increase	HR > 100 bpm	HR per 10-bpm increase		Prior MI or PCI
SBP per 20-mmHg decrease	SBP < 100 mmHg	SBP ≤ 110 mmHg or ≥ 180 mmHg		Diabetes
History of CHF	Killip II–IV	Signs of CHF at presentation		Stent diameter < 3 mm
Initial serum creatinine level per 1 mg/dL increase		Creatinine clearance per 10 mL/min decrease	Serum creatinine per 0.1 mg/dL increase	Smoking
ST changes: ST-segment depression	ST changes: anterior ST elevation or LBBB		ST changes: STEMI	Paclitaxel-eluting stent
History of MI		Prior vascular disease		History of congestive heart failure
	Diabetes	Diabetes		Low ejection fraction
		Baseline hematocrit < 36% (vs. ≥ 36%)		Vein graft intervention
		Female gender	Female gender	Age 65 to < 75 years
No in-hospital PCI				Age ≥ 75 years
Initial cardiac enzyme elevation			NSTEMI with raised biomarkers	
	Weight < 67 kg (150 lbs)			
	Time to treatment > 4 h			
			Elevated white blood cell count	
			Anemia	

ACS acute coronary syndrome, *bpm* beats per minute, *CHF* congestive heart failure, *DAPT* dual antiplatelet therapy, *HR* heart rate, *LBBB* left bundle branch block, *MI* myocardial infarction, *NSTE-ACS* non-ST-elevation acute coronary syndrome, *NSTEMI* non-ST-elevation myocardial infarction, *PCI* percutaneous coronary intervention, *SBP* systolic blood pressure, *STEMI* ST-elevation myocardial infarction

[a]Global Registry of Acute Coronary Events risk score post-discharge to 6 months for full spectrum ACS [110]

[b]Thrombolysis in Myocardial Infarction risk score for STEMI patients [111]

[c]CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) bleeding score for NSTE-ACS [112]

[d]Bleeding score based on ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) and HORIZONS-AMI (The Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction) for full spectrum ACS [75]

[e]DAPT score assessing benefits and harms of continuing dual antiplatelet therapy > 1 year after PCI [81]

because of the inherently greater degree of CV risk in diabetic patients, the absolute reduction in risk of ischemic events was greater in diabetic than non-diabetic patients (1.5 vs. 1.1%, with a 3-year number needed to treat of 67 vs. 91).

In TRITON-TIMI 38, the benefit of prasugrel in patients with diabetes compared with non-diabetic patients tended to be greater, with relative reductions in recurrent MI of 40% (8.2 vs. 13.2%; HR 0.60; $p < 0.001$) and 18% (7.2 vs. 8.7%; HR 0.82; $p = 0.006$), respectively (p value for interaction = 0.02) [94]. There was no significant interaction between treatment effect and diabetes status ($p = 0.009$) [26]. Rates of TIMI major bleeding were similar between patients with and without diabetes (p value for interaction = 0.29). It should be noted that this subset analysis was not powered to detect differences in individual endpoints.

In TRILOGY ACS, patients with diabetes, compared with those without diabetes, had a higher unadjusted and adjusted risk of all ischemic endpoints [88]. However, the frequencies of most ischemic and bleeding endpoints were similar for diabetics treated with prasugrel or clopidogrel (in combination with aspirin).

Intriguingly, a pre-specified subgroup analysis from the DAPT trial showed no benefit from extending dual antiplatelet therapy beyond 1 year in patients with diabetes [95]. The composite endpoint of death, MI or stroke occurred in 6.6% of diabetic patients with continued thienopyridine compared

with 7.0% with placebo ($p=0.55$); for non-diabetic patients, event rates were 3.3 versus 5.2%, respectively ($p<0.001$). There was no mortality benefit with continued thienopyridine therapy versus placebo in either diabetic (2.7 vs. 2.2%, respectively; $p=0.32$) or non-diabetic patients (1.5 vs. 1.2%; $p=0.28$; p value for interaction = 0.96). Overall, the composite endpoint occurred more often in diabetic patients than in those without diabetes (6.8 vs. 4.3%, $p<0.001$), as did the individual endpoints of death (2.5 vs. 1.4%, $p<0.001$) and MI (4.2 vs. 2.6%, $p<0.001$), although bleeding risk was similar regardless of diabetic status (p value for interaction = 0.61).

These findings suggest that caution needs to be exercised in deciding whether diabetic patients benefit more or less from dual antiplatelet therapy compared with non-diabetic patients. However, a recent meta-analysis showed that dual antiplatelet therapy is superior to aspirin alone in diabetic patients with ACS, and that both prasugrel and ticagrelor are better than clopidogrel in terms of CV event reduction, without an increased risk of major bleeding [96].

5.2 Renal Dysfunction

A significant proportion of patients with ACS have renal dysfunction, associated with poorer short- and long-term ischemic outcomes [97, 98]. However, renal dysfunction is associated with an increased risk of bleeding, complicating the net benefit–risk profile of potential antiplatelet therapy [50]. There is also evidence that a severe reduction in glomerular filtration rate may be a determinant of high residual platelet reactivity during clopidogrel maintenance therapy, and that the newer $P2Y_{12}$ inhibitors may overcome this problem [99].

In a subgroup analysis of patients with CKD (creatinine clearance < 60 mL/min) included in the PLATO trial, ticagrelor significantly reduced the primary endpoint (composite of CV death, MI, and stroke) compared with clopidogrel (17.3 vs. 22.0%; HR 0.77, 95% CI 0.65–0.90) [100]. The absolute risk reduction was noted to be greater in patients with CKD than in those without it (7.9 vs. 8.9%; HR 0.90, 95% CI 0.79–1.02), with no differences in rates of major, fatal, or non–CABG-related bleeding. Similarly, in PEGASUS-TIMI 54, the relative reduction in CV events with ticagrelor and aspirin was similar among patients according to estimated glomerular filtration rate (eGFR), but absolute risk reduction was more marked in patients with eGFR < 60 mL/min/1.73 m^2 (2.7 vs. 0.63%) due to a higher overall 3-year risk of CV events in this group [101].

In the TRITON-TIMI 38 trial, prasugrel was shown to be consistently superior to clopidogrel for reducing ischemic events in patients with or without CKD (creatinine clearance < 60 or ≥ 60 mL/min) [26]. In TRILOGY-ACS, however, while prasugrel treatment lowered platelet reactivity at 30 days across all patients regardless of kidney function, compared with clopidogrel, it did not affect either ischemic or bleeding outcomes in any group at 30 months [102].

The SWEDEHEART registry records baseline characteristics, treatments and outcome of consecutive patients with ACS admitted to all hospitals in Sweden. Patients prescribed dual antiplatelet therapy with clopidogrel and aspirin following an ACS were included in a prospective, observational cohort study to determine the optimal duration of treatment in patients with underlying renal disease [103]. Registered death, MI, stroke and bleeding events increased with worsening renal function, regardless of whether dual antiplatelet therapy was stopped at 3 months or continued beyond 3 months. The composite outcome of death, reinfarction, stroke or bleeding was in favor of longer dual antiplatelet therapy than shorter duration (HR 0.84, 95% CI 0.78–0.91).

The benefit of vorapaxar in patients with compromised kidney function is yet to be investigated on a large scale. Focused analyses evaluating the optimal antiplatelet regimen for patients with chronic renal dysfunction is a high priority.

5.3 Polyvascular Disease

Patients with vascular disease in more than one arterial bed are at a greater risk for ischemic events and have poorer prognosis following ACS [1, 57, 104].

Patients with polyvascular disease in CHARISMA had a marked reduction in MACE with clopidogrel and aspirin therapy versus aspirin alone (HR 0.55, 95% CI 0.33–0.91; $p=0.018$) [57]. In PLATO, the benefit of ticagrelor in the subgroup of patients with ACS and PAD was consistent with the overall trial results, but did not reach statistical significance [104]. Similarly, outcomes from TRACER showed a trend toward a reduction in MACE in patients with NSTE-ACS and PAD with vorapaxar, compared with placebo, on background clopidogrel and aspirin, but the difference was not statistically significant [105]. As described above, patients with prior MI, stroke, or PAD in the TRA 2°P-TIMI 50 had a significant reduction in CV event rates with vorapaxar versus placebo, but with significantly increased bleeding risk [52]. Analysis from PEGASUS-TIMI 54 suggests that patients with prior MI and PAD have higher rates of MACE over a 3-year period and consequently experience a greater absolute risk reduction with ticagrelor and aspirin dual therapy versus aspirin alone, compared with patients without PAD, with an absolute excess of TIMI major bleeding of 0.12% (number needed to harm: 834) [106].

5.4 Age

Increasing age is associated with increased CV events and bleeding risk, reduced response to antiplatelet therapy, and a higher rate of HPR [107]. The net benefit of prasugrel was

attenuated in patients > 75 years old in TRITON-TIMI 38 due to increased bleeding, and it is, therefore, not recommended for use in such patients [9, 10, 26]. In contrast, a PLATO substudy found that the overall trial results were consistent among patients < 75 or ≥ 75 years old [108]. Interestingly, PLATO-defined major bleeding with ticagrelor was not increased in older versus younger patients [50, 108]. Apart from these studies, data on the efficacy and safety of dual antiplatelet regimens in older patients are lacking. The ongoing POPular AGE study (NCT02317198) will compare clopidogrel with either ticagrelor or prasugrel (each on a background of aspirin or oral anticoagulant) in approximately 1000 NSTE-ACS patients ≥ 70 years old [109]. The study is due to be completed in January 2017.

6 Conclusion

The availability of new antiplatelet agents and extended or combination therapy has increased the options for secondary prevention among ACS patients. Clinicians should be guided by the results from the studies above and the subsequent clinical guidelines, but are reminded that individual patient circumstances and the benefit of antiplatelet treatment versus the risk of severe bleeding should be considered when deciding appropriate treatment.

Future trials should continue to highlight patient subgroups at high risk for recurrent ischemic events and at low risk for bleeding complications, who are likely to gain the greatest benefit from more potent and prolonged treatment.

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