Platelet Inhibition in Acute Coronary Syndrome and Percutaneous Coronary Intervention: Insights from the Past and Present

Diana A. Gorog¹,² Tobias Geisler³

¹ National Heart and Lung Institute, Imperial College, London, United Kingdom
² Postgraduate Medical School, University of Hertfordshire, Hertfordshire, United Kingdom
³ Department of Cardiology and Angiology, University Hospital, Eberhard-Karls-University Tuebingen, Tuebingen, Germany

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Abstract

Platelet activation and aggregation have a pivotal role in arterial thrombosis and in the pathogenesis of both acute coronary syndromes (ACS) and in the thrombotic complications that occur in patients undergoing percutaneous coronary intervention (PCI). The past 30 years has seen the progress from early trials of clopidogrel and glycoprotein IIb/IIIa inhibitors to the application of more potent P2Y₁₂ inhibitors prasugrel and ticagrelor. Early enthusiasm for newer and more potent antiplatelet agents, which could reduce ischemic events, has led to the understanding of the importance of bleeding and a desire to individualize and optimize treatment. It has increasingly become apparent that the potency and duration of dual antiplatelet therapy (DAPT) has to reflect the balance between ischemic and bleeding risk. Recently, multiple strategies have been proposed to individualize DAPT intensity and duration to reduce the bleeding and ischemic risks. Strategies of de-escalation of DAPT intensity, as well as shorter (less than a year) or more prolonged (beyond a year) treatment have been proposed, as well as platelet function test and genotype guidance of P2Y₁₂ inhibitor therapy. Herein, we provide an overview of the progress in the field of antiplatelet therapy for ACS and PCI over the years, showing the current directions of travel. Ongoing studies focusing on personalized antiplatelet treatment will hopefully yield further insight into ways of optimizing outcomes for the individual.

Keywords

► Acute Myocardial Infarction
► antiplatelet agents
► arterial thrombosis
► thrombosis
► coagulation inhibitors

Importance of Platelets in ACS and post-PCI Complications

Platelet activation and aggregation have a pivotal role in arterial thrombosis and in the pathogenesis of both acute coronary syndromes (ACS) and in the thrombotic complications that occur in patients undergoing percutaneous coronary intervention (PCI). In the 1980s, postmortem studies showed that in the majority of patients who died from sudden death due to ischemic heart disease, plaque disruption with overlying thrombus formation was responsible for the fatal acute myocardial infarction (AMI).¹,² In most cases, the presentation of an ACS is attributable to acute changes in a coronary atheroma, with resultant platelet thrombus formation, which can result in downstream macro- or microinfarction. Furthermore, thrombi are frequently observed at sites other than those of the major culprit lesion in patients with ACS.³ The appreciation that thrombi in patients with ACS are predominantly formed of platelets² led to an increased search for antiplatelet therapy to treat and prevent coronary thrombosis.
Balancing the Risk of Thrombosis against the Risk of Bleeding

Antiplatelet therapy, while reducing thrombosis, also increases bleeding risk. For patients with ACS, there is a strong relationship between bleeding, mortality, and AMI. Major bleeding significantly increases the risk of death\(^3\)\(^,\)\(^4\) and AMI.\(^4\) Bleeding often leads to attenuation or cessation of antithrombotic therapy, thus enhancing the thrombotic risk.

Since both thrombotic and bleeding risks vary from one individual to the next, the benefits and risks of DAPT should be considered when deciding on the intensity and duration of DAPT. There is often a fine balance between benefit and risk, such that decisions on antiplatelet strategy should incorporate an assessment of both ischemic and bleeding risks, with respect to both the intensity and the duration of DAPT. Risk scores can be helpful to guide DAPT treatment, and include the DAPT,\(^5\) the PRECISE-DAPT (PREDicting bleeding Complications In patients undergoing Stent implantation and subEquent Dual Anti Platelet Therapy),\(^6\) and the PARIS (Patterns of non-Adherence to antiplatelet Regimen in Stented patients) scores.\(^7\) However, their use is somewhat limited, and prospective trials have not validated the safety of using these scores to guide DAPT duration. In addition, there is a large overlap between bleeding and thrombotic risk factors in traditional scores, thus preventing a reasonable evaluation of the net benefit. More recently, the Academic Research Consortium for High-Bleeding Risk has proposed a new definition of high-bleeding risk to provide consistency in clinical trials evaluating the safety and effectiveness of devices and drug regimens for patients undergoing PCI, defined as ≥4% risk of Bleeding Academic Research Consortium (BARC) 3 to 5 bleeding or a ≥1% risk of intracranial hemorrhage at 1 year.\(^8\)

Early Antithrombotic Therapy

In 1988, the landmark Second International Study of Infarct Survival trial in 17,187 patients with suspected AMI showed unequivocally that for every 1,000 patients, treatment with aspirin led to a reduction of approximately 25 deaths and 10 to 15 nonfatal reinfarctions or strokes during the first month and that the benefits of early treatment with aspirin were largely independent of, and additive to, those of fibrinolytic therapy (\(\rightarrow\) Table 1).\(^9\) The Antithrombotic Trialists’ Collaboration meta-analysis involving 287 studies established that antiplatelet therapy—primarily with aspirin—reduces the incidence of death, AMI, or stroke in patients at high-vascular risk by 25%.\(^10\) Aspirin became first-line therapy for all patients with cardiovascular disease, including ACS and those undergoing PCI, and remains so in current guidelines.\(^11\),\(^12\) The mechanism of action of aspirin and other antiplatelet medications is shown in \(\rightarrow\) Fig. 1.

P2Y\(_{12}\) Inhibitors

The CURE trial in 2001 showed that the addition of clopidogrel to aspirin in patients with ACS reduced major adverse cardiovascular events (MACE) by 20% compared with aspirin alone in patients suffering from non-ST elevation ACS (\(\rightarrow\) Table 1 and \(\rightarrow\) Fig. 2).\(^13\) Subsequent studies showed that dual antiplatelet therapy (DAPT) comprising of clopidogrel and aspirin reduced MACE after PCI in both stable angina and ACS patients when compared with aspirin alone.\(^14\)

The antiplatelet effect of clopidogrel is relatively modest, however, taking up to 8 hours to achieve maximal effect and did not fully eliminate the recurrent ischemic events post-AMI. Subsequent generations of P2Y\(_{12}\) receptor inhibitors prasugrel (a third-generation thienopyridine) and ticagrelor (a nonthienopyridine P2Y\(_{12}\) inhibitor) both achieve more rapid and significantly higher levels of platelet inhibition compared with clopidogrel.\(^15\),\(^16\) Subsequently, the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38, and the study of Platelet Inhibition and Patient Outcomes trial who were treated with primary PCI (PPCI) revealed that stent thrombosis occurred significantly less often in ticagrelor than in clopidogrel-treated patients\(^18\) demonstrating the importance of platelet inhibition in also preventing stent thrombosis. Prasugrel and ticagrelor have therefore become first-line treatment in ACS,\(^11\),\(^12\) and for many years have been used largely interchangeably assuming similar effectiveness in the absence of head-to-head trials. A very recent head-to-head comparison of prasugrel and ticagrelor in the ISAR-REACT 5 study, demonstrated that in patients with ACS, treatment with prasugrel significantly reduced the risk of the composite of death, myocardial infarction or stroke compared with ticagrelor, without an increase in major bleeding.\(^19\) This highlights the risks associated with assuming similar efficacy of treatments based on pharmacodynamic data and trials of individual drugs in similar patient cohorts, that may be misleading in the absence of direct comparison, which is essential to determine the true comparative effectiveness of medications.

Glycoprotein IIb/IIIa Inhibitors

The final common pathway of platelet aggregation involves the binding of fibrinogen to adjacent platelets by means of glycoprotein IIb/IIIa integrin on the platelet surface. The role of suboptimal platelet inhibition at the time of PCI as a contributor to early stent thrombosis post-PCI is well recognized. Potent intravenous glycoprotein IIb/IIIa inhibitors (GPI) abciximab, tirofiban, and eptifibatide have all been shown to reduce the incidence of death and recurrent AMI in high-risk patients undergoing PCI compared with unfractionated heparin alone, particularly in the setting the ACS.\(^20\),\(^22\) Importantly, this reduction in events was mainly driven by a reduction in periprocedural myocardial infarction.

A large-scale meta-analysis of 221,066 patients with 4,276 episodes of stent thrombosis, reported that early DAPT discontinuation was one of the most important predictors of stent thrombosis.\(^23\) The role of potent platelet...
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<th>Table 1</th>
<th>Landmark trials of antiplatelet therapy in acute coronary syndrome and percutaneous coronary intervention</th>
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<td><strong>Type of antiplatelet therapy</strong></td>
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<td><strong>ISIS-2</strong></td>
<td>MI within 24h</td>
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<td><strong>CURE</strong></td>
<td>ACS without ST-elevation</td>
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<td><strong>PLATO</strong></td>
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<td><strong>TRITON-TIMI 38</strong></td>
<td>Moderate-to-high-risk ACS with scheduled PCI</td>
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<td><strong>CHAMPION PHOENIX</strong></td>
<td>Urgent or elective PCI</td>
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<td><strong>TRACER</strong></td>
<td>ACS without ST-segment elevation</td>
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<td><strong>ISAR-REACT 5</strong></td>
<td>ACS</td>
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| Intensity and duration of DAPT | |
| DAPT | Prior coronary stent with DES after 12 months of DAPT (thienopyridine and aspirin) | RCT double blind | 9,961 | Thienopyridine (clopidogrel 65% or prasugrel 35%) vs. placebo | Co-PEEP stent thrombosis and MACCE (death, MI, or stroke) | 18 months | Thienopyridine vs. placebo: stent thrombosis: 0.4% vs. 1.4% (HR: 0.29; 95% CI: 0.17–0.48; p < 0.001) | MACCE: 4.3% vs. 5.9% (HR: 0.71; 95% CI: 0.59–0.85; p < 0.001) |
| PEGASUS-TIMI 54 | MI 1–3 years earlier | RCT double blind | 21,162 | Ticagrelor 90 mg b.i.d. vs. ticagrelor 60 mg b.i.d. vs. placebo | PEEP: composite of cardiovascular death, MI, or stroke PSEP: TIMI major bleeding | 33 months | Ticagrelor 90 mg b.i.d. vs. 60 mg b.i.d. vs. placebo: PEEP: 7.85 vs. 7.77 vs. 9.04% (Ticagrelor 90 mg b.i.d. vs. placebo: HR: 0.85; 95% CI: 0.75–0.96; p = 0.008) ticagrelor 60 mg b.i.d. vs. placebo: HR: 0.84; 95% CI: 0.74–0.95; p = 0.004) PSEP: 2.60 vs. 2.30 vs. 1.06%; p < 0.001 for each dose vs. placebo | (Continued) |
Table 1 (Continued)

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<tr>
<th>Population</th>
<th>Design</th>
<th>Sample size</th>
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<th>Primary end point</th>
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<th>Outcome</th>
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<tr>
<td>GLOBAL LEADERS</td>
<td>PCI with a biolimus A9-eluting stent for stable CAD or ACS</td>
<td>RCT open label</td>
<td>15,968 Aspirin plus 90 mg ticagrelor b.i.d. for 1 month, followed by 23 months of ticagrelor monotherapy, vs. standard DAPT with aspirin plus either 75 mg clopidogrel o.d. (stable CAD) or 90 mg ticagrelor b.i.d. (ACS) for 12 months, followed by aspirin monotherapy for 12 months</td>
<td>Composite of all-cause mortality or nonfatal new Q-wave MI</td>
<td>2 years</td>
<td>Experimental vs. control: 3.81 vs. 4.37% (RR: 0.87; 95% CI: 0.75–1.01; p = 0.073)</td>
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<tr>
<td>TROPICAL</td>
<td>Biomarker-positive ACS with successful PCI</td>
<td>RCT open label</td>
<td>2,610 Standard treatment with prasugrel for 12 months (control group) vs. step-down regimen (1 week prasugrel followed by 1 week clopidogrel and PFT-guided maintenance therapy with clopidogrel or prasugrel from day 14 (guided de-escalation group)</td>
<td>Composite of cardiovascular death, MI, stroke or bleeding BARC≥ 2</td>
<td>1 year</td>
<td>Guided de-escalation vs. control 7 vs. 9% (p&lt;0.0004; HR: 0.81; 95% CI: 0.62–1.06; p=0.12)</td>
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<tr>
<td>ARCTIC</td>
<td>Scheduled to undergo PCI with stent</td>
<td>RCT open label</td>
<td>2,440 PFT (VerifyNow P2Y12 and aspirin assays), with drug adjustment if poor response to antiplatelet therapy vs. conventional strategy without monitoring and drug adjustment</td>
<td>Composite of death, MI, stent thrombosis, stroke, or urgent revascularization 1 year after stent</td>
<td>1 year</td>
<td>Monitoring vs. conventional group: 34.6 vs. 31.1% (HR: 1.13; 95% CI: 0.98–1.29; p = 0.10)</td>
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<td>GRAVITAS</td>
<td>Patients with high on-treatment reactivity (VerifyNow P2Y12 assay) 12–24 hours after PCI with DES</td>
<td>RCT double blind</td>
<td>2,214 High-dose clopidogrel (600 mg initial dose, 150 mg o.d. thereafter) vs. standard-dose clopidogrel (no additional loading dose, 75 mg o.d.)</td>
<td>Composite of cardiovascular death, nonfatal MI, or stent thrombosis</td>
<td>6 months</td>
<td>High vs. standard dose clopidogrel: 2.3 vs. 2.3% (HR: 1.01; 95% CI: 0.58–1.76; p = 0.97)</td>
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<td>STOP-DAPT2</td>
<td>PCI</td>
<td>RCT open label</td>
<td>3,045 1 month of DAPT followed by clopidogrel monotherapy vs. 12 months of DAPT with aspirin and clopidogrel</td>
<td>Composite of cardiovascular death, MI, stroke, definite stent thrombosis, or bleeding</td>
<td>1 year</td>
<td>Short vs. conventional DAPT duration: 2.3 vs. 3.70% (HR: 0.64; 95% CI: 0.42–0.98), meeting criteria for noninferiority (p &lt; 0.001) and for superiority (p = 0.04)</td>
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<td>SMART CHOICE</td>
<td>PCI with DES</td>
<td>RCT open label</td>
<td>2,993 Aspirin plus a P2Y12 inhibitor for 3 months and thereafter P2Y12 inhibitor alone vs. DAPT for 12 months</td>
<td>Composite of all-cause death, MI, or stroke</td>
<td>12 months</td>
<td>P2Y12 inhibitor monotherapy vs. DAPT group: 2.9 vs 2.5%; one-sided 95% CI: −∞ to 1.3%; p = 0.007 for noninferiority</td>
</tr>
<tr>
<td>SMART DATE</td>
<td>ACS undergoing PCI</td>
<td>RCT open label</td>
<td>2,712 6-month DAPT vs. 12-month or longer DAPT</td>
<td>Composite of all-cause death, MI, or stroke</td>
<td>18 months</td>
<td>6 vs. 12 months DAPT: 4.7 vs. 4.2% (upper limit of one-sided 95% CI: 1.8%; p&lt;noninferiority = 0.03 with a predefined noninferiority margin of 2.0%)</td>
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<td>TWILIGHT</td>
<td>Patients at high risk for bleeding or ischemic event, with PCI 3 months earlier</td>
<td>RCT double blind</td>
<td>7,119 After 3 months of ticagrelor plus aspirin, patients without major bleeding or ischemic event randomized to ticagrelor alone vs. ticagrelor plus aspirin</td>
<td>BARC 2, 3, or 5 bleeding</td>
<td>1 year</td>
<td>Ticagrelor alone vs. ticagrelor plus aspirin: 4.0 vs. 7.1% (HR: 0.56; 95% CI: 0.45–0.68; p &lt; 0.001)</td>
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Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; BARC, bleeding academic research consortium; b.i.d., bis in die (twice daily); CAD, coronary artery disease; CI, confidence interval; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; HR, hazard ratio; MACCE, major adverse cardiac or cerebrovascular event; o.d., once daily; OR, odds ratio; PCI, percutaneous coronary intervention; PEEP, primary efficacy end-point; PFT, platelet function test; PSEP, primary safety end point; RCT, randomized controlled trial; RR, relative risk; TIMI, thrombolysis in myocardial infarction.
Fig. 1  Mechanism of action of antiplatelet medications. ADP, adenosine diphosphate; GP, glycoprotein; PAR, protease-activated receptor; TxA2, thromboxane A2; VWF, von Willebrand factor.

Fig. 2  Evolution of antiplatelet secondary prevention (aspirin plus P2Y12 inhibitor) trials in acute coronary syndrome and percutaneous coronary intervention.
inhibition in reducing stent thrombosis is further supported by the observation that GPI treatment in ACS reduces acute stent thrombosis compared with heparin alone.\textsuperscript{24,25} Although met with initial enthusiasm, GPI significantly increased the risk of bleeding and have not been shown to have net clinical benefit in low-risk ACS or stable coronary disease patients. The appreciation of the risk of bleeding impacting on mortality has led to a significant reduction in GPI use, but these drugs continue to have a role in high-risk ACS patients undergoing PCI.

**Importance of High on Treatment Platelet Reactivity**

The desire to avoid recurrent ischemic events which occurred in some patients despite DAPT led to studies to try and identify “nonresponders” to clopidogrel.\textsuperscript{26,27} In ACS patients treated with PCI and DAPT including clopidogrel, persistent high on-treatment platelet reactivity (HTPR) to adenosine diphosphate was shown to be associated with a significant increase in nonfatal myocardial infarction, stent thrombosis, and cardiovascular mortality.\textsuperscript{28–34}

Furthermore, 20 to 30\% of patients with ACS show an inadequate response to clopidogrel, depending on the platelet function test used.\textsuperscript{35} Some 5 to 12\% of the variation of adenosine diphosphate–induced platelet aggregation is related to genetic polymorphisms encoding \textit{CYP2C19}, the hepatic enzyme responsible for biotransformation of clopidogrel to its active metabolite.\textsuperscript{36} The \textit{CYP2C19} \textit{618G \rightarrow A\textquotesingle 2} allele—carried by approximately 30\% of Caucasians and 50\% of East Asians\textsuperscript{37,35}—is the most common polymorphism, resulting in loss of function (LoF) of \textit{CYP2C19} enzyme activity. Homozygotes for the \textit{CYP2C19}\textsuperscript{2} and less common \textit{CYP2C19}\textsuperscript{3} LoF alleles are poor metabolizers, and heterozygotes are intermediate metabolizers of clopidogrel. These individuals have high-on clopidogrel platelet reactivity and an increased risk of adverse cardiovascular events—including an increased risk of AMI and stent thrombosis—particularly post-PCI.\textsuperscript{37} In the FAST-MI registry, among 2,208 patients receiving clopidogrel—those carrying two \textit{CYP2C19} LoF alleles—\textsuperscript{2,3,4,5} experienced a twofold increase in cardiovascular events compared with those without LoF alleles, an effect most marked among those undergoing PCI.\textsuperscript{38} In a meta-analysis involving 9,685 patients (91\% undergoing PCI and 55\% with ACS), those carrying one or two \textit{CYP2C19}\textsuperscript{2} alleles had increased rates of cardiovascular events compared with noncarriers and an increased risk of stent thrombosis.\textsuperscript{39} Consequently, in 2010, the US Food and Drug Administration announced a boxed warning on clopidogrel stating that the drug has a reduced effect in patients based on their \textit{CYP2C19} genotype. A meta-analysis assessing 32 studies involving 42,016 patients concluded that although there was an association between the \textit{CYP2C19} genotype and clopidogrel responsiveness, there was no significant association of genotype with cardiovascular events.\textsuperscript{40} However, a subsequent meta-analysis showed that the association of \textit{CYP2C19} genotype with adverse cardiovascular outcomes in whites was restricted to those undergoing PCI, and conferred a greater risk in Asians undergoing PCI.\textsuperscript{41} By contrast, the \textit{CYP2C19}\textsuperscript{17} gain-of-function allele appears to confer enhanced response to clopidogrel and increased bleeding risk.\textsuperscript{40,42}

**Individualized Antiplatelet Therapy**

Prasugrel and ticagrelor are not affected by CYP polymorphisms, and these agents can eliminate the HTPR seen with clopidogrel in \textit{CYP2C19}\textsuperscript{2} allele carriers.\textsuperscript{43,44} There is no evidence that escalating antiplatelet therapy based on \textit{CYP2C19} genotyping results in an improvement in clinical outcome and reduction in cardiovascular events. However, the very recently published POPular Genetics study showed that in patients with ST-elevation myocardial infarction (STEMI) undergoing PCI, a genotype-guided de-escalation from prasugrel/ticagrelor to clopidogrel in those who are not \textit{CYP2C19}\textsuperscript{2} or \textit{3} allele carriers results in a reduction in bleeding without an increase in thrombosis risk.\textsuperscript{35}

Studies were also conducted to assess the impact of overcoming HTPR on cardiovascular outcomes. In patients undergoing elective PCI with HTPR on clopidogrel, doubling the dose of clopidogrel in the Gauging Responsiveness with a VerifyNow-Assay-Impact on Thrombosis and Safety (GRAVITAS) trial\textsuperscript{46} or switching from clopidogrel to prasugrel in the Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel (TRIGGER-PCI) trial\textsuperscript{47} failed to translate into an improvement in clinical outcome. Among patients undergoing PCI for stable coronary artery disease or non-ST elevation ACS, intensification of antiplatelet therapy based on the results of the VerifyNow assay by increasing the dose of aspirin, clopidogrel, or switching to prasugrel, or by additional treatment with GPI in the ARCTIC trial,\textsuperscript{48} or using prasugrel or clopidogrel in elderly patients with ACS in the ANTARCITIC trial\textsuperscript{49} failed to reduce the occurrence of adverse cardiovascular events. Thus, we now know that increasing the dose of clopidogrel or using more potent antiplatelet medications can reduce platelet reactivity and overcome HTPR on clopidogrel, but that this does not translate into an improvement in clinical outcomes in low-medium risk patients.\textsuperscript{27,50}

However, it is possible that these neutral results may be explained by trial designs that could not have shown the effectiveness of platelet function-guided P2Y\textsubscript{12} inhibitor intensification. The GRAVITAS and the TRIGGER PCI trials enrolled low-risk patients in whom the observed MACE rate was so small that a difference in outcome could not be detected given the relative sample size, while in the ANTARCITIC trial of higher risk elderly ACS patients, intensification of P2Y\textsubscript{12} inhibitor treatment was only applied to 4\% of patients.

Furthermore, regardless of genotyping or testing for platelet reactivity, the use of ticagrelor or prasugrel is recommended for patients undergoing PCI.\textsuperscript{11,12} Whether assessment of platelet reactivity or genotyping should be performed, remains unclear. Assessment of on-treatment platelet reactivity may be useful to identify high-risk individuals, but does not lead to useful information in terms of altering treatments and cannot be recommended in routine clinical practice. Benefits of genotyping include (1) the ability to use clopidogrel without fear of a higher risk of acute ischemic
events, especially stent thrombosis, in patients who carry two loss-of-function alleles, and potentially more widespread clopidogrel prescribing, which could lead to (2) reduced bleeding complications in these patients compared with the use of newer P2Y12 inhibitors, and (3) reduced prescribing costs, since clopidogrel is cheaper than the newer P2Y12 inhibitors. However, the negative aspects of routine screening include the fact that (1) the majority of ACS patients are now treated with prasugrel and ticagrelor because of their greater efficacy in reducing ischemic events, (2) genotyping is costly, and (3) there are logistic difficulties with implementing genotyping in a timely manner, for example, point-of-care testing, (4) a large number of patients would have to be screened to identify a relatively small cohort who would benefit, and (5) the cost savings associated with cheaper prescribing costs of clopidogrel, in comparison to newer P2Y12 inhibitors, would almost certainly be offset by the costs of genotyping (both testing costs and manpower).

**Speed and Intensity of Platelet Inhibition**

The speed of onset and intensity of platelet inhibition during PCI is an important determinant of PCI-related ischemic complications, and this is particularly relevant in ACS, especially STEMI. However, the onset of action of oral P2Y12 receptor inhibitors is attenuated in STEMI patients due to delayed absorption. Crushing P2Y12 inhibitor tablets has been shown to provide more rapid platelet inhibition than standard oral dosing. Chewed ticagrelor tablets may also result in a similar effect.

The intravenous P2Y12 inhibitor cangrelor has almost immediate onset of effect, is rapidly reversible and could provide the “bridging” antiplatelet effect required before the onset of effect of oral P2Y12 inhibitors. In the CHAMPION PHOENIX trial in 11,145 patients undergoing PCI for the spectrum of coronary disease presentations (STEMI, non-ST-segment elevation ACS, or stable angina) randomized to cangrelor or placebo, in addition to DAPT (aspirin and clopidogrel), showed that cangrelor significantly reduced the rate of ischemic events, including stent thrombosis during PCI without significant increase in severe bleeding. This may be particularly relevant in patients with cardiogenic shock, which is associated with delayed absorption of orally administered P2Y12 inhibitors.

**Opioid and Oral P2Y12 Inhibitor Interaction**

In the last few years, concerns have arisen about a possible negative pharmacodynamic interaction between opiates, such as morphine and fentanyl, used for the relief of chest pain in AMI and oral P2Y12 inhibitors. Several studies have shown that opioids delay the onset of effect and reduce the maximal platelet inhibition achieved by oral P2Y12 inhibitors through delay in gastrointestinal absorption. In patients with stable coronary disease, morphine but not saline, was shown to significantly delay prasugrel absorption and the onset of platelet inhibition. However, the clinical sequelae of this pharmacodynamic interaction is less clear, with no available prospective randomized trials assessing the impact of opioids in ACS on hard clinical endpoints. Small observational studies show varying impact on adverse cardiovascular events such as death and reinfarction with a signal for increased events and larger infarct size with opiate use. An observational study in patients with anterior STEMI showed a trend toward higher reinfarction rate in patients receiving morphine compared with those not receiving morphine, while in the ATLANTIC-Morphine study, STEMI patients treated with ticagrelor and concomitant morphine had reduced pre-PPCI epicardial flow were more frequently given GPI and more frequently underwent thrombus aspiration, indicating larger thrombus burden than patients not receiving morphine. A recent meta-analysis indicates that STEMI patients treated with morphine may have a higher rate of early reinfarction compared with those treated without morphine. The European Society of Cardiology downgraded the level of evidence for the use of intravenous opioids in the setting of STEMI from level I to level IIa.

Options to overcome the opioid-P2Y12 inhibitor interaction include the use of nonopioid analgesics such as intravenous paracetamol. If opioids are used, coadministration of metoclopramide can enhance ticagrelor absorption and platelet inhibition compared with morphine treatment alone. Oral P2Y12 inhibitor absorption can also be improved by giving crushed ticagrelor or prasugrel through a nasogastric tube or using orodispersible ticagrelor. Concomitant platelet inhibition can be achieved until oral medications can reach maximal effect through the use of cangrelor or GPI.

**More Intensive or Prolonged Antiplatelet Therapy**

Following concerns of late stent thrombosis associated with drug-eluting stent (DES) implantation in the late 2000s, prolonged DAPT treatment became recommended following PCI with DES for a minimum of 12 months. In current clinical practice, the default strategy in most centers is 12-months DAPT followed by aspirin for life. The effect of more prolonged DAPT, beyond 1 year, in patients with ACS was assessed in the PEGASUS TIMI 54 study. In 21,162 patients with prior AMI randomized to ticagrelor 90 mg twice daily, 60 mg twice daily, or placebo; in addition to aspirin, the use of ticagrelor 60 mg twice daily significantly reduced the occurrence of the composite of cardiovascular death, AMI, or stroke compared with placebo at the expense of increased major bleeding. More recently, the GLOBAL LEADERS study showed that DAPT for 1 month followed by ticagrelor monotherapy for 23 months was not superior to 12 months of DAPT, followed by 12 months of aspirin monotherapy with regards to mortality, ischemic, or bleeding complications.

**Less Intensive or Shorter Antiplatelet Therapy**

The observation that ticagrelor and prasugrel significantly reduce ischemic events, but increase bleeding risk in ACS patients undergoing PCI led to studies to assess shortened or...
less intensive DAPT regimens to achieve sufficient platelet inhibition with an acceptable bleeding risk.

Following DES implantation, several studies have assessed the shorter DAPT regimens (≤3 months) and showed these to be noninferior to the traditional 12-month regimen with regard to the occurrence of ischemic events.\textsuperscript{76–81} A very recent systematic review and network meta-analysis—including 17 studies and 46,864 patients—concluded that compared with short-term DAPT using clopidogrel, long-term DAPT led to higher rates of major bleeding and noncardiac death, and conventional term DAPT was associated with an increased risk of any bleeding. For patients with ACS, short-term DAPT was shown to have similar efficacy and safety as standard term DAPT.\textsuperscript{82}

The effect of reducing the intensity of antiplatelet medication in ACS patients undergoing PCI was also assessed. The TOPIC trial of 646 patients with ACS evaluated the clinical benefit of unguided DAPT de-escalation by switching from prasugrel or ticagrelor to clopidogrel 1 month after PCI for ACS. The primary end point of cardiovascular death, urgent revascularization, stroke, and bleeding occurred half as often in the switched group as in the unswitched group, with the benefit driven by a reduction in bleeding events.\textsuperscript{83} The TROPICAL-ACS trial in 2,610 patients with ACS undergoing PCI showed that platelet function test-guided early de-escalation of antiplatelet therapy was noninferior to standard prasugrel therapy with similar rates of ischemic events including cardiovascular death, AMI or stroke and a trend toward less bleeding during guided treatment.\textsuperscript{84} However, in a prespecified subanalysis according to diabetic status showed that de-escalation in patients with diabetes was associated with nonsignificant, but numerically higher rate of the net clinical end point (composite of cardiovascular death, myocardial infarction, stroke, or BARC ≥2 bleeding) than standard of care, with no observed reduction in bleeding.\textsuperscript{85} In a small substudy of TROPICAL-ACS,\textsuperscript{86} in which 603 patients were genotyped for \textit{CYP2C19} α2, 3, and 17 alleles, the \textit{CYP2C19} α2 and \textit{CYP2C19} α17 carrier status correlated with platelet reactivity in patients treated with clopidogrel but not, as expected, in those treated prasugrel, and was proposed as a way of identifying patients who may not be suitable for de-escalation of intensive antiplatelet treatment.\textsuperscript{86} The ANTARCTIC trial in 877 ACS patients ≥75 years showed similar ischemic and bleeding rates with low dose prasugrel (5 mg/d), or with platelet function-guided prasugrel dose escalation (10 mg prasugrel) or de-escalation (75 mg clopidogrel).\textsuperscript{87} Thus, in comparison to trials of platelet function-guided intensification of antplatelet therapy whose results were largely neutral, trials of personalized de-escalation of P2Y\textsubscript{12} inhibitor intensity appear to show promising results. In the STOP-DAPT-2 trial, 3,045 patients undergoing PCI (38% with ACS) were randomized either to 1 month of DAPT followed by clopidogrel monotherapy or to 12 months of DAPT with aspirin and clopidogrel.\textsuperscript{87} Compared with patients receiving 12 months of DAPT, patients assigned to 1 month of DAPT had a significantly lower rate of the composite of cardiovascular death, AMI, ischemic or hemorrhagic stroke, definite stent thrombosis, or major or minor bleeding at 12 months, meeting criteria for both noninferiority and superiority. The SMART-CHOICE trial\textsuperscript{88} in which 2,993 patients undergoing PCI were randomized to aspirin plus a P2Y\textsubscript{12} inhibitor for 3 months and thereafter P2Y\textsubscript{12} inhibitor alone or DAPT for 12 months showed that P2Y\textsubscript{12} inhibitor monotherapy after 3 months of DAPT was noninferior to prolonged DAPT with regards to major adverse cardiac and cerebrovascular events at 1 year. However, concerns have also emerged about shorter DAPT duration from the SMART-DATE noninferiority trial conducted in South Korea, in which 2,712 patients with ACS undergoing PCI were randomized to 6-month or 12-month or longer open-label DAPT, predominantly with clopidogrel.\textsuperscript{89} While bleeding was similar in the two arms, the primary endpoint of the composite of all-cause death, myocardial infarction, or stroke at 18 months occurred more often in 6-month than in the 12-month or longer DAPT group (P \textit{noninferiority} = 0.03) driven by more frequent myocardial infarction, indicating that short-term DAPT may not be a safe option in these patients, particularly if clopidogrel is used.

The recently published POPular AGE trial randomized patients aged ≥70 years or older to clopidogrel or prasugrel/ticagrelor, clopidogrel use was associated with significantly less bleeding without a signal for increase in ischemic events.\textsuperscript{90}

The most recent publication in this area was the TWILIGHT study, in which more than 7,000 patients at high risk for bleeding or an ischemic event undergoing PCI were given 3 months DAPT with ticagrelor plus aspirin, and thereafter randomized to aspirin or placebo for 1 year.\textsuperscript{91} Compared with ongoing DAPT, ticagrelor monotherapy was associated with significantly lower occurrence of the primary end point of BARC type II to V bleeding. Although there was no observed increase in the risk of death, myocardial infarction, or stroke with monotherapy, the trial was underpowered to detect differences in the risk stent thrombosis and stroke.

There is, therefore, significant momentum to now not only reduce ischemic risk, but also bleeding risk in patients undergoing PCI, including for ACS, by reducing the intensity and duration of antplatelet therapy where possible. However, it is important to note that most of the studies assessing de-escalation were generally underpowered to reliably assess the safety of de-escalation on hard clinical end points, in particular myocardial infarction and stent thrombosis and the jury remains out regarding the safety of less intense or shorter duration of antplatelet therapy for the majority of patients. It is possible that personalized therapy using genotyping or phenotyping with platelet function testing to assess the potential effectiveness of P2Y\textsubscript{12} inhibitor treatment may allow de-escalation of antplatelet therapy intensity to reduce bleeding while avoiding ischemic events. Apart from the logistic challenges of genotyping ACS patients in a timely manner, this concept is really only applicable to clopidogrel treatment and assessment of platelet reactivity is more generalizable to all P2Y\textsubscript{12} inhibitors, including those currently in development (vide infra) and also more practicable. Furthermore, theoretically, effective platelet inhibition may negate the need for genotyping to assess drug effectiveness. Future large trials would be required to assess the safety and efficacy of such personalized approaches.
Table 2: New antiplatelet agents being evaluated in or beyond phase II clinical trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Phase of study</th>
<th>Comparator Design</th>
<th>Number of subjects</th>
<th>Condition</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anfibatide</td>
<td>GP Ib antagonist</td>
<td>Phase II</td>
<td>Anfibatide i.v. bolus followed by 48 hours infusion vs. placebo</td>
<td>Double blind RCT</td>
<td>240 STEMI</td>
<td>Ratio of TIMI myocardial perfusion grade 2 and grade 3</td>
</tr>
<tr>
<td>BMS-986141</td>
<td>PAR4 inhibitor</td>
<td>Phase II</td>
<td>BMS-986141 4.8 mg orally or 0.8 mg orally vs. placebo</td>
<td>Double blind RCT</td>
<td>16 TIA or stroke</td>
<td>Composite of symptomatic ischemic stroke and unrecognized brain infarction assessed by MRI at day 28 and composite of major bleeding and clinically relevant nonmajor bleeding at 90 days</td>
</tr>
<tr>
<td>PZ-128</td>
<td>Reversible PAR-1 inhibitor</td>
<td>Phase II</td>
<td>PZ-128 0.3 or 0.5 mg/kg as 1 hour i.v. vs. placebo</td>
<td>Double blind RCT</td>
<td>100 Elective PCI</td>
<td>Incidence of bleeding through 30 days</td>
</tr>
<tr>
<td>ACT-246475</td>
<td>Reversible P2Y12 antagonist</td>
<td>Phase II</td>
<td>ACT-246475 subcutaneously vs. placebo</td>
<td>Double blind RCT</td>
<td>346 Stable CAD</td>
<td>Inhibition of platelet aggregation</td>
</tr>
<tr>
<td>Isoquercetin</td>
<td>Protein disulfide isomerase inhibitor</td>
<td>Phase II and III</td>
<td>Isoquercetin vs. placebo in prevention of cancer related VTE</td>
<td>RCT (multiple studies)</td>
<td></td>
<td>VTE</td>
</tr>
<tr>
<td>ACT017</td>
<td>Antibody to platelet GPVI receptor</td>
<td>Phase II</td>
<td>ACT017 as i.v. bolus and infusion vs. placebo (in addition to i.v. thrombolysis)</td>
<td>Double blind RCT</td>
<td>100 Acute ischemic stroke</td>
<td>Symptomatic or asymptomatic (on CT scan) intracranial hemorrhage</td>
</tr>
<tr>
<td>Revacet</td>
<td>Protein made up of an Fc fragment fused to the GPVI receptor</td>
<td>Phase II</td>
<td>Revacet 80 or 160 mg single dose i.v. vs. placebo</td>
<td>Double blind RCT</td>
<td>332 Stable CAD undergoing PCI</td>
<td>Composite of death and myocardial injury within 48 hours</td>
</tr>
<tr>
<td>Revacet</td>
<td>Protein made up of an Fc fragment fused to the GPVI receptor</td>
<td>Phase II</td>
<td>Revacet 40 or 120 mg single dose i.v. vs. placebo</td>
<td>Double blind RCT</td>
<td>158 Symptomatic carotid artery stenosis</td>
<td>Assessment of incidence of microembolic signals within 48 hours treated with transcranial Doppler</td>
</tr>
<tr>
<td>ALX-0081</td>
<td>Humanized anti-vWF immunoglobulin</td>
<td>Phase II</td>
<td>Discontinued for CV indications after phase II due to bleeding concerns</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARC-1779</td>
<td>Aptamer directed against A1 domain of vWF</td>
<td>Phase II</td>
<td>Discontinued for CV indications after phase II due to bleeding concerns</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CAD, coronary artery disease; CV, cardiovascular; GP, glycoprotein; i.v., intravenous; i.v.i. intravenous infusion; MRI, magnetic resonance imaging; PAR, protease-activated receptor; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack; TIMI, thrombolysis in myocardial infarction; VTE, venous thromboembolism; vWF, von Willebrand factor.
Novel Therapeutic Targets

Novel P2Y<sub>12</sub> and P2Y<sub>1</sub> Inhibitors
Novel P2Y<sub>12</sub> inhibitors include selatogrel, AZD1283, and SAR216471 (Table 2).<sup>92,93</sup> Recently, in a phase II study, selatogrel was shown to provide rapid onset of potent, consistent platelet inhibition when given by subcutaneous injection.<sup>93</sup> In animal models, the platelet P2Y<sub>1</sub> inhibitor BMS-884775 demonstrated similar efficacy to clopidogrel with less bleeding.<sup>94</sup> The combined P2Y<sub>12</sub> and P2Y<sub>1</sub> receptor antagonist GLS-409 appears to be a highly potent antithrombotic agent in an animal model, with minimal increase in bleeding time.<sup>95</sup>

Novel GP IIb/IIIa Inhibitors
Currently, available GP IIb/IIIa inhibitors block all circulating platelets, and therefore significantly increase bleeding. RUC-4, a novel small-molecule in development, is a potent antithrombotic agent which can be given by intramuscular injection, but its bleeding profile is unknown.<sup>96</sup> Conformation-specific targeting of GP IIb/IIIa, whereby only activated GP IIb/IIIa is inhibited, results in potent antithrombotic effects without increase in bleeding in preclinical models.<sup>97</sup> A novel approach targeting the GP IIb/IIIa integrin “outside-in” signaling, which normally triggers an intracellular signaling cascade resulting in granule secretion and clot retraction, has been shown in animal models to prevent occlusive thrombus formation without affecting hemostasis.<sup>98</sup>

GPIb–vWF axis Inhibitors
The GP Ib–IX–V complex binds to vWF via its GP Ib subunit at sites of vascular injury and under conditions of high-shear stress. Although inhibitors of the GP Ib–vWF axis exhibit antithrombotic effects, development of two anti-vWF agents (an aptamer, ARC1779 and a single-domain antibody, caplacizumab) was halted due to bleeding concerns.<sup>99,100</sup> Anifabatide is a GP Ib antagonist that also inhibits vWF. Anifabatide has been shown to inhibit platelet adhesion and aggregation in a mouse model<sup>101</sup> and a phase II clinical trial in patients with STEMI is underway (http://www.clinicaltrials.gov. Unique identifier: NCT02495012).

Phosphatidylinositol 3 Kinase B Inhibitors
AZD6482 is an intravenous inhibitor of the lipid kinase PI3Kβ, important in signaling downstream of platelet receptors and mediating platelet adhesion under shear stress. In normal volunteers, AZD6482 exhibited mild antiplatelet effect but inhibited platelet aggregation under shear-stress, with only mild prolongation of bleeding time, but with frequent epistaxis.<sup>102</sup>

Protease-activated Receptor Inhibitors
Thrombin receptors PAR 1 and 4 mediate platelet activation and aggregation at low and high thrombin concentrations, respectively. PAR1 antagonists, such as vorapaxar, are potent antithrombotic agents, but significantly increase bleeding.<sup>103</sup> Parmodulins are a new class of PAR1 antagonists in development which exhibit antithrombotic effects in animal models without affecting hemostasis.<sup>104</sup> The PAR4 antagonist BMS-986120 has similar antithrombotic effects to clopidogrel, albeit with minimal effect on hemostasis<sup>105</sup> and in a phase I study was shown to provide selective and reversible PAR4 antagonism and platelet aggregation.<sup>106</sup> The PAR4 inhibitor BMS-986141 has been evaluated in a phase II clinical study for reduction of stroke recurrence (http://www.clinicaltrials.gov. Unique identifier: NCT02671461).

Protein Disulfide Isomerase Inhibitors
Protein disulfide isomerase is required for thrombus formation, and inhibitors of this such as isoquercetin are being tested in phase II to III clinical trials of venous thrombosis in patients with cancer (http://www.clinicaltrials.gov. Unique identifier: NCT02195232).

GP VI-collagen Inhibitors
Binding of the platelet GP VI receptor to collagen leads to the release of soluble agonists and activation of GP IIb/IIIa, resulting in platelet activation. A monoclonal antibody targeting the collagen-binding site of GP VI has in preclinical studies demonstrated antithrombotic effects without affecting hemostasis.<sup>107</sup> Another monoclonal antibody against GP VI has recently been shown in a phase I study to achieve effective, dose-dependent inhibition of collagen-induced platelet aggregation without affecting hemostasis,<sup>108</sup> and a phase II trial is planned in stroke (NCT03803007). Revacept, another anti-GP VI agent, has also been shown to effectively inhibit collagen-induced aggregation without increase in bleeding<sup>109</sup> and is now being evaluated in phase II studies in coronary artery disease (http://www.clinicaltrials.gov. Unique identifiers: NCT0312855 a) and in symptomatic carotid stenosis (http://www.clinicaltrials.gov. Unique identifier: NCT01645306).

Conclusion
There have been tremendous advances in antiplatelet therapy for ACS and PCI, particularly in the last three decades. The initial excitement about the development of newer and more potent antiplatelet agents, which could reduce ischemic events, has led to an understanding of the importance of bleeding complications and given way to a desire to individualize and optimize treatment to also reduce bleeding risk. The future is also exciting. Ongoing studies focusing on personalizing treatment through the use of platelet function tests genetic testing, and by prolonging and intensifying or by shortening or de-escalating antiplatelet therapy will hopefully yield further insight into ways of optimizing antiplatelet therapy for the individual. Future antiplatelet therapy is likely to be more personalized, with a combination of individualized clinical risk assessment, incorporating perhaps both in vitro tests of thrombotic status as well as genomic studies may be necessary to provide the optimal patient profile to offer personalized antiplatelet therapy.

Conflict of Interest
T.G. reports personal fees from Astra Zeneca, Boehringer Ingelheim, Ferrer, and Pfizer, grants and personal fees.
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