Platelet inhibition in acute coronary syndrome and PCI: Insights from the past and present

Diana A Gorog[1,2] and Tobias Geisler[3]

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

Word count: 4294 (excluding references)

Correspondence to:

Prof. Diana A Gorog MD, PhD, FRCP
National Heart and Lung Institute
Imperial College London
United Kingdom
&
University of Hertfordshire
Hatfield, United Kingdom
Tel: +44 207 0348934
d.gorog@imperial.ac.uk

Abbreviations

ACS = acute coronary syndrome

AMI = acute myocardial infarction

DAPT = dual antiplatelet therapy

DES = drug eluting stent

GP = glycoprotein

HTPR = high on-treatment platelet reactivity

MACE = major adverse cardiovascular events

PPCI = primary percutaneous coronary intervention

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

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 last 30 years has seen the progress from early trials of clopidogrel and glycoprotein IIb/IIIa inhibitors, to the application of more potent $P2Y_{12}$ inhibitors prasugrel and ticagrelor. Early enthusiasm for newer and more potent antiplatelet agents, which could reduce ischaemic events, has led to the understanding of the importance of bleeding and a desire to individualise and optimise treatment. It has increasingly become apparent that the potency and duration of dual antiplatelet therapy (DAPT) has to reflect the balance between ischaemic and bleeding risk. Recently, multiple strategies have been proposed to individualise DAPT intensity and duration, in order to reduce the bleeding and ischaemic 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 $P2Y_{12}$ 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 personalised antiplatelet treatment will hopefully yield further insight into ways of optimising outcomes for the individual.

Word count: 225

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, post-mortem studies showed that in the majority of patients who died from sudden death due to ischaemic 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 micro-infarction. Furthermore, thrombi are frequently observed at sites other than those of the major culprit lesion in patients with ACS.(1) The appreciation that thrombi in patients with ACS are predominantly formed of platelets(2) 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 ischaemic 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 subsEquent Dual Anti Platelet Therapy) ,(6)-and the PARIS (Patterns of non-Adherence to Anti-Platelet 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 (ARC-HBR) 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) 3-5 bleeding or a ≥1% risk of intracranial haemorrhage at 1 year.(8)

Early antithrombotic therapy

In 1988, the landmark Second International Study of Infarct Survival (ISIS-2) trial in 17,187 patients with suspected AMI showed unequivocally that for every 1000 patients, treatment with aspirin led to a reduction of about 25 deaths and 10-15 non-fatal 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 (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 Figure 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 to aspirin alone in patients suffering from non-ST-elevation ACS (Table 1 and Figure 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 ischaemic events post-AMI. Subsequent generations of $P2Y_{12}$ receptor inhibitors prasugrel (a third-generation thienopyridine) and ticagrelor (a non-thienopyridine $P2Y_{12}$ -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 (PLATO) studies demonstrated that prasugrel and ticagrelor, respectively, were superior to clopidogrel in terms of reducing ischaemic events, albeit with a higher risk of bleeding.(15–17) Subsequent studies, including a sub-group analysis of patients from the PLATO 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 to 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 recognised. 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 inhibition in reducing stent thrombosis is further supported by the observation that GPI treatment in ACS reduces acute stent thrombosis compared with heparin alone.(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 ischaemic events which occurred in some patients despite DAPT, led to studies to try and identify "non-responders" to clopidogrel.(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 non-fatal myocardial infarction, stent thrombosis, and cardiovascular mortality.(28–34)

Furthermore, 20-30% of patients with ACS show an inadequate response to clopidogrel, depending on the platelet function test used.(35) Some 5-12% of the variation of adenosine diphosphate-induced platelet aggregation is related to genetic polymorphisms encoding *CYP2C19*, the hepatic enzyme responsible for biotransformation of clopidogrel to its active metabolite.(36) The *CYP2C19* 618G>A*2 allele, carried by about 30% of Caucasians and 50% of East Asians,(35) is the most common polymorphism, resulting in loss of function (LoF) of CYP2C19 enzyme activity. Homozygotes for the *CYP2C19*2* and less common *CYP2C19*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.(37) In the FAST-MI registry, amongst 2208 patients receiving clopidogrel, those carrying two *CYP2C19* LoF alleles *(*2, *3, *4, or *5*), experienced a two-fold increase in cardiovascular events compared to those without LoF alleles, an effect most marked amongst those undergoing PCI.(38) In a meta-analysis

involving 9,685 patients (91% undergoing PCI and 55% with ACS), those carrying one or two *CYP2C19*2* alleles had increased rates of cardiovascular events compared with non-carriers and an increased risk of stent thrombosis.(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 *CYP2C19* genotype. A meta-analysis assessing 32 studies involving 42,016 patients concluded that although there was an association between the *CYP2C19* genotype and clopidogrel responsiveness, there was no significant association of genotype with cardiovascular events.(40) However, a subsequent meta-analysis showed that the association of *CYP2C19* genotype with adverse cardiovascular outcomes in whites was restricted to those undergoing PCI, and conferred a greater risk in Asians undergoing PCI.(41) By contrast, the *CYP2C19*17* gain-of-function allele appears to confer enhanced response to clopidogrel and increased bleeding risk.(40,42)

Individualised antiplatelet therapy

Prasugrel and ticagrelor are not affected by CYP polymorphisms and these agents can eliminate the HTPR seen with clopidogrel in *CYP2C19*2* allele carriers.(43,44) There is no evidence that escalating antiplatelet therapy based on *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 STEMI undergoing PPCI, a genotype-guided de-escalation from prasugrel/ticagrelor to clopidogrel in those who are not *CYP2C19*2* or *3** allele carriers results in a reduction in bleeding without an increase in thrombosis risk.(45)

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^{TM}Assay-Impact On

Thrombosis And Safety (GRAVITAS) trial(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(47) failed to translate into an improvement in clinical outcome. Amongst 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,(48) or using prasugrel or clopidogrel in elderly patients with ACS in the ANTARCTIC trial(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.(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 $P2Y_{12}$ 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, whilst in the ANTARCTIC trial of higher risk elderly ACS patients, intensification of $P2Y_{12}$ 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 over the use clopidogrel in patients with ACS.(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 (i) the ability to use clopidogrel without fear of a higher risk of acute ischaemic events, esp. stent thrombosis,

in patients who carry two loss-of-function alleles, and potentially more widespread clopidogrel prescribing, which could lead to (ii) reduced bleeding complications in these patients compared with the use of newer $P2Y_{12}$ inhibitors, and (iii) reduced prescribing costs, since clopidogrel is cheaper than the newer $P2Y_{12}$ inhibitors. However, the negative aspects of routine screening include the fact that (i) the majority of ACS patients are now treated with prasugrel and ticagrelor because of their greater efficacy in reducing ischaemic events, (ii) genotyping is costly, (iii) there are logistic difficulties with implementing genotyping in a timely manner e.g. point-of-care testing, (iv) a large number of patients would have to be screened to identify a relatively small cohort who would benefit and (v) the cost-savings associated with cheaper prescribing costs of clopidogrel, in comparison to newer $P2Y_{12}$ 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 ischaemic complications, and this is particularly relevant in ACS, especially ST-elevation myocardial infarction (STEMI).(33,51) However, the onset of action of oral $P2Y_{12}$ receptor inhibitors is attenuated in STEMI patients, due to delayed absorption.(51) Crushing $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ inhibitors. In the CHAMPION PHOENIX trial(52) in 11,145 patients undergoing PCI for the spectrum of coronary disease presentations (STEMI, non-ST-segment

elevation ACS, or stable angina) randomised to cangrelor or placebo, in addition to DAPT (aspirin and clopidogrel), showed that cangrelor significantly reduced the rate of ischaemic 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 $P2Y_{12}$ inhibitors(53)

Opioid and oral $P2Y_{12}$ 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 $P2Y_{12}$ inhibitors.(54–57) A number of studies have shown that opioids delay the onset of effect and reduce the maximal platelet inhibition achieved by oral $P2Y_{12}$ inhibitors(54,58–60) through delay in gastrointestinal absorption.(61) In patients with stable coronary disease, morphine but not saline, was shown to significantly delay prasugrel absorption and the onset of platelet inhibition.(62) However, the clinical sequalae of this pharmacodynamic interaction is less clear, with no available prospective randomised 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(63–65) with a signal for increased events and larger infarct size with opiate-use.(66) An observational study in patients with anterior STEMI showed a trend towards higher reinfarction rate in patients receiving morphine compared to those not receiving morphine,(67) whilst 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.(68) A recent meta-analysis indicates

that STEMI patients treated with morphine may have a higher rate of early reinfarction compared to those treated without morphine.(69) 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.(11)

Options to overcome the opioid-$P2Y_{12}$ inhibitor interaction include the use of non-opioid analgesics such as intravenous paracetamol. If opioids are used, co-administration of metoclopramide can enhance ticagrelor absorption and platelet inhibition compared to morphine treatment alone.(70) Oral $P2Y_{12}$ inhibitor absorption can also be improved by giving crushed ticagrelor or prasugrel through a nasogastric tube,(71–73) or using orodispersible ticagrelor.(70) Concomitant platelet inhibition can be achieved until oral medications can reach maximal effect, through the use of cangrelor,(74,75) or GPI(74,75).

More intensive or prolonged antiplatelet therapy

Following concerns of late stent thrombosis associated with drug-eluting stent (DES) implantation in the late 2000's, prolonged DAPT treatment became recommended following PCI with DES for a minimum of 12 months. In current clinical practice, the default strategy in most centres is 12 months' DAPT followed by aspirin for life. The effect of more prolonged DAPT, beyond one year, in patients with ACS was assessed in the PEGASUS TIMI 54 study.(76) In 21,162 patients with prior AMI randomised 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 to placebo, at the expense of increased major bleeding.(76) 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, ischaemic or bleeding complications.(77)

Less intensive or shorter antiplatelet therapy

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

Following DES implantation, a number of 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 ischaemic events.(78–81) 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 non-cardiac 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.(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 one 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.(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 non-inferior to standard

prasugrel therapy with similar rates of ischaemic events including cardiovascular death, AMI or stroke and a trend towards less bleeding during guided treatment.(84) However, in a pre-specified sub-analysis according to diabetic status showed that de-escalation in patients with diabetes was associated with non-significant but numerically higher rate of the net clinical endpoint (composite of cardiovascular death, myocardial infarction, stroke or BARC ≥2 bleeding) than standard of care, with no observed reduction in bleeding.(85) In a small sub-study of TROPICAL-ACS,(86) in which 603 patients were genotyped for *CYP2C19*2, *3* and **17* alleles, the *CYP2C19*2* and *CYP2C19*17* 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.(86) The ANTARCTIC trial in 877 ACS patients ≥75 years showed similar ischaemic 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).(49) Thus, in comparison to trials of platelet function-guided intensification of antiplatelet therapy whose results were largely neutral, trials of personalised de-escalation of $P2Y_{12}$ 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.(87) Compared to 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, ischaemic or haemorrhagic stroke, definite stent thrombosis, or major or minor bleeding at 12 months, meeting criteria for both noninferiority and superiority. The SMART-CHOICE trial(88) in which 2,993 patients undergoing PCI were randomised to aspirin plus a $P2Y_{12}$ inhibitor for 3 months and thereafter $P2Y_{12}$ inhibitor alone or DAPT for 12 months showed that $P2Y_{12}$ inhibitor monotherapy after 3 months of

DAPT was non-inferior 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 non-inferiority trial conducted in South Korea, in which 2712 patients with ACS undergoing PCI were randomised to 6-months or 12-month or longer open-label DAPT, predominantly with clopidogrel.(89) Whilst 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 ($p_{non\text{-}inferiority}$=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 randomised 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 ischaemic events.(90)

The most recent publication in this area was the TWILIGHT study, in which more than 7000 patients at high risk for bleeding or an ischemic event undergoing PCI were given 3 months DAPT with ticagrelor plus aspirin, and thereafter randomised to aspirin or placebo for 1 year.(91) Compared to ongoing DAPT, ticagrelor monotherapy was associated with significantly lower occurrence of the primary end point of BARC type 2-5 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 ischaemic risk, but also bleeding risk in patients undergoing PCI, including for ACS, by reducing the intensity and duration of antiplatelet 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 endpoints, in particular myocardial infarction and stent thrombosis and the jury remains out regarding the safety of less intense or shorter duration of antiplatelet therapy for the majority of patients. It is possible that personalised therapy using genotyping or phenotyping with platelet function testing to assess the potential effectiveness of $P2Y_{12}$ inhibitor treatment may allow de-escalation of antiplatelet therapy intensity to reduce bleeding, while avoiding ischaemic 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 generalisable to all $P2Y_{12}$ 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 personalised approaches.

Novel therapeutic targets

Novel $P2Y_{12}$ and $P2Y_1$ inhibitors

Novel $P2Y_{12}$ inhibitors include selatogrel, AZD1283, and SAR216471 (Table 2).(92,93) Recently, in a phase 2 study, selatogrel was shown to provide rapid onset of potent, consistent platelet inhibition when given by subcutaneous injection.(93) In animal models, the platelet $P2Y_1$ inhibitor BMS-884775 demonstrated similar efficacy to clopidogrel with less bleeding.(94) The combined $P2Y_{12}$ and $P2Y_1$ receptor antagonist GLS-409 appears to be a highly potent antithrombotic agent in an animal model, with minimal increase in bleeding time.(95)

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.(96) 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 pre-clinical models.(97) A novel approach targeting the GP IIb/IIIa integrin "outside-in" signalling, which normally triggers an intracellular signalling cascade resulting in granule secretion and clot retraction, has been shown, in animal models, to prevents occlusive thrombus formation without affecting haemostasis.(98)

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.(99,100) Anfibatide is a GP Ib antagonist that also inhibits vWF. Anfibatide has been shown to inhibit platelet adhesion and aggregation in a mouse model(101) and a phase II clinical trial in patients with STEMI is underway (http://www.clinicaltrials.gov. Unique identifier: NCT02495012).

Phosphatidylinositol 3 Kinase B (PI3Kβ) inhibitors

AZD6482 is an intravenous inhibitor of the lipid kinase PI3Kβ, important in signalling 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.(102)

Protease-activated receptor (PAR) 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.(103) Parmodulins are a new class of PAR1 antagonists in development which exhibit antithrombotic effects in animal models without affecting haemostasis.(104) The PAR4 antagonist BMS-986120 has similar antithrombotic effects to clopidogrel, albeit with minimal effect on haemostasis(105) and in a phase 1 study was shown to provide selective and reversible PAR4 antagonism and platelet aggregation.(106) 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–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 pre-clinical studies, demonstrated antithrombotic effects without affecting haemostasis.(107) Another monoclonal antibody against GP VI has

recently been shown in a phase 1 study to achieve effective, dose-dependent inhibition of collagen-induced platelet aggregation without affecting haemostasis,(108) and a phase 2 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(109) and is now being evaluated in phase 2 studies in coronary artery disease (http://www.clinicaltrials.gov. Unique identifiers: NCT03312855 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 3 decades. The initial excitement about the development of newer and more potent antiplatelet agents, which could reduce ischaemic events, has led to an understanding of the importance of bleeding complications and given way to a desire to individualise and optimise treatment to also reduce bleeding risk. The future is also exciting. Ongoing studies focusing on personalising 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 optimising antiplatelet therapy for the individual. Future antiplatelet therapy is likely to be more personalised, with a combination of individualised 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.

REFERENCES

1. Davies MJ. The birth, growth and consequences of the atherosclerotic plaque. Dialogues Cardiovasc Med. 1999; 4: 115–178.

2. Davies MJ. The pathophysiology of acute coronary syndromes. Heart 2000; 83: 361-366.

3. Moscucci M, Fox KAA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). Eur Heart J 2003; 24: 1815–23.

4. Segev A, Strauss BH, Tan M, et al. Predictors and 1-year outcome of major bleeding in patients with non–ST-elevation acute coronary syndromes: Insights from the Canadian Acute Coronary Syndrome Registries. Am Heart J 2005; 150: 690–4.

5. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention. JAMA 2016; 315: 1735.

6. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet 2017; 389: 1025–34.

7. Abu-Assi E, Raposeiras-Roubin S, Cobas-Paz R, et al. Assessing the performance of the

503 PRECISE-DAPT and PARIS risk scores for predicting one-year out-of-hospital bleeding in
504 acute coronary syndrome patients. Eurointervention 2018; 13: 1914–22.
505
506 8. Urban P, Mehran R, Colleran R, et al. Defining High Bleeding Risk in Patients
507 Undergoing Percutaneous Coronary Intervention: A Consensus Document From the
508 Academic Research Consortium for High Bleeding Risk. Circulation 2019; 140: 240–61.
509
510 9. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187
511 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of
512 Infarct Survival) Collaborative Group. Lancet 1988; 2: 349–60.
513
514 10. Collaboration A. Collaborative meta-analysis of randomised trials of antiplatelet therapy
515 for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;
516 324: 71–86.
517
518 11. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute
519 myocardial infarction in patients presenting with ST-segment elevation: The Task Force for
520 the management of acute myocardial infarction in patients presenting with ST-segment
521 elevation of the European Society of Cardiology (ESC). Eur Heart J 2018; 39: 119–77.
522
523 12. Roffi M, Patrono C, Collet J-PP, et al. 2015 ESC Guidelines for the management of acute
524 coronary syndromes in patients presenting without persistent ST-segment elevation: Task
525 Force for the Management of Acute Coronary Syndromes in Patients Presenting without
526 Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J
527 2016; 37: 267–315.

528

529 13. Yusuf S, Zhao F, Mehta S, et al. Effects of clopidogrel in addition to aspirin in patients
530 with acute coronary syndromes without ST-segment elevation. New Engl J Med 2001; 345:
531 494–502.

532

533 14. Leon M, Baim D, Popma J, et al. A clinical trial comparing three antithrombotic-drug
534 regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study
535 Investigators. New Engl J Med 1998; 339: 1665–71.

536

537 15. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients
538 with acute coronary syndromes. New Engl J Med 2007; 357: 2001–15.

539

540 16. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with
541 acute coronary syndromes. New Engl J Med 2009; 361: 1045–57.

542

543 17. Sibbing D, Angiolillo DJ, Huber K. Antithrombotic therapy for acute coronary syndrome:
544 Past, present and future. Thromb Haemost 2017; 117: 1240–8.

545

546 18. Velders MA, Abtan J, Angiolillo DJ, et al. Safety and efficacy of ticagrelor and
547 clopidogrel in primary percutaneous coronary intervention. Heart 2016; 102: 617–25.

548

549 19. Schüpke S, Neumann F-JJ, Menichelli M, et al. Ticagrelor or Prasugrel in Patients with
550 Acute Coronary Syndromes. New Engl J Med 2019; 381:1524-1534.

551

552 20. Hamm C, Heeschen C, Goldmann B, et al. Benefit of abciximab in patients with

553 refractory unstable angina in relation to serum troponin T levels. c7E3 Fab Antiplatelet
554 Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators. New Engl J Med
555 1999; 340: 1623–9.
556
557 21. PRISM PLUS Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor
558 with tirofiban in unstable angina and non-Q-wave myocardial infarction. New Engl J Med
559 1998; 338: 1488–97.
560
561 22. PURSUIT Trial investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide
562 in patients with acute coronary syndromes. New Engl J Med 1998; 339: 436–43.
563
564 23. D'Ascenzo F, Bollati M, Clementi F, et al. Incidence and predictors of coronary stent
565 thrombosis: evidence from an international collaborative meta-analysis including 30 studies,
566 221,066 patients, and 4276 thromboses. Int J Cardiol 2013; 167: 575–84.
567
568 24. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute
569 myocardial infarction. New Engl J Med 2008; 358: 2218–30.
570
571 25. Dangas G, Aymong ED, Mehran R, et al. Predictors of and outcomes of early thrombosis
572 following balloon angioplasty versus primary stenting in acute myocardial infarction and
573 usefulness of abciximab (the CADILLAC trial). The American Journal of Cardiology 2004;
574 94: 983–8.
575
576 26. Sweeny J, Gorog DA, Fuster V. Antiplatelet drug 'resistance'. Part 1: mechanisms and
577 clinical measurements. Nature Rev Cardiol 2009; 6: 273–82.

578

579 27. Gorog DA, eeny J, Fuster V. Antiplatelet drug 'resistance'. Part 2: laboratory resistance
580 to antiplatelet drugs-fact or artifact? Nature Rev Cardiol 2009; 6: 365–73.

581

582 28. Hochholzer W, Trenk D, Bestehorn H-PP, et al. Impact of the degree of peri-
583 interventional platelet inhibition after loading with clopidogrel on early clinical outcome of
584 elective coronary stent placement. J Am Coll Cardiol 2006; 48: 1742–50.

585

586 29. Geisler T, Zürn C, Simonenko R, et al. Early but not late stent thrombosis is influenced
587 by residual platelet aggregation in patients undergoing coronary interventions. Eur Heart J
588 2010; 31: 59–66.

589

590 30. Morel O, Ghannudi S, Jesel L, et al. Cardiovascular mortality in chronic kidney disease
591 patients undergoing percutaneous coronary intervention is mainly related to impaired P2Y12
592 inhibition by clopidogrel. J Am Coll Cardiol 2011; 57: 399–408.

593

594 31. Cuisset T, Frere C, Quilici J, et al. Relationship between aspirin and clopidogrel
595 responses in acute coronary syndrome and clinical predictors of non response. Thromb Res
596 2009; 123: 597–603.

597

598 32. Frere C, Cuisset T, Quilici J, et al. ADP-induced platelet aggregation and platelet
599 reactivity index VASP are good predictive markers for clinical outcomes in non-ST elevation
600 acute coronary syndrome. Thromb Haemost 2007; 98: 838–43.

601

602 33. Alexopoulos D, Xenogiannis I, Vlachakis P, et al. Peri-Procedural Platelet Reactivity in

603 Percutaneous Coronary Intervention. Thromb Haemost 2018; 118: 1131–40.
604
605 34. de Carvalho LP, Fong A, Troughton R, et al. Prognostic Implications of Dual Platelet
606 Reactivity Testing in Acute Coronary Syndrome. Thromb Haemost 2018; 118: 415–26.
607
608 35. Winter M-PP, Grove EL, Caterina R, et al. Advocating cardiovascular precision medicine
609 with P2Y12 receptor inhibitors. Eur Heart J Cardiovasc Pharmacotherapy 2017; 3: 221–34.
610
611 36. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19
612 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA
613 2009; 302: 849–57.
614
615 37. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to
616 clopidogrel. New Engl J Med 2009; 360: 354–62.
617
618 38. Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to
619 clopidogrel and cardiovascular events. New Engl J Med 2009; 360: 363–75.
620
621 39. Mega JL, Simon T, Collet J-PP, et al. Reduced-function CYP2C19 genotype and risk of
622 adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a
623 meta-analysis. JAMA 2010; 304: 1821–30.
624
625 40. Holmes MV, Perel P, Shah T, et al. CYP2C19 Genotype, Clopidogrel Metabolism,
626 Platelet Function, and Cardiovascular Events: A Systematic Review and Meta-analysis.
627 JAMA 2011; 306: 2704–14.

628

629 41. Sorich M, Rowlan A, McKinnon R, et al. CYP2C19 genotype has a greater effect on
630 adverse cardiovascular outcomes following PCI and in Asian populations treated with
631 clopidogrel: a meta-analysis. Circ Cardiovasc Genetics 2014; 7: 895-902.

632

633 42. Frére C, Cuisset T, Gaborit B, et al. The CYP2C19*17 allele is associated with better
634 platelet response to clopidogrel in patients admitted for non-ST acute coronary syndrome. J
635 Thromb Haemost 2009; 7: 1409–11.

636

637 43. Sorich M, Vitry A, Ward M, et al. Prasugrel vs. clopidogrel for cytochrome P450 2C19-
638 genotyped subgroups: integration of the TRITON-TIMI 38 trial data. J Thromb Haemost
639 2010; 8: 1678–84.

640

641 44. Wallentin L, James S, Storey RF, et al. Effect of CYP2C19 and ABCB1 single nucleotide
642 polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute
643 coronary syndromes: a genetic substudy of the PLATO trial. Lancet 2010; 376: 1320–8.

644

645 45. Claassens DM, Vos GJ, Bergmeijer TO, et al. A Genotype-Guided Strategy for Oral
646 P2Y12 Inhibitors in Primary PCI. New Engl J Med 2019; 381:1621-1631.

647

648 46. Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on
649 platelet function testing after percutaneous coronary intervention: the GRAVITAS
650 randomized trial. JAMA 2011; 305: 1097–105.

651

652 47. Trenk D, Stone GW, Gawaz M, et al. A Randomized Trial of Prasugrel Versus

653 Clopidogrel in Patients With High Platelet Reactivity on Clopidogrel After Elective
654 Percutaneous Coronary Intervention With Implantation of Drug-Eluting Stents Results of the
655 TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement
656 on Clopidogrel to Guide Alternative Therapy With Prasugrel) Study. J Am Coll Cardiol
657 2012; 59: 2159–64.
658
659 48. Collet J-PP, Cuisset T, Rangé G, et al. Bedside monitoring to adjust antiplatelet therapy
660 for coronary stenting. New Engl J Med 2012; 367: 2100–9.
661
662 49. Cayla G, Cuisset T, Silvain J, et al. Platelet function monitoring to adjust antiplatelet
663 therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-
664 label, blinded-endpoint, randomised controlled superiority trial. Lancet 2016; 388: 2015–22.
665
666 50. Gorog DA, Fuster V. Platelet function tests in clinical cardiology: unfulfilled
667 expectations. J Am Coll Cardiol 2013; 61: 2115–29.
668
669 51. Flierl U, Zauner F, Sieweke J-TT, et al. Efficacy of prasugrel administration immediately
670 after percutaneous coronary intervention in ST-elevation myocardial infarction. Thromb
671 Haemost 2017; 117: 99–104.
672
673 52. Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of Platelet Inhibition with Cangrelor
674 during PCI on Ischemic Events. New Engl J Med 2013; 368: 1303–13.
675
676 53. Droppa M, Vaduganathan M, Venkateswaran RV, et al. Cangrelor in cardiogenic shock
677 and after cardiopulmonary resuscitation: A global, multicenter, matched pair analysis with

678 oral P2Y12 inhibition from the IABP-SHOCK II trial. Resuscitation 2019; 137: 205–12.
679
680 54. Silvain J, Storey RF, Cayla G, et al. P2Y12 receptor inhibition and effect of morphine in
681 patients undergoing primary PCI for ST-segment elevation myocardial infarction. The
682 PRIVATE-ATLANTIC study. Thromb Haemost 2016; 116: 369–78.
683
684 55. Bellandi B, Zocchi C, Xanthopoulou I, et al. Morphine use and myocardial reperfusion in
685 patients with acute myocardial infarction treated with primary PCI. Int J Cardiol 2016; 221:
686 567–71.
687
688 56. Kubica J, Adamski P, Ostrowska M, et al. Morphine delays and attenuates ticagrelor
689 exposure and action in patients with myocardial infarction: the randomized, double-blind,
690 placebo-controlled IMPRESSION trial. Eur Heart J 2016; 37: 245–52.
691
692 57. Duerschmied D, Bode C. Life-Saving Therapy versus Symptom Relief: Anti-Platelet
693 Agents and Opioids in Coronary Intervention. Thromb Haemost 2018; 118: 1350–1.
694
695 58. Ibrahim K, Shah R, Goli RR, et al. Fentanyl Delays the Platelet Inhibition Effects of Oral
696 Ticagrelor: Full Report of the PACIFY Randomized Clinical Trial. Thromb Haemost 2018;
697 118: 1409–18.
698
699 59. Parodi G, Valenti R, Bellandi B, et al. Comparison of prasugrel and ticagrelor loading
700 doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of
701 Platelet Inhibitor Drugs) primary PCI study. J Am Coll Cardiol 2013; 61: 1601–6.
702

703 60. Parodi G, Bellandi B, Xanthopoulou I, et al. Morphine is associated with a delayed
704 activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction
705 undergoing primary percutaneous coronary intervention. Circ Cardiovasc Interventions 2015;
706 8: pii: e001593.
707
708 61. Nimmo W, Heading R, Wilson J, et al. Inhibition of gastric emptying and drug absorption
709 by narcotic analgesics. Brit J Clin Pharmacol 1975; 2: 509–13.
710
711 62. Thomas MR, Morton AC, Hossain R, et al. Morphine delays the onset of action of
712 prasugrel in patients with prior history of ST-elevation myocardial infarction. Thromb
713 Haemost 2016; 116: 96–102.
714
715 63. McCarthy CP, Bhambhani V, Pomerantsev E, et al. In-hospital outcomes in invasively
716 managed acute myocardial infarction patients who receive morphine. J Interven Cardiol
717 2018; 31: 150–8.
718
719 64. Puymirat E, Lamhaut L, Bonnet N, et al. Correlates of pre-hospital morphine use in ST-
720 elevation myocardial infarction patients and its association with in-hospital outcomes and
721 long-term mortality: the FAST-MI (French Registry of Acute ST-elevation and non-ST-
722 elevation Myocardial Infarction) programme. Eur Heart J 2016; 37: 1063–71.
723
724 65. Farag M, Spinthakis N, nivasan M, et al. Morphine Analgesia Pre-PPCI Is Associated
725 with Prothrombotic State, Reduced Spontaneous Reperfusion and Greater Infarct Size.
726 Thromb Haemost 2018; 118: 601–12.
727

66. de Waha S, Eitel I, Desch S, et al. Intravenous morphine administration and reperfusion success in ST-elevation myocardial infarction: insights from cardiac magnetic resonance imaging. Clin Res Cardiol 2015; 104: 727–34.

67. Bonin M, Mewton N, Roubille F, et al. Effect and Safety of Morphine Use in Acute Anterior ST-Segment Elevation Myocardial Infarction. J Am Heart Assoc 2018; 7: pii: e006833.

68. Lapostolle F, Hof AW, Hamm CW, et al. Morphine and Ticagrelor Interaction in Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction: ATLANTIC-Morphine. Am J Cardiovasc Drugs 2019; 19: 173–83.

69. Spinthakis N, Gue Y, Farag M, et al. Apixaban Enhances Endogenous Fibrinolysis in Patients with Atrial Fibrillation. Europace 2019; 21: 1297-1306.

70. Sikora J, Niezgoda P, Barańska M, et al. METoclopramide Administration as a Strategy to Overcome MORPHine-ticagrelOr Interaction in PatientS with Unstable Angina PectorIS-The METAMORPHOSIS Trial. Thromb Haemost 2018; 118: 2126–33.

71. Rollini F, Franchi F, Hu J, et al. Crushed Prasugrel Tablets in Patients With STEMI Undergoing Primary Percutaneous Coronary Intervention: The CRUSH Study. J Am Coll Cardiol 2016; 67: 1994–2004.

72. Parodi G, Xanthopoulou I, Bellandi B, et al. Ticagrelor crushed tablets administration in STEMI patients: the MOJITO study. J Am Coll Cardiol 2015; 65: 511–2.

753

754 73. Asher E, Frydman S, Katz M, et al. Chewing versus Swallowing Ticagrelor to Accelerate
755 Platelet Inhibition in Acute Coronary Syndrome - the CHEERS study. For The PLATIS
756 (Platelets and Thrombosis in Sheba) Study Group. Thromb Haemost 2017; 117: 727–33.

757

758 74. Giannopoulos G, Deftereos S, Kolokathis F, et al. P2Y12 Receptor Antagonists and
759 Morphine: A Dangerous Liaison? Circ Cardiovasc Interventions 2016; 9: pii: e004229.

760

761 75. Kubica J, Kubica A, Jilma B, et al. Impact of morphine on antiplatelet effects of oral
762 P2Y12 receptor inhibitors. Int J Cardiol 2016; 215: 201–8.

763

764 76. Bonaca MP, Bhatt DL, Cohen M, et al. Long-Term Use of Ticagrelor in Patients with
765 Prior Myocardial Infarction. New Engl J Med 2015; 372: 1791–800.

766

767 77. Vranckx P, Valgimigli M, Jüni P, et al. Ticagrelor plus aspirin for 1 month, followed by
768 ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months,
769 followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a
770 multicentre, open-label, randomised superiority trial. Lancet 2018; 392: 940–9.

771

772 78. Feres F, Costa RA, Abizaid A, et al. Three vs twelve months of dual antiplatelet therapy
773 after zotarolimus-eluting stents: the OPTIMIZE randomized trial. JAMA 2013; 310: 2510–
774 22.

775

776 79. Kim B-KK, Hong M-KK, Shin D-HH, et al. A new strategy for discontinuation of dual
777 antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet

778 Therapy following Endeavor zotarolimus-eluting stent implantation). J Am Coll Cardiol
779 2012; 60: 1340–8.
780
781 80. Urban P, Meredith IT, Abizaid A, et al. Polymer-free Drug-Coated Coronary Stents in
782 Patients at High Bleeding Risk. New Engl J Med 2015; 373: 2038–47.
783
784 81. Varenne O, Cook S, Sideris G, et al. Drug-eluting stents in elderly patients with coronary
785 artery disease (SENIOR): a randomised single-blind trial. Lancet 2018; 391: 41–50.
786
787 82. Yin S-H-LH, Xu P, Wang B, et al. Duration of dual antiplatelet therapy after
788 percutaneous coronary intervention with drug-eluting stent: systematic review and network
789 meta-analysis. BMJ 2019; 365: l2222.
790
791 83. Cuisset T, Deharo P, Quilici J, et al. Benefit of switching dual antiplatelet therapy after
792 acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary
793 syndrome) randomized study. Eur Heart J 2017; 38: 3070–8.
794
795 84. Sibbing D, Aradi D, Jacobshagen C, et al. Guided de-escalation of antiplatelet treatment
796 in patients with acute coronary syndrome undergoing percutaneous coronary intervention
797 (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet 2017; 390: 1747–57.
798
799 85. Hein R, Gross L, Aradi D, et al. Diabetes and outcomes following guided de-escalation of
800 antiplatelet treatment in acute coronary syndrome patients undergoing percutaneous coronary
801 intervention: a pre-specified analysis from the randomised TROPICAL-ACS trial.
802 Eurointervention 2019; 15: e513–21.

803

804 86. Gross L, Trenk D, Jacobshagen C, et al. Genotype-Phenotype Association and Impact on
805 Outcomes following Guided De-Escalation of Anti-Platelet Treatment in Acute Coronary
806 Syndrome Patients: The TROPICAL-ACS Genotyping Substudy. Thromb Haemost 2018;
807 118: 1656–67.

808

809 87. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-Month Dual Antiplatelet Therapy
810 Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and
811 Bleeding Events in Patients Receiving PCI: The STOPDAPT-2 Randomized Clinical Trial.
812 JAMA 2019; 321: 2414–27.

813

814 88. Hahn J-YY, Song YB, Oh J-HH, et al. Effect of P2Y12 Inhibitor Monotherapy vs Dual
815 Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous
816 Coronary Intervention: The SMART-CHOICE Randomized Clinical Trial. JAMA 2019; 321:
817 2428–37.

818

819 89. Hahn J-Y, Song Y, Oh J-H, et al. 6-month versus 12-month or longer dual antiplatelet
820 therapy after percutaneous coronary intervention in patients with acute coronary syndrome
821 (SMART-DATE): a randomised, open-label, non-inferiority trial. Lancet 2018; 391: 1274–
822 84.

823

824 90. Gimbel ME. Randomised comparison of clopidogrel versus ticagrelor or prasugrel in
825 patients of 70 years or older with non-ST-elevation acute coronary syndrome - POPular
826 AGE. European Society of Cardiology 2019; .

827

828 91. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without Aspirin in High-Risk
829 Patients after PCI. New Engl J Med 2019; 381: 2032–42.
830
831 92. Delesque-Touchard N, Pflieger A, Bonnet-Lignon S, et al. SAR216471, an alternative to
832 the use of currently available $P2Y_{12}$ receptor inhibitors? Thromb Res 2014; 134: 693–703.
833
834 93. Storey RF, Gurbel PA, ten Berg J, et al. Pharmacodynamics, pharmacokinetics, and
835 safety of single-dose subcutaneous administration of selatogrel, a novel P2Y12 receptor
836 antagonist, in patients with chronic coronary syndromes. Eur Heart J 2019
837 https://doi.org/10.1093/eurheartj/ehz807.
838
839 94. Wong P, Crain E, Watson C, et al. Differential effects of P2Y1 versus P2Y12 receptor
840 antagonism on thrombosis and bleeding in rabbits. Eur Heart J 2013; 34: P1431–P1431.
841
842 95. Gremmel T, Yanachkov IB, Yanachkova MI, et al. Synergistic Inhibition of Both P2Y1
843 and P2Y12 Adenosine Diphosphate Receptors As Novel Approach to Rapidly Attenuate
844 Platelet-Mediated Thrombosis. Arteriosclerosis Thrombosis Vasc Biology 2016; 36: 501–9.
845
846 96. Li J, Vootukuri S, Shang Y, et al. RUC-4: a novel αIIbβ3 antagonist for prehospital
847 therapy of myocardial infarction. Arteriosclerosis Thrombosis Vasc Biology 2014; 34: 2321–
848 9.
849
850 97. Schwarz M, Meade G, Stoll P, et al. Conformation-specific blockade of the integrin
851 GPIIb/IIIa: a novel antiplatelet strategy that selectively targets activated platelets. Circ Res
852 2006; 99: 25–33.

853

854 98. McFadyen JD, Schaff M, Peter K. Current and future antiplatelet therapies: emphasis on
855 preserving haemostasis. Nat Rev Cardiol 2018; 15: 181–91.

856

857 99. Markus HS, McCollum C, Imray C, et al. The von Willebrand Inhibitor ARC1779
858 Reduces Cerebral Embolization After Carotid Endarterectomy. Stroke 2011; 42: 2149–53.

859

860 100. Bartunek J, Barbato E, Heyndrickx G, et al. Novel antiplatelet agents: ALX-0081, a
861 Nanobody directed towards von Willebrand factor. J Cardiovasc Transl 2013; 6: 355–63.

862

863 101. Lei X, Reheman A, Hou Y, et al. Anfibatide, a novel GPIb complex antagonist, inhibits
864 platelet adhesion and thrombus formation in vitro and in vivo in murine models of
865 thrombosis. Thromb Haemost 2013; 111: 279–89.

866

867 102. Nylander S, Wågberg F, Andersson M, et al. Exploration of efficacy and bleeding with
868 combined phosphoinositide 3-kinase β inhibition and aspirin in man. J Thromb Haemost
869 2015; 13: 1494–502.

870

871 103. Morrow DA, Braunwald E, Bonaca MP, et al. Vorapaxar in the Secondary Prevention of
872 Atherothrombotic Events. New Engl J Med 2012; 366: 1404–13.

873

874 104. Aisiku O, Peters CG, Ceunynck K, et al. Parmodulins inhibit thrombus formation
875 without inducing endothelial injury caused by vorapaxar. Blood 2015; 125: 1976–85.

876

877 105. Wong PC, Seiffert D, Bird EJ, et al. Blockade of protease-activated receptor-4 (PAR4)

provides robust antithrombotic activity with low bleeding. Sci Transl Med 2017; 9: eaaf5294.

106. Wilson SJ, Ismat FA, Wang Z, et al. PAR4 (Protease-Activated Receptor 4) Antagonism With BMS-986120 Inhibits Human Ex Vivo Thrombus Formation. Arteriosclerosis Thrombosis Vasc Biology 2017; 38: 448–56.

107. Ohlmann P, Hechler B, Ravanat C, et al. Ex vivo inhibition of thrombus formation by an anti-glycoprotein VI Fab fragment in non-human primates without modification of glycoprotein VI expression. J Thromb Haemost 2008; 6: 1003–11.

108. Voors-Pette C, Lebozec K, Dogterom P, et al. Safety and Tolerability, Pharmacokinetics, and Pharmacodynamics of ACT017, an Antiplatelet GPVI (Glycoprotein VI) Fab. Arterioscler Thromb Vasc Biol. 2019 May;39(5):956-964.

109. Ungerer M, Rosport K, Bültmann A, et al. Novel antiplatelet drug revacept (Dimeric Glycoprotein VI-Fc) specifically and efficiently inhibited collagen-induced platelet aggregation without affecting general hemostasis in humans. Circ 2011; 123: 1891–9.

Figure Legends

Figure 1. Mechanism of action of antiplatelet medications.

Abbreviations: ADP = adenosine diphosphate, GP = glycoprotein, PAR = protease-activated receptor, TxA2 = thromboxane A2, VWF = von Willebrand factor

Figure 2. Evolution of antiplatelet secondary prevention (aspirin plus P2Y12 inhibitor) trials in ACS and PCI.

905 **Tables**

906

907 Table 1. Landmark trials of antiplatelet therapy in ACS and PCI.

908

909 Table 2. New antiplatelet agents being evaluated in or beyond Phase 2 clinical trials.