ESC European Society of Cardiology

European Heart Journal (2021) **42**, 339–351
doi:10.1093/eurheartj/ehaa824

STATE OF THE ART REVIEW
Interventional cardiology

Evolution of antithrombotic therapy in patients undergoing percutaneous coronary intervention: a 40-year journey

Davide Cao [1†], Rishi Chandiramani [1†], Mauro Chiarito [1,2,3], Bimmer E. Claessen [1], and Roxana Mehran [1*]

[1]Center for Interventional Cardiovascular Research and Clinical Trials, The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1030, New York, NY 10029-6574, USA; [2]Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20090 Pieve Emanuele, Milan, Italy; and [3]Cardio Center, Humanitas Clinical and Research Hospital IRCCS, Via Alessandro Manzoni 56, 20090 Rozzano, Milan, Italy

Received 17 June 2020; revised 2 September 2020; editorial decision 11 September 2020; accepted 22 September 2020; online publish-ahead-of-print 26 December 2020

Since its introduction in 1977, percutaneous coronary intervention has become one of the most commonly performed therapeutic procedures worldwide. Such widespread diffusion, however, would have not been possible without a concomitant evolution of the pharmacotherapies associated with this intervention. Antithrombotic agents are fundamental throughout the management of patients undergoing coronary stent implantation, starting from the procedure itself to the long-term prevention of cardiovascular events. The last 40 years of interventional cardiology have seen remarkable improvements in both drug therapies and device technologies, which largely reflected a progressive understanding of the pathophysiological mechanisms of coronary artery disease, as well as procedure- and device-related adverse events. The purpose of this article is to provide an overview of the important milestones in antithrombotic pharmacology that have shaped clinical practice of today while also providing insights into knowledge gaps and future directions.

Keywords Coronary stents • Pharmacology • Dual antiplatelet therapy • $P2Y_{12}$ inhibitor • Anticoagulants

Introduction

Tremendous advancements have been made in the field of interventional cardiology since the first successful human percutaneous transluminal coronary angioplasty (PTCA) was performed by Andreas Grüntzig on 16 September 1977.[1] However, any discussion regarding the progress made would be incomplete without acknowledging the vast efforts that were simultaneously dedicated towards improving the therapeutic agents and strategies to prevent recurrent events. Progressing from the era of solely preventing thrombosis to subsequently understanding the prognostic relevance of bleeding complications in stented patients, the primary focus of physicians now is to find the optimal duration and combination of antithrombotic drugs according to individual risk characteristics. With the continuous refinement in stent technologies, novel antithrombotic agents and expanding indication to an older and sicker population with anatomically complex coronary artery disease (CAD), management of patients undergoing percutaneous coronary intervention (PCI) is as challenging as ever. The present review summarizes the extensive evidence base on interventional pharmacology that has been generated over the last 40 years, focusing first on the evolution of intraprocedural anticoagulation followed by post-procedural antithrombotic therapy. Emphasis has been given to the changes that occurred in dual antiplatelet therapy (DAPT) management as a result of improvements in stent design, development of new drugs and a better understanding of the pathophysiology underlying coronary thrombotic events.

Intraprocedural pharmacology: back to the future

As an invasive, intravascular procedure, PCI may lead to bleeding and thrombotic complications. Intraprocedural anticoagulation is necessary to prevent thrombus formation both on the surface of the intravascular equipment and resulting from local plaque rupture and dissection caused by balloon angioplasty or stent implantation.

* Corresponding author. Tel: +1 212 659 9649, Fax: +1 646 537 8547, Email: roxana.mehran@mountsinai.org
†The first two authors contributed equally to the study.

However, bleeding complications after PCI are also associated with substantial morbidity and mortality.[2,3] Therefore, a pharmaceutical regimen providing just the right amount of anticoagulant effect is of paramount importance. Current agents used for periprocedural anticoagulation include inhibitors of factor IIa (thrombin) and/or factor Xa (*Table 1*).[4]

Unfractionated heparin (UFH) was historically the first drug to be used during PCI and remains the most widely used anticoagulant for this indication. Drawbacks of UFH include a variable anticoagulant response sometimes leading to heparin resistance, the inability to inhibit clot-bound thrombin and, although uncommon in a PCI setting, the risk of heparin-induced thrombocytopenia.[5]

Low molecular weight heparin (LMWH) is derived from UFH and has better bioavailability and minimal protein binding, which results in a more reliable dose–response relationship. Mechanistically, LMWH has a higher anti-Xa/anti-IIa ratio than UFH.[6] Enoxaparin is the most studied LMWH to facilitate PCI and is available in subcutaneous and intravenous forms to be administered either upstream in case of acute coronary syndrome (ACS) or only during PCI in stable patients. A meta-analysis of 13 randomized trials comparing intraprocedural LMWH with UFH showed a significant reduction in major bleeding in the LMWH group with similar rates of death or myocardial infarction (MI).[7] The main limitation of enoxaparin remains the inability to effectively monitor the extent of anticoagulation at bedside.

In 1979, Lindahl *et al.*[8] showed that the minimum molecular sequence of heparin required to bind antithrombin was a pentasaccharide. This was synthesized by Choay *et al.*[9] in 1983 as fondaparinux. Fondaparinux has no effect against thrombin but only inhibits factor Xa. In the OASIS 5 trial involving 20 078 patients with non-ST-elevation ACS, fondaparinux markedly reduced major bleeding at 9 days compared to enoxaparin (2.2% vs. 4.1%, $P < 0.001$) with no trade-off in ischaemic events.[10] This resulted in a significant reduction in mortality with fondaparinux at both 30- and 180-day follow-ups. The lower bleeding rates were also reflected in the subgroup of patients who underwent PCI. However, fondaparinux alone was found to inadequately prevent catheter-related thrombosis, a finding also confirmed in the OASIS 6 trial, which investigated patients with ST-elevation myocardial infarction (STEMI).[10,11] This led to the recommendation of administering additional treatment with an anticoagulant possessing anti-IIa activity at the time of PCI.[12] Subsequently, in the FUTURA/OASIS 8 trial, low-dose UFH did not result in decreased peri-PCI major bleeding as compared with standard-dose UFH in high-risk patients with non-ST-elevation ACS initially treated with fondaparinux.[13]

Direct thrombin inhibitors act independent of antithrombin, which means that they can also inhibit thrombin bound to fibrin.[14] Bivalirudin is the most commonly used direct thrombin inhibitor during PCI, while lepirudin (recombinant hirudin), danaparoid and argatroban are mostly limited to patients with heparin-induced thrombocytopenia.

Evolving recommendations on the use of GPIs, heparin and bivalirudin

The history of glycoprotein IIb/IIIa inhibitors (GPIs), heparin and bivalirudin is highly interwoven, and recommendations regarding their use have changed significantly over the last three decades. The currently available GPIs abciximab, eptifibatide and tirofiban inhibit the glycoprotein IIb/IIIa complex, which is a crucial component in the platelet aggregation pathway.[15] Before the current era of routine stenting and $P2Y_{12}$ inhibitor preloading, a number of trials showed a significant reduction in ischaemic events with the routine adjunct use of a GPI during PCI, albeit at the cost of increased periprocedural bleeding.[16–19] By the early 2000s, intraprocedural administration of UFH plus a GPI had become

Table 1 Currently used agents for periprocedural anticoagulation during percutaneous coronary intervention

Drug	Mechanism of action	Route of administration	Bedside effect monitoring	Recommended dose	Reversibility	Risk of HIT
Unfractionated heparin	Anti-IIa Anti-Xa (1:1 Anti-Xa/Anti-IIa ratio)	i.v.	Yes, using ACT	70–100 U/kg bolus to achieve target ACT of 250–350 s (50–70 U/kg bolus with GPI)	Yes, with protamine sulphate (1–1.5 mg/100 U, maximum 50 mg)	+++
Low molecular weight heparin (Enoxaparin)	Anti-IIa Anti-Xa (4:1 Anti-Xa/Anti-IIa ratio)	i.v.	No	0.5–0.75 mg/kg bolus	Partial, with protamine sulphate (1 mg/mg enoxaparin)	+
Fondaparinux	Anti-Xa	s.c.	No	2.5 mg daily before PCI 1.5 mg if CrCl 20–50 ml/min	No	+/−
Bivalirudin	Anti-IIa (direct)	i.v.	Yes, using ACT	0.75 mg/kg bolus, followed by 1.75 mg/kg/h infusion	No	−
Argatroban	Anti-IIa (direct)	i.v.	Yes, using ACT	350 μg/kg bolus, 25 μg/kg/min infusion	No	−

Enoxaparin and fondaparinux can be administered either i.v. or s.c. The table reports the recommended routes of administration and doses for periprocedural anticoagulation.
ACT, activated clotting time; CrCl, creatinine clearance; GPI, glycoprotein IIb/IIIa inhibitor; HIT, heparin-induced thrombocytopenia; i.v., intravenous; PCI, percutaneous coronary intervention; s.c., subcutaneous.

the standard of care. Subsequently, several trials showed lower bleeding rates and significant survival benefit associated with bivalirudin compared to UFH plus a GPI in patients undergoing PCI for chronic coronary syndrome and ACS.[20–24] This led to a class IA recommendation to use bivalirudin in PCI for ACS in the 2014 European Society of Cardiology (ESC) guidelines on myocardial revascularization.[25] However, because of advances in the ever-evolving field of interventional cardiology, such as increased uptake of radial access, safer next-generation drug-eluting stents (DES), routine preloading of $P2Y_{12}$ inhibitors and the advent of novel potent $P2Y_{12}$ inhibitors, a new wave of trials investigated the use of UFH without routine GPI administration as compared to bivalirudin and no longer showed a reduction in bleeding with bivalirudin, but rather an increased risk of acute stent thrombosis (ST).[26–30] Therefore, recent guidelines downgraded the recommendation for bivalirudin in ACS to IIB, while maintaining a class I recommendation for UFH.[31]

Stent technology and antithrombotic therapy: a never-ending story

Origins of antithrombotic therapy after PTCA

Acute intracoronary thrombosis was relatively uncommon (3–5%) in the very early days of PTCA, despite a wide variety of non-standardized antithrombotic regimens being used worldwide, mostly based on periprocedural heparin and dextran, with long-term warfarin or high-dose aspirin.[32,33] Warfarin was originally the most used long-term therapy to prevent abrupt vessel closure after PTCA, as it had been shown to reduce ischaemic events in patients with acute MI.[34] However, indirect comparisons between observational data on different antithrombotic regimens questioned the role of warfarin over aspirin. It was in fact Dr Margaret Thornton, Dr Grüntzig's wife, who first tested this hypothesis in 1984 with a study that randomized 248 patients to 325 mg of aspirin or warfarin post-PTCA.[35] While there was no significant difference in the primary endpoint of recurrent stenoses overall, the subgroup of patients with a long history of angina derived significant benefit from the use of aspirin compared to warfarin (21% vs. 44%; $P < 0.05$), laying the ground for aspirin as the cornerstone of antithrombotic therapy after coronary interventions.[35] Nonetheless, abrupt vessel closure due to acute elastic recoil and flow-limiting dissection remained relatively common after PTCA, irrespective of the antithrombotic regimen, and was tightly linked to an increased risk of MI and sudden death.[32] Metallic coronary stents were therefore conceived with the aim of preventing these dreaded complications of PTCA.[36] However, as coronary stents gained increasing popularity, ST turned out to be the most feared drawback of this pioneering technology.

Stent thrombosis and intensified antithrombotic regimens

Following preclinical observations in animal models,[37] early clinical experience with self-expandable stents in Europe showed that intense post-procedural anticoagulation with warfarin on top of aspirin and dipyridamole compared to antiplatelet drugs alone was effective in reducing the risk of early ST.[38] Similar findings were also reported in the first registry of patients receiving the Palmaz-Schatz balloon-expandable stent in the USA.[39] In this study, patients were treated with intravenous dextran starting 2 h before the procedure followed by aspirin indefinitely and dipyridamole for 3 months. Because post-procedural oral anticoagulation (OAC) was not mandatory in the first 39 patients, this subgroup showed a 18% rate of subacute ST, while the following patients treated with warfarin had a significantly lower risk.[39] Nevertheless, early ST remained a critical issue even with OAC therapy, especially in the case of urgent procedures due to failed balloon angioplasty or acute MI.[40] The first attempt to reduce early ST involved intensifying anticoagulation with high-dose heparin and increasing the target INR (international normalized ratio) range from 1.8–2.4 to 2.5–3.5 with warfarin.[41] This strategy reduced the incidence of ST to 1–5% but with the downside of an unacceptable 10–15% rate of bleeding and vascular complications.[41] Prognostic implications of bleeding were progressively recognized and brought forth the need for simplified antithrombotic strategies. Despite their established antiplatelet properties, dextran and dipyridamole did not show an incremental benefit over aspirin alone and were associated with considerable side effects. Hence, both were gradually abandoned.

The dawn of DAPT

The rationale for DAPT consisting of aspirin and ticlopidine was to reduce the risk of thrombotic complications as observed with aspirin monotherapy without increasing bleeding as observed with aspirin plus OAC.[41] Ticlopidine was originally studied in the 1970s for its analgesic and anti-inflammatory properties until it was unexpectedly found to have antithrombotic properties in rats. After showing a reduction in ischaemic events among patients with unstable angina,[42] ticlopidine started being widely used post-PCI, even though its mechanism of action on the $P2Y_{12}$ receptor was described only in 2001.[43]

As prevention of ST was a clinical priority, intravascular ultrasound became a mainstay in the research of its causes and possible solutions.[44–46] The causative role of stent underexpansion was initially studied by Colombo *et al.*, who demonstrated that intravascular ultrasound-guided high pressure pre- and post-dilation to optimize stent expansion and strut apposition was strikingly effective in reducing the risk of ST among patients discharged on aspirin alone or with ticlopidine.[47] The safety and efficacy of DAPT after PCI was further evaluated in the ISAR trial, which randomized 517 patients to DAPT with aspirin plus ticlopidine or anticoagulant therapy with intravenous heparin (for 5–10 days), phenprocoumon and aspirin.[48] The study reported a 75% risk reduction in the composite of cardiac death, MI or need for surgical or percutaneous revascularization in the DAPT group.[48] Subsequently, the STARS trial definitely ushered in the DAPT era by demonstrating that aspirin with ticlopidine was superior to aspirin alone or with warfarin in reducing ischaemic events at 30 days, albeit at the cost of more haemorrhagic complications with DAPT than with aspirin alone.[49]

The rise of clopidogrel

With the widespread use of DAPT, ST was reported to occur in <1% of patients undergoing coronary stenting and was no longer perceived as a relevant issue, despite its potentially fatal sequelae.[50] Nonetheless, the routine use of ticlopidine was encumbered by an unfavourable adverse reaction profile, particularly bone marrow suppression, in addition to gastrointestinal side effects and cutaneous rashes.[51] Clopidogrel, like ticlopidine, is an oral thienopyridine that requires hepatic metabolism into a biologically active form to irreversibly inhibit the $P2Y_{12}$ subunit of the platelet adenosine diphosphate receptor.[52] Following observations indicating clopidogrel to be at least as effective as ticlopidine and better tolerated, the CLASSICS study randomized patients undergoing stent implantation to different regimens of aspirin plus clopidogrel and aspirin plus ticlopidine.[53] The primary endpoint of major bleeding, neutropenia, thrombocytopenia or treatment discontinuation was found to be significantly lower in patients receiving DAPT with clopidogrel.[53] Subsequent meta-analyses also suggested a possible advantage in terms of ischaemic complications, including mortality, with the use of clopidogrel, likely due to increased patient compliance and faster onset of antiplatelet effect achieved with a loading dose.[54] The role of pretreatment with a clopidogrel loading dose in patients undergoing PCI for non-ST-elevation ACS and STEMI was further clarified by the PCI-CURE and PCI-CLARITY studies, respectively, wherein pretreatment significantly reduced ischaemic events without increasing major bleeding.[55,56]

Early-generation DES

By the beginning of the 21st century, PCI with stent implantation had become the most popular method of coronary revascularization.[57] Notwithstanding, rates of in-stent restenosis and repeat revascularization were still high. Between 2002 and 2004, DES that gradually released cytostatic agents, namely sirolimus and paclitaxel, through a durable polymer coating demonstrated superiority over bare metal stent (BMS) in large-scale randomized trials by reducing restenosis and target-vessel revascularization.[58–60] DAPT was recommended for 3 months after sirolimus-eluting stent placement and for 6 months after paclitaxel-eluting stent placement,[61,62] based on the protocol-mandated antiplatelet regimen used in the trials conducted for marketing approval.[58–60] In the absence of any apparent drawbacks, DES rapidly replaced BMS.

However, the honeymoon of DES ended early. Initial case reports and observational registries reported alarming rates of late (>30 days) and very late (>1 year) ST, but evidence remained limited.[63–65] The 2006 edition of the ESC scientific sessions—popularly renamed the 'ESC firestorm'—was the turning point in the history of early-generation DES. Two meta-analyses[66,67] and a randomized study[68] presented in the same session demonstrated a higher risk of cardiac death and MI with the use of early-generation DES compared to BMS due to an increase in late and very late ST. It soon became clear that the vast majority of these events occurred after DAPT was discontinued.[68,69] Several studies identified DAPT discontinuation as the strongest predictor of ST.[70,71] Accordingly, international guidelines and regulatory bodies arbitrarily extended the recommended DAPT duration after DES implantation to 1 year,[72,73] with many authors advocating for further prolongation in case of low risk of bleeding.[66,74] Hence, device thrombogenicity and need for prolonged DAPT made patients with high thrombotic or bleeding risk unattractive candidates for DES.[74]

Next-generation DES

The ESC firestorm led to a dramatic reduction in DES use and boosted clinical research aimed at explaining this phenomenon. While mechanisms of early ST were largely related to suboptimal stent deployment for both DES and BMS, late and very late ST showed unique and unexpected underlying causes, such as delayed stent endothelialization, hypersensitivity reactions to polymer coating and late strut malapposition (*Figure 1*).[75–77] These findings prompted the development of the next generation of DES, characterized by thinner struts made of different metal alloys to preserve radial strength, use of sirolimus (-analogues) and more biocompatible or biodegradable polymers or even lack of polymers to modulate antirestenotic drug release.[78–80] All these technological advancements allowed for remarkable improvement in the safety of DES, thereby reducing the need for prolonged DAPT, without compromising their efficacy.[81]

Bioresorbable scaffold

The persistence of metallic material in coronary vessel walls represents—at least from a theoretical point of view—a fundamental drawback of DES technology, leading to impaired vasomotor function, chronic local inflammation, negative arterial remodelling, suboptimal results of repeated PCI and preclusion of future bypass surgery. Bioresorbable scaffolds (BRS) were developed to overcome these limitations but have thus far failed to live up to expectations, with trials showing an increased risk of MI and ST in patients treated with BRS compared to next-generation DES.[82,83] Such unexpected and alarming findings have led to the market withdrawal of these devices. The thicker and wider stent struts with the lower radial forces increasing the risk of stent underexpansion and recoil have been considered major contributors to the increased thrombogenicity of BRS. Studies also revealed that the majority of BRS thrombosis occurred while patients were off DAPT,[83] highlighting the need for prolonged DAPT regimens after PCI with current generation BRS.

Balancing bleeding and thrombosis: the sweet spot of DAPT

Any ischaemic benefit achieved with intensification of antiplatelet therapy is almost inevitably counterbalanced by a concomitant increase in bleeding. Moreover, prolonging treatment duration and adding or switching to more potent agents have not always translated into a significant reduction in ischaemic events but have rather led, in some occasions, to higher mortality and worse net clinical outcomes.[84] Contradictory findings have also been observed in landmark trials with overall positive results that have changed contemporary PCI practice. In the TRITON-TIMI 38 trial, each cardiovascular death prevented by the use prasugrel was offset by an almost equivalent number of fatal bleeding events prevented by the use of clopidogrel.[85] Similarly, in the DAPT trial, continuing thienopyridines on top

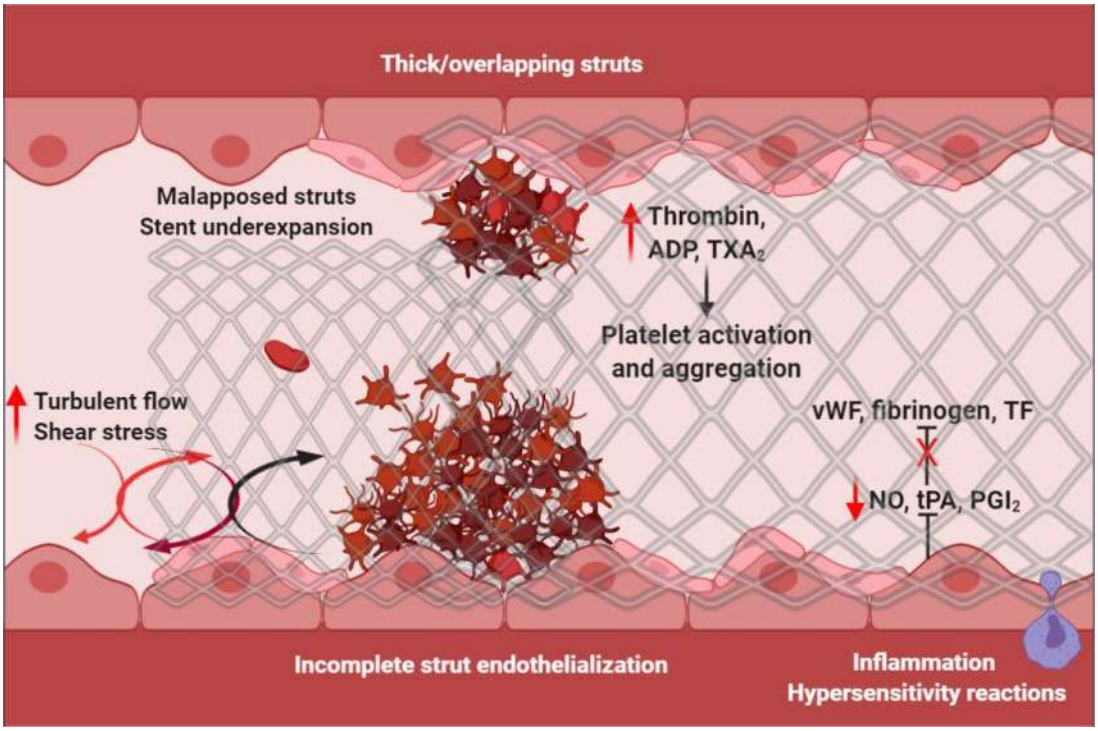

Figure 1 Key elements involved in the pathogenesis of stent thrombosis. Stent- and procedure-related factors, such as increased strut thickness, overlapping stents, and stent malapposition or underexpansion, induce rheological alterations resulting in turbulent flow, increased shear stress, and reduced strut endothelialization. These factors, together with inflammatory and hypersensitivity reactions to foreign material (i.e. metallic struts and polymer), induce platelet activation and aggregation through several mediators, mainly released by platelets and endothelial cells. Created with BioRender.com. ADP, adenosine diphosphate; NO, nitric oxide; PGI_2, prostacyclin; TF, tissue factor; tPA, tissue plasminogen activator; TXA2, thromboxane A2; vWF, von Willebrand factor.

of aspirin beyond 12 months after PCI was associated with higher all-cause mortality as compared with placebo, despite a significant reduction in ischaemic events.[86]

Owing to the double-edged effect of antithrombotic therapies, studies on this subject are often challenging to interpret. Commonly used statistics to weigh the risks and benefits associated with an antithrombotic regimen in randomized trials are the number of patients to be treated to prevent one additional ischaemic event [i.e. number needed to treat (NNT)] and its counterpart, the number of patients to be exposed to the intervention to cause one additional bleeding [i.e. number needed to harm (NNH)]. NNT and NNH are simple and intuitive measures to evaluate the risk–benefit trade-off and clinical relevance of the observed treatment effect, also in terms of public health impact.

Selecting intensity of the $P2Y_{12}$ inhibitor

Prasugrel was the next oral $P2Y_{12}$ inhibitor to be tested in combination with aspirin among PCI patients. Prasugrel exerts a faster, stronger and more consistent platelet inhibitory effect compared to clopidogrel.[87] Ticagrelor is another potent $P2Y_{12}$ inhibitor that belongs to a chemical class different than prasugrel and clopidogrel and acts by reversibly binding to the $P2Y_{12}$ receptor with a more rapid onset and offset of action (*Table 2*).[88] Prasugrel and ticagrelor were tested against clopidogrel in separate large-scale randomized trials involving ACS patients. Despite notable differences in terms of study design and secondary outcome results, both drugs were associated with a reduction in the incidence of cardiovascular death, MI, or stroke at the expense of a variable, albeit consistent, increase in bleeding.[89,90] Accordingly, guidelines state that in the absence of contraindications, patients presenting with ACS should receive DAPT with either prasugrel 10 mg daily or ticagrelor 90 mg twice daily, with the former reserved only for patients undergoing PCI.[91,92] Contraindications to prasugrel include active bleeding disorders or prior cerebrovascular events. Prasugrel is also generally discouraged in patients with advanced age (≥75 years) or low body weight (<60 kg); however, if prasugrel is decided upon in these patients, a reduced dose (5 mg) is recommended on the basis of pharmacodynamic data.[93–95] Ticagrelor, on the other hand, has been traditionally associated with more favourable safety but worse patient tolerability compared with prasugrel. Ticagrelor increases plasma levels of adenosine, which is possibly implicated in its common side effect of dyspnoea.[96] Ticagrelor-related dyspnoea lead to drug discontinuation in about 1 of every 15–20 patients, although lower drug dosages (60 mg) may be associated with reduced occurrence.[97,98] Transient bradycardia secondary to a variable degree of atrioventricular block is another distinct side effect of ticagrelor. Unlike low-dose prasugrel,

Table 2 Antiplatelet agents used in patients undergoing percutaneous coronary intervention

Drug	Structure	Primary mechanism of action	Prodrug	Receptor blockade	Onset of action	Offset of action	Route of administration	Recommended dose
Aspirin	Salicylate	COX-1 inhibition	No	Irreversible	Nonenteric-coated: <1 h Enteric-coated: 3–4 h	5–10 days	Oral i.v.	150–300 mg orally or 75–250 mg i.v. (LD) 75–100 mg daily (MD)
Ticlopidine	Thienopyridine	$P2Y_{12}$ inhibition	Yes	Irreversible	2–4 days	10–14 days	Oral	250 mg twice daily
Clopidogrel	Thienopyridine	$P2Y_{12}$ inhibition	Yes	Irreversible	2–6 h	5–10 days	Oral	300–600 mg (LD) 75 mg daily (MD)
Prasugrel	Thienopyridine	$P2Y_{12}$ inhibition	Yes	Irreversible	0.5–4 h	7–10 days	Oral	60 mg (LD) 10 mg daily (MD) 5 mg daily (RMD)
Ticagrelor	Cyclopentyl-triazolopyrimidine	$P2Y_{12}$ inhibition	No	Reversible	0.5–2 h	3–5 days	Oral	180 mg (LD) 90 mg twice daily (MD) 60 mg twice daily (RMD)
Cilostazol	Quinolinone derivative	PDE3 inhibition	No	Reversible	6 h	12–16 h	Oral	100 mg twice daily
Vorapaxar	Tricyclic himbacine derivative	PAR1 inhibition	No	Reversible	2–7 days	4 weeks	Oral	40 mg (LD) 2.5 mg daily (MD)[a]
Cangrelor	ATP analogue	$P2Y_{12}$ inhibition	No	Reversible	2 min	30–60 min	i.v.	30 μg/kg (bolus) 4 μg/kg/min (infusion)
Abciximab	Fab fragment of the chimeric human-murine mAb 7E3	GP IIb/IIIa inhibition	No	Irreversible	10 min	1–3 days	i.v.	0.25 mg/kg (bolus) 0.125 μg/kg/min (infusion)
Eptifibatide	Cyclic heptapeptide	GP IIb/IIIa inhibition	No	Reversible	5 min	4–8 h	i.v.	180 μg/kg (2 boluses 10 min apart) 2 μg/kg/min (infusion)
Tirofiban	Non-peptide tyrosine derivative	GP IIb/IIIa inhibition	No	Reversible	<10 min	4–8 h	i.v.	25 μg/kg (bolus) 0.15 μg/kg/min (infusion)

ATP, adenosine triphosphate; Fab, antigen-binding fragment; mAb, monoclonal antibody; COX, cyclooxygenase; GP, glycoprotein; PDE, phosphodiesterase; PAR, protease-activated receptor; i.v., intravenous; LD, loading dose; MD, maintenance dose; RMD, reduced maintenance dose.
[a]2.5 mg of vorapaxar sulphate equivalent to 2.08 mg tablets of vorapaxar.

ticagrelor 60 mg has been specifically evaluated in two large-scale randomized placebo-controlled trials involving patients with stable CAD at high ischaemic risk.[97,98]

Robust head-to-head comparisons between ticagrelor and prasugrel have been lacking for nearly a decade. The first attempt to compare these two drugs in patients undergoing primary PCI led to inconclusive results and premature study termination for futility.[99] In 2019, results from the long awaited ISAR-REACT-5 trial became available.[100] Among 4018 ACS patients for whom an invasive strategy was planned, prasugrel was associated with a significant 2.4% absolute reduction in the composite rate of death, MI or stroke at 1 year compared with ticagrelor without any apparent increase in bleeding complications.[100] Hence, the 2020 ESC guidelines on non-ST-elevation ACS endorse the use of prasugrel in preference to ticagrelor among patients who proceed to PCI.[101] However, the mechanisms underlying these remarkable findings remain poorly understood and several caveats about ISAR-REACT-5 must be acknowledged: the open-label design with the two treatments starting at different time points in patients with non-ST-elevation ACS, the relatively high and unbalanced treatment non-adherence between study groups, and a lower than anticipated event rate.[102] Nonetheless, ISAR-REACT-5 raised important questions about the current generalizability of previous landmark trials conducted in subjects treated with obsolete PCI technologies; how the use of upstream $P2Y_{12}$ inhibitor loading dose impacts PCI outcomes; and if a single $P2Y_{12}$ inhibitor is appropriate for all ACS patients, including those medically managed.

In recent years, the array of $P2Y_{12}$ receptor antagonists has broadened to include novel parenteral agents. Among those, cangrelor is the only one currently approved for intravenous use. As it does not require bioactivation, cangrelor ensures almost immediate platelet inhibition by reversibly binding to the $P2Y_{12}$ receptor.[103] Given its short plasma half-life of 3–5 min, the antiplatelet effect of cangrelor lasts 30–60 min after the infusion is discontinued.[103] In terms of intensity of antiplatelet effect, pharmacodynamic data from STEMI patients showed that cangrelor yields greater inhibition of platelet aggregation than chewed and integral prasugrel in the first 30 min after treatment

initiation but not thereafter.[104] Conversely, inhibition of platelet aggregation was lower with cangrelor than with the GPI tirofiban at any time point.[104]

The first two randomized placebo-controlled trials that evaluated the clinical safety and efficacy of periprocedural cangrelor on top of a clopidogrel loading dose in $P2Y_{12}$ inhibitor-naive patients undergoing PCI were prematurely terminated for futility.[105,106] Although these studies did not show any difference in the primary ischaemic endpoint, both reported significant reduction in ST with cangrelor.[105,106] By contrast, in the CHAMPION PHOENIX trial, patients in the cangrelor group were found to have significantly lower rates of 48-h death, MI, ischaemia-driven revascularization or ST compared to placebo (4.7% vs. 5.9%, $P = 0.005$), with no increase in major bleeding.[107]

At present, the existing evidence is not considered sufficient to justify the routine use of cangrelor over standard loading dose of oral agents in $P2Y_{12}$ inhibitor-naive patients undergoing PCI. Nonetheless, cangrelor is sometimes used off-label in high-risk ACS patients for whom rapid and efficacious platelet inhibition is desirable or, in general, when the oral uptake of commonly used $P2Y_{12}$ inhibitors is hampered. Furthermore, cangrelor may be used as bridging strategy in patients undergoing surgery that requires perioperative DAPT discontinuation within 1 month of stent implantation.[108,109] Additional injectable agents for subcutaneous use are under clinical development and have shown promising initial results.[110]

Tailoring duration of DAPT

Current guidelines provide a class IA recommendation for 6 months of DAPT in patients with stable CAD undergoing DES implantation and 12 months of DAPT for those with ACS.[91,92] Dilemmas about the ischaemia-bleeding trade-off with DAPT have led to a multitude of randomized trials aimed at assessing its optimal duration after PCI (*Figure 2*).[111] It is noteworthy that both the design and findings of these trials broadly reflected the concomitant evolution of stent technology at the time they were conducted. While the scope of studies investigating longer DAPT durations was generally to demonstrate superiority in the prevention of ischaemic events, those evaluating shorter regimens were conceived with a non-inferiority hypothesis for ischaemic or, more often, net clinical benefit endpoints that included bleeding as well.[111] More recently, attention has shifted towards tailoring antiplatelet treatment strategies according to individualized ischaemic and bleeding risk assessment. To this end, there has been a surge of risk scores to predict adverse events in patients undergoing PCI (*Table 3*).[112–114] Nonetheless, all risk scores are intrinsically influenced by the characteristics of the patient cohorts used for their development, which often translates into a limited external validity.[115,116] To overcome this limitation and guarantee consistency in clinical research, an Academic Research Consortium initiative proposed a consensus definition of high bleeding risk based on the presence of well-recognized risk criteria.[117]

Studies evaluating patient subgroups with established risk factors for ischaemia and/or bleeding have documented differing results with prolonging or shortening DAPT.[118–121] *Post hoc* analyses of randomized trial data have shown that patients undergoing complex PCI (i.e. with lesions and procedural characteristics known to increase the risk of stent-related adverse events) benefit more from longer DAPT duration (≥12 months).[122,123] Similar findings have been reported in patients with an elevated thrombotic risk due to underlying comorbid conditions such as peripheral artery disease.[124,125] Hence, guidelines state that prolonged DAPT may be considered in selected patient subsets.[91] By contrast, if bleeding risk prevails, shortening DAPT to 3 and 6 months should be considered in stable and ACS patients, respectively,[91,92] with the possibility of being further curtailed to 1 month in the former.[91]

The perceived lower thrombogenicity of BMS has long influenced clinicians to favour this stent type in patients with a contraindication to prolonged DAPT. Recently, investigators have leveraged the ameliorations in DES biocompatibility to demonstrate their superior safety and efficacy over BMS even with an ultra-short (i.e. 1 month) DAPT regimen.[126,127] Hence, the European guidelines now advocate for the use of next-generation DES irrespective of the intended DAPT duration.[91] However, the lack of randomized evidence comparing different antiplatelet regimens in patients at high bleeding risk, together with the non-negligible rates of ST observed in short DAPT trials,[128] leaves uncertainty around the optimal management of these patients. Assessing the harm–benefit trade-off of DAPT is even more challenging in light of the frequent overlap between ischaemic and bleeding risk factors. To this regard, it has been suggested that when both high ischaemic and bleeding risks co-exist, the latter should be prioritized and inform decisions on DAPT duration.[129]

Platelet function test and genotyping

Clopidogrel was originally approved by the Food and Drug Administration in 1997 and still remains the most commonly used $P2Y_{12}$ inhibitor. However, it is also the antiplatelet drug associated with the highest interindividual variability in terms of platelet response,[130,131] a phenomenon that can be ascribed to both genetic (i.e. CYP2C19 *2 and *3 alleles polymorphisms)[132,133] and clinical factors (e.g. drug–drug interactions, age, diabetes and renal insufficiency).[134] Of note, genetic polymorphisms do not seem to affect the antiplatelet efficacy of prasugrel or ticagrelor.[135,136]

There is a wide variety of available assays to monitor platelet function, each measuring specific aspects of platelet physiology.[137] High platelet reactivity (HPR) during treatment with $P2Y_{12}$ inhibitors has demonstrated strong predictive value for thrombotic events among PCI patients, whereas low platelet reactivity identifies those more prone to bleeding.[138–140] The observation of a therapeutic window of platelet reactivity levels wherein both thrombotic and bleeding complications are minimized fostered investigations aimed at exploring the clinical utility of platelet function tests (PFT) to guide the selection of the $P2Y_{12}$ inhibitor.[139,141] Strategies involving PFT-guided dose adjustment (e.g. from clopidogrel 75 to 150 mg) to overcome impaired platelet response to clopidogrel were initially proposed but turned out to be unsuccessful.[142,143] These disappointing findings have been attributed to a number of reasons, such as non-standardized PFTs, varying definitions for HPR, inadequate patient selection, ineffective therapeutic strategies, and improved safety and efficacy of next-generation DES. Adjunctive cilostazol, a reversible phosphodiesterase 3 inhibitor with unique antiplatelet and vasodilatory properties, on top of DAPT with clopidogrel has also been considered to counter HPR.[144] The therapeutic role of cilostazol has been predominantly evaluated among East Asian patients owing to their higher rates of clopidogrel non-responsivness.[145] However, the paucity of data in non-Asian populations, coupled with the relatively

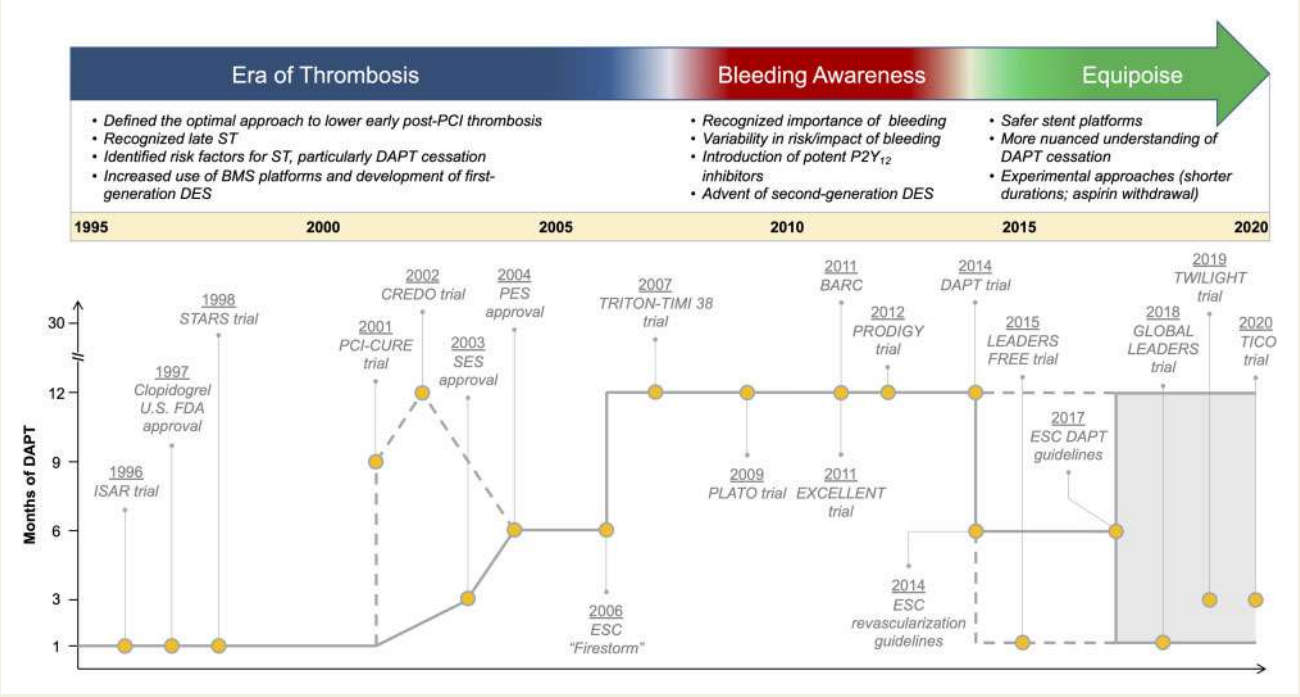

Figure 2 Evolving duration of antiplatelet therapy after percutaneous coronary intervention. BARC, Bleeding Academic Research Consortium; BMS, bare metal stents; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; ESC, European Society of Cardiology; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; ST, stent thrombosis; U.S. FDA, United States Food and Drug Administration.

Table 3 **Risk assessment tools for tailoring antiplatelet therapy after percutaneous coronary intervention**

	DAPT[113]	PARIS CTE[112]	PARIS MB[112]	PRECISE-DAPT[114]	ARC-HBR[117]
Year of publication	2016	2016	2016	2017	2019
Development data set	DAPT trial (n = 11 684)	PARIS registry (n = 4190)	PARIS registry (n = 4190)	Pooled 8 RCTs (n = 14 963)	Consensus definition
Study population	Event free at 12 months post-PCI	Stable and ACS	Stable and ACS	Stable and ACS	–
Ischaemic outcome	MI or definite/probable ST	MI or definite/probable ST	–	–	–
Bleeding outcome	GUSTO moderate or severe	–	BARC 3 or 5	TIMI minor or major	BARC 3 or 5
Follow-up	Between 12 and 30 months	2 year	2 years	Median of 552 (IQR 365–725) days	–
Variable number	9	6	6	5	20 (14 major, 6 minor) criteria
Score range	−2 to 10	0 to 12	0 to 15	0 to 100	–
High score group	≥2	≥5	≥8	≥25	≥1 major or 2 minor criteria
Clinical use	Identify patients who derive the greatest benefit over harm from prolonged (vs. short) DAPT	Predict risk of out-of-hospital CTE	Predict risk of out-of-hospital MB	Predict risk of out-of-hospital MB	Identify patients with a BARC 3 or 5 bleeding risk ≥4% and an intracranial haemorrhage risk ≥1% at 1 year

BARC, Bleeding Academic Research Consortium; CTE, coronary thrombotic events; DAPT, dual antiplatelet therapy; GUSTO, Global Strategies for Opening Occluded Coronary Arteries; IQR, interquartile range; MB, major bleeding; MI, myocardial infarction; RCT, randomized controlled trial; ST, stent thrombosis; TIMI, thrombolysis in myocardial infarction.

common side effects of cilostazol (i.e. headache, diarrhoea, dizziness, and tachycardia), has limited its use worldwide.

Following the spread of potent $P2Y_{12}$ inhibitors, PFT-guided strategies were revised to evaluate the benefit of switching clopidogrel with more potent agents such as prasugrel. Nevertheless, despite initial positive results from small randomized studies, large-scale trials have consistently failed to show any benefit of a PFT-guided escalation strategy.[146,147] More recently, the potential advantages of a de-escalation approach were suggested among ACS patients with an indication to potent $P2Y_{12}$ inhibitors in whom clopidogrel would still guarantee adequate levels of platelet inhibition while reducing bleeding complications and costs. Within this background, the TROPICAL-ACS randomized trial enrolled 2610 ACS patients undergoing PCI and found that PFT-guided de-escalation from prasugrel to clopidogrel was non-inferior to conventional treatment with prasugrel in terms of both ischaemic and net clinical outcomes.[148] From the patient perspective, however, PFT-guided management of antiplatelet therapy may be challenging to implement.[149] The high variability in the results to define HPR status could potentially require multiple switches between $P2Y_{12}$ inhibitors and thus represent a source of confusion.[149] Genotype testing has therefore been suggested to overcome this limitation of PFT.

The use of genotype testing to identify poor clopidogrel metabolizers was first noted in a black box warning issued by the Food and Drug Administration in 2010.[150] Since then, however, evidence in support of this practice has been confined to relatively small or non-randomized studies.[151–154] It was only last year that results from two large-scale randomized trials became available.[155,156] The POPular Genetics trial found CYP2C19-guided de-escalation to clopidogrel to be non-inferior to standard treatment with potent $P2Y_{12}$ inhibitors for the primary endpoint of net clinical benefit in 2700 patients undergoing primary PCI.[155] These positive findings were complemented by the encouraging results of the TAILOR-PCI trial, which instead tested an escalation strategy to ticagrelor in both ACS and stable PCI patients.[156]

At present, the totality of evidence does not support the routine use of PFT or genotyping to guide management of DAPT;[91,92] however, their use may be appropriate in selected contexts such as ACS patients with high ischaemic (i.e. DAPT escalation) or bleeding (i.e. DAPT de-escalation) risk features.[131] Risk scores integrating information on CYP2C19 genotype and clinical factors that are known to affect individual responsiveness to clopidogrel have been developed for tailoring the intensity of $P2Y_{12}$ inhibitor therapy.[157] Yet, the variable penetrance of genetic and environmental factors may significantly curb the clinical performance of such risk assessment tools.[158]

Aspirin-free strategies: when less is more

$P2Y_{12}$ inhibitor monotherapy

Pharmacodynamic studies have questioned the incremental platelet inhibitory effect of aspirin in the presence of potent $P2Y_{12}$ inhibitors, with clinical investigations even suggesting a potential attenuating role of the aspirin maintenance dose in the treatment effect of DAPT with ticagrelor.[159,160] These observations led to the hypothesis that prolonged monotherapy with a potent $P2Y_{12}$ inhibitor (such as ticagrelor) after a short course of DAPT could reduce ischaemic events compared to standard DAPT followed by aspirin monotherapy.[161] This strategy was first tested in an all-comers population of almost 16 000 patients undergoing PCI from the GLOBAL LEADERS trial and showed a numerical, albeit non-significant, reduction in the composite of death or Q-wave MI at 2 years in the experimental arm (3.81% vs. 4.37%; $P = 0.073$).[161] The nearly missed opportunity of GLOBAL LEADERS can be attributed to several limitations including an open-label design, lack of central adjudication, lower than expected event rates and poor treatment adherence.[162] The more recent randomized, placebo-controlled TWILIGHT trial evaluated a strategy of early aspirin discontinuation at 3 months after PCI among high-risk patients being prescribed DAPT with ticagrelor.[163] The trial met its primary objective by demonstrating a significant reduction in clinically relevant bleeding (4.0% vs. 7.1%; $P < 0.001$) without an increase in thrombotic events (3.9% vs. 3.9%, P for non-inferiority < 0.001) with ticagrelor monotherapy compared to ticagrelor plus aspirin.[163] Similar findings with ticagrelor monotherapy initiated at 3 months post-PCI have also been reported in ACS patients.[164] Two additional randomized studies seem to extend the potential advantages of $P2Y_{12}$ inhibitor monotherapy in reducing bleeding without compromising antithrombotic efficacy to clopidogrel.[165,166] Thus far, however, no such evidence exists for prasugrel monotherapy, despite its more consistent antiplatelet effect and greater antithrombotic efficacy in ACS patients compared to clopidogrel and possibly ticagrelor as well.[85,99,135] In addition, a recent meta-analysis suggested only a modest benefit of $P2Y_{12}$ monotherapy over aspirin monotherapy in reducing the risk of MI without a significant impact on mortality in the setting of secondary cardiovascular prevention.[167] In conclusion, aspirin is likely to remain a cornerstone of post-PCI pharmacotherapy; however, the increasing enthusiasm around aspirin-free strategies is justified by a growing body of clinical evidence. Such an approach, however, should not be generalized to all patients but rather be limited to the contexts in which it has been studied.[168] Additional considerations relating to cost-effectiveness, treatment non-compliance and possible side effects of these agents should be accounted for when selecting this treatment strategy.

Patients with atrial fibrillation undergoing PCI

Most clinical trials on DAPT have traditionally excluded patients on concomitant OAC therapy, resulting in a lack of data to inform their optimal management after PCI. Before the advent of direct oral anticoagulants (DOACs), the only randomized evidence available was derived from two relatively small trials suggesting potential harm with prolonged triple antithrombotic therapy comprising of a vitamin K antagonist and DAPT.[169,170] However, results from multiple dedicated studies on PCI or ACS patients with atrial fibrillation have become available since 2016.[171–174] Most of these trials found dual antithrombotic therapy with a DOAC and $P2Y_{12}$ inhibitor started within few days (up to 2 weeks) of PCI to be effective in preventing bleeding complications compared to regimens that included a vitamin K antagonist, aspirin, and $P2Y_{12}$ inhibitor, without an apparent increase in ischaemic events.[171–174] In keeping with these findings, expert consensus documents recommend that triple therapy be limited

to the periprocedural period with a transition to dual therapy soon after discharge, unless thrombotic risk features are predominant.[175,176] In fact, as none of these studies were powered to detect differences in ischaemic events, safety concerns about the routine adoption of a dual antithrombotic regimen remain. Moreover, study-level meta-analyses have reported signals of increased risk of MI and ST with dual therapy and lack of benefit with respect to mortality despite the large reduction in bleeding.[177,178] It is therefore recommended that a tailored approach be utilized in patients on OAC to effectively push the ischaemia-bleeding trade-off of antithrombotic therapy towards the desired direction according to individual risk features. The 2020 ESC guidelines on atrial fibrillation recommend early aspirin withdrawal (≤1 week) followed by dual therapy if concerns about bleeding outweigh those of ST.[179,180] In the opposite scenario, triple therapy should be continued up to 1 month.[179] Furthermore, dual therapy with potent $P2Y_{12}$ inhibitors may be considered as an alternative to triple therapy with clopidogrel in patients with a moderate to high risk of ST.[180] Finally, given that different DOACs have demonstrated varying risk-benefit profiles, it may be suggested that the choice of the appropriate drug be part of the individualized approach, although evidence in this regard is uncertain and possibly biased by trial design and other confounders.

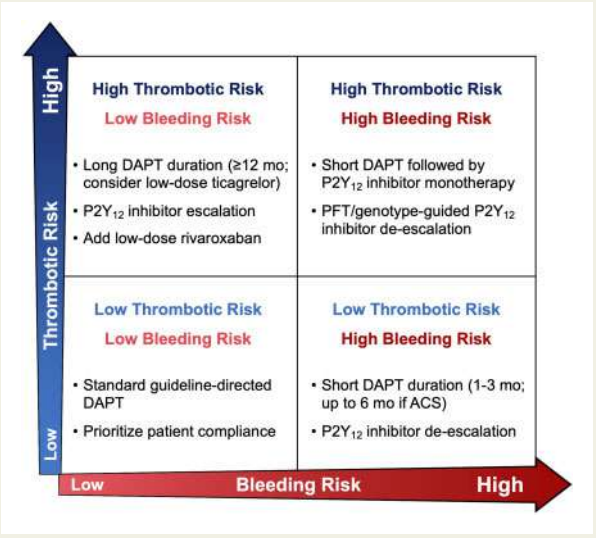

Figure 3 Proposed strategies for tailoring antithrombotic therapy according to individual bleeding and ischaemic risk. ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; mo, months; PFT, platelet function test.

Alternative pathways of platelet inhibition: a new horizon

Recurrent adverse events generate the most concern, especially after an ACS. Evidence of residual and sustained thrombotic risk in patients with ACS steered research towards new possible therapies targeting alternative pathways of platelet inhibition. The idea that a multipronged approach towards platelet inhibition would lead to better prevention of thrombotic events was based on previous experience with DAPT compared to aspirin alone, or with the addition of GPIs.

Thrombin is the most potent platelet agonist and its plasma levels have been shown to correlate with recurrent cardiovascular events after an ACS.[181] Thrombin mediates platelet activation mainly through the PAR (protease-activated receptor) 1, and to a lesser extent via the PAR4.[181] Vorapaxar, a competitive inhibitor of the PAR1, has been tested on top of DAPT in patients with ACS (58% of whom underwent PCI) with disappointing results, showing a non-significant reduction in cardiac events and a disproportionate increase in bleeding with a three-fold higher risk of intracranial haemorrhage.[182]

Blockage of thrombin generation is another way to inhibit platelet activation. DOACs directly inhibit factor Xa or thrombin and have shown to be at least as effective as and globally safer than vitamin K antagonists in various clinical settings.[183] The possibility of achieving a more profound antithrombotic effect with the addition of DOACs to antiplatelet therapy was tested in patients with ACS. Following the positive results of the ATLAS ACS 2-TIMI 51 trial,[184] guidelines state that, in ACS patients at low bleeding and high ischaemic risk receiving aspirin and clopidogrel, low-dose rivaroxaban 2.5 mg twice daily may be considered.[93] While similar studies conducted with other DOACs led to overall negative results,[185,186] mostly because of an unacceptable excess in bleeding risk, a meta-analysis including six randomized trials and almost 30 000 patients suggested that the efficacy of DOACs on top of antiplatelet therapy may vary by ACS type, with a risk–benefit profile more favourable in STEMI patients (NNT: 63, NNH: 96) than in those with non-ST-elevation ACS (NNT: 130, NNH: 137).[187]

Given that many ischaemic and bleeding risk factors coincide, identifying the patient subgroups who will derive the greatest net benefit from the use of intensified antithrombotic regimens remains a major challenge. In general, patients at increased risk for bleeding should not be considered for potent (or prolonged) drug combinations, regardless of the concomitant ischaemic risk (*Figure 3*). Greater focus on appropriate patient selection and treatment duration should guide future randomized trials that aim to address these knowledge gaps (*Table 4*).

Conclusions

Great strides have been made to optimize intra- and post-procedural pharmacological management in the relatively short history of interventional cardiology, but there is still much to be accomplished. Although better understood today, the struggle of finding the right balance between maintaining efficacy of preventing ischaemic events without incurring bleeding-related harm remains a relevant topic in real-world practice. Individualized clinical judgement, now more than ever, taking into account patient comorbidities, coronary anatomy as well as the attributes of the different antithrombotic strategies will yield the best outcomes.

Conflict of interest: R.M. reports institutional research grants from Abbott Laboratories, Abiomed, Applied Therapeutics, AstraZeneca, Bayer, Beth Israel Deaconess, Bristol-Myers Squibb, CERC, Chiesi, Concept Medical, CSL Behring, DSI, Medtronic, Novartis Pharmaceuticals, and OrbusNeich; consultant fees from

Table 4 Ongoing randomized controlled trials on antithrombotic therapies after percutaneous coronary intervention or acute coronary syndrome

Study name	*n*	Study population	Study intervention(s)	Primary outcome(s)
DAPT duration				
MASTER DAPT (NCT03023020)	4300	HBR patients undergoing PCI with the Ultimaster stent	• DAPT without OAC: 1 vs. ≥6 months • DAPT with OAC: 1 vs. ≥3 months (then dual therapy for 5 vs. 11 months)	NACE between 1 and 12 months[a]; MACCE between 1 and 12 mo[a]; BARC 2, 3, or 5 bleeding between 1 and 12 months
DUAL-ACS2 (NCT03252249)	19 519	Patients with ACS	3-month DAPT vs. 12-month DAPT	All-cause mortality at 15 months
PARTHENOPE (NCT04135989)	2106	Patients undergoing PCI with DES	2 × 2 factorial design: • Personalized (3-, 6- or 24-month) DAPT vs. standard (12-month) DAPT • Polymer-free (Cre8) DES vs. biodegradable-polymer (Synergy) DES	• Antiplatelet study: NACE at 12 months • Stent study: TLF at 12 months[a]
TARGET SAFE (NCT03287167)	1720	HBR patients undergoing PCI with the Firehawk stent	1-month DAPT vs. 6-month DAPT	NACE at 12 months[a]
DAPT intensity				
SMART-ATTEMPT (NCT04014803)	3500	Patients undergoing elective complex PCI with DES	12-month DAPT with prasugrel vs. 12-month DAPT with clopidogrel	MACE at 12 months
TALOS-AMI (NCT02018055)	2590	Stabilized patients with acute MI who underwent PCI with DES	After 1-month DAPT with ticagrelor, de-escalation to DAPT with clopidogrel vs. continued DAPT with ticagrelor	NACE at 12 months[a]
TAILORED-CHIP (NCT03465644)	2000	High-risk patients undergoing complex PCI	6-month DAPT with low-dose ticagrelor followed by 6-month clopidogrel monotherapy vs. 12-month DAPT with clopidogrel	NACE at 12 months
Genotyping				
GUARANTEE (NCT03783351)	3780	Patients undergoing PCI with new-generation DES	CYP2C19 genotype-guided DAPT with clopidogrel or ticagrelor vs. standard of care	MACCE at 12 months
P2Y$_{12}$ inhibitor monotherapy				
OPT-BIRISK (NCT03431142)	7700	ACS patients with high ischaemic and bleeding risk who received a new-generation DES and 9–12 months of DAPT	After initial 9–12 months of DAPT, 9 months of clopidogrel monotherapy vs. additional 9 months of DAPT	BARC 2–5 bleeding at 9 months after randomization
SMART-CHOICE 3 (NCT04418479)	5000	Patients at high ischemic risk with prior PCI (≥12 months)	Clopidogrel monotherapy vs. aspirin monotherapy	MACCE at 12 months
STOPDAPT-2 ACS (NCT03462498)	3008	ACS patients undergoing PCI with the XIENCE stent		NACE at 12[a] and 60 months

Continued

Table 4 *Continued*

Study name	*n*	Study population	Study intervention(s)	Primary outcome(s)
			1-month DAPT followed by clopidogrel monotherapy vs 12-month DAPT	
NEOMINDSET (NCT04360720)	3400	Patients undergoing PCI for ACS	• Prasugrel (non-HBR): 12-month monotherapy vs. 12-month DAPT • Ticagrelor (HBR): 12-month monotherapy vs. ≥6 DAPT	MACCE at 12 months[a]; BARC 2, 3, or 5 bleeding at 12 months
A-CLOSE (NCT03947229)	3200	Patients at high ischaemic risk and event free for 12 months after DES implantation	Clopidogrel monotherapy from 12 to 36 months vs. extended DAPT for 36 months	NACE between 12 and 36 months post-PCI[a]
IVUS-ACS and ULTIMATE-DAPT (NCT03971500)	3486	Patients undergoing PCI for ACS	2 × 2 factorial design: (1) One-month DAPT followed by ticagrelor monotherapy for 11 months vs. DAPT for 12 months (2) IVUS guidance vs. angiography guidance	(1) Antiplatelet study: BARC 2–5 bleeding; MACCE between 1 and 12 months[a] (2) Imaging study: TVF at 12 months
SMART-CHOICE II (NCT03119012)	1520	Patients undergoing PCI with BRS and event free for 12 months	P2Y12 inhibitor monotherapy with clopidogrel or low-dose ticagrelor from 12 to 36 months vs. extended DAPT for 36 months	MACCE between 12 and 36 months post-PCI[a]
Periprocedural antiplatelet therapy				
DAPT-SHOCK-AMI (NCT03551964)	304	Patients with acute MI complicated by cardiogenic shock undergoing primary PCI	Periprocedural cangrelor vs. ticagrelor	MACCE at 30 days; periprocedural inhibition of ADP-induced platelet aggregation
Concomitant OAC therapy				
WOEST 3 (NCT04436978)	2500	Patients with ACS and atrial fibrillation	Dual therapy with $P2Y_{12}$ inhibitor for 12 months vs. triple therapy with 12 months of $P2Y_{12}$ inhibitor and 1–12 months of aspirin	Thromboembolic complications at 12 months[a]; ISTH major or clinically relevant non-major bleeding at 12 months
OPTIMA-3, 4 (NCT03234114)	3746	ACS patients with atrial fibrillation undergoing PCI with DES	• Warfarin: triple therapy for 1 month vs. 6 months • Dabigatran 110 mg: 12-month dual therapy with ticagrelor vs. clopidogrel	Warfarin: MACCE at 12 months Dabigatran 110 mg: ISTH major bleeding at 12 months; MACCE at 12 months

[a]Study intervention tested for non-inferiority.
ACS, acute coronary syndrome; ADP, adenosine diphosphate; BARC, Bleeding Academic Research Consortium; BRS, bioresorbable scaffold; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; HBR, high bleeding risk; ISTH, International Society of Thrombosis and Haemostasis; MACCE, major adverse cardiac and cerebral events; MACE, major adverse cardiac events; MI, myocardial infarction; NACE, net adverse clinical events; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; TLF, target-lesion failure; TVF, target-vessel failure.

Abbott Laboratories, Boston Scientific, CardiaWave, Chiesi, Janssen Scientific Affairs, Medscape/WebMD, Medtelligence (Janssen Scientific Affairs), Roivant Sciences, Sanofi, and Siemens Medical Solutions; consultant fees paid to the institution from Abbott Laboratories and Bristol-Myers Squibb; advisory board, funding paid to the institution from Spectranetics/Philips/Volcano Corp; consultant (spouse) from Abiomed, The Medicines Company, and Merck; equity <1% from Claret Medical and Elixir Medical; DSMB Membership fees paid to the institution from Watermark Research Partners; consulting (no fee) from Idorsia Pharmaceuticals Ltd. and Regeneron Pharmaceuticals; and Associate Editor for ACC and AMA. The other authors have nothing to disclose.

References

1. Grüntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med* 1979;**301**:61–68.
2. Mehran R, Pocock S, Nikolsky E, Dangas GD, Clayton T, Claessen BE, Caixeta A, Feit F, Manoukian SV, White H, Bertrand M, Ohman EM, Parise H, Lansky AJ, Lincoff AM, Stone GW. Impact of bleeding on mortality after percutaneous coronary intervention results from a patient-level pooled analysis of the REPLACE-2 (randomized evaluation of PCI linking angiomax to reduced clinical events), ACUITY (acute catheterization and urgent intervention triage strategy), and HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trials. *JACC Cardiovasc Interv* 2011;**4**:654–664.
3. Chhatriwalla AK, Amin AP, Kennedy KF, House JA, Cohen DJ, Rao SV, Messenger JC, Marso SP, National Cardiovascular Data Registry FT. Association between bleeding events and in-hospital mortality after percutaneous coronary intervention. *JAMA* 2013;**309**:1022–1029.
4. Davie EW, Kulman JD. An overview of the structure and function of thrombin. *Semin Thromb Hemost* 2006;**32**:003–015.
5. Salter BS, Weiner MM, Trinh MA, Heller J, Evans AS, Adams DH, Fischer GW. Heparin-induced thrombocytopenia: a comprehensive clinical review. *J Am Coll Cardiol* 2016;**67**:2519–2532.
6. Gray E, Mulloy B, Barrowcliffe TW. Heparin and low-molecular-weight heparin. *Thromb Haemost* 2008;**99**:807–818.
7. Dumaine R, Borentain M, Bertel O, Bode C, Gallo R, White HD, Collet JP, Steinhubl SR, Montalescot G. Intravenous low-molecular-weight heparins compared with unfractionated heparin in percutaneous coronary intervention: quantitative review of randomized trials. *Arch Intern Med* 2007;**167**:2423–2430.
8. Lindahl U, Bäckström G, Höök M, Thunberg L, Fransson LA, Linker A. Structure of the antithrombin-binding site in heparin. *Proc Natl Acad Sci USA* 1979;**76**:3198–3202.
9. Choay J, Petitou M, Lormeau JC, Sinaÿ P, Casu B, Gatti G. Structure-activity relationship in heparin: a synthetic pentasaccharide with high affinity for antithrombin III and eliciting high anti-factor Xa activity. *Biochem Biophys Res Commun* 1983;**116**:492–499.
10. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, Budaj A, Peters RJ, Bassand JP, Wallentin L, Joyner C, Fox KA. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006;**354**:1464–1476.
11. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, Budaj A, Peters RJ, Bassand JP, Wallentin L, Joyner C, Fox KA, OASIS-6 Trial GroupEffects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 2006;**295**:1519–1530.
12. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011;**58**:e44-122–e122.
13. Steg PG, Jolly SS, Mehta SR, Afzal R, Xavier D, Rupprecht HJ, López-Sendón JL, Budaj A, Diaz R, Avezum A, Widimsky P, Rao SV, Chrolavicius S, Meeks B, Joyner C, Pogue J, Yusuf S, The FUTURA/OASIS-8 Trial Group. Low-dose vs standard-dose unfractionated heparin for percutaneous coronary intervention in acute coronary syndromes treated with fondaparinux: the FUTURA/OASIS-8 randomized trial. *JAMA* 2010;**304**:1339–1349.
14. Weitz JI, Hudoba M, Massel D, Maraganore J, Hirsh J. Clot-bound thrombin is protected from inhibition by heparin-antithrombin III but is susceptible to inactivation by antithrombin III-independent inhibitors. *J Clin Invest* 1990;**86**:385–391.
15. Phillips DR, Charo IF, Parise LV, Fitzgerald LA. The platelet membrane glycoprotein IIb-IIIa complex. *Blood* 1988;**71**:831–843.
16. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994;**330**:956–961.
17. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997;**336**:1689–1696.
18. The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet* 1998;**352**:87–92.
19. The ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet* 2000;**356**:2037–2044.
20. Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, Keren G, Carr J, Cohen EA, Betriu A, Desmet W, Kereiakes DJ, Rutsch W, Wilcox RG, de Feyter PJ, Vahanian A, Topol EJ. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 2003;**289**:853–863.
21. Kastrati A, Neumann FJ, Mehilli J, Byrne RA, Iijima R, Büttner HJ, Khattab AA, Schulz S, Blankenship JC, Pache J, Minners J, Seyfarth M, Graf I, Skelding KA, Dirschinger J, Richardt G, Berger PB, Schömig A. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *N Engl J Med* 2008;**359**:688–696.
22. Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, Moses JW, White HD, Pocock SJ, Ware JH, Feit F, Colombo A, Aylward PE, Cequier AR, Darius H, Desmet W, Ebrahimi R, Hamon M, Rasmussen LH, Rupprecht HJ, Hoekstra J, Mehran R, Ohman EM. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;**355**:2203–2216.
23. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Dangas G, Wong SC, Kirtane AJ, Parise H, Mehran R. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008;**358**:2218–2230.
24. Kastrati A, Neumann FJ, Schulz S, Massberg S, Byrne RA, Ferenc M, Laugwitz KL, Pache J, Ott I, Hausleiter J, Seyfarth M, Gick M, Antoniucci D, Schömig A, Berger PB, Mehilli J. Abciximab and heparin versus bivalirudin for non-ST-elevation myocardial infarction. *N Engl J Med* 2011;**365**:1980–1989.
25. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa-Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;**35**:2541–2619.
26. Valgimigli M, Frigoli E, Leonardi S, Vranckx P, Rothenbühler M, Tebaldi M, Varbella F, Calabrò P, Garducci S, Rubartelli P, Briguori C, Andó G, Ferrario M, Limbruno U, Garbo R, Sganzerla P, Russo F, Nazzaro M, Lupi A, Cortese B, Ausiello A, Ierna S, Esposito G, Ferrante G, Santarelli A, Sardella G, de Cesare N, Tosi P, van 't Hof A, Omerovic E, Brugaletta S, Windecker S, Heg D, Jüni P, Campo G, Uguccioni L, Tamburino C, Presbitero P, Zavalloni-Parenti D, Ferrari F, Ceravolo R, Tarantino F, Pasquetto G, Casu G, Mameli S, Stochino ML, Mazzarotto P, Cremonesi A, Saia F, Saccone G, Abate F, Picchi A, Violini R, Colangelo S, Boccuzzi G, Guiducci V, Vigna C, Zingarelli A, Gagnor A, Zaro T, Tresoldi S, Vandoni P, Contarini M, Liso A, Dellavalle A, Curello S, Mangiacapra F, Evola R, Palmieri C, Falcone C, Liistro F, Creaco M, Colombo A, Chieffo A, Perkan A, De Servi S, Fischetti D, Rigattieri S, Sciahbasi A, Pucci E, Romagnoli E, Moretti C, Moretti L, De Caterina R, Caputo M, Zimmarino M, Bramucci E, Di Lorenzo E, Turturo M, Bonmassari R, Penzo C, Loi B, Mauro C, Petronio AS, Gabrielli G, Micari A, Belloni F, Amico F, Comeglio M, Fresco C, Klinieken I, Van Mieghem N, Diletti R, Regar E, Sabaté M, Gómez Hospital JA, Díaz Fernández JF, Mainar V, de la Torre Hernandez JM. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. *Lancet* 2018;**392**:835–848.
27. Navarese EP, Schulze V, Andreotti F, Kowalewski M, Kołodziejczak M, Kandzari DE, Rassaf T, Gorny B, Brockmeyer M, Meyer C, Berti S, Kubica J, Kelm M, Valgimigli M. Comprehensive meta-analysis of safety and efficacy of bivalirudin versus heparin with or without routine glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndrome. *JACC Cardiovasc Interv* 2015;**8**(1 Pt B):201–213.
28. Steg PG, van 't Hof A, Hamm CW, Clemmensen P, Lapostolle F, Coste P, Ten Berg J, Van Grunsven P, Eggink GJ, Nibbe L, Zeymer U, Campo dell' Orto M,

Nef H, Steinmetz J, Soulat L, Huber K, Deliargyris EN, Bernstein D, Schuette D, Prats J, Clayton T, Pocock S, Hamon M, Goldstein P. Bivalirudin started during emergency transport for primary PCI. *N Engl J Med* 2013;**369**:2207–2217.
29. Erlinge D, Omerovic E, Fröbert O, Linder R, Danielewicz M, Hamid M, Swahn E, Henareh L, Wagner H, Hårdhammar P, Sjögren I, Stewart J, Grimfjärd P, Jensen J, Aasa M, Robertsson L, Lindroos P, Haupt J, Wikström H, Ulvenstam A, Bhiladvala P, Lindvall B, Lundin A, Tödt T, Ioanes D, Råmunddal T, Kellerth T, Zagozdzon L, Götberg M, Andersson J, Angerås O, Östlund O, Lagerqvist B, Held C, Wallentin L, Scherstén F, Eriksson P, Koul S, James S. Bivalirudin versus heparin monotherapy in myocardial infarction. *N Engl J Med* 2017;**377**: 1132–1142.
30. Shahzad A, Kemp I, Mars C, Wilson K, Roome C, Cooper R, Andron M, Appleby C, Fisher M, Khand A, Kunadian B, Mills JD, Morris JL, Morrison WL, Munir S, Palmer ND, Perry RA, Ramsdale DR, Velavan P, Stables RH. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet* 2014;**384**:1849–1858.
31. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferović PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO, Wijns W, Glineur D, Aboyans V, Achenbach S, Agewall S, Andreotti F, Barbato E, Baumbach A, Brophy J, Bueno H, Calvert PA, Capodanno D, Davierwala PM, Delgado V, Dudek D, Freemantle N, Funck-Brentano C, Gaemperli O, Gielen S, Gilard M, Gorenek B, Haasenritter J, Haude M, Ibanez B, Iung B, Jeppsson A, Katritsis D, Knuuti J, Kolh P, Leite-Moreira A, Lund LH, Maisano F, Mehilli J, Metzler B, Montalescot G, Pagano D, Petronio AS, Piepoli MF, Popescu BA, Sádaba R, Shlyakhto E, Silber S, Simpson IA, Sparv D, Tavilla G, Thiele H, Tousek P, Van Belle E, Vranckx P, Witkowski A, Zamorano JL, Roffi M, Windecker S, Aboyans V, Agewall S, Barbato E, Bueno H, Coca A, Collet J-P, Coman IM, Dean V, Delgado V, Fitzsimons D, Gaemperli O, Hindricks G, Iung B, Jüni P, Katus HA, Knuuti J, Lancellotti P, Leclercq C, McDonagh TA, Piepoli MF, Ponikowski P, Richter DJ, Roffi M, Shlyakhto E, Sousa-Uva M, Simpson IA, Zamorano JL, Pagano D, Freemantle N, Sousa-Uva M, Chettibi M, Sisakian H, Metzler B, İbrahimov F, Stelmashok VI, Postadzhiyan A, Skoric B, Eftychiou C, Kala P, Terkelsen CJ, Magdy A, Eha J, Niemelä M, Kedev S, Motreff P, Aladashvili A, Mehilli J, Kanakakis I-G, Becker D, Gudnason T, Peace A, Romeo F, Bajraktari G, Kerimkulova A, Rudzitis A, Ghazzal Z, Kibarskis A, Pereira B, Xuereb RG, Hofma SH, Steigen TK, Witkowski A, de Oliveira EI, Mot S, Duplyakov D, Zavatta M, Beleslin B, Kovar F, Bunc M, Ojeda S, Witt N, Jeger R, Addad F, Akdemir R, Parkhomenko A, Henderson R, ESC Scientific Document Group. ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87–165.
32. Bredlau CE, Roubin GS, Leimgruber PP, Douglas JS, King SB, Gruentzig AR. In-hospital morbidity and mortality in patients undergoing elective coronary angioplasty. *Circulation* 1985;**72**:1044–1052.
33. Urban P, Buller N, Fox K, Shapiro L, Bayliss J, Rickards A. Lack of effect of warfarin on the restenosis rate or on clinical outcome after balloon coronary angioplasty. *Br Heart J* 1988;**60**:485–488.
34. Anticoagulants in acute myocardial infarction. Results of a cooperative clinical trial. *JAMA* 1973;**225**:724–729.
35. Thornton MA, Gruentzig AR, Hollman J, King SB, Douglas JS. Coumadin and aspirin in prevention of recurrence after transluminal coronary angioplasty: a randomized study. *Circulation* 1984;**69**:721–727.
36. Grech ED. ABC of interventional cardiology: percutaneous coronary intervention. I: history and development. *BMJ* 2003;**326**:1080–1082.
37. Schatz RA, Palmaz JC, Tio FO, Garcia F, Garcia O, Reuter SR. Balloon-expandable intracoronary stents in the adult dog. *Circulation* 1987;**76**:450–457.
38. Serruys PW, Strauss BH, Beatt KJ, Bertrand ME, Puel J, Rickards AF, Meier B, Goy JJ, Vogt P, Kappenberger L, Sigwart U. Angiographic follow-up after placement of a self-expanding coronary-artery stent. *N Engl J Med* 1991;**324**: 13–17.
39. Schatz RA, Baim DS, Leon M, Ellis SG, Goldberg S, Hirshfeld JW, Cleman MW, Cabin HS, Walker C, Stagg J, Buchbinder M, Teirstein PS, Topol EJ, Savage M, Perez JA, Curry RC, Whitworth H, Sousa JE, Tio F, Almagor Y, Ponder R, Penn IM, Leonard B, Levine SL, Fish RD, Palmaz JC. Clinical experience with the Palmaz-Schatz coronary stent. Initial results of a multicenter study. *Circulation* 1991;**83**:148–161.
40. Foley JB, Brown RI, Penn IM. Thrombosis and restenosis after stenting in failed angioplasty: comparison with elective stenting. *Am Heart J* 1994;**128**:12–20.
41. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P, Belardi J, Sigwart U, Colombo A, Goy JJ, van den Heuvel P, Delcan J, Morel M-A. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med* 1994;**331**:489–495.
42. Balsano F, Rizzon P, Violi F, Scrutinio D, Cimminiello C, Aguglia F, Pasotti C, Rudelli G. Antiplatelet treatment with ticlopidine in unstable angina. A controlled multicenter clinical trial. The Studio della Ticlopidina nell'Angina Instabile Group. *Circulation* 1990;**82**:17–26.
43. Hollopeter G, Jantzen HM, Vincent D, Li G, England L, Ramakrishnan V, Yang RB, Nurden P, Nurden A, Julius D, Conley PB. Identification of the platelet ADP receptor targeted by antithrombotic drugs. *Nature* 2001;**409**:202–207.
44. Moussa I, Di Mario C, Reimers B, Akiyama T, Tobis J, Colombo A. Subacute stent thrombosis in the era of intravascular ultrasound-guided coronary stenting without anticoagulation: frequency, predictors and clinical outcome. *J Am Coll Cardiol* 1997;**29**:6–12.
45. Goldberg SL, Colombo A, Nakamura S, Almagor Y, Maiello L, Tobis JM. Benefit of intracoronary ultrasound in the deployment of Palmaz-Schatz stents. *J Am Coll Cardiol* 1994;**24**:996–1003.
46. Nakamura S, Colombo A, Gaglione A, Almagor Y, Goldberg SL, Maiello L, Finci L, Tobis JM. Intracoronary ultrasound observations during stent implantation. *Circulation* 1994;**89**:2026–2034.
47. Colombo A, Hall P, Nakamura S, Almagor Y, Maiello L, Martini G, Gaglione A, Goldberg SL, Tobis JM. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. *Circulation* 1995;**91**:1676–1688.
48. Schömig A, Neumann FJ, Kastrati A, Schühlen H, Blasini R, Hadamitzky M, Walter H, Zitzmann-Roth EM, Richardt G, Alt E, Schmitt C, Ulm K. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996;**334**:1084–1089.
49. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, Giambartolomei A, Diver DJ, Lasorda DM, Williams DO, Pocock SJ, Kuntz RE. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med* 1998;**339**: 1665–1671.
50. Cutlip DE, Baim DS, Ho KK, Popma JJ, Lansky AJ, Cohen DJ, Carrozza JP, Jr., Chauhan MS, Rodriguez O, Kuntz RE. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. *Circulation* 2001;**103**: 1967–1971.
51. Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. *Circulation* 1999;**100**: 1667–1672.
52. Yousuf O, Bhatt DL. The evolution of antiplatelet therapy in cardiovascular disease. *Nat Rev Cardiol* 2011;**8**:547–559.
53. Bertrand ME, Rupprecht H-J, Urban P, Gershlick AH; for the Classics Investigators. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation* 2000;**102**:624–629.
54. Bhatt DL, Bertrand ME, Berger PB, L'Allier PL, Moussa I, Moses JW, Dangas G, Taniuchi M, Lasala JM, Holmes DR, Ellis SG, Topol EJ. Meta-analysis of randomized and registry comparisons of ticlopidine with clopidogrel after stenting. *J Am Coll Cardiol* 2002;**39**:9–14.
55. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;**358**:527–533.
56. Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, Lewis BS, Murphy SA, McCabe CH, Braunwald E. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA* 2005;**294**:1224–1232.
57. Lenzen MJ, Boersma E, Bertrand ME, Maier W, Moris C, Piscione F, Sechtem U, Stahle E, Widimsky P, de Jaegere P, Scholte Op Reimer WJ, Mercado N, Wijns W. Management and outcome of patients with established coronary artery disease: the Euro Heart Survey on coronary revascularization. *Eur Heart J* 2005;**26**: 1169–1179.
58. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;**349**:1315–1323.
59. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004; **350**:221–231.
60. Morice M-C, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnàr F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;**346**:1773–1780.
61. Smith SC, Feldman TE, Hirshfeld JW, Jacobs AK, Kern MJ, King SB, Morrison DA, O'Neill WW, Schaff HV, Whitlow PL, Williams DO, Antman EM, Smith SC, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B; WRITING COMMITTEE MEMBERS. ACC/AHA/SCAI 2005 Guideline Update for

Percutaneous Coronary Intervention—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation* 2006;**113**: 156–175.
62. Patrono C, Bachmann F, Baigent C, Bode C, De CaterinaR, Charbonnier B, Fitzgerald D, Hirsh J, Husted S, Kvasnicka J, Montalescot G, García RodríguezLA, Verheugt F, Vermylen J, Wallentin L, Priori SG, Alonso Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Fernández Burgos E, Lekakis J, Lindahl B, Mazzotta G, Morais J, Oto A, Smiseth OA, Morais J, Deckers J, Ferreira R, Mazzotta G, Steg PG, Teixeira F, Wilcox R. Expert consensus document on the use of antiplatelet agents. The task force on the use of antiplatelet agents in patients with atherosclerotic cardiovascular disease of the European society of cardiology. *Eur Heart J* 2004;**25**:166–181.
63. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004;**364**:1519–1521.
64. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006;**48**:193–202.
65. Muni NI, Gross TP. Problems with drug-eluting coronary stents–the FDA perspective. *N Engl J Med* 2004;**351**:1593–1595.
66. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. *Circulation* 2007;**115**: 1440–1455; discussion 1455.
67. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. *Eur Heart J* 2006;**27**:2784–2814.
68. Pfisterer M, Brunner-La Rocca HP, Buser PT, Rickenbacher P, Hunziker P, Mueller C, Jeger R, Bader F, Osswald S, Kaiser C. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol* 2006;**48**: 2584–2591.
69. Ellis SG, Colombo A, Grube E, Popma J, Koglin J, Dawkins KD, Stone GW. Incidence, timing, and correlates of stent thrombosis with the polymeric paclitaxel drug-eluting stent: a TAXUS II, IV, V, and VI meta-analysis of 3,445 patients followed for up to 3 years. *J Am Coll Cardiol* 2007;**49**:1043–1051.
70. van Werkum JW, Heestermans AA, Zomer AC, Kelder JC, Suttorp MJ, Rensing BJ, Koolen JJ, Brueren BR, Dambrink JH, Hautvast RW, Verheugt FW, ten Berg JM. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. *J Am Coll Cardiol* 2009;**53**:1399–1409.
71. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;**293**: 2126–2130.
72. Grines CL, Bonow RO, Casey DE, Jr., Gardner TJ, Lockhart PB, Moliterno DJ, O'Gara P, Whitlow P. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *J Am Dent Assoc* 2007;**138**:652–655.
73. Farb A, Boam AB. Stent thrombosis redux—the FDA perspective. *N Engl J Med* 2007;**356**:984–987.
74. Bavry AA, Bhatt DL. Drug-eluting stents: dual antiplatelet therapy for every survivor? *Circulation* 2007;**116**:696–699.
75. Finn AV, Kolodgie FD, Harnek J, Guerrero LJ, Acampado E, Tefera K, Skorija K, Weber DK, Gold HK, Virmani R. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation* 2005;**112**:270–278.
76. Finn AV, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, Gold HK, Virmani R. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation* 2007;**115**:2435–2441.
77. Adriaenssens T, Joner M, Godschalk TC, Malik N, Alfonso F, Xhepa E, De Cock D, Komukai K, Tada T, Cuesta J, Sirbu V, Feldman LJ, Neumann FJ, Goodall AH, Heestermans T, Buysschaert I, Hlinomaz O, Belmans A, Desmet W, Ten Berg JM, Gershlick AH, Massberg S, Kastrati A, Guagliumi G, Byrne RA. Optical coherence tomography findings in patients with coronary stent thrombosis: a report of the PRESTIGE Consortium (Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort). *Circulation* 2017;**136**:1007–1021.
78. Stefanini GG, Holmes DR. Jr., Drug-eluting coronary-artery stents. *N Engl J Med* 2013;**368**:254–265.
79. von Birgelen C, Zocca P, Buiten RA, Jessurun GAJ, Schotborgh CE, Roguin A, Danse PW, Benit E, Aminian A, van Houwelingen KG, Anthonio RL, Stoel MG, Somi S, Hartmann M, Linssen GCM, Doggen CJM, Kok MM. Thin composite wire strut, durable polymer-coated (Resolute Onyx) versus ultrathin cobalt-chromium strut, bioresorbable polymer-coated (Orsiro) drug-eluting stents in allcomers with coronary artery disease (BIONYX): an international, single-blind, randomised non-inferiority trial. *Lancet* 2018;**392**:1235–1245.
80. Chiarito M, Sardella G, Colombo A, Briguori C, Testa L, Bedogni F, Fabbiocchi F, Paggi A, Palloshi A, Tamburino C, Margonato A, Pivato CA, Baber U, Calcagno S, Giordano A, Godino C, Stefanini GG. Safety and efficacy of polymer-free drug-eluting stents. *Circ Cardiovasc Interv* 2019;**12**:e007311.
81. Piccolo R, Bonaa KH, Efthimiou O, Varenne O, Baldo A, Urban P, Kaiser C, Remkes W, Räber L, de Belder A, van 't Hof AWJ, Stankovic G, Lemos PA, Wilsgaard T, Reifart J, Rodriguez AE, Ribeiro EE, Serruys PWJC, Abizaid A, Sabaté M, Byrne RA, de la Torre Hernandez JM, Wijns W, Jüni P, Windecker S, Valgimigli M, Piccolo R, Bonaa KH, Efthimiou O, Varenne O, Baldo A, Urban P, Kaiser C, Remkes W, Räber L, de Belder A, van't Hof AWJ, Stankovic G, Lemos PA, Wilsgaard T, Reifart J, Rodriguez AE, Ribeiro EE, Serruys PWJC, Abizaid A, Sabaté M, Byrne RA, de la Torre Hernandez JM, Wijns W, Jüni P, Windecker S, Valgimigli M. Drug-eluting or bare-metal stents for percutaneous coronary intervention: a systematic review and individual patient data meta-analysis of randomised clinical trials. *Lancet* 2019;**393**:2503–2510.
82. Ali ZA, Serruys PW, Kimura T, Gao R, Ellis SG, Kereiakes DJ, Onuma Y, Simonton C, Zhang Z, Stone GW. 2-year outcomes with the Absorb bioresorbable scaffold for treatment of coronary artery disease: a systematic review and meta-analysis of seven randomised trials with an individual patient data substudy. *Lancet* 2017;**390**:760–772.
83. Wykrzykowska JJ, Kraak RP, Hofma SH, van der Schaaf RJ, Arkenbout EK, IJsselmuiden AJ, Elias J, van Dongen IM, Tijssen RYG, Koch KT, Baan J, Vis MM, de Winter RJ, Piek JJ, Tijssen JGP, Henriques JPS. Bioresorbable scaffolds versus metallic stents in routine PCI. *N Engl J Med* 2017;**376**:2319–2328.
84. Chew DP, Bhatt DL, Sapp S, Topol EJ. Increased mortality with oral platelet glycoprotein IIb/IIIa antagonists: a meta-analysis of phase III multicenter randomized trials. *Circulation* 2001;**103**:201–206.
85. Bhatt DL. Intensifying platelet inhibition–navigating between Scylla and Charybdis. *N Engl J Med* 2007;**357**:2078–2081.
86. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR, Jr., Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;**371**:2155–2166.
87. Ferri N, Corsini A, Bellosta S. Pharmacology of the new P2Y12 receptor inhibitors: insights on pharmacokinetic and pharmacodynamic properties. *Drugs* 2013; **73**:1681–1709.
88. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, Teng R, Antonino MJ, Patil SB, Karunakaran A, Kereiakes DJ, Parris C, Purdy D, Wilson V, Ledley GS, Storey RF. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* 2009;**120**:2577–2585.
89. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;**357**:2001–2015.
90. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**: 1045–1057.
91. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Jû¥ni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;**39**:213–260.
92. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC. Jr., 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2016;**68**: 1082–1115.
93. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P, Collet J-P, Kristensen SD, Aboyans V, Baumbach A, Bugiardini R,

Coman IM, Delgado V, Fitzsimons D, Gaemperli O, Gershlick AH, Gielen S, Harjola V-P, Katus HA, Knuuti J, Kolh P, Leclercq C, Lip GYH, Morais J, Neskovic AN, Neumann F-J, Niessner A, Piepoli MF, Richter DJ, Shlyakhto E, Simpson IA, Steg PG, Terkelsen CJ, Thygesen K, Windecker S, Zamorano JL, Zeymer U, Windecker S, Aboyans V, Agewall S, Barbato E, Bueno H, Coca A, Collet J-P, Coman IM, Dean V, Delgado V, Fitzsimons D, Gaemperli O, Hindricks G, Iung B, Jüni P, Katus HA, Knuuti J, Lancellotti P, Leclercq C, McDonagh T, Piepoli MF, Ponikowski P, Richter DJ, Roffi M, Shlyakhto E, Simpson IA, Zamorano JL, Chettibi M, Hayrapetyan HG, Metzler B, Ibrahimov F, Sujayeva V, Beauloye C, Dizdarevic-Hudic L, Karamfiloff K, Skoric B, Antoniades L, Tousek P, Terkelsen PCJ, Shaheen SM, Marandi T, Niemelä M, Kedev S, Gilard M, Aladashvili A, Elsaesser A, Kanakakis IG, Merkely B, Gudnason T, Iakobishvili Z, Bolognese L, Berkinbayev S, Bajraktari G, Beishenkulov M, Zake I, Lamin HB, Gustiene O, Pereira B, Xuereb RG, Ztot S, Juliebø V, Legutko J, Timóteo AT, Tatu-Chițoiu G, Yakovlev A, Bertelli L, Nedeljkovic M, Studenčan M, Bunc M, García de Castro AM, Petursson P, Jeger R, Mourali MS, Yildirir A, Parkhomenko A, Gale CP; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–177.

94. Erlinge D, Ten Berg J, Foley D, Angiolillo DJ, Wagner H, Brown PB, Zhou C, Luo J, Jakubowski JA, Moser B, Small DS, Bergmeijer T, James S, Winters KJ. Reduction in platelet reactivity with prasugrel 5 mg in low-body-weight patients is noninferior to prasugrel 10 mg in higher-body-weight patients: results from the FEATHER trial. *J Am Coll Cardiol* 2012;**60**:2032–2040.
95. Erlinge D, Gurbel PA, James S, Lindahl TL, Svensson P, Ten Berg JM, Foley DP, Wagner H, Brown PB, Luo J, Zhou C, Moser BA, Jakubowski JA, Small DS, Winters KJ, Angiolillo DJ. Prasugrel 5 mg in the very elderly attenuates platelet inhibition but maintains noninferiority to prasugrel 10 mg in nonelderly patients: the GENERATIONS trial, a pharmacodynamic and pharmacokinetic study in stable coronary artery disease patients. *J Am Coll Cardiol* 2013;**62**:577-583.
96. Cattaneo M, Faioni EM. Why does ticagrelor induce dyspnea?. *Thromb Haemost* 2012;**108**:1031–1036.
97. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O.O, Ophuis, T Budaj, A Theroux, P Ruda, M Hamm, C Goto, S Spinar, J Nicolau, JC Kiss, RG Murphy, SA Wiviott, SD Held, P Braunwald, E Sabatine, MS Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;**372**:1791–1800.
98. Steg PG, Bhatt DL, Simon T, Fox K, Mehta SR, Harrington RA, Held C, Andersson M, Himmelmann A, Ridderstråle W, Leonsson-Zachrisson M, Liu Y, Opolski G, Zateyshchikov D, Ge J, Nicolau JC, Corbalán R, Cornel JH, Widimský P, Leiter LA. Ticagrelor in patients with stable coronary disease and diabetes. *N Engl J Med* 2019;**381**:1309–1320.
99. Motovska Z, Hlinomaz O, Miklik R, Hromadka M, Varvarovsky I, Dusek J, Knot J, Jarkovsky J, Kala P, Rokyta R, Tousek F, Kramarikova P, Majtan B, Simek S, Branny M, Mrozek J, Cervinka P, Ostransky J, Widimsky P. Prasugrel versus ticagrelor in patients with acute myocardial infarction treated with primary percutaneous coronary intervention: multicenter randomized PRAGUE-18 study. *Circulation* 2016;**134**:1603–1612.
100. Schüpke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, Richardt G, Liebetrau C, Witzenbichler B, Antoniucci D, Akin I, Bott-Flügel L, Fischer M, Landmesser U, Katus HA, Sibbing D, Seyfarth M, Janisch M, Boncompagni D, Hilz R, Rottbauer W, Okrojek R, Möllmann H, Hochholzer W, Migliorini A, Cassese S, Mollo P, Xhepa E, Kufner S, Strehle A, Leggewie S, Allali A, Ndrepepa G, Schühlen H, Angiolillo DJ, Hamm CW, Hapfelmeier A, Tölg R, Trenk D, Schunkert H, Laugwitz KL, Kastrati A. Ticagrelor or prasugrel in patients with acute coronary syndromes. *N Engl J Med* 2019;**381**:1524–1534.
101. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2020;doi: 10.1093/eurheartj/ehaa575.
102. Jneid H. Ticagrelor or prasugrel in acute coronary syndromes—the winner takes it all? *N Engl J Med* 2019;**381**:1582–1585.
103. Franchi F, Rollini F, Muniz-Lozano A, Cho JR, Angiolillo DJ. Cangrelor: a review on pharmacology and clinical trial development. *Expert Rev Cardiovasc Ther* 2013;**11**:1279–1291.
104. Gargiulo G, Esposito G, Avvedimento M, Nagler M, Minuz P, Campo G, Gragnano F, Manavifar N, Piccolo R, Tebaldi M, Cirillo P, Hunziker L, Vranckx P, Leonardi S, Heg D, Windecker S, Valgimigli M. Cangrelor, tirofiban, and chewed or standard prasugrel regimens in patients with ST-segment-elevation myocardial infarction: primary results of the FABOLUS-FASTER Trial. *Circulation* 2020;**142**:441–454.
105. Bhatt DL, Lincoff AM, Gibson CM, Stone GW, McNulty S, Montalescot G, Kleiman NS, Goodman SG, White HD, Mahaffey KW, Pollack CV, Jr., Manoukian SV, Widimsky P, Chew DP, Cura F, Manukov I, Tousek F, Jafar MZ, Arneja J, Skerjanec S, Harrington RA. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med* 2009;**361**:2330–2341.
106. Harrington RA, Stone GW, McNulty S, White HD, Lincoff AM, Gibson CM, Pollack CV, Jr., Montalescot G, Mahaffey KW, Kleiman NS, Goodman SG, Amine M, Angiolillo DJ, Becker RC, Chew DP, French WJ, Leisch F, Parikh KH, Skerjanec S, Bhatt DL. Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med* 2009;**361**:2318–2329.
107. Bhatt DL, Stone GW, Mahaffey KW, Gibson CM, Steg PG, Hamm CW, Price MJ, Leonardi S, Gallup D, Bramucci E, Radke PW, Widimský P, Tousek F, Tauth J, Spriggs D, McLaurin BT, Angiolillo DJ, Généreux P, Liu T, Prats J, Todd M, Skerjanec S, White HD, Harrington RA. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med* 2013;**368**:1303–1313.
108. Angiolillo DJ, Firstenberg MS, Price MJ, Tummala PE, Hutyra M, Welsby IJ, Voeltz MD, Chandna H, Ramaiah C, Brtko M, Cannon L, Dyke C, Liu T, Montalescot G, Manoukian SV, Prats J, Topol EJ, Bridge Investigators FT. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. *JAMA* 2012;**307**:265–274.
109. Cao D, Chandiramani R, Capodanno D, Berger JS, Levin MA, Hawn MT, Angiolillo DJ, Mehran R. Non-cardiac surgery in patients with coronary artery disease: risk evaluation and periprocedural management. Nat Rev Cardiol 2020;doi: 10.1038/s41569-020-0410-z.t.
110. Sinnaeve P, Fahrni G, Schelfaut D, Spirito A, Mueller C, Frenoux JM, Hmissi A, Bernaud C, Ufer M, Moccetti T, Atar S, Valgimigli M. Subcutaneous selatogrel inhibits platelet aggregation in patients with acute myocardial infarction. *J Am Coll Cardiol* 2020;**75**:2588–2597.
111. Costa F, Valgimigli M. The optimal duration of dual antiplatelet therapy after coronary stent implantation: to go too far is as bad as to fall short. *Cardiovasc Diagn Ther* 2018;**8**:630–646.
112. Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S, Ariti C, Litherland C, Dangas G, Gibson CM, Krucoff MW, Moliterno DJ, Kirtane AJ, Stone GW, Colombo A, Chieffo A, Kini AS, Witzenbichler B, Weisz G, Steg PG, Pocock S. Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from PARIS. *J Am Coll Cardiol* 2016;**67**:2224–2234.
113. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, Spertus JA, Steg PG, Cutlip DE, Rinaldi MJ, Camenzind E, Wijns W, Apruzzese PK, Song Y, Massaro JM, Mauri L; For the DAPT Study Investigators. 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**:1735–1749.
114. Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, Pilgrim T, Hong MK, Kim HS, Colombo A, Steg PG, Zanchin T, Palmerini T, Wallentin L, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M. 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**:1025–1034.
115. Abu-Assi E, Raposeiras-Roubin S, Cobas-Paz R, Caneiro-Queija B, Martínez-Reglero C, Rodríguez-Rodríguez JM, Baz A, Íñiguez-Romo A. Assessing the performance of the PRECISE-DAPT and PARIS risk scores for predicting one-year out-of-hospital bleeding in acute coronary syndrome patients. *EuroIntervention* 2018;**13**:1914–1922.
116. Song L, Guan C, Yan H, Qiao S, Wu Y, Yuan J, Dou K, Yang Y, Dangas GD, Xu B. Validation of contemporary risk scores in predicting coronary thrombotic events and major bleeding in patients with acute coronary syndrome after drug-eluting stent implantations. *Catheter Cardiovasc Interv* 2018;**91**:573–581.
117. Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, Cuisset T, Cutlip D, Eerdmans P, Eikelboom J, Farb A, Gibson CM, Gregson J, Haude M, James SK, Kim HS, Kimura T, Konishi A, Laschinger J, Leon MB, Magee PFA, Mitsutake Y, Mylotte D, Pocock S, Price MJ, Rao SV, Spitzer E, Stockbridge N, Valgimigli M, Varenne O, Windhoevel U, Yeh RW, Krucoff MW, Morice MC. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Eur Heart J* 2019;**40**:2632–2653.
118. Udell JA, Bonaca MP, Collet JP, Lincoff AM, Kereiakes DJ, Costa F, Lee CW, Mauri L, Valgimigli M, Park SJ, Montalescot G, Sabatine MS, Braunwald E, Bhatt DL. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. *Eur Heart J* 2016;**37**:390–399.
119. Meredith IT, Tanguay JF, Kereiakes DJ, Cutlip DE, Yeh RW, Garratt KN, Lee DP, Steg PG, Weaver WD, Holmes DR, Jr., Brindis RG, Trebacz J, Massaro JM, Hsieh WH, Mauri L. Diabetes mellitus and prevention of late myocardial

infarction after coronary stenting in the randomized dual antiplatelet therapy study. *Circulation* 2016;**133**:1772–1782.
120. Mavrakanas TA, Chatzizisis YS, Gariani K, Kereiakes DJ, Gargiulo G, Helft G, Gilard M, Feres F, Costa RA, Morice MC, Georges JL, Valgimigli M, Bhatt DL, Mauri L, Charytan DM. Duration of dual antiplatelet therapy in patients with CKD and drug-eluting stents: a meta-analysis. *Clin J Am Soc Nephrol* 2019;**14**: 810–822.
121. Lee SY, Hong MK, Palmerini T, Kim HS, Valgimigli M, Feres F, Colombo A, Gilard M, Shin DH, Kim JS, Kim BK, Ko YG, Choi D, Jang Y, Stone GW. Short-Term versus long-term dual antiplatelet therapy after drug-eluting stent implantation in elderly patients: a meta-analysis of individual participant data from 6 randomized trials. *JACC Cardiovasc Interv* 2018;**11**:435–443.
122. Giustino G, Chieffo A, Palmerini T, Valgimigli M, Feres F, Abizaid A, Costa RA, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Gilard M, Morice MC, Sawaya F, Sardella G, Genereux P, Redfors B, Leon MB, Bhatt DL, Stone GW, Colombo A. Efficacy and safety of dual antiplatelet therapy after complex PCI. *J Am Coll Cardiol* 2016;**68**:1851–1864.
123. Yeh RW, Kereiakes DJ, Steg PG, Cutlip DE, Croce KJ, Massaro JM, Mauri L. Lesion complexity and outcomes of extended dual antiplatelet therapy after percutaneous coronary intervention. *J Am Coll Cardiol* 2017;**70**:2213–2223.
124. Bonaca MP, Bhatt DL, Storey RF, Steg PG, Cohen M, Kuder J, Goodrich E, Nicolau JC, Parkhomenko A, López-Sendón J, Dellborg M, Dalby A, Špinar J, Aylward P, Corbalán R, Abola MTB, Jensen EC, Held P, Braunwald E, Sabatine MS. Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. *J Am Coll Cardiol* 2016;**67**:2719–2728.
125. Franzone A, Piccolo R, Gargiulo G, Ariotti S, Marino M, Santucci A, Baldo A, Magnani G, Moschovitis A, Windecker S, Valgimigli M. Prolonged vs short duration of dual antiplatelet therapy after percutaneous coronary intervention in patients with or without peripheral arterial disease: a subgroup analysis of the PRODIGY randomized clinical trial. *JAMA Cardiol* 2016;**1**:795–803.
126. Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrié D, Naber C, Lipiecki J, Richardt G, Iñiguez A, Brunel P, Valdes-Chavarri M, Garot P, Talwar S, Berland J, Abdellaoui M, Eberli F, Oldroyd K, Zambahari R, Gregson J, Greene S, Stoll HP, Morice MC. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N Engl J Med* 2015;**373**:2038–2047.
127. Ariotti S, Adamo M, Costa F, Patialiakas A, Briguori C, Thury A, Colangelo S, Campo G, Tebaldi M, Ungi I, Tondi S, Roffi M, Menozzi A, de Cesare N, Garbo R, Meliga E, Testa L, Gabriel HM, Ferlini M, Vranckx P, Valgimigli M. Is bare-metal stent implantation still justifiable in high bleeding risk patients undergoing percutaneous coronary intervention? A pre-specified analysis from the ZEUS trial. *JACC Cardiovasc Interv* 2016;**9**:426–436.
128. Windecker S, Latib A, Kedhi E, Kirtane AJ, Kandzari DE, Mehran R, Price MJ, Abizaid A, Simon DI, Worthley SG, Zaman A, Hudec M, Poliacikova P, Abdul Ghapar AKB, Selvaraj K, Petrov I, Mylotte D, Pinar E, Moreno R, Fabbiocchi F, Pasupati S, Kim HS, Aminian A, Tie C, Wlodarczak A, Hur SH, Marx SO, Jankovic I, Brar S, Bousquette L, Liu M, Stone GW. Polymer-based or polymer-free stents in patients at high bleeding risk. *N Engl J Med* 2020;**382**:1208–1218.
129. Costa F, Van Klaveren D, Feres F, James S, Raber L, Pilgrim T, Hong MK, Kim HS, Colombo A, Steg PG, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M. Dual antiplatelet therapy duration based on ischemic and bleeding risks after coronary stenting. *J Am Coll Cardiol* 2019;**73**:741–754.
130. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation* 2003;**107**:2908–2913.
131. Sibbing D, Aradi D, Alexopoulos D, Ten Berg J, Bhatt DL, Bonello L, Collet JP, Cuisset T, Franchi F, Gross L, Gurbel P, Jeong YH, Mehran R, Moliterno DJ, Neumann FJ, Pereira NL, Price MJ, Sabatine MS, So DYF, Stone GW, Storey RF, Tantry U, Trenk D, Valgimigli M, Waksman R, Angiolillo DJ. Updated expert consensus statement on platelet function and genetic testing for guiding P2Y12 receptor inhibitor treatment in percutaneous coronary intervention. *JACC Cardiovasc Interv* 2019;**12**:1521–1537.
132. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias W, Braunwald E, Sabatine MS. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med* 2009;**360**:354–362.
133. Mega JL, Simon T, Collet JP, Anderson JL, Antman EM, Bliden K, Cannon CP, Danchin N, Giusti B, Gurbel P, Horne BD, Hulot JS, Kastrati A, Montalescot G, Neumann FJ, Shen L, Sibbing D, Steg PG, Trenk D, Wiviott SD, Sabatine MS. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA* 2010;**304**:1821–1830.
134. Hochholzer W, Trenk D, Fromm MF, Valina CM, Stratz C, Bestehorn HP, Büttner HJ, Neumann FJ. Impact of cytochrome P450 2C19 loss-of-function polymorphism and of major demographic characteristics on residual platelet function after loading and maintenance treatment with clopidogrel in patients undergoing elective coronary stent placement. *J Am Coll Cardiol* 2010;**55**: 2427–2434.
135. Mega JL, Close SL, Wiviott SD, Shen L, Walker JR, Simon T, Antman EM, Braunwald E, Sabatine MS. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. *Lancet* 2010;**376**:1312–1319.
136. Wallentin L, James S, Storey RF, Armstrong M, Barratt BJ, Horrow J, Husted S, Katus H, Steg PG, Shah SH, Becker RC. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet* 2010;**376**:1320–1328.
137. Aradi D, Storey RF, Komócsi A, Trenk D, Gulba D, Kiss RG, Husted S, Bonello L, Sibbing D, Collet JP, Huber K; on behalf of the Working Group on Thrombosis of the European Society of Cardiology. Expert position paper on the role of platelet function testing in patients undergoing percutaneous coronary intervention. *Eur Heart J* 2014;**35**:209–215.
138. Parodi G, Marcucci R, Valenti R, Gori AM, Migliorini A, Giusti B, Buonamici P, Gensini GF, Abbate R, Antoniucci D. High residual platelet reactivity after clopidogrel loading and long-term cardiovascular events among patients with acute coronary syndromes undergoing PCI. *JAMA* 2011;**306**:1215–1223.
139. Aradi D, Kirtane A, Bonello L, Gurbel PA, Tantry US, Huber K, Freynhofer MK, ten Berg J, Janssen P, Angiolillo DJ, Siller-Matula JM, Marcucci R, Patti G, Mangiacapra F, Valgimigli M, Morel O, Palmerini T, Price MJ, Cuisset T, Kastrati A, Stone GW, Sibbing D. Bleeding and stent thrombosis on P2Y12-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. *Eur Heart J* 2015;**36**:1762–1771.
140. Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann FJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Gurbel PA, Xu K, Parise H, Kirtane AJ, Brodie BR, Mehran R, Stuckey TD. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet* 2013;**382**:614–623.
141. Sibbing D, Steinhubl SR, Schulz S, Schömig A, Kastrati A. Platelet aggregation and its association with stent thrombosis and bleeding in clopidogrel-treated patients: initial evidence of a therapeutic window. *J Am Coll Cardiol* 2010;**56**: 317–318.
142. Price MJ, Berger PB, Teirstein PS, Tanguay JF, Angiolillo DJ, Spriggs D, Puri S, Robbins M, Garratt KN, Bertrand OF, Stillabower ME, Aragon JR, Kandzari DE, Stinis CT, Lee MS, Manoukian SV, Cannon CP, Schork NJ, Topol EJ. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA* 2011;**305**: 1097–1105.
143. Collet JP, Cuisset T, Range G, Cayla G, Elhadad S, Pouillot C, Henry P, Motreff P, Carrie D, Boueri Z, Belle L, Van Belle E, Rousseau H, Aubry P, Monsegu J, Sabouret P, O'Connor SA, Abtan J, Kerneis M, Saint-Etienne C, Barthelemy O, Beygui F, Silvain J, Vicaut E, Montalescot G. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med* 2012;**367**:2100–2109.
144. Tang Y-D, Wang W, Yang M, Zhang K, Chen J, Qiao S, Yan H, Wu Y, Huang X, Xu B, Gao R, Yang Y, Yuan X, Ji H, Zhou Z, Liu Z, Chen J, Yuan J, Liu H, Qian J, Hu F, Shao C, Zhao H, Hua Y, Lu J, On behalf of the CREATIVE Investigators. Randomized comparisons of double-dose clopidogrel or adjunctive cilostazol versus standard dual antiplatelet in patients with high posttreatment platelet reactivity: results of the CREATIVE trial. *Circulation* 2018;**137**:2231–2245.
145. Levine GN, Jeong YH, Goto S, Anderson JL, Huo Y, Mega JL, Taubert K, Smith SC. Jr., Expert consensus document: world Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. *Nat Rev Cardiol* 2014;**11**:597–606.
146. Trenk D, Stone GW, Gawaz M, Kastrati A, Angiolillo DJ, Müller U, Richardt G, Jakubowski JA, Neumann F-J. of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) study. *J Am Coll Cardiol* 2012;**59**:2159–2164.
147. Cayla G, Cuisset T, Silvain J, Leclercq F, Manzo-Silberman S, Saint-Etienne C, Delarche N, Bellemain-Appaix A, Range G, El Mahmoud R, Carrié D, Belle L, Souteyrand G, Aubry P, Sabouret P, Du Fretay XH, Beygui F, Bonnet JL, Lattuca B, Pouillot C, Varenne O, Boueri Z, Van Belle E, Henry P, Motreff P, Elhadad S, Salem JE, Abtan J, Rousseau H, Collet JP, Vicaut E, Montalescot G. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. *Lancet* 2016;**388**:2015–2022.
148. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, Orban M, Hadamitzky M, Merkely B, Kiss RG, Komócsi A, Dézsi CA, Holdt L, Felix SB, Parma R, Klopotowski M, Schwinger RHG, Rieber J, Huber K, Neumann F-J, Koltowski L, Mehilli J, Huczek Z, Massberg S, Parma R, Parma Z, Lesiak M, Komosa A, Huczek Z, Koltowski L, Kowara M, Rymuza B, Klopotowski M, Malek L, Aradi D, Veress G, Dézsi AD, Merkely B, Lux Á, Kiss RG, Papp J, Kovács A, Dézsi CA, Amer S, Ruzsa Z, Róna S, Komócsi A, Ili R, Ungi I, Nagy F,

Zweiker R, Tóth-Gayor G, Huber K, Haller P, von Scheidt W, Blüthgen A, Neumann F-J, Trenk D, Leggewie S, Kreider-Stempfle HU, Remp T, Kara K, Mügge A, Wutzler A, Fichtlscherer S, Zeiher AM, Seeger F, Hinterseer M, König A, Lederle S, Jacobshagen C, Czepluch F, Maier L, Schillinger W, Sossalla S, Hummel A, Felix S, Karakas M, Sydow K, Rudolph T, Halbach M, Gori T, Münzel T, May A, Gerstenberg C-M, Pilecky D, Rieber J, Deichstetter M, Sibbing D, Mehilli J, Gross L, Kääb S, Löw A, Orban M, Orban M, Sattler S, Deuschl S, Teupser D, Holdt L, Mudra H, Räder T, Schütz T, Vahldiek F, Divchev D, Ince H, Nienaber CA, Radunski H, Boekstegers P, Horstkotte J, Mueller R, Geisler T, Müller K, Schwinger R, Rasp O. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. *Lancet* 2017;**390**:1747–1757.

149. Angiolillo DJ. Dual antiplatelet therapy guided by platelet function testing. *Lancet* 2017;**390**:1718–1720.
150. Holmes DR, Dehmer GJ, Kaul S, Leifer D, O'Gara PT, Stein CM. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the American Heart Association endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2010;**56**:321–341.
151. Roberts JD, Wells GA, Le May MR, Labinaz M, Glover C, Froeschl M, Dick A, Marquis JF, O'Brien E, Goncalves S, Druce I, Stewart A, Gollob MH, So DY. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. *Lancet* 2012;**379**:1705–1711.
152. Notarangelo FM, Maglietta G, Bevilacqua P, Cereda M, Merlini PA, Villani GQ, Moruzzi P, Patrizi G, Malagoli Tagliazucchi G, Crocamo A, Guidorossi A, Pigazzani F, Nicosia E, Paoli G, Bianchessi M, Comelli MA, Caminiti C, Ardissino D. Pharmacogenomic approach to selecting antiplatelet therapy in patients with acute coronary syndromes: the PHARMCLO trial. *J Am Coll Cardiol* 2018;**71**:1869–1877.
153. Cavallari LH, Lee CR, Beitelshees AL, Cooper-DeHoff RM, Duarte JD, Voora D, Kimmel SE, McDonough CW, Gong Y, Dave CV, Pratt VM, Alestock TD, Anderson RD, Alsip J, Ardati AK, Brott BC, Brown L, Chumnumwat S, Clare-Salzler MJ, Coons JC, Denny JC, Dillon C, Elsey AR, Hamadeh IS, Harada S, Hillegass WB, Hines L, Horenstein RB, Howell LA, Jeng LJB, Kelemen MD, Lee YM, Magvanjav O, Montasser M, Nelson DR, Nutescu EA, Nwaba DC, Pakyz RE, Palmer K, Peterson JF, Pollin TI, Quinn AH, Robinson SW, Schub J, Skaar TC, Smith DM, Sriramoju VB, Starostik P, Stys TP, Stevenson JM, Varunok N, Vesely MR, Wake DT, Weck KE, Weitzel KW, Wilke RA, Willig J, Zhao RY, Kreutz RP, Stouffer GA, Empey PE, Limdi NA, Shuldiner AR, Winterstein AG, Johnson JA. Multisite Investigation of Outcomes With Implementation of CYP2C19 Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention. *JACC Cardiovasc Interv* 2018;**11**:181–191.
154. Tuteja S, Glick H, Matthai W, Nachamkin I, Nathan A, Monono K, Carcuffe C, Maslowski K, Chang G, Kobayashi T, Anwaruddin S, Hirshfeld J, Wilensky RL, Herrmann HC, Kolansky DM, Rader DJ, Giri J. Prospective CYP2C19 genotyping to guide antiplatelet therapy following percutaneous coronary intervention: a pragmatic randomized clinical trial. *Circ Genom Precis Med* 2020;**13**:e002640.
155. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, van 't Hof AWJ, van der Harst P, Barbato E, Morisco C, Tjon Joe Gin RM, Asselbergs FW, Mosterd A, Herrman J-PR, Dewilde WJM, Janssen PWA, Kelder JC, Postma MJ, de Boer A, Boersma C, Deneer VHM, ten Berg JM. A genotype-guided strategy for oral P2Y(12) inhibitors in primary PCI. *N Engl J Med* 2019;**381**:1621–1631.
156. Pereira NL, Farkouh ME, So D, Lennon R, Geller N, Mathew V, Bell M, Bae JH, Jeong MH, Chavez I, Gordon P, Abbott JD, Cagin C, Baudhuin L, Fu YP, Goodman SG, Hasan A, Iturriaga E, Lerman A, Sidhu M, Tanguay JF, Wang L, Weinshilboum R, Welsh R, Rosenberg Y, Bailey K, Rihal C. Effect of genotype-guided oral P2Y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial. *JAMA* 2020;**324**:761–771.
157. Angiolillo DJ, Capodanno D, Danchin N, Simon T, Bergmeijer TO, Ten Berg JM, Sibbing D, Price MJ. Derivation, validation, and prognostic utility of a prediction rule for nonresponse to clopidogrel: the ABCD-GENE score. *JACC Cardiovasc Interv* 2020;**13**:606–617.
158. Bittl JA. The ABCD-GENE score for clopidogrel response: not just another cardiac risk model. *JACC Cardiovasc Interv* 2020;**13**:618–620.
159. Armstrong PC, Leadbeater PD, Chan MV, Kirkby NS, Jakubowski JA, Mitchell JA, Warner TD. In the presence of strong P2Y12 receptor blockade, aspirin provides little additional inhibition of platelet aggregation. *J Thromb Haemost* 2011;**9**:552–561.
160. Mahaffey KW, Wojdyla DM, Carroll K, Becker RC, Storey RF, Angiolillo DJ, Held C, Cannon CP, James S, Pieper KS, Horrow J, Harrington RA, Wallentin L. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation* 2011;**124**:544–554.
161. Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, Chichareon P, Benit E, Möllmann H, Janssens L, Ferrario M, Moschovitis A, Zurakowski A, Dominici M, Van Geuns RJ, Huber K, Slagboom T, Serruys PW, Windecker S, Abdellaoui M, Adlam D, Akin I, Albarran Gonzalez-Trevilla A, Almeida M, Alves Lemos Neto P, Aminian A, Anderson R, Andreae R, Angioi M, Asano T, Barbato E, Barlis P, Barraud P, Benit E, Bertrand O, Beygui F, Bolognese L, Botelho R, Bouwman C, Bressers M, Brunel P, Buszman P, Buysschaert I, Canas da Silva P, Carrie D, Cequier A, Chichareon P, Chin Chang C, Chowdhary S, Collet C, Colombo A, Cotton J, Cruz Ferreira R, Curello S, Curzen N, de Bot J, de Vreede T, Delle Karth G, Dijksma L, Dominici M, Édes I, Eeckhout E, Eitel I, Faluközy J, Fath-Ordoubadi F, Ferrario M, Fontos G, Francisco Diaz J, Freitas Quintella E, Frey B, Friedrich G, Galasko G, Galuszka G, Gama Ribeiro V, Garg S, Gargiulo G, Geisler T, Gelev V, Ghandilyan A, Goicolea J, Gori T, Gragnano F, Guimarães A, Hamm C, Haude M, Heg D, Heijke P, Hernández Antolin RA, Hildick-Smith D, Hillen D, Hoekman I, Hofma S, Holmvang L, Hoole S, Horváth I, Huber K, Hugense A, Ibrahim K, Iñiguez A, Isaaz K, Jambrik Z, Janssens L, Jasionowicz P, Jonk J, Jung W, Jüni P, Katagiri Y, Kogame N, Koh TH, Koning R, Konteva M, Kőszegi Z, Krackhardt F, Kreuger Y, Kukreja N, Ladan B, Lantelme P, Leandro S, Leibundgut G, Liebetrau C, Lindeboom W, Macaya Miguel C, Mach F, Magro M, Maillard L, Manavifar N, Mauri L, McFadden E, Merkely B, Miyazaki Y, Młodziankowski A, Moccetti T, Modolo R, Möllman H, Morelle J-F, Moschovitis A, Munndt Ottesen M, Muurling M, Naber CK, Neumann F-J, Oldroyd K, Ong P, Onuma Y, Palsrok S, Petrov I, Plante S, Prokopczuk J, Rademaker-Havinga T, Raffel C, Rensing B, Roffi M, Royaards K-J, Sabate M, Schächinger V, Seidler T, Serra Peñaranda A, Serruys P, Sikarulidze L, Slagboom T, Soliman OI, Sousa A, Spitzer E, Stables R, Steg G, Steinwender C, Subkovas E, Suryapranata H, Takahashi K, Talwar S, Teiger E, ter Weele A, Teurlings E, Thury A, Tijssen J, Tonev G, Trendafilova-Lazarova D, Tumscitz C, Umans V, Ungi I, Valkov V, van der Harst P, van Geuns RJ, van Meijeren C, Vassilev D, Velchev V, Velthuizen E, Verheugt F, Vlcek N, Vom Dahl J, Vrolix M, Walsh S, Werner N, Windecker S, Witsenburg M, Zaman A, Żmudka K, Zrenner B, Zurakowski A, Zweiker R. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet* 2018;**392**:940–949.
162. Mehran R, Cao D, Baber U. Ticagrelor monotherapy after coronary stenting: is the GLASS half full or half empty? *J Am Coll Cardiol* 2019;**74**:2235–2237.
163. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, Džavík V, Escaned J, Gil R, Gurbel P, Hamm CW, Henry T, Huber K, Kastrati A, Kaul U, Kornowski R, Krucoff M, Kunadian V, Marx SO, Mehta SR, Moliterno D, Ohman EM, Oldroyd K, Sardella G, Sartori S, Shlofmitz R, Steg PG, Weisz G, Witzenbichler B, Han YL, Pocock S, Gibson CM. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med* 2019;**381**:2032–2042.
164. Kim BK, Hong SJ, Cho YH, Yun KH, Kim YH, Suh Y, Cho JY, Her AY, Cho S, Jeon DW, Yoo SY, Cho DK, Hong BK, Kwon H, Ahn CM, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Hong MK, Jang Y. TICO Investigators. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. *JAMA* 2020;**323**:2407–2416.
165. Hahn JY, Song YB, Oh JH, Chun WJ, Park YH, Jang WJ, Im ES, Jeong JO, Cho BR, Oh SK, Yun KH, Cho DK, Lee JY, Koh YY, Bae JW, Choi JW, Lee WS, Yoon HJ, Lee SU, Cho JH, Choi WG, Rha SW, Lee JM, Park TK, Yang JH, Choi JH, Choi SH, Lee SH, Gwon HC; for the SMART-CHOICE Investigators. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA* 2019;**321**:2428–2437.
166. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, Ohya M, Suwa S, Takagi K, Nanasato M, Hata Y, Yagi M, Suematsu N, Yokomatsu T, Takamisawa I, Doi M, Noda T, Okayama H, Seino Y, Tada T, Sakamoto H, Hibi K, Abe M, Kawai K, Nakao K, Ando K, Tanabe K, Ikari Y, Hanaoka KI, Morino Y, Kozuma K, Kadota K, Furukawa Y, Nakagawa Y, Kimura T.; for the STOPDAPT-2 Investigators. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA* 2019;**321**:2414–2427.
167. Chiarito M, Sanz-Sánchez J, Cannata F, Cao D, Sturla M, Panico C, Godino C, Regazzoli D, Reimers B, De Caterina R, Condorelli G, Ferrante G, Stefanini GG. Monotherapy with a P2Y(12) inhibitor or aspirin for secondary prevention in patients with established atherosclerosis: a systematic review and meta-analysis. *Lancet* 2020;**395**:1487–1495.
168. Capodanno D, Mehran R, Valgimigli M, Baber U, Windecker S, Vranckx P, Dangas G, Rollini F, Kimura T, Collet JP, Gibson CM, Steg PG, Lopes RD,

Gwon HC, Storey RF, Franchi F, Bhatt DL, Serruys PW, Angiolillo DJ. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nat Rev Cardiol* 2018;**15**:480–496.
169. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, Adriaenssens T, Vrolix M, Heestermans AA, Vis MM, Tijsen JG, van 't Hof AW, ten Berg JM. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;**381**:1107–1115.
170. Fiedler KA, Maeng M, Mehilli J, Schulz-Schüpke S, Byrne RA, Sibbing D, Hoppmann P, Schneider S, Fusaro M, Ott I, Kristensen SD, Ibrahim T, Massberg S, Schunkert H, Laugwitz KL, Kastrati A, Sarafoff N. Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation: the ISAR-TRIPLE trial. *J Am Coll Cardiol* 2015;**65**:1619–1629.
171. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Birmingham M, Ianus J, Burton P, van Eickels M, Korjian S, Daaboul Y, Lip GY, Cohen M, Husted S, Peterson ED, Fox KA. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;**375**:2423–2434.
172. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, Maeng M, Merkely B, Zeymer U, Gropper S, Nordaby M, Kleine E, Harper R, Manassie J, Januzzi JL, Ten Berg JM, Steg PG, Hohnloser SH. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med* 2017;**377**:1513–1524.
173. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, Goodman SG, Windecker S, Darius H, Li J, Averkov O, Bahit MC, Berwanger O, Budaj A, Hijazi Z, Parkhomenko A, Sinnaeve P, Storey RF, Thiele H, Vinereanu D, Granger CB, Alexander JH. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med* 2019;**380**:1509–1524.
174. Vranckx P, Valgimigli M, Eckardt L, Tijssen J, Lewalter T, Gargiulo G, Batushkin V, Campo G, Lysak Z, Vakaliuk I, Milewski K, Laeis P, Reimitz PE, Smolnik R, Zierhut W, Goette A. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet* 2019;**394**:1335–1343.
175. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm AJ, Heidbüchel H, Lip GYH, Weitz J, Fauchier L, Lane D, Boriani G, Goette A, Keegan R, MacFadyen R, Chiang C-E, Joung B, Shimizu W; ESC Scientific Document Group. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;**39**:1330–1393.
176. Angiolillo DJ, Goodman SG, Bhatt DL, Eikelboom JW, Price MJ, Moliterno DJ, Cannon CP, Tanguay JF, Granger CB, Mauri L, Holmes DR, Gibson CM, Faxon DP. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a north american perspective-2018 update. *Circulation* 2018;**138**:527–536.
177. Gargiulo G, Goette A, Tijssen J, Eckardt L, Lewalter T, Vranckx P, Valgimigli M. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. *Eur Heart J* 2019;**40**:3757–3767.
178. Lopes RD, Hong H, Harskamp RE, Bhatt DL, Mehran R, Cannon CP, Granger CB, Verheugt FWA, Li J, Ten Berg JM, Sarafoff N, Vranckx P, Goette A, Gibson CM, Alexander JH. Optimal antithrombotic regimens for patients with atrial fibrillation undergoing percutaneous coronary intervention: an updated network meta-analysis. *JAMA Cardiol* 2020;**5**:582.
179. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL. ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2020;doi: 10.1093/eurheartj/ehaa612.
180. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.
181. Patrono C, Morais J, Baigent C, Collet JP, Fitzgerald D, Halvorsen S, Rocca B, Siegbahn A, Storey RF, Vilahur G. Antiplatelet agents for the treatment and prevention of coronary atherothrombosis. *J Am Coll Cardiol* 2017;**70**:1760–1776.
182. Tricoci P, Huang Z, Held C, Moliterno DJ, Armstrong PW, Van de Werf F, White HD, Aylward PE, Wallentin L, Chen E, Lokhnygina Y, Pei J, Leonardi S, Rorick TL, Kilian AM, Jennings LH, Ambrosio G, Bode C, Cequier A, Cornel JH, Diaz R, Erkan A, Huber K, Hudson MP, Jiang L, Jukema JW, Lewis BS, Lincoff AM, Montalescot G, Nicolau JC, Ogawa H, Pfisterer M, Prieto JC, Ruzyllo W, Sinnaeve PR, Storey RF, Valgimigli M, Whellan DJ, Widimsky P, Strony J, Harrington RA, Mahaffey KW. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. *N Engl J Med* 2012;**366**:20–33.
183. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;**383**:955–962.
184. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FW, Gibson CM. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;**366**:9–19.
185. Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, Bhatt DL, Goodman S, Verheugt FW, Flather M, Huber K, Liaw D, Husted SE, Lopez-Sendon J, De Caterina R, Jansky P, Darius H, Vinereanu D, Cornel JH, Cools F, Atar D, Leiva-Pons JL, Keltai M, Ogawa H, Pais P, Parkhomenko A, Ruzyllo W, Diaz R, White H, Ruda M, Geraldes M, Lawrence J, Harrington RA, Wallentin L. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med* 2011;**365**:699–708.
186. Oldgren J, Budaj A, Granger CB, Khder Y, Roberts J, Siegbahn A, Tijssen JG, Van de Werf F, Wallentin L; for the RE-DEEM Investigators. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. *Eur Heart J* 2011;**32**:2781–2789.
187. Chiarito M, Cao D, Cannata F, Godino C, Lodigiani C, Ferrante G, Lopes RD, Alexander JH, Reimers B, Condorelli G, Stefanini GG. Direct oral anticoagulants in addition to antiplatelet therapy for secondary prevention after acute coronary syndromes: a systematic review and meta-analysis. *JAMA Cardiol* 2018;**3**:234–241.