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# Pharmacology before, during and after percutaneous coronary intervention

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## INTRODUCTION

Coronary intervention initiates thrombin generation through endothelial damage and plaque disruption. The subsequent thrombotic risk<sup>1</sup> can persist for several weeks and dissipates, but not disappear, after stent endothelialisation. Adjunctive antithrombotic pharmacology, therefore, is a key determinant of acute and long-term outcomes with the range of available options improving outcomes but adding complexity to the decision making process.

This review will focus on antithrombotic pharmacology before, during and after percutaneous coronary intervention (PCI) with stent deployment. The major trials of antithrombotic drugs are listed in [table 1](#) and those of extended and shortened duration in [tables 2 and 3](#), respectively.

## PHARMACOLOGY BEFORE INTERVENTION

Pretreatment refers to pharmacology given (in ambulance or Emergency Department) before coronary anatomy is defined. Given the pathophysiology of coronary revascularisation, pretreatment with P2Y12 inhibitors would be expected to reduce ischaemic events. However, this benefit has to be balanced with increased bleeding risk in patients who have non-obstructive disease or those referred for surgical revascularisation. The evidence base for patient benefit of pretreatment with oral P2Y12 inhibitors is limited but all patients should be given a loading dose of aspirin.

### Stable angina

The evidence for pretreatment arose from the CREDO trial<sup>2</sup> which demonstrated benefit if patients received clopidogrel 300 mg loading at least 6 hours before PCI. However, closer analysis of patient inclusion revealed that most were selected after coronary angiography. The only trial designed to test pretreatment was PRAGUE-8 which failed to show ischaemic benefit between prehospital 600 mg clopidogrel compared with in-laboratory treatment but with a higher risk of minor bleeding.<sup>3</sup> The study finding was consolidated by a meta-analysis showing no mortality benefit from pretreatment.<sup>4</sup>

The absence of benefit from pretreatment loading is reflected in guidelines: The European Society of Cardiology (ESC) giving a IIb C recommendation for pretreatment loading only 'if high chance of PCI'<sup>5</sup> and the American Heart Association/American College of Cardiology (AHA/ACC) questioning its benefit without giving a recommendation.<sup>6</sup> Neither prasugrel nor ticagrelor have been tested in patients with stable angina.

There is no evidence of patient benefit for glycoprotein inhibitors (GPI) in pretreatment. Cangrelor

## Learning objectives

- ▶ To understand the risks and benefits of antithrombotic drug combinations in coronary intervention in different clinical settings.
- ▶ To provide a state-of-the-art review of relevant clinical studies of pharmacology for coronary intervention.
- ▶ To understand options for managing high bleeding risk patients.

is approved but has not been tested in the pretreatment setting against in-laboratory clopidogrel. The CHAMPION-PHOENIX trial (included stable and unstable patients) found cangrelor to significantly decrease the combined primary efficacy endpoint and stent thrombosis within 48 hours compared with clopidogrel in P2Y12 inhibitor naïve patients undergoing PCI<sup>7</sup> without increase in severe bleeding. Its use should be limited to high-risk patients unable to take oral medication.<sup>8</sup>

In summary, for stable angina when coronary anatomy is not known, the evidence does not support pretreatment over in-laboratory loading with clopidogrel. If coronary anatomy is known (or high probability of PCI) then pretreatment with clopidogrel (600 mg) at least 2 hours before procedure is recommended. There is no role for preprocedural anticoagulants.

## Non ST elevation acute coronary syndrome (NSTEMI-ACS)

Data from PCI-CURE showed benefit of pretreatment with clopidogrel and aspirin in NSTEMI-ACS<sup>9</sup> both before and after PCI, even though the median time from randomisation to PCI was 10 days—in contrast to contemporary recommendation for early referral and invasive management (within 48 hours). Subsequent studies in NSTEMI-ACS were equivocal<sup>4 10–12</sup> showing no benefit of clopidogrel pretreatment. A non-randomised study of clopidogrel pretreatment (300 mg loading  $\geq$ 12 hours or a 600 mg loading  $\geq$ 2 hours before angiography) was associated with similar adjusted short-term ischaemic and bleeding outcomes compared with in-laboratory 600 mg clopidogrel loading (<2 hours before or after PCI).<sup>13</sup> Overall, in the setting of early invasive therapy, the evidence supporting pretreatment with clopidogrel in NSTEMI-ACS is limited.

Pretreatment with ticagrelor against in-laboratory treatment has not been tested. In PLATO,<sup>14</sup> treatment before coronary angiography was permitted and did not exclude patients pretreated with clopidogrel before randomisation. Study analysis showed pretreatment to be safe but without ischaemia reduction.



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**Table 1** Summary of pivotal trials for antithrombotic agents

Study	Number of patients	Agent used	Indication	Treatment duration	Primary end point	Safety end point
PLATO 2009	18 624	Aspirin+Ticagrelor vs Aspirin+Clopidogrel	ACS with or without ST elevation	12 months	Death/ MI/stroke 9.8% Ticagrelor 11.7% Clopidogrel P<0.001	Major bleeding 11.6% Ticagrelor 11.2% Clopidogrel P=0.43
TRITON 2007	13 608 (STEMI=3534)	Aspirin+Prasugrel vs Aspirin+Clopidogrel	ACS 99% patients had PCI	6–15 months	Death/MI/non-fatal MI and stroke 9.9%—Prasugrel 12.1% Clopidogrel P<0.001	Major bleeding 2.4%—Prasugrel 1.8% Clopidogrel P=0.03 Life-threatening bleed 1.4%—Prasugrel 0.9% Clopidogrel
CURE 2001	12 562	Aspirin+Clopidogrel vs Aspirin+Prasugrel	ACS without ST elevation	3–12 months	Death/non-fatal stroke & MI 9.3% Clopidogrel 11.4% Prasugrel P<0.001	Major bleeding 3.7% Clopidogrel 2.7% Prasugrel P<0.001
CLARITY TIMI-28 2005	3491 Clopidogrel vs placebo	Fibrinolytic +anticoagulant+clopidogrel vs Fibrinolytic+clopidogrel+placebo	STEMI	1 month	Composite of occlusion of infarct artery/death/MI 15% Clopidogrel 21.7% Prasugrel P<0.001	TIMI major bleed 1.3% Clopidogrel 1.1% Prasugrel P=0.64
OASIS-5 2007	20 078	Fondaparinux vs Enoxaparin	ACS	6 days	Death/MI/refractory ischaemia 5.8%—Fondaparinux 5.7%—Enoxaparin P=0.06	Major bleeding 2.2%—Fondaparinux 4.1%—Enoxaparin P<0.001
ATLANTIC	1862 STEMI	Pretreatment ticagrelor vs in-laboratory ticagrelor	STEMI	End of PCI	>70% ST segment resolution TIMI 3 flow in infarct related artery before PCI	No difference in coprimary endpoints

ACS, acute coronary syndrome; MI, Myocardial Infarction; PCI, percutaneous coronary intervention; STEMI, ST Elevation Myocardial Infarction.

The only randomised study of pretreatment in this population was the ACCOAST study which tested half-dose prasugrel (30 mg) followed by a second in-laboratory 30 mg dose compared with 60 mg before PCI, after coronary anatomy had been defined.<sup>15</sup> The results showed no benefit

**Table 2** Trials of prolonged duration of antithrombotics

Study	No. of patients	Agent used	Follow-up duration	Efficacy endpoints	Safety endpoint
PEGASUS 2015 ACS in previous 1–3 years with high ischaemia risk	21 162	Aspirin+Ticagrelor 60mg two times a day vs Aspirin+Ticagrelor 90mg two times a day vs Aspirin+placebo	33 months	Death/MI/stroke Ticagrelor 90mg: 7.85% 60mg 7.77 % Placebo: 9.04 % P<0.001	TIMI major bleeding 90mg: 2.6% 60mg: 2.3% Placebo: 1.06%
THEMIS 2019 Stable CAD and type 2 diabetes, no history of previous MI/Stroke	19 220	Ticagrelor (60 two times a day)+Aspirin vs Aspirin+placebo	39.9 months	Primary end point: CV death/MI/stroke Ticagrelor+Aspirin = 7.7% Aspirin+placebo = 8.1% p=0.038	TIMI major bleeding Ticagrelor+Aspirin = 2.2% Aspirin+placebo = 1.0% P<0.001
THEMIS-PCI 2019 Subgroup of THEMIS patients who underwent PCI	11 154	Ticagrelor (60 two times a day)+Aspirin vs Aspirin+placebo		Primary end point: CV death/MI/stroke Ticagrelor+Aspirin=7.3% Aspirin+placebo=8.6% P=0.013	TIMI major bleeding Ticagrelor+Aspirin=2.0% Aspirin+placebo=1.1% P<0.001 Net clinical benefit: 15% reduction in Ticagrelor arm
DAPT 2014 ACS with high ischaemia risk	9961	Aspirin+thienopyridine for 12 months vs Aspirin+thienopyridine for 30 months	30 months	Stent thrombosis, 0.4%–30 months 1.4%–12 months death/MI/stroke 4.3%–30 months 5.9%–12 months P<0.001	Moderate–severe bleeding 30 months—2.5% 12 months—1.6% P<0.001
COMPASS 2017 Stable atherosclerotic vascular disease	27 395	Rivaroxaban 2.5 mg two times a day+Aspirin vs Rivaroxaban 5 mg two times a day vs Aspirin	23 months	Death/MI/Stroke 4.1% (Rivaroxaban+Aspirin) 4.9% Rivaroxaban 5.4% Aspirin P<0.001 for (R+A) vs A	Major bleeding 3.1%— (Rivaroxaban+Aspirin) 1.9%—Aspirin P<0.001

DAPT, dual antiplatelet therapy; TIMI, Thrombolysis in Myocardial Infarction.

**Table 3** Trials of short duration DAPT

LEADERS-FREE 2015 ACS+stable angina	2466 HBR patients BioFreedom (DES) vs BMS	1 month of DAPT followed by aspirin alone	12-month follow-up	Target lesion revascularisation: 5.1% BioFreedom 9.8% BMS P<0.001	Death, MI, stent thrombosis 9.4% BioFreedom vs 12.9% BMS P<0.001
ONYX-ONE 2020 ACS+stable angina	1996 HBR patients Resolute Onyx (DES) vs BioFreedom (DES)	1 month DAPT (aspirin+mostly clopidogrel) After 2 months 92% on single APT Aspirin : 55.9% P2Y12 : 44.1%	12-month follow-up	Primary safety endpoint: Cardiac death/MI/stent thrombosis 17.1 vs 16.9% P=0.011 for non-inferiority	Stent thrombosis 0.9% at 12 months for both arms P=0.99 Bleeding, BARC 2–5 P=0.4
SENIOR 2018 ACS+stable angina	1200 patients>75 years Synergy (DES) vs BMS	1 month DAPT for stable angina 6 months DAPT for ACS	12-month follow-up	Primary endpoint: all-cause mortality, MI, stroke or ischaemia-driven target lesion revascularisation DES 11.6% vs BMS 16.4% P=0.02	Stent thrombosis 1% for both arms Bleeding: 5% in both arms
TWILIGHT 2019 ACS+stable angina	7119 patients at HBR or high ischaemic risk	Ticagrelor+Aspirin for 3 months then Ticagrelor+Aspirin vs Ticagrelor+placebo	12-month follow-up	Primary endpoint : BARC 2, 3, 5 Ticagrelor+Aspirin=7.1% Ticagrelor+placebo = 4.0% P<0.001	Death from any cause, non- fatal MI, or non-fatal stroke 3.9% in both arms P<0.001 for non-inferiority

A, aspirin; BARC, bleeding academic research collaboration; BMS, bare metal stent; DAPT, dual antiplatelet therapy; DES, drug eluting stent; HBR, high bleeding risk; T, ticagrelor.

of pretreatment in the ischaemic endpoint but a 90% increased risk of major and life-threatening bleeding. In the PCI subgroup, there was also no evidence of ischaemic benefit.<sup>16</sup> The ACTION group meta-analysis also failed to show a significant mortality reduction with pretreatment with increased major bleeding.<sup>17</sup>

The failure of pretreatment with oral P2Y12 inhibitors in NSTEMI-ACS was surprising given the central role of platelets in atherothrombotic disease and raises questions about whether the mode of delivery—oral versus parenteral—could be important.

The evidence for GPI's pre-dates use of routine oral dual antiplatelet therapy (DAPT) and early invasive treatment. While early trials demonstrated a reduction in ischaemic events (largely reduction in myocardial infarction (MI)) in favour of GPI in combination with unfractionated heparin (UFH) compared with UFH alone,<sup>18</sup> a consistent major bleeding risk was seen. Overall, there is no evidence for benefit of routine upstream GPI in patients scheduled for PCI and receiving DAPT treatment.<sup>19–20</sup> With ticagrelor or prasugrel, randomised data with GPI use are limited; therefore, use of these agents for pretreatment is not recommended. Cangrelor also lacks evidence in the presence of prasugrel or ticagrelor.<sup>7</sup>

In summary, aspirin (loading and maintenance) carries a IA recommendation for pretreatment in NSTEMI-ACS with ticagrelor (180 mg) added as soon as the coronary anatomy is established (IIbC). If ticagrelor is unavailable, then clopidogrel 600 mg can be given but prasugrel is not recommended (IIIa). The use of cangrelor in P2Y12-naïve patients unable to take oral medication carries a IIbA recommendation. If the wait for coronary angiography is longer (>24 hours), antiplatelet pretreatment should be considered.<sup>5</sup>

With respect to anticoagulants, the OASIS-5 trial showed equivalence of fondaparinux

(2.5 mg od subcutaneously) to heparin in reducing composite events but with a reduced risk of bleeding.<sup>21</sup> As a result, fondaparinux carries a class IA recommendation for pretreatment of NSTEMI-ACS but patients should receive UFH during PCI. Where fondaparinux is not available, then enoxaparin (1 mg/kg two times a day, subcutaneously) is preferred (class IB).<sup>5</sup>

### ST elevation myocardial infarction (STEMI)

The only pretreatment study was ATLANTIC<sup>22</sup> which showed no benefit in the composite primary end-points of infarct artery TIMI 3 flow and 70% ST segment resolution. One reason may have been the short median time between the loading doses in the pretreatment and no pretreatment groups (about 30 min) which was likely insufficient to allow for significant separation in platelet inhibition between the two groups at the time of PCI.

Although TRITON-TIMI 38<sup>23</sup> did not allow pretreatment with prasugrel, the consensus has been to accept administration of prasugrel in patients with STEMI undergoing primary PCI within 12 hours from symptoms. Cangrelor lacks evidence in this setting with CHAMPION-PHOENIX including only 18% STEMI patients.

The European Society of Cardiology, European Association of Cardiothoracic Surgeons (ESC-EACTS) guidelines (aspirin IA) recommend ticagrelor or prasugrel before PCI (IA). Cangrelor (IIbA) or GPI (IIbC) may be considered in P2Y12 inhibitor naïve patients unable to take oral medication.<sup>5</sup>

### PHARMACOLOGY DURING INTERVENTION

#### Stable angina

The use of parenteral anticoagulants is standard of care during elective PCI to inhibit thrombin generation with UFH and bivalirudin being the most widely studied.<sup>24–26</sup> Low molecular weight heparin may be considered especially if the patient was on this preprocedure. The recommendation is to use

70–100 U/kg of UFH. Anticoagulant treatment should be stopped once PCI is completed.

### Non-ST elevation acute coronary syndrome and ST elevation MI

UFH is cost effective and trials in the contemporary era of radial access show equivalence<sup>27</sup> or superiority to bivalirudin.<sup>28</sup> Overall, there is no compelling evidence for the benefit of routine use of GPI in NSTEMI-ACS or STE-MI patients undergoing PCI with P2Y12 antiplatelet treatment with use limited to bail out situations. The evidence on cangrelor suggests that the potential benefit (rapid platelet inhibition) is independent of the clinical presentation. Thus, cangrelor may be considered in specific settings in P2Y12-naïve patients undergoing high risk PCI.

### PHARMACOLOGY AFTER INTERVENTION

The duration of DAPT after PCI should consider patient-specific risk, clinical presentation, and procedural factors. Prolonged DAPT for all patients reduces stent thrombosis and MI at the expense of increased bleeding. In certain clinical scenarios, there is evidence for both shortening to 1 month or extending beyond 12 months<sup>29</sup>. There are also data showing safety and efficacy of stopping aspirin at 3 months and continuing with a single P2Y12 antiplatelet agent.

### Stable angina

For all stents, the recommended duration of DAPT (aspirin and clopidogrel) is 6 months and aspirin continued thereafter for life. The COMPASS trial<sup>30</sup> demonstrated the value of low ('vascular') dose rivaroxaban (2.5 mg two times a day) in combination with aspirin. However, this trial was not linked to myocardial revascularisation procedures.

The GLOBAL-LEADERS trial in patients undergoing PCI for both stable and unstable disease, evaluated 1 month of aspirin plus ticagrelor followed by 23 months of ticagrelor monotherapy compared with 1 year of DAPT (aspirin plus clopidogrel in stable or ticagrelor in unstable) followed by 1 year of aspirin monotherapy.<sup>31</sup> The primary outcome showed no significant reduction but safety was confirmed. The findings were similar in multiple tested subgroups.

In THEMIS<sup>32</sup> patients with stable disease and diabetes without history of MI or stroke, ticagrelor plus aspirin had a lower incidence of ischaemic events but a higher incidence of major bleeding. Importantly, in a prespecified PCI patient population, ticagrelor plus aspirin provided a favourable net clinical benefit.<sup>33</sup>

The GLOBAL-LEADERS and THEMIS studies underscore the point that in an unselected patient population undergoing PCI for stable angina, there is no benefit of extending DAPT or substituting aspirin with a more potent P2Y12 agent. However, based on THEMIS-PCI, long-term therapy with ticagrelor in addition to aspirin should be considered in patients with diabetes and a history of PCI who have tolerated antiplatelet therapy, have high ischaemic risk and low bleeding risk.

### Non-ST elevation ACS and ST elevation MI

The guidelines recommend 12 months of DAPT (aspirin with either ticagrelor or prasugrel) post-procedure. However, it is in this subset of high risk patients after ACS where evidence is growing for extending duration beyond 1 year. The PEGASUS-TIMI 54<sup>29</sup> study randomised patients with a history of AMI (most underwent PCI) to aspirin and ticagrelor (60 mg two times a day or 90 mg two times a day) versus aspirin and placebo. After a median follow-up of 33 months, the ticagrelor groups had significantly lower rates of major adverse cardiovascular and Cerebrovascular Events (MACCE) with higher rates of TIMI major bleeding (with higher rates of bleeding with 90 mg two times a day vs 60 mg two times a day) with similar rates of intracranial haemorrhage or fatal bleeding among the three groups. The study is important in demonstrating the efficacy of prolonged DAPT in high-risk patients and supports the safety of this strategy in selected patients. A substudy analysis in patients with diabetes<sup>34</sup> with prior MI demonstrated a reduction in ischaemic events with ticagrelor and aspirin. Taken together with the THEMIS-PCI study, there is growing evidence for extending ticagrelor for secondary prevention in high-risk subgroups.

The ESC guidelines recommend extending ticagrelor 60 mg two times a day beyond 12 months with aspirin in patients with previous MI and high ischaemic risk who have tolerated DAPT without bleeding complications (IIbB).

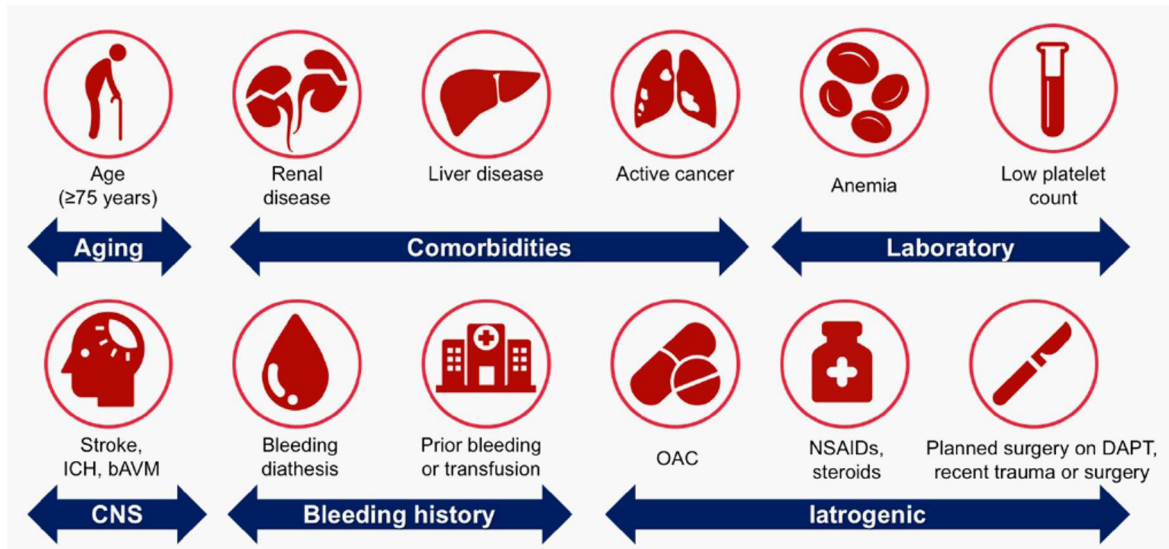
### PHARMACOLOGY IN PATIENTS IN ATRIAL FIBRILLATION ON EXISTING ANTICOAGULANTS UNDERGOING PCI

The main focus in patients with atrial fibrillation (AF) is stroke prevention. Several trials<sup>35–39</sup> guide therapy in this population with all powered for bleeding endpoints compared with vitamin K antagonist (VKA) and not for ischaemic or stroke prevention.

The WOEST study demonstrated safety of using a combination of clopidogrel and warfarin alone in terms of thrombotic events with reduced overall bleeding risk. The PIONEER<sup>36</sup> RE-DUAL,<sup>37</sup> AUGUSTUS<sup>38</sup> and ENTRUST<sup>39</sup> trials further reinforced the concept of redundancy of aspirin due to increased bleeding in patients with AF treated with anticoagulant and P2Y12 inhibitor. The AUGUSTUS trial used a factorial design to specifically evaluate a single P2Y12 inhibitor with an anticoagulant versus triple therapy with aspirin. This trial confirmed first, superiority of apixaban over VKA in reducing bleeding and second, similar efficacy but less bleeding with dual therapy (apixaban and P2Y12 with >92% of patients on clopidogrel).

### Pretreatment

Direct oral anticoagulants (DOAC) should be withheld for 24 hours (48 hours for those with renal impairment on dabigatran – creatinine clearance <50 mL/min).<sup>40</sup> For patients on VKA, this does not



**Figure 1** Markers of high bleeding risk. bAVM, brain arteriovenous malformation; ICH, intracranial haemorrhage; NSAID, non steroidal anti inflammatory drugs; OAC, oral anticoagulant.

need to be interrupted<sup>41</sup> but US guidelines recommend a washout period before PCI using preferably, radial access when international normalised ratio (INR)  $\leq 2$  (or if femoral when INR  $\leq 1.5$ ).<sup>40</sup>

As there is scant evidence for preloading with P2Y12 antiplatelet agents, patients on oral anticoagulants should only receive treatment once coronary anatomy is known and decision made to proceed to PCI. The overwhelming trial evidence is to give clopidogrel (300 mg) in-laboratory.

Patients presenting with NSTEMI-ACS on DOAC should stop treatment for 24 hours before PCI. If the clinical situation demands urgent revascularisation (eg, STEMI), then studies suggest that an uninterrupted strategy is not associated with increased bleeding or major cardiovascular events compared with bridging therapy.<sup>42</sup>

#### Treatment during PCI

There are limited data to guide parenteral anticoagulants during PCI. For patients on VKA, additional parenteral anticoagulants may not be needed if INR is  $> 2.5$  at the time of elective PCI.<sup>43</sup> However, for preservation of radial artery patency, a dosing level of 30–50 U/kg is recommended and it may be prudent to give this at the time of radial sheath removal rather than at procedure start.

With patients on DOAC, use of parenteral heparin (70–100 U/kg) during PCI is recommended regardless of the timing of the last DOAC dose.<sup>41</sup> The use of parenteral antiplatelet agents (cangrelor or GPI) has no evidence base and should be restricted to bail out situations. Cangrelor may be preferred on account of its shorter half-life.

#### Treatment after PCI

The dose of DOAC should reflect the regimen tested in trials of patients with AF undergoing PCI. For

patients who prefer VKA, the INR should be targeted to the lower end of the therapeutic range (2.0–2.5).

In a meta-analysis of four randomised trials, patients on dual antithrombotic therapy (DAT) showed a 47% reduction in TIMI major or minor bleeding compared with triple antithrombotic therapy (TAT) with no difference in major adverse cardiac events or stroke.<sup>44</sup>

Trials of DOAC in patients undergoing PCI build on data from WOEST to add clarity and guide antiplatelet therapy. The consistency of significantly lower bleeding with DAT (clopidogrel has most evidence) across all trials supports its use over TAT and represents the default strategy. In selected patients at high ischaemic/thrombotic and low bleeding risks, low-dose aspirin therapy (triple therapy) may be extended for a limited period of time (1 month) after PCI.

There are some data with ticagrelor, particularly in combination with dabigatran, which showed safety and efficacy consistent with those of clopidogrel but with numerically higher bleeding.<sup>37</sup> As a result, the US guidelines include ticagrelor as an option in patients at high ischaemic/thrombotic and low bleeding risk with omission of aspirin in keeping with the RE-DUAL PCI trial. Indirect support for ticagrelor as antiplatelet monotherapy comes from the TWILIGHT study which reported reduced bleeding without an increase in ischaemic events if aspirin treatment was stopped 3 months after PCI and patients continued on ticagrelor monotherapy alone.<sup>45</sup>

Data on prasugrel with a DOAC are limited to a small study reporting a near fourfold increase in bleeding with TAT and thus, its use is not recommended.<sup>46</sup>

Trials of new generation drug eluting stent (DES) in high bleeding risk patients demonstrating safety and efficacy of short duration dual antiplatelet therapy (see below) have led to guidelines recommending their use in patients with AF undergoing PCI.<sup>47</sup>

## Key messages

- ▶ There is no mortality benefit of pretreatment with P2Y12 inhibitors in patients undergoing percutaneous coronary intervention (PCI).
- ▶ The recommended duration of DAPT after PCI for stable angina is 6 months. Trial data with specific drug eluting stents (LEADERS-FREE, ONYX-ONE) show safety of 1-month duration in high bleeding risk.
- ▶ For certain high ischaemic risk patients, trial (THEMIS-PCI, PEGASUS) data show ischaemic benefit with extended duration DAPT (ticagrelor plus aspirin).
- ▶ Unfractionated heparin remains the anticoagulant of choice during PCI.
- ▶ There is no role for routine use of intravenous glycoprotein inhibitors in PCI and their use is reserved only for bailout scenarios. Cangrelor may be considered in specific settings in P2Y12-naive patients undergoing high-risk PCI.
- ▶ Patients on warfarin for atrial fibrillation do not need to stop therapy before PCI. If on direct oral anticoagulants, this should be withheld 24 hours prior to procedure (or 48 hours if on dabigatran and creatine clearance <50 mL/min).

In summary, after PCI in patients on anticoagulants, a bleeding/ischaemic/stroke risk assessment should be performed. European guidelines recommend dual therapy with clopidogrel and an OAC in high bleeding risk (IIaA). For all others, triple therapy is recommended with aspirin, clopidogrel, and an OAC for up to 1 month (IIaB) after which time aspirin is stopped. In patients at high ischaemic risk, or other anatomical/procedural characteristics and low bleeding risk triple therapy for up to 6 months can be considered (IIaB). After 12 months, antiplatelets should be stopped and oral anticoagulation continued at the dose effective for stroke prevention.

**HIGH BLEEDING RISK PATIENTS**

The treatment options for patients at high bleeding risk (figure 1) have become more focused with trials showing efficacy and safety of DES with short durations of dual antiplatelet therapy.<sup>48–50</sup> In LEADERS-FREE, the polymer free, BioFreedom stent showed superiority to its bare metal counterpart for safety and efficacy. The ONYX-ONE trial compared a polymer based zotarolimus eluting stent to the BioFreedom in high bleeding risk and was non-inferior with regard to safety and efficacy at 1 year. In SENIOR, patients >75 years (rather than specific high bleeding risk) were allocated 1 month DAPT for stable angina or 6 months if presenting with ACS. The results confirmed that DES (Synergy) and short DAPT duration was superior to BMS

with respect to all-cause mortality, MI, stroke and ischaemia-driven target lesion revascularisation. These trials, by confirming safety and efficacy of DES with short duration DAPT, have changed practice with patients at high risk of bleeding undergoing PCI now receiving DES. Nevertheless, it must be remembered that the trade-off between bleeding events and ischaemic protection of prolonging DAPT beyond 1 month in this patient subset has not been tested.

All patients should undergo radial access, where possible and receive a proton pump inhibitor (IB).

**Stable angina**

There is no evidence for pretreatment with P2Y12 agent which should be started in the laboratory (clopidogrel 300mg) once coronary anatomy is known. After PCI, clopidogrel should be continued for 1 month (IIbC). The ESC guidelines give 3 months duration (IIaB) as an option if the balance of bleeding and ischaemic risk favours the latter. The choice of anticoagulation during the procedure is heparin and the lower dose of the recommended 70–100U/kg should be used with additional doses up to the maximum 100U/kg if procedure is prolonged.

**Non ST elevation ACS and ST elevation MI**

Pretreatment and peritreatment are as for stable angina. The choice of P2Y12 agent can be extended to use of ticagrelor both in-laboratory and postprocedure.

The only randomised trial of shortened DAPT (6 months) after ACS in the high bleeding risk group (based only on age >75 years) is SENIOR. A meta-analysis of six trials<sup>51</sup> comparing 3-month and 6-month DAPT against 12 months identified those with ACS and reported a non-significant increase in the risk of MI or stent thrombosis in the 6 months arm but importantly no signal with respect to cardiac or all-cause death. With 3-month duration, ischaemic complications increased substantially leading the ESC to recommend 6-month duration of DAPT following ACS for high bleeding risk (PRECISE-DAPT  $\geq 25$  (IIaB)). However, the TWILIGHT study of contemporary practice provides evidence for safety and efficacy for ticagrelor monotherapy beyond 3 months.

In summary, stable angina patients at high bleeding risk undergoing PCI can receive DES and be safely treated with 1 month of clopidogrel. Following ACS, patients should have 6 months of clopidogrel or in high-ischaemic risk, ticagrelor. In selected cases of acute coronary syndrome where ischaemic risk is judged to be greater than bleeding risk, dual therapy with ticagrelor may be considered and aspirin stopped after 3 months.

**SUMMARY**

The cornerstone of pharmacology for patients undergoing PCI remains oral dual antiplatelet therapy. There is scant evidence for pretreatment before coronary anatomy is known. After PCI, advances in stent technology have reduced DAPT duration from 12 to 6 months in stable patients and

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1 month in high bleeding risk. In high ischaemic, low bleeding risk patients, trial evidence has led to recommendations to extend antiplatelet or low dose anticoagulant (rivaroxaban) therapy beyond 12 months. Although randomised trial evidence of optimal dose is lacking, periprocedural use of anti-coagulant therapy with UFH has extensive clinical experience and safety profile.

Advances in antithrombotic medications and carefully conducted clinical trials have improved outcomes in patients undergoing coronary intervention. Nevertheless, real world evidence<sup>52</sup> showing recurrent ischaemic events in nearly a fifth of patients with ACS gives impetus to search for even more effective pharmacological agents.

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#### REFERENCES

- 1 Yano Y, Ohmori T, Hoshida S, *et al*. Determinants of thrombin generation, fibrinolytic activity, and endothelial dysfunction in patients on dual antiplatelet therapy: involvement of factors other than platelet aggregability in Virchow's triad. *Eur Heart J* 2008;29:1729–38.
- 2 Steinhubl SR, Berger PB, Mann JT, *et al*. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411–20.
- \*3 Widimský P, Motovská Z, Simek S, *et al*. Clopidogrel pre-treatment in stable angina: for all patients > 6 h before elective coronary angiography or only for angiographically selected patients a few minutes before PCI? A randomized multicentre trial PRAGUE-8. *Eur Heart J* 2008;29:1495–503.
- 4 Bellemain-Appaix A, O'Connor SA, Silvain J, *et al*. Association of clopidogrel pretreatment with mortality, cardiovascular events, and major bleeding among patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *JAMA* 2012;308:2507–16.
- 5 Neumann F-J, Sousa-Uva M, Ahlsson A, *et al*. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019;40:87–165.
- 6 Levine GN, Bates ER, Blankenship JC, *et al*. 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.
- 7 Bhatt DL, Stone GW, Mahaffey KW, *et al*. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med* 2013;368:1303–13.
- 8 European Medicines Agency. Kengrexal. Available: <https://www.ema.europa.eu/en/medicines/human/EPAR/kengrexal>
- 9 Mehta SR, Yusuf S, Peters RJ, *et al*. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;358:527–33.
- 10 Di Sciascio G, Patti G, Pasceri V, *et al*. Effectiveness of in-laboratory high-dose clopidogrel loading versus routine pre-load in patients undergoing percutaneous coronary intervention: results of the ARMYDA-5 preload (antiplatelet therapy for reduction of myocardial damage during angioplasty) randomized trial. *J Am Coll Cardiol* 2010;56:550–7.
- 11 Stone GW, White HD, Ohman EM, *et al*. Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the acute catheterization and urgent intervention triage strategy (ACUITY) trial. *Lancet* 2007;369:907–19.
- 12 Wang TY, White JA, Tricoci P, *et al*. Upstream clopidogrel use and the efficacy and safety of early eptifibatid treatment in patients with acute coronary syndrome: an analysis from the early glycoprotein IIb/IIIa inhibition in patients with non-ST-segment elevation acute coronary syndrome (EARLY ACS) trial. *Circulation* 2011;123:722–30.
- 13 Feldman DN, Fakorede F, Minutello RM, *et al*. Efficacy of high-dose clopidogrel treatment (600 Mg) less than two hours before percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes. *Am J Cardiol* 2010;105:323–32.
- 14 Wallentin L, Becker RC, Budaj A, *et al*. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045–57.
- 15 Montalescot G, Bolognese L, Dudek D, *et al*. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *N Engl J Med* 2013;369:999–1010.
- 16 Montalescot G, Collet J-P, Ecollan P, *et al*. Effect of prasugrel pretreatment strategy in patients undergoing percutaneous coronary intervention for NSTEMI: the ACCOAST-PCI study. *J Am Coll Cardiol* 2014;64:2563–71.
- \*17 Bellemain-Appaix A, Kerneis M, O'Connor SA, *et al*. Reappraisal of thienopyridine pretreatment in patients with non-ST elevation acute coronary syndrome: a systematic review and meta-analysis. *BMJ* 2014;349:g6269.
- 18 Boersma E, Harrington RA, Moliterno DJ, *et al*. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet* 2002;359:189–98.
- 19 Giugliano RP, White JA, Bode C, *et al*. Early versus delayed, provisional eptifibatid in acute coronary syndromes. *N Engl J Med* 2009;360:2176–90.
- 20 Stone GW, McLaurin BT, Cox DA, *et al*. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;355:2203–16.
- 21 Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators, Yusuf S, Mehta SR, *et al*. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006;354:1464–76.
- \*22 Montalescot G, van 't Hof AW, Lapostolle F, *et al*. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *N Engl J Med* 2014;371:1016–27.
- 23 Wiviott SD, Trenk D, Frelinger AL, *et al*. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the prasugrel in comparison to clopidogrel for inhibition of platelet activation and Aggregation-Thrombolysis in myocardial infarction 44 trial. *Circulation* 2007;116:2923–32.

- 24 Lincoff AM, Kleiman NS, Kereiakes DJ, *et al.* Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. *JAMA* 2004;292:696–703.
- 25 Kastrati A, Neumann F-J, Mehilli J, *et al.* Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *N Engl J Med* 2008;359:688–96.
- 26 Schulz S, Mehilli J, Neumann F-J, *et al.* ISAR-REACT 3A: a study of reduced dose of unfractionated heparin in biomarker negative patients undergoing percutaneous coronary intervention. *Eur Heart J* 2010;31:2482–91.
- 27 Erlinge D, Omerovic E, Fröbert O, *et al.* Bivalirudin versus heparin monotherapy in myocardial infarction. *N Engl J Med* 2017;377:1132–42.
- \*28 Shahzad A, Kemp I, Mars C, *et al.* Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet* 2014;384:1849–58.
- \*29 Bonaca MP, Bhatt DL, Cohen M, *et al.* Long-Term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;372:1791–800.
- 30 Eikelboom JW, Connolly SJ, Bosch J, *et al.* Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;377:1319–30.
- 31 Vranckx P, Valgimigli M, Jüni P, *et al.* 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;392:940–9.
- 32 Steg PG, Bhatt DL, Simon T, *et al.* Ticagrelor in patients with stable coronary disease and diabetes. *N Engl J Med* 2019;381:1309–20.
- 33 Bhatt DL, Steg PG, Mehta SR, *et al.* Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial. *Lancet* 2019;394:1169–80.
- 34 Bhatt DL, Bonaca MP, Bansal S, *et al.* Reduction in ischemic events with ticagrelor in diabetic patients with prior myocardial infarction in PEGASUS-TIMI 54. *J Am Coll Cardiol* 2016;67:2732–40.
- 35 Dewilde WJM, Oirbans T, Verheugt FWA, *et al.* Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;381:1107–15.
- \*36 Gibson CM, Mehran R, Bode C, *et al.* Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;375:2423–34.
- 37 Cannon CP, Bhatt DL, Oldgren J, *et al.* Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med* 2017;377:1513–24.
- 38 Lopes RD, Heizer G, Aronson R, *et al.* Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med* 2019;380:1509–24.
- 39 Vranckx P, Valgimigli M, Eckardt L, *et al.* 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;394:1335–43.
- 40 Angiolillo DJ, Goodman SG, Bhatt DL, *et al.* Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American Perspective-2018 update. *Circulation* 2018;138:527–36.
- 41 Lip GYH, Collet J-P, Haude M, *et al.* 2018 joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European heart rhythm association (EHRA), European Society of cardiology Working group on thrombosis, European association of percutaneous cardiovascular interventions (EAPCI), and European association of acute cardiac care (ACCA) endorsed by the heart rhythm Society (HRS), Asia-Pacific heart rhythm Society (APHRS), Latin America heart rhythm Society (LAHRS), and cardiac arrhythmia Society of southern Africa (CASSA). *Europace* 2019;21:192–3.
- 42 Kowalewski M, Suwalski P, Raffa GM, *et al.* Meta-analysis of uninterrupted as compared to interrupted oral anticoagulation with or without bridging in patients undergoing coronary angiography with or without percutaneous coronary intervention. *Int J Cardiol* 2016;223:186–94.
- 43 Angiolillo DJ, Goodman SG, Bhatt DL, *et al.* Antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention: a North American Perspective-2016 update. *Circ Cardiovasc Interv* 2016;9:e004395.
- 44 Golwala HB, Cannon CP, Steg PG, *et al.* Safety and efficacy of dual vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of randomized clinical trials. *Eur Heart J* 2018;39:1726–35.
- 45 Mehran R, Baber U, Sharma SK, *et al.* Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med* 2019;381:2032–42.
- 46 Sarafoff N, Martischinig A, Wealer J, *et al.* Triple therapy with aspirin, prasugrel, and vitamin K antagonists in patients with drug-eluting stent implantation and an indication for oral anticoagulation. *J Am Coll Cardiol* 2013;61:2060–6.
- 47 Valgimigli M, Bueno H, Byrne RA, *et al.* 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;39:213–60.
- 48 Urban P, Meredith IT, Abizaid A, *et al.* Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N Engl J Med* 2015;373:2038–47.
- 49 Varenne O, Cook S, Sideris G, *et al.* Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. *Lancet* 2018;391:41–50.
- 50 Windecker S, Latib A, Kedhi E, *et al.* Polymer-Based or polymer-free stents in patients at high bleeding risk. *N Engl J Med* 2020;382:1208–18.
- 51 Palmerini T, Della Riva D, Benedetto U, *et al.* Three, six, or twelve months of dual antiplatelet therapy after DES implantation in patients with or without acute coronary syndromes: an individual patient data pairwise and network meta-analysis of six randomized trials and 11 473 patients. *Eur Heart J* 2017;38:ehw627–43.
- 52 Rapsomaniki E, Thuresson M, Yang E, *et al.* Using big data from health records from four countries to evaluate chronic disease outcomes: a study in 114 364 survivors of myocardial infarction. *Eur Heart J Qual Care Clin Outcomes* 2016;2:172–83.