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 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 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. The study finding was consolidated by a meta-analysis showing no benefit of clopidogrel pretreatment.

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’10 and the American Heart Association/American College of Cardiology (AHA/ACC) questioning its benefit without giving a recommendation.11 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 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 without increase in severe bleeding. Its use should be limited to high-risk patients unable to take oral medication.

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 procedural anticoagulants.

Non ST elevation acute coronary syndrome (NSTE-ACS)
Data from PCI-CURE showed benefit of pretreatment with clopidogrel and aspirin in NSTE-ACS 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 NSTE-ACS were equivocal showing no benefit of clopidogrel pretreatment. A non-randomised study of clopidogrel pretreatment (300 mg loading ≥12 hours or a ≥600 mg loading ≥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). Overall, in the setting of early invasive therapy, the evidence supporting pretreatment with clopidogrel in NSTE-ACS is limited.

Pretreatment with ticagrelor against in-laboratory treatment has not been tested. In PLATO 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.
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. The results showed no benefit...
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. The ACTION group meta-analysis also failed to show a significant mortality reduction with pretreatment with increased major bleeding. The failure of pretreatment with oral P2Y12 inhibitors in NSTE-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, 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. 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.

In summary, aspirin (loading and maintenance) carries a IA recommendation for pretreatment in NSTE-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.

With respect to antiocoagulants, 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. As a result, fondaparinux carries a class IA recommendation for pretreatment of NSTE-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).

**ST elevation myocardial infarction (STEMI)**

The only pretreatment study was ATLANTIC, 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 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.

**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. Low molecular weight heparin may be considered especially if the patient was on this preprocedural. The recommendation is to use

### Table 3 Trials of short duration DAPT

| Trial        | Year | Patient Selection | Treatment | Follow-up | Main Findings |
|--------------|------|-------------------|-----------|-----------|--------------|
| LEADERS-FREE | 2015 | ACS+stable angina | Ticagrelor | 3 months | Targets lesion revascularisation: 5.1% BioFreedom vs 9.4% BMS (P < 0.001) |
|              |      | BMS vs BioFreedom (DES) vs RESOLUTES Synergy (DES) | Ticagrelor | 3 months | Death, MI, stent thrombosis: 1.9% BMS vs 9.4% BMS (P < 0.001) |

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.
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 or superiority to bivalirudin. Overall, there is no compelling evidence for the benefit of routine use of GPI in NSTE-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-naive 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. 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 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. The primary outcome showed no significant reduction but safety was confirmed. The findings were similar in multiple tested subgroups.

In THEMIS 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.

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 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 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 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 RE-DUAL, AUGUSTUS and ENTRUST 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 <30 mL/min). For patients on VKA, this does not
need to be interrupted but US guidelines recommend a washout period before PCI using preferably, radial access when international normalised ratio (INR) ≤2 (or if femoral when INR ≤1.5).

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 NSTE-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.

**Treatment during PCI**

There are limited data to guide parenteral anti-coagulants during PCI. For patients on VKA, additional parenteral anticoagulants may not be needed if INR is >2.5 at the time of elective PCI. 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. 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.

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. 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.

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.

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.
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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. 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 risk favours the latter. The choice of anticoagulation during the procedure is heparin and the lower dose of the recommended 70–100 U/kg should be used with additional doses up to the maximum 100 U/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 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 ≥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...
1 month in high bleeding risk. In high ischaemic, low bleeding risk patients, trial evidence has led to recommendations to extend antplatelet or low-dose anticoagulant (rivaroxaban) therapy beyond 12 months. Although randomised trial evidence of optimal dose is lacking, peri-procedural 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 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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