Changing roles of anticoagulant and antiplatelet treatment during percutaneous coronary intervention

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Heart 2005;91(Suppl III):iii16–iii19. doi: 10.1136/hrt.2004.058511

In the development of percutaneous intervention, Dotter first used unfractionated heparin (UFH) alone when performing peripheral angioplasty.¹ In the 1970s Gruentzig added 1 g of aspirin (ASA) for three days in coronary angioplasty, which was started the day before the procedure.² Over the ensuing years empiric attempts were made to improve patient outcomes using dextran and dipyridamole but without success. More recently, along with ASA and UFH, direct thrombin inhibitors, low molecular weight heparin (LMWH), warfarin, fibrinolytics, thienopyridines, and platelet glycoprotein (Gp) IIb/IIIa antagonists have all been studied in efforts to reduce the thrombotic complications associated with a percutaneous coronary intervention (PCI).

Of the multiple combinations of antithrombotic agents that have been tried and tested, only several have been unequivocally proven to be beneficial in placebo controlled trials. A number of others continue to be studied or have persisted empirically. ASA, thienopyridines, UFH, LMWH, direct thrombin inhibitors, and Gp IIb/IIIa antagonists are currently the most commonly utilised antithrombotic agents. As a result of improvements in the antithrombotic regimen, in conjunction with improvements in equipment and technique, the incidence of periprocedural major adverse cardiac events (MACE) and major bleeding have continued to improve.

ANTIPLATELET THERAPY

Aspirin

Aspirin (acetylsalicylic acid, ASA) has been available for over a century yet its cardiac and vascular benefits have only been realised in the last 50 years. The benefit of ASA as antiplatelet treatment in PCI is frequently under-appreciated, but has been well established in short and long term placebo controlled studies. Schwartz showed that the addition of aspirin to heparin in PCI was associated with a 77% relative risk reduction in MACE ($p = 0.013$).³ Similarly, White showed that aspirin when combined with heparin was associated with a 75% reduction in MACE ($p < 0.001$) compared to heparin alone.⁴ A longer duration of aspirin treatment after PCI is supported by the M-Heart II study. In this case, six months of ASA treatment was associated with less reinfarction when compared with placebo (1.2% v 5.7%).⁵ Lifelong ASA treatment in PCI patients is further recommended on the basis of extrapolating from primary and secondary prevention data.

Ticlopidine

The early experience with ticlopidine alone in PCI patients is limited, but when started four days before the intervention showed similar protection from periprocedural events as did ASA.⁴ In coronary stenting, data from multiple randomised trials have convincingly proven the benefit of dual antiplatelet treatment with the combination of ASA and ticlopidine than either ASA alone or in combination with warfarin.⁶

However, ticlopidine has been noted to cause transient neutropenia in 0.4–2% of patients and thrombotic

thrombocytopenic purpura in approximately 1 in every 1500–4000 patients.⁷ Consequently, clopidogrel has essentially replaced ticlopidine in patients undergoing a PCI.

Clopidogrel

Clopidogrel has been compared to ticlopidine in only one blinded, controlled trial. In the CLASSICS trial, which was powered based on a primary safety end point, clopidogrel was better tolerated in combination with ASA compared to ticlopidine, with similar clinical efficacy.⁸ The combined results of two prospective, non-blinded but randomised trials and multiple registries, which in total included nearly 14 000 patients, also confirmed the better tolerability of clopidogrel and at least similar efficacy to ticlopidine.⁹

Early observational studies suggested that pretreatment with ticlopidine or clopidogrel was associated with a lower rate of periprocedural thrombotic events.¹⁰ Consistent with these early findings, the PCI-CURE subset analysis of the CURE trial also found a similar benefit of pretreatment. In this analysis 2658 patients underwent PCI at a median of 10 days after randomisation, having received ASA 75–325 mg and clopidogrel 300 mg followed by 75 mg daily, or matching placebo starting at the time of randomisation.¹¹ Following PCI, each patient received open label clopidogrel or ticlopidine for ~4 weeks after the procedure followed by a mean total duration of nine months of the previously assigned study medication. Pretreatment with clopidogrel was associated with a 30% relative risk reduction (44% if no open

Abbreviations: ACUTY, a randomized trial of Angiomax versus Clexane in patients undergoing early invasive management for acute coronary syndromes without ST segment elevation; ASA, acetylsalicylic acid (aspirin); BAT, bivalirudin angioplasty trial; CABG, coronary artery bypass grafting; CLASSICS, clopidogrel aspirin stent international cooperative study; CREDO, clopidogrel for the reduction of events during observation; CURE, clopidogrel in unstable angina to prevent recurrent events; EPIC, evaluation of c73 for prevention of ischemic complications; EPILOG, evaluation in PTCA to improve long term outcome with abciximab GpIIb/IIIa blockade; EPISTENT, evaluation of platelet Gp IIb/IIIa inhibitor for stenting; ESPRIT, enhanced suppression of the platelet IIb/IIIa receptor with Integrilin therapy; FANTASTIC, the full anticoagulation versus aspirin and ticlopidine; Gp, glycoprotein; ISAR REACT, intracoronary stenting and antithrombotic regimen-rapid early action for coronary treatment; JUMBO-TIMI, joint utilization of medications to block platelets optimally; LMWH, low molecular weight heparin; MACE, major adverse cardiac events; MATTIS, multicenter aspirin and ticlopidine trial after intracoronary stenting; MI, myocardial infarction; NICE, national investigators collaborating on enoxaparin; PCCURE, percutaneous coronary intervention-CURE; PCI, percutaneous coronary intervention; REPLACE, randomized evaluation in PCI linking Angiomax to reduced clinical events; STARS, stent anti-thrombotic regimen study; STEEPLE, safety and efficacy of enoxaparin in PCI patients, an international randomized evaluation; SYNERGY, superior yield of the new strategy of enoxaparin, revascularization and glycoprotein IIb/IIIa inhibitors; TARGET, do tirofiban and ReoPro give similar efficacy outcomes trial; TENACITY, tirofiban evaluation of novel dosing vs. abciximab with clopidogrel and inhibition of thrombin study; TLR, target lesion revascularisation; TVR, target vessel revascularisation; UFH, unfractionated heparin

labelled thienopyridine treatment) in 30 day cardiovascular (CV) death, MI, or urgent target vessel revascularisation (TVR) (6.4% *v* 4.5%; 95% CI 0.52 to 0.89; *p* = 0.005).

In the CREDO trial, the only prospective, blinded, randomised trial of clopidogrel treatment before PCI, a 300 mg clopidogrel loading dose started 3–24 hours before PCI was associated with only a non-significant ~19% relative risk reduction in 28 day MACE compared with the control arm that received no pretreatment and no loading dose.¹² Based on the findings of a prespecified subgroup analysis, the investigators found a strong relation between the duration of pretreatment and the clinical benefit. Pretreatment with 300 mg of clopidogrel at least 6–24 hours before PCI was associated with a 38.6% relative risk reduction in MACE at 28 days (5.8% *v* 9.4%, *p* = 0.051). Subsequent analysis has suggested that in order to achieve the benefit of a 300 mg clopidogrel loading dose, pretreatment for at least 15 hours is required. In fact an inverse relation between the duration of pretreatment and risk of death, MI, or urgent TVR was found, only in patients randomised to clopidogrel. This benefit was not significant until over 15 hours of pretreatment (odds ratio 0.73, *p* = 0.024), and the magnitude of this benefit increased with an increasing duration of pretreatment.¹³

The optimal dose of clopidogrel needed to minimise the duration of pretreatment is not yet well established, but is likely to be > 300 mg. One study has found a much faster onset, but similar final levels of ADP induced platelet inhibition with 600 mg pre-loading of clopidogrel at least two hours before PCI, compared with 2 × 500 mg loading dose of ticlopidine, or to clopidogrel 300 mg.¹⁴ The clinical value of this higher dose loading regimen was studied in the ISAR-REACT trial involving 2159 low to moderate risk patients undergoing a non-urgent PCI.¹⁵ All patients were pretreated with 600 mg of clopidogrel at least two hours before PCI and then randomised to either abciximab or matching placebo. Importantly, the addition of abciximab following the clopidogrel load did not lead to any incremental benefit in thrombotic events. Unlike the CREDO findings, subsequent analysis of ISAR-REACT suggested no time dependence of the clinical benefit of the 600 mg clopidogrel loading dose (Berger PB, presented at the 2003 Scientific Sessions of the American Heart Association), suggesting that pretreatment should be given as a 600 mg dose if time delay to anticipated PCI is less than 15–24 hours.

The optimal duration of clopidogrel treatment following a PCI is unknown, although all available data suggest that longer durations lead to greater benefit. Arbitrarily, 2–4

weeks has been routinely utilised following treatment with a bare metal stent to treat the time period of greatest risk for stent thrombosis. However, over the long term PCI patients remain at heightened risk for future thrombotic events unrelated to the treated lesion, and, therefore, ongoing treatment with clopidogrel in addition to ASA may be of benefit in decreasing these events. The CURE trial and its substudy, PCI-CURE, have both shown that combination treatment with ASA and clopidogrel for a mean of nine months is associated with a widening reduction in the occurrence of death, MI, and stroke.¹¹ In CREDO, continuing clopidogrel on top of ASA for 12 months also demonstrated a widening benefit over time, with a ~2% absolute risk reduction between 29 days and one year, but a trend towards an increase in major bleeding.¹² With drug eluting stents, at least 3–6 months of clopidogrel has been studied and should be utilised.

Glycoprotein IIb/IIIa antagonists

Gp IIb/IIIa antagonists in combination with ASA have consistently been shown to reduce MACE after PCI compared with placebo (fig 1). In pooled analysis of PCI trials comparing Gp IIb/IIIa antagonists versus placebo, there was a 35% relative risk reduction (RR) in the combined end point of death and MI at 30 days with Gp IIb/IIIa antagonists (7.9% *v* 11.6%, RR 0.65, 95% CI 0.59 to 0.72).¹⁶ Although lesion characteristics do not seem to be predictive of the benefit of a Gp IIb/IIIa antagonist,¹⁷ several serum markers of thrombosis or platelet activation (for example, troponin, plasma CD40 ligand) are able to identify subgroups of patients who do and do not benefit from the addition of a Gp IIb/IIIa antagonist.¹⁸ Diabetic patients also appear to achieve benefits significantly greater than non-diabetics, especially those being treated with a PCI in the setting of an acute coronary syndrome (ACS).¹⁹ In contrast, in patients undergoing saphenous vein graft PCI, there is little evidence to show that these patients are protected from adverse thrombotic events with the use of a Gp IIb/IIIa antagonist.²⁰

The TARGET trial is the only head-to-head study that compared Gp IIb/IIIa antagonists, and while it was designed as a non-inferiority trial, it actually demonstrated a significant 26% higher incidence of 30 day death, MI, and urgent TVR in those patients treated with tirofiban (6.0% *v* 7.6%, *p* = 0.038).²¹ It has been speculated that the dosing of tirofiban led to the inferior results. This is currently being addressed in the forthcoming TENACITY trial.

Figure 1 The effect of glycoprotein IIb/IIIa antagonists on 30 day mortality and myocardial infarction in percutaneous coronary intervention.

ANTICOAGULANTS

Unfractionated heparin

UFH was originally empirically used for the prevention of thrombotic events in patients undergoing PCI and today it remains the most widely used intravenous anticoagulant in modern PCI practice. There are several theoretical shortcomings with its use: wide variability in anticoagulant effect; its limited and uncertain bioavailability; the potential to cause platelet activation, and its inability to inhibit clot bound thrombin.²²

Low molecular weight heparin

Several small non-randomised trials have been performed using LMWH in PCI patients. The series of NICE trials provided observational data on the use of enoxaparin in PCI with or without Gp IIb/IIIa antagonists. In NICE 3, 628 patients with an ACS were treated with enoxaparin and early Gp IIb/IIIa antagonist, with 283 patients eventually undergoing a PCI. In those patients treated with a subcutaneous dose of enoxaparin within eight hours of PCI no additional anticoagulation was given, while in patients who received enoxaparin over eight hours, an additional 0.3 mg/kg of intravenous enoxaparin was given at the time of PCI. Compared with historical controls, efficacy and safety outcomes were favourable with enoxaparin.²³ Preliminary data suggest that the use of low dose intravenous enoxaparin as the primary anticoagulant in the setting of an elective PCI is both safe and efficacious.²⁴ The ongoing prospective, randomised STEEPLE trial will address the safety and efficacy of two doses of enoxaparin (0.5 mg/kg and 0.75 mg/kg) compared with UFH, with or without a Gp IIb/IIIa antagonist, in ~2700 non-urgent PCI patients.

Direct thrombin inhibitors

Although there are several direct thrombin inhibitors available, only bivalirudin has been extensively studied in the setting of modern PCI. In the REPLACE 2 trial, bivalirudin was found to be as efficacious as UFH plus a Gp IIb/IIIa antagonist but with a significantly lower bleeding risk.²⁵ REPLACE 2 was a non-inferiority trial of 6012 urgent or elective PCI patients who were randomised to UFH plus a Gp IIb/IIIa antagonist or bivalirudin with bailout Gp IIb/IIIa use only. The primary, quadruple end point (death, MI, urgent TVR, or major bleeding) at 30 days was equivalent in both arms (9.2% v 10%, $p = \text{NS}$). The role of bivalirudin, with and without a Gp IIb/IIIa antagonist, in ACS patients likely to undergo a PCI, is currently being studied in the ~13 800 patient ACUTITY trial.

Future directions

Antiplatelet treatment is constantly evolving. A new intravenous P2Y₁₂ antagonist (cangrelor) can induce greater platelet inhibition than clopidogrel and it is reversible. Clinical trials are underway and results are eagerly awaited.^{26, 27} An alternative oral thienopyridine agent (CS-747) is being evaluated in the JUMBO-TIMI 26 trial, a phase II PCI study, and these results should be available soon. A reversible, oral P2Y₁₂ antagonist, AZD-6140, is also just starting phase III studies.

Novel antithrombotic treatments include factor Xa antagonists (fondaparinux), and the oral direct thrombin inhibitor ximelagatran. Fondaparinux is currently being evaluated in PCI patients in the OASIS 5 trial.

CONCLUSION

Antiplatelet and anticoagulant treatments are essential in the management of PCI patients. Aspirin should be given to all patients and likely maintained lifelong. Currently, all PCI patients should be pretreated with clopidogrel before PCI whenever possible. Ideally, 300 mg at least 15–24 hours or

600 mg two hours before PCI is preferable. In the long term one year of clopidogrel 75 mg daily provides ongoing clinical benefit in terms of event reduction when combined with aspirin. Glycoprotein IIb/IIIa antagonists reduce adverse events in PCI patients, especially those with high risk features such as an elevated troponin value. UFH remains the most widely used antithrombotic treatment, although never formally studied, and alternative agents such as bivalirudin, which has already been shown to be more effective, and enoxaparin, currently being studied, may change this. Finally, multiple new antithrombotic agents continue to undergo testing in clinical trials and it is likely that what is currently standard of care will evolve notably over the next several years.

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