Anti-thrombotic therapy in non-ST elevation acute coronary syndrome

Title: Platelet activation and thrombin generation are implicated in the pathogenesis of acute coronary syndrome, in the development of major thrombotic complications of the condition, and in the interventional treatments to treat obstructive coronary lesions (principally, percutaneous coronary intervention). Despite treatment with aspirin and heparin there remained a clinically important risk of thrombotic complications both in hospital and following discharge. Newer anti-platelet therapies (thienopyridines and glycoprotein IIb/IIIa inhibitors) reduced platelet mediated complications, but with an increase in bleeding risk. Similarly, low molecular weight heparins reduced thrombotic complications but with a modest increase in bleeding. Newer anti-thrombins (anti Xa inhibitors and direct thrombin inhibitors) demonstrate similar or improved efficacy, but with reduced bleeding. Insufficient attention has been paid to reducing bleeding complications and recent evidence suggests that major bleeding conveys a significant increase in the risk of death. In addition, clearance of antithrombotic agents by the kidney is impaired in those with renal dysfunction, including in the elderly, and this may contribute to the risks of bleeding. In unselected populations with non-ST elevation ACS more than half the population have a creatinine clearance below 60 ml/min. Reducing the doses of anti-thrombins in patients with renal dysfunction may reduce bleeding complications. The optimal anti-thrombotic strategy in patients with non-ST elevation ACS requires the clinician to consider not only the risk of the patient for thrombotic complications, but also the hazards of bleeding. Newer anti-thrombotic agents, for the first time, offer potential benefits in bleeding risk with similar or improved efficacy.

ABSTRACT

INTRODUCTION

The term “acute coronary syndrome” describes the clinical manifestations of disruption of coronary arterial plaque complicated by intra-luminal thrombosis and distal embolization. The plaque disruption is superimposed on a variable degree of obstruction to the coronary lumen. In consequence, the spectrum of severity of the syndrome is determined by the volume of myocardium affected and the extent of ischemia and myocyte necrosis. With total or sub-total coronary occlusion the patient commonly presents with ST elevation myocardial infarction (MI) and emergency primary percutaneous intervention (PCI) is the preferred reperfusion strategy if PCI is unavailable. Thrombolytic therapy substantially improves survival and outcome. In the remaining spectrum of ACS the condition is characterized by partial obstruction of the coronary lumen (occasionally complete obstruction and well developed collaterals) and a variable degree of thrombotic occlusion. This review will focus on non-ST elevation ACS, where clear evidence supports the use of both anti-platelet and anti-thrombin therapy. Such therapies also need to be seen in the context of percutaneous or surgical revascularization.

Previously, the risks of non-ST elevation ACS have been underestimated in comparison to those surviving to hospital with ST elevation MI. A similar proportion of ST and non-ST elevation MI patients die in the first 6 months after presentation (9-12%) and approximately one in five will require emergency re-hospitalization. Thus, there is the need for anti-thrombotic therapy (in addition to secondary prevention measures) during the acute in-hospital and post-discharge phases. Recent advances in anti-thrombotic and revascularization therapies have been shown to reduce serious cardiac complications, re-hospitalizations and deaths in patients with ACS. However, these improvements in outcome require prompt and effective triage systems and consistent application of evidence-based therapies. International studies suggest that a substantial shortfall exists in the application of guideline and evidence based therapies in clinical practice.

ANTI-PLATELET THERAPY

Aspirin

Evidence for the benefit of aspirin is not new, but the evidence base is very substantial and combined analyses remain powerful and compelling. The most recent update of the Anti-Thrombotic Trialists’ Collaboration is based upon 287 studies in 135,000 patients. It demonstrates a highly significant reduction in the risk of myocardial infarction/stroke/vascular death as a result of anti-platelet therapy (principally aspirin), versus control. Overall, the event rates were 13.2% in control patients and 10.7% in those treated with anti-platelet therapy, a 22% relative risk reduction. In acute MI, and in other high risk patients, the absolute and relative risk reductions were greater: 23 per 1,000 fewer vascular deaths and 13 per 1,000 fewer MIs. Thus, abundant evidence supports the use of aspirin in patients with acute coronary syndromes. Additional anti-platelet therapy requires evidence of benefit on top of aspirin, rather than as an alternative to aspirin. For maintenance therapy, recent data suggest that bleeding risk doubles for aspirin doses above versus below 100mg daily, with no improved efficacy.

Thienopyridines (ADP antagonists)

Thienopyridines inhibit ADP mediated platelet aggregation. Initial studies were conducted with ticlopidine but this has been superseded by clopidogrel, on account of superior safety. The CURE trial tested clopidogrel in 12,562 non-ST segment elevation ACS patients on top of background treatment and aspirin. A 2.1% absolute risk reduction (20% relative risk reduction p<0.0001) occurred in the frequency of non-fatal MI, stroke or cardiovascular death. The treatment effect was evident early (within the first 24 hours of starting therapy) and the absolute benefits were greatest in the first 3 months of treatment. Nevertheless, the relative risk reduction was similar beyond 3 months. Approximately 1% more patients experienced major bleeding, but there was no significant excess of life-threatening bleeding nor hemorrhagic strokes. Nevertheless, in view of
the irreversible nature of the ADP antagonism, current guidelines suggest that clopidogrel should be withheld for 5 days prior to CABG surgery (19). In candidates for very urgent CABG a small molecule glycoprotein IIb/IIIa inhibitor (epifibatide or tirofiban) can be used prior to surgery (8).

In non-ST segment elevation ACS, the ESC and AHA/ACC guidelines recommend at least 9 and up to 12 months’ treatment with clopidogrel (8). Longer term treatment in patients with a spectrum of vascular risk was examined in the large scale CHARISMA trial (20). Overall, the results do not support long-term therapy with clopidogrel in addition to aspirin. Those with ischaemic events (MI, stroke or peripheral vascular events) appear to benefit more than patients simply at high vascular risk (3) (primary prevention) but the evidence is not sufficiently robust to form the basis of guideline recommendations. There is evidence for the use of clopidogrel in acute ST elevation myocardial infarction (treated with thrombolysis) from the CLARITY and COMMIT trials.

Thienopyridines reduce the risk of stent thrombotic occlusion and are now part of standard treatment, in combination with aspirin, in all patients undergoing elective PCI. Recent data on late stent thrombosis suggest that with drug eluting stents at least 12 months of clopidogrel and aspirin are required. With PCI in ACS there is evidence for benefit for 1 year of treatment (PCI CURE and CREDO trials) (10).

Glycoprotein IIb/IIIa receptor antagonists

The glycoprotein IIb/IIIa receptor plays a key role in platelet aggregation through linkages involving fibrinogen or von Willebrand Factor. Intravenous glycoprotein IIb/IIIa receptor antagonists have been extensively tested in patients with acute coronary syndromes and in a meta-analysis of all the major randomised trials the absolute risk reduction for death or myocardial infarction at 30 days was 1% (11.8% control versus 10.8% with GPIIb/IIIa) (11-13). The absolute treatment benefit was largest in high risk patients; in particular those with evidence of troponin release or those undergoing acute PCI. Among those without troponin elevation or without PCI no significant benefits were observed with GPIIb/IIIa administration.

The CREDO and ISAR-REACT trials have helped to resolve the question of whether clopidogrel plus glycoprotein IIb/IIIa receptor antagonists may be required in patients undergoing PCI (10-14). In CREDO about half of the patients received glycoprotein IIb/IIIa antagonists (a non-randomized subset) and two-thirds had presented with an acute coronary syndrome. The frequency of MI, stroke or death at one year was reduced with clopidogrel from 11.5% to 8.5% (p=0.02), with similar risk ratios in the presence or absence of GPIIb/IIIa inhibitors. In ISAR-REACT 2 there was additional benefit (relative risk of death, MI, revascularization = 0.75; 95% CI, 0.58-0.97; P=0.03) with abciximab treatment in the presence of background treatment of aspirin and clopidogrel (loading dose 600mg given more than 2 hours prior to PCI) (14).

In summary, aspirin provides clear evidence of benefit in patients with acute coronary syndromes and robust evidence supports the use of clopidogrel in patients presenting with non-ST elevation ACS (at least up to 9-12 months). Extensive evidence supports the use of intravenous glycoprotein IIb/IIIa inhibitors in high risk patients with ACS, especially those in whom the troponin level is elevated and/or who are to undergo acute PCI (12,13).

ANTI-THROMBIN THERAPY

Thrombin is critical in the generation of fibrin and it is also a potent stimulator of platelet activation. Thrombin activation promotes monocyte chemotaxis, mitogenesis, increased permeability of the vascular wall and secretion of cytokines and growth factors from smooth muscle cells. Thus thrombin inhibition should not be seen in isolation. Effective anti-thrombotic treatment requires inhibition of platelet function and inhibition of thrombin (1).

Unfractionated heparin (UFH) and low molecular weight heparin (LMWH)

Although unfractionated heparin has been used extensively in ACS it suffers from practical difficulties in maintaining anti-thrombin activity within the therapeutic range (influenced by acute phase proteins and the binding to anti-thrombins). In many settings it has been replaced by LMWH. There is clear evidence that a form of heparin (either unfractionated or LMWH), is superior to placebo in patients with ACS (8,15,16). The meta-analysis of trials of UFH-LMWH versus control demonstrates a reduction in absolute rates of death or MI from 7.4% to 4.5% (odds ratio 0.53, 95% CI 0.38-0.73) (17). The meta-analysis of all the trials of LMWH versus unfractionated heparin has demonstrated a modest but significant advantage in death or myocardial infarction (odds ratio 0.91 95% CI 0.83-0.99) (18,19). Heterogeneity exists among the low molecular weight heparins and a meta-analysis of the two trials of enoxaparin (ESSENCE and TIMI 11B) has demonstrated a significant reduction in death or myocardial infarction compared with unfractionated heparin (odds ratio 0.82, 95% CI 0.69-0.97). However, these trials pre-dated modern interventional therapy and thienopyridine antagonists. Regarding safety, the combined analysis of LMWH versus UFH suggests a similar safety profile for LMWH and unfractionated heparin in the presence or absence of glycoprotein IIb/IIIa inhibitors (major bleeds: 3.9% LMWH vs 3.7% UFH, odds ratio 1.1, 95% CI 0.96-1.13) (16). SYNERGY was a large-scale trial testing enoxaparin versus UFH in the context of intervention (20). Overall, there was no significant advantage for enoxaparin (similar efficacy) but a modest increase in bleeding. The study strongly suggested that bleeding hazards were greater in those switching from enoxaparin to UFH for catheterization (perhaps due to the combined effect of both anti-thrombins). The risks of bleeding were lower if the patient continued on the same anti-thrombin (20).

Direct thrombin inhibitors

Direct anti-thrombins may provide advantages over the indirect inhibitors (unfractionated and low molecular weight heparin). In earlier trials in ACS patients there was no clear benefit for the direct thrombin inhibitors.GUSTO
In the phase III OASIS-5 study (24), 20,078 patients with NSTE-ACS were randomized to receive subcutaneous fondaparinux (2.5 mg daily), versus enoxaparin (1 mg/kg twice daily) for up to 9 days (average 5.3 days). The primary outcome of death, myocardial infarction or refractory ischaemia at 9 days was very similar (5.7% enoxaparin vs. 5.8% fondaparinux; HR 1.01, 95% CI 0.90-1.13). This satisfied the criteria for noninferiority (24). However, major bleeds were halved with fondaparinux (2.2% fondaparinux vs. 4.1% enoxaparin, HR 0.52, 95% CI 0.44-0.61, p<0.001), and the composite outcome of death, myocardial infarction, refractory ischaemia or major bleeding also favoured fondaparinux, 7.3% compared to 9.0% with enoxaparin (HR 0.81, 95% CI 0.73-0.89, p<0.001) (24). Major bleeding was an independent predictor of death, which was lower with fondaparinux at 30 days (2.9% vs. 3.5%, HR 0.83, 95% CI 0.71-0.97, p=0.02), and at 6 months (5.8% vs. 6.5%, HR 0.89, 95% CI 0.80-1.00, p=0.05). The composite outcome of death, MI or stroke was significantly lower with fondaparinux at 6 months: 11.3% vs. 12.5%, HR 0.89, 95% CI 0.82-0.97, p=0.007 (24).

**ANTI-THEMBOBOTIC THERAPY FOR PCI PROCEDURES IN ACS**

Platelet inhibition with aspirin and systemic anticoagulation with unfractionated heparin (UFH) has been the reference standard for PCI since this therapy was first applied (27). In order to reduce the PCI-related thrombotic complications, this treatment is combined with clopidogrel and GP IIb/IIIa inhibitors. The current guideline recommendation, based only on empiric evidence, is to give UFH as an iv bolus of 100 IU/kg or about 50-60 IU/kg if GP IIb/IIIa inhibitors are used (27). The efficacy of UFH is monitored by activated clotting time (ACT). However, the relation between ACT values with a given bolus of UFH and the rate of clinical events remains uncertain; in consequence the real utility of ACT monitoring remains undetermined.

Direct thrombin inhibition with bivalirudin and GP IIb/IIIa inhibitors has been shown to be at least as effective but with a lower risk of bleeding compared with UFH/LMWH plus GP IIb/IIIa inhibitors (28-29).
Low MW heparins have been used in the setting of PCI, and of these most of the evidence has been obtained with enoxaparin. Previously, due to a lack of clinical studies, patients on LMWH were either switched to UFH, or UFH was added on top of enoxaparin before going to the cathlab. More recent data have shown that no additional UFH is needed if PCI is carried out within 6 to 8 hours following the last subcutaneous injection of enoxaparin (31). After 6-8 hours following the last injection of enoxaparin, an additional 0.3 mg/kg iv bolus of enoxaparin is recommended.

The SYNERGY trial tested enoxaparin (1mg/kg twice daily) or UFH in double blind design in 4,687 NSTE-ACS patients undergoing PCI. It demonstrated similar efficacy in both groups, but with a higher risk of bleeding associated with post-randomization crossover from one anti-thrombotic agent to another (20). In the STEEPLE trial enoxaparin was used at reduced doses of 0.5mg/kg or 0.75mg/kg iv bolus, in comparison with standard iv doses of UFH, in 3,258 patients undergoing elective PCI (31). A significant reduction in the primary endpoint was observed in the 0.5mg/kg of enoxaparin (5.9% vs. 8.5% UFH, odds ratio 0.69, 95%CI -0.7 to -0.6, p=0.01), while the 0.75mg/kg arm was non-inferior to UFH (6.5% vs. 8.5% UFH, odds ratio 0.76 95%CI -0.1 to 0.0, p=0.051). There was a reduction in major bleeding, which was significant in both enoxaparin arms, as compared to the UFH arm, but there was no significant difference in the rate of bleeding complications in patients who received GP IIb/IIIa inhibitors (31). The rate of ischaemic events (death and MI) was not significantly different between the two groups, but the STEEPLE trial had insufficient power to reliably detect a difference in efficacy.

Fondaparinux, the anti-Xa inhibitor, was tested in the setting of PCI in ASPIRE, and in a subset of OASIS 5 and OASIS 6 (24-26). In OASIS 5, there was a trend towards a higher rate of PCI-related coronary complications in the fondaparinux group, (9.5% fondaparinux versus 8.8% enoxaparin, OR 1.11 [0.94-1.29], p=0.21), but without a significant impact on the rate of ischaemic events at 9 and 30 days. There was a significantly lower rate of vascular access site complications (3.3% fondaparinux vs. 8.1% enoxaparin, RR 0.41 [0.33-0.51], p<0.001), and a significantly lower rate of bleeding complications with fondaparinux as compared to enoxaparin (2.2% vs. 4.1%, RR 0.52 [0.44-0.61], p<0.001 at 9 days and 3.1% vs. 5.0%, RR 0.62 [0.54-0.72], p<0.001 at 30 days). However, a higher rate of catheter-related thrombi was observed with fondaparinux compared as with enoxaparin (0.9% vs. 0.4%, RR 3.6 [1.6-7.8], p=0.001). This higher rate of catheter thrombosis was also observed in the setting of primary PCI in STEMI in the OASIS-6 study (32). However, the frequency of catheter-related thrombus was reduced in OASIS-5 and eliminated in OASIS-6 by the administration of UFH prior to or during PCI. Pragmatically, a standard dose of UFH is recommended on top of fondaparinux, if fondaparinux is used as the anti-thrombin prior to PCI.

**BLEEDING IN ACUTE CORONARY SYNDROME**

Although bleeding is recorded as the most common complication of therapy in ACS, the significance of bleeding has not been fully appreciated. In addition, several different definitions have been used in clinical trials to grade bleeding severity. For example, the terms “severe, life-threatening, major or minor”, have different qualifying criteria in trials using TIMI, GUSTO or OASIS definitions (26,33). In consequence, the frequency of bleeding is difficult to compare across studies.

Nevertheless, the frequency of major bleeding ranges from 2% to 8% across the spectrum of acute coronary syndromes (ACS) depending on the frequency of invasive procedures and on the anti-thrombotic and anti-platelet therapy (20,34,35). Data from registries generally reflect a population at higher risk and with greater comorbidity than that seen in clinical trials. In the CRUSADE registry conducted in the US, blood transfusion used as a surrogate marker of major bleeding and transfusion was performed in more than 15% of patients (36). In the multinational GRACE registry the overall incidence of major bleeding was 3.9% in patients with ST-segment elevation myocardial infarction (STEMI) and 4.7% in patients with non-ST segment elevation acute coronary syndromes (NSTE-ACS), and 2.3% in patients with unstable angina (27).

**Is it possible to predict the risk of bleeding in ACS?**

Similar predictors of bleeding were identified in the CRUSADE and GRACE registries (37,38). Independent predictors of major bleeding were advanced age (odds ratio (OR) 1.22 per 10-year increase, p=0.0002), female sex (OR 1.36, p=0.0116), history of bleeding (OR 2.18, p=0.014), percutaneous coronary intervention (OR 1.63, p=0.005), history of renal insufficiency (OR 1.53, p=0.0062), use of IIb/IIIa inhibitors (OR 1.86, p=0.0001) (Table 1) (37). Excessive doses of drugs, especially in elderly patients or those suffering from renal failure, may also lead to an increased risk of bleeding (38). These risk factors have been confirmed in other reports, and are detailed in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR</th>
<th>95%CI</th>
<th>P-value</th>
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<tr>
<td>Age (per 10-year increase)</td>
<td>1.22</td>
<td>1.10-1.35</td>
<td>0.0002</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.36</td>
<td>1.07-1.73</td>
<td>0.0116</td>
</tr>
<tr>
<td>History of renal insufficiency</td>
<td>1.53</td>
<td>1.13-2.08</td>
<td>0.0062</td>
</tr>
<tr>
<td>History of bleeding</td>
<td>2.18</td>
<td>1.14-4.08</td>
<td>0.014</td>
</tr>
<tr>
<td>Mean arterial pressure 1.14</td>
<td>1.02-1.27</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>(per 20mmHg decrease)</td>
<td></td>
<td></td>
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<tr>
<td>Diuretics</td>
<td>1.91</td>
<td>1.46-2.49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LMWH only</td>
<td>0.68</td>
<td>0.50-0.92</td>
<td>0.012</td>
</tr>
<tr>
<td>LMWH and UFH</td>
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<td>0.52-0.98</td>
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<td>GP IIb/IIIa blockers only</td>
<td>1.86</td>
<td>1.43-2.41</td>
<td>&lt;0.0001</td>
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<tr>
<td>Thrombolitics and GP IIb/IIIa blockers</td>
<td>4.19</td>
<td>1.68-10.4</td>
<td>0.002</td>
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<td>IV nitroglyceric agents</td>
<td>1.88</td>
<td>1.35-2.62</td>
<td>0.0002</td>
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<tr>
<td>Right-heart catheterisation</td>
<td>2.01</td>
<td>1.38-2.91</td>
<td>0.0003</td>
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</table>

Hosmer-Lemeshow goodness of fit test P-value=0.70; C-statistic =0.73.
including those from clinical trials. The critical role of renal dysfunction was
confirmed in the OASIS-5 and ExTRACT studies, with the risk of major
bleeding independently linked to the severity of renal dysfunction (9). It is
remarkable that a steep increase in bleeding risk is observed for moderate
to mild levels of renal dysfunction. In OASIS-5, as in the GRACE registry, an
increase in bleeding was observed with only mild impairment of creatinine
clearance (CrCl 80 ml/min). The risk is much higher for creatinine clearance
between 30 and 60 ml/min and higher still for severe renal dysfunction
(CrCl <30 ml/min). Future trials are needed to define the appropriate dose
of anti-thrombotic agents in the context of mild to moderate renal
dysfunction.

The impact of bleeding on prognosis
Evidence from trials and registries demonstrates that major bleeding has a
powerful impact on prognosis. In the GRACE registry, major bleeding predicted
an increased risk of hospital death, with an odds ratio of 1.64
(1.18-2.28, p<0.001) (37). From a large meta-analysis of registries and trials,
including more than 30,000 patients, major bleeding is associated with a
fourfold increase in risk of death, a fivefold increase in risk of recurrent MI
and a threefold increase in risk of stroke at 30 days (5,37,40). Pooled data from
four multicentre randomized clinical trials of patients with ACS, (26,452
patients), demonstrated a stepwise increase of the risk for death depending
on the severity of bleeding (from mild, moderate to severe, using the
GUSTO scale).

The hazard ratios for death at one month were 1.6, 2.7 and 10.6 for mild,
moderate and severe bleeding respectively, and at 6 months 1.4, 2.1 and 7.5
respectively (41). Beyond 30 days, the risks of bleeding are lower, but are still
present, as modern treatment of NSTE-ACS includes the use of dual
anti-platelet therapy for 9 to 12 months (59). A similar impact on prognosis
has been demonstrated for both procedure-related and non-procedure-
related bleeding (41).

The mechanisms of the increase in mortality after bleeding have not been
fully defined. Several factors contribute to the worse outcome associated
with bleeding. The direct haemodynamic complications and immediate
complications of bleeding only contribute part of the risk. Indirect effects,
including the impact on renal function and potential deleterious effect of
transfusion, may contribute to the mortality risk. In addition, bleeding
triggers a pro-thrombotic and pro-inflammatory state. A key component
of the risk may be the consequence of discontinuation of anti-platelet and
anti-thrombotic therapy, leading to activation of the thrombotic cascade
and ischaemic complications.

CONCLUSIONS
Pharmacologic and interventional therapy of acute coronary syndrome has
changed markedly over the past decade. Evidence from large-scale
randomized trials supports the use of dual anti-platelet therapy (aspirin
plus thienopyridine) across the spectrum of ACS, and triple therapy (with
glycoprotein IIb/IIIa inhibitors) in higher risk patients, especially in the context
of PCI. Unfractionated heparin has been the reference standard anti-
thrombin therapy, but recent trial evidence has demonstrated that greater
benefit is derived from newer anti-thrombotic therapy (low MW heparin,
anti-Xa inhibitors, direct anti-thrombins). The OASIS 5 trial demonstrated
improved outcome with fondaparinux (lower bleeding and mortality) in
non-ST elevation ACS patients compared with enoxaparin and OASIS 6
demonstrated improved outcome compared with control (unfractionated
heparin or no heparin) in ST elevation ACS. The optimal balance of efficacy
and safety (predominantly bleeding risk) is critical in improving patient
outcomes. Newer anti-thrombotic therapy (for example fondaparinux,
bivalirudin) produce less bleeding. Tailoring therapy to the individual
patient’s risks and potential benefits is critical.

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