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Review of antithrombotic therapy for percutaneous coronary interventions

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Abstract

Antithrombotic therapy is a cornerstone in the management of acute coronary syndromes and plays a major role during percutaneous coronary interventions. Numerous antithrombotic agents are currently available, showing synergistic effects in combination. In considering the physiological basis of thrombosis, platelets and coagulation are seen as interdependent and cannot be dissociated in therapeutic strategies. Nevertheless, new antithrombotic agents and new protocols are emerging.

The use of potent antithrombotic agents may be associated with increased bleeding complications and additional costs. With this in mind, recommendations and expert consensus documents aim to help interventionists in clinical practice. Currently, dual antiplatelet therapy with aspirin and clopidogrel is the standard treatment after stenting, although development of direct thrombin inhibitors may soon change anticoagulation practices. Indications for intravenous GP IIb-IIIa antagonists need to be redefined according to current management of acute coronary syndromes and reliable tests are needed for the monitoring of antiplatelet activity. Insufficient platelet inhibition with standard therapy should be discussed when subacute stent thrombosis occurs. In addition to technological advances with newer devices, further studies must continue to assess antithrombotic strategies in terms of protective effects and bleeding risks.

Introduction

Percutaneous coronary intervention (PCI) with stent implantation needs appropriate antithrombotic therapy. Thrombosis may influence outcome after PCI, a

procedure that produces vessel injury and induces thrombin generation and platelet activation with intertwined pathways. Numerous antithrombotic agents are currently available (Tables 1 and 2).

Table 1. Current antithrombotic agents for PCI

Heparins

- unfractionated heparin
- low molecular weight heparins

Direct thrombin inhibitors

- bivalirudin

Aspirin

Thienopyridines

- ticlopidine
- clopidogrel

GP IIb-IIIa inhibitors

- abciximab
- eptifibatide
- tirofiban

Guidelines and expert consensus documents aim to help interventionists to weigh up the benefits and risks of procedures.^{1,2} Newer antithrombotic agents are emerging as an alternative to conventional treatments; however, data supporting their use are still limited. Recommendations issued by different organizations are not homogeneous and do not cover all subjects. In addition, burdens and costs of treatments may influence the operator's choices. Finally, individual variability of response to antiplatelet therapy is a recurrent question. This paper summarizes recent recommendations of antithrombotic therapy for PCI and discusses some debated points.

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Table 2. Doses of antithrombotic agents during PCI

Agent	Administration route	Doses and length of treatment
UFH	intravenous	50 to 100 UI/kg bolus
LMWH	subcutaneous ± intravenous	1 mg/kg subcutaneous twice daily ± 0.3 mg/kg bolus
Bivalirudin	intravenous	0.75 mg/kg bolus + an infusion of 1.75 mg/kg/h during PCI
Aspirin	orally	75 to 325 mg prior to PCI following by 75 to 100 mg/day
Clopidogrel	orally	300 to 600 mg prior to PCI following by 75 mg/day
Abciximab	intravenous	0.25 mg/kg bolus + a 12-h infusion of 0.125 µg/kg/mn (10 µg/mn max)
Eptifibatide	intravenous	180 µg/kg double bolus 10 mn apart + a 24-h infusion of 2 µg/kg/mn
Tirofiban	intravenous	0.4 µg /kg/mn (30 mn) + a 24-h infusion of 0.10 µg/kg/mn

LMWH: low-molecular-weight heparins, PCI: percutaneous coronary interventions, UFH: unfractionated heparin.

Trends in the evolution of antithrombotic therapy for PCI

With the progressive introduction of stents, the need for less aggressive anticoagulation has emerged.³ Increased use of stents, as well as decreased use of anticoagulation, has been associated with reduced rates of ischaemic and bleeding complications. More recently, a clear benefit of early revascularisation and aggressive antiplatelet therapy has been demonstrated for high-risk patients who should be identified. Risk markers of NSTEMI-ACS (non-ST-elevation acute coronary syndromes) recognised in ESC guidelines⁴ are listed in Table 3.

Recommendations

Strong clinical recommendations (i.e. evidence that a treatment is beneficial with data derived from multiple randomized clinical trials) are few in number. Recent ESC recommendations on antithrombotic therapy during PCI are summarized in Table 4 and show some differences from the ACCP recommendations.¹² Experts recommend against intra-coronary fibrinolytic agents during PCI, ticlopidine beyond 14 days after stenting, and prolonged heparin infusion after PCI.

Table 3. Characteristics for risk stratification of patients with NSTEMI-ACS²

- Recurrent resting pain
- ST-segment depression ≥ 0.1 mV or transient (< 30 min) ST-segment elevation ≥ 0.1 mV
- Elevated Troponin or CK-MB levels
- Haemodynamic instability
- Ventricular tachycardia, ventricular fibrillation
- Early post-infarction unstable angina
- Diabetes mellitus
- Age > 65 years
- History of known coronary artery disease
- Congestive heart failure
- Elevated CRP or fibrinogen levels
- Elevated BNP levels
- Renal insufficiency

Aspirin

Studies showing a significant reduction of major vascular events with aspirin were generally performed before the widespread use of PCI. These results have been extrapolated to PCI for which aspirin is considered as the cornerstone of antiplatelet therapy. A daily dose

Table 4. Recommendations (ESC guidelines) for antithrombotic therapy during PCI²

Drug	Recommendations in PCI	Level of evidence
UFH	All PCI	Class I C
LMWH	Not recommended	
Bivalirudin	Replaces UFH to reduce bleeding Replaces UFH if HIT	Class IIa C Class I C
Aspirin	Stable angina NSTEMI-ACS STEMI	Class I B Class I C Class I B
Clopidogrel	Pretreatment with 300 mg After bare metal stent (one month) After drug eluting stent (6–12 months)	Class I C Class I A Class I C
Abciximab	High-risk NSTEMI-ACS patients Primary PCI in STEMI	Class I C Class IIa A
Eptifibatide	High-risk NSTEMI-ACS patients	Class I C
Tirofiban	High-risk NSTEMI-ACS patients	Class I C

ACS: acute coronary syndromes, HIT: heparin-induced thrombocytopenia, LMWH: low-molecular-weight heparins, PCI: percutaneous coronary interventions, UFH: unfractionated heparin.

Classes of recommendations

Class I	Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful and effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion

Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

in the range of 75–100 mg is sufficient in association with a thienopyridine,⁵ while higher doses are associated with increase in bleeding complications without supplementary protective effect.

Thienopyridines

By acting on different platelet proteins (COX-1, ADP receptor P2Y₁₂), aspirin and thienopyridines have synergistic effects for platelet inhibition.⁵ This dual antiplatelet therapy has become the standard of care following stent placement.^{6,7} Clopidogrel seems to be at

least as effective as ticlopidine with fewer side-effects.⁸ Consequently, ticlopidine is no longer used in most countries.

Anticoagulation during PCI

PCI without anticoagulation appears unrealistic. However, there are few controlled trials specifically addressing the use of heparin during PCI. The optimal dose of unfractionated heparin (UFH), the most commonly used anticoagulant during PCI, remains unknown⁹ – weight-adjusted low doses appear at least

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as safe as fixed high doses.¹⁰ At the start of PCI, a 50–100 UI/kg bolus of UFH is now recommended. If GP IIb-IIIa inhibitors are given, use of low doses of UFH (50–70 UI/kg) limits bleeding complications.¹¹ During PCI, the objectives of anticoagulation may differ: treatment of ACS and prevention in clot formation on materials do not necessarily require a similar inhibition of coagulation factors IIa and Xa.

Unfractionated heparin versus low-molecular-weight heparins (LMWH)

Use of the same anticoagulant agent seems judicious for NSTEMI-ACS undergoing PCI. The superiority of LMWH over UFH is clear for ACS.¹² The most recent guidelines do not suggest that LMWH may supplant UFH in PCI.¹² Registries generally reported a trend towards increased bleeding complications with LMWH in comparison with UFH.¹³ If PCI is performed within 8 hours of the last subcutaneous injection of LMWH, no further anticoagulation is needed.¹⁴ Yet, despite its limitations, UFH remains the standard heparin therapy during PCI.

Monitoring of anticoagulation activity

The activated clotting time (ACT) is easily measured in the cath lab and gives a global assessment of the level of anticoagulation for UFH and bivalirudin. With UFH regimen, target ACT values in the range of 250–350 s or 200–250 s (if GP IIb-IIIa antagonists are given), are advocated during PCI.¹ The monitoring of UFH activity by ACT is not systematic if weight-adjusted doses are used. The fact that subcutaneous LMWH slightly modifies the ACT is an issue for the monitoring of anticoagulation activity.⁹ On the other hand, ACT may measure anticoagulation activity of LMWH following intravenous administration.¹⁵

Use of intravenous GP IIb-IIIa inhibitors

Based on the results of controlled trials, upstream use of GP IIb-IIIa inhibitors is recommended prior to PCI in moderate-to-high-risk patients with NSTEMI-ACS.^{4,5} Currently, these agents are often started in the cath

lab once the coronary anatomy is known and PCI is planned. The burdens and costs of these agents may explain this practice and a multinational registry showed a relatively infrequent use of GP IIb-IIIa inhibitors in the real world.¹⁶ Recommendations for GP IIb-IIIa inhibitors are often derived from non PCI-trials and the position of these agents needs to be redefined using contemporary studies (i.e. planned PCI with stenting in all patients).

New direct thrombin inhibitors

Thrombin, a key modulator of haemostasis, is a potent activator of platelets while bivalirudin, a direct thrombin inhibitor with a short half-life, has shown encouraging results compared with UFH during PCI in terms of bleeding reduction. However, the heparin regimen in the control group was aggressive compared with current practices.¹⁷ More recently, the investigators of REPLACE-2 described similar antithrombotic effects with bivalirudin when compared with heparin in combination with GP IIb-IIIa antagonists during PCI.¹⁸ In addition, bivalirudin appears useful in patients with heparin-induced thrombocytopenia.

Pretreatment with thienopyridines

A loading dose of 300 mg clopidogrel is recommended before PCI,¹⁹ although such a pretreatment within 3 hours may not be sufficient. A higher initial dose of 600 mg establishes a greater level of platelet inhibition²⁰ and can protect against myocardial injury in patients undergoing PCI.²¹ It is currently recommended that clopidogrel be administered as soon as possible in patients with NSTEMI-ACS. The results from NSTEMI-ACS may be extrapolated to ST-elevation myocardial infarction (STEMI). Immediate administration of clopidogrel (300 mg) appears more effective (CLARITY-TIMI 28 study), as an adjunctive reperfusion therapy when combined with fibrinolytics.²²

Monitoring of antiplatelet activity

Numerous methods using flow cytometry or platelet aggregometry are available for evaluation of biological

efficiency of antiplatelet regimens. These might prove helpful for monitoring efficacy of the treatment, but there are not currently routinely recommended due to the lack of standardization. In addition, specialised laboratories are usually required. However, these tests have shown important individual variability in the degree of platelet inhibition induced by antiplatelet therapy leading to the concept of 'aspirin or clopidogrel resistance'. One-third of patients treated by clopidogrel appeared to be 'unprotected'.²³ Several mechanisms have been suggested for this observation e.g. higher platelet activity, variability in absorption or metabolism, polymorphism of the P2Y₁₂ platelet receptor.

Hypersensitivity to aspirin

A diagnosis of hypersensitivity to aspirin usually implies complete exclusion of the molecule. Rapid aspirin desensitization has been tested recently with a high rate of success observed in patients with a history of allergy to aspirin.²⁴ Most of the patients underwent uneventful coronary stenting under dual antiplatelet therapy.

Antithrombotic therapy during primary PCI in patients with STEMI

Aspirin (160–325 mg), UFH (50–70 UI/kg), and clopidogrel (600 mg) should be administered as soon as possible. The use of GP IIb-IIIa inhibitors during primary PCI in patients with STEMI remains under debate. Abciximab has been well investigated with some significant results^{25,26} and pre-hospital treatment seems logical in this setting.

Facilitated PCI during STEMI

Facilitated PCI is defined as planned intervention within 12 hours following the onset of symptoms and soon after the administration of potent antithrombotic agents (fibrinolytic agents and GPIIb-IIIa inhibitors) alone or in association. So far, there is no evidence for the recommendation of facilitated PCI. However, the results of ongoing trials (FINESSE, ASSENT-4) may change the current indications.

PCI after thrombolysis

If thrombolysis is preferred in patients with STEMI, it should not be considered as the final treatment. Rescue PCI after failed thrombolysis appears superior to conservative treatment.²⁷ ESC guidelines recommend routine coronary angiography and – if needed – PCI early (< 24 hours) post thrombolysis.² Adequate regimens are still to be defined in this setting where too low or too high a degree of anticoagulation may increase the risks of thrombotic and bleeding complications.

Effects of contrast media on coagulation

Contrast media have anticoagulant properties of varying intensity, depending on their chemical structure. *In vitro* anticoagulant effects are more marked with ionic agents.²⁸ However, large multicentre randomised trials showed that non-ionic contrast media do not increase the risk of thromboembolic complications.^{29,30}

Costs of antithrombotic therapy during PCI

Interventionists must take the cost and cost-effectiveness of antithrombotic treatments into consideration, including possible additional costs resulting from any bleeding complications.³¹ Increased use of the radial approach and development of arterial closure devices has led to minimized risks of bleeding at the access site. Economic evaluations can provide substantial information supporting the choices between agents with similar clinical impact.

Antithrombotic therapy and sheath removal

Use of low doses of heparin represents a major advance in the last decade for the management of femoral vascular access following PCI with stent placement. Late sheath removal is associated with a higher rate of bleeding and vascular events.³² Less aggressive anticoagulation allows early and even immediate sheath withdrawal after PCI performed via the femoral route.³³

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Stent thrombosis

Despite the use of dual antiplatelet therapy and better interventional techniques optimising stent implantation, stent thrombosis has not been abolished (~1%). The one-month incidence of subacute stent thrombosis appears similar following the use of bare-metal stents and drug-eluting stents in the real world.³⁴ Biological variations in the response to antiplatelet therapy are potential causes of subacute stent thrombosis. An increased platelet reactivity, which cannot be overcome by ordinary antiplatelet therapy, has been described in patients who suffered subacute stent thrombosis.³⁵

Non-responders to antiplatelet treatment

The strategy for patients with insufficient platelet inhibition with standard therapy remains unclear. An increase in doses of clopidogrel (150 mg daily) or use of another thienopyridine (ticlopidine) is the general practice. An association between inadequate platelet inhibition *ex vivo* and the risks of thrombotic complications has yet to be demonstrated. Prasugrel, a new molecule of the thienopyridine family currently undergoing a Phase III clinical trial (TRITON-TIMI-38),

seems more effective *in vitro* at inhibiting platelet aggregation than clopidogrel.³⁶

Conclusion

As well as the meticulous intravascular techniques necessary to minimize thromboembolic events, an effective and safe antithrombotic therapy is needed during PCI. Understanding of the roles of coagulation and platelets in the complex process of thrombosis has only evolved recently. Data supporting superior benefits of new antithrombotic agents in the setting of PCI may soon change the practices of interventionists. Moreover, new management of ACS with earlier PCI leads to the redefinition of most antithrombotic strategies.

The issue of non-responders to standard antiplatelet therapy has probably been underestimated: simple and reliable tests are needed to identify patients insufficiently protected by antiplatelet therapy. In the future, economic implications of ischaemic and bleeding complications will guide the choice of antithrombotic treatments for PCI. However, the implementation of guidelines in antithrombotic therapy for PCI have yet to be evaluated by contemporary surveys.

Key Learning

- PCI needs adequate antithrombotic therapy to limit thrombin generation and platelet activation
- Recently published recommendations on antithrombotic strategies during PCI are not homogeneous
- During PCI, use of LMWH remains debated and direct thrombin inhibitors are emerging
- Synergistic action of aspirin and thienopyridines has proved its efficiency after stent implantation
- Use of GP IIb-IIIa inhibitors in the real world conflicts with current recommendations
- Biological evaluation shows a large inter-individual variability in response to standard antiplatelet therapy
- Abolition of subacute stent thrombosis remains a major challenge
- Some antithrombotic strategies should be redefined using contemporary practices
- Cost and cost-effectiveness of antithrombotic treatments will guide the interventionist's choices during PCI

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