EuroIntervention

Rationale and use of antiplatelet and antithrombotic drugs during cardiovascular interventions

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Introduction

Recent European Society of Cardiology (ESC) Guidelines have extensively investigated antithrombotic therapy during percutaneous coronary interventions (PCI)[1-3]. However, based on their complexity and partial difference from existing ACC/AHA guidelines, it is sometimes difficult to follow them in individual decisions. Moreover, most of the recommendations are based on prospective randomised trials, which only partially reflect the "real world" situation. Meta-analyses and guideline-based registries might help to guide daily practice. With respect to cardiovascular interventions the combination of both anticoagulant and antiplatelet therapies is mandatory to prevent thrombosis, because activation of both platelets and the coagulation system contribute to thrombus formation. The choice, initiation and duration of antithrombotic strategies is based on the clinical setting (elective, acute or urgent intervention). To optimise efficacy of therapy and reduce the potential bleeding hazard both, ischaemic and bleeding risks, have to be evaluated on an individual basis. The present report aims to give practical solutions to handle antithrombotic therapy for patients undergoing PCI in various clinical conditions.

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Elective percutaneous coronary intervention

a) Antiplatelet therapy	Aspirin 250 mg bolus i.v. followed by 75 to 100 mg p.o. daily for all patients[1]	
	Clopidogrel 300 [600] mg loading dose followed by 75 mg daily for all patients[1]	*– A 600 mg clopidogrel loading dose should be used according to its benefit in term of platelet inhibition over the 300 mg standard dose, even if this is given >6h before PCI[4].* *– Some have suggested the use of a higher maintenance dose (150 mg)[5] in patients with high thrombotic risk (e.g. in diabetics, patients after recurrent infarction, after early and late stent thrombosis or with complex lesions). However, this approach has not been yet validated in prospective randomized trial, which are currently ongoing.*
	GP IIb/IIIa-Inhibitors: Only in "bail-out"-situations (thrombus, no reflow, vessel closure, very complex lesions)[1].	*Recent trials could not demonstrate any additional benefit of GP IIb/IIIa-inhibitors after a clopidogrel loading dose of 600 mg[6,7].*
b) Anticoagulation	UFH is currently the gold standard antithrombotic medication: 70-100 IU/kg i.v. bolus without GP IIb/IIIa-inhibitors, only 50-70 IU/kg with GP IIb/IIIa-inhibitors[1].	*The recent STEEPLE trial has suggested a benefit of enoxaparin (0.75 mg/kg i.v. bolus) over UFH with regard to a reduced bleeding hazard[8].*

Non ST elevation acute coronary syndrome (NSTE-ACS)

See also: Algorithm of NSTE ACS management (Figure 1)

To find the optimal strategy the risk of ischaemic events and the bleeding risk of an individual patient have to be weighed against each other. Thereby, easy to use variables or scores should be preferred.

ASSESSMENT OF PATIENT RISK:

– Higher ischaemic risk:

ST-segment changes, elevated troponin, diabetes, GRACE score >108[9]

– Higher bleeding risk:

Female, >75 years, bleeding history, GFR<30ml/min, femoral access

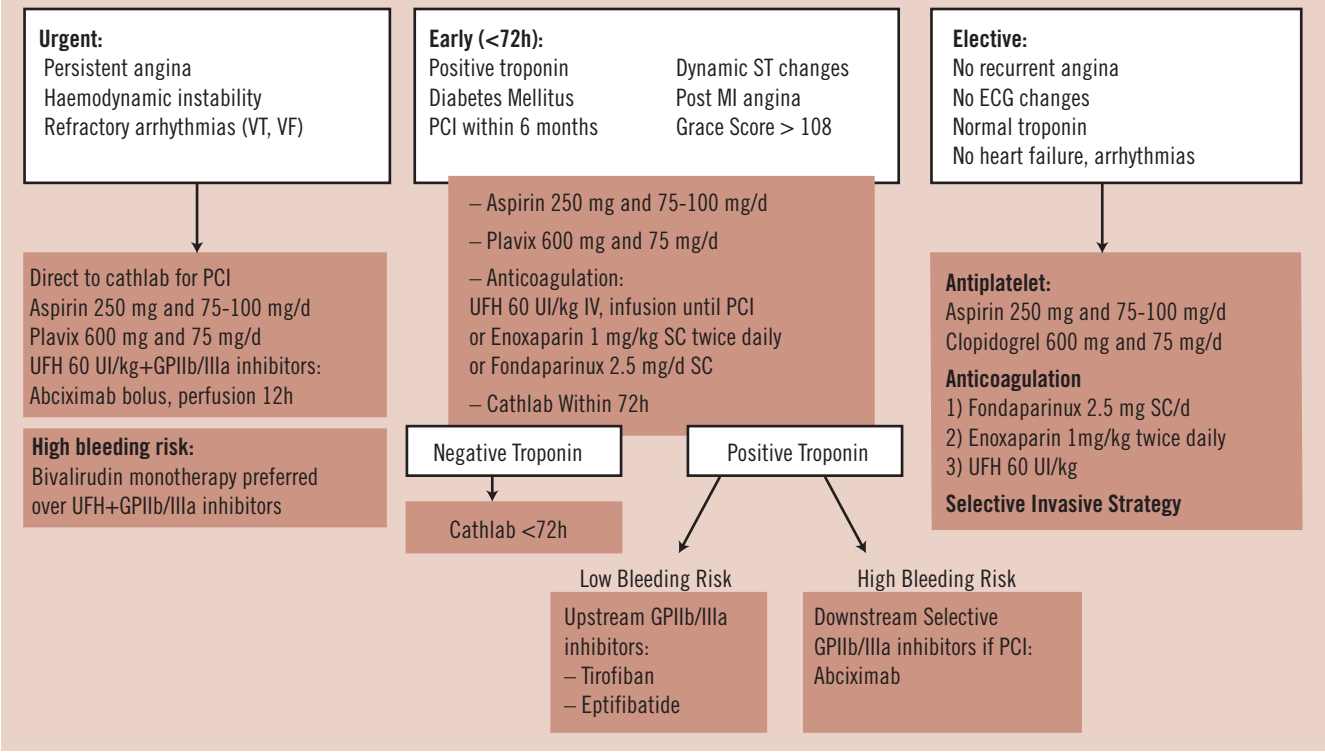

Figure 1. NSTE Acute Coronary Syndrome.

a) Antiplatelet therapy[2]	Aspirin 250 mg i.v. bolus followed by 75 to 100 mg daily.	
	– Clopidogrel 600 mg loading dose followed by 75 mg daily.	*A higher clopidogrel maintenance dose has been discussed also in this setting but definitive proof is still missing (see above).*
	GP IIb/IIIa-inhibitors should be used in patients with high ischemic risk undergoing PCI.	*Although the use of GP IIb/IIIa-inhibitors in this setting is a IA recommendation, "upstream administration" has been mainly investigated in studies without ADP antagonist use[2]. The usefulness of upstream therapy, when clopidogrel is on board is not known and currently investigated in the EARLY-ACS trial.* *GPIIb/IIIa inhibitors have been beneficial only in high-risk NSTE-ACS patients undergoing PCI[2]. However, "upstream use" also includes patients, which in the end are not undergoing PCI, might have less or no benefit from this strategy but an increased bleeding risk[10].* *The selective "downstream administration" of abciximab in combination with a 600 mg clopidogrel loading dose has been shown to be effective for troponin-positive (high-risk) NSTE-ACS patients[11] and might therefore be the better choice.*
b) Anticoagulation[2]	**Golden Rules** Cross-over between different antithrombins should be avoided[2] – Stop antithrombins immediately after PCI except in specific individual situations (e.g. thrombotic complication)	

Pre-cath management

1. In very high risk patients

(e.g. Persistent Angina, Haemodynamic Instability, Refractory Arrhythmias)

Patients are immediately referred to the cathlab:

UFH 60 IU/kg i.v. bolus, then infusion until PCI with GP IIb/IIIa inhibitors (abciximab)

In patients with high bleeding risk: monotherapy with bivalirudin, 0.1 mg/kg i.v. bolus followed by an infusion of 0.25 mg/kg/hr

2. In medium-to-high risk patients (e.g. troponin-positive, recurrent angina, dynamic ST changes)

Primarily invasive strategy is planned <72h:

In patients <75 years

UFH 60 IU/kg i.v. bolus, then infusion (aPTT-controlled) until PCI
or enoxaparin 1 mg/kg s.c. twice daily until PCI
or fondaparinux 2.5 mg daily s.c. until PCI

In patients > 75 years

UFH 60 IU/kg i.v. bolus, then infusion (aPTT-controlled) until PCI
Fondaparinux 2.5 mg daily s.c.
In case of renal failure (GFR<30 ml/min)
UFH 60 IU/kg i.v. bolus, then infusion (aPTT-controlled) until PCI

3. In low-risk patients

Primarily conservative strategy is planned:

Fondaparinux 2.5 mg s.c. daily
or enoxaparin 1 mg/kg s.c. twice daily
or UFH 60 IU/kg i.v. bolus, then infusion (aPTT-controlled) until PCI

Management in the cathlab

Golden Rule:

Continue the initial therapy! (Don't switch except after fondaparinux)

If under UFH: Continue perfusion, ACT measurement might be useful

Target range: - 200-250 sec with GP IIb/IIIa-inhibitors
- 250-350 sec without GP IIb/IIIa-inhibitors

If under enoxaparin:

< 8h of last s.c. application: no additional bolus
within 8-12h of last s.c. application: add 0.30 mg/kg i.v. bolus
>12h of last s.c. application: 0.75 mg/kg i.v. bolus

If under bivalirudin: An additional i.v. bolus of 0.5 mg/kg and an increase of the infusion to 1.75 mg/kg/hour before PCI is performed

If under fondaparinux: UFH 50-100 IU/kg when angiography and PCI is performed

ST elevation myocardial infarction (STEMI)

a) Antiplatelet therapy[3]	Aspirin 250 mg bolus i.v. followed by 75 to 100 mg daily	
	Clopidogrel 600 mg loading dose followed by 75 mg daily	*Although no study data is available (the CIPAMI trial answering this question is still ongoing), clopidogrel should be started as early as possible* *– A possibly higher clopidogrel maintenance dose has been discussed (see above)*
	GP IIb/IIIa-inhibitors: The best data exist for abciximab (0.25 mg/kg i.v. bolus followed by infusion of 0.125 µg/kg/min up to a maximum of 10 µg/min for 12 h)	*Clinical data are heterogeneous about the efficiency of facilitation (early administration) with GP IIb/IIIa-inhibitors before cathlab. While the only published randomised trial[12] showed no benefit, we have positive results from registries and metanalyses[13-15].*
b) Anticoagulation[3]	UFH 60 IU/kg i.v. bolus with GP IIb/IIIa-inhibitor	
	UFH 100 IU/kg i.v. bolus without GP IIb/IIIa-inhibitor	
	ACT might be useful (target ranges see above)	
	Stop perfusion of antithrombin after PCI, except if specific indication force to continue (left ventricular aneurysm and/or thrombus, atrial fibrillation, prolonged bed rest, deferred sheath removal...)	*A recent study suggested bivalirudin as alternative to UFH+IIb/IIIa antagonists[16]. Bivalirudin might be preferred, especially in patients with high bleeding risk.*

Specific points of interest

Prevention of bleeding

– Assessment of bleeding risk
– No crossover of antithrombotic therapy
– No overdosing of antithrombotic therapy
– Radial access should be the preferred option in high bleeding risk
– Stop anticoagulation after PCI unless a specific indication exists
– Selective downstream use of GP IIb/IIIa-inhibitors in NSTE ACS might be better than unselective upstream use
– A consensual bleeding risk score is highly warranted

Duration of dual antiplatelet therapy

– After bare metal stent (BMS) implantation in stable angina: one month
– After drug eluting stent (DES) implantation (all patients): one year
– After ACS (all patients independent of therapeutic strategy): one year

Golden rules to avoid premature discontinuation of antiplatelet therapy

– Avoid DES in patients not expected to comply with therapy
– Avoid DES if surgery is planned within 12 months
– Detailed information and education of the patient might prevent premature cessation of antiplatelet therapy
– Most surgical procedures can be performed under dual antiplatelet therapy with acceptable rate of bleeding: a multidisciplinary approach is required (cardiologist, anaesthesiologist, surgeon).

In surgical procedures with high bleeding risk:

– Stop clopidogrel five days before surgery and stay on ASA, unless high bleeding risk surgery
– The substitution of combined antiplatelet therapy with LMWH is ineffective and useless
– Restart clopidogrel as soon as possible with loading dose
– In very high risk patients (e.g. multivessel DES<1 years, left main stenting...), in whom cessation of antiplatelet therapy before surgery seems to be dangerous, it has been suggested to switch from clopidogrel five days before surgery to a short half-life antiplatelet agent, e.g. the GP IIb/IIIa-inhibitors tirofiban or eptifibatide and stop infusion of these agents four hours before surgery.

Patient under chronic anticoagulation

To avoid long-term triple antithrombotic therapy, BMS implantation or the use of pure balloon dilatation is preferred over the use of DES.

Antiplatelet therapy monitoring

– No consensual test system available
– No consensual definition of "non"– or "low" – response
– No large clinical evidence that tailored antiplatelet therapy improves clinical outcomes
– Monitoring of antiplatelet response by platelet function assays is used at present only in clinical research. Data are not strong enough to support the common use of the available assay systems in daily clinical practice.

Patients with aspirin hypersensitivity

If aspirin is highly required a "rapid desensitisation procedure" should be performed[17]

Heparin induced thrombocytopenia (HIT)

In patient with a history of HIT, neither UFH nor LMWH should not be used (cross reactivity). Bivalirudin is the best option in this case for elective PCI and ACS. Others options are argatroban, lepirudin and danaparoid.

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