EuroIntervention

Rationale and use of antiplatelet and antithrombotic drugs during cardiovascular interventions: May 2010 update

Thomas Cuisset[1]*, MD; Marco Valgimigli[2], MD, PhD; Harald Mudra[3], MD, PhD; Olivier Muller[4], MD, PhD; William Wijns[5], MD, PhD, FESC; Kurt Huber[6], MD, PhD

1. Department of Cardiology, University Hospital La Timone, Marseille, France; 2. Department of Cardiology, University of Ferrara, Cardiovascular Institute, Ferrara, Italy; 3. Department of Cardiology, Pulmonology and Internal Intensive Care Medicine, Klinikum Neupertach, Munich, Germany; 4. Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; 5. Cardiovascular Centre Aalst, OLV Hospital, Belgium; 6. Department of Cardiology and Emergency Medicine, Wilhelminenhospital, Vienna, Austria

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Introduction

Recent European Society of Cardiology (ESC) Guidelines have extensively investigated antithrombotic and antiplatelet therapy during percutaneous coronary interventions (PCI)[1-3]. However, based on their complexity and differences from existing ACC/AHA guidelines, it is sometimes difficult to adhere to evidence-driven recommendations for individual decisions. Most 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. During invasive cardiovascular interventions combined use of both anticoagulant and antiplatelet therapies is mandatory to prevent thrombosis, because activation of both platelets and the coagulation system contribute to thrombus formation. Choice, initiation and duration of antithrombotic strategies are based on the clinical setting (elective, acute or urgent intervention). To optimise the efficacy of therapy and reduce the potential bleeding hazard both ischaemic and bleeding risks have to be evaluated on an individual basis. In 2008, we published a first paper[4] aimed at giving practical solutions to handle antithrombotic therapy for patients undergoing PCI in various clinical conditions. Since that time important data from randomised controlled trials and observational studies have been reported leading to a need for an update of these practical recommendations for antithrombotic therapy during PCI.

Elective percutaneous coronary intervention

a) Antiplatelet therapy	Aspirin 250 mg bolus 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].	*– 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[5].* *– Some have suggested the use of a higher maintenance dose (150 mg)[6] 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 validated in a prospective randomised trial in the context of elective PCI.*

* *Corresponding author: Department of Cardiology, University Hospital La Timone, Boulevard Jean Moulin, Marseille, France*
E-mail: thomascuisset@voila.fr

Elective percutaneous coronary intervention (continued)

	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]. Yet, several studies showed that patients with high residual on treatment platelet reactivity after aspirin and clopidogrel therapy are at increased risk for periprocedural myocardial infarction[9] which can be mitigated by the addition of a GP IIb/IIIa-inhibitors[10,11]. Thus, triple antiplatelet treatment may be selectively considered in patients in whom high on treatment platelet reactivity is identified.*
b) Anticoagulation	UFH is currently the gold standard antithrombotic medication: 70-100 IU/kg i.v. bolus without GP IIb/IIIa inhibitors, while only 50-70 IU/kg with GP Iib/IIIa inhibitors[1].	*The STEEPLE trial has suggested a benefit of enoxaparin (0.5 mg/kg i.v. bolus) over UFH with regard to a reduced bleeding hazard[12].*

Non ST elevation acute coronary syndrome (NSTE-ACS)

a) Antiplatelet therapy[2]	Aspirin 250 mg bolus followed by 75 to 100 mg p.o. daily for all patients[2].	
	Clopidogrel 600 mg loading dose followed by 75 mg for all patients[2].	*A higher clopidogrel loading and maintenance dose has been discussed also in this setting and recent data from the CURRENT OASIS 7 trial suggested benefit of higher dose in ACS patients undergoing PCI[13].*
	Prasugrel 60 mg loading dose followed by 10 mg daily[14].	*Prasugrel, a new more potent thienopyridine, might be used in patients undergoing PCI after coronary angiography with respect to the risk-benefit balance according to the results of the TRITON study[14]. According to subgroups of the TRITON study analysis, prasugrel will be preferred in high risk NSTE-ACS patients (troponin +, ST changes), diabetic patients and avoided in patients with prior stroke or TIA, >75 years old or <60 kg[14].*
	GP IIb/IIIa-inhibitors are recommended in high-risk patients undergoing PCI[3].	*According to recent data[15], the administration of GP IIb/IIIa inhibitors will be initiated selectively "downstream" during PCI, rather than "upstream" in the coronary care unit. This modern strategy will be associated with an early invasive strategy (< 24 h) in high risk NSTE-ACS according to the recent TIMACS trial[16]. **
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, atrial fibrillation...).	

* 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 has been investigated in the EARLY- ACS trial. This study concluded that there was a benefit of selective use of GPIIb/IIIa inhibitors during PCI instead of "upstream use", with similar ischaemic benefit and reduced bleeding hazard[15]. 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[17] and might therefore be the better choice. The residual benefit of GPIIb/IIIa inhibitors with new antiplatelet agents such as prasugrel in NSTE-ACS is debatable and has not been addressed in specific randomised controlled trials.

Pre-cath management for NTSE-ACS patients

1. Patients with very high risk (e.g., persistent angina, haemodynamic instability, refractory arrhythmias), are immediately referred to the cathlab:
   – UFH 60 IU/kg i.v. bolus, then infusion until PCI.
   – Enoxaparin 0.5 mg/kg IV.
   – 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, diabetes, renal dysfunction, LVEF<40%, early post MI angina, PCI < 6 month, prior CABG, intermediate or high GRACE score).

Primarily invasive strategy is planned (<72h), early (< 24h) for high-risk patients:

In patients <75 years	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	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	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:

within 8 h of last s.c. application: no additional bolus
within 8-12 h of last s.c. application: add 0.30 mg/kg i.v. bolus
more than 12 h of last s.c. application: 0.5 mg/kg i.v. bolus.
Recent data suggested the usefulness of bedside monitoring to tailor anticoagulation therapy with enoxaparin during PCI for NSTE-ACS, but effectiveness of these assays has to be validated in prospective randomised trials[18].

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.

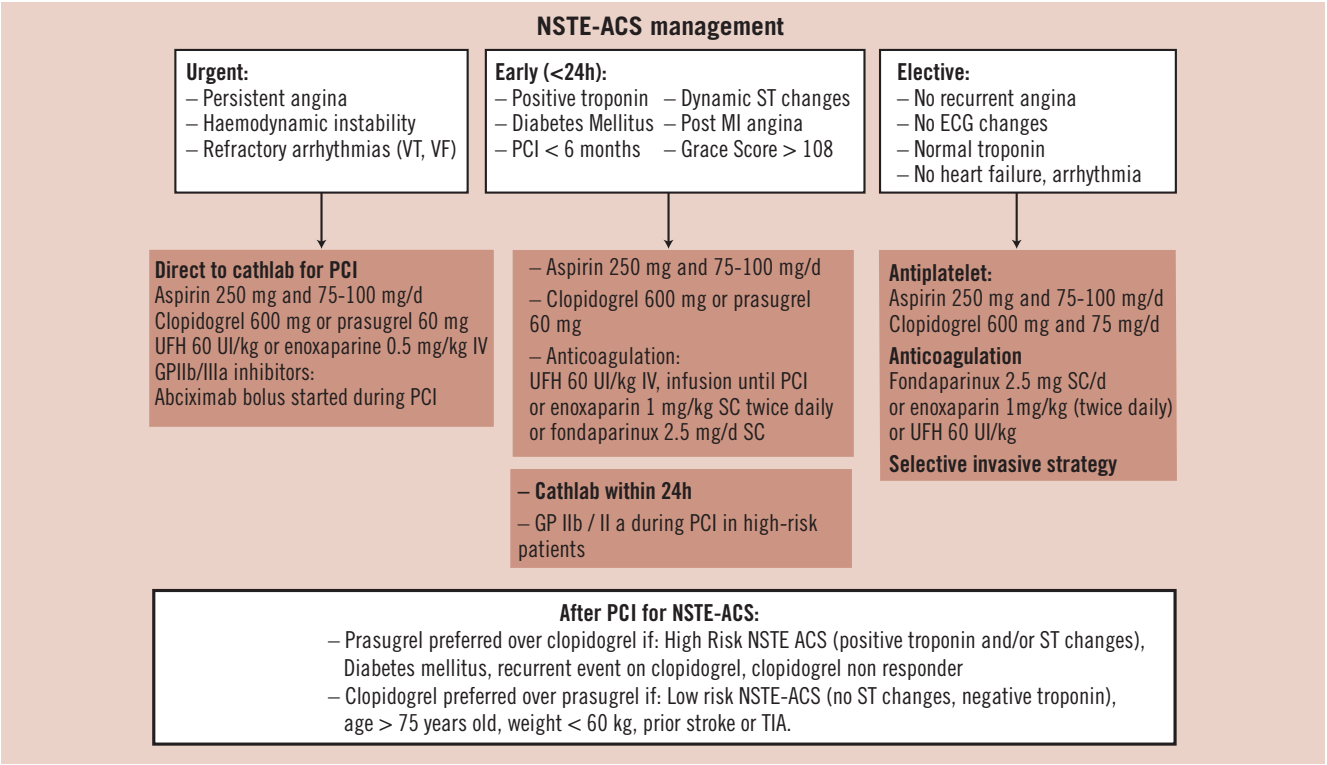

Figure 1. Management of NSTE-ACS.

ST elevation myocardial infarction (STEMI)

a) Antiplatelet therapy[3]	Aspirin 250 mg bolus followed by 75 to 100 mg p.o. daily for all patients[1].	
	Clopidogrel 600 mg loading dose followed by 75 mg daily for all patients[1].	*A higher clopidogrel loading and maintenance dose has been discussed also in this setting and recent data from the CURRENT OASIS 7 trial suggested benefit of higher dose in ACS patients undergoing PCI[13].*
	Prasugrel 60 mg loading dose followed by 10 mg daily[14,19].	*Prasugrel might be preferred over clopidogrel in STEMI patients referred to primary PCI, excluding high bleeding risk (>75 years, <60 kg, prior stroke or TIA). In this setting, prasugrel will be administrated pre-cathlab with a bolus of 60 mg as soon as possible followed by 10 mg daily dose[14]. Indeed, in STEMI patients, prasugrel achieved the same ischaemic benefit without significant increased bleeding risk[19]. Accordingly, prasugrel has been incorporated in the recent ACC/AHA STEMI guidelines[20].*
	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)[3].	*Clinical data are heterogeneous about the efficiency of facilitation (early administration) with GP IIb/IIIa-inhibitors before cathlab.**
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 forces to continue (left ventricular aneurysm and/or thrombus, atrial fibrillation, prolonged bed rest, deferred sheath removal).	*The HORIZON study suggested bivalirudin as alternative to UFH+ GP IIb/IIIa antagonists with same ischaemic benefit and reduced bleeding risk[30].* *The ATOLL study currently addresses the benefit of LMWH (enoxaparin) over UFH in STEMI patients undergoing primary PCI.* *Fondaparinux should not be used for primary PCI[3].*

* While the only published randomised trial[21] showed no benefit, we have positive results from registries, meta-analyses and post hoc analyses of prospective trials[22-25]. However, recent smaller randomised trials with 'reperfusion' endpoints presented in meetings did not succeed to show any benefit of pre-cathlab versus cathlab administration of GP IIb/IIIa inhibitors[26,27]. Moreover, with new fast-acting antiplatelet drugs such as prasugrel (30 min), this strategy seems less promising and specific randomised data are required. Therefore, and according to current guidelines[3], facilitated PCI with GP IIb/IIIa inhibitors cannot be recommended. Based on a recent investigation[25], although a post hoc subgroup analysis, it cannot be excluded that pre-hospital abciximab might be an advantage in patients with STEMI within three hours after symptom onset as a bridging strategy to the cathlab. It has yet to be proven whether the use of more potent ADP receptor blockers for primary PCI before and during primary PCI might be relevant. Therefore, GPIIb/IIIa inhibitors will be used during PCI. When GPIIb/IIIa inhibitors are used in the cathlab, recent studies suggested a benefit to intracoronary administration as compared with intravenous administration[28,29].

Specific points of interest

Prevention of bleeding during hospitalisation and after discharge

- Assessment of bleeding risk.
- No crossover of antithrombotic therapy (except after initial use of fondaparinux).
- 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 seems better than un-selective upstream use.
- Use of PPI in high-risk patients receiving dual antiplatelet therapy[31].
- Use of low aspirin maintenance dose (< 100 mg)[32].
- Monitoring of bleeding risk with platelet function tests has been suggested by recent publications[33,34], but remains at this point-in-time a scientific tool and not recommended for routine clinical use.

Duration of dual antiplatelet therapy

- After bare metal stent (BMS) implantation in stable angina: one month (ASA + clopidogrel).
- After drug eluting stent (DES) implantation (all patients): one year (ASA + clopidogrel or prasugrel).
- After ACS (all patients independent of therapeutic strategy): one year (ASA + clopidogrel or prasugrel).

In a recent, large sample size randomised study, the use of dual antiplatelet therapy for a period longer than 12 months in patients who had received drug-eluting stents was not significantly more

effective than aspirin monotherapy[35]. However, this study was underpowered and included low-risk patients without recurrent events within the first year after DES implantation. Larger ongoing randomised controlled trials will address this issue of the duration of dual antiplatelet therapy after DES.

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.
– Avoid DES in patients requiring oral anticoagulation (artificial valve, atrial fibrillation)[35].
– 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 an acceptable rate of bleeding: a multidisciplinary approach is required (cardiologist, anaesthesiologist, surgeon).

In surgical procedures with high bleeding risk:

– Stop clopidogrel five days or prasugrel seven days before surgery and stay on ASA, unless very 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: 300 to 600 mg according to both bleeding and ischaemic risk.
– In very high risk patients (e.g., multivessel DES <1 years, left main stenting...), in whom the 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. Although these protocols are attractive and have been successfully used in small patient series, there is currently no controlled evidence to support their use[37,38].

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[36]. In patients receiving chronic anticoagulation, the uninterrupted strategy will be preferred in order to avoid bridging therapy with heparin associated with increased ischaemic and bleeding risk[36]. In these patients, radial should be the first choice to lower bleeding complications[36].

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. Small sample size studies have suggested benefit of tailored antiplatelet therapy[10,11]. However, data are not strong enough to support the common use of the available assay systems in daily clinical practice. Results from the ongoing studies of personalised $P2Y_{12}$ inhibitor therapy such as GRAVITAS or ARCTIC will address the issue of the relevance of tailored antiplatelet therapy.

Heparin induced thrombocytopenia (HIT)

In patients with a history of HIT, neither UFH nor LMWH should 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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