Acute myocardial infarction care : developments, pitfalls and prognosis

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Management of acute coronary syndrome: achievements and goals still to pursue

Novel developments in diagnosis and treatment

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ABSTRACT

Acute coronary syndromes contribute a substantial part of the global disease burden. To realise a reduction in mortality and morbidity, the management of patients with these conditions involves the integration of several different approaches. Timely delivery of appropriate care is a key factor, as the beneficial effect of reperfusion is greatest when performed as soon as possible. Innovations in antithrombotic therapy have also contributed significantly to improvements in the prevention of ischaemic complications. However, with the use of such treatment an increase in the risk of bleeding is inevitable. Therefore, the greatest challenge is now to obtain an optimal balance between the prevention of ischaemic complications and the risk of bleeding. In this regard, identification of patients at highest risk of either one is essential.

INTRODUCTION

Acute coronary syndrome (ACS) is a high-risk manifestation of coronary artery disease and represents a substantial proportion of all acute hospitalisations. Although mortality because of ACS has declined in recent years[1], largely attributable to optimisation of timely reperfusion and innovations in pharmacological therapy, ischaemic heart disease remains a leading cause of death and accounted for 7.25 million deaths worldwide in 2008 (World Health Organisation)[2].

ACS is a term that comprises several clinical manifestations of acute ischaemia of the myocardium. The different manifestations are all characterised by a deficiency of oxygen supply to the myocytes, most often due to intracoronary thrombus formation triggered by erosion or rupture of an unstable atherosclerotic plaque. This thrombus partially or completely occludes the epicardial coronary artery and impairs blood flow or results in distal embolisation. Plaque rupture occurs as a result of haemodynamic and biological factors affecting a vulnerable atherosclerotic plaque. These vulnerable plaques, which are prone to rupture, are characterised by a large lipid or necrotic core covered by a thin fibrous cap with few smooth muscle cells but an abundance of macrophages and other inflammatory cells. Remarkably, they do not always occur at the sites of the most severe lumen narrowing[3;4]. In the case of plaque erosion, thrombus formation is triggered by de-endothelialisation of a more organised plaque. Infrequent causes of ACS include arteritis, trauma, congenital anomalies, cocaine abuse, coronary spasm, embolism and coronary or aortic dissection.

The most common clinical manifestations of ACS are unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). UA and NSTEMI are closely related conditions, both characterised by clinical symptoms suggestive of acute ischaemia (e.g. chest pain or discomfort), occurring *de novo* or rapidly increasing in frequency, duration and/or intensity, with or without ST-segment depression or T-wave inversion on the electrocardiogram (ECG). However, distinction between UA and NSTEMI is made by the absence or presence of circulating biomarkers for myocardial necrosis, respectively[5]. STEMI is a clinical condition with symptoms suggestive of acute ischaemia, accompanied by ST-segment elevation on the ECG, indicative of transmural ischaemia.

The term acute myocardial infarction is used to describe evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. The criteria for diagnosis of non-fatal spontaneous myocardial infarction have been universally defined by Thygesen et al.[6] and include detection of a rise and/or fall in biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit. Furthermore, at

least one of the following is obligatory: symptoms of ischaemia, ECG changes typical of new ischaemia (new ST-T changes or new left bundle branch block), development of pathological Q waves on the ECG or imaging evidence of ischaemia (new regional wall motion abnormalities).

The management of ACS has been extensively described in recent guidelines[7-10] with recommendations of how to implement evidence-based medicine in daily clinical practice. The purpose of this review is to provide an overview of novel strategies in the treatment of patients with ACS. The focus will be on early diagnosis and risk stratification, timely mechanical and pharmacological reperfusion, new developments in antithrombotic therapies administered in the acute setting and awareness of bleeding complications, particularly in the treatment of STEMI and NSTEMI. For this purpose, PubMed was searched for relevant published studies. The search strategy is shown in the box below.

Search strategy
PubMed search terms included 'acute coronary syndrome', 'acute myocardial infarction', 'plaque rupture', 'clinical guidelines', 'delay', 'prehospital', 'system', 'troponin', 'angioplasty', 'primary percutaneous coronary intervention', 'fibrinolysis', 'thrombolysis', 'transfer', 'risk score', 'antithrombotic therapy', 'antiplatelet therapy', 'anticoagulant therapy' and 'bleeding'.
Articles cited by those identified by these search terms were also selected if considered to be relevant in the context of this review.

EARLY DIAGNOSIS

Early diagnosis is of paramount importance if there is clinical suspicion of ACS. It has been clearly demonstrated that early diagnosis in acute myocardial ischaemia and the application of early reperfusion strategies to save jeopardised myocardium lead to better survival and less morbidity[11;12]. Especially in patients with recent-onset and ongoing symptoms, timely action is indicated as these patients might have transmural ischaemia, characterised by ST-segment elevation on ECG, and pharmaceutical or mechanical reperfusion should be performed as soon as possible. The duration from onset of symptoms to reperfusion is strongly correlated with infarct size and survival. Therefore, several strategies have been developed to minimise the delay. In addition to in-hospital and outpatient frameworks, educational programmes for timely medical care-seeking behaviour and pre-hospital protocols have been designed to improve outcomes[13-16]. Although the cause of pre-hospital delay in ACS is multifactorial and the duration from onset of symptoms until care-seeking is in part dependent on nonadjustable (patient) characteristics[17], some factors that cause delay in reperfusion after medical care-seeking are modifiable.

Field triage by means of a 12-lead ECG, conducted by trained paramedics of the regional emergency medical service (EMS) and directly transmitted to the nearest primary percutaneous coronary intervention (PCI) centre, has been demonstrated to be valuable for rapid diagnosis, transportation and treatment in STEMI care[18]. Whilst patients eligible for PCI are being transported to the PCI facility, the interventional team is activated, which enables the EMS to bypass noninterventional community hospitals as well as the emergency department at arrival of the PCI centre and deliver the patient directly to the catheterisation laboratory. If the classical features of myocardial necrosis on ECG lack (i.e. ST-segment elevation), additional recordings of V7-8 or V4R might help to diagnose patients with a true posterior infarction or right ventricular infarction, respectively.

Though prehospital triage with a 12-lead ECG is the appropriate diagnostic tool for early diagnosis in STEMI, this is seldom applicable in the case of NSTEMI. NSTEMI is a working diagnosis made by exclusion, due to the lack of typical ECG changes in STEMI. In the absence of the most frequently reported symptom, chest pain or discomfort, NSTEMI is a highly under-recognised condition[19]. Findings on physical examination might suggest other non-ischaemic cardiac or non-cardiac causes of chest pain, such as aortic dissection, pulmonary embolism or pericarditis, but findings specific of NSTEMI are lacking. The most observed ECG abnormalities are ST-segment depression or T-wave inversion, but are often discrete. Serial ECG recording might reveal dynamic ST-T abnormalities during complaints compared with an asymptomatic ECG, but it should be acknowledged that repeated normal ECGs do not rule out the possibility of NSTEMI. The lack of a simple diagnostic out-of-hospital test ensures that cardiac biomarkers play an important role in the identification of NSTEMI and its risk[20]. The measurement of troponin in a blood sample is the preferred laboratory test[6], as it reflects the damage to myocytes and is more specific and sensitive than other markers such as creatine kinase[21-23]. Although there are other causes of abnormal laboratory results, when myocardial infarction is clinically suspected, the elevation of troponin indicates at least myocardial cellular damage irrespective of the underlying mechanism[6]. Recently, high-sensitivity assays have been introduced that enable the detection of circulating troponin within three hours after the onset of symptoms and the sensitivity reaches approximately 100% when performed within three hours after admission, irrespective of the duration of symptoms. As a result, myocardial infarction can be demonstrated earlier and more frequently compared to detection with conventional assays in which troponin elevation can be delayed for 6–12 hours after the onset of symptoms[24].

Pending the laboratory results, two-dimensional echocardiography is a rapid and widely used diagnostic tool that can also be helpful. Regional wall motion abnormalities occur within seconds after coronary occlusion, long before necrosis, and demonstrate jeopardised

myocardium that can even be salvaged in very early presenters. Moreover, it is valuable to differentiate myocardial infarction from other causes of chest pain, as the absence of wall motion abnormalities excludes major myocardial ischaemia[25].

All these diagnostic techniques require equipment that is lacking in the ambulance. However, pre-hospital testing of troponin by paramedics using conventional assays has been assessed and was shown to be feasible with high success rates[26]. This may offer promising opportunities with the newly available high-sensitivity troponin assays for high-risk NSTEMI patients who could benefit from early invasive reperfusion strategies.

REPERFUSION STRATEGIES

A number of parameters are crucial for the determination of the best approach for patients with acute myocardial infarction. Primary PCI has been clearly demonstrated to be the treatment of choice in STEMI patients, compared to fibrinolytic therapy, to achieve coronary reperfusion[27]. It should be performed in all patients with symptoms for less than 12 hours provided a PCI-capable facility is reached in time[9].

However, the preferred strategy in patients delivered to a non-PCI centre is less clear given the accompanying transfer time to a PCI centre (**Figure 1**). The purpose of triage in non-PCI centres (i.e. whether to transfer or to treat with fibrinolytics) is to pursue reperfusion within an acceptable time frame with consideration of patients' baseline risk regarding mortality and bleeding, rather than paradoxically extend this time frame to ensure primary PCI in a higher proportion of STEMI patients[28]. The role of transfer for primary PCI has not been fully elucidated. Several studies have assessed the optimal balance regarding the benefits of primary PCI over fibrinolytic therapy versus the disadvantages because of transfer delay in STEMI patients. Current recommendations state that balloon inflation should be performed within at least two hours after first medical contact and within 90 minutes in very early presenters (within two hours after the onset of symptoms) with evidence of a large infarction[9;29]. If an invasive approach cannot be accomplished within these time periods, the use of fibrinolytic therapy is supported. However, the net balance is highly dependent on patients' characteristics. Therefore, an individualised approach is recommended[30]. Patients with a high bleeding risk, contraindications to fibrinolytic agents or high-risk conditions such as cardiogenic shock or congestive heart failure are likely to benefit from primary PCI irrespective of the extent of delay[31]. However, in any patient with intended transfer for primary PCI, a door-in to door-out (DIDO) time, defined as the duration from arrival to discharge in the referring hospital, should be as

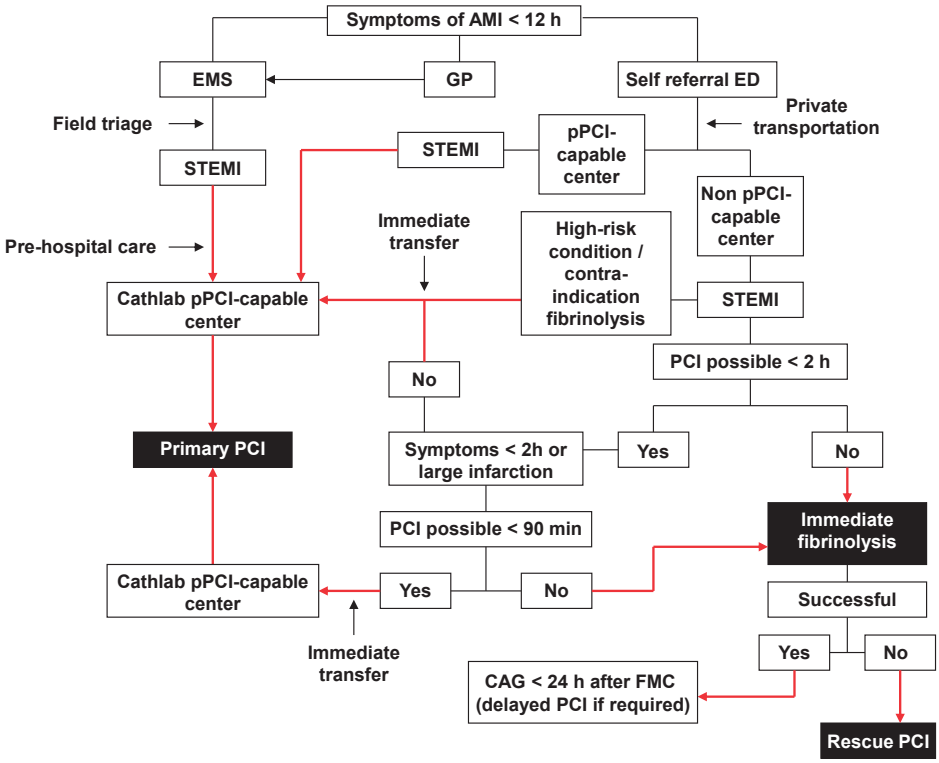

Figure 1. Reperfusion strategies in STEMI

AMI = acute myocardial infarction; EMS = emergency medical services; GP = general practitioner; ED = emergency department; STEMI = ST-segment elevation myocardial infarction; pPCI = primary percutaneous coronary intervention; CAG = coronary angiography; FMC = first medical contact.

short as possible, because a DIDO time of 30 minutes or less has been shown to be associated with lower in-hospital mortality rates[32].

Facilitated PCI, defined as full- or half-dose fibrinolytic therapy prior to immediate intended PCI, has been evaluated as a strategy to bridge the PCI-related time delay. Although early ST-segment resolution seems to be more common in facilitated PCI compared to primary PCI, no mortality benefit is demonstrated, whereas bleeding complications occur more frequently[33;34]. Therefore, facilitated PCI as a primary treatment strategy in unselected STEMI patients irrespective of the time frames is not recommended[9]. However, if a patient receives initial treatment with fibrinolytic therapy, early coronary angiography after stabilisation is preferred rather than waiting for the effect of fibrinolysis[35-37]. If the effect of fibrinolysis is still awaited for any reason and failure of reperfusion is evident in patients with a large infarction and a reasonable delay since symptom onset (<12 hours), rescue PCI should still be considered[38].

In contrast to patients with STEMI, the management of NSTEMI patients has been more conservative to date, partly because of the delay in establishing the diagnosis that is highly dependent on laboratory tests. Patients are generally treated with intensive medical therapy and diagnostic coronary angiography with or without mechanical revascularisation. Although the optimal timing of angiography has been a topic of debate for a number of years, no recent developments in this field have been reported. Several studies have assessed the value of a routine invasive strategy in these patients[39] and demonstrated reduced rates of cardiovascular events after five years of follow-up compared with a selective invasive strategy in which patients were initially treated conservatively and crossed over to early angiography in case of refractory angina, ischaemia detected with a functional test or an unstable condition requiring intervention. Early routine coronary angiography within 24 hours after presentation seems to have an additional beneficial effect in high-risk patients who are likely to benefit from invasive intervention[40;41]. However, favorable outcomes with an immediate invasive strategy (i.e. within the first few hours of admission as in STEMI) have not been demonstrated so far, when compared with an early routine invasive strategy in an unselected population of NSTEMI patients[42].

Risk stratification is crucial for the choice of treatment strategy in NSTEMI. Several risk models (for example the GRACE score) have been developed to predict the risk of death and ischaemic adverse events after ACS, incorporating markers of risk regarding clinical history, delay, physical examination, ECG characteristics and laboratory tests[43-45]. Although STEMI and NSTEMI do not share a common treatment strategy and risk scores are mostly used in the management of NSTEMI, risk stratification is important in both conditions to ensure appropriate treatment and estimation of prognosis. Therefore, it is noteworthy that both the TIMI and GRACE risk scores have also been validated for STEMI[44;46].

Several studies have demonstrated that patients undergoing PCI for STEMI or NSTEMI benefit from peri-procedural administration of a glycoprotein (GP) IIb/IIIa inhibitor such as abciximab, tirofiban or eptifibatide. Abciximab is a monoclonal antibody with a non-specific high platelet affinity and irreversible non-competitive GP IIb/IIIa inhibition. Tirofiban and eptifibatide are the so-called 'small-molecule' GP IIb/IIIa inhibitors with low platelet affinity and reversible competitive inhibition. These agents should be administered in addition to the standard antiplatelet drugs and heparin in patients with ACS. Relative risk reductions of up to 37% in death or re-infarction were demonstrated at long-term follow-up, whilst major bleedings unrelated to fibrinolysis occurred equally frequent[47-49]. However, in conservatively treated NSTEMI patients, the extent of the benefit of abciximab has been seriously questioned[50] and its use is therefore not recommended.

Although the beneficial effects of these drugs as part of an invasive strategy have been recognised, the timing of administration is still uncertain. The value of routine upstream administration remains a topic of debate, as it might increase rates of bleeding. In NSTEMI patients, upstream administration is discouraged because the risk of bleeding outweighs the risk of thrombotic complications[51]. However in STEMI patients, early (pre-hospital) administration seems to be beneficial, in particular following timely presentation (<3 hours) and/or in high-risk patients[52-55].

NOVEL ANTITHROMBOTIC AGENTS AND THE RISK OF BLEEDING

Antithrombotic therapy, consisting of antiplatelet and anticoagulant agents, is an essential element in the treatment of patients with ACS given the involvement of thrombus formation in the pathophysiology of this condition. It should be initiated as soon as ACS has been diagnosed to reduce the risk of ischaemic complications and recurrent thrombus formation. Results of the various trials, assessing antithrombotic agents in the treatment of patients with ACS and STEMI, are summarised in **Tables 1 and 2**, respectively.

Antiplatelet therapy

Aspirin inhibits the synthesis of thromboxane A_2 by targeting cyclo-oxygenase-1 (COX-1) and thereby diminishes platelet aggregation. It has been shown to reduce mortality rates amongst patients with evolving acute myocardial infarction[56] and is the cornerstone of antiplatelet therapy to which other antiplatelet agents have always been compared. However, blocking other pathways is essential for adequate inhibition of platelet activation and aggregation. Inactivation of the adenosine diphosphate $P2Y_{12}$ receptor plays an important role and can be achieved by administration of thienopyridines such as the widely used clopidogrel. Aspirin plus clopidogrel was shown to be superior to aspirin alone in the prevention of ischaemic cardiovascular events in STEMI and NSTEMI[57-59]. Therefore, standard dual antiplatelet therapy (loading and maintenance dose for one year) comprised clopidogrel and aspirin for several years. Upstream administration of dual antiplatelet loading doses was shown to have additional benefits in patients eligible for intervention[60-62]. Although no randomised trial has been conducted to examine exclusively its value in NSTEMI, international guidelines have also incorporated upstream antiplatelet therapy in invasively treated NSTEMI patients as a period of time (at least 30-90 minutes) is needed to reach adequate plasma levels and inhibition of platelet aggregation.

Unfortunately, there is a wide variability in response to clopidogrel partly because of drug interactions and detrimental genotype polymorphisms, such as the *CYP2C19* reduced-function alleles. This dose-independent resistance, which is seen in approximately

Table 1. Trials novel antithrombotic therapy in ACS patients

Main trial (acronym)	Compound	Structure	Compared to	Inclusion	No. of patients	Primary endpoint and results (compound vs. control)	Main secondary endpoint(s)	Bleeding endpoint(s)* and results (compound vs. control)	Ref.
TRITON-TIMI 38	Prasugrel	Irreversible oral P2Y12 receptor antagonist (thienopyridine)	Clopidogrel	ACS with scheduled PCI	13,608	Cardiovascular death, re-MI or stroke (15 months) 9.9% vs. 12.1%, *P*<0.001	Cardiovascular death, re-MI, stroke or re-hospitalisation due to cardiac ischaemic event; major bleeding	Non-CABG-related major bleeding (15 months) 2.4% vs. 1.8%, *P*=0.03 CABG-related major bleeding (15 months) 13.4% vs. 3.2%, *P*<0.001	69
PLATO	Ticagrelor	Reversible oral P2Y12 receptor antagonist (non-thienopyridine)	Clopidogrel	ACS	18,624	Cardiovascular death, re-MI or stroke (12 months) 9.8% vs. 11.7%, *P*<0.001	Primary endpoint exclusively in invasively treated patients; major bleeding	Major bleeding (12 months) 11.6% vs. 11.2%, *P*=0.43 Non-CABG-related major bleeding (12 months) 4.5% vs. 3.8%, *P*=0.03	76
TRACER	Vorapaxar	Competitive protease-activated receptor 1 inhibitor	Placebo	UA / NSTEMI	12,944	Cardiovascular death, re-MI, stroke, ischaemia with re-hospitalisation or urgent revascularisation (2 years) 18.5% vs. 19.9%, *P*=0.07	Cardiovascular death, re-MI or stroke; moderate or severe bleeding	Moderate and severe bleeding (2 years) 7.2% vs. 5.2%, *P*<0.001	81

ISAR-REACT 4	Bivalirudin	Direct thrombin inhibitor	Abciximab + unfraction-ated heparin	NSTEMI undergo-ing PCI	1721	Death, large re-MI, urgent TVR or major bleeding (30 days) 11.0% vs. 10.9%, *P*=0.94	Death, any re-MI or urgent TVR; major bleeding	Major bleeding (30 days) 2.6% vs. 4.6%, *P*=0.02	86
RE-DEEM	Dabigatran (4 dose-arms)	Direct thrombin inhibitor	Placebo	Recent ACS	1861	Major or clinically relevant minor bleeding (6 months) 3,5%;4.3%;7.9%;7.8% vs. 2.2%, *P*<0.001	Reduced D-dimer; cardiovascular ischaemic events	- (primary endpoint)	87
OASIS-5	Fondaparinux	Indirect factor Xa inhibitor	Enoxaparin	UA / NSTEMI	20,078	Death, re-MI or refractory ischaemia (9 days) 5.8% vs. 5.7%, *P*=0.007 (non-inferiority)	Major bleeding; primary endpoint or major bleeding	Major bleeding (9 days) 2.2% vs. 4.1%, *P*<0.001	89
ATLAS ACS 2-TIMI 51	Rivaroxaban	Direct factor Xa inhibitor	Placebo	Recent ACS	15,526	Cardiovascular death, re-MI or stroke (24 months) 8.9% vs. 10.7%, *P*=0.008	Death of any cause, any re-MI or stroke; non-CABG-related major bleeding	Non-CABG-related major bleeding (24 months) 2.1% vs. 0.6%, *P*<0.001	92
AP-PRAISE-2	Apixaban	Direct factor Xa inhibitor	Placebo	Recent ACS	7392 (terminated prematurely)	Cardiovascular death, re-MI or ischaemic stroke (241 days [IQR 132-352]) 7.5% vs. 7.9%, *P*=0.51	Several individual and composite endpoints of ischaemic and bleeding events	Major bleeding (241 days [IQR 132-352]) 1.3% vs. 0.5%, *P*<0.001	93
RUBY-1	Darexaban (6 dose-arms)	Direct factor Xa inhibitor	Placebo	Recent ACS	1279	Major or clinically relevant non-major bleeding (6 months) 6.2%;6.5%;9.3% vs. 3.1%, *P*=0.009	Major bleeding; all-cause mortality, re-MI, stroke or severe ischaemia	- (primary endpoint)	94

* Note: The applied definitions differ between trials

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; re-MI = recurrent myocardial infarction; TVR = target vessel revascularization; UA = unstable angina.

Table 2. Trials novel antithrombotic therapy in STEMI patients (including sub-studies)

Main trial (acronym)	Compound	Structure	Compared to	Inclusion	No. of patients	Primary endpoint and results (compound vs. control)	Main secondary endpoint(s)	Bleeding endpoint(s)* and results (compound vs. control)	Ref.
TRITON-TIMI 38 Sub-study	Prasugrel	Irreversible oral P2Y12 receptor antagonist (thienopyridine)	Clopidogrel	STEMI sub-population	3534	Cardiovascular death, re-MI or stroke (15 months) 10.0% vs. 12.4%, *P*=0.0221	Cardiovascular death, re-MI or urgent TVR; major bleeding	Non-CABG-related major bleeding (15 months) 2.4% vs. 2.1%, *P*=0.6451 CABG-related major bleeding (15 months) 18.8% vs. 2.7%, *P*=0.0033	70
PLATO Sub-study	Ticagrelor	Reversible oral P2Y12 receptor antagonist (non-thienopyridine)	Clopidogrel	STEMI sub-population	7544	Cardiovascular death, re-MI or stroke (12 months) 9.4% vs. 10.8%, *P*=0.07	Cardiovascular death or re-MI; all-cause mortality, re-MI or stroke; all arterial thrombotic events; major bleeding	Major bleeding (12 months) 9.0% vs. 9.2%, *P*=0.76	77
HORIZONS-AMI	Bivalirudin	Direct thrombin inhibitor	Unfractionated heparin + GP IIb/IIIa inhibitor	STEMI undergoing primary PCI	3620	Net adverse clinical events (NACE: major bleeding or major adverse cardiovascular events [death, re-MI, TVR for ischaemia, or stroke]) (12 months) 15.6% vs. 18.3%, *P*=0.022	Major adverse cardiovascular events	Non-CABG-related major bleeding (12 months) 5.8% vs. 9.2%, *P*<0.0001	85
OASIS-6	Fondaparinux	Indirect factor Xa inhibitor	Placebo or unfractionated heparin	STEMI	12,092	Death or re-MI (30 days) 9.7% vs. 11.2%, *P*=0.008	Major bleeding	Major bleeding (9 days) 1.0% vs. 1.3%, *P*=0.13	88

* Note: The applied definitions differ between trials

CABG = coronary artery bypass grafting; GP = glycoprotein; PCI = percutaneous coronary intervention; re-MI = recurrent myocardial infarction; STEMI = ST-segment elevation myocardial infarction; TVR = target vessel revascularization.

one-fifth of all patients[63], eventually may lead to worse clinical outcomes including stent thrombosis and recurrent myocardial infarction[64-66]. To overcome these problems, other potential adenosine diphosphate $P2Y_{12}$ receptor antagonists (e.g. prasugrel and ticagrelor) and platelet thrombin receptor antagonists (e.g. vorapaxar) have recently emerged (**Figure 2**).

Prasugrel is a thienopyridine with a similar mechanism of action to clopidogrel, but it is less susceptible to interindividual variability. Furthermore, its antiplatelet effect is greater and achieved more rapidly due to different pathways in metabolising the pro-drug, which are desirable characteristics in conditions such as STEMI and NSTEMI[67;68]. The TRITON-TIMI 38 trial assessed the performance of both antiplatelet agents in patients with ACS and demonstrated improved platelet inhibition and clinical outcomes with prasugrel compared with clopidogrel, in particular in patients with STEMI or diabetes mellitus, or those undergoing stent implantation[69-73]. Though prasugrel was associated with fewer ischaemic events, an increase in (non)coronary artery bypass graft (CABG)-related major and fatal bleedings was reported as well. A *post hoc* analysis revealed that patients ≥75 years of age, with a weight of <60 kg or with a history of stroke, were at greatest risk of harm, and therefore, prasugrel is not recommended in these patients, at least not at the full

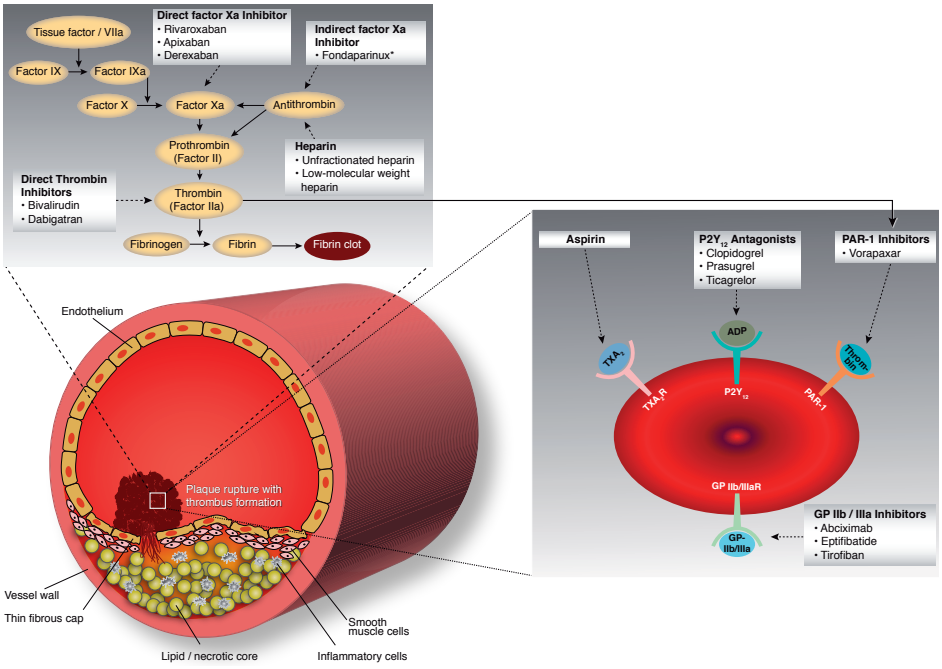

Figure 2. Antithrombotic therapy
Antiplatelet and anticoagulant agents and their targets.

dose. One of the limitations of clopidogrel and prasugrel is that their antiplatelet action is irreversible, which may be detrimental particularly in patients with triple vessel and/or left main disease who require urgent surgical revascularisation.

Ticagrelor is the first reversible oral $P2Y_{12}$ receptor antagonist of a non-thienopyridine class and has been evaluated for the treatment of ACS. It is a direct-acting drug with rapid onset, but administration twice daily is mandatory because of a short half-life of 12 hours. As with prasugrel, outcomes after ticagrelor are not affected by the presence of genotype polymorphisms known to be involved in clopidogrel resistance[74]. Compared with clopidogrel, the antiplatelet effect of ticagrelor appears to be superior in terms of major adverse cardiovascular events in STEMI and NSTEMI patients[75-78], which can be attributed to a greater suppression of platelet activation and aggregation[79]. However, although no increase in overall major bleeding has been demonstrated, ticagrelor has been associated with more non-procedural-related bleeding.

It should be noted, however, that the superiority of both ticagrelor and prasugrel in ischaemic events was based essentially on only one large trial (PLATO and TRITON-TIMI 38, respectively). A recent meta-analysis demonstrated a similar performance of ticagrelor and prasugrel when indirectly compared with each other, but favourable (lower) rates of stent thrombosis were observed with prasugrel versus less bleeding complications with ticagrelor[80]. However, definite conclusions cannot be drawn, as a study comparing these drugs directly has yet to be conducted.

Based on the evidence to date, prasugrel and ticagrelor are promising oral antiplatelet agents with superior efficacy compared with clopidogrel, but at the (limited) price of an increased risk of bleeding. Pre-procedural administration of prasugrel in addition to aspirin seems appropriate in STEMI patients with a low bleeding risk undergoing primary PCI. In high-risk NSTEMI patients undergoing invasive treatment, ticagrelor could be recommended; however, prasugrel should be considered in patients with a known coronary anatomy (especially in diabetic individuals), as it might be more effective in the prevention of thrombotic events, whilst it should be avoided in patients who are likely to undergo urgent CABG. Furthermore, in patients with a history of stroke or transient ischaemic attack or those who have already received fibrinolytic therapy, both prasugrel and ticagrelor are contraindicated.

Vorapaxar is a competitive inhibitor of the principal protease-activated receptor 1 (PAR-1) for thrombin, which is a powerful platelet activator. Recently, the TRACER investigators[81] demonstrated a tendency towards reduced rates of the primary composite ischaemic endpoint with the addition of vorapaxar to standard therapy in patients presenting with UA/

NSTEMI, although statistical significance was not reached. This difference was mainly driven by a reduction in the rate of re-infarction. However, a potential benefit should still be weighed against the significantly increased risk of major and intracranial bleeding. Because standard therapy included the combination of aspirin and a $P2Y_{12}$ receptor antagonist (predominantly clopidogrel) in the majority of patients, the increased risk in this trial might reflect the incremental increase in bleeding risk with the administration of multiple strong antiplatelet agents. Therefore, a trial to compare PAR-1 with $P2Y_{12}$ inhibition (not only clopidogrel but also prasugrel and ticagrelor) in ACS patients receiving aspirin could be appropriate for an accurate evaluation of this novel compound. The role of vorapaxar is currently under investigation in patients with chronic atherosclerotic disease in the TRA 2ºP-TIMI 50 trial[82]. This drug has not yet been studied in STEMI patients.

Anticoagulant therapy

Whereas antiplatelet drugs prevent the activation and aggregation of platelets, anticoagulant drugs interfere with the clotting cascade itself. Several categories of anticoagulants have been evaluated in ACS in addition to standard antiplatelet therapy (to date, standard therapy has usually comprised aspirin and clopidogrel), including heparins, direct thrombin inhibitors and (in)direct factor Xa inhibitors (**Figure 2**).

Heparins – both unfractionated (UFH) and low-molecular weight (LMWH) – bind to antithrombin, which leads to inactivation of several factors, predominantly thrombin and factor Xa. Since its introduction to the treatment of ACS in 1981[83], the use of intravenous heparin has become the gold standard therapy, although there is a paucity of data on its use in the setting of invasively treated ACS. LMWHs were developed more recently to overcome some of the limitations of UFH, including variability in response and susceptibility to heparin-induced thrombocytopenia, and are now implemented as standard care in ACS. Amongst the LMWHs, enoxaparin has been evaluated most extensively and was given a class I recommendation for use in STEMI patients treated with fibrinolysis and for NSTEMI patients as an alternative to fondaparinux (discussed below) when unavailable according to the guidelines of the European Society of Cardiology and the American College of Cardiology / American Heart Association. Although anticoagulation during primary PCI for STEMI has always been supported by UFH, the recently published ATOLL trial[84] demonstrated reduced rates of ischaemic complications with similar rates of bleeding complications and procedural success after peri-procedural intravenous enoxaparin versus UFH.

Direct thrombin inhibitors have been available for several years. These agents have a number of advantages over heparins, including the ability to equally inhibit fibrin-bound and fluid-phase thrombin, a short elimination half-life and no activation of antiheparin /

platelet factor 4 antibodies. Of all direct thrombin inhibitors that have been evaluated as an alternative to heparins, only bivalirudin has been used in a clinical setting. In STEMI patients treated with primary PCI, bivalirudin was shown to reduce the composite of major bleeding or adverse cardiac events (death, re-infarction, revascularisation or stroke), mainly driven by a reduction in major bleeding, compared with heparin combined with a GP IIb/IIIa inhibitor[85]. Therefore, bivalirudin is preferred in STEMI patients with a high risk of bleeding. Although no difference was observed at 30 days, additional analyses revealed an increase in stent thrombosis within 24 hours, in particular in comparison to patients who received heparin pre-randomisation. This finding led to the suggestion that pretreatment with a strong/high-dose thienopyridine, heparin or extension of the duration of bivalirudin might improve outcomes. However, this remains to be investigated. In NSTEMI patients undergoing PCI, the composite primary endpoint of death, large re-infarction, urgent target vessel revascularisation or major bleeding was reached equally frequently after 30 days with bivalirudin and with a GP IIb/IIIa inhibitor (abciximab) plus UFH. Likewise, rates of the composite ischaemic endpoint were similar in the two treatment groups. However, major bleeding was less common in patients treated with bivalirudin[86].

Recently, the RE-DEEM trial[87] reported a dose-dependent increase in major or clinically relevant minor bleeding with the novel direct thrombin inhibitor dabigatran compared with placebo in patients after recent (7.5 ± 3.8 days) STEMI or NSTEMI, whilst no reduction in the occurrence of ischaemic events was observed. When outcomes from patients in the four dose arms were evaluated separately, only those in the groups receiving the two highest doses of dabigatran (110 and 150 mg) reached the composite ischaemic endpoint numerically less frequently, but they also showed a significant small increase in major bleeding. For a proper evaluation of dabigatran in (N)STEMI, a sufficiently powered trial has yet to be conducted.

Fondaparinux is an indirect factor Xa inhibitor that, like LMWHs, binds to antithrombin to inhibit factor Xa. However, in contrast to LMWH-bound antithrombin, fondaparinux-bound antithrombin is not capable of thrombin inhibition, as it is selective for factor Xa. The OASIS-6 trial assessed the upstream use of fondaparinux versus placebo or UFH in STEMI and demonstrated a reduction in the risk of death or re-infarction, as well as major bleeding, in conservatively treated patients. By contrast, no clear benefit compared with heparin was demonstrated in patients undergoing primary PCI, and guiding catheter thrombosis was more common. Bleeding complications were equally frequent with either treatment in these patients[88]. The OASIS-5 trial showed that rates of the composite of death, re-infarction or refractory ischaemia were comparable among UA/NSTEMI patients treated with subcutaneous fondaparinux or enoxaparin. At 30 days, however,

mortality was reduced in the fondaparinux-treated group, which might be explained by the lower rates of bleeding complications[89]. The administration of peri-procedural UFH might prevent the more frequently occurring guiding catheter thrombosis after treatment with fondaparinux[90]. Therefore, fondaparinux is recommended in all NSTEMI patients but adjunctive UFH is appropriate to reduce the risk of catheter thrombosis when invasively treated. Low-dose UFH versus standard-dose in this setting does not reduce the risk of peri-procedural bleeding[91].

In addition to indirect factor Xa inhibitors, several direct-acting factor Xa antagonists have been evaluated in the treatment of ACS, although not in the acute phase. Results of treatment with rivaroxaban in patients with recent ACS (STEMI/NSTEMI/UA ≤7 days) after initial stabilisation were recently published by the ATLAS ACS 2-TIMI 51 investigators[92]. Both regimens of twice-daily 2.5 and 5 mg reduced the composite of death from cardiovascular causes, re-infarction or stroke compared with placebo. Remarkably, the regimen of 2.5 mg twice-daily reduced rates of death, whereas rivaroxaban twice-daily 5 mg did not. This finding may be partly explained by a non-significant increase in fatal bleeding with the higher dose, but a contribution from non-fatal bleeding may also have been important. However, fatal bleeding did not occur more frequently when comparing all patients receiving rivaroxaban to those receiving placebo. Both regimens significantly increased the risk of non-fatal major bleeding and intracranial haemorrhage, with the high dose having more effect than the low dose.

In a relatively high-risk population with recent ACS (≤7 days), the APPRAISE-2 trial compared apixaban to placebo at a dose of 5 mg twice daily[93]. The primary ischaemic endpoint occurred at a similar frequency in both treatment arms, but the primary safety outcome of major bleeding was significantly increased with apixaban. Therefore, the trial was terminated prematurely. Unfortunately, this limits the interpretation of the results regarding the efficacy of apixaban in the prevention of ischaemic events.

In the RUBY-1 trial[94], six different dosage regimens of another direct factor Xa inhibitor, darexaban, were compared with placebo. Bleeding was more frequent with darexaban when pooling all dose arms, but only statistically significant for the darexaban 30 mg dose arm when evaluating all dosages separately. Furthermore, a positive dose–response relationship was observed between bleeding rates and dose. The rate of the composite ischaemic endpoint was not decreased with darexaban; however, this study was underpowered for efficacy endpoints.

In conclusion, the purpose of developing novel anticoagulants was to optimise the prevention of ischaemic events and simultaneously reduce the risk of bleeding. Although the role

of anticoagulants such as bivalirudin and fondaparinux seems to be well established in the treatment of both STEMI and NSTEMI, additional research is required when using either as the sole anticoagulant during intervention because stent and catheter thrombosis seem to occur more frequently. Novel direct factor Xa inhibitors are currently being investigated for use after recent ACS and, so far, only rivaroxaban appears to clearly reduce the risk of ischaemic complications. However, based on studies to date, the dosage should be low to counterbalance the incremental risk of bleeding. Furthermore, it should be noted that these emerging anticoagulants have not yet been tested in combination with novel antiplatelet regimens including prasugrel or ticagrelor.

Table 3. CRUSADE risk score for in-hospital major bleeding in NSTEMI

Predictor	Score	Predictor	Score
Baseline haematocrit (%)		Sex	
<31	9	Male	0
31–33.9	7	Female	8
34–36.9	3	Signs of CHF at presentation	
37–39.9	2	No	0
≥40	0	Yes	6
Creatinine clearance (mL/min) *		Prior vascular disease ¶	
≤15	39	No	0
>15 to 30	35	Yes	6
>30 to 60	28	Diabetes mellitus	
>60 to 90	17	No	0
>90 to 120	7	Yes	6
>120	0	Systolic blood pressure (mmHg)	
Heart rate (bpm)		≤90	10
≤70	0	91–100	8
71–80	1	101–120	5
81–90	3	121–180	1
91–100	6	181–200	3
101–110	8	≥201	5
111–120	10		
≥121	11		
Total score 1–100 points			

Score	Risk of bleeding	Rate of bleeding
≤20	Very low	3.1%
21–30	Low	5.5%
31–40	Moderate	8.6%
41–50	High	11.9%
>50	Very high	19.5%

CHF, congestive heart failure. * Creatinine clearance estimated with Cockcroft-Gault formula; ¶ prior vascular disease is defined as a history of peripheral artery disease or stroke.

Bleeding

Recently, progress has been made in the prevention of thrombotic events, largely due to the development of mechanical revascularisation therapy and novel antithrombotic agents. However, this is inevitably accompanied by an increase in the risk of bleeding. Major bleeding complications have become a serious problem in the treatment of patients with ACS, significantly increasing 30-day mortality[95]. Therefore, patient groups particularly susceptible to bleeding should be identified in order to prevent inappropriate treatment. As in ischaemic risk stratification, models for estimating the risk of bleeding, such as the CRUSADE bleeding risk score (**Table 3**), have been developed[95-97]. Characteristics consistently found to be predictors of bleeding complications include older age, female gender, lower body weight, poor renal function, a history of bleeding complications and treatment with an invasive procedure[98]. For each patient individually, the risk of bleeding should be weighed against the presumed benefits of reducing ischaemic complications.

Additional measures such as proper dose adjustment of antithrombotic drugs, a radial approach to invasive procedures and the use of closure devices may diminish complications whilst preserving the benefits of antiplatelet agents, GP IIb/IIIa inhibitors and anticoagulants in terms of thrombotic events.

CONCLUSION

In the past few years, several emerging therapeutic options have been evaluated for the management of patients presenting with ACS. Recent achievements in ACS treatment include a reduction in treatment delay because of effective systems of care, which ensures early diagnosis and delivery of proper care. New antithrombotic drugs have been developed to provide the most effective prevention of ischaemic complications. Together with raised awareness of the seriousness of the accompanying bleeding risk, these innovations have brought us one step closer to an optimal treatment strategy for each individual patient.

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