



# Invasive management of the acute coronary syndromes

Acute coronary syndromes (ACS) represent a large segment of patients with coronary artery disease. This article discusses the algorithm of risk stratification in ACS and the evidence for selecting the invasive strategy in the management of ACS. Antiplatelet and antithrombotic therapy used in the management of ACS is also reviewed. Individualization of the dual antiplatelet therapy and of the anticoagulation regimen used during percutaneous coronary intervention, in order to balance the anti-ischemic benefit versus the bleeding risk, allows a safe coronary revascularization in the particular patient presenting with ACS.

**KEYWORDS:** acute coronary syndrome • antithrombotic therapy • dual antiplatelet therapy • percutaneous coronary intervention

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Acute coronary syndromes (ACS) represent a large segment of the patients with coronary artery disease. While presenting with various clinical and ECG scenarios, ACS share a common pathophysiological mechanism: atherosclerotic plaque erosion and/or rupture with superimposed thrombosis and microembolism, subsequent myocardial underperfusion, followed by possible myocardial necrosis. The size of the coronary artery involved and the amount of jeopardized myocardium explain the clinical presentation and dictate the appropriate treatment strategy.

This article will review the invasive management in patients presenting with non-ST-T segment elevation myocardial infarction (NSTEMI) and unstable angina.

In light of their common pathophysiology (erosion/rupture of an unstable plaque) all ACS patients should receive medical management including dual antiplatelet therapy, statins, anticoagulation and anti-ischemic agents on their initial presentation to the emergency room. However, risk assessment and patients' characteristics will dictate further management.

## Risk stratification in ACS patients

Risk score models were developed over time in order to better evaluate the prognosis of the patients with ACS and as such, to determine the appropriateness of the invasive management.

The thrombolysis in myocardial infarction (MI) risk score predictor variables (i.e., age  $\geq 65$  years, at least three risk factors for coronary artery disease, prior coronary stenosis of  $\geq 50\%$ , ST-T segment deviation on ECG at presentation,

at least two anginal events in the prior 24 h, use of aspirin (ASA) over the prior 7 days and elevated serum cardiac markers) allow an accurate tool to assess a patient's risk of death and/or ischemic events [1].

The GRACE risk score allows prediction of the cumulative 6-month risk of death or MI and includes age, development (or history) of heart failure, peripheral vascular disease, systolic blood pressure, Killip class, initial serum creatinine concentration, elevated initial cardiac markers, cardiac arrest on admission and ST-T segment deviation [2].

## The invasive strategy in the management of ACS

Over recent years several randomized trials, as well as meta-analyses, have addressed the appropriateness and timing of an invasive management strategy in the setting of ACS, provided the patients studied had, from presentation, a higher risk for future ischemic cardiovascular events [3–7]. The results of these trials have to be critically reviewed, since several variables (e.g., pharmacological regimens used during the percutaneous interventions – percutaneous coronary intervention (PCI), patient population studied, completeness of revascularization, use of different stents during the PCI, rates of crossover, different bleeding noted over the index hospitalization) were addressed differently during the years.

The most contemporary ACS data, including timing of the invasive strategy (early vs delayed) was analyzed in a recent meta-analysis [7] that identified four trials (4013 patients) performed

between 2003–2009. An early coronary angiography followed by potential intervention (1.16 to 14 h vs 20.8–86 h in the delayed strategy group) reduced the risk of recurrent ischemia, and shortened hospital stay in patients with NSTEMI-ACS.

The benefit of an early invasive strategy (the first 24 h of the initial presentation) was observed mostly in the high-risk group patients (risk score above 140 on the GRACE scale), significantly reducing the rate of the composite secondary outcome of death, MI or refractory ischemia [8].

Once the invasive strategy is followed and the coronary anatomy is defined, further risk stratification can be performed regarding the extent of the coronary artery disease, method, timing and extent of revascularization and potential risk of bleeding.

The retrospective calculation of a previously validated angiographic risk score of PCI [9] was performed in 2627 patients with NSTEMI-ACS undergoing PCI in the ACUITY trial [10]. The SYNTAX score emerged as an independent predictor of the 1-year rate of death, cardiac death, MI and target-vessel revascularization in patients with ACS undergoing PCI [10].

No randomized controlled trial has so far compared PCI with coronary artery bypass graft (CABG) in patients with ACS; once the coronary anatomy was defined the revascularization strategy was usually left at the operator's discretion. In general, PCI was performed in 60% of patients, medical therapy alone in 25% and CABG in 15% of patients in most clinical trials in ACS.

A propensity-score matched analysis from the ACUITY trial (performed on 1056 patients) revealed that moderate- and high-risk patients with ACS and multivessel disease treated with PCI rather than with CABG had lower rates of periprocedural stroke, MI, major bleeding and renal injury, with comparable 1-month and 1-year rates of mortality, but more frequently developed recurrent ischemia requiring repeat revascularization procedures during follow-up [11].

The risk of bleeding during the index hospital admission for ACS has been derived from different registries. The CRUSADE bleeding score (range 1–100 points calculated using eight variables: age, sex, heart rate, systolic blood pressure, signs of congestive heart failure at presentation, prior vascular disease, diabetes mellitus, baseline hematocrit and creatinine clearance) quantifies risk for in-hospital major bleeding across all treatment strategies [12]. The ACUITY bleeding

score uses seven variables (i.e., age, sex, baseline anemia, white blood cell count, ST-T segment changes at presentation and anticoagulation regimen used) in order to identify patients at increased risk for non-CABG-related bleeding and subsequent 1-year mortality [13].

### Antiplatelet therapy

Once the invasive strategy is followed and coronary revascularization is contemplated the adjunctive pharmacology regimen (antiplatelets and antithrombotics) has to be adjusted to the particular patient, balancing the antithrombotic advantages versus the bleeding risk.

Dual antiplatelet therapy (ASA – and a second oral antiplatelet agent – clopidogrel, prasugrel or ticagrelor) is considered standard treatment in the management of ACS. Several trials over the last decade have tried to answer several questions regarding the efficiency of these regimens (preventing future cardiovascular events vs the risk of bleeding), optimal loading and maintenance dosing, duration of treatment, drug–drug interactions and metabolism of these drugs according to different genotypes.

Clopidogrel, a second generation thienopyridine that irreversibly inhibits the platelet P2Y<sub>12</sub> receptor, has been proven to significantly reduce major cardiovascular events when added to ASA, and this was not associated with a significant risk of major bleeding [14].

A loading dose of 600 mg (vs 300 mg) of clopidogrel (given 4–8 h before the planned coronary intervention) was shown to significantly reduce the incidence of periprocedural MI during the first 30 days of postprocedural follow-up [15]. The higher (600 mg clopidogrel) loading dose followed by 150 mg orally daily for 1 week after the index PCI (and then by the usual 75 mg daily maintenance dose) was shown to significantly reduce stent thrombosis and ischemic events by 30 days when compared with a regimen of 300 mg loading and 75 mg daily maintenance dose [16]. Of note, a high dose (300–325 mg) did not differ from a low dose (75–100 mg) daily ASA. Secondary to its complex metabolism, requiring absorption regulated by the *ABCBI* gene encoded P-glycoprotein, followed by a two-step CYP450 isoenzymes CYP3A4- and CYP2C19-dependent conversion in the liver to its active metabolic form, clopidogrel was considered to exert a variable pharmacological action secondary to different genotype polymorphisms. Recent data suggest that among patients with stable cardiovascular disease, tripling the maintenance dose of

clopidogrel to 225 mg daily in *CYP2C19*\*2 heterozygotes achieved levels of platelet reactivity similar to that seen with the standard 75-mg dose in noncarriers; in contrast, for *CYP2C19*\*2 homozygotes, doses as high as 300 mg daily did not result in comparable degrees of platelet inhibition [17].

However, a modification of antiplatelet therapy based on platelet function testing failed to improve outcomes when double-dose clopidogrel (150 mg) was used in patients with high on-treatment reactivity after PCI with drug-eluting stents [18]. Despite mostly low-risk patients studied and concerns regarding questionable incremental efficacy of the 150 mg daily dose, this randomized evidence does not support the routine use of platelet function measurement [19].

Adding omeprazole to ASA and clopidogrel did not significantly affect the rate of cardiovascular events (e.g., MI and revascularization) in the only double blinded, randomized, controlled trial conducted [20]. This finding disproved concerns raised from previous (nonrandomized) studies regarding attenuation of clopidogrel conversion to its active metabolite due to hepatic enzyme interference from proton-pump inhibitors.

The optimal duration of dual antiplatelet therapy (ASA with clopidogrel) after the index PCI is controversial, since 24 months of dual antiplatelet therapy failed to be superior to only 6 months in patients receiving first- and second-generation drug-eluting stents and bare metal stents for their index PCI [21]. However, discontinuation of clopidogrel within 12 months was associated significantly with cardiovascular death and nonfatal MI in registry-followed patients [22]. Most cardiovascular events associated with discontinuation of clopidogrel were noted to occur within the first 90 days after stopping the dual antiplatelet therapy, suggesting the possibility of a clopidogrel rebound phenomenon [23].

Prasugrel, a new thienopyridine with a distinct chemical structure that allows its conversion to an active metabolite via a two step metabolic activation (mediated by plasma esterases and subsequently by the liver CYP isoenzymes) has a very low inter-individual variability in the inhibition of the P2Y<sub>12</sub>-dependent platelet responses and its action is not influenced by the CYP genotype. A loading dose of 60 mg prasugrel followed by 10 mg maintenance dose achieved a significantly higher platelet inhibition as well as reduction in cardiovascular events (mostly MI and stent thrombosis) when compared with

clopidogrel 300 mg loading dose (followed by 75 mg maintenance dose) [24]. This was accompanied by higher major bleeding rate [24]. A trend towards a higher benefit without increased bleeding was observed in the diabetic patients; however, there was no significant interaction between treatment effect and diabetes status [24]. The *post hoc* analysis of the data identified three subgroups (patients with previous cerebrovascular events, elderly over 75 years of age and patients with a body weight less than 60 kg) in which the treatment with prasugrel was shown to have less clinical efficacy and greater absolute levels of bleeding than the overall cohort [24]. A lower maintenance dose of 5 mg daily may be recommended for the elderly ( $\geq 75$  years) and for the patients with a weight  $< 60$  kg if prasugrel is considered as part of the combination of the dual antiplatelet therapy.

Cangrelor, an ATP analog with high affinity for the P2Y<sub>12</sub> receptor, does not require conversion to an active metabolite, is immediately active after intravenous (iv.) infusion, has a half-life of 3 to 6 min (with rapid reversal of both the platelet-inhibitory effect and the effect on bleeding time within 20 min after cessation of the infusion) and has a dose-dependent inhibition of ADP-induced platelet aggregation [25]. In the CHAMPION PCI trial, cangrelor when administered iv. 30 min before PCI and continued for 2 h after PCI, was not superior to an oral loading dose of 600 mg of clopidogrel, administered 30 min before PCI, in reducing major adverse cardiac events at 48 h [26].

Ticagrelor belongs to a new chemical class (cyclopentyl-triazolo-pyrimidines), and is an oral, reversibly binding P2Y<sub>12</sub> inhibitor with a plasma half-life of approximately 12 h (requiring twice daily [b.i.d.] administration). Its level of P2Y<sub>12</sub> inhibition is weaker than that achieved by cangrelor and is determined by the plasma ticagrelor level and, to a lesser extent, an active metabolite [25,27]. In the PLATO trial, patients with ACS undergoing an invasive strategy were randomized to ticagrelor and placebo (180 mg loading dose followed by 90 mg b.i.d.), or to clopidogrel and placebo (300–600 mg loading dose or continuation with maintenance dose followed by 75 mg q.d.) for 6–12 months. All-cause and cardiac mortality as well as major adverse cardiac events were significantly reduced with ticagrelor; the mechanisms of the mortality benefit might be related to the reduction in ischemic events (MI and stent thrombosis) without major increase in bleeding [28]; indeed, overall bleeding rate was similar to the clopidogrel control group,

despite higher non-CABG related major bleeding with ticagrelor. The benefits of the ticagrelor treatment in patients with ACS was observed irrespective of *CYP2C19* and *ABCB1* polymorphisms in a genetic substudy from the PLATO trial [29]. A prespecified subgroup analysis demonstrated a significant interaction between treatment and region of the world ( $p = 0.045$ ), with less effect of ticagrelor in North America than in the rest of the world [30]. The lowest risk of cardiovascular death, MI or stroke with ticagrelor compared with clopidogrel is associated with a low maintenance dose of concomitant ASA [30].

The GP2b/3a receptor inhibitors used in ACS are iv. agents belonging to different classes: abciximab (Reopro<sup>®</sup>) is a monoclonal antibody fragment; eptifibatid (Integrilin<sup>®</sup>) is a cyclic peptide; and tirofiban (Aggrastat<sup>®</sup>) is a peptidomimetic molecule. A meta-analysis of major randomized trials of GP2b/3a inhibitors in patients with ACS revealed a significant decrease in ischemic events (death or nonfatal MI) at 30 days in patients treated with GP2b/3a inhibitors when undergoing PCI [31]. No significant benefit was noted in the medically treated patients and/or if the PCI was performed once the Gp2b/3a was discontinued [31]. In two randomized trials the early infusion of these agents was not superior to a delayed, provisional use only after diagnostic coronary angiography, but before starting the PCI (HORIZONS-TIMING and 32); conversely, it was associated with an increased risk of non-life-threatening bleeding [32]. Therefore, GP2b/3a inhibitors should be considered only after defining the coronary anatomy (e.g., extent of disease and thrombotic burden), balancing their anti-thrombotic benefits against their increased risk of bleeding in the particular patient with ACS. Furthermore, abciximab plus unfractionated heparin (UFH), compared with bivalirudin, failed to reduce the rate of death, any recurrent MI, or urgent target-vessel revascularization and increased the risk of bleeding among patients with ACS undergoing PCI [33].

GP 2b/3a inhibitors can still be considered for unstable patients being transferred to a PCI facility from a hospital without a catheterization laboratory.

### Antithrombotics

Anticoagulation represents, together with the antiplatelet therapy, the cornerstone of anti-thrombotic therapy in the ACS population. Several anticoagulants (indirect and direct inhibitors of thrombin and/or Factor Xa) were studied in ACS.

UFH is usually administrated on a weight-adjusted dosing regimen as a means to provide a more predictable and constant level of systemic anticoagulation. In the setting of an ACS, where patients are already on a concomitant regimen of dual antiplatelet therapy and GP 2b/3a may be used liberally during the PCI, UFH may be started at a lower bolus dose (50–60 U/kg iv. bolus), followed by further iv. boluses in order to achieve and maintain an activated clotting time of 200–300 s. After completion of the intervention, the UFH should be discontinued and the arterial sheath has to be removed as soon as possible, to decrease the incidence of access site bleeding complications.

Low-molecular-weight heparins (indirect thrombin and Factor Xa inhibitors) were tested against UFH in ACS patients managed with an early invasive strategy in the SYNERGY trial [34]. No differences in ischemic events (abrupt closure and threatened abrupt closure, unsuccessful PCI, emergency CABG) during PCI were observed between enoxaparin and UFH groups, respectively. Enoxaparin use was associated with statistically significant increase in thrombolysis in myocardial infarction major bleeding [34]. Patients pretreated with enoxaparin (1 mg/kg subcutaneous [sc.] b.i.d.) following an invasive strategy do not usually need additional enoxaparin during PCI; an additional 0.3 mg/kg iv. bolus is recommended if the last sc. enoxaparin injection was administered more than 8 h before PCI or if less than 3 consecutive sc. doses of enoxiparin were used [34,35]. This agent remains a good option for patients treated with a conservative approach in hospitals without a cardiac catheterization laboratory.

Fondaparinux (a selective Factor Xa inhibitor) was studied against enoxiparin in the OASIS 5 trial [36]. In the subgroup of patients who underwent revascularization, the use of fondaparinux was associated with similar rates of death, MI and refractory ischemia at 9 days when compared with the subgroup of patients receiving enoxiparin [36]. Major bleeding 48 h after the procedure was significantly lower with fondaparinux than with enoxaparin and this translated also into a significant reduction of the combined endpoint of death, MI, stroke or major bleeding at 9 and 30 days in the patients treated with fondaparinux [36]. However, in the patients undergoing PCI there was a significant increase in the rate of guiding-catheter thrombus formation with fondaparinux versus enoxaparin prompting the OASIS investigators to recommend the use of UFH as an adjunctive therapy at the time of the PCI [37]. Patients with

ACS treated with fondaparinux and undergoing PCI may receive activated clotting time-guided standard dose of UFH [38].

The iv. direct thrombin inhibitor bivalirudin (Angiomax<sup>®</sup>) has been proven to be at least as safe as UFH in preventing ischemic complications during and after PCI; however, its use is associated with significantly less bleeding complications than the use of UFH [39,40,41]; these observations were confirmed irrespective of the concomitant use of GP 2b/3a inhibitors [40,41]. The ACUITY trial prospectively tested three different anticoagulation regimens in ACS: heparin (UFH or enoxaparin) plus GP 2b/3a inhibitors, bivalirudin plus GP 2b/3a inhibitors, or bivalirudin alone. Anticoagulation with bivalirudin alone suppressed major ischemic events to a similar extent as heparin plus GP 2b/3a inhibitors, while significantly lowering the risk of major hemorrhagic complications [42,43]. Patients that were switched from heparin (UFH or enoxaparin) to bivalirudin monotherapy during the PCI had comparable ischemic outcomes and an approximately 50% reduction in major bleeding compared with the patients who were treated with heparin and a GP 2b/3a inhibitor [44].

In a recently presented trial, very low dose (2.5 mg daily) of the Factor Xa inhibitor riveroxaban provided significant ischemia-free survival benefit and only modest increase in bleeding [45].

In summary, patients with ACS benefit from an early invasive strategy if they are in a medium- and/or high-risk group at their initial

presentation. Individualization of the dual antiplatelet therapy and of the anticoagulation regimen used during the PCI (in order to balance the anti-ischemic benefit vs the bleeding risk) allows a safe coronary revascularization in the particular patient presenting with ACS.

### Future perspective

A better and faster risk assessment of the patients presenting with ACS will be developed over coming years and as such, a better emergency room triage of these patients will be achieved. The choice of the antiplatelet and antithrombotic therapy will be individualized as per the particular clinical characteristics of the presenting patient (e.g., age, sex and comorbidities) and by his/her genotype, balancing the benefit of antithrombotic effect with the risks of bleeding. The wider use of the bioabsorbable stents and of the coating balloons will allow a much safer management of a wider spectrum of patients presenting with ACS.

### Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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### Executive summary

- Acute coronary syndromes (ACS) represent a large segment of the patients with coronary artery disease.
- Risk score models were developed over time in order to better evaluate the prognosis of the patients with ACS and as such to determine the appropriateness of the invasive management.
- The benefit of an early invasive strategy (the first 24 h of the initial presentation) was observed mostly in the high-risk group patients, reducing significantly the rate of the composite secondary outcome of death, myocardial infarction or refractory ischemia.
- Once the invasive strategy is followed and coronary revascularization is contemplated the adjunctive pharmacology regimen (antiplatelets and antithrombotics) has to be adjusted to the particular patient, balancing the antithrombotic advantages versus the bleeding risk.
- Patients with ACS benefit from an early invasive strategy if they are in a medium- and/or high-risk group at their initial presentation. Individualization of the dual antiplatelet therapy and of the anticoagulation regimen used during the percutaneous coronary intervention (in order to balance the anti-ischemic benefit vs the bleeding risk) allows a safe coronary revascularization in the particular patient presenting with ACS.

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