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EDITORIAL

Percutaneous treatment in acute coronary syndromes

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Abstract

Both ST-segment elevation myocardial infarction and non-ST-segment elevation acute coronary syndromes (ACS) are the result of an acute thrombotic lesion obstructing blood flow in the coronary vasculature. Percutaneous treatment has shown to improve clinical outcome in this clinical setting by resolving coronary obstruction with different devices directed to restore coronary blood flow. In comparison with balloon alone angioplasty, implantation of bare metal stents reduced the rate of restenosis and cardiac events, but high rates of restenosis remained, leading to further investigations to develop drug-eluting stents with different pharmacological coatings that reduced restenosis rates and clinical events. In this review, we discuss the current treatment of ACS, reviewing recent randomized clinical trials and advances in medical treatment, including new antiplatelet agents and recent guideline recommendations.

Key words: Coronary revascularization; Acute coronary syndromes; Stent; ST-elevation myocardial infarction; Non-ST-elevation myocardial infarction

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INTRODUCTION

Myocardial revascularization is the key therapy for acute coronary syndromes (ACS). Accordingly, it is in this clinical setting when the expected benefits (increased survival, relief of symptoms, and improvement of quality of life) exceed the potential negative consequences of the procedure[1].

ACS include both ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation (NSTE) ACS. However, coronary vasospastic angina (10%-15% presenting with ST-segment elevation) is commonly included in the NSTE-ACS group. Both STEMI and NSTE-ACS are associated with high morbidity and mortality rates. Risk assessment is crucial in contemporary clinical practice and should hinge on developed risk scores[1] to predict mortality, with EuroSCORE for percutaneous and surgical treatment and SYNTAX for percutaneous coronary interventions (PCI).

Recent guidelines[1] have highlighted that patients should take an active role in the decision-making process especially when offered different types of revascularization procedures, so it is necessary to provide clinical information. This strategy has shown to improve outcomes[1]. A multidisciplinary team (Heart Team) should meet and discuss each patient's characteristics and optimize the objective decision-making process, with consideration of

sex, race, availability, technical skills, local results, referral patterns, and patient preference. Coronary artery bypass graft (CABG) surgery may be considered in some patients according to their clinical characteristics, and number and location of coronary lesions.

REVASCULARIZATION IN NSTE ACS

NSTE-ACS is the most frequent manifestation of ACS and represents the largest group of patients with ACS undergoing PCI. Despite continuous advances in medical and interventional treatments, mortality and morbidity remain high and are frequently equivalent to those of patients with STEMI after the initial month[1].

Patients with NSTE-ACS are very heterogeneous with a highly variable prognosis. Therefore, early risk stratification is essential for selection of the best treatment strategy.

Early invasive vs conservative strategy

Randomized clinical trials have shown that an early invasive strategy reduces ischemic endpoints mainly by reducing severe recurrent ischemia and the clinical need for further rehospitalization and revascularization. These trials have also shown a clear reduction in the rate of mortality or myocardial infarction (MI) in the medium term, while the reduction in mortality in the long term has been moderate and MI rates during the initial hospital stay have even been increased (early hazard) (Table 1). The most recent meta-analysis confirms that an early invasive strategy reduces the rate of cardiovascular death or MI at up to 5 years of follow-up[2]. These benefits were more evident in patients at higher risk. Troponin elevation and ST-segment depression at baseline appear to be the most powerful individual predictors of benefit from invasive treatment. Recently published European Society of Cardiology Guidelines on Coronary Revascularization[1] recommend the use of the Global Registry of Acute Coronary Events (GRACE risk score)[3] to guide clinical management[4,5]. Predictors of high thrombotic risk or of high risk for progression to MI, which constitute indications for emergency coronary angiography are[1,6]: (1) ongoing or recurrent ischemia; (2) dynamic spontaneous ST changes (> 0.1 mV depression or transient elevation); (3) deep ST-segment depression in anterior leads V_2-V_4 indicating ongoing posterior transmural ischemia; (4) hemodynamic instability; and (5) major ventricular arrhythmia.

The 2009 American College of Cardiology/American Heart Association Guidelines on coronary revascularization included a new class IIa recommendation to perform coronary angiography within the first 12-24 h after the onset of symptoms for patients with high risk (GRACE score > 140)[7,8]. In lower risk patients, revascularization can be delayed without increased risk but should be performed during the same hospital stay, preferably within 72 h of admission. Although subgroups of patients, such as women and the elderly, may be at higher risk of bleeding and other complications, they should not be treated differently from other patients included in clinical trials.

Pharmacologic treatment

Aims of pharmacologic treatment in patients with NSTE-ACS undergoing coronary angiography and PCI are: (1) to prevent coronary clot formation or progression; (2) to stabilize atherosclerotic plaques; and (3) to relieve ischemia. Treatment should be decided with consideration of both ischemic (ST-segment changes, elevated troponin, diabetes, GRACE score > 140) and bleeding risk (female sex, age > 75 years, bleeding history, glomerular filtration rate < 30 mL/min and use of femoral access), as they both worsen short- and long-term prognosis.

Angiotensin converting enzyme inhibitors should be initiated as part of the treatment of ACS as they have been shown to reduce left ventricular dilatation and to improve left ventricular ejection fraction. High-dose statin treatment has been shown to improve in-hospital and long-term outcomes in patients presenting with ACS. Up-titration of β-blocker therapy on admission is of critical value for these patients.

Antiplatelet therapy: Dual antiplatelet therapy (DAPT) includes aspirin (ASA) 150-300 mg po or 250-500 mg iv bolus, followed by 75-100 mg daily, and either clopidogrel (600 mg as loading dose, followed by 75 mg daily), or prasugrel (60 mg as loading dose, followed by 10 mg daily), or ticagrelor (180 mg as loading dose, followed by 90 mg twice daily). A higher clopidogrel maintenance dose for 1 or 2 wk immediately following stent implantation has shown some benefit in terms of reduced major adverse cardiac event rates without a significant increase in bleeding[9], but additional studies are necessary in order to confirm preliminary results.

In the TRITON TIMI 38 trial, prasugrel has been tested against a 300 mg loading dose of clopidogrel, with both started in the catheterization laboratory after diagnostic angiography, and proved to be beneficial with respect to a combined thromboembolic-ischemic outcome[10]. Recurrent cardiovascular events were significantly reduced in patients allocated to prasugrel patients. Severe bleeding complications increased with prasugrel, specifically in patients with a history of stroke and transient ischemic attack, in the elderly (≥ 75 years), and in patients with body weight < 60 kg. Bleeding was also increased in prasugrel-treated patients referred for early CABG. Excluding those patients at higher risk of bleeding, prasugrel offers significant benefit over clopidogrel with respect to cardiovascular events without increasing severe bleeding. In diabetic patients presenting with ACS, prasugrel confers a significant advantage over clopidogrel without increased bleeding[11].

Ticagrelor, a non-thienopyridine ADP receptor blocker which reversibly inhibits platelet function, has been compared with clopidogrel. The PLATO study confirmed a significant improvement in combined clinical endpoints,

Table 1 Recommendations for revascularization in non-ST-segment elevation acute coronary syndromes[1]

Situation	Class of recommendation	Level of evidence
An invasive strategy is indicated in patients with: GRACE score > 140 or at least one high-risk criterion Recurrent symptoms Inducible ischemia at stress test	I	A
An early invasive strategy (< 24 h) is indicated in patients with GRACE score > 140 or multiple other high-risk criteria	I	A
A late invasive strategy (within 72 h) is indicated in patients with GRACE score < 140 or absence of multiple other high-risk criteria but with recurrent symptoms or stress-inducible ischemia	I	A
Patients at very high ischemic risk (refractory angina, with associated heart failure, arrhythmias or hemodynamic instability) should be considered for emergent coronary angiography (< 2 h)	IIa	C
An invasive strategy should not be performed in patients: At low overall risk At a particular high-risk for invasive diagnosis or intervention	III	A

GRACE: Global Registry of Acute Coronary Events.

including mortality, in favor of ticagrelor[12]. The rate of severe non-CABG-related bleeding was similar to that of prasugrel in the TRITON-TIMI 38 trial, while CABG-related bleeding was lower than for clopidogrel, most probably a consequence of the faster inactivation of the agent after stopping intake.

The greatest benefit of GP IIb-IIIa inhibitors *vs* placebo was demonstrated in earlier recent clinical trials when ADP receptor blockers were not routinely used[5]. The usefulness of upstream eptifibatide, with or without clopidogrel, was not confirmed in the EARLY-ACS trial. This lack of benefit was associated with a higher bleeding risk[13]. The selective "downstream administration" of abciximab in the catheterization laboratory, in combination with a 600 mg clopidogrel loading dose, has been shown to be effective in troponin-positive NSTE-ACS patients in some studies[14] and may therefore be preferred over upstream use.

Anticoagulation: The golden rule is to avoid crossover especially between unfractionated heparin (UFH) and low molecular weight heparin[5] and to discontinue antithrombinic agents after PCI except in specific individual situations (e.g., thrombotic complications).

Risk stratification in NSTE-ACS patients determines the use of specific agents and doses. Patients at very high ischemic risk (e.g., persistent angina, hemodynamic instability, refractory arrhythmias) should immediately be referred to the catheterization laboratory and receive UFH, combined with DAPT. In patients at high risk of bleeding, bivalirudin (0.75 mg/kg bolus followed by 1.75 mg/kg per hour) can be used instead of UFH.

In patients at intermediate or high risk (e.g. troponin positive, recurrent angina, dynamic ST changes) for whom an invasive strategy is planned within 24-48 h, options for anticoagulation are: (1) in patients < 75 years, either UFH (60 IU/kg iv bolus, then infusion until PCI, controlled by activated partial thromboplastin time) or enoxaparin (1 mg/kg sc twice daily until PCI) or fondaparinux (2.5 mg daily sc until PCI) or bivalirudin (0.1 mg/kg iv bolus followed by infusion of 0.25 mg/kg per hour until PCI); and (2) in patients ⩾ 75 years, either UFH (60 IU/kg iv bolus, then infusion until PCI) or enoxaparin (0.75 mg/kg sc twice daily until PCI) or fondaparinux (2.5 mg daily sc) or bivalirudin (0.1 mg/kg iv bolus followed by infusion of 0.25 mg/kg per hour until PCI).

Management during catheterization: The initial therapy should be maintained, avoiding switching between different anti-thrombotic drugs (with the exception of adding UFH to fondaparinux). The management during PCI depends on the treatment administered prior to the procedure. (1) Previous treatment with UFH: continue infusion, activated clotting time measurement should be used during PCI with the following target range: 200-250 s with GP IIb-IIIa inhibitors, 250-350 s without GP IIb-IIIa inhibitors; (2) Previous treatment with enoxaparin: In patients with less than 8 h since last sc dose, no additional bolus is needed. In contrast, in patients within 8-12 h of the last sc dose, a 0.30 mg/kg iv bolus should be added, and in those with > 12 h since the last sc dose, a 0.75 mg/kg iv bolus should be administered; (3) Previous treatment with fondaparinux: it is indicated that UFH 50-80 IU/kg be added when PCI is performed. Fondaparinux, an indirect factor Xa inhibitor, has been tested against enoxaparin in the OASIS-5 trial[15]. The combined ischemic event rate was similar, but severe bleeding complications were highly significantly reduced with fondaparinux. This favourable net clinical outcome with fondaparinux included lower long-term mortality and stroke rates. Because of a higher rate of catheter thrombosis when fondaparinux alone was used, UFH should be added for patients referred for angiography and PCI[16]; and (4)Previous treatment with bivalirudin: An additional iv bolus of 0.5 mg/kg should be given and the infusion rate increased to 1.75 mg/kg per hour before PCI. Bivalirudin, a direct antithrombin, alone or in combination with GP IIb-IIIa inhibition, was compared with UFH/enoxaparin + GP IIb-IIIa inhibition. Bivalirudin monotherapy was superior to either regimen with respect to reduced bleeding, without increased ischemic events[17].

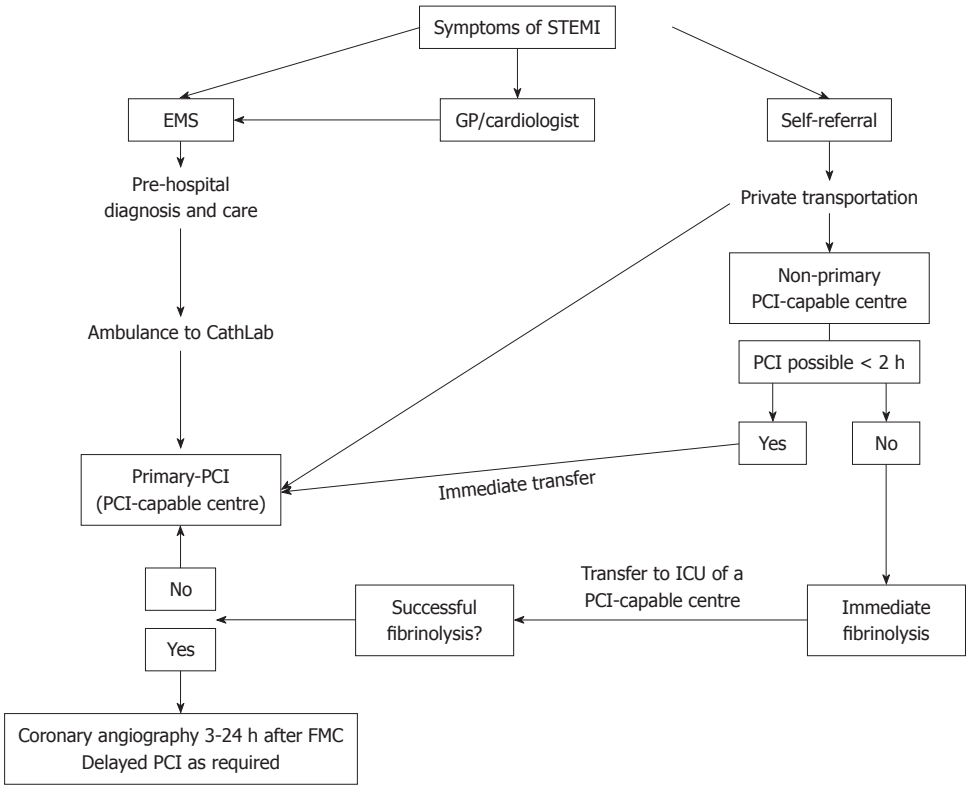

Figure 1 Organization of ST-segment elevation myocardial infarction patient pathway[1]. EMS: Emergency medical service; FMC: First medical contact; GP: General physician; ICU: Intensive care unit; PCI: Percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

REVASCULARIZATION IN ST-SEGMENT ELEVATION ACS

General guidelines

Primary PCI performed within the first 6-12 h after symptom onset has shown to provide more effective restoration of vessel patency, less re-occlusion, improved residual left ventricular function and better clinical outcome compared with fibrinolysis[18-20].

It is essential to minimize all time delays. When the expected delay is > 2 h, patients admitted to a non-PCI centre should receive fibrinolysis and then be transferred to a PCI-capable centre. In cases of persistence of ST-segment elevation after fibrinolysis (more than a half of the maximal initial elevation in the worst ECG lead) and/or persistent ischemic chest pain, rescue PCI should be considered. In the case of successful fibrinolysis, patients may be referred for PCI within 24 h (Figure 1)[7].

In patients presenting > 3 d after the acute event with a fully developed Q-wave MI, revascularization is indicated in those with recurrent angina and/or documented ischemia and viability[1,7].

Cardiogenic shock is the leading cause of in-hospital death for MI patients, even in those treated with primary PCI[21]. Echocardiography should always be performed in the setting of acute heart failure to assess left ventricular function and to rule out life-threatening mechanical complications that may require surgery (mitral regurgitation), ventricular septal defect, free wall rupture or cardiac tamponade[1]. In those patients complete PCI of non-infarcted vessels (i.e. PCI performed in all critically stenosed large epical coronary arteries) should be considered. In the presence of hemodynamic impairment, intra-aortic balloon pumping is recommended[21].

In patients with multivessel disease and STEMI but without cardiogenic shock, early PCI should focus on the coronary artery responsible for the ACS[22,23]. Staged PCI for a complete revascularization is the recommended strategy as it encounters less morbidity and mortality.

PHARMACOLOGIC TREATMENT

Antiplatelet therapy

DAPT consists of ASA 150-300 mg po or 250-500 mg bolus iv, followed by 75-100 mg daily, and either prasugrel (60 mg as loading dose, followed by 10 mg daily), ticagrelor (180 mg as loading dose, followed by 90 mg twice daily), or clopidogrel (600 mg as loading dose, followed by 75 mg daily)[24,25].

Increasing the maintenance dose of clopidogrel to 150 mg/d for 1-2 wk might be effective in STEMI patients, as shown in NSTE-ACS. Prasugrel is superior to clopidogrel (300 mg loading dose, 75 mg maintenance dose) in reducing combined ischemic endpoints and stent thrombosis in STEMI patients without increasing the risk of severe bleeding[24]. A predefined subgroup analysis has demonstrated that STEMI or NSTE-ACS patients referred for PCI significantly benefit from ticagrelor *vs* clopidogrel, with similar bleeding rates[8,26]. Most studies of GP Ⅱb-Ⅲa inhibitors in STEMI have evaluated

abciximab (0.25 mg/kg iv bolus followed by infusion of 0.125 mg/kg per minute up to a maximum of 10 mg/min for 12 h) but more recent trials have also been performed with tirofiban[27]. Findings are mixed regarding the effectiveness of facilitation (early administration) with GP Ⅱb-Ⅲa inhibitors before catheterization. While the only available clinical trial[28] showed no benefit, registries, meta-analyses, and *post hoc* analyses of the APEX-AMI[29] show positive results. The controversial literature data, the negative outcome of the only prospective clinical trial[28], and the beneficial effects of faster acting and more efficacious ADP receptor blockers in primary PCI do not support pre-hospital or pre-catheterization use of GP Ⅱb-Ⅲa inhibitors.

Anticoagulation

Options for anticoagulation include mainly UFH (60 IU/kg iv bolus with GP Ⅱb-Ⅲa inhibitor or 100 IU/kg iv bolus without GP Ⅱb-Ⅲa inhibitor under monitoring with ACT), and bivalirudin (0.75 mg/kg bolus followed by 1.75 mg/kg per hour). Antithrombins can be stopped after PCI for STEMI with few exceptions such as left ventricular aneurysm and/or thrombus, atrial fibrillation, and prolonged bed rest.

A recent study suggested bivalirudin monotherapy as an alternative to UFH plus a GP Ⅱb-Ⅲa inhibitor[30]. Significantly lower severe bleeding rates let to a beneficial net clinical outcome, indicating that bivalirudin may be preferred in STEMI patients at high risk of bleeding. The 1-year outcome of the HORIZONS clinical trial confirmed the beneficial effect of bivalirudin monotherapy *vs* UFH plus a GP Ⅱb-Ⅲa inhibitor. Uncertainty remains in the early phase of primary PCI, when thrombotic complications seem to be higher with bivalirudin monotherapy. Fondaparinux was inferior to UFH in the setting of primary PCI in patients with STEMI (OASIS-6 trial)[31].

DRUG-ELUTING STENTS

Efficacy and safety of drug-eluting stents

Bare metal stents (BMS) were initially designed to treat major dissections, avoid acute vessel closure and prevent restenosis. However, due to a 20%-30% rate of recurrence of angiographic stenosis within 6-9 mo after implantation, restenosis with BMS has often been considered the Achilles' heel of PCI. In native vessels, drug-eluting stents (DES) significantly reduce angiographic restenosis and ischemia-driven target vessel revascularization[32,33]. In recent clinical trials, no significant differences were observed in the long-term rates of death or MI after DES or BMS use for either off-label or on-label indications[33,34]. First-generation DES are safe and efficacious for both on-label and off-label use, when implanted in the native circulation, in spite of a slightly increased propensity for late and very late stent thrombosis[32].

DES with proven efficacy should be considered by default in nearly all clinical conditions and lesion subsets, except if there are concerns or contraindications for prolonged DAPT. Indications for DES in a few specific patient or lesion subsets remain a matter of debate[35]. In selected STEMI patients[36-38], SES and PES were shown to be safe and effective in follow-up extending from 2 to 4 years. Studies based on angiographic endpoints favor the use of DES with strong antiproliferative properties (late lumen loss $\leqslant$ 0.2 mm)[39-42].

CONCLUSION

ACS are a common manifestation of atherosclerotic disease. Continuous advances have reduced morbidity and mortality risks, but there remain elevated rates of complications and mortality. Risk assessment is crucial in the setting of NSTE-ACS. Coronary revascularization is the major treatment of patients presenting with ACS. Optimal medical treatment including dual or triple antiplatelet therapy and anticoagulation are mandatory in this clinical setting. BMS have been used to alleviate coronary stenosis but high rates of restenosis developed. DES are the state-of-the-art treatment for coronary stenosis, excluding patients with elevated bleeding risk with prolonged DAPT. Further investigations will help us determine better pharmacologic regimens to minimize bleeding risk and thrombotic events.

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