
Implementation of reperfusion therapy in ST-segment elevation myocardial infarction A policy statement from the Belgian Society of Cardiology (BSC), the Belgian Interdisciplinary Working Group on Acute Cardiology (BIWAC) and the Belgian Working Group on Interventional Cardiology (BWGIC)

Marc J. CLAEYS, MD, PhD; Sofie GEVAERT, MD; Antoine DE MEESTER, MD; Patrick EVRARD, MD, PhD; Victor LEGRAND, MD, PhD; Chris VRINTS, MD, PhD; Guy BERKENBOOM, MD, PhD; Walter DESMET, MD, PhD; Glenn VAN LANGENHOVE, MD; Pascal VRANCKX, MD; Herbert DE RAEDT, MD; Frans VAN DE WERF, MD, PhD; Frank VAN DEN BRANDEN, MD

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Background

Acute heart attacks are a major healthcare problem with continuing high mortality and morbidity rates.

The major goal in the treatment of acute myocardial infarction (AMI) is the rapid restoration of blood flow and myocardial perfusion in the infarct zone. This can be achieved by either a pharmacological approach (fibrinolysis) or by a mechanical approach (immediate coronary angiography and coronary dilatation of the occluded infarct artery, the so-called primary percutaneous coronary intervention or PCI). A timely application of reperfusion therapy has been shown to influence favourably short- and long-term patient outcome.

Data from several large registries have, however, shown that reperfusion therapy is insufficiently implemented in many countries¹. A considerable number of patients with ST-segment elevation myocardial infarction (STEMI) do not receive any reperfusion therapy, for a wide variety of reasons, despite its availability and the absence of any contra-indication. In addition, for patients who do have access to reperfusion, pre- or in-hospital delays can adversely influence the outcome.

In this context, a policy conference was organised in Brussels on 30 September 2006 to review the status quo of reperfusion strategies, taking into account existing guidelines and data from registries. In addition, strategies to optimize reperfusion therapy were

discussed in regional meetings during 2007. This policy statement presents a summary of the topics discussed at the policy conference and subsequent regional meetings and also refers to the recently published European Society of Cardiology (ESC) guidelines on the management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. This document has been reviewed and approved by the board members of the Belgian Society of Cardiology and its working groups on acute cardiology and interventional cardiology.

Reperfusion therapy: review of the evidence

DIAGNOSIS OF STEMI

Early recognition of STEMI is a prerequisite for the timely initiation of reperfusion therapy. In all ACS patients a 12-lead ECG should be recorded and interpreted as quickly as possible after the first medical contact and ideally within a maximum of 10 minutes. Accordingly, the mobile care units (MUG-SMUR) should be equipped with appropriate ECG recorders and with medical staff trained in interpreting ECG recordings. Teletransmission of ECG recordings for final validation by a cardiologist may help to accelerate the decision for reperfusion therapy.

ST-segment elevation at the J-point with the cut-off points $>+0.2$ mV in precordial leads and >0.1 mV in the other leads are considered as diagnostic, as well as presumably new left bundle-branch block. In addition, careful analysis of the ST segment can help to predict the site of occlusion and to assess the amount of myocardium at risk (e.g. proximal LAD occlusion vs. more distally located LAD occlusion).

Address for correspondence: Prof. dr. Marc Claeys, Dept. of Cardiology, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium.
E-mail: marc.claeys@ua.ac.be

REPERFUSION THERAPY

The European Society of Cardiology (ESC) as well as the American College of Cardiology/American Heart association (ACC/AHA) have published guidelines for the management of ACS with ST elevation^{2,3}. The treatment algorithms of these guidelines advocate reperfusion therapy for all patients with STEMI within 12 hours after the onset of symptoms.

Fibrinolysis has been the standard treatment for more than 20 years, preserving left ventricular function and resulting in improved survival. Mechanical reperfusion techniques were introduced more than 15 years ago and have been improved by the application of stents and glycoprotein IIb/IIIa antagonists. The superiority of PCI over fibrinolysis has been documented in several randomised trials, provided the intervention can be performed by an experienced team and within 90 minutes after the first medical contact (FMC)^{4,5}. First medical contact must be understood as the time of the diagnosis of STEMI, whether in the pre-hospital setting, in the emergency room, or in the coronary care unit. The benefit of PCI over thrombolysis is most striking for high-risk patients (Killip class > 1) and for patients with an ischaemic time of more than 3 hours⁵. In deciding whether the patient should be treated by PCI or thrombolysis, the PCI-related time delay plays an important role and is defined as the theoretical difference between the time of FMC to balloon minus the time from FMC to the start of fibrinolysis (= door-to-balloon minus door-to-needle time). However, the PCI-related time delay that mitigates the benefit of mechanical intervention over thrombolysis varies considerably (between 60 and 120 minutes) and is influenced by age, symptom duration, fibrinolytic use, location and extent of infarction⁶. This implies that if PCI cannot be performed within a short time delay an individualised rather than a uniform approach for selecting the optimal reperfusion therapy is recommended. For instance, for young patients presenting early (< 2 h) with a large infarction, thrombolysis will be more appropriate if the PCI-related time delay exceeds 60 minutes. On the other hand, for older patients presenting late with non-anterior infarction, PCI will be the preferred therapy unless PCI-related time delay exceeds 120 minutes.

There is currently no evidence that facilitated PCI (upstream fibrinolysis followed by immediate PCI) improves outcome⁷. Figure 1 depicts a flow chart for the management of STEMI patients (< 12 h after onset of pain), taking into account the availability of coronary intervention facilities. Nitrates and aspirin should be given to all patients as soon as possible after the diagnosis is deemed probable. In addition, clopidogrel is started with a loading dose of 300 mg (or, preferably, 600 mg in case of primary PCI). If thrombolytic

therapy is given in patients older than 75 years, a maintenance dose of clopidogrel (75 mg) should be administered without loading dose. Unfractionated heparin is the preferred initial treatment for patients scheduled for primary PCI. If fibrin-specific thrombolytic therapy is initiated, enoxaparin is recommended (weight-adjusted and with reduced doses for patients > 75 y)⁸. STEMI patients who were admitted to a PCI centre should be referred as fast as possible to the cath lab for invasive evaluation and primary PCI with target door-to-balloon time of 90 ± 30 minutes. In addition, aggressive antiplatelet therapy with GIIb/IIIa antagonists (abciximab) should be initiated. The direct thrombin inhibitor, bivalirudin, can be used as an alternative anti-thrombotic treatment (instead of heparin + GIIb/IIIa antagonists)⁹.

For patients admitted to a non-PCI centre or for patients with a first medical contact outside the hospital, a more tailored strategy is recommended, taking into account cardiac risk profile and transfer time to PCI centres. Patients with a contra-indication for thrombolysis; patients at high risk because of haemodynamic instability (Killip class > 1 and/or malignant arrhythmias); patients with an anticipated transfer time of < 60 min, should be transferred to the nearest catheterisation centre for urgent invasive evaluation. In the other cases, the decision between thrombolysis and transfer to a PCI centre should be made individually and depends on several factors including anticipated time of transfer, patient condition, duration of ischaemia and medical transport system. In general, short transfer time (< 90 min) and long ischaemia time (> 3 h) favour transfer to a PCI centre. On the other hand, long transfer time (> 90 min) and short ischaemia time (< 3 h) are favourable factors for thrombolysis. Time to initiation of lytic therapy can be shortened by pre-hospital administration. If thrombolysis is chosen as the reperfusion strategy, it must not be considered as the end of treatment. Careful electrocardiographic and clinical evaluation should be used for a timely identification of patients with failed reperfusion who are candidates for rescue PCI¹⁰. After successful fibrinolysis patients should be scheduled for elective coronary angiography, if there are no contra-indications and preferably within a time window of 3 to 24 hours¹¹.

Lessons learned from registries

The same messages arise from registries and surveys in Europe and in the USA.

Patients seen in routine clinical practice differ significantly from those selected for participation in clinical trials as they are older, more often female, have a more severe cardiac condition and more often suffer from concomitant disease. As increasing age and severe

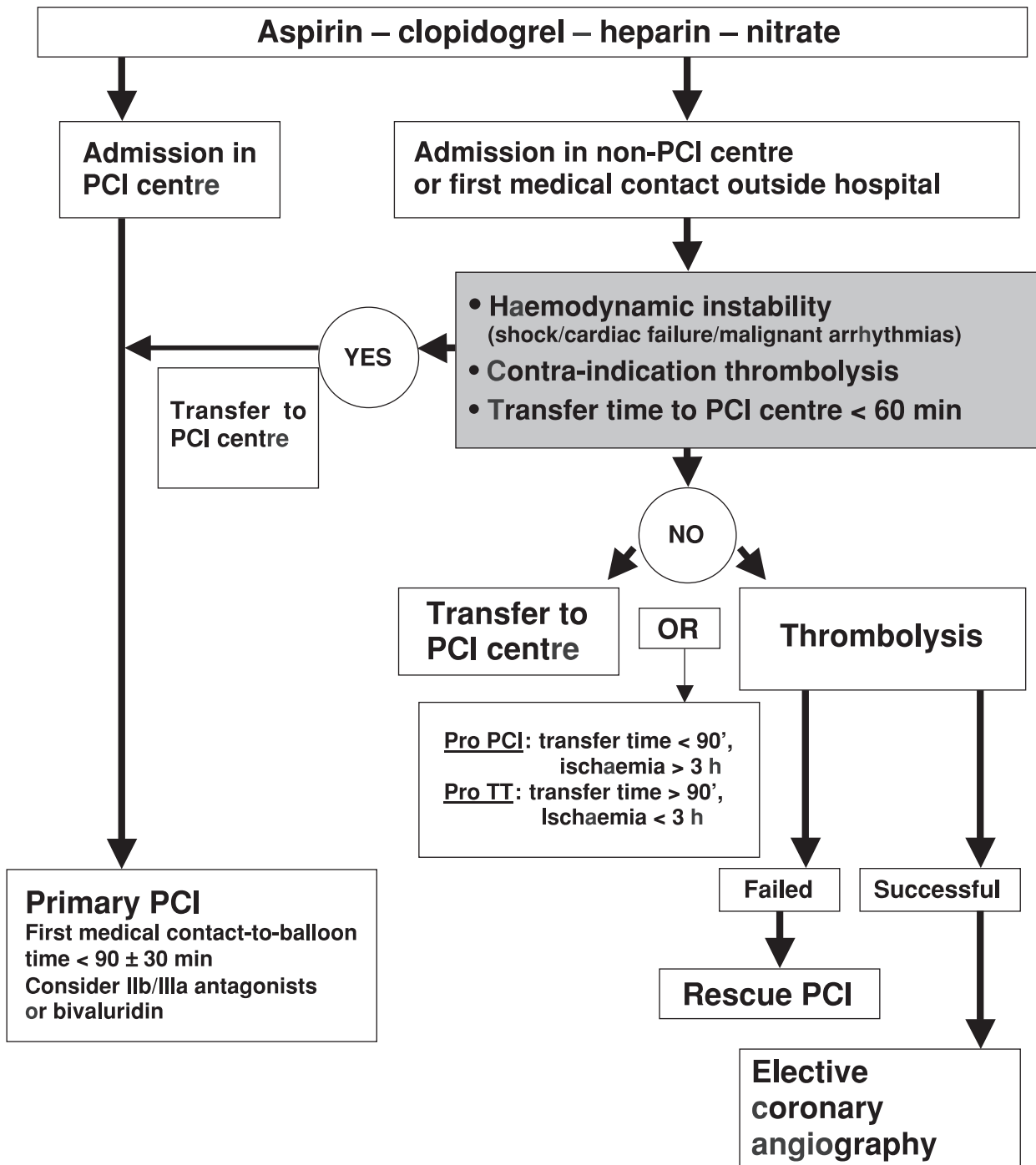


Fig. 1. – STEMI management flow chart.

co-morbidity are strong determinants of outcome, it is not surprising that reported mortality rates in registries are higher than in the clinical trials. In addition, several large registries have consistently shown that reperfusion therapy is insufficiently implemented. But, over time, a consistent increase in reperfusion therapy is observed which is linked to a significant reduction in mortality¹².

Data from the Euro Heart Survey on acute coronary syndromes II, collected in 2004, demonstrated that, at that time, 61% of included STEMI patients

received reperfusion therapy as compared to 56% in the first Euro Heart Survey on ACS in 2000. Thrombolysis, as a method of a reperfusion therapy, predominantly used in 2001, decreased from 63% to 41%, whereas the use of primary PCI increased from 37% to 59%. The impact on mortality was impressive, with a 23% risk reduction between ACS 1 en ACS 2 for mortality at 7 days and a 19% risk reduction at 30 days. Withholding reperfusion therapy was associated with a nearly doubled hospital mortality rate.

We emphasize that the data from the Euro Heart Survey come from a collection of well-equipped and highly trained departments of cardiology and may not therefore be representative of all regions in Europe. In fact, data from other more nationwide registries (Germany, Spain, USA) reveal a variability in clinical practice and adherence to guidelines.

In Belgium, clinical data on STEMI are available from the national registry of STEMI patients admitted to Belgian hospitals and from the Belgian registry of percutaneous coronary interventions. The overall mortality for the period 2007-2008 was 7%. Based upon the available data on the use of primary PCI, we estimate that PCI is performed in 60% and thrombolysis in 30% of STEMI patients. In 10% of patients no reperfusion therapy was initiated (mostly because of late presentation). Without reperfusion therapy mortality was more than double: 15% vs. 6.5%. The presence of cardiogenic shock, long-lasting ischaemia and older age were the most important other prognostic factors of in-hospital mortality.

Networks for STEMI and medical transport

To optimize treatment and meet the recommended timeframes for initiating reperfusion therapy, there needs to be an efficient, co-ordinated system of regionalised cardiac care. Such a system would encourage pre-arranged transfer agreements and protocols between referring hospitals and the PCI centre. In addition, valuable time can be saved if the ambulance can transfer the patient directly from the patient's home to the catheterisation laboratory, bypassing the ICU/CCU¹³.

There are many examples of well-established networks of reperfusion in Europe and recent reports (e.g. the Vienna experience) show that implementation of these networks reduces treatment delay, facilitates the use of primary PCI and results in a substantial reduction in mortality¹⁴.

In Belgium, the organisation of such networks is hampered by insufficient communication among the healthcare providers and by a lack of regulation for transferring critically ill STEMI patients from one hospital to another. Today, mobile coronary care units, located in PCI centres, still pick up critically ill patients in community centres, thereby doubling the transfer time. In addition, the national emergency medical system (by calling 100 or 112) is obliged to transport patients to the nearest hospital with an accredited emergency department (and not to the nearest PCI centre). Informing politicians and health authorities about this issue is of key importance. Fortunately, a recent circular of the federal minister of Public Health has been published that permits the transfer of critically ill STEMI patients with the public emergency

medical transport system (MUB/SMUR) to the nearest PCI centre, as long as this can be organised with the authorisation of both the referring and the accepting hospital (full text available on the BIWAC website: www.biwac.be). This measure, while representing a positive step forward, will only bring optimum benefit if sufficient financial resources are given to allow for the further expansion of the emergency medical transport system.

There is also a need to organise public information campaigns, as most of the time delay between the onset of symptoms and the start of reperfusion therapy is the result of a delay in patients seeking medical attention. The primary target of public information campaigns should be patients with a high cardiovascular risk profile who need to understand that they should seek urgent medical support if they experience prolonged chest pain.

Quality control

Quality control is a key issue for monitoring the efficacy of the management of STEMI patients. Registries should provide information on baseline risk factors (age, Killip class), time delays and modalities of reperfusion therapy, as well as outcome parameters such as mortality. Feedback in the form of benchmark reports should be part of the registries, as this is the strongest tool for encouraging the implementation of guidelines.

In addition, cardiac care programmes should stipulate quality criteria for performing primary PCI. Previous large-scale registries have shown a strong association between institutional and individual procedural volumes and clinical outcome, including mortality¹⁵. Hence, volume criteria have been established to ensure optimal quality care (experience leads to skills): operators should be experienced interventional cardiologists who regularly perform elective coronary interventions (at least >75 cases/year and optimally >150 cases/year) and should do a minimum of 12 PPCI/year. In addition, the institution should meet the volume criteria for PCI (>400 PCI/year) and should have a formalised protocol for immediate and safe transfer of patients for emergency cardiac surgery.

Conclusions

Over the last decades, a dramatic improvement in reducing STEMI mortality resulted from a more rapid reperfusion of the infarct-related artery. However, it is clear that implementation of the guidelines and improvements in clinical practice are still not ideal. We believe it is therefore time to establish a national policy with recommendations for achieving a more timely reperfusion in STEMI patients.

References

- Bassand JP, Danchin N, Filippatos G, Gitt A, Hamm C, Silber S, Tubaro M, Weidinger F. Implementation of reperfusion therapy in acute myocardial infarction. A policy statement from the European Society of Cardiology. *Eur Heart J* 2005; **26**: 2733-41.
- Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, Hochman JS, Krumholz HM, Lamas GA, Mullany CJ, Pearle DL, Sloan MA, Smith SC, Jr., Anbe DT, Kushner FG, Ornato JP, Pearle DL, Sloan MA, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B, Tarkington LG, Yancy CW: 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2008; **51**: 210-47.
- Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, Filippatos G, Fox K, Huber K, Kastrati A, Rosengren A, Steg PG, Tubaro M, Verheugt F, Weidinger F, Weis M, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Silber S, Aguirre FV, Al Attar N, Alegria E, Andreotti F, Benzer W, Breithardt O, Danchin N, Di Mario C, Dudek D, Gulba D, Halvorsen S, Kaufmann P, Kornowski R, Lip GY, Rutten F. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2008; **29**: 2909-45.
- Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003; **361**: 13-20.
- Thune JJ, Hoefsten DE, Lindholm MG, Mortensen LS, Andersen HR, Nielsen TT, Kober L, Kelbaek H. Simple risk stratification at admission to identify patients with reduced mortality from primary angioplasty. *Circulation* 2005; **112**: 2017-21.
- Pinto DS, Kirtane AJ, Nallamothu BK, Murphy SA, Cohen DJ, Laham RJ, Cutlip DE, Bates ER, Frederick PD, Miller DP, Carrozza JP, Jr., Antman EM, Cannon CP, Gibson CM. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. *Circulation* 2006; **114**: 2019-25.
- Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. *Lancet* 2006; **367**: 579-88.
- Antman EM, Morrow DA, McCabe CH, Murphy SA, Ruda M, Sadowski Z, Budaj A, Lopez-Sendon JL, Guneri S, Jiang F, White HD, Fox KA, Braunwald E. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 2006; **354**: 1477-88.
- Stone GW, Witzembichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Dangas G, Wong SC, Kirtane AJ, Parise H, Mehran R. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008; **358**: 2218-30.
- Gershlick AH, Stephens-Lloyd A, Hughes S, Abrams KR, Stevens SE, Uren NG, de Belder A, Davis J, Pitt M, Banning A, Baumbach A, Shiu MF, Schofield P, Dawkins KD, Henderson RA, Oldroyd KG, Wilcox R. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 2005; **353**: 2758-68.
- Fernandez-Aviles F, Alonso JJ, Castro-Beiras A, Vazquez N, Blanco J, Alonso-Briales J, Lopez-Mesa J, Fernandez-Vazquez F, Calvo I, Martinez-Elbal L, San Roman JA, Ramos B. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. *Lancet* 2004; **364**: 1045-53.
- Eagle KA, Nallamothu BK, Mehta RH, Granger CB, Steg PG, Van de WF, Lopez-Sendon J, Goodman SG, Quill A, Fox KA. Trends in acute reperfusion therapy for ST-segment elevation myocardial infarction from 1999 to 2006: we are getting better but we have got a long way to go. *Eur Heart J* 2008; **29**: 609-17.
- Rokos IC, Larson DM, Henry TD, Koenig WJ, Eckstein M, French WJ, Granger CB, Roe MT. Rationale for establishing regional ST-elevation myocardial infarction receiving center (SRC) networks. *Am Heart J* 2006; **152**: 661-7.
- Kalla K, Christ G, Karnik R, Malzer R, Norman G, Prachar H, Schreiber W, Unger G, Glogar HD, Kaff A, Laggner AN, Maurer G, Mlczoch J, Slany J, Weber HS, Huber K. Implementation of guidelines improves the standard of care: the Viennese registry on reperfusion strategies in ST-elevation myocardial infarction (Vienna STEMI registry). *Circulation* 2006; **113**: 2398-405.
- Vakili BA, Kaplan R, Brown DL. Volume-outcome relation for physicians and hospitals performing angioplasty for acute myocardial infarction in New York state. *Circulation* 2001; **104**: 2171-6.