EuroIntervention 2012;8:P36-P43

Acute coronary syndromes: is there a place for a real pre-hospital treatment for patients "en route" to the coronary intensive care unit?

Nathalie Assez, MD; Grégoire Smith, MD; Christophe Adriansen, MD; Wissam Aboukais, MD; Eric Wiel, MD, PhD; Patrick Goldstein*, MD

Emergency Department and SAMU, Lille University Hospital, Lille, France

Abstract

Acute initial management of patients with acute coronary syndrome (ACS) is based on a precise clinical and electrocardiographic diagnosis. Initial risk stratification in the pre-hospital phase is the key step. The last step, adequate patient routing, is decided based on emergency level and reperfusion strategies, considered right from the pre-hospital phase. The management of a patient with an ACS requires close collaboration between emergency physicians and cardiologists, according to simplified protocols for easier access to catheterisation. The next challenges for the pre-hospital management of ACS are based on:

– precise knowledge of new antiplatelet and anticoagulant drugs by the emergency physicians, in order to adjust their prescriptions to the patient profile;
– developing co-operation between hospitals, according to regional specificities (geographic considerations and distribution of PCI centres) in order to reduce access time to catheterisation rooms;
– organising the healthcare network, where the SAMU has an essential role in coordinating the different medical actors;
– regular analysis of the evolution of our professional practices, considering, e.g., the guidelines of the "HAS" (French official healthcare guidelines institute);
– integrating pre-hospital medicine in health prevention programmes;
– improving our understanding of the population's presentations of coronary artery disease, in order to encourage the patients and their families to call the EMS as soon as possible.

The challenge of the emergency physician is to adapt the strategies to the patient's needs.

Introduction

Cardiological activity represents on average 20% to 40% of the activity of the French Mobile Intensive Care Unit (MICU), of which 30% is acute coronary syndrome (ACS). This activity is not limited to ST-elevation myocardial infarction (STEMI). Indeed, the incidence of STEMI has decreased[1], but proactive strategies for management of ACS without ST-elevation (NSTEMI) are now a major issue. ACS care is constantly changing and evolving, due to better understanding of the pathophysiology and major therapeutics over recent years[2]. Many studies have led to changes in the diagnostic and prognostic approach by comparing the efficacy and safety of drug therapies and/or interventional therapies. Paradoxically, the growing number of clinical trials has sometimes made the choice more difficult for practitioners dealing with coronary emergencies. European and American guidelines have

*Corresponding author: Emergency Department and SAMU, Lille University Hospital, FR-59037 Lille cedex, France. E-mail: Patrick.Goldstein@chru-lille.fr

DOI: 10.4244/EIJV8SPA7

clarified the situation for STEMI, and stressed the essential role of the MICU[3]. Early administration of a combination of antiplatelet therapy before reperfusion (thrombolysis or angioplasty) has demonstrated its effectiveness[43,44]. The pre-hospital therapy for NSTEMI is far more complex. In these patients the balance between reperfusion quality and haemorrhagic risk is very delicate. The use of a risk score (GRACE, CRUSADE) in the pre-hospital setting cannot be done easily.

In this highly innovative context, a major challenge for the emergency physician is to adapt his strategies to the international guidelines and to stay as close as possible to the patient's needs, before sending him to the cardiologist, as soon as possible and in an adapted structure. STEMI patients and high-risk non-STEMI patients must be sent directly to an institution with cathlab facilities available 24 hours per day avoiding inter-hospital transfers[45,46].

First challenge: act fast

Apart from the choice of reperfusion technique, giving early treatment and activating the coronary emergency network's actors (emergency physicians and cardiologists) as soon as possible is a key factor in the success of reperfusion[4]. It is therefore essential for the MICU teams to intervene as soon as the patient calls. However, up to 2010, delays before support were often still unacceptable, and very few patients received all recommended treatments timeously[5]. Only 15% of patients referred for primary percutaneous coronary intervention (PCI) were treated within two hours[6,7].

Second challenge: recognising and identifying patients at risk

THE DOCTOR'S PERSPECTIVE

To adapt the means and avoid sending unnecessary MICU teams, the ideal system for sorting calls must have a high sensitivity and high specificity. Some data are needed after the first call to get through to the medical dispatching centre or emergency medical system (EMS) call centre (personal and family history, characteristics of pain, age, cardiovascular risk factors, and current medications). So far, however, the decision support software (algorithms) is disappointing: excellent sensitivity (99%) but low specificity (2%), and no data is in favour of a system based on estimation and subjectivity of experts to determine the sending of a MICU[8].

THE PATIENT'S PERSPECTIVE: DO NOT WAIT

The time taken for a patient to decide is usually the most critical period. Part of the delay in treatment occurs before the first medical contact and is often attributable to the patient himself. Patients calling late have certain individual characteristics: they are more often elderly, female, diabetics, they have atypical symptoms, or have a lower social status. Things are changing positively through public initiatives undertaken in the United States[9] and Europe[4]. Repeated information campaigns, delivering an easy-to-understand message on the characteristics of symptoms and the importance of time to "save the heart", are effective[10]. They encourage calling the emergency number of the local EMS directly in case of chest pain to shorten time to reperfusion[11]. Their impact led to an increased use of the EMS. Unfortunately, the effects of public campaigns are temporary. Despite mixed results, other methods to raise public awareness and to motivate an earlier call in coronary patients are tested in prevention programmes[12]. Indeed, a better understanding of how patients and families make the decision to alert the emergency services is essential. Awareness of the population's presentations and beliefs of coronary disease is useful to assess the individual risk perception, and thus to understanding better the severe underestimation by the patient especially in the elderly and women. These patients wait a long time after onset of pain before calling and the first call is often to their GP and not to the local EMS.

Third challenge: quick diagnosis

In France and many other European countries, the decision to initiate treatment relies on early diagnosis by the pre-hospital emergency physician, based on physical examination and ECG.

The qualifying ECG is the key to the diagnosis, regardless of where it is performed[13]. Its interpretation by an experienced physician will allow the diagnosis of STEMI or NSTEMI. It is the key determinant of a time for reperfusion of STEMI, either by pre-hospital thrombolysis (PHT) and/or by primary angioplasty. We can consider the first ECG as the first medical contact, and the delay between first medical contact and reperfusion according to the guidelines determines the choice of reperfusion[3]. If the delay is more than 120 minutes, lytic therapy must be administered as soon as possible, and PHT in these conditions seems to be the best option. Telemedicine offers new perspectives. For hospitals far away from specialised centres, tele-expertise can be performed by a specialist remotely, and a quick transfer by a medical team to the catheterisation laboratory can be organised.

THE USE OF A BIOLOGICAL DIAGNOSTIC TEST

As far as STEMI is concerned, the revascularisation decision must be immediate, because waiting for any biological blood test would delay reperfusion. Started in the MICU before reaching the hospital thanks to an on-board laboratory, and repeated in hospital, troponin measurement is an important diagnostic element. It influences the therapeutic strategy for NSTEMI but requires more than two hours after symptom onset before the markers can be detected[2]. A biomarker rising almost immediately could be useful to detect "high-risk" NSTEMI patients. The ultrasensitive troponins available in the emergency department cannot be exported to the pre-hospital setting[14]. Copeptin, the vasopressin prohormone, could improve early diagnosis of NSTEMI (within the first four hours). Combining troponin and copeptin may eliminate the diagnosis of infarction with greater security[15].

Fourth challenge: ischaemic and haemorrhagic risk stratification

Risk stratification is the cornerstone of the therapeutic management of NSTEMI[13]. Accurate stratification of the ischaemic risk (death and acute thrombotic complications) predictive scores (TIMI, PURSUIT, GRACE) is recommended[16]. However, they remain

difficult to use in the pre-hospital environment. Also, the validation of a clinical risk score remains a challenge: not only ischaemic risk but also haemorrhagic risk (inherent to choosing appropriate antiplatelet and anticoagulant drugs) should be evaluated in the pre-hospital phase[2,13]. Indeed, bleeding is steadily leading to increased mortality in a "dose-dependent" way[17]. The good regimen of dual antiplatelet therapy in the pre-hospital setting is balanced between two options: a simple choice for all patients, or a more complex strategy adapted to the age, weight and clinical history of the patients.

Fifth challenge: deciding on the optimal reperfusion strategy

IN STEMI

Optimal emergency treatment is now well codified[3]. The guidelines highlighted the essential role of the MICU to initiate the choice of the reperfusion strategy[3]. Access to angioplasty within less than 90-120 minutes after first medical contact is the main discriminating factor **(Figure 1)**. Accessibility to the catheterisation laboratory must take into account local conditions (distance, traffic conditions, weather)[7,18]. PPCI is recommended, if performed by an experienced operator within 120 min after the qualifying electrocardiogram. This acceptable delay should in some patients be reduced to 90 min (young subject, anterior necrosis, very high-risk patient)[3]. Data from registries show that in real life these time goals are extremely difficult to achieve. Pre-hospital thrombolysis is an alternative when primary PCI cannot be guaranteed within 120 min[4]. Its benefit and superiority when administered within two hours has been demonstrated[41]. The management strategy after thrombolysis remains controversial. The European Society of Cardiology (ESC) suggests performing a coronary angiography in all thrombolysed patients within 24 hours[19], while the American College of Cardiology/American Heart Association (ACC/AHA) restricts this strategy to high-risk patients only[20]. While some studies clearly demonstrated the interest of PHT followed by PCI, the "optimal" time to perform coronary angiography remains controversial[21]. It may be delayed to between three and 24 hours to avoid the prothrombotic period and thus reduce the risk of re-occlusion[3]. In case of no signs of reperfusion after thrombolysis, "rescue" PCI must be performed as soon as possible.

IN NSTEMI

Despite the updated guidelines, it is often difficult for the clinician to determine optimal management for these patients[13]. Faced with a NSTEMI, choosing an appropriate therapeutic strategy leads to

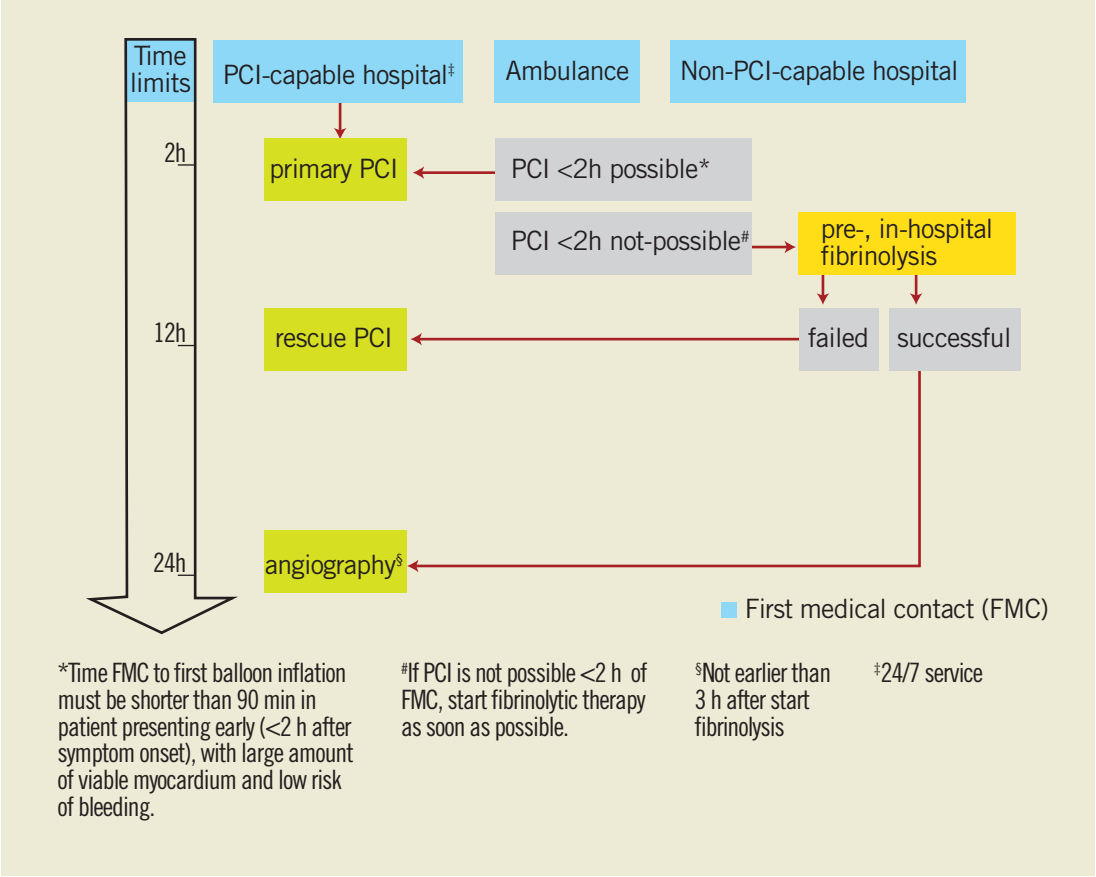

Figure 1. *STEMI management strategies in 2010*[3].

three questions: 1) the pharmacological environment; 2) routing the patients to the appropriate structure (with or without "cathlab"); and 3) delay before diagnostic coronary angiography[2]. Any patient suspected of a NSTEMI should be evaluated immediately by a qualified physician, routed according to risk, transported by a MICU with a physician on board and re-evaluated later in hospital. Taking an individual and personalised treatment decision based on risk/benefit is a new challenge for emergency physicians. The emergency physician must weigh the comorbidities and the clinical findings, and evaluate the pharmacological and interventional environment. The decision can translate into performing coronary angiography in immediate life-threatening emergencies or ideally within 48 hours in patients with medium to high risk[13].

Sixth challenge: the right use of anticoagulant and antiplatelet agents

The management of ACS should be integrated into up-to-date therapeutic strategies involving early use of anticoagulants and antiplatelet agents. The aim is to facilitate spontaneous reperfusion to stabilise atherosclerotic plaque and to limit thrombus extension, while ensuring pharmacological impregnation at the time of mechanical reperfusion. Numerous international studies have attempted to clarify their impact on morbidity and mortality because of a real risk of bleeding. Therefore, combining antiplatelet agents and anticoagulants (two or three) has become a major issue. Moreover, optimal combined dose has rarely been tested[22]. Three major therapeutic classes are available: anti-ischaemic agents, in particular beta-blockers and nitrates, anticoagulants (unfractionated heparin [UFH] , low molecular weight heparin [LMWH], fondaparinux or bivalirudin), and antiplatelet agents (aspirin, clopidogrel, prasugrel, ticagrelor, and glycoprotein IIb/IIIa inhibitors). The prescription depends on the initial risk, as perceived by the emergency physician, the recurrence of symptoms and biological data.

The antiplatelet agents

Aspirin is the routine treatment given as soon as possible to all patients, orally (150-325 mg) or intravenously (250 mg).

Among associated therapy, thienopyridines and new inhibitors of platelet aggregation may legitimately be used by emergency physicians. **Clopidogrel** - a bolus of 300 mg is recommended for patients less than 75 years old receiving PHT[23]. The ESC guidelines recommend 600 mg of clopidogrel in patients undergoing PPCI[3,24]. Administration of clopidogrel two hours before the procedure is associated with faster ST-segment resolution (90-180 minutes), increased incidence of TIMI 2-3 and a lower rate of recurrence and death[25]. Earlier on, attitudes were more controversial. Some considered routine clopidogrel before diagnostic coronary angiography useless or even dangerous[26]. Others argue that to wait until diagnostic coronary angiography to avoid bleeding risk in case of CABG (bypass surgery) is unfounded[27]. In 2012, the question as to whether there should or should not be a pre-treatment with clopidogrel is unresolved (ARMYDAS, CIPAMI). It is therefore important to reassess this practice considering the arrival of new, more powerful drugs. These issues are a real clinical challenge for a more rational use of these new oral antiplatelet agents in the pre-hospital setting. Prasugrel and ticagrelor are both recommended by the ESC guidelines for STEMI and high-risk NSTEMI as soon as possible for patients undergoing PCI but their use in the pre-hospital phase is still under investigation.

Prasugrel is a new P2Y12 inhibitor, twice as powerful as clopidogrel for inhibiting platelet aggregation (with a lower rate of non-responders), and it has a faster onset of action. The results of TRITON TIMI 38 showed a significant reduction of ischaemic events in the STEMI subgroup of patients treated with PCI (9.9% vs. 12.1%) and a similar rate of bleeding[28]. Therefore, it seems reasonable to consider prasugrel in pre-hospital STEMI patient care, carefully respecting the precautions (bleeding, prior stroke or TCI, low body weight and patients over 70 years old) for use. Clinical trials are currently underway in NSTEMI with elevated troponin to clarify the use of prasugrel in the pre-hospital phase (ACCOAST).

Ticagrelor is a "rapid and reversible" antiplatelet agent. With its effectiveness in relation to total mortality (4.5% vs. 5.9% for clopidogrel), it could be the preferred pre-hospital treatment of tomorrow[29]. Its short half-life, its reversibility and its safety profile appear particularly suitable for pre-hospital use. The effect of a loading dose for STEMI patients in the pre-hospital setting is currently being tested in an on-going trial (ATLANTIC).

Glycoprotein IIb/IIIa inhibitors (GPI) should probably be used in the cathlab only according to the guidelines[30]. The FINESSE trial was negative but the delay between onset of pain and administration of abciximab was quite long. On the other hand, ON-TIME 2[41] with tirofiban, using a surrogate endpoint, was positive. For a young patient with a large infarct and a delay from onset of pain to primary PCI of less than one hour, there could still be a benefit of pre-administration of glycoprotein inhibitors, but this hypothesis must be reinforced by new trials.

Anticoagulants integrated into early pre-hospital strategy

Unfractionated heparin (UHF)

UHF is the recommended anticoagulant as the primary therapy in the actual STEMI guidelines[3].

Enoxaparin

– In STEMI: enoxaparin is an interesting approach. Its effectiveness and safety has emerged as the reference low molecular weight heparin (LMWH), with established clinical benefit and a significant reduction in death or reinfarction. Its safety was confirmed in a large meta-analysis[31]. It is currently recommended in pre-hospital use for all patients receiving fibrinolytic therapy[32]. For patients undergoing primary PCI, the ATOLL trial was close to demonstrate superiority over UFH (net clinical benefit 10.2% vs. 15% for UFH) (0.5 mg/kg followed by 0.1 ml/kg subcutaneously)[33].

– In NSTEMI: LMWH has been validated, with or without associated coronary angiography. SYNERGY (enoxaparin vs. UFH) in an up-to-date design (aspirin + clopidogrel + PCI) confirmed the efficacy and relative safety of subcutaneous enoxaparin adjusted

to the weight (0.6 to 1.0 IU/ml). In unselected patients, it significantly reduced the death or infarction risk, and suggested that lower doses could decrease the bleeding risk in case of selective PCI[34].

Fondaparinux appears to be as effective in terms of ischaemic risk, and improves long-term morbidity and mortality, reducing bleeding and stroke risk, but is not recommended in patients requiring emergency angioplasty.

In the ESC NSTEMI guidelines, fondaparinux is recommended as the reference anticoagulant in patients where the need for angiography is not urgent[13,35].

Bivalirudin: this hirudin analogue proved to be a life-saving drug in patients with STEMI when given in the cathlab to patients treated by PPCI, but it has not yet been evaluated in the pre-hospital setting. The clinical benefit of bivaluridin (vs. UFH + glycoprotein inhibitors) results in lower bleeding risk (39%) with a similar reduction in antithrombotic efficacy. This benefit was still present at one year (absolute risk reduction 1.7%) and was also associated with a decrease in mortality[36]. In moderate or high-risk NSTEMI, ischaemic performance is equivalent to UFH + GPI but the bleeding profile is favourable (ACUITY, ISAR REAC 4)[13,37]. EUROMAX (bivalirudin vs. UFH + PCI <2 hours) is a randomised study designed to evaluate bivalirudin in pre-hospital STEMI patients. Results are expected in 2012.

Seventh challenge: to provide proper patient routing

– In STEMI: direct transfer to the catheterisation laboratory reduces mortality. It is thus essential to promote direct admission to these units by the MICU teams. Everything must be done to offer PPCI as soon as possible to STEMI patients.

PPCI is a IA recommendation in the current guidelines.

If the delay of two hours between first medical contact and PPCI cannot be respected, pre-hospital thrombolysis or a pharmaco-invasive approach followed by direct transfer to the cathlab for early PCI reduces morbidity and mortality compared to conservative ischaemia-guided treatment[39,42]. It is therefore essential for the physician to identify from among the thrombolysed patients those who should be transferred as soon as possible to the cathlab. OPTIMAL's goal was to identify quickly the 40%-45% of patients who will not respond to fibrinolysis, in order to organise their immediate transportation to the cathlab[38]. The results of several recent studies argue for an early transfer to the cathlab after thrombolysis, but the optimum time period between "successful" fibrinolysis and PCI is not yet clear[21,39]. A time span of three to 24 hours provides the best results, with a lower mortality, when PCI was performed more than three hours after fibrinolysis (1.6% vs. 3.7% when the PCI was performed within the first three hrs)[25]. The STREAM study, comparing fibrinolysis with delayed PCI to primary PCI may give useful information on this optimal time.

– In NSTEMI: the timing of an invasive strategy for high-risk patients should be tailored as soon as possible according to risk in three categories: urgent, early and conservative, depending on the patient's risk (GRACE score)[13]. Ideally, all high-risk non-STEMI patients must be transported by the MICU to cathlab facilities avoiding a second inter-hospital transfer.

Eighth challenge: building an efficient healthcare network

The current situation can be improved by setting up networks in which the local EMS organisation, cardiac intensive care units and cathlabs cooperate closely. This system will offer PCI access to the majority of patients within the recommended time.

Ninth challenge: involving a broader range of populations in our studies

Actual clinical research is often limited to relatively homogeneous groups, and some individuals (elderly >75 years) are systematically excluded from research protocols without justification. In the future, including elderly patients in these protocols should allow a more realistic approach, considering reduced ischaemic events vs. increased haemorrhagic risk phenomena in our ageing population.

Conclusion

The benefits of accurate diagnosis and risk stratification followed by treatment in the ambulance have been demonstrated. Powerful new drugs constantly enlarge the therapeutic possibilities for the emergency physician, but we still need more randomised trials adapted to the pre-hospital setting. Nevertheless, before discussing these "revolutionary" drugs, we should apply validated practices to improve catheterisation laboratory access, to comply with the guidelines in terms of delay. Through the national registries (FAST-MI, Stent for Life), evaluation of professional practice is possible and will enable us to compare the new strategies in order to optimise ACS management. These registries are the vital link between clinical trials and daily practice. Beyond their innovative qualities, these studies should take into account ethics, collective constraints and local conditions. Better coordination of local health facilities and specialised services should ensure access to quality care for all. Reflection on structured networks for coronary emergencies should continue. Tomorrow's coronary emergency management will be more "targeted" and individualised and therefore more complex. Emergency physicians will have to cope with interesting therapeutic innovations.

Conflict of interest statement

C. Adriansen is a speaker for Lilly, and Boehringer Ingelheim. P. Goldstein is a speaker and consultant for Lilly, Daiichi Sankyo, Boehringer Ingelheim, Astra Zeneca, The Medicines Company, Bayer, and Sanofi. The other authors have no conflicts of interest to declare.

References

1. Fox KA, Cokkinos DV, Deckers J, Keil U, Maggioni A, Steg G. The ENACT study: a pan-European survey of acute coronary syndromes. European Network for Acute Coronary Treatment. *Eur Heart J.* 2000;21:1440-9.

2. Bertrand ME, Simoons ML, Fox KA, Wallentin LC, Hamm CW, McFadden E, De Feyter PJ, Specchia G, Ruzyllo W; Task Force on the Management of Acute Coronary Syndromes of the European Society of Cardiology. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2002;23:1809-40.

3. 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; ESC Committee for Practice Guidelines (CPG). 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.

4. 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; Vienna STEMI Registry Group. 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.

5. Eagle KA, Nallamothu BK, Mehta RH, Granger CB, Steg PG, Van de Werf F, López-Sendón J, Goodman SG, Quill A, Fox KA; Global Registry of Acute Coronary Events (GRACE) Investigators. 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.

6. Fox K, Steg P, Eagle KA, Goodman SG, Anderson FA, Jr, Granger CB, Flather MD, Budaj A, Quill A, Gore JM; GRACE Investigators. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. *JAMA.* 2007;297:1892-900.

7. Nallamothu BK, Bates ER, Herrin J, Wang Y, Bradley EH, Krumholz HM; NRMI Investigators. Times to treatment in transfer patients undergoing primary percutaneous coronary intervention in the United States: National Registry of Myocardial Infarction (NRMI)-3/4 analysis. *Circulation.* 2005;111:761-7.

8. Steinbuch R. Regulatory changes for the treatment of patients with heart attacks. *Am J Cardiol.* 2007;99:1166-7.

9. Fox KA, Huber K. A European perspective on improving acute systems of care in STEMI: we know what to do, but how can we do it? *Nat Clin Pract Cardiovasc Med.* 2008;5:708-14.

10. Chevalier V, Alauze C, Soland V, Cuny J, Goldstein P. Impact of a public-directed media campaign on emergency call to a mobile intensive care units center for acute chest pain. *Ann Cardiol Angeiol (Paris).* 2003;52:150-8.

11. Cambou JP, Simon T, Mulak G, Bataille V, Danchin N. The French registry of Acute ST elevation or non-ST-elevation Myocardial Infarction (FAST-MI): study design and baseline characteristics. *Arch Mal Coeur Vaiss.* 2007;100:524-34.

12. Luepker RV, Raczynski JM, Osganian S, Goldberg RJ, Finnegan JR, Jr, Hedges JR, Goff DC, Jr, Eisenberg MS, Zapka JG, Feldman HA, Labarthe DR, McGovern PG, Cornell CE, Proschan MA, Simons-Morton DG. Effect of a community intervention on patients delay and emergency medical service in acute coronary heart disease. The Rapid Early Action for Coronary Treatment (REACT) trial. *JAMA.* 2000;284:60-7.

13. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D; ESC Committee for Practice Guidelines, Bax JJ, Auricchio A, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Poldermans D, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S; Document Reviewers, Windecker S, Achenbach S, Badimon L, Bertrand M, Bøtker HE, Collet JP, Crea F, Danchin N, Falk E, Goudevenos J, Gulba D, Hambrecht R, Herrmann J, Kastrati A, Kjeldsen K, Kristensen SD, Lancellotti P, Mehilli J, Merkely B, Montalescot G, Neumann FJ, Neyses L, Perk J, Roffi M, Romeo F, Ruda M, Swahn E, Valgimigli M, Vrints CJ, Widimsky P. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2011;32:2999-3054.

14. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, Tjora S, Domanski MJ, Gersh BJ, Rouleau JL, Pfeffer MA, Braunwald E; Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial Investigators. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med.* 2009;361:2538-47.

15. Keller T, Tzikas S, Zeller T, Czyz E, Lillpopp L, Ojeda FM, Roth A, Bickel C, Baldus S, Sinning CR, Wild PS, Lubos E, Peetz D, Kunde J, Hartmann O, Bergmann A, Post F, Lackner KJ, Genth-Zotz S, Nicaud V, Tiret L, Münzel TF, Blankenberg S. Copeptin improves early diagnosis of acute myocardial infarction. *J Am Coll Cardiol.* 2010;55:2096-106.

16. Ramsay G, Podogrodzka M, McClure C, Fox KA. Risk prediction in patients presenting with suspected cardiac pain: the GRACE and TIMI risk scores versus clinical evaluation. *QJM.* 2007;100:11-8.

17. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation.* 2006;114;774-82.

18. Ferrier C, Belle L, Labarere J, Fourny M, Vanzetto G, Guenot O, Debaty G, Savary D, Machecourt J, François P. Comparison of mortality according to the revascularisation strategies and the symptom-to-management delay in ST-segment elevation myocardial infarction. *Arch Mal Coeur Vaiss.* 2007;100:13-9.

19. Wagner GS, Macfarlane P, Wellens H, Josephson M, Gorgels A, Mirvis DM, Pahlm O, Surawicz B, Kligfield P, Childers R, Gettes LS, Bailey JJ, Deal BJ, Gorgels A, Hancock EW, Kors JA, Mason JW, Okin P, Rautaharju PM, van Herpen G; American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; American College of Cardiology Foundation; Heart Rhythm Society. AHA/ACCF/HRS

recommendations for the standardization and interpretation of the electrocardiogram: part VI: acute ischaemia/infarction: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. *Circulation.* 2009;119:e262-70.

20. Kushner FG, Hand M, Smith SC, Jr, King SB 3rd, Anderson JL, Antman EM, Bailey SR, Bates ER, Blankenship JC, Casey DE, Jr, Green LA, Hochman JS, Jacobs AK, Krumholz HM, Morrison DA, Ornato JP, Pearle DL, Peterson ED, Sloan MA, Whitlow PL, Williams DO; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2009 focused update: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guidelines and the 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guidelines and 2007 focused update): a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. *Circulation.* 2009;120:2271-306.

21. Di Mario C, Dudek D, Piscione F, Mielecki W, Savonitto S, Murena E, Dimopoulos K, Manari A, Gaspardone A, Ochala A, Zmudka K, Bolognese L, Steg PG, Flather M; CARESS-in-AMI (Combined Abciximab RE-teplase Stent Study in Acute Myocardial Infarction) Investigators. Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomised, multicentre trial. *Lancet.* 2008;371:559-68.

22. Lapostolle F, Catineau J, Lapandry C, Adnet F. Excess dosing of antithrombotic therapy in non-ST-segment elevation acute coronary syndromes. *JAMA.* 2006;295:1896-7.

23. Sabatine MS, Morrow DA, Montalescot G, Dellborg M, Leiva-Pons JL, Keltai M, Murphy SA, McCabe CH, Gibson CM, Cannon CP, Antman EM, Braunwald E; Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI) 28 Investigators. Angiographic and clinical outcomes in patients receiving low-molecular-weight heparin versus unfractionated heparin in ST-elevation myocardial infarction treated with fibrinolytics in the CLARITY-TIMI 28 Trial. *Circulation.* 2005;112:3846-54.

24. Mehta S. CURRENT-OASIS 7 Trial Results: A randomized comparison of a clopidogrel high loading and maintenance dose regimen versus standard dose and high versus low dose aspirin in 25,000 patients with acute coronary syndromes. "Hot line Session – Annual Congress of the European Society of Cardiology. Barcelona August 29-September 2, 2009". Available at http://www.escardio.org//esc-2009/congress-reports/Documents/706003-mehta-slides.pdf

25. Danchin N, Coste P, Ferrières J, Steg PG, Cottin Y, Blanchard D, Belle L, Ritz B, Kirkorian G, Angioi M, Sans P, Charbonnier B, Eltchaninoff H, Guéret P, Khalife K, Asseman P, Puel J, Goldstein P, Cambou JP, Simon T; FAST-MI Investigators. Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment-elevation acute myocardial infarction: data from the french registry on acute ST-elevation myocardial infarction (FAST-MI). *Circulation.* 2008;118:268-76.

26. Widimsky P, Motovská Z, Simek S, Kala P, Pudil R, Holm F, Petr R, Bílková D, Skalická H, Kuchynka P, Poloczek M, Miklík R, Maly M, Aschermann M; PRAGUE-8 Trial Investigators. Clopidogrel pre-treatment in stable angina: for all patients > 6 h before elective coronary angiography or only for angiographically selected patients a few minutes before PCI? A randomized multicentre trial PRAGUE-8. *Eur Heart J.* 2008;29:1495-503.

27. Szük T, Gyöngyösi M, Homorodi N, Kristóf E, Király C, Edes IF, Facskó A, Pavo N, Sodeck G, Strehblow C, Farhan S, Maurer G, Glogar D, Domanovits H, Huber K, Edes I. Effect of timing of clopidogrel administration on 30-day clinical outcomes: 300-mg loading dose immediately after coronary stenting versus pretreatment 6 to 24 hours before stenting in a large unselected patient cohort. *Am Heart J.* 2007;153:289-95.

28. Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, Antman EM; TRITON-TIMI 38 investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet.* 2009;373:723-31.

29. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361:1045-57.

30. Ellis SG, Tendera M, de Belder MA, van Boven AJ, Widimsky P, Janssens L, Andersen HR, Betriu A, Savonitto S, Adamus J, Peruga JZ, Kosmider M, Katz O, Neunteufl T, Jorgova J, Dorobantu M, Grinfeld L, Armstrong P, Brodie BR, Herrmann HC, Montalescot G, Neumann FJ, Effron MB, Barnathan ES, Topol EJ; FINESSE Investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med.* 2008;358:2205-17.

31. Silvain J, Beygui F, Barthélémy O, Pollack C Jr, Cohen M, Zeymer U, Huber K, Goldstein P, Cayla G, Collet JP, Vicaut E, Montalescot G. Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. *BMJ.* 2012;344:e553.

32. Antman EM, Morrow DA, McCabe CH, Murphy SA, Ruda M, Sadowski Z, Budaj A, López-Sendón JL, Guneri S, Jiang F, White HD, Fox KA, Braunwald E; ExTRACT-TIMI 25 Investigators. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med.* 2006;354:1477-88.

33. Montalescot G, Zeymer U, Silvain J, Boulanger B, Cohen M, Goldstein P, Ecollan P, Combes X, Huber K, Pollack C Jr, Bénezet JF, Stibbe O, Filippi E, Teiger E, Cayla G, Elhadad S,

Adnet F, Chouihed T, Gallula S, Greffet A, Aout M, Collet JP, Vicaut E; ATOLL Investigators. Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: the international randomised open-label ATOLL trial. *Lancet.* 2011;378:693-703.

34. Zeymer U, Gitt A, Jünger C, Koeth O, Zahn R, Wienbergen H, Gottwik M, Senges J; ACOS-Registry Participants. Clinical benefit of enoxaparin in patients with high-risk acute coronary syndromes without ST elevations in clinical practice. *Am J Cardiol.* 2006;98: 19-22.

35. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, Budaj A, Peters RJ, Bassand JP, Wallentin L, Joyner C, Fox KA; Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med.* 2006; 354:1464-76.

36. Mehran R, Lansky AJ, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Wong SC, Nikolsky E, Gambone L, Vandertie L, Parise H, Dangas GD, Stone GW; HORIZONS-AMI Trial Investigators. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. *Lancet*. 2009;374:1149-59.

37. Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, Moses JW, White HD, Pocock SJ, Ware JH, Feit F, Colombo A, Aylward PE, Cequier AR, Darius H, Desmet W, Ebrahimi R, Hamon M, Rasmussen LH, Rupprecht HJ, Hoekstra J, Mehran R, Ohman EM; ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med.* 2006;355: 2203-16.

38. Bongard V, Puel J, Savary D, Belle L, Charpentier S, Cottin Y, Soulat L, Elbaz M, Miljkovic D, Steg PG; OPTIMAL Investigators. Predictors of infarct artery patency after prehospital thrombolysis: the multicentre, prospective, observational OPTIMAL study. *Heart.* 2009;95:799-806.

39. Cantor WJ, Fitchett D, Borgundvaag B, Ducas J, Heffernan M, Cohen EA, Morrison LJ, Langer A, Dzavik V, Mehta SR, Lazzam C, Schwartz B, Casanova A, Goodman SG; TRANSFER-AMI Trial Investigators. Routine early angioplasty after fibrinolysis for acute myocardial infarction. *N Engl J Med.* 2009;360:2705-18.

40. Bonnefoy E, Steg PG, Boutitie F, Dubien PY, Lapostolle F, Roncalli J, Dissait F, Vanzetto G, Leizorowicz A, Kirkorian G; CAPTIM Investigators, Mercier C, McFadden EP, Touboul P. Comparison of primary angioplasty and pre-hospital fibrinolysis in acute myocardial infarction (CAPTIM) trial: a 5-year follow-up. *Eur Heart J.* 2009;30:1598-606.

41. Van't Hof AW, Ten Berg J, Heestermans T, Dill T, Funck RC, van Werkum W, Dambrink JH, Suryapranata H, van Houwelingen G, Ottervanger JP, Stella P, Giannitsis E, Hamm C; Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. *Lancet.* 2008;372:537-46.

42. Bøhmer E, Hoffmann P, Abdelnoor M, Arnesen H, Halvorsen S. Efficacy and safety of immediate angioplasty versus ischemia-guided management after thrombolysis in acute myocardial infarction in areas with long transfer distances results of the NORDISTEMI (NORwegian study on DIstrict treatment of ST-elevation myocardial infarction. *J Am Coll Cardiol.* 2010;55:102-10.

43. Verheugt FW, Montalescot G, Sabatine MS, Soulat L, Lambert Y, Lapostolle F, Adgey J, Cannon CP. Prehospital fibrinolysis with dual antiplatelet therapy in ST- elevation acute myocardial infarction: a substudy of the randomized double blind CLARITY-TIMI 28 trial. *J Thromb Thrombolysis.* 2007;23:173-9.

44. Tubaro M, Danchin N, Goldstein P, Filippatos G, Hasin Y, Heras M, Jansky P, Norekval TM, Swahn E, Thygesen K, Vrints C, Zahger D, Arntz HR, Bellou A, De La Coussaye JE, De Luca L, Huber K, Lambert Y, Lettino M, Lindahl B, McLean S, Nibbe L, Peacock WF, Price S, Quinn T, Spaulding C, Tatu-Chitoiu G, Van De Werf F. Pre-hospital treatment of STEMI patients. A scientific statement of the Working Group Acute Cardiac Care of the European Society of Cardiology. *Acute Card Care.* 2011;13:56-67.

45. Huber K, Goldstein P, Danchin N, Fox KA. Network models for large cities: the European experience. *Heart.* 2010;96:164-9.

46. Goldstein P, Lapostolle F, Steg G, Danchin N, Assez N, Montalescot G, Charpentier S, Wiel E, Juliard JM. Lowering mortality in ST-elevation myocardial infarction and non-ST-elevation myocardial infarction: key prehospital and emergency room treatment strategies. *Eur J Emerg Med.* 2009;16:244-55.