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Review article

Primary angioplasty in Europe: From trials to practice

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ABSTRACT

This manuscript is focused around two key messages from the current Guidelines of the European Society of Cardiology on ST elevation myocardial infarction; the need to use primary angioplasty whenever timely and effectively applicable and the importance of organisational changes in the emergency system to implement this indication. Based on a review of the trials motivating these guidelines and the successful experience of many European countries, practical indications are provided on the methods to overcome resistances and malpractices that prevent the delivery of optimal care in these critically ill patients.

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INTRODUCTION

There are few issues in medicine less controversial than treatment of acute myocardial infarction. Unlike in stable coronary syndromes there is no discussion whether patients should be better off in terms of prognosis and long term relief of symptoms after bypass surgery or coronary angioplasty or simply remaining on medical therapy, a difficult decision in individual cases that often leads to fierce discussions in our multidisciplinary meetings. For primary angioplasty there is unanimous consent that a direct immediate mechanical opening of the occluded artery with angioplasty is preferable to fibrinolysis and far preferable to no reperfusion treatment, as often occurs when patients have contraindications to fibrinolysis. This article reports the indications coming from Guidelines supported by large trials, meta-analysis and large registries and reviews the reasons why this clear message has not led to a generalised application in most European countries, addressing the changes in clinical practice required to implement this winning strategy.

"PRIMARY ANGIOPLASTY IS THE PREFERRED TREATMENT IF PERFORMED BY AN EXPERIENCED TEAM <90 MINUTES AFTER FIRST MEDICAL CONTACT: CLASS I A"

The first ESC guidelines clearly indicating that primary angioplasty was the treatment of choice when performed in good time, by an experienced team, were published in 2003 [1]. Retrospectively, we can ask ourselves whether it was timely enough since the first two large randomised trials using streptokinase [2]. or rtPA [3]. were published 10 years before, followed by a compelling meta-analysis of more than 3000 patients showing advantages in mortality [4]. We must remember that at the time there was still heated discussion on the value of third generation fibrinolytics and questions coming from poorly interpreted registry data. The 2003 Guidelines should be considered as highly innovative, because they gave the strongest possible recommendation (Class I, Level of Evidence A) to a practice that many still felt to be inapplicable in most situations. In countries with an advanced health service it was seen as a distraction, or as an excuse to delay or prevent the application of fibrinolysis, the other treatment truly available everywhere within minutes from diagnosis. With minimal changes in subsequent updates, this guideline has become the cornerstone of STEMI treatment. We must gratefully thank Professor van der Werf and his coauthors for having given an official approval to a therapy still felt experimental, or not practically applicable, by many at the time. This guideline faced the dilemma of defining an acceptable time delay of PCI in order to remain superior to fibrinolysis. The issue is complicated by the basic knowledge that a minimal delay in the first hours after symptom onset causes much greater damages than the same delay after 6 or 9 h. An incorrect interpretation of some early PCI trials suggested similar mortality, irrespective of the time delay after symptom onset when PCI was used, a very different outcome than after fibrinolytics, that also become less effective on old thrombi. More recently this mistake has been corrected, based on the evidence of a worsening in outcome according to the time delay between symptoms onset and PCI, more evident in high-risk patients [5]. The 2008 Guidelines have identified a cohort of patients with large anterior infarctions and low bleeding risk in whom a lower threshold (no more than 90 minute delay) should be used, while the general time delay has been prolonged to 2 h, including also the delay between first medical contact and the transport to the hospital door [6]. Despite its clear formulation, the application of primary angioplasty has been very slow, to the point that an immediate Past-President of the ESC, Jean Pierre Bassand, felt the need to create a task force for promoting its implementation. The results of the survey, conducted in 2005, observed a large gap between guideline recommendations and clinical practice, with none of the large European countries having greater than 50% application of primary angioplasty. The treatment looked suitable for small, well-organised countries such as the Netherlands, Belgium, Czech Republic or Switzerland, but impractical elsewhere [7]. This was the driving force of the first Stent for Life (SfL) initiative and a repeated survey led by Petr Widimsky in 2008, showed that Germany, Poland, Sweden, Hungary, Croatia, Slovenia and others had come on board and much progress was made in France and Italy too [8]. No data could be obtained on the quality of the PCI performed and, in particular, on the respect of the 90-minute door-to-balloon time suggested at the time. A large, ongoing survey is being coordinated by Dr Kristensen on behalf of the SfL group and data are expected to be concluded in 2013. What can we expect based on current knowledge? A major increase in penetration of primary angioplasty will emerge, probably showing the fastest pace of progress since its introduction. The biggest positive surprise is certainly the UK and we will not express more than admiration for a stunning performance moving from $<40\%$ in 2006 to $>90\%$ PCI in 2011. The UK has a unified national health care system and decisions taken in Whitehall apply to the entire country, a

situation very different from Italy or France, where the patchy application mirrors different regional directives. Hospitals in the UK respond to authorities with the power to decide which hospital should perform PCI and regulate patient transfer accordingly. Secondly, the UK had already developed an excellent system to timely administer fibrinolysis based on dedicated nurses in A&E. The system worked equally well when these resources have been allocated upstream, in the ambulance, with the personnel performing and interpreting the ECG and informing the closest primary PCI centre of the arrival of a STEMI patient. Thirdly, auditing was fully implemented via the MINAP ACS and BCIS PCI databases, offering the advantage of constant monitoring of quality indicators such as time delays and outcomes such as mortality. This advantage is shared with Sweden and it is interesting to know that data from both countries indicate impressive mortality benefit after the implementation of the universal primary PCI program, together with cost reduction mainly generated by shorter hospital stays and immediate patient triage. Equally impressive results have been achieved in most of the 13 countries participating to the SfL initiative. It is obviously impossible to distinguish the natural process of diffusion of a new therapeutic treatment from the additional push the participation of SfL gave to the program. In Italy and Spain, wide regional differences remain, with large regions such as Lombardy in Italy and Catalonia in Spain close to universal application of primary angioplasty and others much further behind. Similar considerations can be repeated for France with the additional complication in interpreting figures that pre-hospital thrombolysis is still occasionally applied in the country. It is seen not as an alternative to, but as a preparation for, angioplasty. Characteristics specific to the country are the reluctance of the SAMU, the very efficient equipped ambulances with an anaesthetist on board, to play a passive role simply shipping the patient to the closest angioplasty centre where mechanical recanalization is performed. The results of CAPTIM [9]., at odds with all the other thrombolysis vs primary PCI randomised comparisons because they saw superiority of thrombolysis within 2 h from symptoms onset must be interpreted in the context of a very atypical 80% use of angioplasty in the hours after fibrinolysis. Unlike in ASSENT IV [10]. there were no signals of higher morbidity and mortality when PCI immediately followed the administration of lytics, possibly because of the timely use with fibrinolysis of dual antiplatelet treatment. Unlike almost all the other trials of facilitated PCI (FINESSE [11]., etc) there was no excess of bleeding, possibly because of the frequent adoption of a radial approach. The real surprise, however, comes from the other countries participating in the SfL program, starting from a very low penetration and expected to be limited by an insufficient number of 24/7 primary PCI centres and equipped mobile units for pre-hospital diagnosis. Serbia, Bulgaria, Romania, Turkey made impressive steps forward, thanks to the ability of their country champions to make primary angioplasty an absolute priority in receiving ample resources to meet the goals.

"IMPLEMENTATION OF A WELL FUNCTIONING NETWORK BASED ON PRE-HOSPITAL DIAGNOSIS AND FAST TRANSPORT TO THE CLOSEST AVAILABLE PRIMARY PCI CAPABLE CENTRE: CLASS I A"

The process of integration between EMS and 24/7 hospitals to provide a seamless delivery of care throughout a geographical area irrespective of the time of the day, or day of the week, was already strongly advocated in the 2008 STEMI Guidelines [6]. This point acquired dignity of a specific recommendation, however, only in the 2010 ESC Myocardial Revascularisation Guidelines [12]. and in the last update of the ACC/AHA/SCAI STEMI guidelines [13]. Again a Class 1 Level of evidence A was indicated, based on large series showing how individual changes in service organisation have impacted morbidity and mortality. The principle is the identification of a geographical area where delivery of care for STEMI patients is provided by a single EMS system, connected to well-identified 24/7 primary centres. The practical application sees enormous differences from country-to-country and region-to-region, in terms of dimension of population served, organisation of EMS service and modalities of offer of the primary angioplasty service.

First Medical Contact: A unified telephone number for emergency calls with an operator promptly available and able to identify symptoms possibly related to acute myocardial infarction, is the first essential requirement for a timely delivery of P-PCI. In Europe there is large variability in the education of the public to use such an emergency service, which is key to ensure the smoothest and most rapid access to primary angioplasty. Occasionally patients rely on their GP and waste precious time to wait for him to be available to give advice, or come to see them. More often, relatives or neighbours believe they can speed up diagnosis and treatment by bringing the patient directly to the A&E. This is not only a dangerous exercise because of the possible complications arising *en route*, but also hardly the best

way to immediately get the full attention of overcommitted staff in a crowded A&E department. It is almost certainly bound to lead to delays when compared to the "ideal" path described below. The operator on the line will probably have the most difficult job in the many steps leading to a successful recanalization: identify the symptoms of an acute cardiac ischaemic syndrome from the broken voice of an emotional relative or from the words of an old patient trying to minimise the severity of his/her symptoms to the outside world. Constrictive chest pain with classical irradiation lasting more than 10 minutes is not the way symptoms always manifest. As shown in the article by Chieffo et al [14]. older women often only complain of the dyspnoea secondary to left ventricular failure, and many patients have pain limited to the jaw or the epigastrium and/or profuse vomiting and diaphoresis. All these symptoms, especially when they develop in a patient within an age group at risk, or in a patient with clear risk factors for CAD, or with known cardiac pathology, should trigger the dispatch of an ambulance with the equipment and personnel able to perform and interpret/transmit an ECG, perform resuscitation, transfer him if needed to the closest primary PCI centre available, not stopping in the A&E but bringing the patient directly to the Cath Lab.

Emergency Medical System: The organisation of an efficient, yet affordable, emergency system is a complex task. The guidelines stress the word "integration", which means that the Intensive Care specialists, nurses and drivers of the ambulance offering first physical contact with a doctor or a paramedic after the phone call, should feel like part of the team involved in a very special diagnosis and treatment – facing one of the relatively few medical emergencies where a timely and appropriate treatment can make the difference between life and death. After having checked vital signs and pressure, when the suspect of an STEMI is present, an ECG should be performed immediately and the interpretation obtained either directly by the ambulance personnel, using clear thresholds of abnormality to trigger a primary PCI call, or via teletransmission to a dedicated specialist giving feedback as a first priority. There are many ways of fulfilling this task. There are advantages in having an expert central operator coordinating the entire metropolitan area, because he is aware of possible unusual circumstances (road blocks, unavailability of the closest centre engaged in other calls) and may suggest transfer to a different primary PCI centre. If the ambulance personnel has an appropriate background knowledge, or has attended a well-structured training course on ECG interpretation targeted to the recognition of ST-segment elevation, then this is a simple, but appealing, alternative and ensures the full attention of the ambulance crew towards this demanding choice. The experience in London is that courses organised and repeated in the main P-PCI hospitals achieve their educational goal and help in creating the team approach and the strive for excellence these sick patients desperately need. A correct STEMI diagnosis of 94%, as achieved in London, is even more valuable when you consider that most of the other diagnoses (pericarditis, aortic dissection, etc) still require urgent cardiological input. Besides pain control, many other treatments can be started in the spacious modern well-equipped ambulances, provided protocols are well defined and the ambulance personnel is authorised to administer drugs. While nobody will argue for aspirin, decisions on the association of clopidogrel, prasugrel or ticagrelor and the use of pre-hospital thrombolysis when the anticipated delay is greater than 2 h, are obviously dependent on the duration of the transfer.

24/7 Primary Angioplasty Hospital: In principle, the population served must be sufficient to maintain competency of the primary angioplasty centre. The absolute number is equally important as the annual incidence of STEMI. There has been a progressive and, at times, rapid decrease in the incidence of STEMI, attributed to better control of risk factors [15,16]. The decline of STEMI is a quite recent phenomenon and is probably related to the almost complete abolition of the smoking habit in high-risk groups in some European countries. Early recognition and treatment of new onset angina and NSTEMI is probably equally responsible, but more difficult to quantify. Epidemiology of acute coronary syndrome (ACS) is outside the scope of this paper, but it is important to realise that these rapid changes require equally rapid adjustments. A gross estimate of 1000 STEMI per million inhabitants was initially used as average European prevalence to set the goal of the Stent for Life initiative to offer primary angioplasty to at least 600 patients out of a million inhabitants served. This estimate is probably applicable only in some Eastern European countries such as Ukraine or Russia. Northern European countries, with a historically very high prevalence of coronary artery disease (CAD), see only pockets of epidemics in more deprived areas, while densely-populated regions such as South-East England are down to 500-600 STEMI cases/million/year. The rapid rise of obesity and diabetes limits

the contraction of CAD and determines a change in the groups at risk with women > 70 years of age becoming a more frequent target. Assuming an average STEMI population of 500 patients/million inhabitants which is probably closer to the current incidence in many European countries, a single hospital providing service should not have less than 250–300,000 inhabitants in its served territory, in order to be able to provide 125–150 STEMI cases per year, as in some lucky areas of Southern Europe such as Catalonia or some regions in Southern France. In rural or mountainous areas lower basins can be an acceptable choice. The ESC Guidelines do not indicate minimal numbers to maintain competency of hospital and operators, and this is probably a reflection of the extreme geographical variations across Europe that makes difficult to set meaningful thresholds [12]. The US ACC/AHA/SCAI Guidelines [13]. are of help but their targets are also very loose, with a minimum of 36 primary PCI/year to maintain competency as a centre. More importantly, they reaffirm that a primary PCI centre should have a reasonable volume of at least 400 PCIs/year with each operator performing a minimum of 75 PCI/year. These are numbers nobody can argue with: a PCI centre with a volume below 400 cases/year makes no sense economically and is unlikely to offer adequate safety to patients when its personnel is exposed to an average of <8 PCI/week. This is especially so when the patient in question has an occluded artery that requires rapid recanalization and is prone to arrhythmias and haemodynamic complications. Also the number per operator of 75 PCI/year (all PCIs, not only primary angioplasties) fits well these calculations because you need a minimum of 4 to 6 operators to maintain a sustainable rota and 400-450 PCIs are sufficient to maintain this level, if evenly split among the operators. If this is a meaningful general rule, exceptions have to be accepted and sometimes encouraged. The operators' and possibly the paramedics' competency can be maintained performing angioplasties in a different centre and you may accept a centre with a suboptimal number of 75–100 primary angioplasties/year if this is the only solution to ensure a timely offer of primary angioplasty in a homogeneous region sufficiently remote and this is compatible with the economic resources available for the health system. Where possible, however, and this includes all the urban/metropolitan areas of Europe and probably 2/3 of its population, the encouragement should be to move in the opposite direction and encourage the development of large primary angioplasty hubs with 300-500 patients/year. Obviously, there are no possible randomised trials comparing outcomes in low volume and high volume centres but all data coming from matched comparisons suggest success increases and complications fall in larger volume centres. Clearly there is an inherent cost in maintaining an on-call service which is relatively inactive, and this also plays a role in suggesting to limit the number of active primary PCI centers. There are also challenges in the smooth running of high volume centres. Impersonal service, with the operator seen during the acute treatment not showing up thereafter, and occasional instances of excessive pressure to retransfer or discharge the patient are potential drawbacks to consider. Much more difficult to accept, is that the hard work of the EMS to quickly bring the patient for primary angioplasty is wasted because of unacceptable delays to the Cath Lab because of several simultaneous cases of primary angioplasty. This is a problem likely to occur especially at nights or during weekends if only one lab is used for primary angioplasty. A good balance can be maintained when various centres are active within the same metropolitan areas and there is a central allocation unit able to accommodate patients to the nearest hospital with a Cath Lab available to immediately start angioplasty. There is great creativity in the way the primary angioplasty service is organised across Europe and the solutions are often a compromise to satisfy all of the hospitals involved, not necessarily those offering the most efficient or cost-efficient solution. In most European cities, all centers able to offer a round the clock service are allowed to offer primary angioplasty. The advantage is that ambulances are spoilt with choices and can shorten the drive to the hospital and the competition creates an incentive to raise standards. The disadvantage is that this often drives numbers below the minimal acceptable figures indicated above. A solution which is possibly acceptable in remote areas, but not in the heart of a large city. Rotation of the hospitals on call for providing service is a possible alternative to maintain all hospitals involved, but is applicable only when the hospitals in question are strategically placed to meet the needs and not creating another problem of insufficient experience being built up in some of the participating centres. In order to maintain an active 24/7 service, centres may need to attract operators not routinely working in the hospital, which may create difficulties dealing with acute cases in a foreign environment.

Provisions after angioplasty: Primary angioplasty has drastically changed the treatment and prognosis of STEMI patients. The risks of acute arrhythmias and late ventricular tachycardia, mechanical complications, pericarditis and Dressler's syndrome, haemodynamic compromise,

recurrence of angina or reocclusion have all become rare events. Patient triage is performed during primary angioplasty and patients with multivessel disease are identified and scheduled for further treatment. The use of radial approach and the elimination of the most heroic antithrombotic and antiplatelet cocktails, substituted by weight-adjusted doses of less dangerous drugs, potentially allow rapid transfer after P-PCI. Transfer is an absolute must in some units with very limited bed capacity. Transfer can be positive when it offers access to departments where the patient completes up-titration of beta-blockers and ACE-inhibitors, receives detailed instructions on diet, pressure and cholesterol control, and the importance of physical activity. Transfer can help to balance patient flow, compensating hospitals that have accepted not to promote P-PCI facilities because they are redundant for the territory in question or they have transferred the patient after having performed diagnosis. Conversely, staying in the same unit where angioplasty was performed, speaking with the operator and receiving reinforcement messages on the importance of double antiplatelet treatment, can work equally well or better if the situation allows. The important message to convey is that the stent is only the first of a series of measures to implement in order to transform the risk profile. Again, multiple models have been developed, but it is essential that the patient cannot be transformed into a postal package to move when and where convenient and that the patient's safety and well-being must remain the centre of the treatment strategy.

CONCLUSIONS

Primary angioplasty can be performed in the vast majority of patients with ST elevation myocardial infarction, with the possible exception of patients living in remote regions who are unable to reach the hospital within the first 90–120 minutes after diagnosis. In all other areas, covering more than 85% of the European population, the poor penetration of primary angioplasty is caused by the lack of a coherent organisation, revolving around a coordination centre and a network of cleverly placed primary PCI hospitals.

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