Hospital networks for the treatment of acute myocardial infarction

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Patients with ST-elevation myocardial infarction (STEMI) may have a survival benefit, as well as a reduced occurrence of reinfarction and stroke, if treated with primary percutaneous coronary intervention (PCI) instead of fibrinolysis. Furthermore, there are no other reperfusion options for patients with absolute contraindications to fibrinolysis or after failed fibrinolysis or in shock. Unfortunately, primary PCI programs require a relatively high number of experienced interventional cardiologists as well as other specialized personnel to guarantee a 24-hour call schedule together with a high level of skill. Since these conditions may be achieved only in a minority of hospitals with high volumes of interventional procedures, most of the patients with STEMI will be admitted to hospitals without a primary PCI program. The implementation of hospital networks based on a Hub-and-Spoke model is the only way to allow the choice of a reperfusion treatment on the basis of clinical needs and not only on the basis of the hospital characteristics. In Italy this process should be driven by regional authorities that have to establish the distribution of Hub centers, in close cooperation with cardiologists and physicians involved in emergency departments and 118 Service. Several key points, such as the collaboration between cardiologists and emergency physicians, common diagnostic and therapeutic protocols, prehospital diagnosis and treatment, transportation difficulties, overflow of the patients in the Hub centers, public campaigns for the use of the 118 Service and registries for all patients with STEMI, should be adequately addressed and implemented. In hospitals with well established primary PCI programs, all patients with STEMI should receive a mechanical reperfusion. The selection of patients with STEMI who might benefit most from mechanical reperfusion even after transfer, should be made considering the patient's risk profile, the time interval from symptom onset and the time interval to a primary PCI: in late comers (> 3 hours of symptom onset) and in the elderly, primary PCI should be the treatment of choice, but in early comers and younger patients, if an excessive time delay is necessary to perform a primary PCI, fibrinolysis might be a good initial option. In the latter, a systematic immediate transfer of high-risk patients to a primary PCI center for facilitated or rescue PCI should be considered.

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The superiority of primary angioplasty over fibrinolysis in the treatment of ST-elevation myocardial infarction (STEMI) was demonstrated for the first time in 1993[1,2]. Ten years later a quantitative review of all of the 23 randomized trials comparing primary percutaneous coronary intervention (PCI) with fibrinolysis[3] confirmed that mechanical reperfusion was superior to pharmacological reperfusion in reducing the short-term rates of death (7 vs 9%, $p < 0.001$) and the combination of death, non-fatal reinfarction and stroke (8 vs 14%, $p < 0.0001$).

The current guidelines for the management of patients with STEMI, developed by the European Society of Cardiology and the American College of Cardiology/American Heart Association[4,5], and the Italian Federation of Cardiology in a dedicated Consensus Document[6], recommend primary PCI as the reperfusion therapy in class I with level of evidence A in a large spectrum of clinical and logistic situations.

Furthermore, primary PCI is the only available reperfusion treatment for patients with STEMI and absolute contraindications to fibrinolysis.

The task of the cardiological community is to contribute to enable all of the patients with STEMI to receive primary PCI, on the basis of their clinical needs and independently of the characteristics of the admitting hospital.

How to make primary percutaneous coronary intervention available for all of the patients who might benefit most from mechanical reperfusion?

An inverse relationship between the annual number of patients treated with PCI in a specific cath lab and the rate of mortality

and complications, even after the introduction of coronary stents, has been documented[7]. The same findings were reported for primary angioplasty, with significantly lower mortality rates, in hospitals with the highest volumes of procedures if compared to hospitals performing a low volume of procedures[8]. This relationship was not observed for fibrinolysis. Indeed, only in high volume hospitals, patients undergoing primary angioplasty had a higher survival rate than those undergoing fibrinolysis[9]. If compared with patients treated at low-volume hospitals by low-volume physicians, patients treated at high-volume hospitals by high-volume physicians had a lower mortality rate[10].

The current guidelines for the management of patients with STEMI[4,5] emphasize that primary PCI should be performed by skilled operators, supported by experienced personnel in an appropriate laboratory environment with a 24-hour, 365-day call schedule. The latter conditions require the availability of at least 4 experienced operators as well as a relevant number of specialized personnel[11]. The solution could be that of programming the number of primary PCI centers, that should perform high volumes of procedures, serve an area with 300 000-1 million inhabitants[11] and receive patients with STEMI transferred from other hospitals in the same area.

This, of course, rises the question whether the mechanical reperfusion after transfer to a PCI center is superior to fibrinolytic therapy administered at the referral hospital. A quantitative overview of 5 randomized trials that have addressed this point[12] showed that primary PCI after transfer was still superior to fibrinolysis with a significant reduction in the rates of death (6.8 vs 9.6%, $p = 0.01$) or of the combination of death, non-fatal reinfarction and stroke (8.5 vs 15.5%, $p < 0.001$).

Therefore, the regionalization of care for acute ischemic heart disease and a need for specialized centers have been claimed by many opinion leaders[13,14]. This approach has already been validated for specialized "trauma centers", although the prevalence of death due to all-cause trauma is 7-fold lower than that of death due to myocardial infarction and 20-fold lower in subjects ≥ 65 years[15].

Therefore, the only way to offer the best treatment options to the patients presenting with STEMI is to organize hospital networks based on Hub-and-Spoke models.

How to develop the hospital networks?

The Hub-and-Spoke model takes into account different levels of treatment complexity and is organized to allow the selection and transfer of patients from hospitals without PCI facilities (Spoke) to PCI centers (Hub), as well as the return of the patients to the Spoke center as soon as possible.

The implementation of the Hub-and-Spoke model is difficult for several reasons:

a) tendency to concentrate in a single location (coronary care unit of the nearest hospital) all the diagnostic and therapeutic pathways, performed only by cardiologists. It should be considered that in patients with chest pain calling the 118 Service an immediate ECG should be performed and some of those with STEMI might be treated with prehospital fibrinolysis (and possibly rescue PCI), with survival rates similar to those of subjects treated with primary PCI[15]; in this context, the final destination for every single patient should be based on his/her risk profile and will not necessarily be the nearest coronary care unit. If the diagnosis of STEMI is made in the emergency room of a Spoke hospital, patients with indications to primary PCI should be immediately transferred in a catheterization laboratory of a Hub center. Therefore, the site of diagnosis and the selection of the initial treatment may not be the coronary care unit, provided that experienced personnel is available on site;
b) lack of common treatment protocols. The previously described model can work only if detailed treatment protocols are developed by cardiologists and shared with all the physicians and the personnel involved in the emergency departments and in the 118 Service and with the cardiac surgeons who might be involved in some critical situations. These protocols should be discussed with all personnel involved in the treatment of STEMI in the area of hospital network. This implies the need for periodic meetings, with the aim to improve the specific knowledge but also to improve a cooperation between the operators from different areas of specialization;
c) lack of facilities for the transportation of patients. The transfer of the patients from the Spoke to the Hub center is frequently the main obstacle to the realization of the program, due to the fact that most hospitals do not have a dedicated personnel on a 24-hour basis and the 118 Service usually does not consider this transfer as red code (hopefully the latter will change in a near future). As the logistic conditions may vary widely among hospitals there is not a single solution to this problem. In every hospital, the most effective organization for the transportation should be investigated, on the basis of local ambulance and personnel availability;
d) overflow of patients in the Hub centers. In the Hub centers an overflow of patients receiving primary PCI may occur and this should be taken into account when hospital network programs and treatment protocols are developed. One of the solutions is to retransfer the patient to the Spoke center, if clinically feasible, in the first 24 hours following primary PCI. Although there are no available statements from scientific societies, a consensus between expert cardiologists and emergency physicians (Boccanelli A., Greco C., 2003, unpublished data) stated that patients with optimal angiographic results can be retransferred without an accompanying physician;
e) lack of political authorities that should program, organize, support and control the outcomes of this mod-

el. The organization of new and complex models of hospital networks, being able to assure the prompt cooperation between physicians of different specialties and hospitals, exceeds the competence and the possibilities of physicians involved in the process. Although interesting experiences on STEMI treatment in the setting of hospital networks have been reported in Italy[16-19], all of them are based on local initiatives of deeply involved physicians, without any change in the existing logistic and availability of resources. To develop a stable and "structured" network, a public authority should be involved in a process of programmation, organization and outcome control. In Italy, according to the Constitutional Law and the recently approved article 34[20] all these duties are conferred to the Regional Government.

The regional authorities, in close cooperation with experts appointed by the scientific societies, should:
- establish the number of Hub centers on the basis of the existing laboratories, geographical situations, epidemiological needs and operative standards of 24-hour available catheterization laboratories. With regard to the epidemiological issue, the number of patients with STEMI and candidates to reperfusion therapy (those with < 12 hours of symptom onset) admitted to cardiology departments, seems to be roughly in the range of 650-750 patients/million inhabitants/year[21-23] with 25-50% (depending on the definition criteria) of them at high risk; these estimates are lower than previously reported. Therefore, considering that the operative standards of 24-hour cath labs are really difficult to develop due to a need for a high number of skilled operators and other experienced personnel that impose a high-volume practice, caution must be addressed to plan the correct number of Hub centers;
- solve the transportation difficulties implementing the existing organizations, when necessary;
- support or implement, with specific indicators, a registry on STEMI (or all acute coronary syndromes), in order to monitor the process of care, clinical outcome and cost-effectiveness issues;
- promote interdisciplinary meetings (cardiologists and emergency physicians);
- set up dedicated regionwide educational public campaigns, in order to sensitize citizens and to shorten the decisional time in case of chest pain and increase the access to the 118 Service;
- change the current distribution of resources, because of different pathways of patient treatments.

In the real life, effective regional measures based on the requests made by medical communities may be hard to obtain, due to the gap between the technical (physicians) and executive (politicians) levels. One example that may help to fill this gap is the ongoing Veneto Region experience. The preliminary basis was the existence of a Regional Emergency Center, that was initially contacted by cardiologists interested in this issue. Subsequently, the Coordinator of the Regional Emergency Center set up a Technical Committee formed by the experts appointed by the scientific societies of cardiologists (the Italian Association of Hospital Cardiologists, the Italian Society of Cardiology, the Italian Society of Invasive Cardiology) and emergency physicians (118 Service, the Italian Society for Emergency Medicine). This Committee elaborated a document regarding the standards of treatment of STEMI and the steps necessary to develop a hospital network, with particular regard to the organization of a regional registry on STEMI, of educational meetings for all the figures involved in the process (cardiologists and emergency physicians) and of a public campaign to increase the use of the 118 Service in case of chest pain. This document constituted the bases of the final regional law with earmarked funds for the realization of the priority points[24].

If the target of setting up a hospital network is centered, should all patients with STEMI be treated with primary PCI?

Which patients with ST-elevation myocardial infarction may benefit most from hospital networks?

In some STEMI patients (regardless if admitted to a Hub or Spoke center), primary PCI is currently recommended as the treatment of choice[4-6]: a) STEMI lasting < 12 hours and contraindications to fibrinolysis; b) failed fibrinolysis in patients with large myocardial infarctions and/or Killip class 3 and/or shock; c) shock developed within 36 hours of myocardial infarction.

The current experience teaches us that when the catheterization laboratory develops a 24-hour interventional program (Hub center), almost all STEMI patients admitted directly to that center within 12 hours of symptom onset, will receive a primary PCI, regardless of their risk profile. Moreover, this approach is recommended by the current guidelines[4] and is considered as one of the performance criteria for the cath lab involved in a primary PCI program.

For other patients who need to be transferred from Spoke to Hub centers, it seems reasonable to introduce some selection criteria, either because "offering primary PCI to every patient with acute myocardial infarction coming to any hospital at all times is a luxury we cannot afford"[25] but also because primary PCI may not be really life-saving for some groups and may even be harmful for others if an excessive time delay is required to perform it.

Although the rates of combined events (death, reinfarction, stroke) favor primary PCI in all subgroups of patients[26,27], the net survival benefit may be less evident in some of them who therefore can be candidates to pharmacological reperfusion, if admitted to a Spoke center. These patients include:

• those with STEMI and low-risk characteristics treated with fibrinolysis: these patients will have a low in-hospital mortality and may be identified by means of a very simple tool such as a TIMI risk index (calculated using age, heart rate and systolic blood pressure), initially derived from a randomized trial[28] and then validated in 153 486 all-comers with STEMI[29]. In the latter study, according to the TIMI risk index, the in-hospital mortality in a low-risk group of patients who had undergone reperfusion treatments was < 1.5% and this group represented about 45% of all patients with STEMI[29]. Probably, in those patients the type of reperfusion (pharmacological or mechanical) will unlikely influence the immediate survival;
• those enrolled in randomized trials within 2 or 3 hours of symptom onset: in these patients minor (or none) survival benefits can be demonstrated in favor of primary PCI, if the time required to perform it exceeds by 60 min the time required to perform a fibrinolysis[15,30-33]; in Italy, 49% of patients with STEMI are admitted within 2 hours of symptom onset[21].

It seems reasonable to estimate that a large number of patients with STEMI, approaching 50% of those admitted to cardiology departments, will not have a relevant immediate survival disadvantage if treated with fibrinolysis.

Nevertheless, other important clinical points regarding the rates of reinfarction and stroke should be addressed.

The reinfarction rate is significantly reduced in primary PCI vs fibrinolysis (3 vs 7%)[3], and is even lower (0.9%) after stent implantation[34]. On the other hand, out of 20 101 patients enrolled in thrombolytic trials (TIMI 4, 9, 10b and InTIME II) 4.2% had a symptomatic recurrent myocardial infarction occurred during the index hospitalization, associated with a significantly higher 30-day mortality at univariate (16.4 vs 6.2%, $p < 0.001$) as well as at multivariate analysis (hazard ratio 2.55, $p < 0.001$)[35]; in 4281 of those patients treated with a PCI at a median of 4 days after fibrinolysis, reinfarction occurred less frequently (1.6 vs 4.5%, $p < 0.001$) as well as in 1021 patients who had undergone coronary artery bypass surgery (0.7 vs 4.3%, $p < 0.001$), with a significant reduction of mortality in both revascularized groups[35]. Is it possible to reduce the reinfarction rate in patients undergoing pharmacological reperfusion performing a PCI not immediately, but shortly after fibrinolysis? In the GRACIA-1 trial, comparing the strategy of routine angiography within 24 hours of fibrinolysis vs ischemia-driven indication to angiography, the 30-day reinfarction rate was not significantly lower in the former group (1 vs 2%)[36]. In the SIAM III trial, the 30-day reinfarction rate in patients undergoing stenting within 6 hours of fibrinolysis was the same as in those undergoing stenting after 2 weeks (2.4 vs 2.5%)[37]. On the other hand, in the GRACIA-2 trial (unpublished data) no difference in the rate of combined events (death, reinfarction and ischemia-driven revascularization) was observed between patients undergoing primary PCI and those undergoing routine PCI 3-12 hours after full-dose fibrinolysis with tenecteplase. The number of patients enrolled in the GRACIA-1, 2 and SIAM III trials were too low to address this point, therefore, the hypothesis regarding the possibility of reducing the reinfarction rate after fibrinolysis performing a PCI shortly (hours-days) after the pharmacologic treatment, has still to be properly investigated.

The rate of total stroke is halved in patients undergoing primary PCI if compared to those treated with fibrinolysis (1 vs 2%, $p = 0.0004$), mainly due to the fact that in patients treated with primary PCI a hemorrhagic stroke was virtually abolished (0.05 vs 1%)[3]. Even if a 1% rate of hemorrhagic stroke after fibrinolysis can be considered a relatively rare complication, it may obviously have dramatic consequences and therefore in the selection of candidates to fibrinolytic therapy all efforts should be made to exclude subjects at intermediate or higher risk of stroke, if primary PCI may be a therapeutic option. For this reason, in elderly patients fibrinolysis should be considered with caution.

Furthermore, in patients with STEMI > 70 years enrolled in randomized trials comparing primary PCI with fibrinolysis, the mortality and reinfarction rates strongly favored primary PCI (13.3 vs 23.6%)[26]. In the "real world" too, a similar superiority of primary PCI over fibrinolysis in reducing the mortality rate was observed in patients > 75 years (14.3 vs 24.4%, $p < 0.03$)[27]. These data are still more important if we consider that in patients > 75 years, fibrinolysis confers a limited but statistically significant (26 vs 29.4%, $p = 0.03$) survival benefit, if compared to placebo[38]. So, it seems reasonable that elderly patients should be more extensively considered for mechanical rather than pharmacological reperfusion.

Protocols regarding the selection of treatment for patients with STEMI, admitted to a Spoke center, should consider for every single patient his/her risk profile, the time of symptom onset and the overall delay associated with the transfer to the Hub center. The same holds true for the patients referring to the 118 Service: similar algorithms should be applied to decide which treatment should be immediately undertaken and to which hospital a patient should be transferred.

The choice of the graduation of the selection of patients to be transferred for primary PCI should be decided in every single network according to the local possibilities: it may vary from selecting only high-risk and elderly patients where the number needed to treat (NNT) to avoid one hard event such as death or reinfarction will be as low as 8-9 patients[26,27], or extending the indications also to patients at intermediate or low risk for whom the NNT will be much higher (in the range of 15-76)[26,27].

When the results of ongoing randomized trials comparing different strategies will be available, it will be

easier to understand if the clinical outcome after PCI may be further improved by anticipating the recanalization with pharmacological tools.

Conclusions

Primary angioplasty has improved our possibilities of treatment of STEMI and is superior to fibrinolysis in a broad spectrum of clinical situations. Conditions should be created to assure the best treatment option driven by evidence-based clinical decisions and not by the type of admission hospital. Setting up hospitals and pre-hospital networks is the only way to achieve this objective. This process imposes some relevant transformations, moving sometimes the site of acute treatment to the home of the patient, to the emergency room or to the cath lab, and forcing the cooperation between cardiologists and other emergency physicians and public authorities. Scientific societies may play a relevant role in this process. In Italy, every single Region should face this problem separately and organize hospital networks according to local geography and existing interventional cath labs, solve the transportation difficulties and support the registry of STEMI, necessary for monitoring the whole process and outcomes. The selection of patients to treat with primary PCI may vary according to different logistic situations and the initial objective should be to assure, for all high-risk STEMI patients, the possibility of reaching a Hub center in the shortest time, without excessive delay and without excluding an immediate fibrinolytic treatment if indicated.

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