Editorial comment

MISTRAL whispers: STEMI trials forecast storm, registries blow breeze

Michele Galli, Alberto Genovesi Ebert

Division of Cardiology, Spedali Riuniti, Livorno, Italy

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Address:

Dr. Michele Galli

Divisione di Cardiologia
Spedali Riuniti
Viale Alfieri, 34
57100 Livorno
E-mail: m.galli@nord.usl6.toscana.it

There are wide variations regarding the routine approach to patients presenting with acute ST-elevation myocardial infarction (STEMI), and several management strategies, including local fibrinolysis vs primary percutaneous coronary intervention (PCI), local fibrinolysis vs immediate transfer to primary PCI centers, as well as pre-hospital fibrinolysis vs transfer to primary PCI have been evaluated in randomized clinical trials, with diverging results. A recent comprehensive meta-analysis of randomized trials comparing local thrombolysis with primary PCI showed that primary PCI is superior to thrombolysis due to a significant reduction in reinfarction and stroke, with a trend in mortality reduction[1].

Among the several factors driving invasive procedures in STEMI patients, local availability and expertise play the major role. Worldwide, ≤ 20% of patients with acute STEMI are initially treated with primary PCI; the majority receives fibrinolytic therapy or even no acute reperfusion therapy. On the contrary, in hospitals with on-site cath lab facilities, primary PCI is now preferred to the common fibrinolysis-based medical treatment that confines coronary angiography and revascularization only to patients who present with high-risk features. The recent Italian BLITZ survey, that prospectively collected data on epidemiology, therapeutic strategies and 30-day outcome of patients with acute myocardial infarction (MI) consecutively admitted to 296 Italian coronary care units from October 15 to 29, 2001, did not find any relationship between rates of primary PCI, patients' age and pre-hospital delay, thus suggesting that when cath lab facilities are available, primary PCI is the preferred reperfusion strategy, independent of potential harms or reduced thrombolysis efficacy, as in the case of older patients or those presenting late[2].

Hours are golden, and minds confused

The issue of the best reperfusion strategy remains one of the hottest topics in cardiology: coherently, the two writers of the present editorial share different opinions regarding the fact that primary PCI might, or not, be the best option for all STEMI patients and cardiologists. Primary PCI vs local fibrinolysis trials were generally performed at high-volume centers, where PCI facilities were readily available at the time of randomization and performed by experienced operators achieving high success rates. Even in well-resourced countries, however, the majority of patients present initially to their emergency ambulance service and/or to local hospitals rather than to an angioplasty center. According to the data collected in BLITZ, currently in Italy only 45% of the patients with acute coronary syndromes reach hospitals by the emergency territorial services[2]. In this situation, the clinical decision needs to be made between early thrombolysis and transfer to a PCI center with delayed, but more complete, reperfusion. The clinically relevant question with regard to reperfusion strategy must therefore take into account the delay in triage and transfer for primary PCI, if available, when judging it against rapid thrombolysis.

On the other hand, even when transfer to an angioplasty center is necessary, primary PCI still confers a significant mor-

bidity and mortality benefit superior to immediate local thrombolysis[3,4]. The recent meta-analysis of six transfer trials shows that transfer to outside centers for primary PCI remains a superior strategy to immediate local in-hospital thrombolysis, despite the fact that transfer clearly adds delay to reperfusion[5]. These findings are in keeping with the observation that time to reperfusion is much less critical with primary PCI than with thrombolysis, lending further credit to the "primary PCI supremacy" in STEMI management[6,7]. On the basis of all these data, the European Society of Cardiology (ESC) recently updated its guidelines on the management of patients presenting with STEMI[8]. The revised ESC guidelines recommend angioplasty and/or stenting without prior or concomitant fibrinolytic therapy as *the preferred therapeutic option when it can be performed within 90 min after the first medical contact.*

How fast and how effectively you can restore blood flow in a patient with MI is crucial. Both pharmacological and mechanical approaches designed to limit infarct size by recanalization of the infarct-related artery have reduced STEMI mortality. Early efforts to combine the two were attenuated because of complications encountered. Since time to recanalization and adequacy of restoration of perfusion are pivotal determinants of a favorable outcome with either approach, primary PCI and thrombolysis cannot be viewed as alternative, rather than complementary modalities, and optimal advantage may accrue from the use of both approaches in combination in selected cases. Thus, studies focusing on the temporal window available for efficacy of subsequent optimally timed therapeutical interventions, and the identification of pharmacological regimens that start prompt recanalization and minimize bleeding are eagerly awaited.

It seems ingenuous to expect a therapeutic model that fits everyone needs, young heavy males and old thin females, large acute inferior MI with impending hemodynamic and electrical failure or first Killip class 1 apical infarction, in-hospital STEMI onset vs late presentation of patients with previous MI or bypass surgery, etc. Certainly, the clinical presentation and the delay from symptom onset currently represent the driving criteria to optimize treatment individually. Subgroup analysis of two recent transfer trials shows that in patients treated within 2 to 3 hours of chest pain onset, the 30-day mortality was lower or no worse with thrombolysis (2.2 vs 5.7% with primary PCI in the French CAPTIM study, 7.4% with thrombolysis and 7.3% with primary PCI in PRAGUE-2), whereas in patients presenting > 2-3 hours, primary PCI is strongly favored (mortality of 3.7 and 6% respectively in the two trials, compared with 5.9 and 15.3% with thrombolysis)[4,9,10]. Organization of ambulance systems, pre-hospital management, immediate risk stratification, and adequate PCI capacity are now the key issues in providing the best reperfusion therapy for STEMI.

MISTRAL: fresh wind or stuffed air?

In the current issue of the Journal, Steffenino et al.[11] report MISTRAL, a national survey started in 1998 by the Italian associations ANMCO and GISE and aimed at describing the clinical epidemiology, therapeutic strategies and outcome of consecutive STEMI patients. Between May 1998 to June 1999, 3074 consecutive patients admitted to 47 Italian coronary care units were enrolled, 2227 (72.4%) of whom found at higher risk according to a set of demographic (female sex, age > 70 years) and clinical variables (diabetes, previous MI, heart rate, blood pressure, site and ECG extent of acute MI, impaired left ventricular ejection fraction at entry, contraindication to thrombolysis). Among the subgroup at higher risk according to the above-mentioned criteria, 82% of the patients had a large MI (i.e., ST-segment elevation in more than 4 ECG leads), 36% were > 70 years old, and 28% were women.

Some MISTRAL findings are unexpected. In particular, despite the "high-risk" profile of the surveyed population, the investigators found a substantially similar outcome among patients treated with thrombolysis or with primary PCI, both at short- and long-term follow-up: the in-hospital combined incidence of death, non-fatal MI or stroke events was 9.2% after thrombolysis, and 10.7% after primary PCI (odds ratio 1.19, 95% confidence interval 0.86-1.63). At 1-year follow-up, primary PCI was no better than thrombolysis in terms of mortality (12.9 vs 13.0%) or recurrent infarction, but it was associated with less angina.

Surveys monitor and verify the transposition of trial results to the everyday clinical practice. MISTRAL is a huge registry that encompassed the clinical practice of 47 major Italian hospitals (17/47 also performing primary PCI) just few years ago. In order to better understand some "strange" MISTRAL results and establish their applicability, first we should verify how much MISTRAL registry still reflects the current care pattern in acute MI management countrywide. To this aim, we compared the database from MISTRAL with that from BLITZ, the last snapshot on current nationwide practice on STEMI management in > 90% of the Italian coronary care units (> 30% with on-site primary PCI facilities)[2] (Table I). In view of the striking similarities in demographic, clinical and outcome data of the two surveys, most MISTRAL thoughts seem contemporary and applicable.

Although the MISTRAL study is subject to the well-known methodological limitations as any registry, it is relevant to note that groups receiving either thrombolysis or primary PTCA were substantially similar with regard to baseline descriptors. The slight excess of Killip class > 2 among patients who had primary angioplasty (9.3 vs 2.5% in thrombolysis), a finding that might reflect a selective use of PCI in such patients, is

Table I. Demographic, management and outcome data of the MISTRAL and BLITZ populations.

	MISTRAL (n=3074)	BLITZ (n=1275)
Age (years)	64 ± 12	66 ± 13
Female sex (%)	23.5	29
Diabetes (%)	17.5	20
Prior acute MI (%)	15.5	15
Previous PCI/CABG (%)	5.7	5.2
Delay to admission (min)	180 ± 160	120§ (IQR 60-300)
Acute anterior MI (%)	43.0	46.7
Killip class 1 (%)	82.8	79.6
Killip class 3-4 (%)	4.9	4.5
No reperfusion treatment (%)	18.7*	35
Pre-hospital thrombolysis (%)	0*	0
In-hospital thrombolysis (%)	48.9*	50
Door-to-needle time (min)	30§ (IQR NA)*	45§ (IQR 26–85)
Contraindications to thrombolysis (%)	10.2*	28
Primary PCI (%)	32.3*	15
Door-to balloon time (min)	50§ (IQR NA)*	85§ (IQR 60-135)
In-hospital mortality (%)	7.7	7.5

CABG = coronary artery bypass graft; IQR = interquartile range; MI = myocardial infarction; NA = not available; PCI = percutaneous coronary intervention. * data are limited to the 2227/3074 MISTRAL patients at higher risk; § median.

counterbalanced by the older age and the larger prevalence of women in the thrombolysis group. Whatever the case, multivariate adjustments failed to show any advantage for primary PCI in terms of in-hospital survival, and the use of primary PCI was not significantly correlated with a lower mortality at 1 year.

The overall in-hospital mortality rates of Italian patients with STEMI enrolled in the MISTRAL and BLITZ registries are strikingly similar (7.7 and 7.5% respectively)[2,11]. Of note, the in-hospital mortality of higher-risk MISTRAL patients who were treated with thrombolysis (7.2%) is not too far from that observed after thrombolysis in all-comers BLITZ patients (5.6%), as well as in modern reperfusion trials, such as ASSENT-3 (6.2%) and GUSTO V (5.7%), which included only thrombolysis-eligible patients within 6 hours of symptom onset[12,13]. The in-hospital mortality rate of higher-risk MISTRAL patients who underwent primary PCI (8.5%) was substantially greater than the 30-day mortality in all patients treated with primary PCI in BLITZ (6.5%), in the 1994-1998 German MITRA-MIR survey (6.4%), and in modern primary PCI trials, such as CADILLAC (2.1%), ADMIRAL (5.0%), and ACE (3.7%)[14-17].

For those of us working in cardiac centers with limited access to emergency intervention facilities, when reading the results of ongoing primary PCI trials is a sort of an excursion into a clinical Alice Wonderland. Yet convinced that "small is large", then registries wake up us suddenly: maybe, or likely, the benefit is not that large in the real world. If primary PCI has emerged as the reperfusion strategy of choice in acute MI, how can we explain the diverging results reported in the registries?

Trials and registries: the reality is more real

Steffenino et al.[11] correctly pointed out that the lack of superiority from a primary PCI-based strategy in comparison to pharmacological reperfusion is mainly to ascribe in MISTRAL to the very high percentage of patients who underwent thrombolysis in the "golden hours": > 85% of them were treated within 2 hours of symptom onset.

The fact that several lytic ineligible MISTRAL patients underwent primary PCI could also explain the outcome findings. In any case, other surveys of real-world practice indicated no survival benefit for patients treated with primary angioplasty compared with those who received thrombolysis. In the MITI registry, the 1-year survival was 89% for thrombolysis and 85% for primary PCI[18]. In the smaller registry of all STEMI patients admitted in French intensive care units in November 1995, the 30-day mortality was 7.6% in the 721 patients who received thrombolytic therapy, compared with 9.2% in the 152 patients who were treated with primary PCI[19]. Of note, the rate of rescue angioplasty among patients receiving thrombolysis in the MITI and French surveys was 26 and 9%, respectively. On the contrary, it is not possible from the MISTRAL data now reported to determine how many patients treated with thrombolysis subsequently underwent rescue or urgent PCI: this is a major pitfall when translating MISTRAL findings into our daily practice.

Different results (hospital mortality of 11.3 and 6.4% after thrombolysis and primary PCI, respectively) were found in the large German MITRA-MIR survey in 9906 lytic-eligible patients[14]. This survey also documented between 1994 and 1998 a substantial in-hospi-

tal mortality decrease after primary PCI (from 13.9 to 3.8% at the end of survey) but not after thrombolysis (from 10.2 to 12.7%)[20]. PCI techniques have undoubtedly improved since the MITI and French surveys. But also thrombolysis improved. "Modern thrombolysis" now comprises careful coagulation management and aggressive reperfusion monitoring with urgent post-fibrinolysis transfer for rescue PCI, thus substantially reducing the risk of both intracranial hemorrhage and early reinfarction. Of note, current in-hospital mortality rates of Italian STEMI patients in the BLITZ registry look strikingly similar (5.6% both after thrombolysis and primary PCI).

When favorable results of trials are translated into clinical practice, several relevant issues arise. Patients recruited in trials differ from "real-world" patients, since the inclusion/exclusion criteria adopted in randomized clinical trials may select a subset of patients at lower risk. In particular, elderly patients, those with late hospital presentation, uncertain diagnosis and unfair co-morbidities are generally excluded from trials, while they are an increasing component of the clinical scenario. It has been shown that patients who met the selection criteria for inclusion into a randomized trial of coronary angioplasty vs coronary surgery fared better than those actually randomized, which casts doubt on the applicability of such randomized trials in clinical practice[21]. Moreover, research projects are frequently conducted in selected institutions, where the overall healthcare system is different from that available in a "real-world" setting. Unfortunately, physicians and community hospitals substantially differ from investigators and centers participating in clinical trials. In the case of acute coronary syndromes, the feasibility of revascularization procedures is exceedingly less common in community hospitals.

Randomized trials and registries describing current practices and outcomes bring different types of information and are affected by different limitations. Randomized trials of interventions document the efficacy of a given type of therapy or intervention in an optimal setting, rising however the concern of the applicability of the results on a larger scale, given the major selection bias in selecting patients. In contrast, registries document whether new therapeutic modalities used in the real world are correlated with improved clinical outcomes, but suffer the major methodological bias of the limited comparability of different groups of patients receiving different kinds of treatment.

To obviate the limitations of both types of studies, we must consider them complementary to improve our clinical decision. Of note, when both trials and registries give concordant results, we consider their clinical applicability as extremely likely. Not infrequently, however, trial and registry results are conflicting: further evaluation is then necessary before we can definitely recommend any specific management policy.

As a matter of fact, the "reperfusion supremacy *querelle*" is scientifically far from being settled. Supporters of primary PCI emphasize the ongoing improvement in PCI techniques and materials. On the contrary, detractors point out that based on the available evidence, clinical advantages of primary angioplasty are small and limited to a reduction in early reinfarction and intracranial hemorrhage risk. Many of the primary PCI vs thrombolysis trials included in meta-analyses have limitations that could have favored primary PCI: reinfarctions associated with invasive procedures were generally omitted; obsolete reperfusion protocols with 3-4 hour infusions of alteplase or duteplase "unfair to modern thrombolysis" were used, as well as obsolete antithrombotic regimens with dosages of unfractionated heparin substantially exceeding what current guidelines recommend and regimens used in recent clinical trials[8,22].

Among the reasons for the discrepancies between randomized studies and registries, motivation for participating in a randomized trial as well as center experience (which has been shown to influence the results of direct angioplasty in the acute phase of MI) might represent a partial explanation. We doubt, however, that center inexperience in primary PCI played any role in the MISTRAL results, given the blazon of most of the PCI centers enrolled in this survey.

Can Italians do it better or worse?

The finding that, in MISTRAL, despite similar risk profiles, STEMI patients who underwent thrombolysis or primary PCI showed similar fatality rates is not the sole remarkable finding. Other MISTRAL results deserve consideration.

• In MISTRAL, as well as in BLITZ registries, reperfusion treatment was administered in > 60% of all STEMI patients. Among high-risk MISTRAL patients, reperfusion treatment was administered in > 85% of patients in centers with and in > 76% of those admitted in centers without on-site cath labs. Overall, this represents a very high rate of reperfusion treatment, considering the not negligible fraction of patients with long pre-hospital delay. In 1990, the GISSI-Ritardo Evitabile registry documented a very low rate (40%) of reperfusion therapy performed in the Italian hospitals[23]. Current Italian reperfusion rates favorably compare with those recently reported in other international STEMI registries: 55, 59 and 56% of patients enrolled in RIKS-HIA, ENACT and Euro Heart Survey ACS, respectively, received thrombolysis or primary PCI[24-26]. Even higher rates of reperfusion therapy have been reported in the United States: in the NRMI-3 survey, 48% of STEMI patients presenting within < 12 hours of symptom onset received thrombolysis and 24% primary PCI[27]. In MISTRAL centers without on-site cath lab, a slightly higher prevalence of no reperfused patients was recorded (23 vs 14%). Thus, we can do it even better, also taking into

consideration the poor clinical profile and outcome of patients who do not receive any reperfusion treatment: they are generally older, with a higher prevalence of previous MI and stroke; they receive less aspirin, beta-blockers and statins both at entry and at discharge, and their mortality rate is 3 times higher. One possible explanation of current "no-reperfusion" strategy adopted *de facto* in one fourth to one third of STEMI patients is the late hospital presentation of most of them, with delays that often exceed the critical reperfusion window. The high number of patients with contraindications to thrombolysis who are not treated with primary PCI represents a major target of intervention for our Associations.

• The door-to-needle time documented in MISTRAL (median 30 min) was better than in BLITZ (median 45 min). This suggests that the "reperfusion track" operating in our hospitals is still far from being settled. Shorter door-to-needle delays have been documented in the NRMI-3 survey (median 38 min)[27]. We can do better.

• The door-to-balloon time was also shorter in MISTRAL (median 50 min) than in BLITZ (median 85 min). In other surveys, it was longer (110 min in RIKSHIA year 2000, 111 min in GRACE, and 108 min in NMRI-3)[24,27,28].

• The long duration of hospital course in MISTRAL patients must be underscored. The 10 days of median hospital stay documented in BLITZ reconfirms our *lento pede* in managing STEMI patients, different from what happens in other European countries (8 days of median total length in the Euro Heart Survey ACS and GRACE registries, 5 days for acute MI patients in Sweden in the year 2000) and in the United States, were the duration of hospital stay of patients with acute MI declined in the last 10 years from 8.3 days in 1990 to 4.3 days in 1999, independent of any kind of reperfusion strategy[24-28].

Is Alice leaving Wonderland?

The MISTRAL data add further fuel to the *querelle* regarding "the best reperfusion strategy" in patients with STEMI. The topic is hot, as well as the enthusiasm, that often seems to ignore major logistic issues and the increasing resource restriction. Wisely, Dr. Ardissino, co-author of the ESC guidelines on STEMI treatment, has recently admitted that even in his top-quality Parma cardiac center "we cannot afford costs and managing implications of treating with primary PCI all patients presenting with STEMI" (Como, May 2003, personal communication). For most Italian centers less favorite in terms of funds, medical and nursery staff availability, the performance of a primary PCI implies a substantial resource shortage for other elective coronary and electrophysiology interventions, with unfair consequences in the daily activity of our overcrowded departments.

Countrywide, several self-made primary PCI programs have been established in the last years with local networks driving STEMI patients to cath labs with skilled personnel or to tertiary cardiac centers. These are mostly the results of strenuous efforts put by passionate cardiologists, luckily dealing with illuminate administrators collaborating to solve all the cumbersome logistics of transfer. Of note, 13 Italian regions are currently setting possible network strategies on how to make emergent angiography and primary PCI more readily available and timely (Boccanelli A., January 2004, personal communication). ANMCO is putting concrete and coordinate efforts toward politicians and administrators in order to regionalize the care of patients with acute MI, to implement the 118 Service by standardizing both first as well as secondary transfer to tertiary cardiac centers for any emergent ("primary", "rescue", "facilitated", etc.) angiography or PCI, and initiating pre-hospital thrombolysis in counties without cath labs and longer transfer delays.

Treatment options must be tailored to each patient in order to optimize the benefits and minimize both the risk of detrimental effects and management costs. It is now clear that pre-treatment delay must be largely reduced with expected clinical benefits independent of further medical or invasive management. Early patient reaction and health service response are at least as important as the type of strategy. Then, the choice of this latter crucially requires four major answers to the following questions: a) is the presentation delay > 3 hours? b) is the transfer delay to implement PCI > 90 min? c) what is the risk profile? d) what is the bleeding risk?

Treatment methods do not compete for patients and should be selected according to individual patients' needs. Instead of wondering which strategy theoretically would offer the greatest advantage, most of us wish to be put in condition to implement effectively the results of major trials, in order to optimize the care of the single individual presenting with STEMI.

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