Editorials
Primary angioplasty, instead of thrombolysis, for all patients with acute ST-elevation myocardial infarction?

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Randomized clinical trials

Evidence has grown in the last decade, showing that primary angioplasty (P-PTCA) is superior to thrombolysis (TL) in the treatment of acute ST-elevation myocardial infarction (MI). A meta-analysis of 10 randomized trials, published in 1997[1], showed a relative reduction in mortality of 34% (6.5% for TL vs 4.4% for P-PTCA). Incidentally, that meta-analysis was recently extended to 7739 TL-eligible patients included in 23 randomized trials[2]; it confirmed a lower short-term mortality for P-PTCA vs TL (7 vs 9%) and lower re-infarction (3 vs 7%) and stroke rates (1 vs 2%).

In the American College of Cardiology/American Heart Association (ACC/AHA) guidelines of 1999[3] the recommendation was made that "*P-PTCA should be used as an alternative to thrombolytic therapy only if performed in a timely fashion by individuals skilled in the procedure and supported by experienced personnel in high-volume centers*".

Recent registries

Data from randomized clinical trials corroborating the need for both a "timely fashion", and "individuals skilled in the procedure and supported by experienced personnel in high-volume centers" as stated in the ACC/AHA guidelines, have been replicated in analyses of recent registries.

In their report of the NRMI-2 and -3 data (62 299 patients with acute MI treated with P-PTCA or TL in 446 US centers between 1994 and 1999), Magid et al.[4] found that at high-volume centers (> 49 procedures/year) the in-hospital mortality was lower among patients treated with P-PTCA (3.4%) than among those submitted to TL (5.4%); this was also true for medium-volume P-PTCA centers (17-48 procedures/year), where the mortality rates were 4.5 vs 5.9% respectively. The analysis of the NRMI-2 data (27 080 patients with acute MI treated with P-PTCA in 661 US hospitals) published by Cannon et al.[5] some months earlier had illustrated the relationship between an increased mortality and a delay in the door-to-balloon time > 2 hours, suggesting that the door-to-balloon time is a valid quality-of-care indicator.

In a German study[6], 9906 lysis-eligible patients with an acute MI < 12 hours were evaluated by pooling two registries from 271 centers (18% performing P-PTCA). Of the 1327 patients treated with P-PTCA, 18% were transferred from other hospitals; of the 8579 patients treated with TL, 50% received streptokinase. At hospitals with P-PTCA facilities, TL was used in 58% of patients: at these hospitals the mortality rates were 6.6% for P-PTCA and 11.3% for TL. The mortality was lower at hospitals with P-PTCA facilities than at those without (9.3 vs 11.2%). Overall, in this registry, when patients with shock were excluded, the hospital mortality with P-PTCA (4.7%) was similar to other registry reports, while for those patients treated with TL it was much higher (9.7%) than in most other studies.

Many patients are just not fortunate enough

These data from the contemporary real world have been taken to confirm the superior effectiveness of P-PTCA over TL, and have sustained a widely held outlook, synthesized by Every and Lehmann[7] in 2001: "*Based on a number of prospective trials, it appears clear to us that, on average, moderate-to-high-risk patients presenting early in the course of an evolving infarction do better with P-PTCA than with TL – provided the patient is treated expeditiously by an experienced operator in a high-volume center. The proper course of action for the large majority of patients who are not fortunate enough to present at the optimal time of day to such a facility is less clear*".

Suggestions about what should be done with the "majority of patients who are not fortunate enough …" have come from new randomized studies showing that emergency transfer of patients to a tertiary center to receive P-PTCA may be preferable to treatment with TL at a community hospital.

Patients on the move

In the PRAGUE trial, 300 patients were randomized to on-site TL with streptokinase, transfer for P-PTCA, or both[8]; at 30 days, the mortality rates were 14, 7 and 12% respectively, and the combined endpoint of death, reinfarction and stroke was 23, 8 and 15% ($p < 0.02$) – with reinfarction being observed in 10% of the patients in the on-site TL group.

In the Air-PAMI trial, 138 lysis-eligible patients with a high-risk acute MI were randomized to either transfer for P-PTCA or on-site TL[9]. The trial was stopped prematurely due to recruitment difficulties; in the transfer vs on-site TL patients, the mortality was 8.4 vs 12.1%, the incidence of reinfarction was 1.4 vs 0%, and that of stroke was 0 vs 4.5%, and the incidence of the composite endpoint was 8.4 vs 13.6% ($p = 0.33$).

In the DANAMI-2 trial (presented at the American College of Cardiology Scientific Sessions, Atlanta, GA, USA, 2002), 1129 patients admitted to 22 non-invasive referring hospitals in Denmark were randomized to either transfer for P-PTCA at the nearest (on average 56 km) of five invasive centers, or to local TL with recombinant tissue-type plasminogen activator (rt-PA); 443 additional patients admitted to the P-PTCA centers were randomized to either P-PTCA or TL. The trial was stopped before its conclusion by its Safety and Data Monitoring Board, after a clear benefit was seen in the P-PTCA patients; in fact, in patients treated with TL vs P-PTCA, the combined 30-day endpoint of death, reinfarction and stroke was observed in 13.7 vs 8.0%, respectively – with 14.2 vs 8.5% in patients from referring hospitals, and 12.3 vs 6.7% in patients from invasive centers. The incidence of death alone at 30 days was 7.6% in the TL group vs 6.6% in the P-PTCA group. It is noteworthy that a reinfarction occurred in 1.6% of the P-PTCA patients vs 6.3% of the TL patients, and in the latter non-scheduled myocardial revascularization was as low as about 7% at 5 days and 12% at 10 days. Rescue PTCA was performed in 2.5% of patients only. "*The take home message from this trial* – in the very words of its principal investigator[10] – *is that the strategy of transferring patients with ST-elevation acute MI for P-PTCA is superior to accelerated alteplase treatment when the transport can be completed within 3 hours*".

In the PRAGUE-2 trial (presented at the European Society of Cardiology Congress, Berlin, Germany, 2002), 850 patients with an acute MI admitted to community hospitals were randomized to on-site TL (streptokinase) or transport to a tertiary center for P-PTCA. The primary endpoint of the 30-day mortality in the TL vs P-PTCA patients was 10 vs 6.8% ($p = 0.12$) as analyzed by the intention to treat, and it was 10.4 vs 6.0% ($p < 0.05$) as analyzed by the actual treatment received. The analysis by the time to treatment showed that the mortality was identical in patients randomized to both treatments within 3 hours of the onset (7.4 vs 7.3% respectively), but it was 15.3 vs 6% ($p < 0.02$) in those treated at 3-12 hours from the onset.

Moving angioplasty

Diverging suggestions about what should be done with the "majority of patients who are not fortunate enough …" have come from the C-PORT trial[13]. In this trial, 451 patients with acute MI < 12 hours admitted to 11 US community hospitals without on-site cardiac surgery or extant PTCA programs were randomized to on-site P-PTCA or TL with rt-PA. A formal P-PTCA development program had previously been completed at all sites[11]. The trial was stopped prematurely due to funding problems. The composite incidence of death, reinfarction and stroke was significantly lower in the P-PTCA group at 6 weeks (10.7 vs 17.7%) and 6 months (12.4 vs 19.9%). The median door-to-treatment time for TL vs P-PTCA was 46 vs 55 min respectively; it is of note that, at discharge, the incidences of death, recurrent acute MI and stroke were 6.2, 8.8, and 3.5 vs 5.3, 4.0, and 1.3% respectively.

Last year, new ACC/AHA guidelines for percutaneous coronary interventions were published. According to these guidelines, hospitals without on-site cardiac surgery could perform P-PTCA as long as they met specified criteria, including a minimum volume of 36 P-PTCA per year[12].

Provocative registry data from the NRMI-3 and -4 were presented by Sanborn et al. at the last AHA Scientific Sessions (Chicago, IL, USA, 2002). The in-hospital mortality and door-to-balloon times were examined for 26 764 reperfusion-eligible patients who were treated with P-PTCA in the United States from 1998-

2001. Approximately 2000 of these patients received P-PTCA in 97 hospitals without cardiac surgery, and the P-PTCA volume was ≥ 50/year in 13% only of those centers. There were no significant differences in mortality between hospitals with and without cardiac surgery, and the door-to-balloon times were even shorter in the latter, suggesting a more efficient treatment. P-PTCA was used in a higher proportion of acute MI patients at hospitals without surgery. About 70 and 25% of patients treated with P-PTCA were low-risk and moderate-risk, respectively, in both hospital settings, and 25% of reperfusion-eligible patients received no reperfusion treatment.

Primary angioplasty for everybody

The results from all these trials and registries have fueled enthusiasm by the international cardiological community. An authoritative overview of evidence-based treatment options for the reperfusion of an ST-elevation acute MI has recently been published in the "Clinician Update" section of a major cardiology journal[13]. The authors conclude: "*In summary, available evidence suggests that the patient described above, who presented in the early hours of anterior infarction with evidence of hemodynamic compromise, should have undergone reperfusion. Although clear benefit would have been obtained by thrombolytic administration, ample data point toward a greater benefit from catheter-based intervention (P-PTCA with stent implantation) either at a qualified community hospital, or by transfer to a tertiary center"*. In a 2002 editorial in *JAMA*, Cannon[14] comes to an even more explicit conclusion: "*At present, the available evidence suggests that transfer for or performance on-site of primary percutaneous coronary intervention, even at the community hospital, appears to lead to better outcomes than thrombolytic therapy for acute MI"*.

Using better glasses

Although there is little doubt that for most, or even all, acute MI patients P-PTCA is the best reperfusion treatment, the results of the PRAGUE-1 and -2 and DANAMI-2 trials should be interpreted with some caution. They showed that the transfer of patients with acute MI to a P-PTCA center, instead of TL in the local hospital, was feasible and safe, and was beneficial in that setting. The outcomes of patients treated with TL in a community hospital basically depend on at least three patient-related factors, i.e. 1) the probability that TL can achieve adequate reperfusion – which is related to the time from symptom onset[15,16] and to the type of lytic drug used; 2) the probability that the acute MI is fatal or disabling if reperfusion from TL fails – which is related to the extent of muscle in jeopardy and to the residual left ventricular function; 3) the probability that TL causes severe bleeding – which is related to body weight[17], blood pressure, and other less predictable characteristics. Additional hospital-related factors do influence the outcomes of these patients, namely 4) the probability that the patient is referred for emergency rescue PTCA in case of unsuccessful TL[18-20] or early reocclusion[21]; 5) the probability that the patient is referred for early elective coronary angiography and myocardial revascularization after successful TL[22,23]; and 6) the global quality of care offered in the community hospital. The overall modest survival advantage of P-PTCA transfer over TL, and the high reinfarction rates in the on-site TL arm of those trials contributing to a substantial share of the observed benefit from P-PTCA, should be re-considered under this viewpoint. There may be much room for improving the outcomes of most patients treated with TL at a community hospital even without emergency transfer for P-PTCA, and the latter can probably be reserved for selected high-risk patients for whom it may be life-saving. The subject of the selection and pre-treatment of patients with acute MI for emergency transfer to P-PTCA centers was exhaustively addressed in a recent editorial by Dalby and Montalescot[24].

On the other side, the message from the C-PORT trial also seems to deserve special attention: provided adequate quality assurance programs are implemented, high-quality results with P-PTCA can be obtained in centers without previous experience, and even in those with persistently low P-PTCA caseloads. This is also part of the lesson from DANAMI-2. In fact, before the trial, only two of the five P-PTCA centers in DANAMI-2 had performed P-PTCA, but in a few cases and only during daytime, while the other three had never performed this procedure. Before starting the trial, the three new hospitals had to be trained and certified, after having performed at least 25 procedures, by the trial safety committee[10]. This should mean that the attention of the scientific societies, and of the regulatory organs, should be shifted from "caseloads" to more appropriate – and mandatory – quality assurance programs and indicators for P-PTCA in all centers where it is performed.

Translation into clinical practice in Italy

How the input from all these studies should be translated into clinical practice in our country is a crucial question. A 2001 survey (presented at the Italian Association of Hospital Cardiologists Congress, Florence, Italy, 2002) showed that only 31% of about 300 coronary care units (CCU) nationwide have an interventional cath lab on-site, varying from 40 to 21% – and with a mean reference population varying from 387 000 to 781 000 – in the northern as compared to the southern regions. That survey also showed that, of

1959 patients with acute MI, only 28% were transported to hospital by the "118" emergency ambulance system, that the delay from symptom onset to admission was < 2 hours and 2-6 hours in 49 and 26% respectively, and that about 50, 15, 10 and 30% of reperfusion-eligible patients received TL, P-PTCA, rescue PTCA, and no reperfusion treatment respectively.

If, on the one hand, the way to go in Italy seems to be long and steep, on the other the enthusiasm for P-PTCA has translated into a myriad of local initiatives whereby patients with acute MI are either transferred from community hospitals to a nearby P-PTCA center (with or without pre-treatment with TL and/or IIb/IIIa antagonists), or else P-PTCA is performed locally in low-volume cath labs by (or under the supervision of) experienced operators who are on call at nearby PTCA centers.

A recent consensus document by the Italian Federation of Cardiology[25] should be appreciated for having provided the national cardiological community with a comprehensive, broad perspective on the treatment of patients with acute MI. It is recognized that improving the outcomes of patients with acute MI requires interventions at all steps in their diagnostic and therapeutic pathways, starting with those patients who are admitted to hospitals without a CCU, or who are not admitted at all. It is recommended that patients with a large, or otherwise high-risk, ST-elevation MI are considered for emergency transfer to a center with a consolidated P-PTCA program, if it can be reached within 3 hours or less. As for P-PTCA, the recommendation is made that these interventions should be performed in centers with a caseload of at least 60 P-PTCAs/year and which have on-site cardiac surgical facilities, or a rapid access to them. A quality assurance plan is proposed as mandatory for P-PTCA centers. Similar recommendations for the use of P-PTCA are made in the 2002 Task Force report from the European Society of Cardiology[26] where it is stated that: 1) only hospitals with an established interventional cardiology program should use primary percutaneous coronary intervention as a routine treatment option; 2) for patients admitted to a hospital without catheterization facilities on site, a careful individual assessment should be made of the potential benefits of mechanical reperfusion in relation to the risk and treatment delay of transportation to the nearest interventional laboratory.

We would like to add the following considerations which reflect our personal views. As to Italy, the only large prospective multicenter registry of patients with a high-risk acute MI treated with P-PTCA or TL at centers with and without P-PTCA facilities[27] performed in 1999 unexpectedly failed to document any benefit of P-PTCA over TL, except for a lower incidence of recurrent angina during the year following enrolment.

The practice of P-PTCA has evolved in Italy, probably even faster than elsewhere: nationwide activity data[28] of 2001, as compared to 1999, show a 90% increase in P-PTCA procedures (from 3584 to 6843), and a 55% increase in the number of centers (from 86 to 133) performing P-PTCA; however, the number of centers with ≤ 10, < 36, and ≥ 60 procedures/year in 2001 vs 1999 were 40 (30%) vs 29 (34%), 75 (56%) vs 50 (58%) and 41 (31%) vs 21 (24%) respectively. Thus, even if both the number and the proportion of centers with large (≥ 60) P-PTCA caseloads have increased in the last 2 years, the majority of centers in 2001 were still performing lower volumes of P-PTCAs than indicated in the most recent recommendations in the United States[12] and in Italy[25].

The outcomes of patients currently treated with P-PTCA may have substantially improved in the last 2 years in Italy, but the results of contemporary P-PTCA in our country have not been reassessed. On one hand, traditional observational studies may have become simply too slow to be of help in understanding a rapidly evolving practice; on the other hand, registry reports have spread the awareness that the outcomes of P-PTCA in whatever setting can be properly evaluated only if data are collected upstream, i.e.: if the risk profile and outcomes of all reperfusion-eligible patients at each site are considered. The implementation of a national database of the CCUs, similar to that used in Sweden[23], seems to be the only effective instrument for monitoring the changing practice of acute MI treatment. Ongoing efforts by the Italian Association of Hospital Cardiologists to implement this database should be welcomed as a top priority.

The Italian Society for Interventional Cardiology (GISE) may also have a role to play in this nationwide effort, by: 1) preparing detailed quality assurance protocols for the interventional treatment of acute MI patients to be implemented in all centers; 2) expanding beyond bare activity data the data-set that all centers should provide yearly.

Although pre-hospital TL[29] may be a very interesting option, the overall impact of this strategy in our country may be limited by the small proportion of patients with acute MI currently conveyed to the CCUs by the emergency ambulance system.

When it comes to the emergency transfer for P-PTCA, several factors may reduce the advantage of this strategy over immediate TL: the most commonly experienced obstacle being excessive delay in transfer, due to poor organization. Thus, the use of the DANAMI-2 approach in a different setting may well fail to yield the modest – yet appealing – benefit of one life saved for 100 patients treated, as reported in that trial. All programs involving the transfer for P-PTCA instead of local TL should, therefore, include the monitoring, auditing and reporting of both the delays and outcomes for all (transferred or non-transferred) patients, and the involved cardiologists should be as committed to data collection as if it were part of a trial.

Reperfusion treatment still underused

Finally, it should be considered that all recent registries[4-6,27] and surveys[30] uniformly show that reperfusion treatment is persistently underused in patients with acute MI, with one quarter to one fifth of eligible patients being left untreated. This also holds true when P-PTCA programs are run at small community hospitals without cardiac surgery facilities, suggesting that this is probably no solution to the insufficient use of reperfusion. Registry data uniformly show also that non-reperfused patients have a very high incidence of adverse outcomes[31]. Despite the impressive growth of P-PTCA in Italy in the last 2 years[28], the percentage of patients who do not receive reperfusion treatment has remained unchanged[27]. P-PTCA has virtually no contraindication in patients with acute MI, and is probably safer and more effective than TL in most situations where reperfusion treatment is currently being omitted (e.g. age > 75 years, onset of symptoms > 4 hours, acute heart failure). P-PTCA, possibly by transfer to tertiary centers, could have a strong impact on the mortality and disability of acute MI in the population if it were used first of all for offering reperfusion to patients who – especially in community hospitals[27] – are frequently excluded from this treatment. In the few places where rapid transfer to an interventional center is not feasible for geographic or other reasons, the initiation of a small-volume P-PTCA program – with the same quality assurance instruments and prescriptions as anywhere else – would be a workable alternative, and should be encouraged.

Back to the headline

In concluding this review, we would like to return to the question in the title. Offering P-PTCA to every patient with acute MI coming to any hospital at all times is a luxury we cannot afford. A local policy – where feasible – of simply shifting as many patients as possible from TL to P-PTCA, either by transfer to tertiary centers or by starting P-PTCA programs in community hospitals, is not an appropriate solution. Many, or even most, of these patients would be well served by TL, if followed by accurate surveillance of reperfusion and prompt intervention when necessary; emergency transfer for P-PTCA in all these cases means inappropriate resource use. On the other hand, every effort should be made in all community centers: 1) to identify by adequate protocols those patients who are less likely to benefit – or more likely to be harmed – from TL and in whom P-PTCA may be highly advantageous; 2) to develop adequate, effective pathways for the rapid and safe emergency transfer of acute MI patients to the nearest interventional center at any time – when necessary – after admission; 3) to increase the use of reperfusion treatment as close as possible to 100%, even by resorting to transfer for P-PTCA; 4) to collect data and monitor results. Patient transfer for P-PTCA appears to be a specially rewarding effort in those cases (and many are to be found) where it makes a great difference, the more so where the alternative is between reperfusion treatment and no reperfusion treatment at all.

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