Primary Percutaneous Coronary Intervention for All?

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REPERFUSION THERAPY WITH THROMBOLYSIS OR PRIMARY percutaneous coronary intervention (PCI) has been a major advance in the treatment of acute ST-segment elevation myocardial infarction (MI), with a 25% reduction in mortality with thrombolysis.[1] Primary PCI has been considered in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines in 1999 to be an alternative to thrombolysis.[2] Since then, the number of trials and number of patients randomized has more than doubled to 21 trials and 6800 patients, all of which show clear benefit of PCI over thrombolysis. A meta-analysis of the randomized trials carried out through 1997 showed a clear reduction in mortality, recurrent MI, stroke, and intracranial hemorrhage. Mortality was reduced a relative 34% (6.5% for thrombolysis vs 4.4% for primary PCI), suggesting that 20 patients' lives would be saved for every 1000 patients treated with primary PCI instead of thrombolytic therapy.[3] Nonfatal reinfarction was reduced nearly 50% (5.3% for thrombolysis and 2.9% for PCI) and intracranial hemorrhage was essentially eliminated (1.1% with thrombolysis and 0.1% with PCI).[3] In addition, cost appears to be similar between the 2 strategies,[4] largely because many patients receive PCI following initial thrombolysis. Thus, based on these initial 10 randomized trials, primary PCI is considered a superior strategy both for efficacy and safety.

The caveats to this conclusion were that these excellent results were obtained in the setting of clinical trials with experienced interventionists. Could these benefits be accomplished in the real world? Initial data from 2 registries actually suggested otherwise, with no difference in outcomes between patients treated with primary PCI vs thrombolysis.[5,6] However, interventional cardiology has advanced dramatically during the last decade with the advent of stents and glycoprotein IIb/IIIa inhibitors, which have appeared to make a difference in outcomes in patients treated with an invasive strategy with unstable angina and non–ST elevation MI.[7]

More recent registry data show a benefit of primary PCI over thrombolysis. A study of more than 62 000 thrombolytic-eligible patients in the National Registry of Myocardial Infarction compared patients treated with primary PCI with those treated with thrombolysis.[8] Because hospital volume is an important marker of overall skill, experience, and outcomes in performing primary PCI,[9] patients were stratified into groups reflecting low-, intermediate-, and high-volume centers, based on primary PCI volume of the hospital at which they were treated. At high-volume centers, in-hospital mortality was lower among patients treated with primary PCI (3.4%) than with thrombolysis (5.4%)—ie, 20 lives saved for every 1000 patients treated with primary PCI.[8] Mortality at intermediate-volume hospitals was also lower for patients who received PCI than for those who received thrombolysis (4.5% vs 5.9%). At low-volume hospitals, mortality was similar between thrombolytic-treated and primary PCI-treated patients. However, across all hospitals, primary PCI had a safety advantage, with nonfatal stroke occurring in 0.4% vs 1.1%.[8] Thus, even at low-volume centers, which performed 16 or fewer primary PCI procedures per year, there was an overall advantage for primary PCI.

Another major issue involves time delays that might attenuate any benefit of primary PCI. In an analysis of more than 27 000 primary PCI-treated patients, increasing door-to-balloon time (time from hospital arrival to angioplasty balloon inflation) was found to be a significant factor related to increased mortality.[10] Comparing patients who had an ideal door-to-balloon time of less than an hour, patients who had door-to-balloon times of more than 2 hours had a 40% to 60% increase in adjusted mortality.[10] In accord with these data, the ACC/AHA guidelines recommend that patients undergoing primary PCI should have a door-to-balloon time of 90 minutes ±30 minutes.[2]

Another key issue has been the need for surgical backup in the event of any complications of the primary PCI procedure. Registry data have suggested that immediate surgical capabilities may not be absolutely required because complication risks of primary PCI are quite low in the current era of coronary stenting.[11]

It is in this overall setting that the Atlantic Cardiovascular Patient Outcomes Research Team (C-PORT) study re-

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ported in this issue of THE JOURNAL was conducted. In this trial, Aversano et al[12] posed the question of whether patients who present at community hospitals that do not have cardiac surgical facilities and, hence, have not traditionally carried out primary PCI, could be successfully managed with a primary PCI strategy. Investigators at 13 institutions set out to establish a full critical pathway for the performance of primary PCI. They had multidisciplinary training, standardized order sets, checklists, training procedures at tertiary care hospitals, and quality assurance measures that were a key component of the overall primary PCI program.

After this training program, 226 patients were randomly assigned to receive either front-loaded tissue plasminogen activator (the best available fibrinolytic regimen at the time) and 225 were assigned to undergo primary PCI. The study demonstrates a significant reduction in both early and late cardiac events in patients treated with primary PCI as opposed to thrombolytic therapy. At 6 weeks, the incidence of the composite end point of death, recurrent MI, and stroke was 10.7% in the PCI group and 17.7% in the thrombolytic therapy group. At 6 months, the rates were 12.4% vs 19.9%, respectively ($P=.03$).

In the as-treated analysis, mortality at 6 months was reduced by an absolute (albeit nonsignificant) 2.3%, or 1 life saved for every 43 patients treated with PCI. Recurrent MI and stroke were each reduced by more than 50%, from 10.9% to 4.7%, and from 3.8% to 1.8%, respectively, at 6 months. These data are consistent with findings in previous randomized trials conducted at experienced cardiac centers and provide evidence that after a careful training program, primary PCI can be performed successfully at community hospitals.

Moreover, the findings of Aversano et al are supported by 3 other recent trials. In the European PRAGUE trial, in which 300 patients were randomized to on-site thrombolysis, transfer for primary PCI, or thrombolysis and transfer for PCI,[13] patients transferred for primary PCI had the lowest rate of death, MI, or stroke at 30 days, 8% compared with 23% for on-site thrombolysis and 15% for patients treated with thrombolysis and primary PCI.[13] In the Air PAMI study, in which high-risk patients were randomized to on-site thrombolysis vs transfer for primary PCI,[14] there was a non–statistically significant 38% reduction (13.6% vs 8.4%) in the end point of death, MI, or disabling stroke in patients treated with primary angioplasty. However, the study included only a portion of planned enrollment because of difficulty recruiting patients. Most recently, in the DANAMI-2 study, 1572 patients were randomly assigned to thrombolysis vs primary PCI, with three quarters of patients enrolled at hospitals without on-site catheterization facilities, who were transferred for primary PCI.[15] The preliminary results show a 45% reduction in the primary end point of death, MI, or stroke at 30 days favoring primary PCI: 13.7% for thrombolysis vs 8.0% for primary PCI ($P<.001$). This benefit was similar for patients who were transferred and for those treated at hospitals with on-site catheterization facilities. The mortality difference was an absolute 1%, 7.6% for thrombolysis vs 6.6% for primary PCI (not a statistically significant difference).

What changes are on the horizon that might alter the relative benefits of these 2 strategies? For primary PCI, the advent of glycoprotein IIb/IIIa inhibition has improved outcomes.[16] One randomized trial of coronary stenting with glycoprotein IIb/IIIa inhibition compared with front-loaded tissue plasminogen activator showed a 66% reduction in death, MI, or stroke with the primary PCI strategy.[17] These benefits will become further amplified with the advent of coated stents that help eliminate restenosis.[18] Immediate treatment with clopidogrel in patients being referred for primary angioplasty may provide additional benefit.[19-21]

For thrombolysis, glycoprotein IIb/IIIa inhibition combined with reduced-dose fibrinolytic therapy was expected to improve mortality but did not in 2 large randomized trials.[22,23] Furthermore, a new trial has just compared primary PCI with glycoprotein IIb/IIIa inhibition to enhanced thrombolysis with half-dose thrombolysis with glycoprotein IIb/IIIa inhibition, and found improved myocardial salvage and clinical outcomes with primary PCI.[24] A trend toward an approximately 15% lower mortality rate with the use of enoxaparin rather than unfractionated heparin was noted in the ESSENCE, TIMI 11B, and ASSENT-3 trials.[23,25] If confirmed in the large, upcoming ExTRACT-TIMI 25 trial, this approach could warrant direct comparison with primary PCI.

The Atlantic C-PORT study has several limitations. These include the small sample size, the fact that the trial was stopped early due to lack of funding, and the limited availability of angioplasty after regular work hours. Although the results of the Atlantic C-PORT study are not definitive, this study is the 21st consecutive trial to show a benefit of primary PCI over fibrinolysis.[26] At present, the available evidence suggests that transfer for or performance on site of primary PCI, even at the community hospital, appears to lead to better outcomes than thrombolytic therapy for acute MI.

The implications of these trials are profound. The first is that if a community hospital makes a strong institutional commitment to establishing a comprehensive program, performance of primary PCI will be beneficial to patients. This commitment must involve all levels of caregivers, including the emergency medical services, nurses, physicians, and cardiac catheterization laboratory personnel, such that the overall program can be implemented with quality as high as the Atlantic C-PORT study.[12]

Second, the related positive data on transfer of patients for primary PCI[13-15] suggest that it may be time to change the approach of the emergency medical response system for acute MI. It has been the practice that patients with acute MI are transported to the nearest acute-care hospital so that they can be stabilized and treated appropriately. However, given the results of these 5 recent trials,[12-15,24] and the 16

that preceded them,[3,17,26] this policy may need to be modified so that patients are transferred to a cardiac center that offers primary PCI as the optimal reperfusion strategy. If this can be accomplished in a timely fashion, such an approach clearly would be optimal to improve outcomes, based on current evidence. Of note, this would not apply to patients without ST-elevation MI, for whom an early invasive strategy involves cardiac catheterization within 48 hours, which could be accomplished with initial management at a noncatheterization facility and subsequent transfer.[7,27]

Such a strategy would take a great deal of planning. As outlined several years ago by the National Heart Attack Alert Program,[28] this might be accomplished using the trauma center model, in which patients with major trauma are triaged not to the nearest hospital but to the nearest trauma center. Trauma centers also require ongoing quality assurance and accreditation, which is probably a key component of their overall successful treatment of these patients. This would need to be a part of any program for transfer for primary PCI to ensure high-quality care. In addition, primary PCI would need to be available 24 hours a day, 7 days a week. Such a major change on a national level would likely only follow changes in national guidelines regarding the triage of patients between centers providing the 2 reperfusion strategies. However, at a regional level, pilot programs are already in progress in Florida and Boston, Mass.[29] Data from their implementation should be considered carefully before this approach is adopted nationwide.

The time is now to reevaluate the optimal approach to treatment of patients with acute MI, with an interventional approach appearing to be the optimal strategy. The task for cardiologists and other physicians is to make the best possible therapy available to every patient with acute MI.

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