Primary Stenting in Acute Myocardial Infarction

The Promise and the Proof

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With the demonstration that the timely administration of thrombolytic therapy after coronary arterial occlusion results in myocardial salvage and improved survival, the treatment of patients with evolving AMI has forever been changed. To overcome the inherent limitations of thrombolytic therapy (TIMI 3 flow rates of \( \approx \)55% at best, and rare but unavoidable life-threatening or incapacitating hemorrhagic complications), mechanical reperfusion by balloon angioplasty without antecedent thrombolysis (primary PTCA) has been adopted at many centers. Ten prospective, randomized trials comparing primary PTCA and lytic therapy in 2606 patients have now been performed and examined in a recent meta-analysis by Weaver et al, demonstrating that compared with thrombolytic therapy, primary PTCA results in reduced rates of mortality, reinfarction, and stroke. Other randomized trials have shown that primary PTCA, by reducing early and late recurrent ischemic events and facilitating earlier discharge, is as or more cost-effective than thrombolysis.

Despite these attributes, balloon-induced medial disruption and platelet activation result in recurrent ischemia in 10% to 15% of patients treated with primary PTCA before hospital discharge, including reinfarction in 3% to 5% of patients. Although improvements in operator technique, exclusive use of ionic contrast, and attention to anticoagulation status can minimize these complications, the significant residual stenosis remaining in many patients after balloon angioplasty, in concert with intimal hyperplasia, unopposed vessel recoil, and late remodeling, results in angiographic restenosis in 30% to 50% of infarct vessels within 6 months. As a result, \( \approx \)20% of patients after primary PTCA require TVR with repeat angioplasty or bypass surgery during this time period. Furthermore, not all operators have been able to achieve optimal results of primary PTCA at their institutions.

With the demonstration that the implantation of balloon-expandable slotted-tube stents can reduce clinical and angiographic restenosis compared with PTCA in patients undergoing elective intervention, it might be natural to conclude that shifting from primary PTCA to a primary (routine) stent strategy in patients with AMI would similarly improve late outcomes. However, these early randomized trials of elective stenting were careful to exclude patients with acute ischemic syndromes (including AMI) and lesions containing thrombus, given the prior demonstration that subacute thrombosis rates are increased with the implantation of a metallic endoprosthesis into a thrombotic environment. With the reduction in subacute thrombosis rates realized with improved stent technique and the application of more effective antiplatelet regimens, including ticlopidine, the thrombus-laden lesion no longer represents a strict contraindication to stenting.

As a prelude to initiation of randomized trials, the feasibility, safety, and efficacy of primary stenting in AMI have been examined in a number of observational and registry studies, the largest of which is the prospective PAMI Stent Pilot Trial. In this 9-center international cooperative effort, stenting (primarily with the Johnson & Johnson Palmaz-Schatz stent) was found to be feasible in 240 (77%) of 312 consecutive patients undergoing primary PTCA, with a 98% procedural success rate. Among the stented patients, 93.7% were event-free (alive, without reinfarction or TVR) at 30 days, and 83.3% were event-free at 6 months. When outcomes in the PAMI Stent Pilot Trial were compared with the 1100-patient PAMI-2 trial (99% of patients treated with PTCA only), the routine stent strategy was associated with improved clinical outcomes. Similarly favorable results were reported from the 18-center PAMI Heparin Coated Stent Pilot Trial, in which the 30-day and 7-month event-free rates in 101 patients with AMI were 97.0% and 81.2%, respectively, after implantation of heparin-coated Palmaz-Schatz stents.

While the PAMI investigators were toiling with pilot studies, Suryapranata and colleagues from the Hospital De Weezenlanden, Zwolle, The Netherlands, were boldly per-
forming the first randomized trial of primary PTCA versus primary stenting (using the Palmaz-Schatz stent), the results of which are published in this issue of *Circulation*. Because this group has previously demonstrated the ability to achieve superb outcomes with primary PTCA alone, any findings favoring a primary stent strategy by these investigators would be particularly meaningful. At first glance, it is therefore quite remarkable that among the 227 randomized patients, the 6-month cardiac event–free rates were 95% after primary stenting versus 80% after primary PTCA (P<0.002). This difference in the composite primary end point was driven by reduced rates of reinfarction (1% versus 7%; P<0.04) and TVR (4% versus 17%; P<0.002) in the stent cohort, with no difference in mortality. Does this study represent the proof of the promise of primary stenting in AMI?

Before we banish primary balloon angioplasty to the basement of the Museum of Natural History (along with other well-known interventional dinosaurs), the present report must be carefully analyzed in terms of its limitations and questions left unanswered. The authors would be the first to acknowledge the small sample size of the study (resulting in wide CIs) and the fact that it was performed at a single institution by operators highly experienced with acute infarct intervention. As such, the favorable results of the present study must be reproduced in larger, multicenter trials. In addition, the appropriately cautious entry criteria used resulted in a relatively low-risk population being enrolled. In this regard, the authors are to be commended for carefully registering and tracking outcomes of the patients excluded during the course of the study. Of note, only 50% of the patients with AMI undergoing primary PTCA by Suryapranata et al were considered to be clinically and anatomically eligible for stenting (in contrast to 77% of screened patients in the PAMI Stent Pilot Trial). As demonstrated in Tables 1 and 2 of their article, randomized patients compared with excluded patients were younger, more frequently male, more likely to have single-vessel disease, and less likely to be hemodynamically unstable. Reference-vessel size, a major determinant of late outcome after percutaneous intervention, was also significantly larger in the randomized cohort. Indeed, 124 patients (27%) were excluded for small vessel size or diffuse disease, in contrast to 11% of screened patients in the PAMI Stent Pilot. The results of the present study cannot therefore be necessarily extended to the sizable group of patients with excluded characteristics.

Perhaps more importantly, given sample-size considerations, the possible play of chance cannot be ignored. In this regard, the 5% incidence of adverse cardiac events at 6 months in the stent arm of the present study (including 4% bypass surgery and 0% repeat PTCA) is among the lowest event rates (if not the lowest) ever reported after stenting in any population, and markedly less than the 17% to 19% rate of 6- to 7-month adverse outcomes in the 341 stented patients from the two PAMI pilot trials, which also used the Palmaz-Schatz stent. Moreover, despite the low-risk nature of the randomized population and the fact that 13% of patients assigned to primary PTCA received stents for suboptimal results, in-hospital reinfarction in the PTCA group still occurred in 3.5% of patients. In contrast, no patient in the first Zwolle randomized trial developed reinfarction after primary PTCA, despite enrollment of a higher-risk cohort who were treated with PTCA only without stent availability. Furthermore, intra-aortic balloon counterpulsation was used in 9 more patients (8%) in the stent group than in the PTCA group in the present study, which may also have contributed to the lower incidence of recurrent ischemia.

In addition to requiring that these favorable results be confirmed in other large-scale trials, many additional questions remain to be answered before primary stenting is routinely adopted. What patient and lesion characteristics respond best to acute infarct stenting? Given the obligatory amount of neointimal hyperplasia that occurs after stenting, will certain lesion subtypes, such as small vessels or long lesions, have equivalent or even worsened outcomes after primary stenting compared with PTCA? If an optimal PTCA result is obtained (eg, stenosis <30% without major dissection), is there any benefit to stent implantation? Will routine stenting improve or degrade the outcomes achieved with primary PTCA by the low-volume or less-experienced AMI interventionist? Compared with PTCA alone, stenting is more technically demanding and carries its own set of complications. Does stenting improve myocardial salvage compared with PTCA? No data have been presented yet from any study in this regard. Importantly, is primary stenting alone superior to primary PTCA plus glycoprotein IIb/IIIa receptor blockade? Of note, only 1% of the patients in the present report received abciximab. Results from the recently completed RAPPORT trial suggest that abciximab may also improve the early safety profile of primary PTCA. Is glycoprotein IIb/IIIa inhibition beneficial if a stent is implanted during AMI? What is the optimal stent design for AMI use, and are procedural success and clinical outcomes affected by stent configuration? What are the trade-offs in this setting of flexibility and deliverability versus scaffolding and radial strength versus wall coverage and side-branch access? Does stenting reduce the rates of angiographic restenosis compared with primary PTCA (follow-up angiographic data were not reported in the present study), and in this regard, are all stents created equal? Does an inherently thromboresistant device, such as the heparin-coated stent, offer significant clinical benefits compared with noncoated stents? What is the optimal anticoagulation and antiplatelet regimen after primary stent-
ing? Is postprocedural heparin or enoxaparin required? Finally, is primary stenting cost-effective compared with primary PTCA?

Fortunately, at least 7 additional randomized trials comparing primary stenting and PTCA have either been completed or are actively enrolling patients, including 2 large international studies designed with adequate statistical power and geographic representation to ascertain whether primary stenting indeed results in improved outcomes and is more cost-effective than primary PTCA. In the PAMI Heparin Coated Stent Trial, 900 patients with AMI at 65 sites were randomized to either primary PTCA or stenting with the heparin-coated Palmaz-Schatz stent, with angiographic follow-up planned in all patients. Given the properties of local stent-bonded heparin to resist platelet and thrombus deposition, stented patients in PAMI received no additional postprocedural intravenous heparin, postprocedural complications and promote early discharge. The PAMI 30-day results were to be available in March 1998, with the 6-month primary end-point data to be reported in November 1998. In the CADILLAC trial, 2000 patients with AMI at 90 sites are being randomized in a 2×2 factorial design to primary PTCA alone, PTCA plus abciximab, primary stenting alone, or stenting plus abciximab, with routine angiographic follow-up in a subset of 700 patients. The stent used in CADILLAC is the ACS Multi-Link, which is available to treat lesions ≤65 mm in length in vessels from 2.5 to 4.1 mm in diameter. It is thus anticipated that >80% of screened patients will be randomized. Patients receiving abciximab in CADILLAC (after either PTCA or stent) will receive no postprocedural heparin and, if stable, will be discharged on the second hospital day (day 3 in high-risk patients), making CADILLAC the most ambitious early-discharge study yet attempted. The CADILLAC trial began enrolling patients in late 1997, and results are expected in 1999. In addition, formal substudies in both PAMI and CADILLAC are examining the usefulness of intravascular ultrasound imaging after mechanical reperfusion of AMI, and the role of thrombectomy in occluded vein grafts is being investigated in CADILLAC.

One fact is clear: as the 21st century approaches, we have entered an age in which clinical practice is powerfully influenced by the results of well-designed, prospective randomized trials. It is no small irony that after the introduction of primary PTCA, 17 years were required to randomize 2606 patients with AMI to PTCA versus thrombolytic therapy, whereas in the course of <3 years, ≈4000 patients will have been prospectively randomized to primary PTCA versus stenting. The intense global interest expressed in these ongoing trials attests to the conviction that primary stenting holds promise to be the next major breakthrough in the treatment of patients with AMI. Suryapranata and colleagues deserve credit for being at the forefront of this effort.

References


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