

# Provisional Stenting Strategies: Systematic Overview and Implications for Clinical Decision-Making

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Coronary stents reduce the rates of abrupt closure, emergency coronary artery bypass graft surgery and restenosis, but do not prevent myocardial infarction or death at six months. The financial burden of increased stent use and the difficulty in managing in-stent restenosis have provided the impetus to develop provisional stenting strategies. Patients at low risk for restenosis after balloon angioplasty may not derive additional benefit from stent implantation and may be successfully managed with percutaneous transluminal coronary angioplasty (PTCA) alone. Numerous patient, lesion and procedural predictors of restenosis have been identified. Postprocedural assessment using quantitative coronary angiography, intravascular ultrasound (IVUS), coronary flow velocity reserve (CVR) or fractional flow reserve (FFR) may further enhance the ability to predict adverse outcomes after PTCA. Several studies have been performed to investigate the feasibility of provisional stenting strategies using various modalities to identify low risk patients who could be managed with PTCA alone. An optimal or “stent-like” angiographic result after PTCA is associated with favorable clinical outcomes. Preliminary results of studies using IVUS or CVR to guide provisional stenting appear promising. Angiography alone may be inadequate to identify truly low risk patients and may need to be combined with clinical factors, assessment of recoil, IVUS or physiologic indexes. Strategies that avoid unnecessary stenting in even a small proportion of patients may have large impacts on health care costs. Provisional stenting may potentially reduce costs and rates of in-stent restenosis without compromising the quality of health care delivery. (J Am Coll Cardiol 2000;36:1142–51) © 2000 by the American College of Cardiology

As health care costs continue to rise, physicians are increasingly being called on to practice cost-effective, evidence-based medicine. The struggle to maintain the quality of health care in the face of increasing financial pressures has surfaced in the field of interventional cardiology. Specifically, although coronary stents improve procedural outcomes, they also add significant cost to the initial procedure, which is offset by a later reduction in repeat procedures (1,2). However, this later financial benefit is frequently not realized by the hospital; instead, the cost of the initial procedure is usually carried by the hospital, which does not receive higher reimbursement for procedures that could provide lower long-term costs. Stents are being used for an increasingly broad population of patients. The high cost to hospitals created by increased stent use has prompted a reevaluation of the indications for stenting (3,4). This report will briefly review the known benefits and limitations of stents, discuss the concept of provisional stenting and its cost implications and present various strategies for provisional stenting and the results of recently completed studies.

## BENEFITS AND LIMITATIONS OF STENT USE

**Benefits.** Stents lower the rates of abrupt closure, emergency coronary artery bypass graft surgery and restenosis (5–10). Two large multicenter trials—the STent REStenosis Study (STRESS) (9) and the BELgium NETHERlands STENT (BENESTENT) study (10)—compared elective stenting with angioplasty alone in native coronary arteries with short (<15 mm in length) de novo lesions and showed a 25% to 30% reduction in restenosis. Later stent trials confirmed reduced rates of restenosis and target lesion revascularization (TLR) (10–21) (Table 1). The STRESS and BENESTENT results led to a marked enthusiasm for stent use and a dramatic rise in the number of stent procedures performed worldwide (22). For example, stent use in 12 U.S. centers rose 12-fold from 1994 to 1997 (from 5.4% to 69%) (23). Although stenting carries reduced rates of restenosis and abrupt closure, a recent meta-analysis of stent trials found no reduction in the rates of myocardial infarction (MI) or death during six-month follow-up (24). A recent analysis of a large Canadian data base has also confirmed that the major clinical benefit conferred by stenting is a reduction in repeat revascularization procedures (25).

**Limitations.** The use of stents is not without limitations and complications. Stent thrombosis occurs in <1% of cases, but may result in MI, urgent TLR and death. Stent implantation achieves larger lumen dimensions and prevents early recoil, but stimulates neointimal proliferation, result-

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**Abbreviations and Acronyms**

- CVR = coronary flow velocity reserve
- FFR = fractional flow reserve
- IVUS = intravascular ultrasound
- LAD = left anterior descending coronary artery
- MI = myocardial infarction
- MLD = minimum lumen diameter
- PTCA = percutaneous transluminal coronary angioplasty
- QCA = quantitative coronary angiography
- TLR = target lesion revascularization

ing in higher rates of late lumen loss, as compared with angioplasty alone. Restenosis rates after stent implantation range from <10% to 58%, depending on lesion, stent, patient and procedural characteristics, definitions and angiographic surveillance (26,27). Diffuse in-stent restenosis appears to be much more difficult to manage than restenosis after percutaneous transluminal coronary angioplasty (PTCA) (26,28). Treatment strategies for in-stent restenosis (PTCA, atheroablation or additional stent implantation) are associated with high recurrence rates (29). However, intracoronary radiation therapy is a promising new investigational approach to treat in-stent restenosis (30).

**Generalizability of clinical trial results.** The initial STRESS and BENESTENT trials enrolled highly selected subjects with favorable patient and lesion characteristics. Less than 30% of patients undergoing stenting in current clinical practice would have been eligible for these trials (31-34). It is not surprising, therefore, that clinical outcomes in "real-world" stenting have not been as consistent as those seen in randomized studies (31-35). More recent trials have extended the findings of STRESS and BENESTENT to vein graft lesions (17), total occlusions (19,20), restenotic lesions (16) and acute MI (36). However,

the results of stenting in small vessels, diffuse disease and bifurcations remain unsatisfactory, and the benefit of stents over balloon angioplasty in these lesion types has not been clearly established (37,38).

**Newer stent designs and deployment techniques.** Since the time of the STRESS and BENESTENT studies, considerable advances have been made in the design of stents and in the techniques used to deploy them. Second- and third-generation stent designs have improved flexibility and lower profiles, facilitating their delivery. Optimal stent expansion, achieved with the use of high pressure inflations or intravascular ultrasound (IVUS), or both, results in larger postprocedural lumen areas and lower rates of subacute stent thrombosis (39). However, the impact of these advances on restenosis rates is unclear. Table 2 lists the restenosis and TLR rates observed in studies of modern stent designs and deployment techniques (40-47). The Multicenter Ultrasound Stenting in Coronaries (MUSIC) study used IVUS to optimize stent expansion in low risk patients and observed remarkably low TLR and restenosis rates of 4.5% and 8.3%, respectively. The restenosis rates in two other trials of IVUS-guided stent implantation ranged from 23% to 25% (48,49). The Multicenter STent (MUST) registry evaluated stenting using high pressure inflations without IVUS guidance and observed a low TLR rate of 6%. In contrast, the STRESS-3 registry found no significant difference in six-month restenosis rates (31.4% vs. 31.6%) (3) or one-year TLR rates (8.3% vs. 12.2%, p = 0.2) (42), as compared with the stent arm of the first STRESS study. A recent randomized trial showed no difference in restenosis rates with high pressure inflations during stent deployment (50). High pressure inflations can cause increased arterial wall trauma, which may accelerate intimal hyperplasia and offset the larger lumen area initially achieved. Randomized trials comparing newer stents with Palmaz-Schatz stents have

**Table 1.** Randomized Trials of Stenting Versus Balloon Angioplasty

Study	Indication	n	Angiographic Restenosis			Target Vessel Revascularization		
			Stent Group	PTCA Group	p Value	Stent Group	PTCA Group	p Value
STRESS-I + II (11)	Discrete, de novo lesions	596	30%	45%	0.0001	10%	18%	0.003
BENESTENT (10)	Discrete, de novo lesions	520	22%	32%	0.02	14%*	23%*	0.005
BENESTENT-II (12)	Discrete, de novo lesions	827	16%	31%	0.0008	5%†	12%†	0.001
START (13)	Discrete, de novo lesions	452	22%	37%	0.001	9%	19%	< 0.01
TASC-1 (14,15)	De novo and restenotic lesions	270	31%	46%	0.01	4%	10%	0.08
REST (16)	Restenotic lesions	383	18%	32%	0.03	10%	27%	0.001
SAVED (17)	Saphenous vein grafts	220	37%	46%	0.24	17%	26%	0.09
Versaci et al. (18)	LAD lesions	120	19%	40%	0.02	7%	23%	0.01
SICCO (19)	Chronic occlusions	119	32%	74%	<0.001	22%	42%	0.03
TOSCA (20)	Chronic occlusions	410	55%	70%	<0.01	8%	15%	0.03
EPISTENT (21)‡	Wide range	1590	NA	NA	NA	9%	15%	0.001
Total		5507	28%	43%	0.001	9%	18%	0.001

\*Repeat PTCA only, does not include bypass surgery. †For patients assigned to clinical follow-up only (n = 411). ‡For the two abciximab groups only.

BENESTENT = Belgian Netherlands STENT study; EPISTENT = Evaluation of Platelet glycoprotein IIb/IIIa inhibitor for STENTing; LAD = left anterior descending coronary artery; NA = not available; PTCA = percutaneous transluminal coronary angioplasty; REST = REstenosis STent study; SAVED = SApheNous VEin De novo trial; SICCO = Stenting in Chronic Coronary Occlusion; START = Stent Versus Angioplasty Restenosis Trial; STRESS = STent REStenosis Study; TASC = Trial of Angioplasty and Stents in Canada; TOSCA = Total Occlusion Study of CANada.

**Table 2.** Studies of Newer Stent Designs and Stent Deployment Techniques

Stent Type	Study	Study Design	n	Target Lesion Revascularization	Angiographic Follow-Up	Angiographic Restenosis
Palmaz-Schatz	MUST (40)	Registry	260	6.2%	—	—
	MUSIC (41)	Registry	161	4.5%	92%	8.3%
	STRESS III (42)	Registry	250	8.3%*	NA	31%
ACS Multi-link	ASCENT (43)	RCT	520	7.5%	60%	15.6%
NIR	NIRVANA (44)	RCT	420	7.4%	70%	20.0%
	FINESS (45)	Registry	255	11.9%	—	—
AVE Micro Stent II	SMART (46,47)	RCT	330	8.4%	NA	25%
Cook GR-II	GR-II (46,47)	RCT		27%*	75%†	45%

\*Rate applies to one-year follow-up. †Follow-up angiography obtained in 75% of first 300 consecutive patients.

ASCENT = ACS Multi-Link™ Stent Clinical Equivalence in de novo Lesions Trial; FINESS = First International New intravascular rigid-flex Endovascular Stent Study; GR-II = Gianturco-Roubin-II; MUSIC = Multicenter Ultrasound Stenting in Coronaries study; MUST = Multicenter Stent; NIRVANA = Medinol NIR primo stent Vascular Advances North America Trial; RCT = randomized controlled trial; SMART = Study of AVE-Micro Stent Ability to Limit Restenosis Trial; other abbreviations as in Table 1.

found similar restenosis rates, with the exception of the GR-II stent (47). However, these small studies may not have been adequately powered to detect subtle differences in clinical and angiographic outcomes (51). In summary, modern stent designs and deployment techniques have likely improved procedural success rates and lowered the risk of subacute stent thrombosis. However, the effect of stent design, IVUS and high pressure inflations on restenosis rates remains unclear.

**Cost implications.** Stent implantation greatly increases the cost of PTCA. Early observational studies estimated that stenting increased in-hospital costs by 50% to 100% (52,53). In randomized trials, these excess costs were only partially recovered by the lower rate of repeat procedures for patients receiving stents during follow-up (1,54). Using data from the 1994 STRESS study, Cohen et al. (1) estimated a one-year net excess cost of \$1,200 (U.S.) per patient for stenting as compared with PTCA alone.

Advances in stent deployment techniques and adjuvant pharmacotherapy have eliminated the need for intense oral anticoagulation after stenting, resulting in fewer bleeding complications and shorter hospital stays (39,55). Despite these improvements, the cost of stent procedures at one center increased over time (56), due to increased numbers of balloon catheters and stents used per patient. Another institution documented declining costs despite increased equipment use (57). In the BENESTENT-II study, which used modern stent deployment techniques and antiplatelet regimens, the average cost of stent procedures was approximately \$1,300 more than that of PTCA procedures (12). An economic analysis of the Evaluation of Platelet glycoprotein IIb/IIIa inhibitor for STENTing (EPISTENT) study showed that the use of stents and abciximab was cost-effective, with a favorable cost-effectiveness ratio of \$5,291 per added life-year for stents plus abciximab as compared with balloon angioplasty plus abciximab (58). Nevertheless, a strategy of provisional stenting with clinical outcomes similar to those of elective stenting would be even more cost-effective.

A recent analysis from Duke University found that the in-hospital costs for stent procedures were \$3,268 more per

patient than the costs for PTCA alone (2). Because there are an estimated 500,000 stent procedures performed in the U.S. in 1998 (59), a strategy that could eliminate the use of stenting in even 10% of procedures could save over \$160 million per year. If the use of stents could be reduced by 50%, the savings would exceed \$800 million per year. The implicit assumption in these calculations is that clinical outcomes with these strategies are equivalent to those seen with elective stenting. Otherwise, the initial cost savings may be offset by the costs of additional repeat revascularization procedures (2).

### PROVISIONAL STENTING—PATIENT IDENTIFICATION

The primary benefit of stents after successful angioplasty is the reduction in clinical and angiographic restenosis. Given that <20% of patients undergoing angioplasty alone require TLR (12), many patients with successful angioplasty probably do not gain any additional clinical benefit from stenting. When stent use is reserved for patients most likely to benefit, it is referred to as “provisional stenting,” in contrast to “elective” or “obligatory” stenting, in which all technically eligible patients receive a stent. Many provisional stenting strategies have been proposed, using a variety of assessment techniques. Patient, lesion and procedural characteristics can be used to predict the risk of restenosis (Table 3) (60–62). In addition, IVUS (63,64) and physiologic flow and pressure measurements (65,66) are predictive of adverse outcomes. These predictors can be used individually or together to identify patients who would have excellent clinical outcomes with PTCA alone and would be unlikely to derive further benefit from stent implantation. Provisional stenting could deliver clinical outcomes equivalent to those with elective stenting, but with substantially reduced costs and rates of in-stent restenosis.

**Baseline clinical and angiographic characteristics.** Several baseline patient and lesion characteristics are associated with higher rates of restenosis (Table 3) (60–62). These predictors may assist in selecting the patients at highest risk for restenosis and thus most likely to benefit from stent insertion. Stenting reduces restenosis rates for high risk

**Table 3.** Patient-, Lesion- and Procedure-Related Predictors of Restenosis

Patient Factors	Lesion Factors	Procedural Factors
Age	Bypass graft	Postprocedural percent stenosis
Male gender	LAD location	Postprocedural MLD
Diabetes mellitus	Preprocedural percent stenosis	Final gradient >15 mm
Hypertension	Preprocedural MLD	Increased relative gain
High cholesterol	Arterial diameter	Lack of dissection
Current smoking	Lesion length	Number of sites dilated
No previous myocardial infarction	Total occlusion	Duration of inflation
Angina class/severity	Calcification	Increased stretch
Unstable angina	Eccentric lesion	Lower balloon/artery ratio
Shorter duration of angina		Elastic recoil
Multivessel disease		
End-stage renal disease		

Adapted from Miller et al. (61), with permission.

LAD = left anterior descending coronary artery; MLD = minimal lumen diameter.

groups, such as patients with proximal left anterior descending coronary artery (LAD) lesions (18), vein graft interventions (17) and chronic total occlusions (19) (Table 1). In contrast, stents may not improve outcomes in low risk groups, such as the non-LAD subgroup of the STRESS trial (67). In the BENESTENT-2 study, stenting had the greatest benefit and was most cost-effective in patients with unstable angina, LAD lesions or vessel size >3 mm (68). The utility of baseline characteristics to guide stent use has not been prospectively studied.

**Postprocedural angiographic factors.** Several postprocedural variables are associated with increased risk of restenosis after PTCA (61). These variables are listed in Table 3 (60). Multivariate models combining preprocedural and postprocedural angiographic factors for predicting restenosis have been developed, albeit with modest predictive strength (c-index of 0.67) (61). Postprocedural angiographic factors may help to predict which patients are most likely to benefit from stent insertion.

**EARLY LUMEN LOSS.** Early lumen loss, presumably due to elastic recoil, is an angiographic predictor of restenosis (69). Two randomized pilot trials have compared elective stenting with provisional stenting based on assessment of recoil 20 to 30 min after successful PTCA (Table 4) (70,71). In the Optimal Coronary Balloon Angioplasty with provisional Stenting (OCBAS) study (70), patients were randomized to elective stenting or to angioplasty with stenting only for early lumen loss. Importantly, 86 (42%) of the 206 eligible patients were excluded owing to suboptimal results or acute complications. Patients were enrolled only if the final diameter stenosis was ≤30% by on-line quantitative coro-

nary angiography (QCA) and no major dissections were present. Only eight of the 59 patients assigned to PTCA required stenting for early loss. The patients who had elective stenting had better early angiographic results, but clinical and angiographic outcomes did not differ significantly at six months. The Balloon Optimization vs. Stent Study (BOSS) also found similar rates of TLR in the stent and angioplasty groups (71). These studies, although small, suggest that assessment of recoil can identify patients who might benefit from stenting, despite their optimal angioplasty results. Unfortunately, the additional 20 to 30 min of procedure time may be impractical in many catheterization laboratories and may limit acceptance of this technique.

**FINAL MINIMAL LUMEN DIAMETER (MLD).** Kuntz et al. (72) popularized the “bigger is better” paradigm of restenosis by showing the relation between postprocedural MLD and the risk of restenosis. The MLD immediately after PTCA strongly correlated with the MLD at six-month follow-up. This implies that when a large lumen can be achieved with PTCA, the low risk of restenosis may obviate the need for stenting.

**FINAL DIAMETER STENOSIS.** It has generally been assumed that patients with suboptimal PTCA results (high residual diameter stenosis) derive greater benefit from stent implantation than do patients with optimal PTCA results. This premise is supported by the results of a randomized trial in which stenting for patients with suboptimal results (residual stenosis ≥15%) reduced restenosis from 53% to 24% (p = 0.02) (73). Patients with optimal results were not randomized but were treated with balloon angioplasty and had a low

**Table 4.** Studies Using Early Lumen Loss Criteria

Study	n	Criteria for Crossover to Stenting	Crossover	Restenosis	Target Lesion Revascularization
OCBAS (70)	116	MLD loss >0.3 mm or >10% increase in diameter stenosis at 30 min	14%	16%	18%
BOSS (71)	97	MLD loss >0.3 mm at 20 min	36%	38%	21%

BOSS = Balloon Optimization vs. Stent Study; MLD = minimal lumen diameter; NA = not available; OCBAS = Optimal Coronary Balloon Angioplasty with provisional Stenting study.

**Table 5.** Stent-like Results Versus Elective Stenting

Study	Criteria for SLR	Patients With SLR, n/N (%)	Restenosis		Target Lesion Revascularization	
			SLR	Stent	SLR	Stent
BENESTENT (74)	Diameter stenosis $\leq$ 30% by QCA*	90/255 (35%)	16%	22%	20%	20%
REST (75)	Diameter stenosis $\leq$ 30% by QCA†	98/180 (54%)	NA	NA	12%	11%
TOSCA (76)	Diameter stenosis $\leq$ 35% by QCA	74/196 (38%)	55%	55%	8%	8%
EPISTENT (21,77)	Operator discretion	642/796 (81%)	NA	NA	15%‡	9%
OPUS (79)	Diameter stenosis $\leq$ 30% by QCA* or $\leq$ 20% by visual assessment	157/249 (63%)	NA	NA	10%‡	3%
NHLBI Registry (79)	Diameter stenosis $\leq$ 10% by visual assessment	225/1989 (11%)	NA	—	23%§	—
Espinola-Klein et al. (80)	Diameter stenosis $\leq$ 25%	246/417 (59%)	NA	—	35%	—

\*No major dissection. †No dissection/thrombus. ‡Includes patients who received stents for suboptimal results. §Percentage of lesions, not patients. ||Ten-year follow-up. NHLBI = National Heart, Lung and Blood Institute; OPUS = Optimal PTCA versus primary Stent strategy; QCA = quantitative coronary angiography; SLR = stent-like results; other abbreviations as in Table 1.

restenosis rate of 14%. Several studies have assessed outcomes for patients with optimal, or “stent-like,” PTCA results on the basis of low residual diameter stenosis after the procedure (Table 5) (21,74–80). The BENESTENT investigators compared patients with “stent-like” results after PTCA (defined as a final residual diameter stenosis  $\leq$ 30% with no major dissection) with patients assigned to elective stenting (74). Of the 255 patients in the PTCA arm of the trial, 90 (35%) met these criteria. The rates of death, MI and repeat revascularization at six months in these patients were similar to those in the stented patients. The angiographic restenosis rate was 16% in the stent-like PTCA group, as compared with 22% in the stent group ( $p = 0.3$ ). These findings have been confirmed in subgroup analyses of the REstenosis STent (REST) study and the Total Occlusion Study of CANada (TOSCA) (16,76). The National Heart, Lung and Blood Institute (NHLBI) PTCA Registry investigators reported long-term outcomes in patients with stent-like results, defined as a final diameter stenosis by visual assessment of  $\leq$ 10% (79). Stent-like results were achieved in 225 (11%) of the 1,989 patients who had successful PTCA. At 10-year follow-up, the rate of TLR was significantly lower for patients with stent-like initial results (22.5% vs. 31.5%,  $p = 0.003$ ). No differences were seen in the rates of death and MI. Espinola-Klein et al. (80) reported lower rates of repeat revascularization and trends toward reduced death and MI in patients with stent-like results. The EPISTENT study randomized 2,399 patients to one of three arms: stenting with placebo, stenting with abciximab or PTCA with abciximab (77). In the PTCA group, provisional or bailout stenting was performed for suboptimal results. Although criteria were suggested for stent implantation (e.g., reduced flow, long dissection,  $>70\%$  residual diameter stenosis), this was largely left to the discretion of the physicians. Stenting was performed in 154 (19%) of the 796 patients in the PTCA group. Compared with patients randomized to elective stenting plus abciximab, the patients in the PTCA group had higher rates of TLR (15.4% vs. 8.7%,  $p < 0.001$ ) and death (1.8% vs. 0.5%,  $p = 0.02$ ) at six months (21). In

elderly women, however, event rates were higher with elective stenting (81).

The Optimal PTCA versus Primary Stent strategy (OPUS) study was the first randomized trial of provisional stenting (based on final diameter stenosis) as compared with elective stenting. The study included short lesions ( $\leq 20$  mm) in arteries  $\geq 3.0$  mm in diameter and excluded more complex lesions such as angulated, calcified or ostial lesions. In addition, patients were excluded if a multivessel intervention was planned or if they had an MI within the previous 24 h. For patients randomized to provisional stenting, stents were used if the final diameter stenosis was  $>20\%$  by visual estimation (or  $>30\%$  by on-line QCA) or if the intervention was complicated by abrupt closure or sustained or flow-limiting dissection. Stents were implanted in 99% of the elective stent group and in 37% of the provisional stent group. In a preliminary analysis (78), the primary composite end point of death, MI or TLR occurred more often in the provisional stent group than in the elective stent group (14.9% vs. 6.1%,  $p = 0.003$ ). Most of the difference was due to a significantly higher rate of TLR with provisional stenting (10.1% vs. 3.0%,  $p < 0.005$ ). The costs at six months were similar between the groups, owing to more readmissions in the provisional stent group. The OPUS results suggest that elective stenting leads to improved clinical outcomes at six months as compared with provisional stenting, according to angiography alone. Of note, 63% of patients assigned to the optimal PTCA/provisional stenting strategy achieved the criteria for stent-like results, which is higher than the incidence of stent-like results observed in previous studies (74–76,79,80). The less frequent use of stents in OPUS may therefore partly account for the discrepant findings, compared with previous studies. Visual estimation may be too imprecise to discriminate optimal angioplasty results from those that indicate stenting. Alternatively, angiographic criteria may need to be combined with other assessment techniques.

**IVUS-guided strategies.** Coronary angiography may overestimate postprocedural lumen size, when extravasation of contrast agent into the fractured atheromatous plaque re-

**Table 6.** Studies Using Intravascular Ultrasound Criteria

Study	IVUS Criteria of Success	Stented Lesions n/n (%)	TLR, Nonstented Lesions n/n (%)
Haase et al. (84)	CSA gain $\geq 20\%$ and/or nonocclusive dissection	0/152 (0%)	13/152 (9%)
Abizaid et al. (85)	CSA $\geq 65\%$ and no dissection	150/284 (53%)	11/134 (8.0%)
Yasukawa et al. (86)	CSA $>70\%$ and no dissection	26/60 (42%)	NA

CSA = cross-sectional area of lumen relative to reference lumen area; NA = not available; TLR = target lesion revascularization; IVUS = intravascular ultrasound.

sults in hazy angiographic images. In addition, when the angiographically normal reference segment is diffusely narrowed, the vessel size may be underestimated. Intravascular ultrasound enables visualization of the vessel wall and lumen and more accurately displays the extent of atherosclerotic involvement and effects of interventions on the vessel wall. It was therefore anticipated that IVUS would be more predictive of restenosis than angiography, but studies to date have provided conflicting results (63,64,65,82). Use of IVUS to guide balloon size may allow the safe use of larger balloons to achieve larger final lumens (83). Several studies have been performed to assess whether PTCA guided by IVUS yields clinical outcomes comparable with those of stenting (Table 6) (84–86). A recent single-center, nonrandomized study reported outcomes of 144 selected patients undergoing IVUS-guided PTCA (84). The balloon size was based on IVUS measurements of the external elastic membrane at the lesion site. Although there was a high rate of dissection, none of the dissections led to abrupt closure or required stenting. At one year, the rates of angiographic restenosis and repeat revascularization were 21% and 9%, respectively. Two other centers have reported series of IVUS-guided PTCA with provisional stenting (85,86). Criteria for “crossing over” to stenting included a cross-sectional lumen area that was  $<70\%$  of the reference lumen area, or  $<5.5 \text{ mm}^2$ , or lumen-compromising dissections. Stenting was required in about half of the patients. The rates of restenosis and TLR were low as compared with those in historic control subjects. Although these preliminary reports support the use of IVUS to guide balloon sizing and provisional stenting, the optimal criteria for crossing over to stenting have not been determined (87). To date, there have been no direct comparisons of IVUS-guided provisional stenting with elective stenting, although randomized trials are in progress. The Gradual Inflation at optimal Pressure vs. Stent Implantation (GIPSI) trial is comparing IVUS-guided, prolonged balloon inflations with

a perfusion balloon catheter versus stent implantation. It remains to be seen whether IVUS provides an incremental benefit over angiography for provisional stenting, or whether the benefit outweighs the additional cost of IVUS equipment.

**Coronary flow reserve: pressure gradients.** As opposed to QCA and IVUS, which assess the structural outcome of percutaneous interventions, coronary flow reserve provides a means to assess the functional significance of residual stenosis. Coronary flow velocity reserve (CVR) is the ratio of maximal hyperemic to basal flow velocities. The distal CVR has been used as a physiologic measure of coronary stenosis severity and correlates well with myocardial perfusion imaging (88). The advent of the Doppler guide wire has permitted continuous assessment of blood flow velocity during percutaneous interventions. Although CVR improves in most patients after angioplasty, it does not always normalize, most likely because of residual stenosis (89). The Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) correlated angiographic and Doppler endpoints after PTCA with clinical outcomes in 297 patients (65). The postprocedural CVR was most useful in predicting recurrence of symptoms. However, 45% of patients with recurrent symptoms did not have angiographic restenosis, and stenting would not be expected to alter their outcomes. Patients with a residual diameter stenosis  $\leq 35\%$  and distal CVR  $>2.5$  after PTCA had the lowest rates of restenosis, repeat intervention and recurrent symptoms. The combined angiographic and Doppler criteria have been tested prospectively in five randomized studies (Table 7) (65,90–92). These trials were similarly designed, such that patients undergoing PTCA were randomly allocated to a elective stenting strategy or to PTCA guided by Doppler and QCA. In the DEBATE-2 study, patients in the guided angioplasty group were subrandomized to either stop the procedure or go on to stenting. In the other trials, stenting was performed only if the criteria for optimal results were not

**Table 7.** Studies Using Coronary Doppler Criteria

Study	n	Criteria for Optimal Result	SLR, n/n (%)	End Points	TLR
DEBATE (65)	297	CVR $>2.5$ and final diameter stenosis $\leq 35\%$	44/202 (22%)	Symptoms, restenosis, TLR	16%
DEBATE-2 (90)	616	CVR $>2.5$ and final diameter stenosis $\leq 35\%$	249/519 (48%)	MACE at 12 months	NA
DESTINI (91)	700	CVR $>2.0$ and final diameter stenosis $\leq 35\%$	(43%)	MACE at 6 months	14%
FROST (92)	251	CVR $\geq 2.2$ and final diameter stenosis $\leq 35\%$	65/126 (52%)	MLD at 6 months	15%
CRUSADE	200	CVR $\geq 2.0$ or final diameter stenosis $\leq 35\%$	NA	MACE, restenosis at 6 months	NA

CRUSADE = Coronary Revascularization UltraSound Angioplasty DEvice trial; CVR = coronary flow velocity reserve; DEBATE = Doppler Endpoints Balloon Angioplasty Trial Europe; DESTINI = Doppler Endpoints STenting INternational Investigation; FROST = French Optimal Stenting Trial; MACE = major adverse clinical event; MLD = minimal lumen diameter; NA = not available; SLR = stent-like result; TLR = target lesion revascularization.

achieved; otherwise, the procedure was stopped. Preliminary results have been presented for three of these studies (90-92). Surprisingly, the proportion of patients meeting the combined Doppler and angiographic criteria was significantly greater than that seen in DEBATE, ranging from 43% to 52%. The FRENCH Optimal Stenting Trial (FROST) evaluated angiographic end points at six months and found no difference in restenosis or MLD. The clinical outcomes at six months did not differ significantly for elective stenting and guided angioplasty in any of the trials. However, the DEBATE-2 guided PTCA group subrandomized to receive a stent had better outcomes than the group randomized to stop after PTCA; the six-month rates of major adverse cardiac events were 1% with stenting and 11% without stenting ( $p < 0.05$ ). The FROST and Doppler Endpoint STenting INTERNATIONAL Investigation coronary flow reserve (DESTINI) results indicate that compared with elective stenting, provisional stenting based on CFR and angiographic criteria can avoid the costs and complications of stenting in ~50% of patients, with no compromise in clinical or angiographic outcomes. Preliminary findings from a cost analysis of DESTINI revealed significantly lower in-hospital and six-month follow-up costs with the provisional stenting strategy (93). The DEBATE-2 findings suggest that although patients with optimal PTCA results have low rates of adverse events, stenting in these patients leads to a further reduction of events. The explanation that has been put forth is that optimal PTCA may in fact be the ideal substrate for optimal stenting. The final data from these trials, including subgroup analyses, will be needed before making any definitive conclusions about provisional stenting using the combination of angiographic and Doppler results.

The pressure-derived myocardial fractional flow reserve (FFR), a new index of coronary flow reserve, has also been used to assess the functional significance of coronary stenoses. As measured by a pressure sensor mounted on a 0.014-in. guide wire, the pressure distal to the stenosis during maximal hyperemia ( $P_d$ ) is divided by the aortic pressure ( $P_a$ ). Values  $< 0.75$  are considered hemodynamically significant and have been correlated with myocardial perfusion imaging and exercise-induced ischemia. The advantage of FFR is that it is less sensitive to hemodynamic changes as compared with CVR (94). Bech *et al.* (68) recently analyzed the prognostic utility of FFR and QCA in 60 consecutive patients undergoing angioplasty. The two-year event-free survival rate for patients with postprocedural residual diameter stenosis  $\leq 35\%$  and a FFR  $\geq 0.90$  was significantly better than that for patients with suboptimal values of either of these variables (88% vs. 59%,  $p = 0.014$ ). No randomized trials of provisional stenting guided by FFR have been performed to date.

**Conclusions.** Coronary stents have revolutionized percutaneous coronary interventions; however, like many new technologies, initial enthusiasm has led to a very high use of stents. Stents provide superior angiographic results and more predictable short-term outcomes. Although random-

ized trials of stenting have shown lower restenosis rates, caution must be exercised when extrapolating trial results to clinical practice (95). As in thrombolytic trials (96), stent trials generally have enrolled patients with more favorable clinical and angiographic characteristics, leading to better outcomes than those in patients commonly treated in clinical practice (3,31-34).

Given the accumulating evidence supporting the feasibility of provisional stenting strategies, it may be difficult to justify routine stent implantation if similar clinical outcomes may be obtained with a provisional stenting strategy. In view of the potential for cost savings and prevention of diffuse in-stent restenosis, priority must be given to the development of an evidence-based optimal stenting strategy. Unresolved issues include: 1) what is the best means to identify patients who do not require stenting? and 2) what is the most appropriate rate of stent use in typical clinical practice?

The OPUS results indicate that angiography alone may be too insensitive a tool to identify patients requiring stenting. Incorporation of baseline clinical and angiographic data may further refine the discriminatory power of angiography. Intravascular ultrasound, coronary Doppler imaging and FFR may be used to provide additional prognostic information. However, these techniques prolong procedure times, and the additional equipment costs may offset any potential cost savings. Patients with excellent angiographic results after angioplasty appear to be a heterogeneous group. Further research is needed to determine which clinical, angiographic, IVUS or physiologic variables are most useful and cost-effective in predicting event-free survival for patients with excellent angiographic results. It would appear from the OPUS and EPISTENT results that provisional stenting strategies in which  $< 40\%$  of patients undergo stenting are unlikely to result in long-term outcomes equivalent to elective stenting. In the Canadian data base study, the rates of target vessel revascularization declined over a three-year period as the rates of stent implantation increased from 14% to 59% (25). Although the optimal threshold for stent use remains to be determined, the evidence to date supports the use of stents in the majority of patients. Nevertheless, with over 500,000 stent procedures performed each year (59), a strategy that could prevent unnecessary stent implantation in even a small proportion of patients could have a large impact on health care costs while retaining the ability to use stents for the patients most likely to derive clinical benefit.

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