Percutaneous Coronary Revascularization:

A Therapy in Evolution

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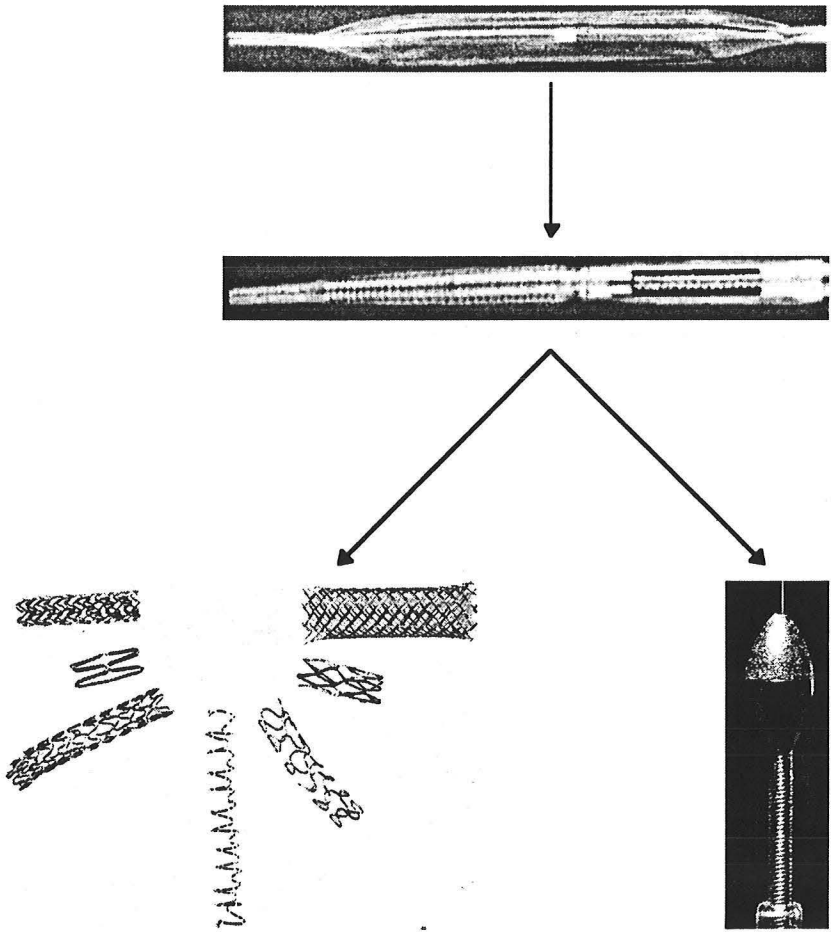

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The era of percutaneous coronary revascularization began over 20 years ago when Andreas Gruentzig performed the first balloon angioplasty in the left anterior descending artery of a patient (1). The technique gained wide acceptance in the United States during the early 1980s as a treatment for symptomatic coronary artery disease. The number of angioplasty procedures continues to rise annually with an estimated 500,000 having been performed in 1997. Initially limited to proximal, focal stenoses in stable patients, percutaneous interventions are now used to treat a wide variety of coronary lesion types in patients spanning the entire spectrum of acute and chronic ischemic syndromes (2).

Much of the initial progress in angioplasty technology related to refinements in the design of the three major components of an angioplasty system: 1) The guiding catheter, which provides a portal for access to the coronary tree from its entry site in the femoral artery, 2) the guide wire, which is manipulated across the stenosis into the distal vessel and 3) the balloon dilation catheter, which is passed over the wire and across the stenosis where expansion of the balloon results in an increased cross sectional area for blood flow. Over the past several years, the introduction of new devices and pharmacologic agents have resulted in enhanced safety and efficacy of percutaneous revascularization procedures, leading to a continued expansion in the universe of approachable lesions with the promise of improved clinical outcomes.

In order for a new technique to supplant the use of stand-alone balloon angioplasty, it must offer an advantage over a procedure which is technically simpler to perform, enjoys widespread acceptance, and is bolstered by long-term follow up data in thousands of patients. In addition, because balloon dilations are a requisite adjunct to achieve optimal results with newer devices, procedural costs with second generation techniques are always greater than with balloon angioplasty alone. In order to appreciate the potential of new techniques, it is necessary to review the success and limitations of balloon angioplasty in the modern era.

BALLOON ANGIOPLASTY

Indications for percutaneous revascularization

Percutaneous revascularization is an effective therapy for patients with chronic stable angina, unstable angina, acute myocardial infarction, and provokable ischemia following a Q wave myocardial infarction. In the Angioplasty Compared to Medicine (ACME) trial (3) 212 patients with stable angina, provocable myocardial ischemia, and single-vessel coronary artery disease were randomized to either PTCA or medical therapy. Although PTCA was initially successful in only 80 percent of those assigned to it, these subjects exercised longer on treadmill testing, were treated with fewer anti-anginal medications, and were more likely to be free of angina than those treated with medication (64 versus 46 percent, respectively, $p < 0.01$) at the cost of a 4% rate of procedural-related infarctions. In addition, PTCA treated patients had fewer admissions for

unstable angina over the ensuing 5 years, although there was no reduction in mortality or infarction in this low risk cohort (4). In a similar trial of 101 patients with two vessel disease, PTCA and medical therapy yielded equivalent in rates of death, MI, and exercise treadmill times. In addition, angioplasty patients required less anti-anginal treatment and were less symptomatic at 6 months (53% angina free vs. 36%, p=0.09). Of note, 37% of these patients were incompletely revascularized, most often due to the presence of a chronically occluded vessel (4).

In the RITA-2 trial, 1018 patients with single (60% of subjects) or multivessel coronary disease were randomized to PTCA or medical therapy and followed for an average of 2.7 years. Success rates in the angioplasty group exceeded 90% for non-occluded vessels with a 1.4% incidence of both emergent CABG and Q wave MI related to the procedure. Angioplasty patients had improved exercise tolerance, took fewer antianginal medications, and experienced less severe angina, even though a 25.4% crossover to revascularization in the medical group led to diminished differences over time. Due to the inherent risks of the procedure, the primary endpoint, death or MI, was 6.3% in PTCA patients vs. 3.3% for those treated medically (p=0.02). Subgroup analysis revealed that the physiologic benefits of PTCA were limited to those patients with an anginal class $\geq$ 2 or with exercise times of $<$ 9 minutes on a Bruce protocol (5). This suggests that patients with mild stable angina or excellent exercise performance are unlikely to derive a clinical benefit from percutaneous intervention over medical management unless there is a degradation in one of these parameters.

In the MASS trial, patients with ischemia and an isolated proximal stenosis of the left anterior descending artery were randomized to CABG, angioplasty, or medical therapy. There was no difference in the endpoint of death or MI at 3 years among the groups, although revascularized patients enjoyed greater symptomatic relief and improved performance on exercise testing (6). Angioplasty patients, as a result of restenosis, had less complete anginal relief and required more frequent repeat procedures than their surgical counterparts, a finding later confirmed by multiple trials directly comparing angioplasty and bypass surgery (7).

The efficacy of PTCA for unstable angina was addressed in the TIMI IIIB trial which randomized 1473 patients with rest pain to the invasive strategy of catheterization and revascularization or to a conservative strategy of angiography only for refractory ischemia. In a 2 x 2 factorial design, patients were also randomized to tPA or placebo therapy (8). At one year there was no difference in the rates of death or nonfatal MI among the invasive vs. conservative strategies (7.2% vs. 7.8%) and no significant differences in anginal symptoms or the need for anti-ischemic medications . The rates of revascularization were higher in the invasive group (64% vs. 58%, p<0.001), but repeat hospitalizations were less frequent (26% vs. 33%, p<0.001) (9). Hence these two strategies appear equivalent. The issue of timing for intervention in unstable angina was explored in a study of 263 unstable patients who underwent PTCA within 4 hours of

chest pain vs. stabilization for > 72 hours prior to intervention. In-hospital and 6 month outcomes were similar, although stenting was utilized in 22% of early treatment patients vs. 11% of stabilized patients to achieve this equivalence. These findings suggest that if an invasive strategy is elected, prompt therapy does not increase risk and can shorten hospital stay (10).

The routine use of PTCA in the acute infarct setting remains controversial. There is, however, wide agreement that acute infarct angioplasty should be considered only in institutions with appropriate expertise, when prompt reperfusion is logistically feasible, or in circumstances where thrombolytic therapy is contraindicated. In a meta-analysis of first generation trials involving 1145 randomized patients, a benefit accrued to those treated with primary angioplasty with a 6 week mortality rate of 3.7% vs. 6.4% ($p<0.05$) and a 6 week rate of death or nonfatal MI of 6.1% vs. 11.0% ($p<0.005$). For the 393 patients followed for 1 year, these outcome differences were no longer significant (11). The single largest trial to address this question, Gusto IIb, was a multicenter study where 1138 patients presenting within 12 hours of symptom onset were randomized to PTCA or front-loaded intravenous tPA therapy. The composite endpoint of death, nonfatal reinfarction, or nonfatal disabling stroke occurred in 9.6% and 12.7 % of PTCA and tPA patients, respectively at 30 days ($p<0.04$), with no significant difference (14.1% vs. 16.1%) noted at 6 months (12).

The utility of PTCA in post-Q wave MI patients with spontaneous or provokable ischemia was demonstrated in the Danish trial in Acute Myocardial Infarction (DANAMI) (13). In this study, 1008 streptokinase treated patients with post-MI angina or a positive exercise test were randomized to medical therapy or revascularization. Patients with 3 or more lesions or left main disease were treated with CABG (29%), the remainder received PTCA (53%) or medical therapy due to the absence of a significant lesion.

End Point	Conservative n=505	Invasive n=503	p
Mortality	4.4%	3.6%	NS
Reinfarction	10.5%	5.6%	0.004
Unstable angina	29.5%	17.9%	<0.00001
Composite	40.4%	26.9%	<0.00001

Table 1: Primary endpoints in DANAMI, 2.4 years of follow-up.

Although patients treated with PTCA were not analyzed separately, use of this revascularization paradigm appears to offer clinical benefit in this subgroup of patients.

Stand-alone balloon angioplasty in the current era

Balloon angioplasty yields an increase in lumen size by several mechanisms, including fissuring of the atherosclerotic plaque; dehiscence of the intima and plaque from the underlying

media; and stretching or tearing of the media and adventitia, with resultant aneurysmal dilation (14-17). This barotrauma-induced injury results in dissection of the arterial wall which can provide the mechanical or rheologic stimulus for abrupt vessel closure, one of the major limitations of this technique. Balloon inflations also initiate the vascular biological events responsible for restenosis, the loss of the initial luminal gain over the 6 months following the initial procedure. The need for repeat procedures after a successful angioplasty is the second and more common limitation of balloon technology.

The early evolution of percutaneous revascularization is documented by data reported in the two NHLBI registries of balloon angioplasty which included 1345 patients from 1977 to 1981, and 2136 patients from 1985 to 1986. During this first decade of balloon angioplasty, improvements in equipment and techniques resulted in an enhanced clinical success (post PTCA stenosis < 50% with no in-hospital death, MI, or CABG) of 83% vs. 55%, leading to improved 5 year outcomes for patients treated during the latter period (18). Repeat revascularization at 1 year in this cohort was 19% (19). A series of recent restenosis trials provide insight into rates of acute procedural success, complications, and restenosis rates using current generation balloon technology. The most common definition of restenosis, a percent diameter stenosis ≥ 50% at 6 month follow-up was used for this analysis.

Study	n	Ref Diam	% stenosis	Success	Death	Q MI	Em CABG	Restenosis	Revasc
ERA (20)	458	2.85	32%	NA	0.40%	2%	NA	44%	11%
EMPAR (21)	658	2.52	48%	88%	0.60%	1.2%	NR	39%	20%
Angiopeptin(22)	553	2.75	34%	87%	0.90%	2.9%	3.2%	36%	28%
REDUCE (23)	612	NR	NR	93%	0%	1.0%	NR	NR	24%
ACCORD (24)	700	2.88	34%	93%	0.20%	2.0%	NR	42%	28%
STRESS (25)	205	2.99	34%	90%	1.50%	3.4%	2.4%	42%	12%
BENESTENT (26)	258	3.01	33%	93%	0.40%	1.9%	1.6%	32%	23%
BOAT (27)	491	3.2	28%	97%	0.40%	1.2%	2.0%	40%	20%
TOTALS	3935	2.85	36%	91%	0.46%	1.8%	2.4%	39.6%	21.9%

NA= not applicable (only successful patients enrolled), NR=not reported

Table 2: Balloon angioplasty success and complications in recent trials

Acute success rates have continued to improve compared with the earlier experience. Despite the inclusion of higher risk subgroups in many of these trials, the rates of death and MI have remained low with a favorable 22% rate of repeat revascularization.

Restenosis

Although initially attributed solely to neointimal proliferation, it is now recognized that maladaptive vessel constriction, a process termed remodeling, plays an important role in the

restenosis process. Insights into the relative contributions of these complimentary processes have been provided by high resolution intravascular ultrasound (IVUS), which provides a cross-sectional view of the coronary artery from a probe placed within the vessel lumen (17). In a series of patients treated with a variety of interventional techniques, 73% of the decrease in lumen area from the time of intervention to 6 months of follow up was due to a decrease in the outer area of the vessel (Figures 1 and 2). Furthermore, among the 22% of lesions associated with an adaptive increase in vessel area, there was no net decrease in lumen area at 6 months (28). These findings provide a clue as to the failure of pharmacologic techniques targeted to attenuating smooth muscle cell migration and proliferation to reduce the incidence of restenosis (29), and suggest that alterations in remodeling mechanisms would provide a more promising approach.

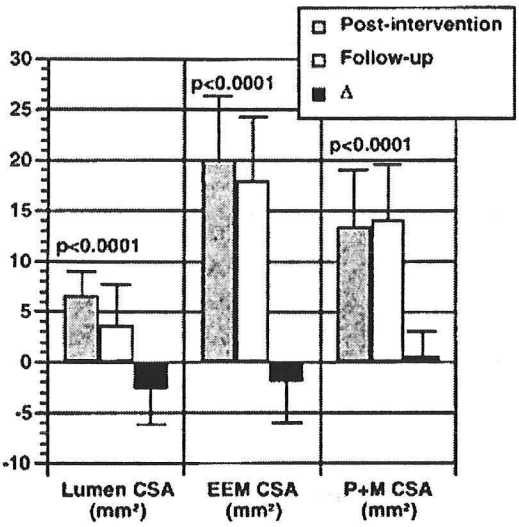

Figure 1: Changes in cross sectional areas (CSA) of the lumen, external elastic lamina (EEM) and plaque +media (P+M) after PTCA. From (28)

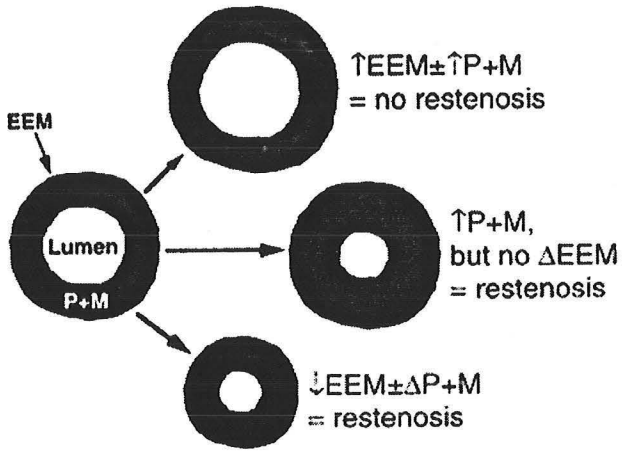

Figure 2: Influence of vessel component changes on late lumenal dimensions. See Fig 1 for abbreviations. From (28)

The prediction of restenosis in patients undergoing balloon angioplasty remains imperfect. Numerous clinical and angiographic risk factors have been identified by various investigators due to relatively small numbers in individual databases (2). In a well designed study involving 4006 patients using a training and validation group, Weintraub et al identified class III-IV angina, diabetes mellitus, hypertension, age> 60, left anterior descending lesion site, pre-PTCA diameter stenosis >70%, absence of an intimal dissection and eccentric lesion morphology as restenosis risk factors. Individually, the relative risk of restenosis in the presence of these variables ranged from 1.1 to 1.3 with a 59% predictive accuracy of the entire model(30). Another approach to identifying operator dependent factors which can influence restenosis utilizes lumen measurements as continuous variables. In multivariable analysis, the post - procedure diameter and percent

stenosis were the only independent predictors of the lumen diameter at 6 months, regardless of the interventional technique utilized during the initial procedure (31). These findings have been confirmed for balloon angioplasty by others, and also extended to include the IVUS derived measures of lumen, vessel, and plaque areas (32). The implication of these data are that maximizing the acute luminal result will decrease the risk of lesion recurrence, although vessel size (reflected in the percent stenosis) is an intrinsic factor which also plays a role in defining restenosis risk. One potential strategy to achieve this goal is suggested by data from the CLOUT trial, where balloon size was chosen on the basis of IVUS measurements following optimal angioplasty using standard, angiographically determined vessel dimensions. As a result, a larger balloon was used in 76% of patients which yielded a larger final lumen diameter (33). Whether the predicted decrease in restenosis as a consequence of an improved initial result does occur will require confirmation in a randomized trial.

The influence of new devices on percutaneous revascularization

Ellis et al compared acute and one-year outcomes in a matched group of multivessel coronary disease patients treated from 1986-7 with balloon angioplasty alone and in 1991 with angioplasty or new devices (17% of lesions). With the use of rotablation (8%), directional atherectomy (6%), stenting (2%) and excimer laser (1%), procedural success rates increased from 83% to 90% ($p=0.04$), bypass surgery during the index hospitalization decreased from 5.5% to 1.0% ($p=0.006$) and event free survival at one year increased from 63.6% to 73.3% ($p=0.02$) (34). Thus, selected use of new devices in patients with similar clinical characteristics leads to significant improvements in clinical outcomes.

The favorable influence of stent availability on acute outcomes was demonstrated in a comparison of procedures performed before and after FDA approval of the first stent, the Gianturco-Roubin device, in 1993. Despite its selected use in only 4% of procedures, emergency CABG rates were decreased from 2.9% to 1.1% ($p<0.01$). There was no decrease in the rates of death or MI, although the incidence of the latter was inexplicably low at 0.9% in this study (35).

In a study comparing acute results and in-hospital outcomes of consecutive patients treated during the periods 1990-91 and 1994-95, the only difference in techniques was the availability of stents during the latter period, where 12% of patients received a stent for acute closure or suboptimal results (a post-balloon angioplasty stenosis of >50%). Patients treated in the latter epoch had more high risk characteristics, including greater age, more complex lesions, a greater burden of coronary artery disease, and a higher incidence of unstable angina. Despite a less favorable population, the 1994-95 group enjoyed a higher initial success rate (92% vs. 84%, $p<0.001$) with a lower rate of death or MI (2.7% vs. 5.7%, $p=0.01$) and fewer emergent bypass surgeries (0.4% vs. 1.4%, $p=0.13$) (36).

The major reason for an unsuccessful coronary intervention remains the presence of an occluded vessel, and indeed such patients are frequently excluded from clinical trials. The success rate in this group ranges from 65-70%, a rate which has not improved significantly over the last decade (37-39). In lesions that can be crossed with a guidewire, the availability of new devices has clearly altered percutaneous coronary revascularization by addressing the major limitations of balloon angioplasty: 1) Inability to cross a lesion with a balloon catheter, 2) abrupt closure of the vessel following balloon dilatation, and 3) restenosis. Stents have played a major role in enhancing the safety and efficacy of balloon procedures and rotational atherectomy has expanded the universe of approachable lesions. Other FDA-approved devices are complementary or equivalent to balloon dilation with potential utility in specific circumstances: 1) Directional coronary atherectomy (DCA), 2) Transluminal extraction atherectomy (TEC), and 3) Excimer laser coronary angioplasty (ELCA). These latter two devices will not be discussed further since they comprise a small fraction of interventional practice. TEC is rarely used due to 1) a lack of comparative or prospective trials and 2) observational data suggesting no significant benefit over PTCA(40, 41). ELCA is available in few centers nationally due to the expense of the laser console and the lack of superiority to balloon angioplasty in randomized trials (42, 43).

INTRACORONARY STENTING

The concept of stenting, or the use of a permanent intravascular appliance to radially buttress the dimensions of the vessel wall and treat a luminal narrowing, was first enumerated by Dotter in 1969 (44). Stenting provides three major enhancements compared to standard balloon angioplasty: 1) It seals intimal flaps and dissections, thus providing a smooth, circular lumen without encroachment by vessel wall constituents, 2) it prevents acute vessel recoil following balloon deflation, resulting in a larger post-intervention luminal diameter, and 3) it abolishes late vascular remodeling, thus eliminating one of the mechanisms responsible for balloon angioplasty-induced restenosis.

Use of the first intracoronary device, the Wallstent, was reported in 1986 with disappointing results due to an unacceptable 24% rate of stent thrombosis (45). The first stent available in the US, the Gianturco-Roubin stent, was FDA approved in 1993. Design refinements and alterations in post-stent medical therapy have lead to an explosion of stenting since FDA approval of the Palmaz-Schatz stent in August, 1994. This device, which accounts for the majority of stents placed in the US to date, is actually two 7 mm stents attached by a central 1 mm articulation site which increases the flexibility of the device to allow passage through tortuous coronary arteries. Current stent use is displayed in Figure 3, and the stents currently available in the US are listed in Table 3.

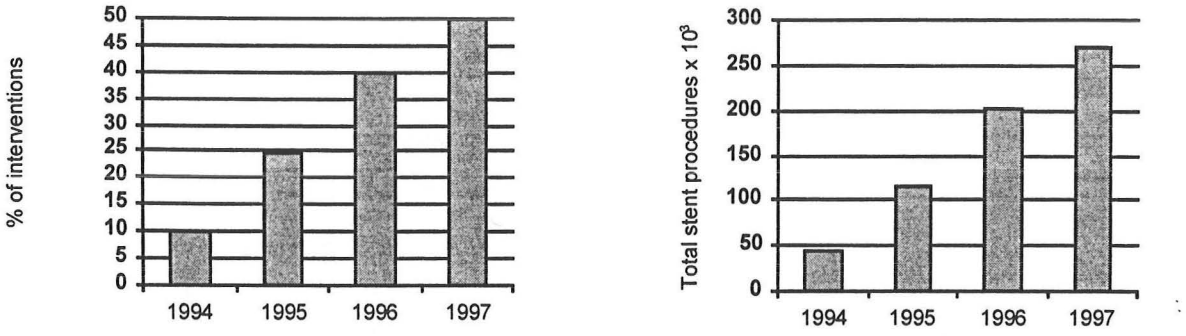

Figure 3: Current US stent use

Stent Type	Structure	Material
ACS multilink	Rings joined by linked, etched tube	Stainless steel
AVE Microstent	Wire zigzags, welded in series	Stainless steel
Crown (Cordis)	Slotted tube	Stainless steel
Gianturco-Roubin II (Cook)	Flat coil with longitudinal spine	Stainless steel
Palmaz-Schatz (Cordis)	Slotted tube with central articulation	Stainless steel
Wiktor (Medtronic)	Single wire sinusoidal helix	Tantalum

Table 3: Stents currently available in the US

All approved designs utilize a metal device which is compressed onto a balloon catheter. Following pre-dilation of a coronary stenosis with an angioplasty balloon, the stent is positioned at the lesion site and permanently delivered into the artery by inflation of the balloon which is encircled by the stent. When the balloon is deflated, the expanded stent remains anchored to the wall of the artery. To ensure adequate stent expansion, additional high pressure dilations using specially designed balloons are usually performed. This practice improves the probability that stent components are in firm contact with the vessel and not protruding into the lumen. As a result, luminal dimensions are enlarged and the risk of stent thrombosis is reduced.

Indications for stenting

Clinical scenarios where stents are utilized are identical to those enumerated above for balloon angioplasty. Historically, stenting was initially used as an unplanned or emergent measure to treat threatened or abrupt closure following routine balloon angioplasty, circumstances that would ordinarily result in urgent bypass surgery or myocardial infarction. In a multicenter series of 518 such patients, the Gianturco Roubin stent was successfully deployed in 95% of patients,

2% died, 4% underwent emergent CABG, 3% developed a Q wave MI, and 9% developed post-procedural stent thrombosis. Of those discharged, 15 % required repeat revascularization and restenosis occurred in 39% (46). In a similar set of 339 patients implanted with the Palmaz-Schatz stent, deployment was successful in 97%, with rates of death, emergent CABG, Q-wave MI and stent thrombosis of 1%, 1%, 4% and 7%, respectively. These rates compare favorably with the 20% rate of emergent CABG in the pre-stent era (47). Following discharge, 19% required repeat revascularization with restenosis in 30% (48). The use of aggressive post-stent anticoagulation with coumadin resulted in major bleeding rates of 9-14%.

Comparison trials of stenting vs. PTCA did not specifically address symptomatic status or exercise tolerance, however the clinical efficacy of stenting was demonstrated by rates of revascularization lower than those treated with balloon angioplasty (see below). Stenting has also been utilized in clinical scenarios where the limitations of balloon angioplasty are especially apparent. As opposed to the case of balloon angioplasty where outcomes are less favorable in patients with unstable angina (49-52), stenting leads to in-hospital event rates that are equivalent to those with stable anginal symptoms (53, 54).

In patients with prior restenosis from a balloon PTCA, stenting is associated with rates of angiographic restenosis (37% vs. 15%, p=0.05) and target vessel revascularization (31% vs. 9%, p=0.01) that are higher than those undergoing the procedure for a de novo lesion (55). Others have not confirmed these findings (56).

Stenting has also been utilized in the acute infarct setting to improve the limitations of acute angioplasty which include recurrent ischemia (10-15%), reinfarction (3-5%) (57) and late luminal loss, resulting in restenosis rates of 37% to 49% (58). Early experience revealed success rates in excess of 90% with recurrent ischemia in <5% (59-61). This strategy was tested in the larger PAMI stent trial involving 312 patients with an ST elevation MI presenting with <12 hours of symptoms in whom antegrade flow was restored, vessel size was 3.0-4.0 mm, and lesion length was < 30mm. Stenting with the Palmaz-Schatz device was attempted in 77% of enrolled patients and was successful in 98%. In-hospital and 30 day rates of death (0.8%, 0.8%), reinfarction (1.7%, 1.7%), CABG (2.9%, 3.3%) and target vessel revascularization (1.3%, 1.7%) were low in the stent group. Compared to the 23% of patients who underwent PTCA alone for technical reasons, there was a significant decrease in the need for urgent or in-hospital CABG and for revascularization at 30 days (58). Preliminary data from the PAMI-stent trial which randomized 900 acute MI patients to either PTCA or stenting with a heparin coated Palmaz-Schatz stent revealed no significant differences (balloon vs. stent) in the rates of death (1.8% vs. 3.5%) or reinfarction (1.1% vs. 0.4%) at 30 days, although there was a higher rate of target vessel revascularization in balloon-treated patients, 3.5% vs. 0.9%, p<0.01. Data collection for 6 month follow-up events, the primary endpoint, is continuing (62).

Theoretically, the use of stenting to treat multivessel disease would result in improved event-free survival compared to PTCA due to lower restenosis rates (see below). In a series of 100 patients with 2 vessel (86%) or 3 vessel (14%) stenting, the in hospital composite endpoint of death (0%), MI (8%) and emergent CABG (2%) was comparable to that of patients undergoing PTCA for multivessel disease (7, 63). At 21 months of follow-up, repeat intervention was required in 28% and CABG in 2%, rates lower than 34% and 18%, respectively, reported for balloon angioplasty (7). In a higher risk population in whom 53% of stented sites were in saphenous vein grafts, event free survival at one year was 80% with only 9% requiring revascularization of the stented vessel (64). Several randomized trials comparing CABG to stenting are currently underway to definitively address this issue.

Results with stenting vs. balloon angioplasty

The theoretical advantages of stenting were confirmed clinically with the publication of two randomized trials comparing balloon angioplasty with implantation of the Palmaz-Schatz intracoronary stent; the STRESS (n= 407) and BENESTENT (n= 516) trials (25, 26). The results were confirmed in a smaller group of patients with stenting confined to the LAD (n=120) (65). Patients with vessels < 3 mm, lesions > one stent length, vein graft stenoses, ostial disease, intracoronary thrombus or a recent MI were excluded. The acute and long term outcomes of patients enrolled in these studies are tabulated in Table 4.

	PTCA			STENT		
	STRESS	BENESTENT	VERSACI	STRESS	BENESTENT	VERSACI
Unstable angina	48%	8%	18%	47%	6%	17%
Diabetes mellitus	16%	6%	17%	15%	7%	13%
Procedural success	89.6%	93.1%	93.0%	96.1%	93.8%	95.0%
Crossover	6.9%	5.1%	3.3%	3.9%	5.4%	3.3%
Subacute closure	1.5%	2.7%	0.0%	3.4%	3.5%	1.7%
Death	1.5%	0.4%	0.0%	1.5%	0.8%	0.0%
Q-wave MI	3.4%	1.9%	1.7%	3.5%	2.7%	1.7%
Emergent/Urgent CABG	2.4%	1.6%	3.4%	4.0%	1.9%	3.4%
All CABG	8.4%	4.2%	5.1%	4.9%	6.2%	5.1%
Restenosis	42.1%	32.0%	40.0%	31.6%	22.0%	19.0%
Repeat PTCA	12.4%	23%	22%	11.2%	13.5%	6.7%
Minimal luminal diameter(post)	1.99	2.05	2.10	2.49	2.48	2.80
Minimal luminal diameter(6 mo)	1.56	1.73	1.40	1.74	1.82	1.80

Table 4: Clinical characteristics, in hospital and chronic outcomes in PTCA vs. stent trials

Compared with balloon angioplasty, acute procedural success, defined as a final diameter stenosis <50% without death, MI, or emergent CABG, was greater with stents. Use of stenting also resulted in greater luminal dimensions immediately following the procedure, and at 6 month follow-up. The final success rates in the angioplasty groups were enhanced by crossover to stenting in an average of 5 % of patients. Rates of death, MI, or emergent CABG were comparable with either strategy, but restenosis and the need for repeat intervention were reduced

with stenting after 6 months of follow-up. The durability of these findings was also confirmed at 1 year with a net decrease of approximately 10 repeat interventions for every 100 patients stented (66, 67).

Cost analysis for stenting reveals the expected increase in initial hospital expenditures due to stent costs. Despite a decrease in follow-up care costs for the stent group, overall resource use was greater in stented patients (66), although the $300 per patient difference is likely to diminish as stent prices diminish with greater competition. Longitudinal follow-up in a non-randomized population followed for up to three years showed no late decrement in luminal dimensions, suggesting that stenting does not merely delay the restenosis process (68), a finding confirmed with clinical follow up to 4.5 years (69).

To further tailor stent therapy, it would be useful to identify those patients most likely to benefit from the device. In a series of trials involving 4608 patients treated with planned balloon angioplasty who crossed over to stenting in 14% of cases due to complications , excellent long term results have been achieved, with a target vessel revascularization rate of 17.5% (70). A randomized trial is required to answer the question of whether this strategy of provisional stenting is truly equivalent to stenting all eligible patients.

Coronary interventions in saphenous vein grafts present a challenge for balloon angioplasty, especially lesions located in older (> 4 years) grafts or at the ostium of the conduit. Balloon angioplasty of these stenoses differs from that in native vessels due to lower success rates, an increased number of complications related to embolization of graft material, and higher restenosis rates (71). In the SAVED trial, balloon angioplasty was compared to stenting in vein grafts implanted 9-10 years earlier. The study included patients with de novo lesions, treatable with up to two stents, in grafts with a reference diameter of 3 to 5 mm. Exclusion criteria were a) acute myocardial infarction, b) contraindications to anticoagulation, c) ejection fraction of less than 25%, d) evidence of thrombus, and e) evidence of outflow obstruction. Procedural success rates were substantially higher in the patients assigned to stenting (92% vs. 69%, $P<0.001$). The 8 month cardiac event rate (death, myocardial infarction, and repeat revascularization) was significantly lower after stent implantation than that after balloon angioplasty (27% vs.42%, $p = 0.03$). Although there was no improvement in angiographic restenosis following stent placement (37% vs. 46%, $p = 0.24$), there was a trend towards fewer target vessel revascularizations (17% vs. 26%, $p=0.09$) (72).

It is important to realize that patients enrolled in these clinical trials were highly selected, and represent only 7-30 % of patients undergoing coronary interventions (73, 74). The use of stents in over 50% of interventions nationwide means that many stents are being implanted in circumstances where clinical trials have not shown a clear benefit. In a series of patients with 93% angiographic follow-up, restenosis and target lesion revascularization rates were substantially

higher in the 85% of stented patients with lesion characteristics that would have excluded them from the STRESS and BENESTENT trials (Table 5) (73).

	n	SAT (%)	Restenosis (%)	TLR (%)
STRESS/BENESTENT	152	1.3	11	9
Reference Diameter < 3.0mm	236	1.5	30*	19*
Length > 15 mm	125	1.6	32*	15
Ostial location	97	2.1	40*	14
Total occlusion	40	0	40*	8
Vein graft	52	0	34*	21*
Restenosis lesion	301	1.0	27*	15*

* $p < 0.05$

SAT=subacute thrombosis, TLR=target lesion revascularization

Table 5: Clinical outcomes in stented patients with non-ideal lesion characteristics

The issue of stenting is small vessels was addressed by the STRESS group which analyzed results in vessels < 3.0 mm (mean diameter 2.67 mm) by core lab angiographic analysis in the original cohort and an additional 188 randomized patients, providing a study population of 331 lesions. The clinical characteristics and success rates were similar to the initial group (see Table 4). Rates of restenosis (34% vs. 55%, $p<0.001$) and target vessel revascularization (16% vs. 27%, $p<0.02$) were lower in stented lesions with a subacute closure rate at 30 days of 3.6% in both groups. Significant improvement in 6 month luminal dimensions and restenosis was seen among all vessel sizes, including those < 2.5 mm (75). The role for stents in restenosis lesions was explored in the REST trial. In patients previously treated with balloon angioplasty only, stenting lead to a lower repeat restenosis rate compared to re-angioplasty (18% vs. 32%, $p<0.01$) in 383 randomized patients (76).

Stenting has also been tested against balloon angioplasty for chronic total occlusions, lesions which historically have restenosis rates of 44 to 77% and reocclusion rates of 14 to 40%; values that are higher than those of non-occluded vessels (37-39). The SICCO study randomized 119 patients with a vessel occluded for > 2 weeks and who were successfully recanalized. Palmaz-Schatz stenting resulted in a larger minimal luminal diameter acutely (2.78 mm vs. 2.13 mm, $p<0.001$), and at 6 months (1.92 vs. 1.11, $p<0.001$), a lower incidence of restenosis (32% vs. 74%, $p<0.001$) and reocclusion (12% vs. 26%, $P=0.06$) and less need for target vessel revascularization (22% vs. 42%, $p<0.05$) (37). Similar results were reported by Mori et al in a non-randomized consecutive series of 96 patients (77).

Stent restenosis

The process of restenosis within stents differs from that observed with balloon angioplasty. Because stent dimensions are stable over time, the maladaptive vessel constriction does not occur, meaning that loss of luminal area is due solely to intimal proliferation (78). This proliferative response tends to be distributed axially along the entire stented segment, including the border of the stent and adjacent native vessel (79). The degree of intimal proliferation is actually increased by stenting compared to balloon angioplasty. In the STRESS and BENESTENT trials, the decrement in luminal diameter from post-intervention to follow up was 0.35 mm for balloon and 0.70 mm for stents ($p<0.001$). The larger lumen in the stent group at 6 months was therefore due to a greater acute gain in stented vessels.

Predictors of angiographic restenosis following stenting derived from large consecutive series include diabetes mellitus, prior PTCA, an initially occluded vessel, placement of multiple stents, LAD lesion, ostial location, reference vessel diameter, and a small luminal diameter following stenting (80-82). In multivariate analysis, intravascular ultrasound measurements of the reference segment, lesion severity and post-intervention lumen dimensions are more predictive than angiographic parameters (80). Restenosis has been classified as focal or diffuse (> 10mm in length) within the stent, limited to the stent margin, and proliferative (diffuse pattern extending beyond the stent margins. In Palmaz-Schatz stents, focal restenosis occurs most frequently at the central articulation site (78).

Initial attempts at treating stent restenosis were limited to repeat balloon inflations within the lesion, resulting in recurrent angina in 26% of patients and target vessel revascularization in 14% (83). Similar long-term outcomes have been reported by others with initial success rates in excess of 95%. In the largest series with follow-up catheterization, angiographic restenosis occurred in 22% of patients. Risk factors for recurrent restenosis include vein graft lesions, multivessel disease, an interval < 3 months from stent implantation to first restenosis, diffuse restenosis > 10 mm in length, and a diameter stenosis > 70% at the time of stent restenosis (84, 85). Patients with diffuse or proliferative stent restenosis present an especially challenging subset, with target vessel revascularization in several small series reported in 35% to 85% of patients while patients with focal disease had rates of 12-19% (86-88). Intravascular ultrasound studies reveal that the increase in luminal dimensions with balloon angioplasty are due in equal parts to additional stent expansion and extrusion of neointimal tissue both axially and through the stent to the outer regions of vessel (89). However, over half the neointimal tissue remains within the lumen with suggestions that there is continued inward migration of this material within minutes (90).

The optimal therapy of stent restenosis remains a topic of active investigation. If the original deployment was limited by inadequate stent expansion or if the intimal proliferation advancing from the vessel wall through the stent struts is focal, additional balloon inflations alone

are likely to yield a durable improvement in luminal dimensions. In those circumstances where the tissue proliferation involves most of the stent length, ablative strategies are successful at removing tissue, and could theoretically be of benefit (91-93).

Post-stent medical therapy

Early stent implantation trials were plagued by unacceptable rates of stent thrombosis, leading to aggressive anticoagulation regimens including intra-procedural dextran, periprocedural heparin, aspirin and dipyridamole, and 1-3 months of post-implantation coumadin. As a result, stent thrombosis decreased to 3-5% (94), but vascular complications and the requirement for a therapeutic PT prior to discharge remained major limitations of stenting. In a landmark study, Colombo et al documented a 0.9% rate of subacute stent thrombosis with IVUS-guided stent deployment using high pressure balloon expansion combined with antiplatelet therapy using aspirin and ticlopidine (95). The ISAR trial (96) confirmed the superiority of antiplatelet over anticoagulation therapy using only aggressive deployment techniques without IVUS (Table 6).

	ASA+Ticlid n=257	Coumadin n=260	p
Diabetes mellitus	15.6	19.6	NS
Unstable angina	46.3	43.1	NS
Acute MI	23.7	23.8	NS
Restenotic lesion	13.9	11.4	NS
Dissection before stenting	59.0	57.3	NS
Death	0.4	0.8	NS
Myocardial infarction	0.8	4.2	0.02
Repeat PTCA	1.2	5.0	0.02
Vascular complication	0.8	6.2	0.001
Hemorrhagic event	0	6.5	0.001
Occlusion of stented vessel	0.8	5.4	0.004

Table 6: Antiplatelet vs. Anticoagulation Therapy following stenting

Despite enrolling a high risk group of patients, combined therapy with aspirin and ticlopidine (250 mg BID) vs. aspirin plus coumadin (INR 3.5-4.5) for 4 weeks resulted in fewer stent occlusions, fewer bleeding events, and a decreased rate of vascular complications at 30 days of follow-up. The STARS trial used a similar design, randomizing 1652 successfully stented patients without a recent MI to either aspirin, aspirin + coumadin (INR2-2.5), or aspirin + ticlopidine (250 mg BID) with rates of subacute thrombosis of 2.9%, 2.5%, and 0.6%, respectively (97). Aspirin alone is therefore insufficient therapy following intracoronary stenting.

ticlopidine will likely be replaced by clopidogrel (75 mg QD), an agent which also irreversibly inhibits ADP-induced platelet aggregation, but is not limited by the side effects of ticlopidine. These include reversible neutropenia occurring from 3 weeks to 3 months following initiation of therapy (severe in 1%, moderate in 1.6%), rash (3.4%) and diarrhea (6.3%) (98).

With the use of antiplatelet therapy, subacute stent thrombosis occurs a mean of 9 days following the procedure (range 3-27) and is predicted by low ejection fraction, use of stent combinations, abnormal coronary flow, and persistent dissections (99). The benefit of antiplatelet therapy also extends to stented patients with acute infarction (100) and results in a 1% risk of subacute thrombosis even in those lesions with gross angiographic evidence of thrombus (101).

The ISAR investigators also assessed the effect of antiplatelet vs. anticoagulation therapy on angiographic and clinical outcomes at 6 months. They found no difference in restenosis rates (26.8% vs. 28.9%) or target lesion revascularization (14.6% vs. 15.6%) (102)].

ROTATIONAL ATHERECTOMY

Rotational atherectomy, or rotablation, utilizes a diamond-embedded ablative burr ranging in size from 1.25 to 2.50 mm in diameter which rotates at 160-180,000 rpm. It enlarges the lumen by plaque abrasion and pulverization. In vitro testing suggests that the device preferentially cuts inelastic, atherosclerotic artery components, presumably causing minimal trauma to less diseased portions of the vessel wall. With proper technique in native coronaries (103), plaque fragments are of sufficiently small size, with 2-10% larger than 10 μm, (104), that they pass through the capillary bed without causing flow limitation. Intravascular ultrasound studies have confirmed that rotablation enlarges luminal dimension by plaque removal (105), and intracoronary angioscopy in human coronaries confirmed animal studies indicating that rotablation leads to fewer and less severe dissections than routine angioplasty (106). The luminal diameter following passage of a burr is approximately 80% of the device diameter (107), suggesting some degree of recoil. Balloon angioplasty is therefore a frequent adjunctive therapy. In a typical series of patients, rotablation decreased the percent diameter stenosis from 68% to 44%, and angioplasty resulted in a final 18% residual stenosis (108). Rotablation does "prepare" the artery for adjunctive balloon inflation since the ratio of luminal diameter/inflated balloon diameter is 0.78 following rotablation compared to 0.69 following balloon inflation alone. This results in a lower post-rotablation residual stenosis (109).

Until recently, there were few direct comparisons of rotablation with other techniques since patients undergoing rotablation are usually not optimal candidates for balloon angioplasty due to complex lesion characteristics that increase the risk for vessel closure. The AHA/ACC rating scale for lesion severity is reproduced in Table 7. B lesions are subclassified into those with 1 (B1) or

≥2 characteristics (B2). Procedural outcomes and clinical follow-up results are summarized in Table 8. In the largest series with angiographic follow-up, the restenosis rate was 38% with diabetes and higher post-procedural percent stenosis identified as predictors of this complication (113).

Type A Lesions (High Success, >85%; Low Risk)

- Discrete (<10 mm length)
- Concentric
- Readily accessible
- Nonangulated segment, <45°
- Smooth contour
- Little or no calcification
- Less than totally occlusive
- Nonostial in location
- No major branch involvement
- Absense of thrombus

Type B Lesions (Moderate Success, 60 to 85%; Moderate Risk)

- Tubular (10 to 20 mm length)
- Eccentric
- Moderate tortuosity of proximal segment
- Moderately angulated segment, >45°, <90°
- Irregular contour
- Moderate to heavy calcification
- Total occlusions <3 months old
- Ostial in location
- Bifurcation lesions requiring double guidewires
- Some thrombus present

Type C Lesions (Low Success, <60%; High Risk)

- Diffuse (>2 cm length)
- Excessive tortuosity of proximal segment
- Extremely angulated segments >90°
- Total occlusions >3 months old
- Inability to protect major side branches
- Degenerated vein grafts with friable lesions

Table 7: AHA/ACC lesion classification.
Reproduced from Ryan TJ, et al. (110)

Study	n	Years	% B2/C	Success	Death	MI	Em. CABG	Perforation
Ellis (111)	400	1989-92	36	90%	3.0%	7.9%	0.9%	1.5%
Reisman (112)	2953	1988-93	51	95%	1.0%	7.3%	2.5%	0.6%
Brown (107)	525	1990-94	71	91%	0.8%	6.3%	0.4%	0.2%
Reisman (112)	200	1994	67	96%	3.0%	6.5%	2.5%	0.5%

Table 8: Procedural results and complications with rotational atherectomy

Early experience by Ellis et al identified the issues of "no reflow" and perforation which occur more frequently with rotablation compared to balloon-based interventions (111). No-reflow, which is delayed filling of the distal coronary bed in the absence of a flow-limiting lesion, occurred in 9.1% of patients and was associated with a 33% incidence of MI and a 43% incidence of ischemic ECG changes. This phenomenon is presumably due to platelet aggregation or a large burden of oversized plaque particles released during passage of the activated device, leading to microvascular compromise. Alterations in technique, such as reduced burring times, avoiding rpm drops, continuously flushing the coronary artery with nitrates and verapamil, and using multiple and progressively larger burrs have reduced this complication to 1.8% of cases (114). Perforation,

while rare, is a severe complication which can lead to pericardial tamponade and/or abrupt vessel closure. Lesion angulation, non-LAD location, eccentricity, tortuosity, and length > 10 mm are weakly correlated with perforation (111, 115). Other complications include dissection (10.5%), abrupt closure (3.1%), arrhythmias (1.9%), and spasm (1.6%) (113).

Even in the most complex lesion subtypes, success rates are approximately 90%. Calcified lesions, which are an independent factor for complications with balloon angioplasty(116-118), have a similar success and complication rate compared to noncalcified lesions when treated with rotablation (119). Despite an increasing complexity of treated lesions as more experience with the device is acquired, success and major complication rates have remained stable (112).

Rotablation vs. Balloon angioplasty

Several small randomized trials have addressed the relative efficacies and complications of these two techniques. In BAROCCO, this comparison was made for 100 patients with occluded vessels, demonstrating a success rate of 66% for rotablation vs. 52% for balloon, a nonsignificant difference. After crossing over to rotablation, the balloon success rate was 60% (120). Guerin et al randomized 64 patients with type B2 stenoses and found no difference in procedural success rates (94% rotablation, 87% balloon), complications, or restenosis rates (39% vs. 42%) (121). In the ERBAC trial, 222 patients were randomized to balloon angioplasty and 231 to rotablation. There was also an excimer laser arm which included 232 patients. The results are summarized in table 9.

	PTCA (n=222)	ELCA (n=232)	Rotablation (n=231)	p
Unstable angina	12	16	18	NS
Diabetes Mellitus	16	17	15	NS
B2/C lesion	73	75	79	NS
Calcified	37	41	38	NS
Reference diameter (mm)	2.93	2.91	2.91	NS
% stenosis pre	75	75	76	NS
% stenosis post	35	33	33	NS
Procedural success	80	77	89	0.019
Success with crossover	83	91	91	0.025
In hospital Death	0.9	0.9	0.9	NS
MI	3.5	3.9	3.9	NS
CABG	0.5	2.2	0.9	NS
Restenosis	47	59	57	0.14
Target lesion revascularization	32	46	42	0.013

All numbers represent percentages, ELCA=excimer laser coronary angioplasty

Table 9: Randomized trial of balloon, laser, and rotational atherectomy (42)

Success rates in this group with complex lesions was highest with rotablation, but this technique also resulted in higher rates of restenosis and repeat revascularization. This limitation may be partly explained by a conservative use of rotablation plus adjunctive angioplasty, with a burr:artery ratio = 0.58 and a residual stenosis of 33%, identical to patients in the PTCA group (42) whereas others have demonstrated lower post procedural percent stenosis with rotablation. The optimal burr size for rotablation was explored in the 500 patient STRATAS trial which randomized patients to a standard group (burr:artery ratio=0.68) or an aggressive group (ratio=0.78) prior to adjunctive PTCA. Preliminary data revealed no difference in post-intervention residual stenosis (26.5% conservative vs. 27.8%), target vessel revascularization (20% vs. 25%), or luminal dimensions at 6 month follow up. In the conservative group, there was a trend towards more major in-hospital complications (3.6% vs. 2.0%) and perforation (1.2% vs. 0.4%)(76).

In summary, rotational atherectomy provides higher initial success rates compared to balloon angioplasty in selected complex lesions. If an adequate lumen can be achieved with the combination of burring and adjunctive angioplasty, long term results are likely to be comparable to balloon angioplasty of simpler lesions. This is still a relatively young technique, and additional studies exploring variations in technique may achieve the goal of reducing restenosis rates.

DIRECTIONAL ATHERECTOMY

The directional coronary atherectomy (DCA) device is a windowed cylindrical housing which is compressed against the stenosis using an attached balloon that is inflated against the opposite wall of the artery. Once positioned, a rotating metal cutting blade inside the housing is advanced, shaving plaque from the vessel wall and depositing the shaved debris in the catheter's nosecone. Directional atherectomy enlarges the lumen by a combination of plaque excision, balloon angioplasty effect, and device-related vessel stretching (Dotter effect) (122, 123).

Two early randomized trials compared atherectomy and PTCA. In CAVEAT, atherectomy had a higher incidence of angiographic success, but those receiving atherectomy more often had acute complications. In 512 patients treated with atherectomy and 500 with PTCA, restenosis occurred in 50 and 57 percent, respectively (P = 0.06). Nevertheless, reintervention and mortality were similar in the 2 groups, although at 6 months those undergoing atherectomy were more likely to have a myocardial infarction (124). The CCAT (Canadian Coronary Atherectomy Trial) investigators compared atherectomy in 138 patients to PTCA in 136 patients, all with stenoses of the proximal left anterior descending artery. Although atherectomy had a higher incidence of initial success, clinical outcome at 6 months was similar (125). The major criticism of these trials was that atherectomy was inadequately performed, as assessed by the post atherectomy residual stenosis of 29% in CAVEAT and 26% in CCAT, resulting in no identifiable benefit for DCA. This hypothesis was tested in the BOAT trial which randomized patients to aggressive atherectomy followed by adjunctive balloon

inflations to maximize lumen diameter vs. treatment with angioplasty alone. The results are displayed in Table 10 (27).

		DCA (n=497)	PTCA (n=492)	p
Unstable angina		12	18	NS
Left anterior descending site		50	47	NS
Reference diameter (mm)		3.25	3.20	0.07
% stenosis pre		67	67	NS
% stenosis post		15	28	0.001
Procedural success (%)		93	87	0.001
Success with stent crossover		99	97	0.025
In hospital	Death	0	0.4	NS
	MI (CKMB>3x)	16	6	0.001
	CABG	1.0	2.0	NS
Restenosis		31	40	0.016
One year	Death	0.6	1.6	NS
	Q MI	2.0	1.6	NS
	TVR	17.1	19.7	NS

TVR=target vessel revascularization

Table 10: Results of the BOAT trial

This data reveals that DCA in large vessels with aggressive techniques reduces restenosis, although no difference in clinical outcomes is associated with this benefit. There is a significantly increased risk of non-Q wave MI with DCA compared to balloon angioplasty, a finding that was not associated with excess mortality in BOAT but was in the earlier CAVEAT trial (126).

The use of DCA was also examined in saphenous vein grafts. In CAVEAT-II, which compared outcomes after directional atherectomy and balloon angioplasty in patients with focal (length < 12 mm) de novo lesions, a greater initial success rate and luminal gain were achieved with directional atherectomy. However, distal embolization was also higher (13% vs. 5%, p=0.012) with a trend toward an increase in non-Q-wave myocardial infarction (16% vs. 10%, p=0.09) in the DCA group. The restenosis rate (46% for DCA vs. 51% for PTCA) was equivalent with a trend towards a lower target vessel revascularization rates (18.6% vs. 26.2%, p=0.07) in DCA treated patients (127).

In summary, DCA offers some minor advantages over PTCA in terms of acute results and late angiographic dimensions, but the expense, technical difficulties, and continued uncertainty regarding the influence of procedure-related non Q myocardial infarction on long term prognosis has tempered its use in clinical practice(128-130).

FUTURE DIRECTIONS

Since balloon technology is mature, current work is focusing on restenosis issues and on improving stent technology. Small studies have suggested that probucol therapy and intracoronary radiation can reduce restenosis, findings that must be confirmed with larger numbers of patients and broader populations (131-134). New stent designs employing pharmacologically active coatings and local gene/drug delivery techniques aimed at limiting thrombosis and neointimal proliferation are also now in clinical trials. In addition, a device which can aspirate intracoronary thrombus by producing a saline flow-induced vacuum (Angiojet catheter) was recently FDA approved and may prove useful in the treatment of this difficult subset of patients (135, 136). Lastly, the feasibility of transmyocardial laser revascularization, which previously required a thoracotomy, has been demonstrated using percutaneous systems (137). In conclusion, percutaneous coronary revascularization continues to evolve in exciting and unpredictable directions with the promise of providing ever more-effective therapy to patients with myocardial ischemia.

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