

## Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy

Kuntz RE, Gibson CM, Nobuyoshi M, Baim DS

*J Am Coll Cardiol.* 1993;21:15-25

The demonstration that stenosis after angioplasty, minimal lumen diameter (MLD), or change in MLD are all continuous variables—and not divided into a bimodal population representing restenosis or no restenosis—produced a profound change in the thinking behind the restenosis process. The fact that the artery has a limited response to injury, based primarily on neointima formation, recoil, and geometric remodeling, implies that other interventions used to treat atherosclerosis, such as atherectomy or stenting, may also result in a continuous distribution of angiographic variables. As atherectomy and the use of other devices also result in a continuous distribution of stenosis of vessels, with no improvement in restenosis rates over conventional angioplasty, the authors have examined whether this lack of benefit of the newer modalities was due to the classification of patients into restenosis or nonrestenosis at follow-up.

To address these questions, the authors enrolled 524 patients to undergo Palmaz-Schatz stenting, directional coronary atherectomy (DCA), or angioplasty, with follow-up angiography at 3 and 6 months. The DCA and stenting procedures were performed in the USA, and the conventional angioplasty in Japan. Because of this, and the nonrandom allocation of patients to treatment groups, there were differences in patient characteristics (age, sex), anatomy (preponderance of left anterior descending artery lesions), or percentage of restenotic lesions treated, although it is unlikely that these would affect interpretation of the data. The results show that DCA or stenting resulted in a larger initial gain following the procedure. At 6 months, conventional angioplasty showed a smaller MLD than the other two modalities. Interestingly, stenting provided the highest final MLD at 6 months, although it was associated with the highest overall loss of MLD. This implies that the reason stents perform better than the other two treatments is that a wider lumen can be achieved with stents immediately after the procedure. In fact, there was a good positive correlation between initial gain and late loss, implying that the more damage is done to the vessel, the greater the arterial response in terms of late narrowing.

This study has important implications for the actual clinical practice of these interventions. First, it suggests that the best way to improve restenosis following any intervention would be to minimize immediate stenosis (maximize postprocedural MLD). However, this implies that unless postprocedural MLDs for angioplasty can be achieved similar to the other modalities, conventional angioplasty will always have a higher restenosis rate. Second, the concept of “bigger is better” is applicable to all modalities, and should be practiced clinically. Third, as the results (late percentage stenosis, immediate gain, and late loss) all follow normal distributions for continuous variables, the ability to detect small differences in outcome among experimental treatments is far greater if selected continuous variables are used rather than binary models of restenosis based on an arbitrary cutoff point for restenosis. Finally, although the late loss was related to the immediate gain, treatments which interrupt this relationship, allowing a smaller late loss despite a large initial gain, should still provide further improvements in rates of restenosis.

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1993

Rolls Royce opens its first Russian showroom in Moscow;  
Bill Clinton has a controversial \$200 haircut;  
and Audrey Hepburn dies, aged 63



## Randomized trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months

*Topol EJ, Califf RM, Weisman HF, et al, on behalf of the EPIC Investigators*

*Lancet.* 1994;343:881-886

Numerous studies have used antiplatelet agents to prevent restenosis. In fact, angioplasty is routinely performed using heparin and aspirin, although neither treatment reduces long-term restenosis. This may be due to the fact that both these agents have weak antiplatelet actions, and platelet stimulation can occur in the presence of aspirin therapy. The final common path for platelet aggregation involves the platelet receptor for the glycoprotein IIb/IIIa integrin, and earlier studies have shown that treatment of vessels with an antibody to this receptor can render them unable to activate platelets after injury. The antibody 7E3 is a humanized murine monoclonal chimeric antibody Fab fragment that selectively binds the platelet IIb/IIIa receptor, and thus represents a more potent method of inhibiting platelet function than conventional pharmacological agents. The present study was based on the premise that platelets are important in both acute vessel closure after angioplasty and long-term restenosis. The study evaluated the efficacy of profound suppression of platelet activity using 7E3 on these clinical end points.

This study included nearly 2100 patients; all patients were of a high-risk type (evolving or recent myocardial infarction, unstable angina, or high-risk angiographic lesion morphology or clinical characteristics). All patients received aspirin and heparin, but were then divided into three groups: (i) placebo bolus (>10 minutes before coronary procedure) + placebo infusion for 12 hours; (ii) 7E3 bolus + placebo infusion; or (iii) 7E3 bolus + 7E3 infusion for 12 hours. Patients underwent either coronary angioplasty or directional atherectomy. The primary end points were the composite 30-day or 6-month incidence of death from any cause, myocardial infarction, the need for repeat revascularization (30 days and 6 months), or the need for stent or intra-aortic balloon pump insertion for ischemia (30 days only).

The main clinical findings were that at 30 days there was significant reduction in all events in patients who received the 7E3 bolus and infusion compared with placebo bolus and infusion. This reduction was accounted for predominantly by a reduced need for revascularization of the target vessel by repeat angioplasty. At 6 months of follow-up,

there was still a significant difference in all events in the 7E3 bolus + 7E3 infusion group compared with placebo bolus + infusion, again made up primarily by the reduction in need for repeat angioplasty. This reduction in need for repeat angioplasty was evident at 48 hours, indicating that 7E3 treatment reduces acute closure of the artery. Interestingly, there was no reduction in events at any time with the 7E3 bolus alone. In contrast to these favorable outcomes, 7E3 treatment, either as a bolus or as a bolus + infusion, was associated with a significant increase in bleeding complications requiring approximately twice the volume of blood transfusion in the first 48 hours.

This study is remarkable as it shows a favorable outcome for a therapeutic agent in the suppression of restenosis. In fact, figures for 3-year follow-up are now available that show a maintained benefit of the 7E3-treated patients. However, the trial actually tells us more than this.

The success of 7E3 in the suppression of acute closure is not unexpected; platelets are well known to play a significant role in the acute thrombotic events precipitating vessel occlusion. However, it is less clear why an antiplatelet agent given for only 12 hours has a beneficial effect on restenosis. If restenosis is primarily due to remodeling (see page 166), why should antiplatelet agents affect long-term remodeling? The answer may lie in the nonspecific nature of the antibody used. There is now good evidence that 7E3 also binds to other integrins, many of which are involved in the cell-matrix interactions which mediate wound contracture or chronic recoil. This may be the true mechanism of 7E3 in restenosis, although, as the trial did not use follow-up angiography, this is only speculation at present.

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1994

Cambridge beats Oxford  
in the 140th University boat race;  
Quentin Tarantino's "Pulp Fiction" wins  
the Palme d'Or at the Cannes film festival;  
and Melina Mecouri, Greek actress and politician,  
dies, aged 68

## Restenosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 229 patients

Nobuyoshi M, Kimura T, Nosaka H, Mioka S, Ueno K, Yokoi H, Hamasaki N, Horiuchi H, Ohishi H

*J Am Coll Cardiol.* 1988;12:616-623

**A**ngioplasty results in overexpansion of the vessel, with dissection of the intimal plaque, often extending into the media. This injury induces a characteristic reparative response, with both neointima formation and geometric remodeling (see Narins and Topol's article in this issue). Both of these processes result in lumen narrowing, but the natural history of lumen changes was largely unknown prior to the study of Nobuyoshi et al. The timing of lumen narrowing is critically important for prevention of restenosis, as animal studies have underlined the fact that treatment immediately after angioplasty, extending only for a few days, can affect long-term arterial patency. However, the failure of pharmacological agents that are effective in animals to inhibit restenosis in humans raised the prospect that restenosis in humans was due to low-grade, chronic processes over the months following intervention.

To address this problem, Nobuyoshi et al performed angioplasty on 229 patients with angiography at day 1 and at 1, 3, 6, and 12 months following angioplasty. Success rates for the initial procedure were approximately 80%. Quantitative angiography was used to assess the diameter of the reference and stenotic segments of the artery, and restenosis was classified as more than 50% of the loss of gain immediately after the procedure (change in diameter from postprocedure to follow-up). The study managed to follow up 219 patients at 3 months, 149 patients at 6 months, and 73 patients at 1 year. The main reason for the reduced numbers of patients at follow-up was restenosis of the target lesion requiring further angioplasty. Symptom status was recorded by the patients subjectively.

Using the definition of restenosis outlined above, 15% of patients had restenosed by day 1, with no change to 1 month. However, thereafter there was a rapid increase in restenosis to 43% at 3 months, and then very gradual increases to 6 and 12 months (50% and 53%, respectively). Subgroup analysis of patients who had previous angioplasty, multivessel angioplasty, and acute myocardial infarction showed a similar time course of restenosis. Recurrence of symptoms paralleled restenosis, with most symptoms recurring within 3 months. However, there was

a poor correlation between patients' symptoms and angiographic restenosis. Similar to the STRESS and BENESTENT studies (see pages 164 and 167), a small number of lesions (<4%) showed regression during the follow-up period.

Although this study does not analyze the separate processes contributing to the restenotic process, the time course of changes which have been accurately established in this study do give clues as to the processes involved. Thus, the immediate "restenosis" seen at day 1 is likely to be due to elastic recoil of the artery, possibly superimposed with thrombus on the lesion. More recent definitions of restenosis have in fact excluded this early time point and these processes from the classification. However, most of the restenosis occurs within 3 months, with little change between 3 and 12 months. This has profound implications for the prevention of restenosis, implying that a short-term treatment, with effects possibly only for a few weeks, can suppress restenosis. The study by O'Brien et al (see page 163) has identified that there is no peak of cell proliferation between 1 and 3 months. However, the study by Mintz et al (see page 166) demonstrates that geometric remodeling accounts for most of the changes in lumen diameter over this period. The implications of this are that any treatment that induces favorable arterial remodeling short-term can suppress restenosis. The success of 7E3 in the EPIC trial (see page 159), which was only given for 12 hours after the procedure, further endorses the scientific validity of this concept.

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1988

Enzo Ferrari, Italian racing car magnate, dies aged 90;  
Sir Alexander Issigonis, British designer of  
the "Mini" motor car, dies aged 81;  
and George Bush wins the US presidential election



## Inhibition of vascular smooth muscle cell proliferation in vitro and in vivo by *c-myc* antisense oligodeoxynucleotides

Bennett MR, Anglin S, McEwan JR, Jagoe R, Newby AC, Evan GI

*J Clin Invest.* 1994;93:820-828

The failure of conventional pharmacological agents to inhibit restenosis has spawned a whole series of studies dedicated to using gene therapy to prevent restenosis. The premise for these studies is that interruption of the cascade of gene expression in vascular smooth muscle cells (VSMCs) following arterial injury can prevent those cells undergoing cell proliferation or cell migration and thus inhibit neointima formation. A number of techniques have been tried, with variable success. However, the majority have made use of antisense oligonucleotides—short sequences of DNA that irreversibly bind to the mRNA of a chosen gene, and thereby inhibit formation of a specific protein product critical to cell proliferation or migration.

The study by Bennett et al examined the use of antisense oligonucleotides to *c-myc*, a proto-oncogene that regulates cell proliferation, in the proliferation of rat VSMCs. The authors first used antisense oligonucleotides to *c-myc* and showed that these oligonucleotides could inhibit VSMC proliferation. To control for nonspecific toxic effects of the oligonucleotides, the authors used control oligonucleotides encoding the sense *c-myc* sequence, irrelevant oligonucleotides (to glyceraldehyde-phosphate dehydrogenase (GAPDH) and actin, both genes whose function is unrelated to proliferation), and a 2-base pair mismatch antisense sequence which had been shown to be ineffective in other studies in cancer cells. None of these control oligonucleotides affected rat VSMC proliferation. To demonstrate that the antisense oligonucleotides were acting on the *c-myc* target, the authors showed inhibition of *c-myc* mRNA and protein with the antisense oligonucleotide, but not with any of the other sequences. As a further control, the study used overexpression of *c-myc* to block the effect of the antisense oligonucleotides. Thus, rat VSMCs were engineered with very high levels of *c-myc*; the antisense oligonucleotides to *c-myc* had no effect on the cell proliferation or *c-myc* expression of these cells.

The authors then used antisense oligonucleotides to *c-myc* to inhibit cell proliferation in the rat carotid artery model

of injury. Sense or antisense oligonucleotides to *c-myc* were applied in a gel to the adventitia of the artery immediately after injury. Northern blots demonstrated that after injury, *c-myc* mRNA peaks in the vessel wall at 2 to 4 hours. Application of the antisense oligonucleotide inhibited this induction of *c-myc* expression. Arterial morphometry was analyzed at 2 weeks after injury. This showed that there was a significant inhibition on neointima formation in the antisense treated group, with the effect limited to the segment of the vessel which had been treated.

The study by Bennett et al was not the first to use antisense oligonucleotides in vivo to inhibit neointima formation. However, it differs from other studies in several important aspects. First, while there is considerable debate about the specificity of antisense oligonucleotides, particularly as used here containing specific 4 G motifs, this study provides extensive controls to show that at least some of the effect observed is specific. Furthermore, the study shows that suppression of gene expression at very early times (2 to 4 hours after injury) is sufficient to inhibit neointima formation in this model. While it is debatable how representative this model is of human disease, the long-term efficacy of a single agent applied immediately after angioplasty is an essential prerequisite of any treatment aimed at inhibiting restenosis. Finally, this and subsequent studies demonstrate that gene therapy for restenosis is feasible, if the correct target can be found.

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1994

Canada wins the World Ice-hockey  
Championship in Milan;  
Manchester United beats Chelsea  
4-0 to win the FA cup;  
and shops in Britain open legally on Sundays

## Lumen narrowing after percutaneous transluminal coronary balloon angioplasty follows a near-Gaussian distribution: a quantitative angiographic study in 1445 successfully dilated lesions

Rensing BJ, Hermans WRM, Deckers JW, de Feyter PJ, Tijssen JGP, Serruys PW

*J Am Coll Cardiol.* 1992;19:939-945

Clinical classifications of restenosis are based on a number of criteria; primarily, the patient has a return of symptoms, with demonstrable narrowing of the previously dilated vessel. About 30% of patients in clinical practice present again after angioplasty with this scenario. The 70% of patients who do not have a return of symptoms (and may or may not have a similar re-narrowing), are classified as not having restenosed. Thus, the perception has grown of two populations of patients, those who do and those who do not undergo restenosis. Such a division would have profound significance. If patients had similar clinical and angiographic characteristics of the lesion, then a (presumed genetic) susceptibility would predispose a subset of patients to restenosis. While this may partly still be true, the study by Rensing et al debunked the idea that “restenosis” and “nonrestenosis” were distinct entities, and were actually part of an overlapping spectrum of disease. Thus, like most landmark studies, this changed the way we view the disease process.

Rensing et al performed angioplasty on 1445 lesions in 1427 patients, with a primary success rate of 94.8%, defined as <50% residual stenosis and no in-hospital complications (death, acute myocardial infarction, coronary artery bypass grafting, repeat angioplasty, or symptom recurrence). Patients with both stable and unstable angina were included. Follow-up angiograms were performed at 6 months, and quantitative angiography with edge detection in a central core laboratory was performed for all angiographic measurements.

Minimal lumen diameter (MLD) preangioplasty, immediately after angioplasty, and at 6 months of follow-up all followed a normal (Gaussian) distribution with no evidence of a bimodal distribution. The change in MLD between the immediately postangioplasty and follow-up angiograms also showed a Gaussian distribution, including some lesions which appeared to regress. Percentage diameter stenosis at follow-up also showed a Gaussian distribution. This study yielded other interesting and valuable results. First, if the data were analyzed to exclude the lesions that progressed to total occlusion, then the distribution of

change in MLD more closely followed the Gaussian plot. This suggests that the lesions that progress to occlusion are not necessarily those with the poorest angiographic result post procedure, and occlusion may be associated with other variables. The authors suggest that as lesion diameters below 0.5 mm are impossible to sustain because of unphysiologically high blood pressures required to maintain flow, the last reduction in lumen size, from 0.5 mm to zero, occurs due to thrombosis. Second, only a very small percentage (approx. 1%) of lesions showed evidence of angiographic regression, indicating that, without adjunctive therapy, the healing response of the vessel is only to narrow the lumen back towards its pretreatment size.

This study is important as it emphasizes the continuous variation in response to the angioplasty, rather than an “all or none” response. This underlines the fact that the incidence of angiographic restenosis in a population of patients is critically dependent upon which arbitrary cutoff point one uses for percentage reduction in lumen size. Continuously distributed variables in medicine are always difficult to interpret, as the arbitrary cutoff point not only defines the disease incidence, it also usually decides when to intervene. For coronary stenosis, the cutoff point has usually been 50%, because it represents the approximate point at which coronary flow reserve is reduced in animal arteries. However, restenosis is the tail end of a near-Gaussian distribution, with some lesions crossing an arbitrary cutoff point, rather than representing a specific disease entity that only occurs in some lesions, or some patients. This fact also means that the change in MLD rather than percentage restenosis should be used when comparing the efficacy of new antirestenosis treatments.

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1992

Boutros Boutros Ghali becomes  
UN Secretary-General;  
Agassi wins the Mens' Singles at Wimbledon;  
and the last survivor of the Titanic,  
Marjorie Robb, dies aged 103



## Proliferation in primary and restenotic coronary atherectomy tissue: implications for antiproliferative therapy

O'Brien ER, Alpers CE, Stewart DK, Ferguson M, Tran N, Gordon D, Benditt EP, Hinohara T, Simpson JB, Schwartz SM

*Circulation.* 1993;73:223-231

For the last 20 years, vascular smooth muscle cell proliferation has been considered to be an indispensable part of the pathogenesis of atherosclerosis, and more recently, of angioplasty restenosis. Consequent upon this premise and encouraging data from animal models of both diseases, numerous trials of antiproliferative agents have been done, particularly to prevent restenosis. These agents have universally been unsuccessful. This failure has led many investigators to question the preeminent role of smooth muscle cell proliferation in either disease.

The study by O'Brien et al follows up a study from the same group which showed that there are very low levels of cell proliferation in primary atherosclerotic plaques (<0.5%) (Gordon et al. *Proc Natl Acad Sci USA.* 1990;87:4600-4604). O'Brien et al used directional atherectomy to examine primary (118 specimens) and restenotic (100 specimens) lesions from human coronary arteries, including those from aortocoronary-saphenous vein bypass grafts. These specimens were obtained from a range of patients, with stable or unstable angina, from various sites within the coronary tree, and at various times after angioplasty (to 1 year). Specimens were stained with an antibody to proliferating cell nuclear antigen (PCNA), which stains cells in the cell cycle, and cell type-specific antibodies to recognize vascular smooth muscle cells, macrophages, and endothelial cells. Over 4000 cells/slide were counted for both primary and restenotic specimens.

The study found that the vast majority of primary or restenotic specimens had no evidence of cell proliferation, and where this was present, it was at very low levels. Proliferating cells were smooth muscle cells (approximately 70%), macrophages (approximately 20%), and endothelial cells (approximately 10%). Furthermore, there was no difference in cell proliferation in restenotic specimens when analyzed 0 to 3, 4 to 6, 7 to 9, or >9 months after angioplasty.

This study occupies a very important place in the development of knowledge regarding restenosis. In particular, as there is no difference in rates of

proliferation between primary and restenotic tissues, it provides prima facie evidence disputing the preeminent role of smooth muscle cell proliferation in restenosis. Indeed, subsequent studies have found that neointima formation per se plays only a minor role in restenosis, and the major player appears to be geometric remodeling of the artery. The study by O'Brien et al changes the paradigm for the pathogenesis of restenosis, and redirects our studies to different biological processes and different therapeutic opportunities. In addition, the lack of evidence of a wave of proliferation following human angioplasty corresponding to that seen in animal models further underlines the growing feeling that animal models of restenosis—which involve traction withdrawal of balloon catheters in normal arteries—do not accurately reflect the human disease. This means that better models of restenosis need to be developed before therapeutic trials are extended to humans.

It should be borne in mind that this study is at odds with a similar study on human restenosis material (Pickering et al. *J Clin Invest.* 1993;91:1469-1480), which showed levels of proliferation of 15% to 20% in restenotic lesions. A number of technical differences may account for these discrepancies, as well as the fact that most of the tissue obtained in the study by Pickering et al was from peripheral arteries. It may well be therefore that different biological processes have different contributions to restenosis in the coronary or peripheral circulations.

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1993

“The Piano” wins the Palme d’Or  
at the Cannes film festival;  
Toni Morrison becomes the first black American  
to win the Nobel prize for literature;  
and Alfred Butts, American inventor of  
the boardgame Scrabble, dies aged 93

## A randomized comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease

Fischman DL, Leon MB, Bairn DS, et al, for the STent REStenosis Study Investigators

*N Engl J Med.* 1994;331:496-501

Restenosis following angioplasty has been the Achilles' heel of the technique since its inception. As described in the CAVEAT trial (page 165), newer devices such as directional coronary atherectomy (DCA), excimer laser, or rotablation have not been associated with lower incidences of restenosis. This is likely to be because all these techniques induce arterial injury, with no way of preventing late contraction of the vessel by constrictive remodeling. The advent of coronary stents, metal scaffoldings that brace the vessel in an open and, in many cases, an overdilated state, offer the prospect of directly tackling constrictive remodeling. The findings of two trials (here and Serruys et al, see page 167), which were direct comparisons of stenting versus angioplasty, were thus eagerly awaited.

The STRESS trial, conducted in the USA, randomly assigned 410 patients with symptomatic coronary artery disease to receive elective placement of a Palmaz-Schatz stent or standard balloon angioplasty. Lesions needed to be primary, with no previous intervention, in vessels >3 mm in diameter and producing at least a 70% stenosis. Angiography was performed before, immediately after, and 6 months after the procedure. Procedural success rates were high for both stent placement and angioplasty, although stents were significantly better and produced fewer dissections. In contrast, stenting had more vascular and bleeding complications than angioplasty, with patients staying over twice as long in hospital.

At 6 months' follow-up, stent restenosis was significantly lower than after balloon angioplasty (31.6% to vs 42.1%, respectively). When the authors studied the mechanisms by which improved outcome occurred after stenting, it appeared that stenting results in a greater minimal lumen diameter after the procedure. Although the stented group also had a larger loss of lumen, the higher initial gain resulted in an overall greater lumen diameter in the stented group at 6 months. Indeed, the most important predictor of lumen diameter at 6 months was the lumen after the procedure, whatever the procedure itself. Smaller vessels and left anterior descending lesions

tended to fare worst, whatever the intervention chosen. The angiographic benefits of stenting also translated into clinical events for the patients. Stented patients required less revascularization, and had less angina than the angioplasty group. There was, however, no difference in mortality or rates of myocardial infarction between stented and angioplasty groups at 6 months.

In addition to demonstrating that elective stenting reduces restenosis, this trial also partly suggests the mechanism of this effect. The concept of "bigger is better" in minimal lumen diameter post intervention was mentioned in the discussions of the papers by Kuntz et al and Topol et al (see pages 158 and 165). One major reason why stenting appears to be advantageous is that larger lumens can be achieved safely with this procedure. A larger lumen, with less constrictive remodeling, appears to be the secret of the stent's success.

A word of caution is, however, necessary with this trial. A significant number of stents thrombosed. Indeed, over 20% of stents used as a bailout after failed angioplasty were associated with stent thrombosis. This thrombosis occurred despite the intense anticoagulation regimens employed, regimens which themselves were associated with bleeding complications and a longer hospital stay. Thus, stenting buys a reduction in restenosis; there is, however, a morbid and economic price to pay.

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1994

Austria, Sweden, and Finland join the EU;  
Queen Elizabeth II and Boris Yeltsin  
attend the Bolshoi Ballet;  
and Burt Lancaster dies, aged 80



## A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease

Topol EJ, Leya F, Pinkerton CA, et al, for the CAVEAT Study Group

*N Engl J Med.* 1993;329:221-227

The high rate of restenosis following balloon angioplasty has acted as a driving force for the development of a number of different interventions in an attempt to improve overall long-term patency rates.

Directional coronary atherectomy (DCA) was invented by Simpson in 1984 and involves the introduction of a catheter-based cutting blade across the atherosclerotic plaque, and with a combined closure of the blade and retraction, part of the plaque is excised. If one considers that restenosis is due to neointima formation, then removal of the plaque mass from which the neointima arises is a conceptually elegant solution to the problem of restenosis. Indeed, from 1988, there was a rapid expansion of the use of DCA, due mainly to its high procedural success rate. However, until this study by Topol et al, there was no randomized comparison of the long-term outcome of DCA versus angioplasty. This study effectively puts the nail in the coffin for routine DCA.

Topol et al recruited 1012 patients in a multicenter study in the USA and Europe, and randomly assigned them to DCA or angioplasty. Patients had symptomatic coronary artery disease (although most had unstable angina), without previous intervention, in vessels at least 3 mm in diameter, and >60% stenosis on angiography. Both DCA and angioplasty had good initial procedural success rates, with a slight but significant benefit of DCA over angioplasty. This was due to the increased lumen diameter achieved with DCA versus angioplasty. However, there was a marked difference in the rates of myocardial infarction, with 19% of DCA patients suffering a clinical, ECG, and biochemical infarct. This resulted in higher hospital cost for DCA versus angioplasty.

Angiography was performed in 90% of the original patients at 6 months. This showed no significant difference in restenosis for DCA versus angioplasty patients. However, for either procedure, the single most important determinant of restenosis was the minimal lumen diameter after the procedure, with a larger diameter being associated with a lower restenosis rate. Other minor predictors of restenosis included smaller

vessels, the presence of diabetes mellitus, and a lesion located in the proximal left anterior descending (LAD) artery. There was no significant difference in survival or the need for revascularization between DCA and angioplasty groups at 6 months, although all of the deaths in the DCA group occurred shortly after the procedure. There was still a significant increase in myocardial infarction rates in the DCA group at 6 months.

So what does this study tell us? The main finding of this study is that DCA, despite its conceptual simplicity, does not reduce restenosis, and can produce high levels of procedural complications, including early myocardial infarction and death. Although there is a small subgroup of patients with LAD disease who do better with DCA, most patients do not, and overall, routine DCA in unselected cases increases the total costs of the intervention. However, one important concept has come from this study. Until this time, it had been difficult to assess what size of vessel one should aim to produce with any intervention. This study endorsed the concept that "bigger is better," in that the greater the final minimal lumen diameter, the lower the restenosis. This concept has now been adopted with the advent of stent technology (see page 164).

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1993

The Canadian and Turkish governments are headed  
by women for the first time;  
A Turner landscape is sold to the Getty museum  
for a record £11 million;  
and Rudolf Nureyev dies, aged 54

## Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study

Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Wong SC, Hong MK, Kovach JA, Leon MB

*Circulation.* 1996;94:35-43

The emerging viewpoint over recent years has been that human angioplasty restenosis is attributable to a number of processes, specifically, neointima formation, subacute recoil, and geometric remodeling.

While suppression of neointima formation has been addressed by numerous animal models, and found to be a poor predictor of clinical efficacy of therapeutics, the role of arterial remodeling has not been studied in depth. In fact, it was not until animal models used angioplasty of diseased arteries that arterial remodeling became apparent. Arterial remodeling is defined as a change in overall arterial size, as measured from the internal or external elastic lamina, without necessarily a change in arterial lumen size. It has been known for many years that an artery can expand to accommodate increasing amounts of atherosclerotic intima. However, equally important is the concept that constrictive remodeling of an artery can reduce lumen size with no change in neointima. While this concept has been proven in animal arteries after angioplasty, the study by Mintz et al was the first demonstration that remodeling is the predominant reason that human arteries restenose.

Mintz et al used intravascular ultrasound to measure lumen size, and the proportion of the vessel area occupied by plaque + media (P+M). In addition, they measured the area of the vessel circumscribed by the external elastic lamina. Thus, changes in P+M (or tissue mass) could be discriminated from changes in overall vessel size without changes in mass. These measurements were made prior to angioplasty, immediately after angioplasty, and at an average interval of 6 months after angioplasty. In addition, other forms of vessel manipulation were studied including directional coronary atherectomy, rotational atherectomy, or excimer laser angioplasty.

The results of this study are highly illuminating. The authors found that whatever the nature of the initial procedure, 75% of the restenosis (lumen narrowing) was due to a decrease in the total cross-sectional area of the vessel, ie, due to constrictive remodeling. Only 25% of restenosis could be attributed to neointima formation.

In fact, there was no difference between the amount of neointima found in the vessels that restenosed compared with those that did not. There was a correlation between increasing neointima and lumen loss, but the degree of correlation was far less than that between the reduction in vessel cross-sectional area and lumen loss. Interestingly, there was also a correlation between increase in neointima and increase in vessel cross-sectional area, confirming observations that vessels compensate for atherosclerosis by expanding. When the authors examined the role of remodeling in each of the separate interventions, remodeling accounted for most of the restenosis if the procedure was angioplasty, rotablation, atherectomy, or excimer laser.

This study represents a huge increase in our understanding of restenosis. It may explain why therapies aimed at blocking neointima formation have consistently failed to inhibit restenosis. The study thus provides the rational basis for testing drugs which promote favorable remodeling of arteries. It may also explain why stenting, which is not associated with chronic recoil, does inhibit restenosis, despite the almost universal presence of neointima in stents. Furthermore, it suggests that the range of arterial responses to injury is very limited. We are dealing with a small number of biological processes involved in restenosis, which are similar irrespective of how the artery is injured. This underscores the clinical finding that predictors of restenosis relate more to the vessel characteristics at the time of the procedure than to the nature of the procedure itself.

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1996

The statue of Liberty celebrates its 110th birthday;  
China agrees to lend San Diego Zoo  
two giant pandas for 12 years;  
and Claudette Colbert dies, aged 90



## A comparison of balloon-expandable–stent implantation with balloon angioplasty in patients with coronary artery disease

Serruys PW, de Jaegere P, Kiemeneij F, et al, for the BENESTENT Study Group

*N Engl J Med.* 1994;331:489-495

As the STRESS trial (see page 164) was being conducted, an almost identical European trial was also recruiting, and the results of both STRESS and BENESTENT were published back to back in the *New England Journal of Medicine*. This is appropriate, since the overall message from both is identical: that elective stenting improves clinical and angiographic outcomes versus conventional angioplasty, but at a cost of increased vascular complications. However, there are some very interesting findings to be made in the comparison of the two trials.

BENESTENT recruited 520 patients with stable angina and single-vessel disease, and randomly assigned them to elective stent implantation or balloon angioplasty. Small numbers of patients (approximately 5%) crossed over from each treatment, primarily due to failure to cross the lesion with a stent, or dissection following angioplasty. Angiographic and procedural success rates were similar. The primary clinical end points were death, cerebrovascular accident, myocardial infarction, and need for subsequent revascularization (by coronary artery bypass graft or percutaneously). As in STRESS, quantitative angiography was used to assess minimal lumen diameter (MLD) at follow-up at 7 months. No difference was found in the clinical events between the two groups in hospital, with small numbers of patients suffering myocardial infarctions or requiring revascularization. Stent thrombosis and vessel closure after angioplasty were also similar. However, as in STRESS, stent implantation was associated with a higher risk of bleeding or vascular complications, predominantly groin hematomas or pseudoaneurysms). At 7 months, clinical events were significantly lower in the stented group, due again to a reduction in revascularization of the target vessel. Furthermore, MLD at follow-up was significantly reduced by stenting compared with conventional angioplasty, with a significant reduction in restenosis (defined as >50% stenosis) in the stented patients.

Comparison with STRESS reveals some interesting results. Although lesion characteristics were similar in both trials (>15 mm in length, in a vessel that was at least 3 mm in diameter), lesions were significantly severer in the STRESS

trial (75% vs 64% stenosis). Despite this, US operators achieved significantly greater lumen diameters compared with European operators, although, paradoxically, the percentage stenosis actually calculated after the procedure is similar for both angioplasty and stenting in both studies. In both studies, stenting achieved a far greater MLD after the procedure compared with angioplasty, which, despite an increased late loss in the stented group, still produced a larger vessel overall following stenting.

BENESTENT and STRESS thus lay the foundations for the modern practice of elective stenting. However, both trials offset the clinical reduction in end points (from approximately 30% to 20% with stents) against a longer hospital stay, and a higher incidence of bleeding and vascular complications in the stented group. The bleeding complications are due to the aggressive anticoagulation regimens in stented patients, with both heparin and warfarin after the procedure, with the latter continuing for 3 months. This predictable increase in complications after stenting can be reduced by minimal anticoagulation, and many units now anticoagulate their patients with a similar regimen to that used for angioplasty (heparin during the procedure and aspirin thereafter). This policy has reduced vascular complications, with no significant reduction in the efficacy of stents to prevent restenosis. A word of caution is still necessary, however. Restenosis after angioplasty can be successfully treated with further angioplasty, accepting an approximately 30% restenosis risk of the second procedure. Although the initial rate of restenosis is lower after stenting, we are creating a disease (stent stenosis) with a high subsequent restenosis rate (>50%), and also making surgical access for bypass grafting difficult. Thus, the incidence of restenosis is lower after stents, but the ones that do restenose are harder to deal with.

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1994

The Blackpool Tower is 100;  
 “Schindler’s List” wins 7 Oscars; and Marcel Bich,  
 inventor of the Bic ballpoint pen dies, aged 79