In-stent restenosis

Flavio Ribichini

Department of Cardiology and Cardiovascular Surgery, S. Croce e Carle Hospital, Cuneo, Italy

Key words:
Coronary angioplasty; Restenosis; Stent.

Even after optimal immediate results, restenosis still occurs in a relevant percentage of patients after stent implantation. This disappointing outcome has strong clinical and socio-economical implications and has become a major target of research in cardiology.

The conceptual difference between the mere resolution of the restenotic lesion and the understanding of the mechanisms of restenosis creates a dichotomy between daily practice in the catheterization laboratory and questions raised in the research laboratory that commonly divides people (clinicians and researchers) and budgets (industries and academic institutions). As a consequence, efforts are aimed at treating the consequences of unsuccessful stenting on the one hand, and to understand the causes of excessive neointimal proliferation on the other. However, the commitment of researchers and the large clinical experience accumulated in these years are by-products of the symbiosis between manufacturers and scientists, and it seems as though the fight against restenosis is about to be won with the further setting-up of adequate means that act effectively on the target, even though it has not been clearly understood or identified. Such a pragmatic position, although possibly effective, should remind us that the ancient peoples used natural medicines to cure diseases that they never understood.

(Ital Heart J 2001; 2 (10): 728-735)

Received March 19, 2001; revision received August 9, 2001; accepted August 31, 2001.

Address:

Dr. Flavio Ribichini

Laboratorio di Emodinamica Divisione di Cardiologia Ospedale S. Croce e Carle Via M. Coppino, 26 12100 Cuneo E-mail: flavio_ribichini@hotmail.com

Introduction

The mission of cardiologists and of researchers in the field is to improve survival and the quality of life of the population by reducing the burden of cardiovascular diseases. Stented angioplasty is seen as one of the major advances in cardiovascular medicine during the past 25 years[1]. However, progress is often associated with the creation of new problems that emerge as a consequence of the medical intervention itself. This is the case of in-stent restenosis, a new presentation of coronary artery disease that appears in a subgroup of patients undergoing the intracoronary implantation of a metallic stent.

Restenosis after stent implantation still represents a major clinical and socio-economical problem. While in the majority of cases, we can entertain the dream of defeating coronary artery blockage by a simple, semi-invasive procedure performed during a 24-hour hospital admission, the occurrence of later in-stent restenosis represents a painful return to reality. The quantitative dimension of the problem is readily understandable if one takes a look at the number of percutaneous coronary interventions (PCI) performed worldwide. In 1999 more than 1 million people were treated with PCI and over 70% received an average of 1.7 stents, each of which costs on average $1000. A restenosis rate of 30% would generate 357 000 cases of in-stent restenosis; even if the restenosis rate were only 20%, 238 000 cases would still emerge[2-4].

Research efforts aimed at fighting restenosis have been relentless, both on clinical cardiologists and basic scientists' part. In fact, PCI has rekindled a growing interest in the field of vascular biology as common practice now allows us to have access to "human material" that was not accessible before. However, the phenomenon of restenosis soon appeared to be more complex than was initially suspected. In hindsight, these two research paths seem to have been running towards a common goal but via different routes. Basic scientists have dissected the pathophysiological mechanisms that embrace the interfaces lying between the blood and the adventitia; clinicians on the other hand have responded by "pushing" the mechanics of "luminology" to its limit whilst neglecting the role of the arterial wall to the boundaries of safety[5].

Funding for research in interventional cardiology is frequently provided by industries with a vested interest in leading medical care. Often, research is aimed at direct-

ly improving the clinical outcome, which at the same time is financially profitable. The extraordinary advances achieved in cardiology are in part the result of this symbiosis: the use of PCI as a means of myocardial revascularization is one of the most effective medical interventions developed and performed in the last 25 years[1,6]. However, restenosis after PCI appeared at the same time and efforts to understand its mechanisms became an important subject for study in cardiology. Research has allowed the identification of some variables associated with an increased propensity for restenosis, the description of the pathologic changes and repair mechanisms that follow vessel injury and the development of new drugs and devices in the search for the restenosis-free stent.

The battle against restenosis: much effort, few results

For more than two decades, nearly all possible drugs have been tested in combination with balloon angioplasty in the hope of reducing the restenosis rates. Unfortunately little success has been achieved. The availability of coronary stents has enhanced the initial safety of PCI which has translated into long-term benefit over conventional balloon angioplasty and other kinds of alternative devices. Coronary stents reduced recurrences by preventing the constrictive remodeling of the vessel. The coronary lumen remains widely patent despite an increased stimulus for neointimal formation within the stent[7,8]. When in-stent restenosis nevertheless occurs, its mechanism is one of excessive neointimal proliferation, which is relatively "simple" compared to the complex processes involved with restenosis after balloon injury. When coronary stents were first used, the relative contribution of vessel remodeling versus proliferation to the restenosis process was not known. Pioneers such as Dr. Sigwart had already envisaged that this scaffolding device could reduce acute complications and at the same time prevent restenosis, as testified by the title of the princeps publication in 1987: "Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty"[9].

Searching for the words "angioplasty" and "restenosis" in the Medline with the Service of the National Library of Medicine discloses 4265 articles published since 1980. Despite these immense efforts, for more than 20 years it seemed that nothing would help. Some even argued that we "aimed at the wrong target"[10]. However with the advent of vascular brachytherapy and the use of locally delivered drugs, it now seems that the "restenosis-free" PCI is on the horizon.

The main achievements and milestones of these years of research will be reviewed, while the interested reader will find detailed information on specific issues in the reference list. Obviously, this article may reflect some biases, as opinions may differ according to personal experience and conviction and areas of interest.

Step I. The study of the role of conventional risk factors and coronary stenosis morphology. The long-term outcome after PCI was shown to depend loosely on a number of clinical and angiographic variables that were identified in the early years of interventional cardiology. Interestingly, with the exception of diabetes, none of the conventional risk factors for coronary artery disease has been clearly associated with recurrence after PCI[11-13]. This suggests that restenosis is not "functionally" linked to atherosclerotic coronary disease, but rather results from a non-specific healing response to the unavoidable vessel injury that is induced when the lumen is being enlarged at the expense of the wall.

Another key step was the recognition that recurrences often followed procedures that were suboptimal in the first place ("pseudo-restenosis"). Accordingly, the "bigger is better" paradigm[14] was endorsed. Although the mechanisms by which restenosis developed (or did not develop) remained largely unknown, this pragmatic approach resulted in a significant improvement in clinical outcome, particularly with the availability of stents which are the most effective and safest devices by means of which the coronary lumen diameter can be maximized.

Step II. Improving the results of stented angioplasty and living with in-stent restenosis. The available data regarding the potential for stents to reduce clinical recurrence after the publication of the STRESS and BENESTENT trials can hardly justify the "chain reaction" that followed which resulted in an explosive increase in the use of stents[15-17]. The use of stents was soon extended to clinical and angiographic settings that overstepped the available evidence of their usefulness. With the current antiplatelet regimen, there is no doubt that stented angioplasty is remarkably safe, the rate of complications is extremely low and the initial stability of the angiographic outcome is greatly improved compared to other modalities. However, the long-term outcome is often less satisfactory than the nice immediate angiographic result.

Stents offer no clear benefit in specific but common lesion subsets such as smaller or larger vessels, bifurcation branches and long lesions[18-23]. Indeed, in long lesions the rate of restenosis after stenting is higher the longer the stented segment. However, despite a similar clinical outcome, stents have shown better angiographic results compared to balloon angioplasty as recently demonstrated in a yet unpublished trial[24]. Moreover, stented angioplasty was not proven superior to balloon dilation in patients achieving a "stent-like" angiographic result with balloons only in the WIDEST study[25] although elective stent implantation after the achievement of an optimal result by means of balloon

angioplasty may further improve the clinical outcome of PCI as has been suggested by the DEBATE II investigators[26]. Lastly, in some patients, stent implantation induces, for unknown reasons, aggressive, diffuse and repeated recurrences [4,27,28]. In-stent restenosis presents a diffuse or proliferative angiographic pattern in nearly 50% of cases and, unlike restenosis after balloon angioplasty, in-stent restenosis has a dismal prognosis because the risk of repeated failure is high, no matter which method is used for re-dilation[4,27,28]. This unfortunate event tends to develop unexpectedly, despite the achievement of an optimal immediate result. Although the "bigger is better" dogma resisted in time, the use of high pressures for better balloon and stent expansion may cause deeper damage to the vessel wall which stimulates a more aggressive reparative proliferation[29]. A larger lumen can also be achieved by a debulking procedure prior to stent implantation at low expansion pressures[30] but the histopathologic response of the vessel wall to this approach has not been described and randomized clinical trials are still underway.

As a consequence, it becomes desirable to understand which patients are at a higher risk of developing in-stent restenosis and why. This implies the identification of those subjects more likely to develop a diffuse form of in-stent restenosis in whom other forms of revascularization therapy may be preferable[31]. The current practice of direct stenting, however, implies the exact opposite of such an approach. Initially, it was hoped that direct stenting might reduce the restenosis rates, which it did not. In fact, the clinical results of direct stenting refer mostly to non-complex lesions in which the use of stents is unlikely to offer results different from those observed following optimal balloon angioplasty or conventional stenting (i.e. after adequate balloon dilation) albeit with some marginal advantages in terms of a reduction in the procedural time, fluoroscopy, and use of contrast media[32,33]. The main consequence of direct stenting is the fact that one no longer attempts to obtain a satisfactory result by resorting to the plain old balloon angioplasty. Used indiscriminately, this strategy will put an even greater proportion of patients at a risk of developing in-stent restenosis, an entity that, unlike post-balloon restenosis, is perceived as a troublesome situation.

Step III. Anything new about the mechanisms causing in-stent restenosis? The mechanisms involved in the restenosis process, although multifactorial, may be conditioned by a smaller number of factors and pathophysiological interactions than atherosclerosis and therefore better lend themselves to understanding or eventually, an accurate prediction (Fig. 1). The most recent findings indicate that the inflammatory "foreign body" reaction plays a central role in the genesis of in-stent restenosis.

Inflammation. Growing evidence supports the concept that restenosis is mainly a non-specific inflammatory response to vessel wall damage, potentially enhanced by the sustained insult caused by the presence of a permanent metallic body[34-38]. The elevation of the serum markers of systemic inflammation, the presence of inflammatory cells in the plaque, and the proven role of local mediators in the processes of cell aggregation, migration and proliferation confirm this hypothesis. Inflammation directly follows the injury caused by the procedure, but may also be related to the stimulation, by injury, of latent infectious agents. The infectious theory was proposed years ago[49-51] and is now supported by some clinical findings[52-54].

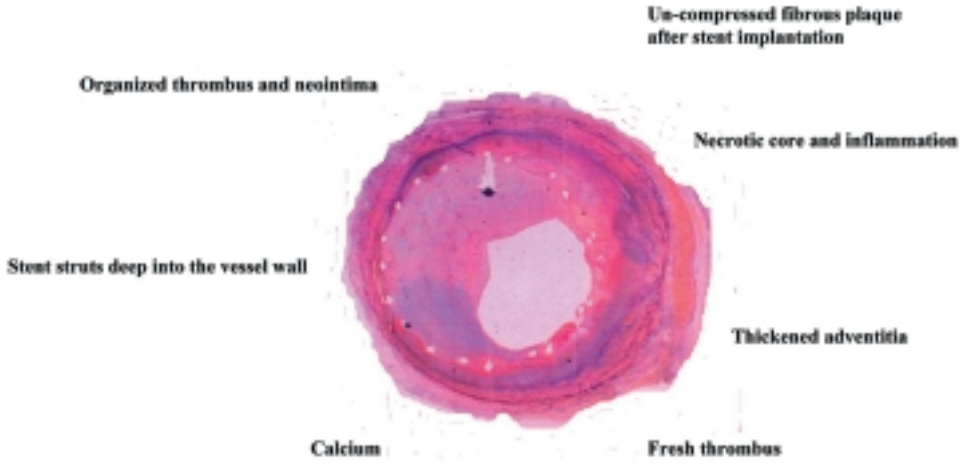

Figure 1. *In-stent restenosis as it really looks. Histologic image of a human coronary vessel stained with Movat pentachrome showing in-stent proliferation that causes a severe reduction of the vessel lumen. Unlike post-balloon restenosis, the chronic lumen reduction is the consequence of neointimal growth and thrombus organization following stent implantation and not of vessel wall shrinkage. The deeper the damage of the vessel wall, the thicker the proliferative reaction that starts from platelet aggregation and thrombus formation, release of growth factors and infiltration by inflammatory cells in the acute phase. In the chronic phase, there is cell migration and differentiation of proliferative cells; calcium deposits and necrotic cores add some more ingredients to the substratum of the interventionalist's vain efforts. Indeed, it seems likely that to avoid such a complex reaction may offer better prospects than trying to "treat" the consequences of in-stent proliferation depicted in the figure.*

Infection. Infection caused by pathogens may be almost completely latent in a host organism because both coexist in equilibrium; any alteration of this balance may facilitate the expression of the infectious agent. Atherosclerosis itself as well as restenosis have been proposed as possible examples of this phenomenon. In the first case, the microorganism slowly interacts with the host and eventually causes damage. In the second, an external factor (such as high blood pressure, free radical generation or mechanical wall injury) starts the process. In support of this theory, a recent randomized trial has shown that the non-selective use of roxithromycin in patients who received a coronary stent does not prevent restenosis, but is effective in those patients with evidence of a latent infection as suggested by elevated titers of the *Chlamydia pneumoniae* antibody[54]. Another important variable in this puzzle is the genetic environment where the whole process takes place[55]; indeed, the concept that the patient rather than lesion specific predisposition leads to restenosis is an emerging point of view[31,56].

Genetics. As with many other individual traits, the inflammatory reaction may not be equivalent in all subjects. Evidence for the interaction between the environment and the genes is of outstanding relevance and further supports the theory of the multifactorial etiology of coronary artery disease according to which a given factor may have a different weight in different subjects. The proliferative response of the vessel wall to mechanical injury differs in individuals who apparently share common baseline characteristics. This has stimulated the quest for those genetic markers which are indicative of an augmented risk for in-stent restenosis, which at the same time permits a rational approach to the selection of good candidates for PCI[22,31,57-59]. Results in this field are still controversial but markers of an enhanced activity of pathways potentially linked to restenosis have already given clinical support to some of the theoretical assumptions[60-68]. Indeed, biological mechanisms potentially involved in in-stent restenosis are under intensive investigation: platelet-mediated aggregation and coagulation systems, the nitric oxide synthase pathway, the renin-angiotensin system, the oxidative chain and NADH/NADPH oxidase polymorphism, the methylenetetrahydrofolate reductase gene, the haptoglobin phenotype, and, more recently, the target of rapamycin protein signaling[65,69-82]. Table I[65,67,68,73,76,81] summarizes the genes that have been published as markers of risk for the occurrence of in-stent restenosis.

New approaches to the treatment of in-stent restenosis

Until the ultimate goal of restenosis prevention is achieved, if ever this is possible in all patient/lesion subsets, two different approaches can be applied to the management of in-stent restenosis. The first is to treat the consequences of unsuccessful stenting, the second is to treat the cause of excessive neointimal proliferation. In a certain way, these two approaches also reflect the different viewpoints of the clinician on the one hand and the basic scientist on the other hand; the former is funded by practice, the latter builds on the understanding of vascular biology.

A better understanding of the genetic basis for cardiovascular diseases will allow to design "gene-guid-

Table I. Genetic polymorphisms proposed as markers of risk for in-stent restenosis.

Gene polymorphism	Mechanism	Alleles	Incidence (%)	ISR rate (%)	Population at risk
I/D polymorphism of the ACE gene[67,68]	Cell proliferation and vasoconstriction	D/D	35	28	Low risk patients
		I/D	45	18	
		I/I	20	10	
Platelet glycoprotein IIIa PlA1/A2[65]	Enhanced platelet aggregation and vascular thrombosis	A1/A1	72	38	Higher in women
		A1/A2	25	46	
		A2/A2	3	53	
Interleukin-1 receptor antagonist mutation[73]	Counteracts the pro-inflammatory effects of interleukin-1	1/1	52	36	Unselected
		1/2	40	30	
		2/2	8	29	
Haptoglobin phenotype[81]	Reduces Hb-mediated oxidative tissue damage	1/1	15	21	Diabetics
		1/2	44	31	
		2/2	41	36	
Polymorphism of the MTHFR gene[76]	Higher levels of homocysteine in 677 C-T subjects	C/C	31	10	Unselected
		C/T	42	14	
		T/T	29	29	

ACE = angiotensin-converting enzyme; Hb = hemoglobin, ISR = in-stent restenosis; MTHFR = methylenetetrahydrofolate reductase.

ed" treatment strategies in those patients in whom a certain genotype can be held responsible, at least in part, for a specific pathophysiological state. However, the value of a genetic marker associated with a certain phenotype may differ among different populations as a consequence of the evolutive interaction that exists between individuals and the environment. Furthermore, the degree of linkage with a given disease may change as well, and this likely accounts for the sometimes discordant reports about the predictive accuracy of genetic markers and disease prevalence.

A new observation is that the evaluation of a given genetic marker in a "current practice" population treated according to the "state of the art" care in 2001 has become an elusive goal. In fact, more and more patients are being treated routinely with drugs that have a strong impact on the process of in-stent restenosis, although such effects were not known until now; for example statins[83], ticlopidine[84], ACE-inhibitors[59] and glycoprotein IIb/IIIa inhibitors in diabetic patients[85]. These drugs may have the potential to blunt the effect of a single genetic factor in the mulifactorial process of in-stent restenosis.

All devices used to treat in-stent restenosis, including the implantation of a new stent within the restenotic one, have yielded poor results[86,87]. Indeed, stenting in-stent restenosis appears to be more of a provocation of vascular biology rather than a search for a solution through understanding *(errare humanum est perseverare diabolicum …)*. Neither does combining debulking by rotational atherectomy with balloon dilation help[88,89]. Directional atherectomy is also under study and the availability of more effective cutting devices and the combined use of stents have anticipated promising results[30]; such an approach will at least offer important information regarding the composition of the in-stent restenotic plaque until its clinical efficacy is determined.

So far, the only effective percutaneous treatment of in-stent restenosis requires the application of vascular brachytherapy, with either gamma or beta radiation, as substantiated by several clinical trials[90-92]. The limitations and potential long-term adverse effects are, however, still under study[93-95].

Interfering with the causes of restenosis requires the discovery of a "universal" antirestenotic drug or device able to work in every subject as a single cure for all situations. The development of glycoprotein IIb/IIIa receptor inhibitors was initially viewed with optimism. These antiplatelet agents have been shown to offer additional clinical benefit when used with coronary stents and initial trials suggested a favorable effect on symptom recurrence[96], in particular in diabetic patients[97]. Subsequent studies involving repeat angiographic examinations have practically excluded the antirestenotic effect of this type of drug[97-102].

Today's hopes are focused on the use of drug-eluting stents. In this context, the very preliminary results obtained with Placlitaxel and the rapamycin-coated stent are quite impressive. Placlitaxel (Taxol) is a microtubule-stabilizing compound with potent an antitumor activity exerted through changes in the cytoskeleton. It induces cellular structural modifications that cause reduced cell proliferation, migration and signal transduction. Preliminary results of Taxol-coated stent implantation on 14 patients have shown a 0% rate of new target vessel revascularization at 2 year follow-up[103]. As to the rapamycin-eluting stent, striking results from a consecutive series of 45 patients treated in Rotterdam or Sao Paolo, in whom no restenosis was observed so far have been published recently[104]. Rapamycin is a naturally occurring macrocyclic lactone produced by streptomyces hygroscopicus and, because of its inhibitory action on the cell cycle, is currently used in kidney transplant recipients to prevent rejection. These effects are exerted both through immunosuppressive and antiproliferative properties that give this intriguing molecule the potential to address the cause and the consequence of in-stent restenosis[105,106] by simultaneous multiple mechanisms of action[82,105-107].

If a universal antirestenotic effect can be confirmed, the molecule may be attributed a role in the conservation of life through a natural antibiotic protection against acquired "silent" infections, as indicated by its natural occurrence. Such a hypothesis would close the loop of an evolutionary point of view of the disease and underscores the pivotal role of infectious and/or inflammatory processes in the pathogenesis of in-stent restenosis and, eventually, of coronary artery disease.

References

1. Lefkowitz RF, Willerson JT. Prospects for cardiovascular research. JAMA 2001; 285: 581-7.
2. Topol EJ. Coronary artery stents - gauging, gorging, and gouging. N Engl J Med 1998; 339: 1702-4.
3. Goy JJ, Eeckhout E. Intracoronary stenting. Lancet 1998; 351: 1943-9.
4. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis. Classification and implications for long-term outcome. Circulation 1999; 100: 1872-8.
5. Haase K, Athanasiadis A, Mahrholdt H, et al. Acute and one-year follow-up results after vessel size adapted PTCA using intracoronary ultrasound. Eur Heart J 1998; 19: 263-72.
6. Callahan D. La medicina impossibile. Milano: Baldini e Castoldi Editori, 2000.
7. Mintz GS, Popma JJ, Pichard A, et al. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. Circulation 1996; 94: 35-43.
8. Hoffmann R, Mintz GS, Dussaillant GR, et al. Patterns and mechanism of in-stent restenosis. A serial intravascular ultrasound study. Circulation 1996; 94: 1247-54.
9. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med 1987; 316: 701-6.
10. Currier JW, Faxon DP. Restenosis after percutaneous transluminal coronary angioplasty: have we been aiming at the wrong target? J Am Coll Cardiol 1995; 25: 516-20.

11. Holmes DR Jr, Vietstra RE, Smith HC, et al. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA Registry of the National Heart, Lung, and Blood Institute. Am J Cardiol 1984; 53: 77C-81C.
12. DeFeyter PJ, Suryapranata H, Serruys PW, et al. Coronary angioplasty for unstable angina: immediate and late results in 200 consecutive patients with identification of risk factors for unfavorable early and late outcome. J Am Coll Cardiol 1988; 12: 324-33.
13. Ellis SG, Vandormael MG, Cowley MJ, et al. Coronary morphologic and clinical determinations of procedural outcome with multivessel coronary artery disease: implications for patient selection. Circulation 1990; 82: 1193-202.
14. Kuntz RE, Gibson CM, Nobuyoshi M, Baim DS. A generalized model of restenosis following conventional balloon angioplasty, stenting and directional atherectomy. J Am Coll Cardiol 1993; 21: 115-25.
15. Serruys PW, de Jaegere P, Kiemeneij F, et al, for the BENESTENT Study Group. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994; 331: 489-95.
16. Fischman DL, Leon MB, Baim D, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med 1994; 331: 496-501.
17. Rodriguez A, Ambrose JA. Do we require a cure for "stent-mania"? J Am Coll Cardiol 1996; 28: 827-9.
18. Waksman R, Mehran R, Saucedo JF, et al. Balloon PTCA is equivalent to stent in patients with small coronaries; a comparative retrospective matching study. (abstr) J Am Coll Cardiol 1998; 31: 275A.
19. Moussa I, Moses J, Wang X, et al. Does "the bigger the better" hypothesis after coronary stenting apply in small vessels? (abstr) J Am Coll Cardiol 1998; 31: 141A.
20. Di Mario C, Colombo A. Trousers-stents: how to choose the right size and shape? Cathet Cardiovasc Diagn 1997; 41: 197-9.
21. Kobayashi Y, DeGregorio J, Reimers B, et al. The length of the stented segment is an independent predictor of restenosis. (abstr) J Am Coll Cardiol 1998; 31: 366A.
22. Narins CR, Holmes DR, Topol EJ. A call for provisional stenting. The balloon is back! Circulation 1998; 97: 1298-305.
23. Serruys PW, Di Mario C, Piek J, et al. Prognostic value of intracoronary flow velocity and diameter stenosis in assessing the short- and long-term outcomes of coronary balloon angioplasty. The DEBATE Study. Circulation 1997; 96: 3369-77.
24. Serruys PW. The ADVANCE trial. In: Ferguson JJ, ed. Highlights of the 22nd Congress of the European Society of Cardiology. Circulation 2001; 103: E41-E45.
25. Fluck DS, Chenu P, Mills P, et al. Is provisional stenting the effective option? The WIDEST study (Wiktor stent in de novo stenosis). WIDEST Trial Investigators' Group. Heart 2000; 84: 522-8.
26. Serruys PW, de Bruyne B, Carlier S, et al. Randomized comparison of primary stenting and provisional balloon angioplasty guided by flow velocity measurement. Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) II Study Group. Circulation 2000; 102: 2930-7.
27. Reimers B, Moussa I, Akiyama T, et al. Long-term clinical follow-up after successful repeat percutaneous intervention for stent restenosis. J Am Coll Cardiol 1997; 30: 186-92.
28. Bauters C, Banos JL, Van Belle E, et al. Six-month angiographic outcome after successful repeat percutaneous intervention for in-stent restenosis. Circulation 1998; 97: 318-21.
29. Farb A, Sangiorgi G, Carter AJ, et al. Pathology of acute and chronic coronary stenting in humans. Circulation 1999; 99: 44-52.
30. Hopp HW, Baer FM, Ozbek C, et al, for the AtheroLink Study Group. A synergistic approach to optimal stenting. Directional coronary atherectomy prior to coronary artery stent implantation. The AtheroLink Registry. J Am Coll Cardiol 2000; 36: 1853-9.
31. Ribichini F, Wijns W. Genetic predictors of in-stent restenosis. Remedica Publishing 1999; 2: 8-15.
32. Taylor AJ, Broughton A, Federman J, et al. Efficacy of direct stenting in coronary angioplasty. J Invasive Cardiol 2000; 11: 560-5.
33. Briguori C, Sheiban I, De Gregorio J, et al. Direct stenting without predilation. J Am Coll Cardiol 1999; 34: 1910-5.
34. Ross R. Atherosclerosis. An inflammatory disease. N Engl J Med 1999; 340: 115-26.
35. Moreno PR, Falk E, Palacios I, et al. Macrophage infiltration in acute coronary syndromes. Circulation 1994; 90: 775-8.
36. Moreno PR, Bernardi VH, Lopez-Cuellar J, et al. Macrophage infiltration predicts restenosis after coronary intervention in patients with unstable angina. Circulation 1996; 94: 3098-102.
37. Pietersma A, Kofflard M, de Wit LE, et al. Late lumen loss after coronary angioplasty is associated with the activation status of circulating phagocytes before treatment. Circulation 1995; 91: 1320-5.
38. Piek JJ, van der Wal A, Meuwissen M, et al. Plaque inflammation in restenotic coronary lesions of patients with stable or unstable angina. J Am Coll Cardiol 2000; 35: 963-7.
39. Moreno PR, Palacios IF, Leon MN, et al. Histopathologic comparison of human coronary in-stent and post-balloon angioplasty restenotic tissue. Am J Cardiol 1999; 84: 462-6.
40. Sangiorgi G, Taylor AJ, Farb A, et al. Histopathology of postpercutaneous transluminal coronary angioplasty remodeling in human coronary arteries. Am Heart J 1999; 138: 681-7.
41. Komatsu R, Ueda M, Naruko T, Kojima A, Becker AE. Neointimal tissue response at sites of coronary stenting in humans. Circulation 1998; 98: 224-33.
42. Ohishi M, Ueda M, Rakugi H, et al. Upregulation of angiotensin-converting enzyme during the healing process after injury at the site of percutaneous transluminal coronary angioplasty in humans. Circulation 1997; 96: 3328-37.
43. Okamura A, Rakugi H, Ohishi M, et al. Upregulation of the renin-angiotensin system during differentiation of monocytes to macrophages. J Hypertens 1999; 17: 537-45.
44. Liuzzo G, Buffon A, Biasucci LM, et al. Enhanced inflammatory response to coronary angioplasty in patients with severe unstable angina. Circulation 1998; 98: 2370-6.
45. Gaspardone A, Crea F, Versaci F, et al. Predictive value of C-reactive protein after successful coronary artery stenting in patients with stable angina. Am J Cardiol 1998; 82: 515-8.
46. Buffon A, Liuzzo G, Biasucci LM, et al. Preprocedural serum levels of C-reactive protein predict early complications and late restenosis after coronary angioplasty. J Am Coll Cardiol 1999; 34: 1512-21.
47. Biasucci LM, Liuzzo G, Buffon A, Maseri A. The variable role of inflammation in acute coronary syndromes and in restenosis. Semin Interv Cardiol 1999; 4: 105-10.
48. Ribichini F, Pugno F, Ferrero V, et al. Angiotensin-converting enzyme tissue activity in the diffuse in-stent restenotic plaque. Circulation 2000; 101: E33-E35.
49. Saikku P, Leinonen M, Mattila K, et al. Serological evidence of an association of a novel Chlamydia, TWAR, with chronic coronary heart disease and acute myocardial infarction. Lancet 1988; 2: 983-6.

50. Zhou YF, Leon MB, Waclawiw MA, et al. Association between prior cytomegalovirus infection and the risk of restenosis after coronary atherectomy. N Engl J Med 1996; 335: 624-30.
51. Danesh J, Collins R, Peto R. Chronic infections and coronary heart disease: is there a link? Lancet 1997; 350: 430-6.
52. Danesh J, Wong Y, Ward M, Muir J. Chronic infection with Helicobacter pylori, Chlamydia pneumoniae, or cytomegalovirus: population based study of coronary heart disease. Heart 1999; 81: 245-7.
53. Gurfinkel E, Bozovich G, Daroca A, Beck E, Mautner B. Randomised trial of roxithromycin in non-Q wave coronary syndromes: ROXIS pilot study. ROXIS Study Group. Lancet 1997; 350: 404-7.
54. Neumann FJ, Kastrati A, Miethke T, et al. Treatment of Chlamydia pneumoniae infection with roxithromycin and effect on neointima proliferation after coronary stent placement (ISAR-3): a randomised, double-blind placebo-controlled trial. Lancet 2001; 357: 2085-9.
55. Task Force Report. Prevention of coronary artery disease in clinical practice. Eur Heart J 1998; 19: 1434-503.
56. Cho L, Ellis SG, Chew DP, Topol EJ, Penn MS. Patient rather than lesion specific predisposition for restenosis. (abstr) J Am Coll Cardiol 2001; 37: 38A.
57. Ribichini F. Controversies in coronary stenting: conditional stenting is the way to go. G Ital Cardiol 1999; 29: 495-504.
58. Ribichini F. The BetAceStent Trial. In: Ferguson JJ, ed. Highlights of the 22nd Congress of the European Society of Cardiology. Circulation 2001; 103: E43-E45.
59. Meurice T, Bauters C, Hermant X, et al. Effect of ACE inhibitors on angiographic restenosis after coronary stenting (PARIS): a randomised, double-blind, placebo-controlled trial. Lancet 2001; 357: 1321-4.
60. van Bockxmeer FM, Mamotte CDS, Gibbons FA, Burke V, Taylor RR. Angiotensin-converting enzyme and apolipoprotein E genotypes and restenosis after coronary angioplasty. Circulation 1995; 92: 2066-71.
61. Weiss EJ, Bray PF, Tayback M, et al. A polymorphism of a platelet glycoprotein receptor as an inherited risk factor for coronary thrombosis. N Engl J Med 1996; 334: 1090-4.
62. Neumann FJ, Gawaz M, Ott I, May A, Mossmer G, Schomig A. Prospective evaluation of hemostatic predictors of subacute stent thrombosis after coronary Palmaz-Schatz stenting. J Am Coll Cardiol 1996; 27: 15-21.
63. Abbate R, Marcucci R, Camacho-Venegas O, et al. Role of platelet glycoprotein PlA1/A2 polymorphism in restenosis after percutaneous transluminal coronary angioplasty. Am J Cardiol 1998; 82: 524-5.
64. Mamotte C, van Bockxmeer FM, Taylor RR. PlA1/A2 polymorphism of glycoprotein IIIa and risk of coronary artery disease and restenosis following coronary angioplasty. Am J Cardiol 1998; 82: 13-6.
65. Kastrati A, Schomig A, Seyfarth M, et al. PlA polymorphism of platelet glycoprotein IIIa and risk of restenosis after coronary stent placement. Circulation 1999; 99: 1005-10.
66. Hamon M, Amant C, Bauters C, et al. Dual determination of angiotensin-converting enzyme and angiotensin-II type 1 receptor genotypes as predictors of restenosis after coronary angioplasty. Am J Cardiol 1998; 81: 79-81.
67. Amant C, Bauters C, Bodart JC, et al. D allele of the angiotensin I-converting enzyme is a major risk factor for restenosis after coronary stenting. Circulation 1997; 96: 56-60.
68. Ribichini F, Steffenino G, Dellavalle A, et al. Plasma activity and insertion/deletion polymorphism of angiotensin I-converting enzyme. A major risk factor and a marker of risk for coronary stent restenosis. Circulation 1998; 97: 147-54.
69. Behague I, Poirier O, Nicaud V, et al. β-fibrinogen gene polymorphisms are associated with plasma fibrinogen and coronary artery disease in patients with myocardial infarction. Circulation 1996; 93: 440-9.
70. Carter AM, Ossei-Gerning N, Wilson IJ, Grant PJ. Association of the platelet Pl(A) polymorphism of the glycoprotein IIb/IIIa and the fibrinogen Bβ 448 polymorphism with myocardial infarction and extent of coronary artery disease. Circulation 1997; 96: 1424-31.
71. Moncada S, Palmer RM, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol Rev 1991; 43: 109-42.
72. Nathan C, Xie QW. Nitric oxide synthases: roles, tolls, and controls. Cell 1994; 78: 915-8.
73. Kastrati A, Koch W, Berger PB, et al. Protective role against restenosis from an interleukin-1 receptor antagonist gene polymorphism in patients treated with coronary stenting. J Am Coll Cardiol 2000; 36: 2168-73.
74. von der Leyen HE, Gibbons GH, Morishita R, et al. Gene therapy inhibiting neointimal vascular lesions: in vivo transfer of endothelial cell nitric oxide synthase gene. Proc Natl Acad Sci USA 1995; 92: 1137-41.
75. Janssens S, Flaherty D, Nong Z, et al. Human endothelial nitric oxide synthase gene transfer inhibits vascular smooth muscle cell proliferation and neointima formation after balloon injury in rats. Circulation 1998; 97: 1274-81.
76. Kosokabe T, Okumura K, Sone T, et al. Relation of a common methylenetetrahydrofolate reductase mutation and plasma homocysteine with intimal hyperplasia after coronary stenting. Circulation 2001; 103: 2048-54.
77. Yamasaki M, Kazuhiro H, Ikari Y, et al. Effects of cilostazol on late lumen loss after Palmaz-Schatz stent implantation. Cathet Cardiovasc Diagn 1998; 44: 387-91.
78. Cote G, Tardif JC, Lesperance J, et al. Effects of probucol on vascular remodeling after coronary angioplasty. Circulation 1999; 99: 30-5.
79. Sekiya M, Funada J, Watanabe K, Miyagawa M, Akutsu H. Effects of probucol and cilostazol alone and in combination on frequency of poststenting restenosis. Am J Cardiol 1998; 82: 144-7.
80. Schachinger V, Britten MB, Dimmeler S, Zeiher AM. NADH/NADPH oxidase p22 phox gene polymorphism is associated with improved coronary endothelial vasodilator function. Eur Heart J 2001; 22: 96-101.
81. Roguin A, Hochberg I, Nikolsky E, et al. Haptoglobin phenotype as a predictor of restenosis after percutaneous transluminal coronary angioplasty. Am J Cardiol 2001; 87: 330-2.
82. Chan TF, Carvalho J, Riles L, Zheng FS. A chemical genomics approach toward understanding the global functions of the target of rapamycin protein (TOR). Proc Natl Acad Sci USA 2000; 97: 13227-32.
83. Walter DH, Schachinger V, Elsner M, et al. Statin therapy is associated with reduced restenosis rates after coronary stent implantation in carriers of the Pl(A2) allele of the platelet glycoprotein IIIa gene. Eur Heart J 2001; 22: 587-95.
84. Steinhubl SR, Ellis SG, Wolski K, Lincoff AM, Topol EJ. Ticlopidine pretreatment before coronary stenting is associated with sustained decrease in adverse cardiac events: data from the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial. Circulation 2001; 103: 1403-9.
85. Marso SP, Lincoff MA, Ellis SG, et al. Optimizing the percutaneous interventional outcomes for patients with diabetes mellitus: results of the EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting trial) diabetic substudy. Circulation 1999; 100: 2466-8.
86. Mintz GS, Barghava B, Merhan R, et al. Does "stent-on-stent" for in-stent restenosis exaggerate intimal hyperpla-

sia? A volumetric intravascular ultrasound analysis. (abstr) J Am Coll Cardiol 2000; 35: 84A.
87. Lefevre T, Benslimane A, Premchand RK, et al. Treatment of in-stent restenosis. Shall we balloon or stent the stent? A prospective single center randomized study. (abstr) J Am Coll Cardiol 2000; 35: 85A.
88. Di Mario C, Marsico F, Adamian E, et al. New recipes for in-stent restenosis: cut, grate, roast, or sandwich the neointima? Heart 2000; 84: 471-5.
89. von Dahl J, Dietz U, Silber S, et al. Angioplasty versus rotational atherectomy for treatment of diffuse in-stent restenosis: clinical and angiographic results from a randomized multicenter trial (ARTIST study). (abstr) J Am Coll Cardiol 2000; 35: 7A.
90. Teirstein PS, Massullo V, Jani S, et al. Catheter-based radiotherapy to inhibit restenosis after coronary stenting. N Engl J Med 1997; 336: 1697-703.
91. Waksman R, White RL, Chan RC, et al. Intracoronary gamma-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis. Circulation 2000; 101: 2165-71.
92. Leon MB, Teirstein PS, Moses JW, et al. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. N Engl J Med 2001; 344: 250-6.
93. Waksman R, Bhargava B, Mintz GS, et al. Late total occlusion after intracoronary brachytherapy for patients with in-stent restenosis. J Am Coll Cardiol 2000; 36: 65-8.
94. Costa MA, Sabaté M, Giessen WJ, et al. Late coronary occlusion after intracoronary brachytherapy. Circulation 1999; 100: 789-92.
95. Waksman R. Late thrombosis after radiation. Sitting on a time bomb. Circulation 1999; 100: 780-2.
96. The EPIC Investigation. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994; 330: 956-61.
97. The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Lancet 1998; 352: 87-92.
98. The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. Lancet 1997; 349: 1429-35.
99. Kong DF, Califf RM, Miller DP, et al. Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. Circulation 1998; 98: 2829-35.
100. Topol E, Mark DB, Lincoff AM, et al. Outcomes at 1 year and economic implications of platelet glycoprotein IIb/IIIa blockade in patients undergoing coronary stenting: results from a multicentre randomised trial. Lancet 1999; 354: 2019-24.
101. Bhatt DL, Marso SP, Lincoff A, et al. Abciximab reduces mortality in diabetics following percutaneous coronary interventions. J Am Coll Cardiol 2000; 35: 922-8.
102. The ERASER Investigators. Acute platelet inhibition with abciximab does not reduce in-stent restenosis (ERASER study). Circulation 1999; 100: 799-806.
103. Grube E, Gerckens U, Rowold S, et al. Inhibition of in-stent restenosis by the Quanam drug eluting polymer stent. Two-year follow-up. (abstr) J Am Coll Cardiol 2001; 37: 74A.
104. Sousa JE, Costa MA, Abizaid A, et al. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries. A quantitative coronary angiography and three-dimensional intravascular ultrasound study. Circulation 2001; 103: 192-5.
105. Ikonen TS, Gummert JF, Serkova N, et al. Efficacies of sirolimus (rapamycin) and cyclosporine in allograft vascular disease in non-human primates: trough levels of sirolimus correlate with inhibition of progression of arterial intimal thickening. Transpl Int 2000; 13 (Suppl 1): S314-S320.
106. Saunders RN, Metcalfe MS, Nicholson ML. Rapamycin in transplantation: a review of the evidence. Kidney Int 2001; 59: 3-16.
107. Shamji AF, Kuruvilla FG, Schreiber SL. Partitioning the transcriptional program induced by rapamycin among the effectors of the TOR proteins. Curr Biol 2000; 10: 1574-81.