

MINIREVIEW SERIES FOR THE 50TH VOLUME

Percutaneous coronary intervention: current perspective

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(Received for publication on May 30, 2001)

Abstract. More than 20 years have passed since percutaneous transluminal coronary angioplasty (PTCA) was introduced for the treatment of coronary artery disease. During the first decade, PTCA outcome had improved significantly. However, acute occlusive complications and restenosis remained as significant limitations of the procedure. During the second decade, new procedures, such as stents and atherectomy (directional coronary atherectomy, and Rotablator) had been introduced and had a significant impact on the outcome of percutaneous coronary intervention (PCI). In addition to the improvements in the equipment, the use of glycoprotein IIb/IIIa inhibitors to prevent platelet aggregation has reduced procedure-related complications. PCI continues to evolve with new developments such as distal protection devices to prevent distal embolism, brachytherapy and drug-eluting stents to prevent restenosis. These new technologies may play a significant role in expanding the applications of PCI in the future. (Keio J Med 50 (3): 152–160, September 2001)

Key words: PTCA (percutaneous transluminal coronary angioplasty), PCI (percutaneous coronary intervention), stent, atherectomy, restenosis

Introduction

Percutaneous Transluminal Coronary Angioplasty (PTCA), first attempted in humans for the treatment of coronary artery disease more than 20 years ago, has evolved significantly over these past two decades. The term percutaneous coronary intervention (PCI) became more appropriate than PTCA because of the use of various non-balloon devices and this is now the most frequently performed procedure for the treatment of coronary artery disease (CAD). This article summarizes the evolution of PCI: the past, present and future.

PTCA in the First Decade

The first PTCA using an inflatable balloon for the treatment of CAD was attempted by Andreas Gruentzig in 1977. He subsequently published the summary of his early experiences in the *New England Journal of Medicine*.¹ Initially he faced many criticisms that this procedure was too dangerous and unpredictable. How-

ever, within a couple of years, the procedure had spread worldwide and revolutionized the treatment of CAD. During the first several years of PTCA, procedural outcome improved significantly. This occurred with the enhancement of technical skills and increased knowledge of operators, as well as significant improvements in the equipment used for PTCA (Fig. 1). These improvements in equipment included better torque and support of the guiding catheters, lower profile balloons, over-the-wire balloon systems and shapeable and torqueable guide wires. Initial PTCA success (usually defined as <50% residual stenosis without major complication) was approximately 67% in the early experiences published in the first National Institute of Health (NIH) Registry.² Of note, the NIH Registry was quickly established to evaluate the efficacy, safety and trends of PTCA in the US. The quick establishment of the NIH registry helped assess the practice pattern and procedure outcome accurately and this information was extremely educational. The success rate improved from 67% to 88% over the next ten years.³

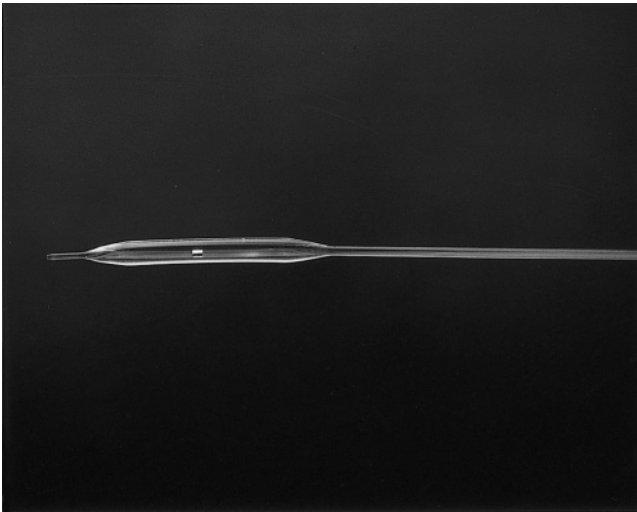


Fig. 1 PTCA Balloon.

The mechanisms of balloon dilatation of stenotic lesions are multifactorial. High pressure (8-15 atmospheres) balloon dilatation at a stenotic lesion results in dissection and laceration of the intima, media and often adventitia, stretching of the vessel wall and some compression of soft atherosclerotic material.⁴⁻⁶ These changes create a wider lumen size in many lesions. Although the overall success rate was high, there were significant limitations with this procedure associated with uncontrolled balloon injury, such as elastic recoil of dilated segments resulting in suboptimal improvement of vessel size, or uncontrolled dissection causing acute vessel occlusion.⁷⁻⁹ In addition to these limitations of the acute outcome, restenosis of treated segments occurred in 30-50% despite successful initial dilatation, during the first six months following the procedure.¹⁰⁻¹² To overcome these limitations, many second generation non-balloon devices were developed. These included directional coronary atherectomy (DCA), Rotablator and stents. The Food and Drug Administration (FDA) in the US also approved other devices, such as laser and TEC, but these devices are currently used very infrequently.

Second Generation Devices

Atherectomy

Directional Coronary Atherectomy (DCA) was the first non-balloon coronary device that was approved by the FDA in the US in 1989 (Fig. 2). The device effectively removes atherosclerotic obstructive tissue (atheroma + removal = atherectomy) with a rotating cutter within a cylindrical housing. By removing tissue, a smoother and much wider lumen was obtained

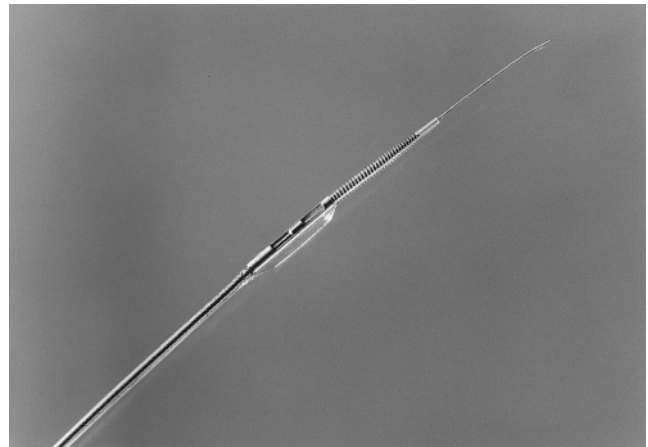


Fig. 2 Directional coronary atherectomy catheter. Atherosclerotic plaque invaginated into the window by low pressure balloon dilatation is excised by a rotating cutter and excised material is stored in the distal nosecone.

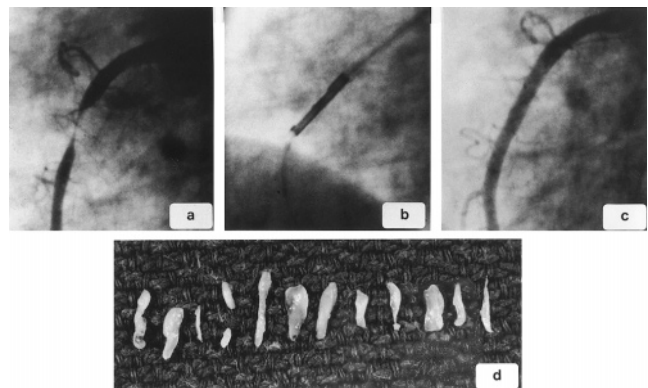


Fig. 3 A case of directional coronary atherectomy (DCA). a) Angiogram of right coronary artery: pre-treatment. b) Directional coronary atherectomy device in the artery. c) Angiogram: post DCA. d) Excised tissue.

(Fig. 3). Early preliminary non-randomized studies suggested the potential for improving acute outcome and reducing restenosis.¹³⁻¹⁵ It was hypothesized that a bigger post interventional lumen retained a wider lumen in the chronic recovery phase, thus reducing restenosis. CAVEAT (Coronary Angioplasty Versus Excisional Atherectomy Trial), which compared DCA and PTCA, was the first device-related randomized trial performed.¹⁶ The results demonstrated no significant improvement of the restenosis rate with DCA over conventional PTCA. It was a historical study since this was the first device-related multi-center randomized trial to evaluate efficacy in a scientific manner. This study, however, revealed some of the limitations and difficulties of device-related trials. These include use of

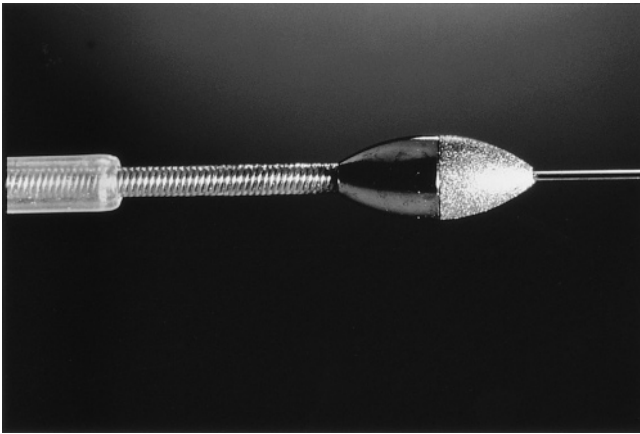


Fig. 4 Rotablator: The burr, with small particles of diamonds, rotates at high speed and ablates atherosclerotic plaque.

first generation devices that are still in their developmental phase, limited operator experience, and non-established operator methods. A subsequent study, BOAT (Balloon vs. Optimal Atherectomy Trial) with more experienced operators and established procedural methods using second generation devices, demonstrated superior results for acute outcome and restenosis with DCA compared with PTCA (residual stenosis was 14.7% vs. 28.1%; $p < 0.001$ and the restenosis rate was 32% vs. 40%; $p < 0.02$).¹⁷ These experiences demonstrated some of the difficulties of device-related trials, but also showed the importance of randomized trials to scientifically evaluate efficacy without biases.

Another effective device for ablation of atherosclerosis is the Rotablator (Fig. 4). Balloon dilatation has a limited efficacy in heavily calcified lesions which are very hard and non-compliant, due either to a failure to dilate or from resulting significant dissections. The Rotablator burr, which is covered with small particles of diamonds, spins at approximately 150–180,000 rpm and this procedure effectively ablates calcified plaque. This is an effective method to treat calcified lesions and to improve the initial procedural outcome (Fig. 5).^{18,19} Subsequent studies, however, (including non-calcified lesions) failed to demonstrate the superiority over PTCA on the restenosis rate.²⁰

Stent Era

In contrast to the “debulking” approach, another approach to overcome the limitations of PTCA was stent placement in stenotic lesions to support the vessel wall from inside the lumen. Self-expandable stainless steel stents (Wallstent®) were implanted in human coronary arteries in Europe with acceptable initial results.²¹ Subsequently, the Gianturco-Roubin stent was the first stent approved by the FDA for use in the

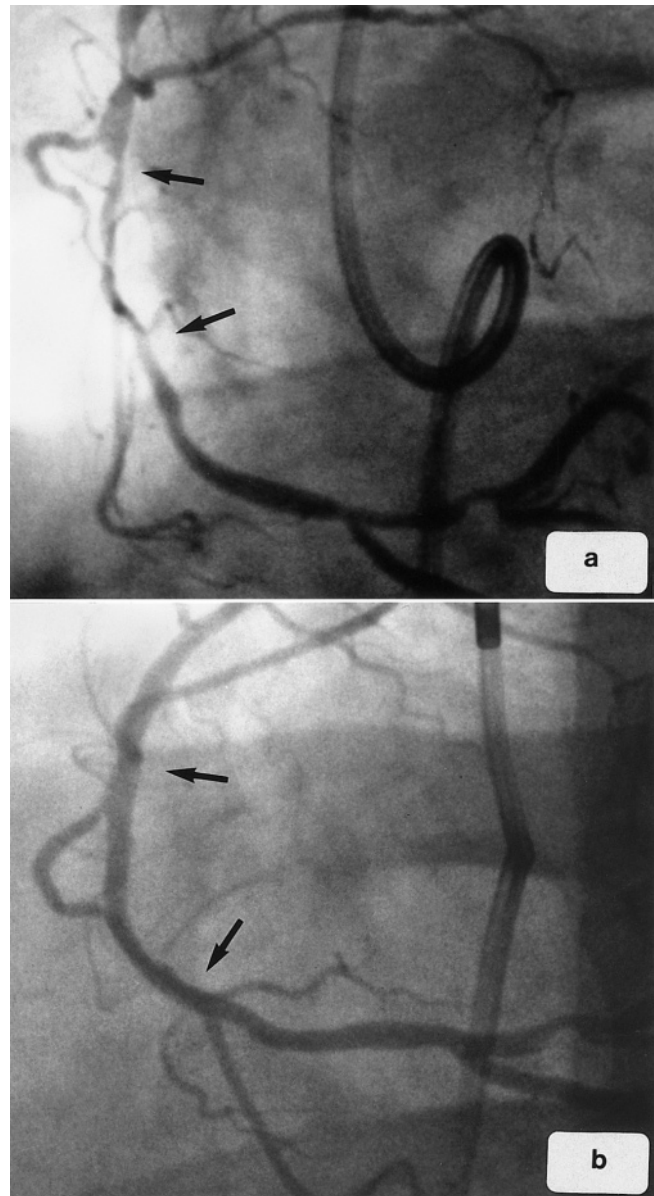


Fig. 5 A case of Rotablator. a) Angiogram of right coronary artery prior to Rotablator. b) Angiogram treated with Rotablator initially followed by balloon dilatation.

US.²² This stent was a balloon-expandable stainless steel coil and was indicated as a “bail-out” device following failed attempted PTCA. This coil stent had more elastic recoil because of less than ideal hoop strength and initial experience suggested a rather high restenosis rate. The other balloon-expandable stent was a slotted tube stent (laser cut patterns from stainless steel tubing) and this had more hoop strength; the Palmaz-Schatz stent was the first slotted tube stent tested in humans. This first generation stent was rather rigid with a larger profile and had significant limitations in its

Table 1 Stents

Balloon Expandable Stents	
Penta multilink*	(Guidant)
Multilink Ultrastent*	(Guidant)
NIR stent, NIR Royal*	(Boston Scientific)
Velocity*	(Cordis)
S660, S670, BeStent*	(Medtronic)
Self Expandable Stents	
Radius stent*	(Boston Scientific)
Magic Wallstent*	(Boston Scientific)

*These are primarily second or third generation stents and are not approved in Japan at the present time.

deliverability. Despite some limitations as a first generation device, stent placement clearly improved acute outcome, with fewer acute occlusions and a larger post procedure lumen size. Subsequently, the first randomized trial using the Palmaz-Schatz stent showed a significant reduction in the restenosis rate compared with PTCA (31% vs. 42%; $p = 0.04$).²³ The BENESTENT (Belgium-Netherland Stent) Trial also confirmed this favorable result.²⁴ Although stents had a significant advantage over PTCA for reducing the restenosis rate, they did have their own limitations. One of the major limitations was subacute thrombosis and the requirement of a complex anticoagulation regime that was associated with bleeding complications at the femoral access site. To prevent subacute thrombosis, which was a risk during the first two to three weeks until the stent was covered by endothelial cells, patients were initially treated with aspirin and warfarin. Despite aggressive anticoagulation, the subacute thrombosis rate was 2–3%. Major breakthroughs were the use of an additional anti-platelet agent, ticlopidine, with Aspirin but without warfarin, as well as high pressure stent delivery for complete apposition of the stent struts against the vessel wall, to prevent subacute thrombosis. With these approaches, the subacute thrombosis rate was reduced to <1% and significant groin access site complications were reduced.^{25–27} With further improvements of stent technology, stents are now more flexible, have better surface coverage with improved hoop strength and lower profile with better deliverability. It is estimated that approximately 80% of PCI cases are stented in the US. More than 20 types of stents are now available in the world. The stents currently available in the US are listed in Table 1 (Fig. 6).

Restenosis

Although stents and to a lesser degree DCA, reduce the incidence of restenosis, this remains the Achilles' heel of PCI. Restenosis is the reactive response to

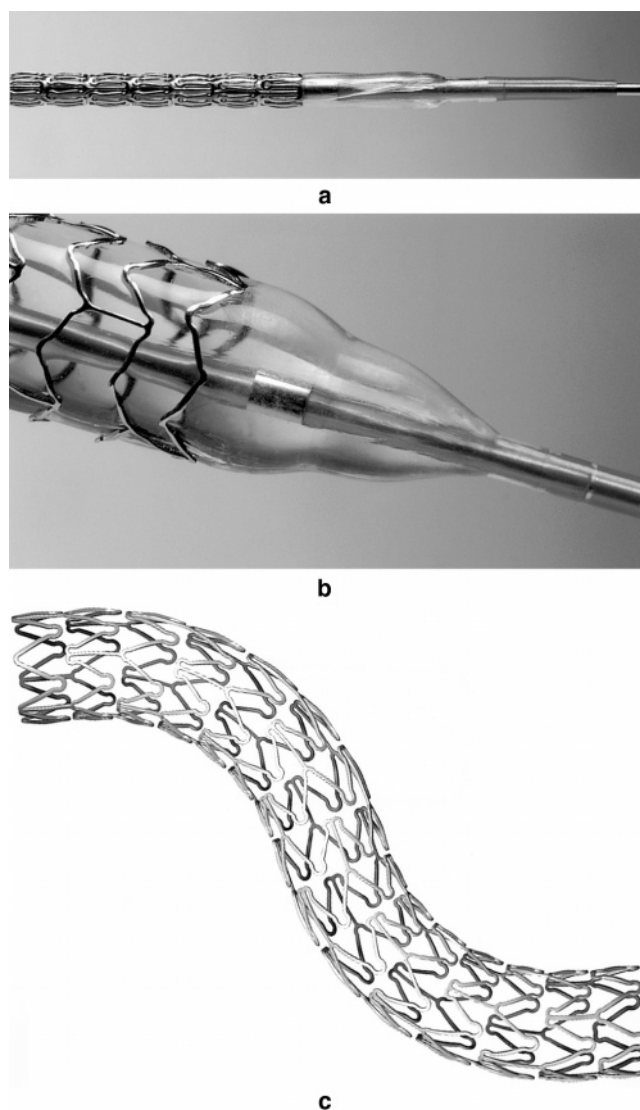


Fig. 6 Tetra® stent. (Guidant) a) Collapsed stent mounted on a balloon. b) Stent expanded on tip of balloon. c) Expanded stent.

tissue injury created by a PCI procedure and usually occurs between 2 and 6 months following a procedure. The restenosis rate following PTCA is 30–45%.^{10–12} Elastic recoil plays some role in restenosis, but the main cause of restenosis following PTCA or DCA was considered to be intimal hyperplasia associated with smooth muscle proliferation. Use of intravascular ultrasound, which gives a cross-sectional ultrasonic view of the vessels from inside the lumen, has provided us with some surprising findings. In addition to intimal hyperplasia, remodeling of the artery, causing shrinkage of the whole vessel size, plays as important a role as intimal hyperplasia in the cause of restenosis.^{28,29} In contrast to the restenosis process following PTCA and DCA, restenosis following stenting is purely due to

intimal hyperplasia since remodeling of the vessel is prevented by the stent itself.

Over the last 2 decades, many pharmacological agents have been tested to reduce restenosis by preventing intimal hyperplasia from occurring. Unfortunately none of these has been shown to be effective clinically. At the present time, one of the most potentially effective treatments to prevent restenosis is brachytherapy. Appropriate dosage of β - or γ - radiation delivered through specially designed catheters effectively suppresses the process of intimal hyperplasia without causing significant radiation injury in the animal model. Gamma radiation was tested first in humans; a single-center randomized trial demonstrated a significant reduction of intimal hyperplasia and clinical restenosis following PCI. The late loss of lumen size was reduced from 1.03 mm to 0.38 mm and the restenosis rate reduced from 54% to 17% with radiation.³⁰ This result was confirmed by a much larger scale randomized trial (GAMMA I Trial).³¹ β -radiation was tested for the treatment of in-stent restenosis; a multicenter, placebo-controlled, randomized trial (START: Sr Treatment of Angiographic Restenosis) demonstrated a significant reduction in the restenosis rate (radiation 29% vs. placebo 45%; $p < 0.05$) and target vessel revascularization rate (16% vs. 24%; $p < 0.05$).³² Based on these data, both γ - and β -radiation treatments were approved by the FDA for the treatment of in-stent restenosis in coronary arteries in the US.

Although brachytherapy clearly reduces the incidence of restenosis, some unique adverse events have been observed. When brachytherapy was utilized during new stent implantation, there was an increase in the incidence of late (>3 month) acute thrombosis, which is an extremely rare event with stent implantation itself without radiation.³³ This is most likely due to the lack of endothelial cell coverage over the stent struts caused by complete suppression of smooth muscle cell proliferation and endothelial cell growth by brachytherapy. Another unusual effect is the “candy wrapper” effect.³⁴ Restenosis at the center of the area treated by radiation is effectively prevented, but both edges of the radiated segment may have significant intimal hyperplasia, creating significant stenoses. Lower dosage of radiation at the edge of the treated segment may cause stimulation rather than suppression of intimal hyperplasia. Little is known of the longer-term effects of brachytherapy at the present time. Brachytherapy may only slow down the process of intimal hyperplasia and restenosis may eventually occur. Another concern is the effect of radiation on the acceleration of atherosclerosis. Since radiation therapy is very new and potentially hazardous, longer-term information is necessary to evaluate this new therapeutic treatment for a much wider application.

Glycoprotein IIb/IIIa Receptor Inhibitors

Many pharmacological agents have been developed to improve the outcome of PCI procedures. Aspirin was the first medication proven to be necessary during PTCA to prevent acute occlusion associated with platelet aggregation. As described, oral anti-platelet agents, ticlopidine (Ticlid[®]) and clopidogrel (Plavix[®]), have become important agents in addition to aspirin, in preventing subacute thrombosis following stenting. Introduction of glycoprotein IIb/IIIa receptor inhibitors, which block the interaction between the glycoprotein IIb/IIIa receptor and its principal adhesive ligand, fibrinogen, have become important agents for PCI. By inhibiting the IIb/IIIa receptor site, these agents, abciximab (ReoPro[®]), eptifibatid (Integrilin[®]) and tirofiban (Aggrastat[®]), inhibit approximately 90% of platelet activity.^{35,36} Initially, the efficacy of abciximab was tested during PCI without stenting. This multicenter, placebo-controlled, randomized trial (EPILOG: Evaluation in PTCA to Improve Long Term Outcome with Abciximab GP IIb/IIIa Blockade Study Group) demonstrated a significant reduction of MACE (major adverse cardiac event: death, myocardial infarction, revascularization) within 30 days.^{37,38} There was no statistical difference in death or revascularization. However, myocardial infarction, defined by CK elevation associated with the procedure, was significantly lower with abciximab. This agent was then tested during stenting procedures (EPISTENT: Evaluation in PTCA to Improve Long Term Outcome with Abciximab GP IIb/IIIa Blockade Study Group). The study was designed with 3-way randomization; stent alone, stent with abciximab and PTCA with abciximab. Death or large myocardial infarction (documented by significant CPK elevation) in the first 30 days was highest in the stent alone group followed by PTCA with abciximab and Stent with abciximab (7.8%, 4.7%, 3.0%).³⁹ This was a somewhat surprising result since it was generally felt that stenting for uncomplicated cases did not require abciximab. This result was confirmed with a subsequent study using eptifibatid (Integrilin) (ESPRIT: Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy).⁴⁰ These studies demonstrated the importance of scientifically well-designed randomized trial to evaluate efficacy. Based on these data, use of IIb/IIIa in the USA has been rising as a part of routine PCI.

New Devices

In the past, many devices were developed to improve the outcome of stenotic lesions and to reduce restenosis. Recently, the concept of “distal protection” during PCI procedures was introduced. In saphenous vein

grafts, the incidence of distal embolism causing myocardial infarction or slow flow was high. Distal embolism is normally caused by dislodgement of friable atherosclerotic material or thrombus when lesions are intervened with PTCA or stenting. Distal protection devices prevent distal embolisms by capturing debris from the lesions during interventions; this is either accomplished by a basket on a wire or a distal occlusion balloon with aspiration of material. The randomized trial (SAFER: Saphenous Vein Graft Angioplasty Free of Emboli Randomized Study) using an occlusion balloon with an aspiration catheter (PercuSurge) demonstrated a significant reduction of peri-procedural myocardial infarction during stenting procedures (8.4% with protection device vs. 16.5% with control) (Fig. 7).⁴¹ Captured material, with this protective device, is usually fine atherosclerotic debris or thrombus. The FDA in the US recently approved this device. In addition to intervention of SVG, distal protection devices will play a pivotal role for carotid stenting since any small dislodgement of material can cause stroke during carotid intervention. Currently, use of distal protection devices during emergency PCI for evolving acute myocardial infarctions are under investigation. Distal protection devices are likely to play a significant role, for both coronary and non-coronary vascular intervention, in the future.

One of the most exciting recent developments is drug-eluting stents to prevent restenosis. The stents are used as the vehicle of drug delivery for a prolonged time. The stents are coated with a thin layer of polymer that carries a pharmacological agent. The drugs are then gradually released to the lesion over periods (usually 30 days). Stents coated with sirolimus (Rapamycin[®]), an immunosuppressive agent used for post renal transplants, demonstrated a significant reduction of neo-intimal hyperplasia in the animal model. Early human studies using Rapamycin-coated stents (<50 patients) showed very favorable results in preventing restenosis following stenting.⁴² Other agents, such as an anti-proliferative agent (Taxol), have also been tested in humans. These early and favorable data need to be confirmed with a large-scale randomized trial in the future. This approach may be a major breakthrough for the prevention of restenosis that remains the Achilles' heel of PCI. If this approach significantly reduces restenosis, the indications and use of stents will be much wider than current use and an increasing number of patients will be treated with PCI rather than CABG.

Current Trends in the US

In the US, the number of PCIs continues to increase and it is estimated that more than 600,000 cases were performed in 1999. The estimated number of CABG

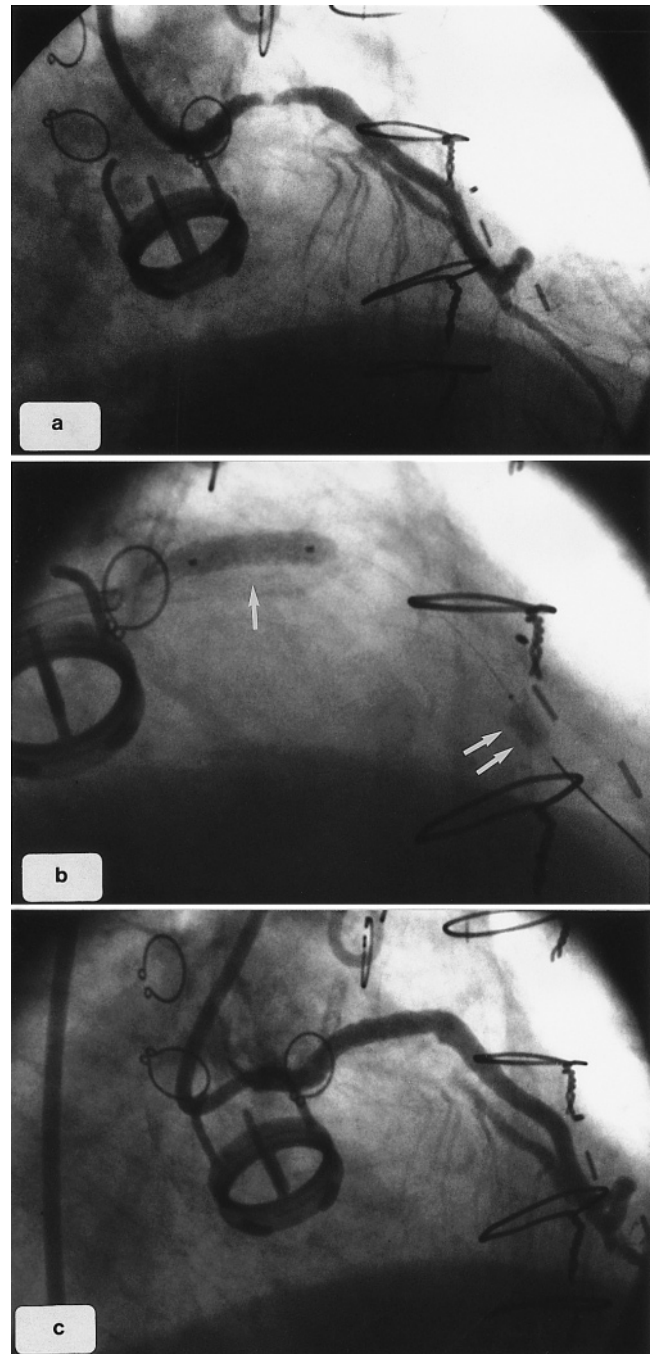


Fig. 7 A case of stenting using a distal protection device. a) Angiogram of saphenous vein graft to the left anterior descending coronary artery, pre-stent. b) 4 mm × 23 mm length Tetra[®] stent deployment with balloon inflation (↑). This procedure was performed using a PercuSurge distal protection device (↑↑). c) Angiogram post stenting.

operations is approximately 350,000/year, thus the estimated ratio of PCI/CABG is about 2:1. Of note, this ratio is much lower than that of 6-7:1 in Japan.

Currently available devices in the US are listed in Table 2. Most of the lesions which are accessible with stents and have a reference vessel size of ≥ 2.5 mm, are

Table 2 Devices Currently Available in the U.S.

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1. PTCA balloon
 2. Cutting Balloon
 3. Stents
 4. Directional Coronary Atherectomy (DCA)
 5. Rotablator
 6. Laser
 7. Transluminal Extraction Catheter (TEC)
 8. Angiojet (thrombus aspiration catheter)
 9. Beta and gamma radiation catheters
 10. Distal protection device (Guardwire)
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treated with stenting and it is estimated that currently more than 80% of PCI are stent procedures. Other devices such as DCA, Rotablator and the cutting balloon are considered to be “niche” devices, their use being limited to selective cases and specific indications. DCA is indicated for left anterior descending (LAD) ostial lesions or bifurcation lesions involving a large side branch. Debulking prior to stenting is an attractive strategy to prevent restenosis. Based on an initial observational study,⁴³ two randomized studies (AMIGO: Atherectomy before Multilink Improves Lumen Gain Outcome, in the US and DESIRE: Debulking and Stenting in Restenosis Elimination, in Japan) are currently under investigation. The results from these trials will soon be available to evaluate the role of debulking prior to stenting. Rotablator is generally used for heavily calcified lesions and is very effective in this setting. This device is used as a stand-alone with post balloon dilatation or as an adjunctive treatment prior to stenting to improve stent expansion. The cutting balloon, which has small blades on the balloon, was introduced in the US recently. It is still too early to determine what role this device will play. Currently, the cutting balloon is used mostly for in-stent restenosis, ostial lesions or diffuse disease.

Although radiation (β and γ) has been approved in the US recently, it is difficult to predict how widely this procedure will be accepted. Due to logistical reasons (isotope license, need for radiation oncologist and physicist) the institutions that will allow brachytherapy to be performed will be limited. In addition, longer-term information is limited and this is a rather significant concern. Most likely, this procedure will be used for refractory in-stent restenosis or diffuse in-stent restenosis, which have a known high recurrent restenosis rate with any other interventional approaches.

The quality of operators is important to obtain excellent PCI outcome. Similar to coronary artery bypass surgery, the experience of the operators and the institution has a significant impact on its outcome. Evaluation of more than 60,000 PTCA cases in New York state between 1991 and 1994, demonstrated the striking relationship between institutional and operator volume

and PTCA outcome.⁴⁴ Institutions with less than 600 cases/year, particularly less than 200/year, were associated with higher significant complication rates. Similarly, operators with less than 75 cases/year had a higher complication rate. No definitive statistics are available but it is estimated that the number of average cases per physician is less than 50 cases/year.

To improve the outcome and to maintain the high quality of the PCI procedure, recent guidelines from the American Heart Association and the American College of Cardiology recommend the minimum of 250 cases/year for the institution and 75 cases/year for the operator. Recently, the Interventional Cardiology Subspecialty Board was established by the American Board of Internal Medicine and the first certification examination was offered in 1999. To be qualified for the “appropriate experience and training”, either at least more than 500 life-time experience or >75/year for two consecutive years or one year of interventional cardiology training at an accredited program with at least 250 procedures are required. Although these guidelines and subspecialty do not have legal restraint on the institutions or physicians, these will help to improve the overall outcome of PCI.

Summary

Since the introduction of PTCA in 1977, PCI has evolved significantly. PCI treatment has become mainstream for the treatment of CAD. In addition to significant improvements of basic PTCA equipment, new generation procedures such as DCA, Rotablator and most significantly stents, have improved the outcome of PCI procedures. Although restenosis remains one of the major limitations of this procedure, new approaches including radiation have improved its outcome. Exciting technologies such as drug-eluting stents will have significant impact on outcome. It is likely the indications for PCI will continue to expand and PCI will become more effective in the future. Evidence-based medicine will play a more important role to evaluate and guide PCI procedures in the future.

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