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Percutaneous coronary intervention in the management of coronary artery disease

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Modern invasive cardiology stems from a legacy dating back more than a century and a half (Table 1). Cardiac catheterization was first performed in a horse by the French physiologist Claude Bernard in 1844.[1] Human cardiac catheterization did not occur until 1929, when Dr. Waner Forssmann (a surgical intern at a small German hospital) passed a catheter through his antecubital vein and, guided by fluoroscopy, entered the right atrium.[2] This landmark discovery, which at the time was seen more as an act of youthful belligerence, carved a path for future discoveries. Selective coronary angiography was later performed by Dr. Mason Sones in 1958 and modified by Judkins in 1967.[3] Initially, cardiac catheters were used only to measure pressures within cardiac chambers, thereby remaining solely diagnostic tools until Dr. Gruentzig launched the field of percutaneous transluminal angioplasty in 1977.[1-3] In the ensuing years, this new technique was widely adopted. In the United States alone, over 1 million diagnostic catheterizations and more than 300,000 balloon angioplasties are performed annually.[3] Progressive advances in equipment, in techniques, along with adjunctive technologies (such as stents and antiplatelet therapy), have led to the modern era of safe and effective therapeutic percutaneous coronary intervention (PCI).

Stents

In 1996, The American College of Cardiology published a consensus document on coronary artery stenting, based on two randomized controlled trials (RCTs) that compared stent implantation to conventional balloon angioplasty.[4,5] Shortly thereafter, the FDA in the US approved coronary stent implantation for elective coronary procedures.[6] There have been more than 12 RCTs comparing stents with balloon angioplasty in more than 6300 patients. The results have consistently demonstrated a 30%-50% reduction in repeat revascularization with stents, a benefit that persists over time.[6] There are now numerous stents available to interventional cardiologists, ranging in length from 8 to 38 mm, and in diameter from 2.0 to 5.0 mm. By preventing early recoil[7] and late vessel constriction (negative remodeling),[6] stents optimize the initial vessel diameter that can be achieved and reduce the likelihood of subsequent restenosis, as well as the need for repeat revascularization (Table 2).

Indications for stenting

Original registry studies confirmed that stents were the most effective treatment for acute or impending closure or dissection after balloon angioplasty.[6] Currently, coronary stents are deployed in over 85%-90% of coronary interventions and have rapidly become a routine part of

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Table 1: Milestones in the development of PCI

- Cardiac catheterization first performed in a horse in 1844
- First human attempt at cardiac catheterization in 1929
- Selective coronary angiography performed as diagnostic tool in 1958 and modified in 1967
- Percutaneous transluminal angioplasty launched in 1977
- Advances in equipment, techniques, and adjunctive technologies (ie, stents in 1996) in modern era
- >300,000 balloon angioplasties and 1 million diagnostic catheterizations performed annually in the US alone

Table 2: The advent of stents

Advantages

- Prevent early recoil and late vessel constriction in a variety of lesion types
- 30%-50% reduction in repeat revascularization compared with balloon angioplasty
- Large variety of styles, lengths, and diameters available
- Currently used in 85%-90% of coronary interventions
- Optimal long-term outcomes in the setting of acute MI
- Coated stents facilitate local drug delivery to vessel wall (ie, sirolimus, an immunosuppressive agent; taxol to inhibit restenosis)

Disadvantages

- Unproven benefit in small lesions (<2.5-3 mm)
- Lesion length (>20 mm), multiple stents, bifurcation and anastomatic lesions increase risk of early and late complications
- Increased risk of neointimal hyperplasia and stent thrombosis and reocclusion

elective percutaneous coronary interventions (PCI). Data from numerous RCTs suggest improved long-term clinical outcomes associated with elective routine stenting of several lesion types, including discrete native artery lesions, restenotic lesions, saphenous venous graft lesions, infarct–related arterial occlusions, and chronic total occlusions.[6] In the REST trial,[8] stenting of restenotic lesions was associated with improved technical success, reduced restenosis rates (18% vs 32%, P=0.03) and fewer repeat revascularization procedures (10% vs 27%, P=0.001). Two RCTs have evaluated the role of stenting in vein graft lesions.[6] The SAVED[9] and VENESTENT[10] trials confirmed that routine elective stenting of vein graft lesions resulted in better initial outcome and a reduction in the combined long-term end-point of death, MI, or target vessel revascularization. In total, at least 9 RCTs[6] have shown that stent placement is associated with less restenosis and better immediate angiographic outcomes compared with angioplasty alone. Stenting has a particular role in addressing chronic total occlusions, where success rates after balloon angioplasty alone have been lower than in non-occluded arteries and restenosis more likely.[11,12] Based on the recently reported Stent-PAMI,[13] CADILLAC,[14] and STOP-AMI[15] trials, primary stenting has also proven to be associated with more optimal long-term outcomes in the setting of acute myocardial infarction (MI) when performed by experienced operators within a few hours of the onset MI. PCI now remains the gold standard for acute reperfusion therapy. The initial benefit of primary angioplasty reported in PAMI-1 persisted at the 2-year follow-up, including a decreased rate of reintervention and improved infarct free survival.[14]

Despite the demonstrated efficacy and safety of coronary stenting, there are still lesions for which stenting is of unproven benefit,[6] such as small vessels (<2.5-3.0 mm). Lesion length (>20 mm), the use of multiple stents, bifurcation and anastomotic lesions, all increase the risk of early and late complications after coronary stenting.

Antiplatelet therapy

Five randomized trials[6,16] (MATTIS , ISAR , STARS, FANTASTIC and Hall's study), have shown that the combination of ASA and a thienopyridine (ticlopidine or clopidogrel) significantly reduces the rate of cardiac events after coronary artery stent implantation and is superior to ASA plus oral anticoagulation (Table 3). The CLASSICS[17] study has shown that the combination of clopidogrel (for 28 days) plus ASA was associated with fewer adverse events compared with ticlopidine and ASA. This study and other observational studies have confirmed the efficacy of the clopidogrel/ASA combination, rendering them routine as a post-stenting regimen. Although current practice is to discontinue the clopidogrel after 1 month, results from two

Table 3: Therapies to reduce cardiac events after stent implantation

- Antiplatelet therapy with a combination of ASA plus a thienopyridine (ticlopidine or clopidogrel)
- Platelet GP IIb/IIIA antagonists (ie, abciximab, eptifibatide or tirofiban) block the final common pathway to platelet aggregation
- "Facilitated PCI" (combination of reduced-dose fibrinolytic + full dose IV GP IIb/IIIa antagonist + PCI) shown in some trials to improve patency
- Intravascular ultrasound (IVUS) can provide accurate vessel sizing, define plaque morphology and ensure optimal stent deployment
- Gamma and beta catheter-based intracoronary brachytherapy for in-stent restenosis

recently completed RCTs[18,19] may force cardiologists to consider longer-term clopidogrel administration.

Platelet glycoprotein IIb/IIIa receptor inhibition

Platelet receptor glycoprotein (GP) IIb/IIIa antagonists block the final common pathway to platelet aggregation. Several RCTs with over 40,000 patients, have confirmed that potent platelet inhibition with a parenteral GP IIb/IIIa antagonist is associated with a significant reduction in the risk of major adverse cardiac events after coronary artery stenting. Current regimens of intravenous abciximab, eptifibatide or tirofiban appear to be safe, with little effect on bleeding risk when heparin dosing is reduced.

Facilitated PCI for acute MI

Recent advances in our understanding of the pathophysiology of acute MI have led to the new concept of facilitated PCI. Platelets play a major role in the pathogenesis of an acute coronary syndrome. An intracoronary thrombus is rich in platelets, not simply fibrin, and therefore will sometimes resist fibrinolysis. Although fibrinolytic therapy can restore patency in 81% of patients by 90 minutes, failure to achieve TIMI 3 flow, which may occur in 45%-70% of patients, is associated with reduced survival[20] and even after successful reperfusion, reocclusion occurs in up to 20% of patients.[21] In contrast, primary PCI has a higher patency rate, greater TIMI 3 flow, and fewer complications. The triple combination of reduced-dose fibrinolytic therapy, full dose intravenous GP IIb/IIIa receptor inhibitors, and PCI has been evaluated in several recent RCTs (TIMI 14 and SPEED)[22,23] and was termed " facilitated PCI." However, the mortality benefits and safety of this approach must be investigated in larger RCTs before any final recommendations .

Intravascular ultrasound (IVUS)

Since Colombo's seminal observation that the majority of stents are not fully expanded with routine inflation despite favorable angiographic results, IVUS has been used to ensure optimal stent deployment.[24] Although the exact indications for IVUS are controversial, the technique is particularly helpful in providing accurate vessel sizing, defining plaque morphology (thrombus, dissection, or calcification), and ensuring optimal stent expansion. RCTs evaluating the incremental clinical benefits of IVUS, in addition to angiography, have shown conflicting results. The MUSIC[25] and CRUISE[26] studies showed that stent deployment guided by IVUS resulted in improved clinical and angiographic outcomes. However, the OPTICUS[27] study failed to show a reduction in restenosis with the use of IVUS. The RESIST[28] study recently reported a non-significant 6.3% decrease in the restenosis rate in patients receiving IVUS-guided stenting. The AVID[29] study, while showing improved stent expansion with IVUS, failed to demonstrate a significant difference in 30-day adverse events. Although these results fail to justify the routine use of IVUS, it remains an invaluable tool when a clearer definition of vessel architecture is required.

In-stent restenosis

Since stents minimize elastic recoil and negative geometric remodeling, the predominant mechanism of in-stent restenosis is intimal hyperplasia. Incomplete stent expansion may also contribute to restenosis. When restenosis is confined to a discrete, short length within the stent (focal restenosis), simple balloon redilation is quite effective, with recurrent restenosis occurring in 25%-30%. However, when there is a diffuse pattern of in-stent restenosis, the treatment is challenging and the restenosis recurrence rate is high (60%-80%). Debulking strategies using atherectomy catheters or the excimer laser have not been shown to reduce recurrent restenosis within stents.[6] Thus far, the only proven effective treatment for in-stent restenosis is brachytherapy.

Brachytherapy (local intracoronary radiation)

The U.S. FDA recently approved both gamma and beta catheter-based intracoronary brachytherapy for the treatment of in-stent restenosis. Encouraged by animal studies, Teirstein et al were the first to prove the clinical efficacy of this approach in humans.[30] Teirstein randomized 55 patients with in-stent restenosis to receive either intracoronary γ-radiotherapy or placebo. They reported a dramatic 73% reduction in repeat revascularization at 6 months, and a 48% reduction at 3 years.[30,31] No perforations, aneurysms, pseudoaneurysms, or other long-term safety concerns have been observed in this cohort after more than 3 years of follow-up.[31] Several other RCTs[32,33] followed, confirming that significant reductions in clinical and angiographic restenosis could be safely achieved in both long and short lesions, including vein graft lesions, with the use of intracoronary radiation. The enthusiasm for brachytherapy has been somewhat tempered by a higher rate of subacute stent thrombosis (~8%), likely resulting from radiation-induced endothelial dysfunction. This has led to the use of prolonged (6-9 months) clopidogrel and ASA therapy, and the avoidance of recurrent stent implantation during the brachytherapy procedure. Such strategies appear to reduce stent thrombosis to levels that are comparable to routine stenting.[34]

As the routine use of brachytherapy for *de novo* lesions has yet to be proven, this technique is only an option for treating in-stent restenosis. Despite their conceptual appeal, radioactive stents have not been approved in humans due to their tendency to induce stenosis at the stent edges ("candy-wrapper" or "edge effects").[35]

Coated stents

Stents have always been an attractive platform for facilitating local drug delivery to the vessel wall. Sirolimus, a potent immunosuppressive agent used for preventing renal transplant rejection, can now be delivered locally on a stent platform to prevent intimal hyperplasia. Sousa et al,[36] recently demonstrated the feasibility and safety of implanting sirolimus-coated stents. Preliminary results with this and other coated stents (ie, taxol) suggest that restenosis may be substantially inhibited. If proven efficacious and safe in larger, ongoing clinical trials, coated stent technology could be the next revolution to have a favorable impact on interventional cardiology. The results of these ongoing studies are eagerly awaited.

Has contemporary PCI fulfilled its potential?

The technique of PCI has undergone tremendous improvements in the last 15 years. Despite its widespread use and documented efficacy, it has some limitations. Coronary stenting prevents early recoil and late remodeling at the cost of increased neointimal hyperplasia, stent thrombosis, and reocclusion. In view of these limitations, the search for more effective and safe alternatives continues. Dual antiplatelet therapy has been found useful in preventing stent thrombosis and reocclusion. The potential of brachytherapy and coated stents has enormous appeal for fulfilling the original mission of PCI. The radioisotope stents resulted in increased neointimal hyperplasia at the edges. However, catheter-based intravascular brachytherapy has shown its efficacy and safety. The future looks even more promising after the encouraging results reported from drug-coated stents, and this option may become the newest treatment of choice.

Summary

The forefathers of interventional cardiology had no way of predicting how their contributions would redefine the treatment of coronary artery disease. In the last 20 years alone, PCI has risen from a cumbersome and risky procedure limited to carefully selected patients, to a routine, safe procedure with success rates in excess of 95%. Despite these advances, restenosis continues to prevent PCI from achieving its fullest potential. With recent developments to minimize restenosis, particularly in the area of stent-based local drug delivery and brachytherapy, the future of this truly minimally-invasive intervention remains bright.

References:

1. Cournand A. Cardiac catheterization; development of the technique, its contribution to experimental medicine, and its initial applications in man. *Acta Med Scand Suppl* 1975;579:3-32.
2. Mueller RL, Sanborn TA. The history of interventional cardiology: cardiac catheterization, angioplasty and related interventions. *Am Heart J* 1995;129:146-172.
3. Baim DS, ed. *Cardiac catheterization, angiography, and intervention*. 5th ed. Baltimore, MD: Williams and Wilkins; 1996:3-7.
4. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med* 1994;331:496-501.
5. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable –stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994; 331:489-495.
6. Al Suwaidi J, Berger PB, Holmes DR Jr. Coronary artery stents. *JAMA* 2000;284(14):1828-1835.
7. Holmes DR Jr, Hirshfeld J Jr, Faxon D, Vlietstra RE, Jacobs A, King SB 3rd. ACC Expert Consensus document on coronary stents. *J Am Coll Cardiol* 1998;32:1471-1482.
8. Erbel R, Haude M, Hopp HW, et al. Coronary artery stenting compared with balloon angioplasty for restenosis after initial balloon angioplasty. *N Engl J Med* 1998;339:1672-1678.
9. Savage MP, Douglas JS Jr, Fischman DL, et al. Stent placement compared with balloon angioplasty for obstructed coronary bypass grafts. *N Engl J Med* 1997;337:740-747.
10. Hanekamp CEE, et al. The VENESTENT study (abstract). *J Am Coll Cardiol* 2000;35:9A.
11. Ishizaka N, Issiki T, Saeki F, et al. Angiographic follow-up after successful percutaneous coronary angioplasty for chronic total coronary occlusion: experience in 110 consecutive patients. *Am Heart J* 1994;127:8-12.
12. Violaris AG, Melkert R, Serruys PW. Long-term luminal narrowing after successful elective coronary angioplasty of total occlusions. *Circulation* 1995;91:2140-2150.
13. Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. *N Engl J Med* 1999;341:1949-1956.
14. Stone GW. CADILLAC trial results. Paper presented at: Transcatheter Cardiovascular Therapeutics 2000; October 17-22, 2000; Washington, DC, U.S.A.
15. Schomig A, Kastrati A, Dirschinger J. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. *N Engl J Med* 2000;343:385-391.
16. Kloner R, Birnbaum Y. *Cardiovascular Trials Review* 2000. 5th ed. Pfizer USA; 2000:497,527-531.
17. Bertrand ME, Rupprecht HJ, Urban P, et al. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study. *Circulation* 2000;102:624-629.
18. Mehta SR, Yusuf S, the CURE Study Investigators. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme; rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. *Eur Heart J* 2000;21:2033-2041.
19. Moore SA, Steinhubl SR. Clopidogrel and coronary stenting: what is the next question? *J Thromb Thrombolysis* 2000;10(2):121-126.
20. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993;329:1615-1622.
21. Ohman EM, Califf RM, Topol EJ, et al. Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction. *Circulation* 1990;82:781-791.
22. Antman EM, Gibson CM, de Lemos JA, et al. Combination reperfusion therapy with abciximab and reduced dose reteplase: results from TIMI 14. *Eur Heart J* 2000;21:1944-1953.
23. The SPEED Group. Trial of abciximab with and without low-dose reteplase for acute myocardial infarction. Strategies for Patency Enhancement in the Emergency Department (SPEED). *Circulation* 2000;101:2788-2794.
24. Colombo A, Hall P, Nakamura S, et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. *Circulation* 1995;91:1676-1688.
25. de Jaegere P, Mudra H. Figulla H, et al. Intravascular ultrasound-guided optimized stent deployment. Immediate and 6 months clinical and angiographic results from the Multicenter Ultrasound Stenting in Coronaries (MUSIC) study. *Eur Heart J* 1998;19(8):1214-1223.
26. Fitzgerald PJ, et al. Can Routine Intravascular Ultrasound Influence Stent Expansion? Analysis of outcomes. *J Am Coll Cardiol* 1998;31(supplA):396A.
27. Mudra H, et al. Acute and preliminary follow up of the optimization with intra-coronary ultrasound to reduce stent restenosis. *J Am Coll Cardiol* 1998;31(suppl A):494A.
28. Schiele F, Meneveau N, Vuillemenot A, et al. Impact of intravascular ultrasound guidance in stent deployment on 6-month restenosis rate: a multicentre, randomized study comparing two strategies — with and without intravascular ultrasound guidance. RESIST Study Group. *J Am Coll Cardiol* 1998;32(2):320-328.
29. Russo RJ, et al. Angioplasty Versus Intravascular ultrasound-Directed stent placement: Observation from the AVID study. *J Am Coll Cardiol* 1998;31(supplA):387A.
30. Teirstein PS, Massullo V, Jani S, et al .Catheter-based radiotherapy to inhibit restenosis after coronary stenting. *N Engl J Med* 1997; 336(24):1697-1703.
31. Teirstein PS, Massullo V, Jani S, et al. Three-year clinical and angiographic follow-up after intracoronary radiation: results of a randomized clinical trial. *Circulation* 2000;101:360-365.
32. 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(4):250-256.
33. Verin V, Popowski Y, de Bruyne B, et al. Endoluminal beta-radiation therapy for the prevention of coronary restenosis after balloon angioplasty. *N Engl J Med* 2001;344(4):243-249.
34. Waksman R, Ajani AE, White RL, et al. Prolonged antiplatelet therapy to prevent late thrombosis after intracoronary gamma-radiation in patients with in-stent restenosis. *Circulation* 2001; 103:2332-2335.
35. Albiero R, Nishida T, Adamian M, et al. Edge restenosis after implantation of high activity (32)P radioactive beta-emitting stents. *Circulation* 2000;101:2454-2457.
36. 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 3-dimesional intravascular ultrasound study. *Circulation* 2001; 103:192-195.

Abstract of Interest

One year follow-up after PCI of chronic total occlusions: results from a multicentre prospective study (TOAST)

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The effectiveness of PTCA in chronic total occlusions (CTO) is limited by low success rate and high incidence of restenosis. The availability of new specific guide wires and stents may have a favourable impact in this setting.

TOAST (Total Occlusion Angioplasty Study) is a multicenter prospective observational study, enrolling consecutive patients with at least one CTO (TIMI flow 01, estimated time from occlusion > 30 days) on native vessels treated with PCI in 30 Italian centers.

AIM OF THE STUDY is to establish immediate and late outcome of PCI in these patients in an era in which specific guide wires and stents are available. Angiographic analysis of all the procedures is ongoing in a central core lab and all patients will be followed for 5 years.

OBJECTIVE of this report is to focus on one year clinical outcome after PCI in patients with successful or unsuccessful procedures.

RESULTS: 458 CTO were attempted in 432 pts; 87,3% had angina symptoms and 65,3% had a previous MI; successful PCI (final TIMI 3 flow and < 50% residual stenosis, no MACE) was obtained in 334 pts (77,3%); 14 pts (3,2%) had in-hospital MACE (1 death, 7 non-Q wave MI, 3 emergent CABG, 3 repeat PTCA) and were excluded from further analysis. One year clinical follow-up is complete for 369/418 pts (88,3%) and results are summarized in the table.

	Successful PCI (286)	Failed PCI (83)	p
Death	4 (1.4%)	2 (2.4%)	ns
MI (Q and non Q)	3 (1.0%)	4 (4.8%)	< 0.05
RePTCA (TLR)	33 (11.5%)	4 (4.8%)	ns
CABG	10 (3.5%)	16 (19.3%)	< 0.01
Event free	236 (82.5%)	57 (68.7%)	< 0.01
Angina free	206/236 (87.3%)	40/57 (70.2%)	< 0.01
Negative stress test	137/159 (86.2%)	23/36 (63.9%)	< 0.01

TLR= target lesion revascularization

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