

Drug-Eluting Stents in Angina

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Guest Editorial

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PERCUTANEOUS CORONARY INTERVENTION: A CONTEMPORARY ASSESSMENT

It has been known for more than three centuries that chronic stable angina pectoris is most commonly caused by narrowing of one or more epicardial arteries. Andreas Grüntzig's brilliant development of percutaneous transluminal coronary angioplasty (PTCA) in 1977 to relieve coronary obstruction was the first and most important step in the development of modern percutaneous coronary intervention (PCI), and represents one of the triumphs of twentieth-century medicine. Coronary revascularization by PTCA soon became a widely used and effective approach for the treatment of angina. When compared with coronary artery bypass surgery (CABG), PCI proved to be equally efficacious in the majority of patients. To the chagrin of cardiac surgeons, an increasing fraction of patients with disabling chronic stable angina selected PCI over surgery because it causes little discomfort and requires only a brief hospitalization and convalescence. Furthermore, it does not exclude subsequent surgery, should it be necessary.

As a result of the development of PCI, an important new specialty, interventional cardiology, developed and interventional cardiologists quickly became the "darlings" of both the profession and the public. In the early 1980s in North America and to a lesser extent in Western Europe, coronary angiography and PCI were carried out in patients with progressively less disabling angina. The "oculostenotic reflex" soon became widespread, viz, if a stenosis on the coronary arteriogram was visualized, then its immediate relief by PCI would be carried out almost reflexly by the interventional cardiologist.

However, three problems with PTCA soon emerged. The first was the development of restenosis caused by neointimal hyperplasia of fibromuscular tissue in the dilated coronary artery. This occurred in 35% to 40% of patients, requiring one and in some instances multiple repeat procedures. The second problem, fortunately much less ●●●

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frequent, was the development of acute coronary occlusion secondary to procedurally induced coronary arterial dissection and/or thrombosis of the coronary artery. This serious complication, if not corrected immediately, would lead to acute myocardial infarction or death, and required emergency CABG. PTCA required the “standby” of an operating room and cardiac surgical team—obviously an expensive and inconvenient requirement. The third problem was the growing realization that coronary atherosclerosis is usually a multifocal, not a unifocal disease; a focal stenosis visualized angiographically was just the tip of the iceberg. Therefore, relieving these obstructions in patients with chronic angina, while greatly reducing or even abolishing symptoms, did not seem to alter the natural history of the disease.

The development, in 1986, of metal stents, at first bare-metal stents (BMS), inserted into the coronary artery following balloon angioplasty, was the second of the three major advances of PCI, since it essentially eliminated procedural coronary occlusions. Although BMS reduced coronary restenosis by one third, to about 20% to 25%, this remained a stubborn residual problem that did not yield to a large number of pharmacologic approaches that were explored. BMS also brought with them an uncommon, but often devastating, early complication—platelet-driven stent thrombosis. To avoid this, dual antiplatelet therapy, ie, aspirin and a thienopyridine, first ticlopidine and more recently clopidogrel, was required. This treatment was associated with its own risk—bleeding that was spontaneous or which accompanied cardiac (or other) surgery.

The development of drug-eluting stents (DES) in 2001 represents the third important advance of PCI. DES are coated by a carrier polymer and anti-inflammatory antiproliferative agents and have been successful in reducing restenosis substantially, to between 5% and 10%. DES have not eliminated the early stent thrombosis with its attendant high risk that was noted with BMS. Indeed, it appears that late stent thrombosis, ie, between 30 days and 1 year, and very late stent thrombosis (after 1 year), may actually be more frequent with DES than with BMS. Such late thromboses may occur because the antiproliferative activity of the coating, which reduces the risk of restenosis, also inhibits reendothelialization, leaving the stent as a nidus for platelet aggregation. This complication may occur despite prolonged dual antiplatelet therapy, although patients who develop stent thrombosis despite such therapy often exhibit hyporesponsiveness to one or both of the antiplatelet drugs.

Moreover, patients with DES who discontinue dual antiplatelet therapy prematurely are at especially high risk of stent thrombosis, which, like coronary occlusion after PTCA, is associated with a very high incidence of mortality or massive nonfatal myocardial infarction. Long-term compliance with dual antiplatelet therapy is problematic and the need to interrupt it because of the occurrence of serious bleeding or because of refusal of payers to continue long-term reimbursement for thienopyridines may become re-



sponsible for a growing number of DES thromboses in the future. The duration of dual antiplatelet therapy required to minimize the risk of DES thrombosis has not yet been determined, but probably exceeds 1 year. In addition, DES may also cause local hypersensitivity reactions.

Where do we go from here? First, a rededication to meticulous deployment regardless of the composition or configuration of the stent is necessary. Second, continued research on DES should be strongly encouraged. New stents must steer a course between the Scylla of inadequate reendothelialization and the Charybdis of excessive neointimal hyperplasia. Ultimately, fully resorbable DES are likely to become standard. Formal prospective registries to ascertain long-term outcomes of patients with newly approved stents are essential to ensure maximum patient safety.

Second, a new look at the platelet P2Y₁₂ component of dual antiplatelet therapy is indicated. Detection of hyporesponsiveness to clopidogrel and/or aspirin with a number of portable devices is now possible. In the not inconsiderable number of patients who exhibit hyporesponsiveness, the doses of these drugs could be increased. Prasugrel, a novel thienopyridine, has been shown to reduce both early and late stent thrombosis by half, albeit at the cost of an increased risk of bleeding. This drug is now wending its way through the regulatory process. Very potent nonthienopyridine P2Y₁₂ blockers are also under active investigation.

Finally, and perhaps most importantly, a reconsideration of the indications for PCI is in order. While this procedure successfully eliminates or reduces the severity of stable angina pectoris, PCI has never been demonstrated to improve survival or reduce the incidence of acute myocardial infarction in these patients. Intensive medical management of angina has improved considerably since the introduction of PCI in the 1970s, and a trial of such therapy should be attempted before allowing the “oculostenotic reflex” to prevail. A medical strategy could be even more important when patients with asymptomatic or mildly symptomatic coronary obstruction are identified in increasing numbers as multislice computed tomographic coronary angiography becomes more widespread. Of course, if optimum medical therapy fails in a patient with severe angina, mechanical reperfusion is required; the specific method—PCI or CABG—depends on the coronary anatomy and left ventricular function.

The situation differs in patients with acute coronary syndromes. PCI, if carried out without delay after the onset of symptoms in patients with ST-segment–elevation myocardial infarction (STEMI) has been shown to be life saving and is now the treatment of choice for patients with this condition. When the thrombosis occurs in a large proximal coronary artery, as is often the case, late lumen loss and restenosis may be of less concern than when it occurs in a smaller coronary artery. Since PCI must be carried



out immediately on presentation of patients with acute STEMI, it is often difficult in the very few minutes available to ascertain if the patient is likely to adhere to dual anti-platelet therapy for a prolonged period. Thus, DES may not be the stents of choice in these patients. In patients with unstable angina and non-ST-segment–elevation myocardial infarction, the need for PCI is also clear, since the composite end point of death or myocardial infarction is reduced by this procedure; DES may be quite useful in patients with this condition.

A number of dazzling advances in cardiovascular therapeutics have occurred during the last half century. However, none of these have been free of problems, either limitations of efficacy and/or the development of adverse effects. All have required continuous reassessment. PCI certainly stands tall among these advances. This issue of *Dialogues in Cardiovascular Medicine* provides a thoughtful, contemporary assessment of this important therapy.

