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EDITORIAL

What Will Be the Impact of Drug-Eluting Stents on Hybrid Coronary Revascularization?

Dr. Karamanoukian

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Treatment of coronary artery disease (CAD) has evolved considerably since the advent of coronary artery bypass grafting (CABG) in 1962 and the introduction of percutaneous coronary intervention (PCI) a decade and a half later. Despite advances from the traditional median sternotomy CABG, such as minimally invasive direct coronary artery bypass (MIDCAB) and endoscopic and robotic modifications of the MIDCAB, median sternotomy CABG remains the gold standard for coronary revascularization. The major reason for this preference is that application of MIDCAB is limited to anastamosis of the left internal mammary artery (LIMA) to the left anterior descending artery (LAD). Occlusion of other vessels within the coronary circulation requires either saphenous vein grafts (SVGs) or percutaneous coronary intervention. Thus, with multiple vessel disease involving the LAD, we are left with the option of median sternotomy CABG or the novel combination of MIDCAB and PCI, so-called hybrid coronary revascularization or integrated coronary revascularization (ICR). Here too there are numerous obstacles to overcome. First, the majority of cardiac surgeons lack proper training in performing MIDCAB, and neither the commonness nor the total number of procedures is known [Karamanoukian, 2002]. Second, there is widespread skepticism among surgeons regarding the efficacy and success of PCIs [Karamanoukian, 2002]. In fact, in patients with multiple-vessel disease, no survival benefits of CABG over PCI have been demonstrated, thus far [BARI 1996]. Randomized trials, however, have shown benefits of CABG over PCI in reducing recurrent angina and lowering reintervention rates [BARI 1996, Hlatky 1997]. Of note is the fact that these trials were done before the advent of stents. When compared to traditional percutaneous transluminal coronary angioplasty (PTCA), the use of stents in PCIs show improved long-term results and angiographic restenosis rates of only 10% to 20% (in focal lesions and vessels >3.0 mm in diameter) [Serruys 1994, Williams 2000]. Yet the use of stents also has drawbacks. Stents have not been greatly successful in high-risk patients. In-stent restenosis (ISR) rates of 30% to 60% occur in diabetics, in patients with diffuse lesions, and in patients with vessels <3.0 mm in diameter [Mehran 1999]. The only treatment to date for ISR has been brachytherapy, approved by the FDA at the start of 2001. Two trials showed reduction of restenosis rates by 43% to 61% and by 36% in patients treated with radiation for ISR compared to patients given a placebo treatment at 9 and 8 months, respectively [Henney 2001]. These results, although substantial, are by no means the definitive answer to ISR. Clearly, if we are to control ISR we must turn to prevention rather than treatment. The latest line of stents—the drug-eluting stents—may hold the answer, not only to ISR but also to the driving force that could propel ICR to becoming the gold standard for the treatment of CAD.

The new drug-eluting stents have been hailed as the possible "holy grail" and "promised land" of interventional cardiology [Hiatt 2002]. They have become the standard therapy for PCIs, although, until now, the use of stents has faced the major obstacle of restenosis. Stenting prevents restenosis by preventing recoil and negative remodeling, but it is well known that stents also contribute to restenosis by increasing intimal hyperplasia. Mechanical arterial injury and foreign body response to the stent induces acute and chronic inflammation of the intima, leading to smooth muscle cell migration and proliferation [Hoffman 1996]. In theory, drug-eluting stents should prevent neointimal hyperplasia by targeting the final common pathway of all cells, the cell cycle. The stents are coated with either a pure drug or, more commonly, a drug-polymer matrix, with a ratio of 30% drug-to-polymer, and although the drugs may also have antiinflammatory and antiproliferative properties, they all target this final pathway to prevent smooth muscle proliferation [Hiatt 2002]. The idea is to work toward a purely cytostatic approach of modulating cell cycle regulatory proteins and away from therapy that would also be cytotoxic (ie, killing proliferating cells), thus avoiding cell necrosis and the associated consequences of inflammation and vessel wall thinning [Hiatt 2002].

Briefly, the leading drug candidates are sirolimus, an immunosuppressive drug used in renal transplant rejection;

Address correspondence and reprint requests to: Dr. Hratch L. Karamanoukian, Center for Less Invasive Cardiac Surgery and Robotic Heart Surgery, Kaleida Health, Buffalo General Hospital, 100 High Street, Buffalo, NY 14203; phone 716-859-1080; fax 716-859-4697 (e-mail: Lisbon5@yahoo.com).

taxol and its derivatives paclitaxel and 7-hexanolytaxol, microtubule inhibitors used for the treatment of ovarian cancer; and actinomycin-D, an antibiotic used in the treatment of various malignancies. The drug showing most promise is sirolimus. In a 6- and 12-month follow-up study of 30 patients with single sirolimus-eluting stent implantation, Sousa et al [2001] demonstrated the virtual absence of neointimal proliferation in all subjects. In the RAVEL study by the same group of investigators, the sirolimus-stent continued to show incredible promise. The randomized trial of 238 patients again exhibited virtual elimination of neointimal hyperplasia and the absence of angiographic stenosis in the sirolimus-eluting stent group at 6 months and a very low rate of cardiac events at 1 year [Morice 2002]. Of particular importance is the success of the sirolimus-eluting stent in diabetics, a subgroup in whom stents have been particularly ineffective [Mehran 1999, Morice 2002]. The results can best be explained by the cytostatic inhibition of cytokine and growth factor–mediated cell proliferation [Gregory 1993]. Other drug candidates have not shown similar results mainly because of concurrent cytotoxic effects. Animal studies of paclitaxel-eluting stents by Heldman et al [2001], Farb et al [2001], and Drachman et al [2000] demonstrated that the stents can inhibit neointimal growth, but at the expense of incomplete intimal healing and arterial cytotoxicity that is dose-dependent, further suggesting a narrow therapeutic window [Hiatt 2002]. No preclinical data is yet available on actinomycin-D.

Stents have big shoes to fill when it comes to occlusion of the LAD. The efficacy of PCI in maintaining perfusion of the LAD is yet to be proven. The LAD has a higher restenosis rate following PCI than non-LAD vessels [Kurbaan 1998]. This point is cardinal because the LAD is the principal vessel to the left ventricle, supplying up to 70% of the ventricle [Mahmarian 1991]. LIMA graft to the LAD, on the other hand, has been found to be the most important determinant of long-term survival in patients with CAD, with patency rates of 95% at 5 years [Loop 1996]. Whereas the LIMA graft has long-term patency, early occlusion rates (≤6 months) in non-LAD vessels for SVG and PTCA are both similar and significant [Lytle 1985, Nobuyoshi 1988]. In addition, CABG and PTCA were found not to differ with respect to the occurrence of the composite primary end point of death, Q-wave MI, and large ischemic defect, imparting further evidence that SVG may not be superior to PCI in determining survival [King 1994].

Thus, the evidence lends itself to the prospect of hybrid revascularization. There exists no alternative to surgical anastomosis of the LIMA to the LAD. Cameron et al [1996] suggest that "it should not be withheld from any subgroup of patients." So paramount is the function of the LAD that a total occlusion of this vessel has been classically termed the "widow maker." The role of the LAD in perfusing the heart, therefore, cannot be taken for granted and deviations from proven interventions should be undertaken warily, only after evidence from solid studies and perhaps only after new methods of intervention have been proven in non-LAD coronary vessels. If an occluded LAD is to be reperfused surgically, we are left with the question of which surgical technique to use.

MIDCAB has obvious advantages to traditional median sternotomy CABG. These advantages include, but are not limited to, performance "off-pump" and avoidance of all the risks concurrent to cardiopulmonary bypass such as stroke, systemic inflammatory responses, postoperative organ dysfunction, and coagulation disorders [Amodeo 2002]. Furthermore, MIDCAB is simpler, quicker, and more cost-efficient, decreases patient morbidity, hastens recovery, and avoids median sternotomy with its associated postoperative complications [Amodeo 2002]. In a study by Calafiore et al [1998] midterm (16 ± 9 months) angiographic follow-up of MIDCAB performed through a left anterior small thoracotomy (LAST) found that 95.6% of anastomoses were both patent and nonrestrictive. In another study by Diegeler et al [1999], 6-month follow-up showed a patency rate of 95.4% of the LAD following MIDCAB. Preliminary results from the Patency Outcomes and Economics of MIDCAB (POEM) trial showed a patency at 6 months of 98.4% for MIDCAB and 96.3% for CABG [Mehran 2000]. Other studies have also proven MIDCAB to be as effective as CABG in producing patency of LIMA to the LAD [Borst 1999, Inderjit 1997, Possati 1998]. Long-term results of the success of MIDCAB should not differ much from those obtained with CABG. In fact, because of the advantages already discussed, we would expect MIDCAB to be an improvement on median sternotomy CABG. The end result of both procedures is, in the truest sense, one and the like—anastamosis of the LIMA to the LAD. Worth mentioning, and surely to have an impact on the future coronary revascularization, are the recent application of endoscopy and/or robotics with and without MIDCAB [Subramanian 2001, Zenati 2001] and the utilization of sutureless coronary anastamosis in coronary bypass grafting [Buijsrogge 2002]. We will relinquish these topics, however, for discussion at a later time. For now, our focus will turn to the hybrid of MIDCAB and PCI.

Independently, MIDCAB and drug-eluting stents are emerging as the new leaders in coronary revascularization. Several studies thus far have demonstrated the safety and efficacy of ICR, combining MIDCAB and PCI with bare metal stents for complete coronary revascularization in individuals with multiple-vessel disease [de Canniere 2001, Cohen 1998, Lloyd 1999, Wittwer 2000]. Clearly, hybrid revascularization has a place in the future of cardiac surgery. In the most recent study, de Canniere et al [2001] claim ICR to be viable and cost-effective and may even prove superior to CABG because of fewer complications and faster recovery. The authors of all the studies agree conclusively on the necessity of randomized, prospective clinical trials comparing ICR and CABG in multivessel disease.

The leading role in ICR, however, has yet to be filled and may very likely be awaiting the drug-eluting stents. It is difficult to contain one's enthusiasm when looking at early results from Sousa et al [2001] and Morice et al [2002] and their work on the sirolimus-eluting stent. Paul Teirstein [2001] terms the results from Sousa et al "the dream of no restenosis." And, although he cautions us to maintain skepticism, he himself can not remain subdued in the wake of such promising news and prospects for the treatment of CAD. In 40 years

of research of surgical, interventional, drug, and dietary treatments, restenosis has consistently and persistently smirked in the face of cardiologists and cardiac surgeons alike, until now. There is reason to smile. The studies have shown that the majority of early restenosis in PCI occurs within the first 6 months and we are now past that mark. What we have to look forward to are follow-up reports by Sousa et al and Morice et al and future studies with promising drugs and stent-coating technologies that have yet to be investigated or even discovered.

Stent-coating technologies are still in their infancy. One novel method creates a polymer sheath with embedded drug, which is then wrapped around the stent and, on deployment, the sheath (with drug) is trapped between the stent and arterial wall, allowing for a larger drug reservoir and more complete contact between drug and intima [Gurbe 2001]. Another aspect that must be addressed is long-term prevention of in-stent restenosis. Currently, we are managing this prevention through drugs, whose role in maintaining long-term patency of all coronary vessels is undisputed and ever-growing. However, such treatment is effective only with aggressive management and depends to a great extent on patient compliance. To attack the problem more thoroughly, we need to look toward stents that are resistant to plaque and thrombus formation. Logically, this step will follow once we have neointimal formation well controlled.

Although the evolution of drug-eluting stents is almost as recent as hybrid revascularization itself, serious consideration should be given to incorporating the sirolimus-eluting stent into prospective clinical trials of ICR, thus simultaneously assessing their synergistic and independent effects on CAD. The impact of minimally invasive surgery combined with interventional procedures that together yield results that are not only comparable to but will very likely surpass the success of CABG over the last generation is immeasurable. No one has more to benefit from such advances than those suffering from CAD. At essence here is the improvement of patients' quality of life. In other words, implementation of hybrid revascularization may lead not only to a longer life but, more important, to a life better lived. Regardless of our field, humanism reaches each one of us individually as physicians. And if humanism in medicine had one voice it would speak to the eradication of barriers between surgeons and interventionalists. As a result, we may witness a new era in the treatment of CAD, with outcomes we could not have imagined on our own.

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Hratch L. Karamanoukian, MD, Pierre S. Aoukar

Center for Less Invasive Cardiac Surgery and
Robotic Heart Surgery, Kaleida Health,
Buffalo General Hospital, Buffalo, New York