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Implications of coronary artery bypass grafting and percutaneous coronary intervention on disease progression and the resulting changes to the physiology and pathology of the native coronary arteries

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Summary

Myocardial revascularization can be achieved through 2 different methods: coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). Clinical trials comparing PCI and CABG generally use the composite end points of death, stroke, myocardial infarction and target vessel revascularization to determine superiority. Other effects of these interventions, including the preservation of normal coronary physiology, the response of the coronary tree to stressors and the response of the vessel wall to the revascularization intervention, are not routinely considered, but these may have significant implications for patients in the medium and long term. For PCI, relatively small differences in clinical outcomes have been reported between bare metal and drug-eluting stents, and the latter seems to have inconsistent and somewhat unpredictable effects on the vascular biology of the coronary arteries. In coronary bypass, the use of arterial conduits is associated with superior clinical outcomes, better long-term patency and the preservation of essentially normal coronary function after intervention. This review assembles the clinical, physiological, angiographic and pathological literature currently available and attempts to provide a more complete picture of the effects of CABG and PCI on coronary arteries.

Keywords: Coronary artery bypass grafting • Percutaneous coronary intervention • Arterial revascularization • Drug-eluting stent • Coronary artery disease

INTRODUCTION

Revascularization through either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) is the standard of care for patients with significant, multivessel coronary artery disease (CAD), particularly those with a high SYNTAX score [1]. The vast majority of PCIs today involve the deployment of drug-eluting stents (DESs) or bare metal stents (BMSs) [2]. Clinicians make choices about revascularization strategies based on patients' acuity, comorbidities and age; however, the impact of these approaches on the coronary artery biology is not completely clear. For patients presenting with acute coronary syndrome (ACS), PCI of the culprit lesion has become the gold standard over the past decade with excellent results [2–4]. In cases of non-ACS CAD, however, the impact that either PCI or CABG will have on the vascular biology of the coronary artery should be

incorporated into the decision-making algorithm alongside patient preferences [5] and the clinical judgement of referring physicians.

For PCI, the need for better protection against vessel reocclusion brought the field of interventional cardiology from balloon angioplasty to BMS, and the challenge of stent restenosis led to the evolution of the DES [6]. Further improvements have focused on mitigating problems related to the stent itself and expanding the clinical indications for PCI [6]. For at least the past 15 years, PCI has been performed at 2–3 times the rate of CABG [7]. The early successes and improved procedural techniques observed in coronary stenting trials on low-risk lesions has resulted in the continued expansion of these devices into higher-risk populations such as patients with ACS or with unprotected left main CAD [6].

For CABG, much of the evolution has been focused on decreasing complications related to the surgery itself and improving postoperative management [8]. The scrutiny imposed

by government and institutional monitoring bodies on patient outcomes has been instrumental in decreasing the operative mortality rate to approximately 2%, where it has remained for the past 10 years [9]. There has been significant evidence published over the last several years suggesting that patients who undergo CABG with arterial grafts have improved graft patency and long-term survival when compared with patients receiving vein grafts [10, 11]. However, the adoption of multiarterial revascularization has been slow, and in most countries, just 5–10% of patients receive a full arterial revascularization.

This article's objective is to assemble and describe published clinical, angiographic, pathological and physiological data behind PCI and CABG. We will also integrate these findings into the clinical context, in an effort to support a better understanding of the long-term implications that these revascularization strategies have for patients.

STENTS

Herein, we provide an overview of the evolution of PCI, but readers may wish to refer to the more comprehensive review of the history of stents by Garg and Serruys [6]. The first BMS, deployed in the mid-1980s, was designed to improve the suboptimal outcomes of balloon angioplasty, which had vessel restenosis rates of 16–44% and reocclusion rates between 30% and 80% [6]. BMS was an improvement over balloon angioplasty; however, the arterial injury caused by stent deployment could generate a continuous and progressive growth of smooth muscle cells described as neointimal hyperplasia [2]. This process led to in-stent stenosis and occlusion in 25–30% of patients [2, 12].

DESs, which elute drugs to inhibit neointimal hyperplasia, were introduced in the late 1990s. The first-generation DES demonstrated restenosis rates in the range of 5–10%, significantly lower than those seen with BMS [6]. By 2005, the vast majority of revascularizations in the USA used DES [7, 13]. This rapid adoption slowed around 2006 with the publication of 2 studies that questioned the benefits of DES over BMS [6]. A meta-analysis found no difference in mortality for DES over BMS at 5 years [14], and a large Swedish registry-based study suggested that DES may be associated with slightly higher mortality than BMS [15]. Similar results were recently demonstrated in the NORSTENT trial, which reported on 9000 patients randomly assigned to receive DES or BMS [16]. After 5 years, no difference was observed in the rates of all-cause mortality or spontaneous myocardial infarction (MI), although the DES group had a slightly lower rate of repeat revascularization.

The latest evolution for PCI is the introduction of bioresorbable stents, an attempt to mitigate the problems associated with the presence of a rigid metallic scaffold inside the coronary artery. In these stents, the scaffold is absorbed over time, theoretically allowing the opened coronary artery to return to its normal physiology. Unfortunately, early results of randomized trials did not confirm the enthusiasm generated by registries; a randomized trial of 500 patients who received either a second-generation DES or a bioresorbable stent failed to produce any improvement in vessel function and had a worse rate of target vessel MI [17].

Patency

Coronary angiography is the gold standard for evaluating the placement and patency of stents. It also allows the evaluation of

the progression of CAD and vasomotor function in the coronary artery. Given the relative rarity of death and major adverse events among patients who have undergone PCI, stent patency and reintervention rates are often used as outcomes in clinical trials. The utility of these measures is complicated by the fact that many studies rely on symptom-driven, rather than routine, angiography.

Routine surveillance of stent patency is relatively rare, which makes the true prevalence of stent restenosis difficult to determine. A large-scale study was conducted at centres in Germany where routine angiography 6–8 months after PCI is the standard of care. Approximately 10 000 patients who had undergone primary PCI and follow-up angiography were included, and the authors found that restenosis rates for BMS, first-generation DES and second-generation DES were 30.1%, 14.6% and 12.2%, respectively [12]. This study has a relatively short follow-up but may represent a more accurate estimate of stent restenosis than large-scale clinical trials, which rely on symptom-driven angiography.

Krasuski *et al.* [18] used angiography to evaluate the progression of CAD in stented coronary arteries and found that DES was associated with a reduced progression of downstream CAD when compared with BMS. This study was limited by the use of a highly selective cohort of patients with a single stent in an artery with no downstream disease, representing only 1.6% of the patients who were stented at the Cleveland Clinic in an 18-year period. Another study, published by Zhang *et al.* [19], examined patients who underwent revascularization of the left anterior descending (LAD) territory and had symptom-driven angiography at least 6 months after the initial procedure. These authors found significant progression of CAD in stented arteries, with no significant difference between stent types.

Pathology studies

Stents can become stenosed, occluded or thrombosed for many reasons, and the aetiologies of these adverse outcomes vary by stent type and change over time. To learn more about these processes, particularly the causes of stent failure, we must consider evidence from pathology studies.

Acute and subacute in-stent thromboses, defined as thrombosis within the first 24 h and the first 30 days after PCI, respectively, are generally attributable to periprocedural factors, such as inadequate sizing, edge dissection or incomplete apposition of stent struts against the vessel wall [20]. The risk of stent thrombosis in the post-procedural time period can be mitigated by the use of dual antiplatelet therapy, which is a standard of care for all patients undergoing PCI [21].

After a stent is deployed, the coronary artery responds to arterial injury by activating vascular smooth muscle cells to cover the stent [2, 22]. An abnormal, continuous activation of this response can induce neointimal hyperplasia, where smooth muscle cell proliferation causes progressive narrowing of the stent (Fig. 1A). The process of endothelialization for BMS has been clearly described, and the stent will be fully covered by endothelial cells 3–4 months after deployment [20]. In the case of DES, the eluted drugs temporarily inhibit neointimal hyperplasia. After the drug dissipates, it can take up to a year for the DES to be covered by endothelium and that coverage may be incomplete (Fig. 1B) [20, 23]. This delayed healing pattern may be inconsistent or patchy and represents a state of vascular instability when compared with

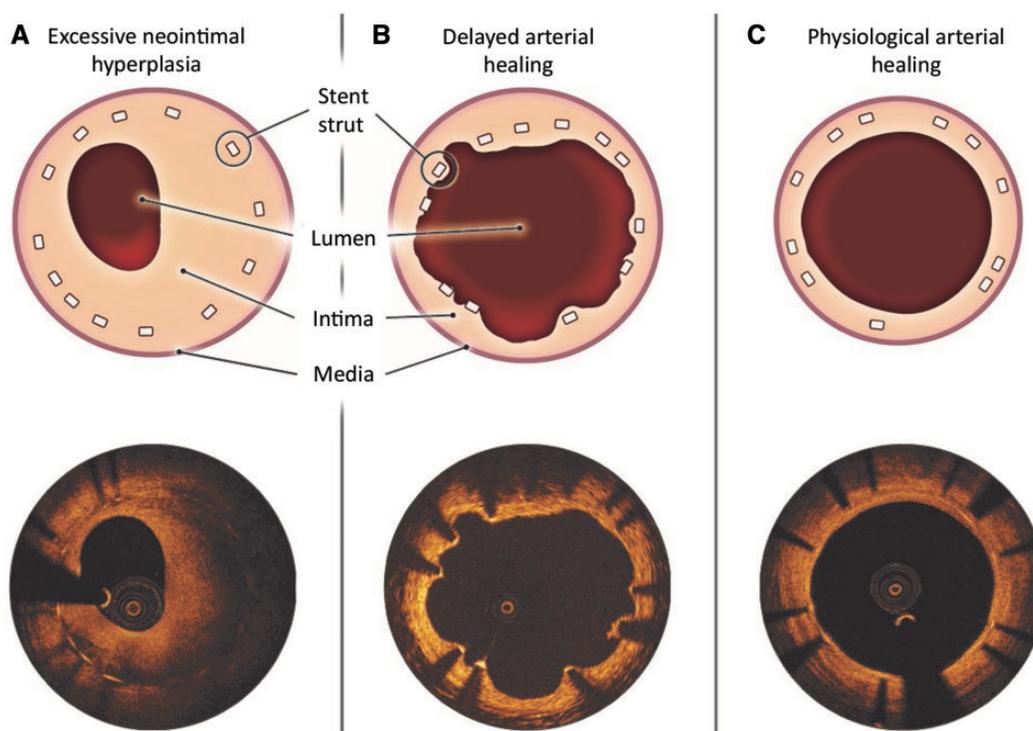


Figure 1: Three distinct patterns of healing observed (A) after the deployment of a coronary stent, including excessive neointimal hyperplasia, (B) delayed arterial healing with protruding stent struts and (C) normal arterial healing. Reproduced with permission from Stefanini and Holmes [2].

normal arterial healing after stent deployment (Fig. 1C) [20]. This healing occurs in the presence of both acute and chronic inflammation that has been observed at the site of, and distal to, the stent [24, 25].

The neointimal layer that forms on all stents may be subject to atherosclerosis [26]. Pathology studies call this as neoatherosclerosis as it is separate from the atherosclerotic plaque of the native coronary artery. When the stent is completely and consistently covered by smooth muscle cells (Fig. 1C), the plaques that form are relatively stable. However, when endothelial coverage is patchy (Fig. 1B), vascular plaques are more prone to rupture. Pathological analyses suggest that DES is more likely to show evidence of neoatherosclerosis when compared with BMS, and it is observed earlier after stent deployment [26]. The second-generation DES seem to be less prone to patchy endothelial coverage [2], but large trials have yet to show improvements in outcomes such as mortality [16].

Late-stent thrombosis is a complex problem with several contributing factors [27, 28]. After 1 year, stent thrombosis is often attributed to progression of neoatherosclerosis, extensive fibrin deposition or a rare inflammatory hypersensitivity response to the stent's polymer [29]. The risk of thrombosis is uncommon in BMS after the artery heals, but DES thrombosis is a concern for at least 4 years after stent implantation [20, 27]. Published data suggest that late-stent thrombosis rates are additive, at a rate of 0.2–0.6% per patient per year. The risk of in-stent thrombosis seems to be higher in patients who undergo stenting to treat ACS, as their stents have an increased proportion of uncovered struts and more inflammation [30, 31]. Significant strides have been made in improving stent patency, but the issue of in-stent thrombosis remains a significant concern [20, 28].

Coronary physiology

The coronary tree is a reactive network of vessels that respond to stimuli such as exercise and stress. During exercise, for example, the normal response of the coronary tree is vasodilatation to increase coronary flow and meet the demands of the heart. A functional endothelium plays a central role in this responsive process, synthesizing and excreting potent vasodilatory molecules, such as nitric oxide (NO) [32].

Many studies have examined endothelial function after coronary stenting. These include measurements of vasomotion and response to exercise, rapid atrial pacing and chemical stressors such as acetylcholine [33]. In a review, studies that evaluated different DES and BMS were pooled, and the response to stressors was examined [34]. The authors reported a variable but consistently abnormal response to acetylcholine injection or exercise among DES; the stented coronary arteries vasoconstricted rather than vasodilated in response to these stressors [35–37]. In contrast, BMS had a more typical response, with the downstream coronary bed vasodilating in response to exercise and acetylcholine.

The literature does not report a uniform response of all stents to all types of coronary stressors. Rather, it suggests that DES seem to be consistently associated with different, inappropriate responses to at least one of the coronary stressors mentioned above [33–35, 37]. In contrast, the oft-maligned BMS seems to leave coronary endothelial function intact.

CORONARY ARTERY BYPASS GRAFTING

CABG was first introduced in the mid 1960s [8]. Early CABG was a risky procedure, with mortality rates of up to 10% and perioperative

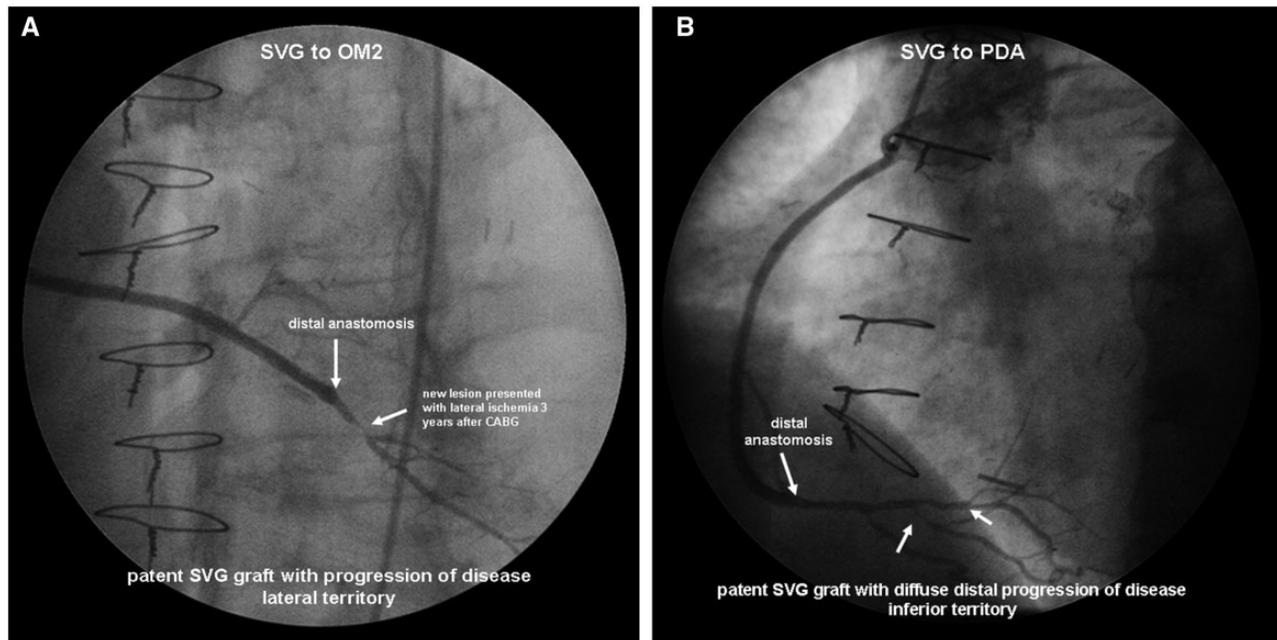


Figure 2: Angiographic images of observed disease progression that is distal to patent SVGs to (A) a lateral territory and (B) an inferior territory. Reproduced with permission from Dimitrova *et al.* [44]. CABG: coronary artery bypass grafting; OM2: second obtuse marginal; PDA: posterior descending artery; SVG: saphenous vein graft.

MI rates of 15%. Patients who survived the initial procedure, however, reported improved symptoms in 70–95% of cases. For the 1st 30 years after it was introduced, research focused on identifying populations in which the potential benefits of CABG outweighed the substantial risks, but as techniques improved, CABG was indicated for a broader population of patients with CAD [8].

Despite the fact that the very first CABG was performed using an internal mammary artery (IMA), saphenous vein grafts (SVGs) were the conduit of choice until the late 1970s [8]. In 1978, FitzGibbon *et al.* [38] described the early failure of venous grafts, at a rate of up to 11% in the first 2–3 weeks after surgery. The failure of SVGs was an area of the literature to which FitzGibbon *et al.* [10] would contribute until at least the 1990s, with little improvement in the observed rates of SVG failure.

The use of arterial grafts – particularly the left internal mammary artery (LIMA) to graft the LAD artery – was initially limited to only a few centres, but became more common in the late 1970s and 1980s. The state of the art with respect to conduit selection seems to favour arterial grafts over venous grafts, with most studies indicating superior long-term patency and equivalent or better survival outcomes for patients who receive multiarterial CABG. This may be due, in part, to the innate qualities of the IMAs, which appear to have ‘striking resistance to the development of atherosclerosis’ [39].

An understanding of the progression of disease within grafts, particularly SVG, has led to attempts to improve the durability of these conduits, from surgical techniques to postoperative medical therapy. Surgically, no-touch harvesting techniques, pump status and the use (or non-use) of endoscopy for SVG harvesting have all been discussed in detail by others [40]. Postoperatively, studies have evaluated medical therapies to increase long-term graft patency. Aspirin and clopidogrel improve vein graft patency in the 1st year after CABG, but there is presently no high-quality evidence of any improvement in SVG patency beyond 3 years for any medical therapy [40]. No surgical technique or medical therapy to date has allowed a vein to exhibit the complex biological properties of an artery.

Angiography

Angiographically, the progression of CAD after CABG has been described in large populations. SVGs are more prone to the development and progression of CAD. As with stenting, a major shortcoming in studies on patients who have undergone CABG is that the angiograms are often symptom driven, and the true prevalence of graft failure is difficult to assess.

A long-term study completed in the 1990s on the patency of 5065 grafts over 25 years found that only 23% of SVGs were free of atherosclerosis by 10 years, a rate that decreased to 14% at 12.5 years [10]. This is an improvement over the rates observed by FitzGibbon *et al.* in the 1970s [38] but is still suboptimal. In a more recent follow-up study published in 2007, just over 36% of vein grafts were free of disease at 10 years, despite more modern surgical techniques and medical therapies [41]. Arterial grafts, on the other hand, have superior patency rates, with 62.5% of LIMA and 56.1% of RIMA grafts found to be patent at 10 years [41]. The use of radial arteries has varied over time due to concerns about arterial spasm and potentially poorer patency than IMAs, but studies have suggested that approximately 90% of radial artery grafts are patent at 5 years [42]. The gastroepiploic and the inferior epigastric arteries are even less commonly used conduits for CABG, but again, patency rates are reported to be approximately 86% after 5 years and 70% after 10 years in selected series [43].

Just as with stenting, the effects of CABG do not seem limited to the graft itself, and there may be an impact on the distal coronary beds. Dimitrova *et al.* [44] examined almost 800 patients undergoing coronary angiography for recurrent symptoms. Angiograms were conducted on an average of 5.5 years after CABG. In the presence of patent graft conduits, the use of SVGs was associated with significantly more progression of downstream CAD progression when compared with the LIMA or radial artery (Fig. 2). As mentioned previously, Zhang *et al.* [19] examined patients undergoing revascularization of the LAD artery with either stents or CABG using the LIMA; they also found

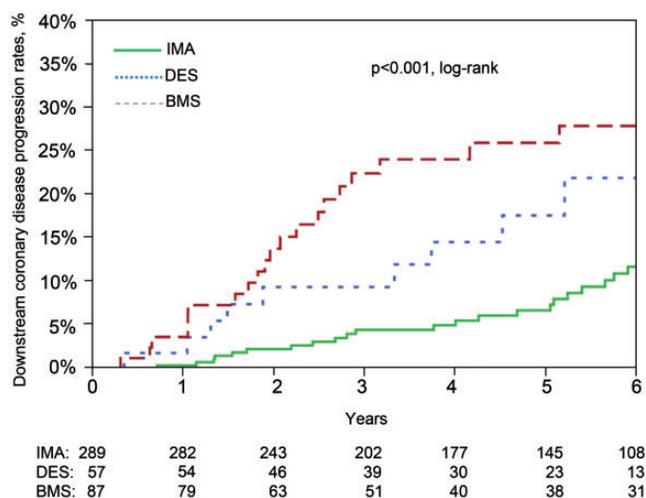


Figure 3: The Kaplan-Meier estimated cumulative downstream coronary disease progression rates in patients who underwent revascularization of the left anterior descending artery (the left internal mammary artery versus BMS versus DES; log-rank test, $P < 0.001$). Reproduced with permission from Zhang *et al.* [19]. BMS: bare metal stent; DES: drug-eluting stent; IMA: internal mammary artery.

significantly lower downstream progression of CAD in the LIMA group when compared with PCI (Fig. 3). This is consistent with a genomic analysis of both IMAs, which suggested that the pathways associated with atherosclerosis and inflammation are downregulated in these conduits [45].

Pathology studies

In the first 30 days after CABG, grafts are vulnerable to thrombotic occlusion, as demonstrated in early pathology studies [46]. After 1 month, SVGs are subject to an evolving disease process that begins with neointimal hyperplasia, an accumulation of smooth muscle cells and extracellular matrix that can significantly reduce the lumen [40, 47]. This may progress to the accumulation of atherosclerotic plaque that leads to stenosis or occlusion of bypass grafts [47].

Pathological studies of venous conduits have shown that narrowing of SVG is relatively common, with narrowing of 75% or greater seen in almost half of patients who died of cardiac causes and one-fifth of patients who died of non-cardiac causes [48]. Interestingly, narrowing of the SVG conduit was also significantly associated with luminal narrowing of the coronary artery distal to the conduit anastomosis. Early work from Lawrie *et al.* [46] suggests that intimal proliferation is responsible for narrowing of the graft but rarely for occlusion. Pathological analysis of SVGs from normal versus hyperlipoproteinaemic patients showed greater progression of intimal proliferation over time in patients with poor lipid control, underscoring the importance of guideline-driven medical therapy after CABG [49].

Coronary physiology

As with stenting, coronary artery endothelial function, vasomotion and response to stressors changes after CABG. Nishioka *et al.* [50] injected acetylcholine into the LIMA or SVG during angiographic assessment. In addition to quantification of coronary diameter, the metabolites of NO metabolism were measured in

the coronary arteries distal to the graft site. The authors demonstrated that the LIMA responded in a way similar to a normal coronary artery, with vasodilation and increased NO production, whereas the SVG response was abnormal, with vasoconstriction and no increase in NO metabolites.

Further evidence on the preservation of endothelial function with arterial grafts was provided by Glineur *et al.* [51]. These authors injected an NO-dependent vasodilatory stimulus, substance P, or normal saline into the proximal limb of the Y construct with 2 mammary arteries. They observed an appropriate vasodilatory effect in the substance P group, which suggests functioning endothelium in the IMA grafts.

Overall, CABG with arterial grafts seems to preserve endothelial function in a way that neither SVGs nor stenting can. Arteries are complex, functional units that vasodilate to meet the needs of the coronary tissues they perfuse [52], and it is logical that grafting a coronary artery with an arterial conduit would be more likely to preserve this function than grafting with a vein or inserting a stent. Although surgical techniques, the skill of the surgeon and postoperative medical management will all affect graft patency and function, the evidence suggests that arterial grafts are more conducive to the normal function of the coronary artery upon which we have intervened.

DISCUSSION

When we intervene on a coronary artery, the effects of that intervention can be long-lasting and may not always benefit the patient. Beyond the short-term benefit intuitively expected from the restoration of a myocardial perfusion, the potential consequences related to the mode of coronary revascularization should be considered. These are 2 profoundly different attempts to address the consequences of advanced CAD, and this review summarizes clinical, angiographic, pathological and physiological evidence in an attempt to raise awareness of the complex, responsive nature of coronary arteries and suggests the need for a significant shift in the way we make decisions about coronary revascularization.

The success of coronary revascularization strategies is currently measured by clinical outcomes such as survival, major adverse cardiovascular events and the need for reintervention. This is understandable given the invasive nature of most functional measures of arterial function, such as the acetylcholine stress testing described above, and the potential ethical concerns with subjecting asymptomatic patients to routine angiographic assessments. By clinical metrics, it appears that CABG is superior to PCI in the long term, with only a small increase in the risk of stroke and a longer length of hospitalization. Large meta-analyses have demonstrated a continuously improving safety profile of CABG, with lower perioperative morbidity and mortality, and significant improvement in long-term survival and the need for repeat intervention. There is, however, variability in the way the operation is being performed, particularly with respect to conduit choice. The progressive adoption of multiarterial CABG has maintained the quality of the outcomes with significant improvement in long-term disease-free survival and decreased the need for repeat intervention.

With regard to PCI, despite an evolution in the technology, the fundamental outcome of survival has not improved. The NORSTENT trial is the latest among many studies that failed to detect any survival difference between BMS and DES [16]. The

recent introduction of next-generation bioresorbable stents has also, to date, failed to live up to high expectations [17].

Clinical outcomes are one way to measure performance, but they provide only a limited assessment. The success of cardiovascular interventions is generally quantified using imaging such as echocardiography. Yearly monitoring is considered the standard of care for valvular interventions, but patients who have undergone myocardial revascularization are seldom subject to routine imaging. This represents a major shortcoming in our ability to evaluate the long-term durability of our interventions after either PCI or CABG. Ideally, patients who have PCI or CABG should be regularly monitored using computed tomography (CT) perfusion scan, intravascular ultrasound or coronary angiogram.

For revascularized patients, coronary angiography assesses the sites of interest, the distal coronary bed and the functional status of the coronary artery and conduit. Angiograms demonstrate superior patency rates for CABG with arterial versus venous grafts and a linear rate of graft failure that relates fundamentally to the SVG bypasses. In the cardiology literature, DES seems to represent an improvement over BMS with respect to patency measured angiographically [6]. The newest generation of DES has a lower incidence of thrombotic complications when compared with the first-generation DES and BMS; this may be due to improvements in stent design, polymer characteristics, the anti-proliferative drugs or more aggressive medical therapy.

Angiography also allows us to observe the functional status of the coronary arteries after the intervention. Although there is variability between types of stents and their responses to stressors such as exercise and acetylcholine injections, overall there is a consistent dysfunction in the vasomotion of stented coronary arteries. In CABG, on the other hand, there are clear differences between venous and arterial conduits [53]. This is not surprising, as the structure of a vein significantly differs from that of an artery. Arterial grafts are designed to sustain systemic pressures and have a functional endothelium. Veins are ill-equipped to sustain systemic pressures and lack endothelial function. Predictably, coronary territories that are bypassed with arterial grafts have an appropriate response to stressors, which is not observed with venous grafts.

Angiography is very informative for clinicians during the diagnosis, treatment and follow-up of patients who have undergone coronary revascularization but offers little insight into the state of the arterial wall. The angiographic findings would seem to suggest underlying pathological processes that have been extensively studied after PCI and examined to a lesser degree after CABG. DESs were designed to reduce the rates of stent restenosis observed with BMS, but the innate qualities of the drugs they elute affect endothelial coverage of the stent. Patchy coverage may create an unstable vascular environment, and when it is subject to neoatherosclerosis, the resulting plaques are more prone to rupture and thrombosis. DES addressed one problem with earlier devices but inadvertently created another that is more unpredictable.

In CABG, there is much less information about the pathological implications of bypassing a vessel with arteries versus veins. Our current evidence suggests that a properly-constructed arterial bypass is vastly superior to a venous graft and demonstrates less progression of CAD, a normal vasomotor response to coronary stressors and evidence of NO production by the functioning endothelium.

The less-invasive nature of PCI is appealing to patients, and studies have shown that a majority of patients would choose PCI

over CABG even if the risk of death or repeat intervention is 2 or 3 times higher, respectively [52]. Patients also seem to be somewhat misinformed about the primary role of PCI, with many believing that it will reduce their risk of death or MI [54]. In contrast, clinicians show a greater understanding of the limitations of PCI and were more likely to choose CABG over PCI when the risk of mortality and repeat intervention increased [52]. Interestingly, even brief explanations on the limitations of PCI have been shown to significantly affect preferences of patients [55]. A greater awareness of the clinical and physiological implications and limitations of PCI and CABG would undoubtedly help patients and clinicians to make more informed choices based on their individual values and preferences.

The acuity of the case and the age and comorbidities of the patient are important when deciding which coronary intervention should be undertaken. PCI has been instrumental in saving the lives of patients with ACSs over the past decades. The use of PCI in this setting will never be replaced by a surgical intervention due to the speed and efficiency that PCI can provide. PCI is also well suited to treat coronary lesions in elderly patients with limited life expectancy, where the benefits of a less-invasive procedure may outweigh the need for a durable 10- or 15-year outcome.

One of the fundamental problems with decision-making in revascularization is our relatively poor understanding of the broader impacts of interventions. A stent does not simply open a coronary artery, and a bypass graft does not simply route blood around a blockage. PCI and CABG can significantly affect the complex, dynamic functioning of the coronary arteries, in ways that we do not fully understand. This leaves interventional cardiologists and cardiac surgeons with an incomplete picture and hampers true evidence-based medicine.

When dealing with an elective situation and a younger patient, a clinician's goal should be an intervention that provides a durable long-term outcome and preserves the coronary physiology. With the current safety profile of surgical revascularization, CABG using arterial grafts represents a very durable option that should be strongly considered as the first choice for patients with a reasonable life expectancy.

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