Coronary Arterial Revascularization: Past, Present, Future: Part I—Historical Trials

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Summary: Advances in coronary artery revascularization have been accompanied by clinical trials evaluating these advances. From the Coronary Artery Surgery Study and Bypass Angioplasty Revascularization Investigation to the more recent Arterial Revascularization Therapy Study (ARTS1) and the Medicine, Angioplasty, or Surgery Study (MASS2), these clinical trials provide us with a rationale for the way we conduct clinical practice. This paper reviews the data supporting historical revascularization strategies for our patients, including medical therapy, angioplasty, and bare metal stents. Several recurrent themes emerge. These include a need for increased revascularization in patients who undergo percutaneous treatments, the durability of surgical arterial revascularization, and the importance of medical therapy as the mainstay of treatment. Part II will address newer therapies.

Key words: coronary artery bypass surgery, bare metal stents, balloon angioplasty, clinical trials

Introduction

Technological advances in percutaneous and surgical coronary artery revascularization techniques have led to improvements in the quality of life of patients with ischemic coronary disease. Landmark papers demarcating the role of revascular-

ization for ischemic coronary disease have accompanied these advances. This paper reviews the history of these procedures and provides an overview of the landmark clinical trials. It then addresses the data of more controversial areas of coronary arterial revascularization, including off-pump bypass surgery and left main coronary artery stenting.

History of Catheterization and Bypass Surgery

Revascularizing the myocardium is built on three centuries of research. Stephen Hales described catheterization in 1711; modern cardiac catheterization extended the work of Drs. Werner Forssmann, Andre Cournard, and Dickinson Richards, for which they shared the 1956 Nobel Prize in Medicine. Dr. Mason Sones discovered selective coronary angiography accidentally in 1958. Dr. Grüntzig performed the first catheterization laboratory percutaneous transluminal coronary balloon angioplasty (PTCA) in 1977,¹ initiating the modern era of percutaneous coronary artery revascularization.

The development of surgical coronary revascularization was also being conceptualized in the early twentieth century. In 1910, Alexis Carrel presented a paper to the American Surgical Association describing the principles of coronary artery bypass surgery (CABG); he was awarded the Nobel Prize in Medicine in 1912. In 1953, Dr. John Gibbon performed the first heart-lung bypass. By 1968, Dr. Rene Favaloro first reported using a saphenous vein graft for coronary artery disease;² Garrett *et al.* performed the first such surgery, reporting on it in 1973.³

Coronary Artery Bypass Surgery versus Medical Therapy

The Coronary Artery Surgery Study (CASS)⁴ delineated the role of CABG in the early 1970s. It randomized 790 patients between 1975 and 1979 to surgical and medical therapy and followed them for 5 years. The average annual mortality rate was 1.1% in the surgical arm and 1.6% in the medical arm ($p = \text{NS}$). At 10-year follow up,⁵ 40% of medically treated patients had crossed over, and there was no difference in

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survival (79 vs. 82%); patients with ejection fractions (EF) < 50% had better survival if initially treated with surgery (61 vs. 79%, $p = 0.01$).

Most patients in CASS were not receiving aspirin or beta blockers, and the trial was conducted before the era of 3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase inhibitors (statins) and angiotensin-converting enzyme (ACE) inhibitors. Patients with triple-vessel disease (TVD) and EF between 35 and 50% had a 7-year survival rate of 88% in the surgical arm versus 65% in the medical arm ($p = 0.009$).⁶ Patients who had only single- or double-vessel disease or normal EF had similar mortality in the two treatment arms. The high crossover rate to surgery underestimated the benefits of CABG.

In a meta-analysis combining 2,649 patients in seven trials enrolled from 1972–1984, Yusuf *et al.*⁷ defined high-risk groups benefiting from CABG. At 5 years, 25% of patients had crossed over to CABG; at 10 years, 41% had crossed over. Patients were mostly male (average age 51 years) and had a mean EF of 59% (19% of patients had EF < 50%). Triple-vessel disease was present in 51% of patients; 59% of patients had proximal left anterior descending (LAD) artery disease and 7% had left main coronary artery (LMCA) disease. Only 10% of patients undergoing surgery had a left internal thoracic artery (LITA) graft, which subsequently has been shown to be independently associated with survival. Table I demonstrates the results of the meta-analysis. It shows that there were statistically significant reductions in mortality with surgery at 5, 7, and 10 years. Only patients in the lowest risk tertile, as defined in the Veterans Administration Cooperative Study,⁸ had no demonstrable benefit from surgery. Patients with significant LMCA disease and treated with medical therapy had a 5-year mortality rate of 36.5%, with surgery strongly benefiting these patients. Patients with low EF had a 5-year medical mortality rate of 25%, and surgery was a survival benefit, demonstrating the advantage of CABG in high-risk populations.

TABLE I Results of coronary artery bypass graft (CABG) and mortality meta-analysis evaluating surgery and high-risk subgroups.

	CABG	Med Rx	p Value
5-year mortality (%)	10.2	15.8	<0.0001
7-year mortality (%)	15.8	21.7	<0.001
10-year mortality (%)	26.4	30.5	0.03
5-year follow-up	Medical mortality	Odds ratio favoring CABG	p Value
Triple-vessel disease (%)	17.6	0.58	<0.001
Left main artery (%)	36.5	0.32	0.004
Normal EF (%)	13.3	0.61	<0.001
Low EF (%)	25	0.59	0.02
Highest-risk tertile (%)	23	0.50	0.001
Lowest-risk tertile (%)	5.5	1.18	0.7

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Abbreviation: EF = ejection fraction.

Coronary Artery Bypass Graft Compared with Percutaneous Transluminal Coronary Angioplasty

As PTCA developed as a method for revascularizing patients in the 1980s, the National Heart, Lung, and Blood Institute funded the Bypass Angioplasty Revascularization Investigation (BARI).⁹ This study was designed to demonstrate the noninferiority of PTCA and, from 1988–1991, randomized 1,829 patients with multivessel coronary artery disease (MVD) and qualitative or quantitative ischemia to CABG or PTCA, following them for an average of 5.4 years. Revascularizations were required to be amenable to both PTCA and CABG (i.e., no LMCA disease and no target vessel < 1.5 mm in diameter); only 15% of screened patients were enrolled. The primary endpoint was all-cause mortality with new Q-wave myocardial infarction (MI) as the secondary endpoint. Medical therapy for the two groups was not specified.

The patients were well matched, and 99% underwent the intended treatment. Of these, 36% had proximal LAD disease, and there was an average of 3.4 lesions with > 50% stenosis. Mean bypass time was 90 min, and the LITA was used 82% of the time, a significant improvement over the arterial revascularization in CASS. Percutaneous transluminal coronary angioplasty was performed on an average of 2.4 vessels per patient, and at least one vessel was dilated in 88% of patients.

The 1-year survival rate was 96% for CABG and 94% for PTCA; 5-year survival rate for CABG was 89% and 86% for PTCA ($p = 0.76$). A post-hoc subgroup analysis of patients with diabetes had 5-year survival rates of 81% with CABG and 66% with PTCA; those free of diabetes had a 91% survival.

Over the 5-year period, 8% of patients who had undergone CABG required repeat revascularization, as against 54% who had undergone PTCA. Results from this trial define clinical practice today: patients with MVD and diabetes tend to be referred for surgery.

A recent BARI substudy¹⁰ demonstrates the importance of aggressive medical therapy, regardless of revascularization techniques. In this angiographic follow-up of a subgroup of patients in BARI, native coronary artery disease (CAD) rather than disease progression at the site of angioplasty or within grafts more commonly was the cause of recurrent angina. This suggests that interventions that reduce atherosclerotic progression (i.e., smoking cessation, control of diabetes, and use of beta blockers, ACE inhibitors, and statin therapy) play a significant role in revascularized patients with CAD.

In 1995, prior to BARI, Pocock *et al.*¹¹ published a meta-analysis of eight trials comparing PTCA and CABG. These trials differed between single- and multivessel disease; mean follow-up was 2.7 years. In all, 3,371 patients were randomized (1,661 CABG and 1,710 PTCA). Coronary anatomy had to be amenable to surgery and PTCA—large numbers of patients were screened prior to randomization. Use of repeat coronary angiography and intervention varied from clinical indication to protocol requirement. There was no difference in the combined endpoint of cardiac death and nonfatal MI, but the PTCA arm needed markedly more revascularizations (34 vs. 3.3% in the first year). Fatal events in this low-risk patient

population were few. Each group had a 1-year mortality of 2.8%. High-risk patients with LMCA disease or TVD were excluded from these trials, which favored PTCA results. Because of the need for repeat revascularization, costs equalized over time.

Coronary Artery Bypass Surgery Compared with Bare Metal Stents

The need for revascularization in the PTCA arm was driven by restenosis, which occurred in 30–50% of patients who had undergone angioplasty within the first 6 months after the procedure. In 1986, working in Toulouse, France, Jacques Puel and Ulrich Sigwart inserted the first stent into a human coronary artery;¹² in 1994, the Palmaz-Schatz stent was approved for use in the United States. Bare metal stents (BMS) reduced restenosis rates to approximately 25% in 6 months. A second series of trials was initiated to determine whether this reduction in restenosis changed the risk benefit equation in revascularization therapy.

Stent or Surgery (SoS)¹³ was an international trial between 1996 and 1999 and randomized 988 patients to CABG (n = 500) and percutaneous coronary intervention (PCI) with stents (n = 488). Symptomatic patients were enrolled if the coronary anatomy was amenable to both surgery and PCI and had no additional indication for surgery (e.g., valve disease). Any stent could be used, but companies sponsoring the trials supplied their stents free. All patients were followed for a mean of 2 years; 97% underwent the planned intervention. The primary outcome was rate of repeat revascularization; secondary outcomes were death, Q-wave MI, all cause mortality, angina, left ventricular ejection fraction (LVEF), and medication requirements.

The average age of patients was 61 years; 79% were men. Severe angina was present in 46% of patients; 24% presented with an acute coronary syndrome; 42% had TVD; mean EF was 55% in both groups. In patients who underwent PCI, 94% of attempted lesions were revascularized; stents were implanted in 78% of lesions (mean 2). The mean number of bypass grafts was 2.8; an arterial graft to the LAD was used 93% of the time (81% were LITAs); mean bypass time was 70 min.

Over 2 years, 21% of patients in the PCI group and 6% of the CABG group required repeat revascularization. Death and nonfatal Q-wave MI were similar in both groups. Death was significantly greater in the PCI group—hazard ratio (HR) 2.91 (confidence interval: 1.29–6.53, $p = 0.01$)—although the absolute numbers were small: PCI 5% (n = 22), CABG 2% (n = 8). When cancer deaths were eliminated, the difference became nonsignificant.

A similar trial, the Arterial Revascularization Therapy Study (ARTS)¹⁴ was also conducted in Europe. Between 1997 and 1998, patients were randomized to CABG (n = 605) or PCI (n = 600). Inclusion criteria were anatomy equally amenable to either surgery or PCI; angina or silent ischemia; and lesions in two different territories (at least one in the LAD). Patients were excluded if they had been previously revascular-

ized; had a prior stroke, LMCA disease, or MI in the prior week; or had concomitant medical illness prohibiting surgery. The trial included prospective evaluations of cost effectiveness and quality of life assessments.

In each arm, 2.8 lesions with at least a 50% stenosis were identified for treatment. In the stent arm, an average of 2.6 lesions were treated, 89% by stents; 15% of patients had prospectively identified lesions left untreated. In the surgery arm, an average of 2.6 anastomoses were made, using an average of 2.5 conduits; 95% of patients received an arterial conduit to the LAD. In 4.5% of patients, the intended surgical procedure was not performed.

Five-year follow-up for the ARTS trial¹⁵ found that overall mortality was statistically similar: 8% in the stent arm and 7.6% in the CABG arm. There was no statistical difference in the overall rate of death, MI, or stroke (18.2% in the stent arm and 14.9% in the CABG arm). The stent group underwent significantly greater repeat revascularization (30.3% for stent arm and 8.8% for CABG arm); 10.5% of patients with stents underwent CABG within 5 years of enrollment. There was a trend toward mortality benefit in diabetic patients who underwent CABG (8.3%) compared with those who received stents (13.4%) ($p = 0.27$). An anastomosis to the LAD was the most significant predictor of survival.

Compared with nondiabetic patients, diabetic patients undergoing CABG showed no significant difference in mortality or major adverse cardiac events (MACE). Diabetic patients with stents had a significant increase in both mortality (13.4 vs. 6.8%, $p = 0.03$), and MACE (42.9 vs. 27.5%, $p = 0.002$) compared with nondiabetic patients undergoing PCI. Patients with stents had greater need for antianginal medications. The subacute stent thrombosis (SAT) rate for stents was 1.1% within the first 3 months and accounted for 40% of MACE for the PCI arm. The most significant predictor of survival free of MACE in the stent arm was high-pressure stent deployment.¹⁶

A meta-analysis¹⁷ of four major stent versus surgery trials—ARTS1, the Stent or Surgery trial (SoS), the Estudio Randomizado Argentino de Angioplastia vs. Cirugía trial (ERACI)2, and the Medicine, Angioplasty, or Surgery Study (MASS)2—was presented in 2003. There were 1,518 patients in the PCI arm and 1,533 patients in CABG arm. At 1 year, there was 3% mortality in the PCI arm and 2.8% mortality in CABG arm (NS). There was no difference in MACE at 1 year (9.1% CABG vs. 8.7% stent); however, there was a greater revascularization rate in the PCI arm than in the CABG arm (24 vs. 13%, HR 1.94, range 1.6–2.3). These results suggest that compared with PTCA, stents reduced the need for revascularization, but with a continued significant advantage in the bypass surgery arm. The average follow-up was only 1 year and the benefit of arterial revascularization seen in the earlier surgery studies was not demonstrated until 3 years later.

Previous trials excluded high-risk patients; Angina With Extremely Serious Operative Mortality Evaluation (AWE-SOME)¹⁸ was designed to determine whether patients with medically refractory ischemia and one of the following high-risk features—prior heart surgery, age > 70 years, LVEF < 35, intra-aortic balloon pump (IABP) requirement prior to sur-

ger, or MI within 1 week before CABG—would benefit from surgery or PCI. Patients with LMCA disease were excluded. The AWESOME trial, a VA study, screened 22,662 patients of whom 454 were randomized to either PCI or CABG; 54% received stents; LITAs were used in 70%. Medical therapy was shown to be better than in previous trials (88% of patients were receiving aspirin and 76% beta blockers).

Survival at 3 years was identical: 79 versus 80% ($p = 0.46$). Patients with CABG had significantly less repeat revascularization ($p = 0.001$), and those who underwent PCI were as likely to be free of unstable angina as those who underwent CABG (65 vs. 59%).

With improvements in surgery, PCI, and medical therapy, the Medicine, Angioplasty or Surgery Study (MASS-II)¹⁹ screened 20,769 Brazilian patients and randomized 611 low-risk patients between 1995 and 2000 to medicine, CABG, or PCI. Patients with unstable angina, prior revascularization, EF < 40%, and LMCA disease > 50% were excluded. The primary endpoint was incidence of cardiac mortality, MI, and refractory angina requiring revascularization. In patients with CABG, an internal thoracic artery graft (ITA) was used 92% of the time and an average of 3.3 vessels were grafted; 74% of patients had all intended vessels grafted.

Patients were provided free medical therapy; a surprising number of patients post surgery and post PCI did not receive optimal medical therapy; this therapy (aspirin, beta blockers, statins, and ACE inhibitors) was far more likely to be used in the medical arm. Although there were fewer deaths in the medical therapy arm (1.5% medical arm, 4.5% PCI arm, 4.0% CABG arm), these differences were not statistically significant. Patients in the PCI arm had a significantly greater event rate, driven mainly by Q-wave MI (5.0% medical arm, 8.3% PCI arm, 2.0% CABG arm, $p = 0.01$). Repeat revascularization secondary to angina was significantly less frequent in the CABG group. Limited 1-year follow-up masked the potential survival benefit of CABG.

Analysis of the New York State Cardiac Registries, which enrolled all patients in New York State undergoing CABG or multivessel PCI from 1997–2000, suggests that clinicians have incorporated this information.²⁰ Patients who underwent CABG were older, had worse LVEF, had increased comorbid conditions, and were more likely to have TVD. When adjusted for severity of disease, patients with TVD including proximal LAD lesions had a 3-year survival with CABG of 89.3% versus 84.4% for PCI. Adjusted hazard ratios favored CABG in most subgroups.

Stents Compared with Medical Therapy

Although PTCA has been shown to reduce angina, the ability of stents to reduce MACE (death, MI, or repeat revascularization) in stable angina has not been shown. A recent meta-analysis of trials, randomly assigning patients to medical therapy versus PCI, included a total of 2,950 patients from 11 different trials.²¹ Overall, the patients were mostly men with angina and normal LVEF; most patients received stents. Fol-

FIG. 1 Improvements in coronary artery disease (CAD) mortality over time; note that the stent data are for 1-year and follow-up only. CASS = Coronary Artery Surgery Study, BARI = Bypass Angioplasty Revascularization Investigation, PTCA = percutaneous transluminal coronary angioplasty, PCI = percutaneous coronary intervention.

low-up varied between 1 and 7 years. Regardless of whether patients received stents, there was no significant difference in MACE or components of MACE. Patients who underwent PCI had no increased need for CABG, as had been suggested by earlier studies. The study did not have the ability to analyze different anatomical subgroups (e.g., proximal LAD disease). This study reinforces the concept that PCI improves quality of life for patients with stable angina, but does not alter morbidity or mortality outside of angina. The benefit of performing PCI in patients with silent ischemia and without acute coronary syndromes is unclear.

Summary of Older Revascularization Studies

From the original CASS study to the more recent ARTS study, several trends become obvious. Higher-risk subsets, such as those with LMCA disease or ischemic cardiomyopathies did better with surgery. The longevity and durability of a surgical arterial graft to the LAD provided patients with significant anginal relief and the need for fewer revascularizations. Overall, BMS reduced the revascularization rates by half compared with those in the PTCA trials, and with medical therapy, mortality rates also seem to show a downward trend (Fig. 1). The rate of urgent CABG in the PCI arm decreased from 5–10% in the early PTCA trials to < 1% in the stent trials.

Newer technologies will alter these trends. The potential role of off-pump bypass surgery in reducing morbidity and mortality is being actively explored. The use of drug-eluting stents for LMCA stenosis has been advanced as a potential percutaneous solution to a previously exclusively surgical disease. Part II of this article will review some of the recent literature evaluating these newer therapies.

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