Myocardial Revascularization by Coronary Arterial Bypass Graft: Past, Present, and Future

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Abstract: The history of coronary artery bypass graft surgery is an amazing story that evolved from a basic understanding of the etiology of coronary artery disease to highly sophisticated methods of restoring blood flow to the myocardium. Adjunctive techniques of anticoagulation, coronary artery imaging, and cardiopulmonary bypass contributed greatly to our ability to provide surgical revascularization. Today, coronary artery bypass graft surgery is the treatment of choice for many patients with complex coronary artery disease. The future will certainly bring improved results with better graft patency with less operative insult and morbidity as the final chapter in the story remains untold. (Curr Probl Cardiol 2011;36:325-368.)

The present state of myocardial revascularization by coronary artery bypass graft (CABG) surgery evolved from the intersection of 5 critical areas of knowledge:

1. An understanding of the pathophysiology of coronary artery disease;
2. An ability to anticoagulate the blood to allow cardiopulmonary bypass and bypass graft construction;
3. An ability to image the coronary arteries;
4. Development of safe and effective cardiopulmonary bypass;
5. Development of techniques to perform coronary artery bypass surgery.

The story began several hundred years ago, reached a critical level of interaction in the 1960s and 1970s, and has continued to be refined up through present day. Our review includes many of the important historical
developments, focuses on current major aspects of myocardial revascularization by CABG surgery, and highlights areas of possible future development.

The Past

Pathophysiology of Coronary Artery Disease

In 1768, William Heberden stated, “. . . there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare. The seat of it, and sense of strangling and anxiety with which it is attended, may make it not improperly be called angina pectoris.” Heberden appropriated the term “angina” from the Latin word for strangling. His classic description marks the beginning of our understanding of angina pectoris and the future association with coronary artery disease.

In 1816, Samuel Black reported on the results of 2 autopsies and put forth several general remarks about angina pectoris that hold true today. He recognized “that the primary and original cause of the disease, is, perhaps, in every instance an ossification of the coronaries.” Further, Black identified risk factors associated with angina pectoris, including male gender, “there is nothing in the history of this disease more remarkable, or to me more inexplicable, than the exemption of the female sex from its attacks.” He may have also made the association between coronary artery disease and obesity and possibly type 2 diabetes stating, “the disease appears in general to have some relation to obesity, or to a plethoric habit,—that the great majority of the subjects of it seem to have belonged to such a rank of society, that we must presume they sat down daily to a plentiful table . . . .”

By the late 19th century, physicians linked angina pectoris with coronary artery disease, although there was confusion between angina pectoris and myocardial infarction. Most physicians thought coronary artery disease was uncommon at the time. In 1901, Osler called the anterior branch of the coronary artery the “artery of sudden death,” later stating that “the tragedies of life are largely arterial.” The correlation between the narrowing and sclerosis of the coronary arteries and angina pectoris or sudden death from “coronary failure” was not fully accepted until Herrick brought forth the connection in 1912. Herrick was also the first to grasp the variable course of myocardial infarction. By the 1930s, the clinical-pathologic correlations of coronary atherosclerosis and
thrombosis with infraction were more widely accepted and they formed the foundation of our current understanding of coronary artery atherosclerosis.¹

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D. R. Holmes: This is a superb article with wonderful historical vignettes. The quote “that the great majority of the subsets seem to have belonged to such a rank of society, that we must presume that they sat down daily at a plentiful table” still resonates but now applies not to a single class but to an increasing majority of all patients in developing nations. Certainly, Herrick popularized the connection between coronary narrowing, angina, and myocardial infarction. However, it must be remembered that this connection had been described in Russian Federation in 1910 by Obraztsov and Strazhesko [Am J Cardiol 1977;40:269-71].

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Anticoagulation

In 1916, at Johns Hopkins University Medical School, Baltimore, MD, under the direction of the physiologist, William Henry Howell, medical students, Jay McLean and L. Emmet Holt Jr, extracted several phosphatides from canine liver that appeared to demonstrate anticoagulant properties. One of these phosphatides Howell termed “heparin,” from the Greek word “hepar,” or liver, the tissue from which it was first isolated. Additional refinements to Howell’s protocol produced the water-soluble heparin compound, which unfortunately caused several side effects, including headaches, fevers, and nausea. Investigators at Connaught Laboratories in Toronto attempted to purify heparin. Finally, in 1933, the team of Best, Charles, and Scott produced a purified bovine heparin preparation that was not pure in the chemical sense but rather free from toxic components.⁴,⁵ Subsequently, in 1938, Murray and Best reported heparin to be a safe and effective anticoagulant for vascular surgery and, ultimately, cardiopulmonary bypass.⁶

Coronary Angiography

Detailed anatomic study of the coronary anatomy is paramount to successful myocardial revascularization. The beginning of cardiac catheterization occurred in the summer of 1929 when Werner Theodor Otto Forssman, through a self-made venous cutdown in his left elbow region, passed a 65-cm-long ureteral catheter into the heart. He then walked over to the radiology department where an x-ray confirmed that the tip of the catheter was in the right ventricle. For his achievement, he received the Nobel Prize in Medicine in 1956.⁷
It would be another 30 years before the diagnostic basis for coronary artery bypass grafting would shift from history, electrocardiogram, and surgical palpation to cine coronary angiography. The need for imaging the coronary arteries was well recognized by Murray, who in 1954 stated, “therefore, in some cases of coronary stenosis with an adequate diagnosis, the development of coronary occlusion might be prevented and symptoms of stenosis completely eliminated . . . to obtain this information, angiography might be necessary . . . when injecting an opaque substance into the coronary artery would demonstrate the state of the lumen of the vessel . . . regarding the site of the stenosis and the state of the vessel both proximally and distally.”

The inadvertent selective injection of contrast media into the right coronary artery of a patient at the Cleveland Clinic by Sones on October 30, 1958 ushered in the new era of cine coronary angiography. Cardiologists and surgeons rapidly adopted the procedure and soon thereafter diagnostic coronary angiography routinely preceded myocardial revascularization with bypass graft surgery. So popular was this new procedure that, by 1964, the Cleveland Clinic team reported that over 2000 patients underwent selective cine coronary arteriography. As a side note, the Cleveland Clinic team also confirmed the accuracy of clinical assessment as they found a close correlation existed between the clinical diagnosis of angina pectoris without rest pain and significant arterial obstruction (95%), and similarly between electrocardiogram evidence of myocardial infarction and severe arterial obstruction (99%).

**Cardiopulmonary Bypass**

The concept of cardiopulmonary bypass may date its origin to the physiologist Le Gallois, who wrote in 1812 that, “if one could substitute for the heart a kind of injection . . . of arterial blood, either natural or artificially made . . . one would succeed easily in maintaining alive indefinitely any part of the body whatsoever.” Fast forward over 100 years, and Alexis Carrel and Charles Lindbergh were experimenting with an extracorporeal support apparatus that could provide 60 pulsations per minute, a systolic pressure of 120 mm Hg, and a diastolic pressure of 60 mm Hg. They reported thyroid glands kept more than 20 days with pulsating arteries and active circulation and concluded that they maintained an entire organ alive in vitro. Personal, institutional, and other world events interacted to render further development of their apparatus impossible.

In 1937, John Gibbon reported his experience short-circuiting blood around a partial obstruction of the pulmonary artery in cats by means of
a new perfusion apparatus. In 21 experiments, he showed that, “the blood pressure was maintained at an adequate level, and the animal continued to breathe and the heart to beat while the pulmonary artery was completely closed for periods varying from 15 minutes to 2 hours and 51 minutes.” He remarked that 1 of the main problems encountered during the tests was that of marked acute anemia secondary to pump-prime hemodilution, a problem that continues today. Gibbon’s successful experiment provided a critical starting point for the clinical development of cardiopulmonary bypass.16

In 1950, Bigelow and colleagues from the University of Toronto reported on their experience with general hypothermia as a means of reducing the oxygen requirement of the body sufficiently to allow exclusion of the heart from the circulation. He found in a canine model that at a body temperature of 20°C, oxygen consumption, cardiac output, blood pressure, and heart rate reduced to about 15% of normal. At that temperature, he excluded the heart from the circulation for periods of 15 minutes, during which he performed exploratory right atriotomy without cardiopulmonary bypass and without any associated intracardiac procedure. Eleven of 23 dogs (48%) survived to normal body temperature.17 Bigelow’s study demonstrated the important direct relationship of oxygen consumption and temperature, a relationship used to the heart surgery patient’s benefit on a regular basis.

In the 1950s, numerous advances in cardiopulmonary bypass paved the way for the more precise, and more complete, techniques of coronary artery operations that enable operation on the nonbeating heart.11 On April 1, 1951, Clarence Dennis and the University of Minnesota group became the first to use cardiopulmonary bypass in a young girl with an atrial septal defect. To say that it was labor-intensive is an understatement as the procedure required 2 anesthesiologists, 4 surgeons, 4 people to run the oxygenator and pumps and to switch over the suction apparatus, 1 person to run the intra-arterial transfusion apparatus, 1 person to draw and manage samples, 2 technicians, and 2 nurses.18,19 The team was able to complete the cardiac repair, but, unfortunately, the patient died of cardiac failure during the procedure.

The first reported successful clinical use of left heart bypass was in 1952 by Dodrill’s group from Detroit. The pump produced a maximal blood flow of 4.5 L per minute, during which the surgeon digitally explored the left atrium and mitral valve via a purse-string suture in the left atrial appendage. Dodrill reported, “the mitral valve was regurgitant, with no palpable evidence of stenosis. The finger was kept within the valve and in the left ventricle for a period of 14 minutes while manipulative proce-
dures were carried out.” The total bypass time was 50 minutes from which the patient recovered without apparent complication. The case represented the first instance of survival of a patient treated with cardiac operation (albeit a closed procedure with no specific intervention performed) during support with a mechanical heart mechanism.20

John H. Gibbon and his team at the University of Pennsylvania were instrumental in the successful development of the first effective cardiopulmonary bypass machine. Using a screen oxygenator, the first cardiopulmonary bypass procedure occurred in February 1952, on a 15-month-old child thought to have an atrial septal defect. Cardiac catheterization had been attempted but not completed because of her small size and heart failure. Gibbon placed the child on cardiopulmonary bypass and opened the right atrium, but he found no atrial septal defect. Her condition rapidly deteriorated and she developed cardiac arrest. Autopsy revealed a large patent ductus arteriosus. The preoperative diagnosis was wrong.21,22

D. R. Holmes: This 15-month old child represents an issue that was perhaps not uncommon—whereby a diagnosis was reached by excellent physicians and surgeons but by virtue of either suboptimal imaging techniques or wrong assumptions that led to poor outcome.

The classic such case was that of a man aged 47 years who was a patient of Professor John Goodwin. The presumptive diagnosis was severe valvular aortic stenosis. Cardiac catheterization by Arthur Hollman (Cardiology Registrar) showed a gradient of 70 mm Hg. Surgery on November 26, 1958 at Hammersmith Hospital in London, UK by William Cleland showed hypertrophic obstructive cardiomyopathy. The patient had a limited myomectomy (Goodwin JF, Hollman A, Cleland WP, et al. Obstructive cardiomyopathy simulating aortic stenosis. Br Heart J 1960;22:403-14). This was the “first” such case; the patient was free of angina and exercised freely for “many years” (Coats CJ, Hollman A. Hypertrophic cardiomyopathy: lessons from history. Heart 2008;94:1258-63).

The second operation occurred on May 6, 1953. The patient was an 18-year-old woman with an atrial septal defect diagnosed at cardiac catheterization. During the procedure, thrombus began to form on the oxygenator screen. Gibbon planned to close the atrial septal defect with a pericardial patch, but because of the oxygenator screen thrombus, proceeded to close the defect with a continuous suture to end the period of cardiopulmonary bypass as rapidly as possible. The patient was on partial cardiopulmonary bypass for 45 minutes and total cardiopulmonary bypass for 26 minutes. On review, the patient received an inappropriately low dose of heparin of 10 mg instead of the planned 25 mg before the initiation of cardiopulmonary bypass. The patient recovered without
apparent sequelae and was alive and well on the 50th anniversary of her operation in May, 2003. Unfortunately, the next 2 patients operated by Gibbon with cardiopulmonary bypass died in the operating room.

Following the death of the last patient, Dr Gibbon decided to end all open-heart operations for a year and used the time to obtain a trained cardiologist and a cardiac catheterization laboratory because 2 of his 4 patients had an incorrect or incomplete diagnosis. He also decided not to personally attempt any more heart operations. The 4 operations were not reported until the following year and then not in a major surgical journal. John W. Kirklin would write the next chapter in cardiopulmonary bypass.

In 1952, Dr Kirklin and colleagues, Earl Wood and David Donald from the Mayo Clinic, Rochester, decided that a cardiopulmonary bypass machine was a necessity to do accurate and safe cardiac surgery. The Mayo Clinic engineering department built a machine based on the Gibbon design. The Mayo-Gibbon cardiopulmonary bypass machine was expensive to construct and quite complex. Kirklin and colleagues scheduled 8 patients for operation with the agreement that they would do all 8 operations even if the first 7 patients died. In the end, 4 patients survived and 4 died, and from that time forward, the Mayo Clinic team had a continuous schedule of open-heart operations.

If you wanted a cardiopulmonary bypass machine in the early 1950s, you built it yourself. By the 1960s, however, several companies began to produce machines. As cardiac surgery evolved, the technology of cardiopulmonary bypass shifted from a very complex machine to a more straightforward device. Better oxygenators and training to include a single full-time specialist, the perfusionist, combined to make cardiopulmonary bypass an asset rather than a liability.

Safe bypass of the heart and lungs allowed operation on an arrested heart in a bloodless field, which greatly contributed to the success of myocardial revascularization with CABG surgery. It did not take long for the new technology to gain popularity, for in 1959 Dubost became the first to perform a coronary artery operation in a human using cardiopulmonary bypass when he performed coronary ostial reconstruction on a patient with syphilitic aortitis.

**Surgical Methods of Myocardial Revascularization**

The history of myocardial revascularization had its beginnings in the early 1900s with extracardiac operations, such as sympathetic denervation and thyroid ablation, for treatment of angina pectoris. From there, indirect
methods evolved from neovascularization via exploitation of collateral channels and pericardial poudrage and cardiopexy in the 1930s to mammary artery implantation in the 1940s. Operations to directly revascularize the coronary arteries included endarterectomy in the 1950s and direct coronary artery revascularization with saphenous vein and mammary artery bypass grafting in the 1960s with refinements in the techniques continuing today.

**Extracardiac Operations for Angina Pectoris**

Treatment of angina pectoris began with amyl nitrite used by Lauder Brunton (1867) and nitroglycerine by William Murrell (1879). It was not long thereafter before surgeons began to propose methods to treat angina, although many had no effect on the underlying coronary artery disease. Kocher observed in 1902 that a patient with angina became asymptomatic after total thyroidectomy. Recognizing the ability of thyroid hormone and its excess to increase myocardial demand and induce ischemia, Boas, in 1926, was the first to perform subtotal thyroidectomy on patients in an effort to treat angina with induction of myxedema.

In 1899, Francois-Frank proposed sympathetic denervation of the heart to treat angina and recommended sympathetic ganglionectomy of the upper thoracic ganglia to relieve symptoms. In 1916, Jonnesco performed the first cardiac sympathectomy reporting on his work in 1920. He performed bilateral extirpation of the cervical sympathetic trunk and first dorsal ganglia. Such denervation not only was reasonably effective in relieving the sensation of angina, it also potentially produced a state of coronary vasodilation. Other means of achieving denervation included paravertebral alcohol injection, posterior rhizotomy, and even cardiac irradiation. Variations of such procedures persisted into the early 1960s.

**Indirect Attempts at Myocardial Revascularization**

In 1880, Langer described the existence of extensive, minute vascular communications between the normal coronary circulation and the vascular supply of surrounding extracardiac structures, such as the diaphragm, bronchi, and pericardium. In 1939, at the suggestion of Fieschi, Zoja and Cesa-Bianchi ligated the internal mammary arteries bilaterally in the second interspace in a patient who was suffering from intractable angina in an attempt to shunt blood flow through branches of the pericardiophrenic arteries back to the heart through vascular anastomoses with the epicardium. Two years later, they reported the patient was alive and comfortable; similarly, others described favorable outcomes of internal
mammary artery ligation. Subsequently, in 1959, Cobb and colleagues reported in a double-blind, placebo-controlled (sham operation) study, that internal mammary ligation had no effect on the pathophysiology of coronary artery disease. This study is notable not only because it demonstrated the lack of effectiveness of an indirect method of revascularization, but also because it was 1 of the first randomized trials of surgical treatment of coronary artery disease.

D. R. Holmes: This trial was also unique in that it included a sham operation.

In 1934, Beck noted brisk bleeding from both ends of a transected pericardial scar, and this stimulated an interest in devising methods of coronary revascularization. He developed several procedures for increasing vascular collateralization between the coronary arteries and surrounding tissues, beginning in 1932 with animals and in 1935 with patients. In the first of these procedures, he induced sterile pericarditis by mechanically abrading the parietal and visceral pericardium, producing vascular adhesions and neovascularization that might communicate with myocardial vessels. The procedure was termed cardio-pericardiopexy or pericardial poudrage. Other irritants for poudrage included talc, sand, phenol, silver nitrate, and even asbestos. O’Shaughnessy modified Beck’s cardiomyopexy procedure in 1937 by bringing in a variety of vascular organs into contact with the abraded epicardium.

Several other investigators proposed techniques to improve myocardial perfusion through manipulation of coronary sinus blood flow. Gross and coworkers reported ligation or partial occlusion of the coronary sinus in dogs in 1937 and found that blood escaped from the venous system into the 4 chambers of the heart; unfortunately, the mortality rate following ligation of the coronary sinus was 42%. Subsequently, in 1939 Fauteux and Palmer used Gross’s technique of great cardiac vein ligation in a 54-year-old man with angina. Except for an episode of postoperative atrial fibrillation, the patient recovered uneventfully and 1 year later was able to walk 5 miles without limitation.

Pratt in 1897 suggested that insertion of an artery into the coronary sinus reversed blood flow, thereby enhancing myocardial perfusion. In 1946, Beck and Leighninger performed arterialization of the coronary sinus in dogs using the common carotid or intercostal artery as well as free autografts of the internal jugular vein. Beck used the technique in humans in 1948 with either free vein or brachial artery autografts.
Subsequently, this technique evolved into the Beck II procedure where the surgeon first ligated the coronary sinus and then 10-14 days later sutured an arterial segment or venous conduit between the aorta and the coronary sinus. Unfortunately, permanent obstruction of coronary sinus venous drainage caused other problems, including myocardial edema, fibrosis, and hemorrhage and the procedure was abandoned.\textsuperscript{38,39}

Griffith and Bates first reported the direct implantation of vessels into the myocardium in 1938. During an operation, they accidentally perforated the left ventricle and attempted repair by suturing part of the pectoralis muscle together with the mammary arteries into the opening. The operation presaged the Vineburg procedure.\textsuperscript{11,40} Murray reports to have carried out canine experiments in 1935 designed to provide a collateral circulation to the heart using grafts of pectoralis major, triangularis sterni, greater omentum, or lung. In unpublished reports, he claimed that there was communication between the somatic and coronary circulations, and that animals had better survival after this operation when he later tied off the coronary artery. He also claimed to have made attempts in 1937 to bring the internal mammary artery into the cardiac muscle, but he believed that the vessel occluded and that there was no improvement of coronary circulation.\textsuperscript{41}

In 1946, Arthur Vineberg of McGill University reported implantation of the internal mammary arteries directly into ventricular myocardium of dogs to increase myocardial blood flow.\textsuperscript{42} He hypothesized that the myocardium contained relatively large venous sinusoids that would absorb the flow from the mammary vessel and avert myocardial hemorrhage or rupture. On April 28, 1950, Vineburg performed the first human internal mammary artery myocardial implantation.\textsuperscript{43} The Cleveland Clinic group proved the merits of the procedure when in 1968 they reported on the angiographic assessment of 1100 internal mammary artery implants; the vessel was patent in 92% of cases, and internal mammary artery-to-coronary artery communication was observed in 54% of patients.\textsuperscript{44,45} The procedure was often effective in relieving angina and was in use until the early 1970s when direct coronary artery revascularization replaced internal mammary artery implantation as the method of choice.

\textbf{D. R. Holmes:} This last sentence is not clear to me.
Direct Myocardial Revascularization

The direct approach to myocardial revascularization involved 2 major techniques, including coronary artery endarterectomy and bypass grafting, with most of the initial work conducted in the 1950s.

Coronary Artery Endarterectomy

Direct removal of an obstructing atheromatous plaque by endarterectomy appealed to surgeons because of its simplicity. It was in 1955 that May performed the first experimental retrograde endarterectomy on dog and cadaver coronary arteries using a special curette to extract atheroma. On October 29 of the next year, Bailey performed the first retrograde coronary artery endarterectomy on a man using May’s specially designed curette. The patient recovered but 2 months later had left-sided pleuritis and a subsequent electrocardiogram showed new Q-waves in the distribution of the vessel treated. A second patient underwent a similar procedure on October 31 without complications.

In 1958, Senning reported experimental use of coronary endarterectomy with direct-vision excision of plaque followed by patch grafting of the defect in the vessel with a split segment of autologous internal mammary artery. During that same year, Longmire reported an antegrade, open coronary endarterectomy procedure, performed on humans without cardiopulmonary bypass. Longmire may have been the first to use the internal mammary artery to bypass a lesion in the right coronary artery. During an endarterectomy, he found that it was not possible to repair the coronary artery, and in desperation, he anastomosed the internal mammary artery to the right coronary artery beyond the endarterectomized segment.

In 1961, Senning reported clinical use of coronary endarterectomy with patch grafting. The operation used hypothermia but not cardiopulmonary bypass and involved the use of autogenous saphenous vein segments as patches. Importantly, his patient was the first to undergo diagnostic coronary arteriography before revascularization.

Donald Effler and his associates reported in 1964 their modification of Senning’s technique in which they used pericardial patches on endarterectomy sites instead of mammary artery or saphenous vein patches. The group performed the operation using hypothermia and cardiopulmonary bypass. Legend states that the technique developed in 1962 when someone dropped a prepared vein patch on the operating room floor, causing the surgeon to use the pericardium instead. Regardless of its
origin, the technique became the preferred method of revascularization until Favaloro pioneered the use of saphenous vein bypass graft surgery in the late 1960s.\textsuperscript{11,51} 

In current practice, there is infrequent use of coronary endarterectomy, but there has been renewed interest in the method because patients referred for operation often have a large atherosclerotic burden due to diabetes, hyperlipidemia, and advanced age.\textsuperscript{52} Most commonly, the need for endarterectomy arises intraoperatively when no soft site is available for arteriotomy or a vessel inadvertently opened in an extensively diseased area is not amenable to grafting. Occasionally, patients with diffuse and extensive coronary disease with no other treatment option receive elective endarterectomy.

\textbf{D. R. Holmes:} There may be an expanded need for such a procedure when very long stents have been used, which then failed. However, the length of the stent prevented locating an appropriate size vessel for coronary bypass.

The perioperative risk of coronary artery bypass with endarterectomy is higher than that for isolated coronary artery revascularization. In a study of 1478 patients, the reported mortality rate with endarterectomy was 3.2\% compared with 2.2\% for isolated CABG surgery. In this study, perioperative myocardial infarction rate was also higher in the endarterectomy group, 4.2\% vs 3.4\%, respectively. The risk of mortality appears to increase when multiple vessels require endarterectomy, 5.5\% vs 1.8\% for single vessel endarterectomy.\textsuperscript{53,54} There is also controversy regarding the risk of endarterectomy of the left anterior descending coronary artery with some studies showing higher mortality, while others demonstrate no increased risk.\textsuperscript{53-55}

Patency of bypass grafts to endarterectomized vessels is lower than that of nonendarterectomized coronary arteries. The reported 3-year patency for internal mammary artery-to-endarterectomized left anterior descending coronary artery is only 74-80\%.\textsuperscript{56,57} Early relief of angina is remarkably good, but the rate of recurrent angina is higher after endarterectomy (25\%) than after insolated CABG surgery at 5 years of follow-up.\textsuperscript{53,58} The reported 5-year survival following coronary endarterectomy ranges from 76\% to 83\%.\textsuperscript{53,58} Among patients in whom bypass to more distal nondiseased segments is not possible, coronary endarterectomy with subsequent bypass offers a viable alternative to leaving a territory not grafted.
Coronary Artery Bypass

During the same era as Herrick’s presentation on the pathophysiology of coronary artery disease, a seminal event occurred when Carrel (1910) reported that, “an arterial wall can be patched with a piece of artery, of vein, or even . . . a piece of peritoneum . . . these operations present very little danger, and their results, observed many months after the graft, were excellent.” For his work on vascular suture and the transplantation of blood vessels and organs, Carrel received the Nobel Prize in Medicine in 1912.\(^7\)\(^{,}\)\(^{59}\)\(^{,}\)\(^{60}\) His experiments would form the foundation of techniques used for direct coronary artery revascularization almost 40 years later.

At the University of Toronto in 1940, Gordon Murray described what would be the precursor of saphenous vein bypass graft technique when he reported the case of a saphenous vein graft interposition in the treatment of a human popliteal artery aneurysm under heparin anticoagulation. The circulation remained normal 14 months after the operation.\(^61\) He later reported that during the same year, he “assisted by J. Janes, McGregor, and Smith” divided the coronary arteries of experimental animals and repaired the vessels with venous interposition grafts.\(^{41}\)\(^{,}\)\(^{62}\) In 1954, he reported the first arterial autograft interpositions in dog coronary arteries using the subclavian, carotid, and internal mammary arteries.\(^8\)

Other investigators made important contributions to the field of CABG surgery, including Demikhov, who, on July 29, 1953, performed the first successful anastomosis of the internal mammary artery to the left anterior descending coronary artery in dogs.\(^63\) Thal, in 1956, performed experimental internal mammary artery grafting onto coronary arteries, carried out on a beating dog heart using a suture technique.\(^64\) Furthermore, in 1957, Julian performed direct coronary artery bypass grafting using internal mammary arteries or homologous arterial grafts in dogs under cardiopulmonary bypass.\(^65\) These experiments set the stage for the application of such techniques in man.

Robert Goetz receives credit with performing the first planned right internal mammary artery-to-right CABG using a tantalum ring for anastomosis in a 38-year-old man on May 2, 1960. Cardiac catheterization on postoperative day 14 showed a patent stented anastomosis. The patient was anticoagulated with warfarin and remained free of angina for over a year. He died at Jacoby Hospital, Bronx, NY, on June 23, 1961, of a posterior wall myocardial infarction. Unfortunately, an autopsy was not performed and the long-term patency of the anastomosis was not established.\(^66\)\(^{,}\)\(^{68}\)
David Sabiston performed the first human saphenous vein-CABG procedure on April 4, 1962; this end-to-end distal anastomosis was performed without cardiopulmonary bypass. The patient died 3 days later of a stroke and an autopsy revealed a thrombus at the graft’s proximal anastomosis, which Sabiston presumed had embolized. Sabiston was discouraged enough by this experience that he did not try vein bypass again until 1968 and did not report this landmark event until 1974, well after the widespread acceptance of saphenous vein bypass surgery.69

Kolesov performed the first sutured internal mammary artery-to-coronary artery bypass in a human subject, grafting the left mammary artery to the left anterior descending artery in a 44-year-old man, without cardiopulmonary bypass, on February 25, 1964. The patient had no recurrence of angina on 3 years’ follow-up.63,70,71 Kolesov’s many significant contributions to cardiac surgery included mechanical suturing of the anastomosis (March 22, 1967), mammary artery grafting for the management of an acute myocardial infarction (February 5, 1968), and unstable angina (May 17, 1968), as well as the placement of retrograde (December 11, 1968) and bilateral mammary artery grafts (July 10, 1969).11

The world’s second human saphenous vein-coronary artery bypass operation, and the first successful 1, occurred on November 23, 1964 by Garret, Dennis, and DeBakey, at Methodist Hospital in Houston, TX. Angiography 7 years later showed a patent vein graft and occluded native vessel. Like Sabiston who performed the first vein bypass operation, Garret inexplicably did not report this historic operation until 1973. The patient died 1 year later after that report as the result of occlusion of the grafted vessel distal to the insertion of the still patent vein graft.11,72

Although many surgeons contributed to the techniques of coronary artery bypass surgery, it was Rene Favaloro at Cleveland Clinic who appreciated the importance of the therapy and applied it widely. On May 9, 1967, he used a free saphenous vein autograft interposed end-to-end to the 2 transected ends of a right coronary artery after excision of an atherosclerotic lesion in a 51-year-old woman. He originally planned endarterectomy and patch-grafting, but the segment was unsuitable for repair, so Favaloro interposed autologous vein in a procedure similar to Murray’s experimental work.41,61,62

Favaloro and colleagues were the first to use autologous saphenous vein as the conduit of choice, and these surgeons then began using the ascending aorta as the site for the proximal vein graft anastomosis.73 Subsequently, he performed vein grafts with an end-to-side distal anastomosis, which quickly became the standard operation throughout the
world. Initial operations were on the right coronary artery with the heart beating, but when grafts were extended to branches of the left coronary artery, Favaloro and others adopted cardiopulmonary bypass to support the circulation and facilitate construction of the distal anastomosis.

Although not the first or even the second to employ vein bypass grafting in human subjects, it was the broad clinical application of the techniques by Favaloro and others in 1967 and 1968 that revolutionized the treatment of ischemic heart disease. Initially Favaloro combined saphenous vein grafting of the right coronary artery with single or double internal mammary artery myocardial implantation. It was because of their tendency to combine the Vineburg procedure with saphenous vein bypass of the right coronary artery that Favaloro’s team initially avoided using the internal mammary artery and left-sided coronary artery anastomoses. This group was also the first to perform vein bypass in patients with unstable angina or acute infarction, and the first to combine vein bypass with valve replacement or aneurysmectomy.11

Dudley Johnson and colleagues from Milwaukee expanded the application of saphenous vein bypass when, in September 1969, they described use of saphenous vein bypass grafts to all major coronary branches to specifically include left-sided vessels.74 They reported double vein grafts used in over 40% of their patients near the end of the study period that started in February 1967 and included 301 patients. Their experience indicated that 5 factors were important in direct CABG surgery:

1. Do not limit grafts to proximal portions of large arteries.
2. Do not work with diseased arteries.
3. Always do end-to-side anastomosis.
4. Always work in a dry quiet field.
5. Do not allow hematocrit to fall below 35%.

In our current experience we maintain the hematocrit above 20%, but would otherwise agree with Johnson and apply his rules in our daily practice.

In 1968, Bailey reported the use of the internal mammary artery as an alternative conduit to saphenous vein when he anastomosed the right internal mammary artery to the right coronary artery.75 During the same year, Green performed an internal mammary artery to left anterior descending coronary artery anastomosis. Later, Green went on to operate on 18 patients, placing the internal mammary artery graft to a 1.5 mm in diameter segment of the distal one-third portion of the left anterior descending coronary artery. Green would become a champion of the use of the internal mammary as a conduit.46,76,77
In 1975, Trapp and Bisarya reported on a series of 63 patients treated with right coronary artery and left anterior descending CABG surgery on the beating, functioning heart, a procedure commonly referred to now as off-pump coronary artery bypass. They reported no mortality related to the cardiac operation and felt the procedure offered benefit to patients because it avoided the potential morbidity related to the use of extracorporeal circulation, including bleeding, renal dysfunction, and neurologic injury. Although some surgeons remain strong advocates of the technique, no conclusive arguments demonstrate that off-pump CABG surgery provides any significant benefit over on-pump CABG surgery. In the end, the technique remains controversial and factors influencing its widespread adoption include training and experience of the surgeon more so than the specific merits of the procedure.

D. R. Holmes: The authors are very correct in this area of practice. There are some surgical practices that focus on this approach as often as possible, believing that it lessens complications and improves outcomes; other authors and institutions use it infrequently.

Although most CABG surgery procedures are performed via median sternotomy, Cheung et al. reported left thoracotomy as an alternative approach to isolated circumflex coronary bypass reoperation. Benetti combined this exposure with video-assisted internal mammary artery harvest and off-pump coronary artery bypass techniques and in 1995 introduced the technique of minimally invasive direct coronary artery bypass surgery, or MIDCAB. Soon thereafter in July 1999, Reichenspurner and his associates from Munich-Grosshadern, Germany reported on the first of 2 cases of completely endoscopic anastomosis of the left internal mammary artery to the left anterior descending coronary artery in man. Both patients recovered without sequelae and had patent anastomoses at angiography 6 weeks postoperative.

Conduits

**Single Internal Mammary Artery Graft.** Although the use of the saphenous vein helped popularize coronary bypass grafting, approximately 15% of vein grafts occlude in the first year postoperatively, and 40% or more occlude by 10 years after operation. In 1985, Barner and colleagues reported superior durability of internal mammary artery grafts compared to saphenous vein grafts, 5-year patency 88% vs 74%, and 10-year patency of 83% compared to 41%. The following year, Loop
and colleagues reported that superior patency translated into improved 10-year survival with internal mammary artery-to-left anterior descending coronary artery bypass (83%) vs saphenous vein bypass (71%) (Fig 1). Patients with internal mammary artery grafts also experienced fewer late myocardial infarctions and had lower risk of hospitalization for cardiac events and reoperations.\textsuperscript{86}

The superior performance of internal mammary artery grafts was also apparent in the more recent bypass angioplasty revascularization investigation (BARI) trial, where patency rates for internal mammary artery grafts at 1 and 4 years were 98% and 91% compared with 87% and 83% for vein grafts.\textsuperscript{87,88} It appears that the superior patency of the internal mammary artery becomes even more apparent with longer follow-up. In an angiographic study of 1408 patients, patency rates for internal mammary artery-to-left anterior descending CABGs at 10 and 15 years were 95% and 88%, while saphenous vein graft patency rates were 61% and 32%.\textsuperscript{89}
**Bilateral Internal Mammary Artery Grafts.** In contrast to the easily demonstrated survival benefit conferred by an internal mammary artery-to-left anterior descending CABG, incremental survival benefit with a second arterial graft has been more difficult to prove. Buxton and colleagues demonstrated a 15% absolute improvement in actuarial survival 10 years after operation (86% vs 71% for a single internal mammary artery). Lytle and colleagues also demonstrated an improvement in survival at 12 years (79 vs 71%) as well as superior reoperation-free survival (77 vs 62%) among 2001 bilateral and 8123 single internal mammary artery graft patients (Fig 2). While some surgeons have embraced bilateral internal mammary artery grafting, the technique represents a small minority of cases reported to the Society of Thoracic Surgeons database. Of the 541,368 CABG surgery procedures reported in the database from 2002 through 2005, only 4% used bilateral internal mammary artery grafts, whereas 92% used a single internal mammary artery graft.

**Complete Arterial Revascularization.** The better long-term results achieved using bilateral internal mammary artery grafts and the well-known time-related attrition of venous conduits encouraged the exclusive use of arterial conduits for myocardial revascularization. Complete arterial revascularization is possible by a variety of strategies, including composite grafting using internal mammary arteries or secondary arterial conduits, such as the radial artery or the gastroepiploic artery and extensive use of sequential anastomotic techniques (Fig 3). Although technically demanding, sequential grafting appears safe and has excellent long-term results with reported 96% patency rates of 7.5 years of follow-up on 1150 sequential internal mammary artery anastomoses.

D. R. Holmes: Although the use of a variety of arterial grafts, such as T configuration described or the gastroepiploic artery, no adequately powered randomized trials have been performed to document unequivocal significant improvement.

Tector and coworkers championed complete arterial revascularization using bilateral internal mammary arteries in a T-configuration with end-to-side anastomosis of 1 internal mammary artery as a free graft to the side of the second internal mammary artery, which is left as a pedicled graft combined with liberal use of sequential anastomoses (Fig 4). In their series of 897 patients, overall survival was 75%, and freedom from reintervention was 92% at 8 years after revascularization.
reported similarly encouraging results with composite grafting using 1 internal mammary artery and 1 radial artery.95

Data from randomized studies support improvement in early outcomes with complete arterial revascularization compared to conventional CABG surgery. Muneretto and associates randomized 200 patients to complete arterial revascularization vs conventional CABG surgery (left internal mammary artery and saphenous vein bypass grafts). At 20 months follow-up, there was superior event-free survival (freedom from nonfatal
MI, angina recurrence/graft occlusion/need for subsequent revascularization/late death) in the complete arterial revascularization patients.\textsuperscript{96}

Muneretto’s group conducted a second randomized trial comparing complete arterial revascularization to conventional CABG surgery (internal mammary artery and saphenous vein bypass) in 160 patients older than 70 years of age. Early mortality was similar, but at 16 months follow-up, there were significantly fewer graft occlusions and recurrences of angina among the complete arterial revascularization group. Independent predictors of graft occlusion and angina recurrence were the use of saphenous vein bypass grafts, or the presence of diabetes, and dyslipidemia.\textsuperscript{97}

\textbf{FIG 3.} Composite Y-graft with total arterial revascularization. The Y-graft consists of the right internal mammary or radial artery sutured to the midportion of the left internal mammary artery. Liberal use of sequential grafting allows for complete arterial revascularization with grafts to each of the 3 coronary artery territories. (Color version of figure is available online.)
Radial Artery. Carpentier originally described the use of the radial artery as a conduit for coronary bypass in 1973. Spasm of the artery was common during surgery and he treated it with mechanical dilation. The initial results with use of the conduit were disappointing with 32% of grafts occluded at 2 years. Accordingly, he abandoned the radial artery as a conduit for CABG at that time. Acar and colleagues revived the use of the radial artery after several grafts, angiographically demonstrated as occluded early postoperatively, were patent during restudy 15 years later. Acar postulated that harvest injury was responsible for the early graft occlusion. Proponents of the radial artery as a conduit have demonstrated encouraging mid- and long-term results with a pedicled harvesting technique and pharmacologic manipulation to prevent radial artery vasospasm. As a result, this conduit has enjoyed a resurgence of interest as a supplementary arterial conduit for coronary revascularization.

Acar and associates in 1992 reported 100% patency of 122 radial artery grafts studied 2 weeks postoperatively and 93% patency at 9 months after operation. These early and good results persistent with reported patencies at 48 months of 89%. Several factors may affect radial artery graft patency, however, including both target artery runoff and competitive flow. In the prospective, randomized Radial Artery Patency Study, more severe target coronary artery stenosis (a surrogate measure of competitive flow, eg, more severe target artery stenosis equals less...
competitive flow) was associated with better graft patency, >90% target artery stenosis, 94% patency vs 70-89% target artery stenosis, 88% patency. The graft failure rate is highest if the target vessel is the right coronary artery system, but this may relate more to the coronary artery than the bypass conduit as one study showed equal patency of radial artery and saphenous vein bypass grafts to the right coronary artery. Importantly, it appears that the overall patency of radial artery grafts to ideal targets may be superior to that of saphenous vein bypass grafts at 5 years.

**Refining Indications for Operation**

The development of standardized operative techniques and reliable cardiopulmonary bypass established coronary artery bypass grafting as a safe and effective treatment of ischemic heart disease. Subsequent clinical investigation has focused on patient selection and late outcomes. The randomized Veterans Administration Cooperative, European Coronary Surgery Study Group (ECAS), and coronary artery surgery study (CASS) studies compared the long-term benefits of CABG surgery against medical therapy. Each study showed no overall difference in survival, but each study identified subgroups of patients that benefited from operation. The common theme was that the highest risk patients benefited the most from CABG surgery.

**VA Study**

In 1976, the Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group reported results in 686 patients with stable angina randomly assigned to either medical or surgical treatment. The study demonstrated a significant survival benefit in patients with left main coronary artery disease, especially those with additional significant disease involving the right coronary artery, with or without left ventricular dysfunction. A follow-up report in 1984 showed improved survival of surgically treated patients without left-main coronary artery disease who had high angiographic risk (eg, 3-vessel disease and impaired left ventricle function), high clinical risk (eg, at least 2 of the following: ST segment depression, history of myocardial infarction, or history of hypertension) or who had combined angiographic and clinical markers of high risk.

**ECAS**

The results of the ECAS, published in 1982, evaluated 768 men under age of 65 years with mild to moderate angina, greater than 50% stenosis
in at least 2 major coronary arteries, and good left ventricle function. Survival was significantly better following surgical revascularization compared to medical therapy in patients with 3-vessel disease and in patients with stenosis in the proximal third of the left anterior descending coronary artery. The group concluded that the greatest survival benefit of surgery occurred in patients at high risk.109

CASS

In November 1983, the CASS published its results in which 780 patients were randomly assigned to either surgical or nonsurgical treatment. After 5 years of follow-up, there was no difference in overall survival.110 However, subsequent subgroup analysis (1985) reported that after 7 years of follow-up, a significant advantage favoring surgery was observed in patients with 3-vessel disease and reduced ejection fractions (less than 50% but greater than 35%). Survivals of medical and surgical patients with normal resting ejection fractions were identical after 7 years. The authors concluded there was a significant advantage of surgical therapy in patients with 3-vessel disease and impaired ventricular function.111

D. R. Holmes: It must be remembered that medical therapy in the CASS was extremely different from in today’s environment. It remains possible that superb medical therapy in a patient with 2 vessel focal coronary artery disease and stable angina and normal left ventricular function but no LMCA stenosis might have similar hard endpoints as surgery—similar to the COURAGE trial.

The Present (and Relative Past)

Diabetes and Coronary Artery Bypass Graft Surgery

After the benefits of CABG surgery were demonstrated in the VA, ECAS, and CASS studies, surgical revascularization has been repeatedly examined against each new less invasive coronary artery revascularization technology, including percutaneous transluminal coronary angioplasty (BARI study), percutaneous coronary intervention with bare-metal stents (arterial revascularization therapies study (ARTS) I study) and, most recently, drug-eluting stents (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study). Much like studies that compare coronary bypass graft surgery to medical treatment, these more recent trials demonstrate little overall survival benefit to surgery in patients who are otherwise good candidates for
percutaneous interventions. However, the subgroup of patients with diabetes appears to benefit greatly from CABG surgery.

**Coronary Artery Bypass Graft Surgery vs Percutaneous Therapy**

**BARI.** The BARI study randomly assigned symptomatic patients with multivessel coronary artery disease (n = 1829) to initial treatment with angioplasty (n = 915) or CABG surgery (n = 914). Subgroup analysis of 353 patients with diabetes (angioplasty, 173 patients; CABG surgery, 180 patients) showed that the 5- and 10-year survival rates were 79.6% and 57.9%, respectively, for the CABG surgery group and 66.5% and 45.5% for the angioplasty group, $P = 0.025$ (Fig 4). Diabetic patients who benefited most included those with severe multi-vessel disease and those who received 1 arterial bypass graft.

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**D. R. Holmes:** I had thought that only diabetic patients with a LIMA had improved survival.

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Cardiac mortality rates at 5.4 years were higher in the angioplasty group than coronary artery bypass group (20.6% vs 5.8%), and need for repeat revascularization 10 years postprocedure was greater after angioplasty (79.7% vs 18.3%).

**EAST and CABRI.** The Emory Angioplasty Versus Surgery Trial (EAST) randomized 392 patients with multivessel coronary artery disease to initial angioplasty or CABG surgery, and subgroup analysis of 59 patients with diabetes supported the findings in BARI. Among diabetic patients, survival 8 years after intervention favored surgery (75.5% vs 60.1%, $P = 0.23$). Furthermore, in the CABRI study, at 4 years follow-up, the absolute risk of mortality was 12.5% in the surgical group and 22.6% in the angioplasty group. The relative risk of mortality among diabetics with angioplasty vs CABG surgery was 1.81.

Importantly, in the CABRI trial, compared with CABG surgery, there was increased residual coronary artery disease after angioplasty, a finding reflective of less complete revascularization. The authors suggested that a possible explanation for better outcome of surgery in diabetic patients was that surgical revascularization bypasses a much larger portion of the coronary artery anatomy, which may make the patient less vulnerable to the consequences of coronary artery disease progression. In fact, most stenoses or plaque ruptures occur within the proximal portion of the coronary arteries, a location usually bypassed with CABG surgery.
Coronary Artery Bypass Graft Surgery vs Percutaneous Coronary Intervention with Bare-Metal Stents

MASS II. The Medicine, Angioplasty, or Surgery Study (MASS) II trial randomized 611 patients with stable multivessel coronary disease from 1995 to 2000 to medical therapy, percutaneous coronary intervention, or CABG surgery. Retrospective review of 190 patients with diabetes showed that those randomized to medical therapy had an increased rate of death after approximately 1 year, which was maintained throughout the follow-up period. At 5 years, mortality in the percutaneous coronary intervention (10.7%) or surgery (8.5%) groups was significantly lower as compared to the medical treatment group (22.7%, \(P = 0.039\)). Rates of complete revascularization were significantly lower in the percutaneous coronary intervention group as compared to the surgery group and only 80% of patients in the percutaneous group received a stent.\(^{118}\)

ARTS. Another comparison of bare-metal stents vs surgery was the ARTS trial. Among 1205 randomized patients, 208 had diabetes (stent, 112 patients; CABG surgery, 96 patients). Five-year mortality was higher in diabetic patients treated with stents (13.4%) vs CABG surgery (8.3%, relative risk 1.61, \(P = 0.27\)). There was also a higher rate of myocardial infarction in the stent group (10.7% vs 7.3%, relative risk 1.47, \(P = 0.47\)). Repeat revascularization was also more common in the stent group than the CABG surgery group (30.3% vs 8.8%, \(P < 0.001\)). The authors stated that surgery should continue to be the preferred therapy for diabetic patients with multivessel disease when using bare-metal stents.\(^{113}\)

BARI 2D. Outcome of diabetic patients with coronary artery disease was the primary focus of study in the BARI 2 D trial in which 2368 patients with both type 2 diabetes and coronary artery disease received random assignment to prompt coronary artery revascularization with intensive medical therapy or intensive medical therapy alone. A key feature of the trial was that randomization was stratified according to the method of revascularization (percutaneous coronary intervention or CABG surgery), as determined a priori by the responsible physician.\(^{119}\) The process is very similar to that which occurs daily where clinical judgment rather than randomization is used to direct patients to CABG surgery or percutaneous coronary intervention.

D. R. Holmes: It must be remembered that BARI 2D was not designed to compare CABG vs percutaneous coronary intervention in diabetics with multivessel disease.
Selection of CABG surgery rather than percutaneous coronary intervention was by angiographic characteristics related to severity of coronary artery disease, including the presence of triple vessel disease, proximal left anterior descending coronary artery stenosis ≥50%, any left anterior descending stenosis ≥70%, total arterial occlusion, and 2 or more class C lesions. The more comprehensive revascularization required for patients in the CABG surgery group resulted in more vessels bypassed (average 3.0 ± 1.0 compared with 1.5 ± 0.8 for patients having percutaneous intervention). Of the percutaneous procedures, only 20.7% involved multivessel intervention. Furthermore, only 34.7% of the patients received a drug-eluting stent, and 9.3% of patients did not receive a stent.

Patients were followed for an average of 5.3 years during which time there were 316 deaths; 136 (43%) were attributed to cardiac causes, and 94 of these (69.1%) were sudden deaths. The risk of death during the entire follow-up was 5.2 times higher after a myocardial infarction compared with those with no myocardial infarction. In the percutaneous coronary intervention group, there was no significant difference in the rates of myocardial infarction between the revascularization and the medical therapy groups (12.3% vs 12.6%, P = 0.42). Also, composite endpoints of all-cause death or myocardial infarction (21.1% vs 19.6%, P = 0.19) and cardiac death or myocardial infarction (16.0% vs 14.2%, P = 0.45) were not different. Cardiovascular events among patients in the percutaneous coronary intervention stratum who were assigned to the revascularization group (23%) did not differ significantly from those who were assigned to the medical-therapy group (21.1%, P = 0.15).

Among patients having surgical revascularization, however, rates of myocardial infarction were significantly reduced compared to medical therapy (10.0% vs 17.6%, P = 0.003) (Fig 5). Importantly, when procedure-related events were excluded, late risks of myocardial infarction were even lower in the surgical patients, 5.9% vs 14.8% (P < 0.001). The composite endpoint of all-cause death or myocardial infarction (21.1% vs 29.2%, P = 0.010) and cardiac death or myocardial infarction (15.8% vs 21.9%, P = 0.03) were also less frequent in the surgical group. Patients had significantly fewer major cardiovascular events (22.4%) with CABG surgery than those who were assigned to medical-therapy only (30.5%, P = 0.01). In addition, nonfatal myocardial infarction occurred in markedly fewer patients in the CABG surgery revascularization group (7.4%) than in the medical-therapy group.
FIG 5. Time to first myocardial infarction in the percutaneous coronary intervention stratum (top) and in the coronary artery bypass graft surgery stratum (bottom). The incremental risk of myocardial infarction was continuous over time in the intensive medical therapy groups. In the coronary artery bypass graft surgery stratum, the difference in myocardial infarction rates between initial revascularization with coronary artery bypass graft surgery and an initial intensive medical therapy strategy was significant ($P = 0.003$). [Modified with permission.121]

(Color version of figure is available online.)
(14.6%). The BARI 2D trial demonstrates clearly that diabetic patients with more extensive coronary disease benefit from prompt CABG surgery and intensive medical therapy.

**Coronary Artery Bypass Graft Surgery vs Percutaneous Coronary Intervention with Drug-Eluting Stents**

**SYNTAX.** The potential improvement in outcomes with drug-eluting stents was the focus of study in the SYNTAX trial that randomized 1800 patients with left main or 3-vessel coronary artery disease to receive paclitaxel-eluting stents or CABG surgery. In the subgroup of 452 patients with medically treated diabetes, the rate of complete revascularization was lower in the percutaneous coronary intervention group (49.1%) compared with CABG surgery (60.7%). At 1-year follow-up of patients with the most severe disease (SYNTAX score ≥33), mortality was 3-fold higher in the percutaneous coronary intervention group (13.5%) vs the CABG surgery group (4.1%, P = 0.04) (Fig 6). In the same cohort of patients, rates of subsequent revascularization were also higher in the percutaneous coronary intervention group (24.3% vs 5.4%, P = 0.001). This study suggested that 1-year major adverse cardiac and cerebrovascular event rates are lower in diabetic patients with left main and/or 3-vessel disease treated with surgical revascularization compared to percutaneous coronary intervention with drug-eluting stents. \(^{114,122}\)

**CARDia.** In another study of diabetic patients and drug-eluting stents, investigators in the CARDia trial (Coronary Artery Revascu-
larization in Diabetes) randomized 510 diabetic patients with multi-vessel or complex single-vessel coronary disease to percutaneous coronary intervention (Cypher stents 69%, bare-metal stents 31%) or CABG surgery. In the percutaneous coronary intervention group, 65% of patients had 3-vessel disease and 88% received complete revascularization. In the CABG surgery group, 60% of patients had 3-vessel disease and 90% received complete revascularization of which 17% received at least 2 arterial grafts. At 1-year follow-up there was no difference in mortality (stent, 3.2%; CABG surgery, 3.2%, \( P \neq 0.97 \)). However, the rate of late myocardial infarction occurring >7 days after the index revascularization procedure was higher in the percutaneous coronary intervention (5.5%) vs CABG surgery group (1.2%, \( P = 0.016 \)). Further revascularization was also higher in the percutaneous coronary intervention group (11.8%) vs CABG surgery (2.0%, \( P < 0.001 \)). Also, after 1 year, patients randomized to percutaneous coronary intervention had significantly more angina (28.7%) compared with CABG surgery (11.5%, \( P = 0.001 \)). This study again suggests that diabetic patients with extensive coronary artery disease do better with surgical revascularization.\(^{123}\)

D. R. Holmes: It must be remembered that the studies of CABG vs percutaneous coronary intervention have in general identified that stroke rates are increased in patients undergoing CABG. This raises the issue of hierarchical endpoints. That is, do all endpoints have the same value? What is the relative value of a procedural stroke vs the need for an additional revascularization procedure?

Cedars-Sinai Medical Center Study. To examine outcomes in contemporary clinical practice, Lee et al reviewed prospectively collected data on 205 consecutive diabetic patients who underwent either drug-eluting stent placement (102 patients) or CABG surgery (103 patients). The surgery group had smaller vessel size and more complex and longer lesions. At 1-year follow-up, major adverse cardiac event rates were higher in the drug-eluting stent group (27% vs 12%, \( P = 0.0006 \)). Myocardial infarction was also more common in the drug-eluting stent group (7% vs 2%) as was the need for repeat revascularization (20% vs 3%, \( P < 0.001 \)). Of importance, in-stent restenosis accounted for 12 of the 20 cases of repeat revascularization and 4 of the 6 cases of myocardial infarction between 31 days and 1 year.\(^{124}\)
Patients with diabetes mellitus carry a greater risk profile and atherosclerotic burden than those without diabetes. Diabetic patients more often have heart failure, cerebrovascular disease, peripheral vascular disease, and renal dysfunction compared to nondiabetic patients. In addition, coronary artery lesions in diabetic patients are frequently complex due to the small size and diffuse involvement with atherosclerosis, necessitating long stent length during percutaneous treatment. It is not surprising, therefore, that diabetics fare worse following any form of revascularization with increased rates of cardiac death, stroke, and need for subsequent revascularization.

The best treatment strategy for diabetic patients with coronary artery disease remains controversial, and the focus of this section of the article is to analyze the important aspects of the previous reviewed studies to identify which patients benefit from surgical revascularization.

Coronary Revascularization and Medical Management

The understanding that coronary artery revascularization confers a survival advantage in diabetic patients was established in the MASS II trial, which reported the long-term benefits of coronary artery revascularization over medical therapy in 190 diabetic patients with stable multivessel coronary artery disease. At 1-year follow-up, patients randomized to medical therapy had an increased rate of death, which continued through the follow-up period. At 5 years, mortality in the angioplasty (10.7%) or surgery (8.5%) groups was dramatically lower than the medical therapy group (22.7%, \( P = 0.039 \)). The investigators emphasized that medical therapy was not optimal in this trial, but it is unlikely that this accounts for the relatively poor outcome of medically treated diabetic patients.

The BARI 2D trial provided robust support of CABG surgery in diabetic patients with extensive coronary artery disease (eg, 3-vessel disease). Compared to medical therapy, patients in the surgical group experienced reduced risks of myocardial infarction, the composite of all-cause death or myocardial infarction, and cardiac death or myocardial infarction. However, in patients treated with percutaneous intervention (who had less extensive disease) there was no difference in composite endpoints compared to patients initially managed medically. The importance of myocardial infarction in relation to survival is the fact that the risk of death during the entire follow-up was 5.2 times higher after a myocardial infarction compared with those with no myocardial infarction.

Results of the BARI 2D trial support the use of intensive medical
therapy as the preferred initial treatment strategy for diabetic patients with less extensive coronary artery disease (eg, 2-vessel disease). This conclusion is generally consistent with findings of the COURAGE trial where an initial strategy of percutaneous coronary intervention in patients with stable coronary artery disease did not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical therapy.127

Coronary Artery Bypass Graft Surgery or Percutaneous Coronary Intervention

The BARI study was the first randomized trial to suggest a survival benefit to CABG surgery over angioplasty in patients with diabetes.112,128 In the initial report from 1996 and in the 10-year follow-up report, overall survival of patients with multivessel disease was similar for patients assigned to CABG surgery or angioplasty (74% vs 71%). Among patients with treated diabetes, however, 10-year survival was superior in the surgery group (58% vs 46% for angioplasty) (Fig 5). As noted previously, these findings were similar to those in the EAST trial in which the 8-year survival of diabetic patients who had bypass graft surgery was 76% compared to 60% for angioplasty patients.129

Other notable results of the original BARI study included the finding that revascularization was more often complete after CABG surgery than angioplasty (87% vs 76%).130 Also of importance is that patients who received 1 arterial graft had a 64.3% 10-year survival, compared with 39.4% in CABG surgery patients who received only vein grafts, and 45% in angioplasty patients.112

Where the BARI and EAST studies compared initial surgical revascularization to percutaneous angioplasty, the ARTS I trial compared surgical revascularization to percutaneous therapy with bare-metal stents.113 In the subgroup of patients with diabetes, 5-year mortality was higher in patients treated with stents (13%) vs CABG surgery (8%). There was also a higher rate of myocardial infarction in the stent vs surgery groups.

Surgical revascularization appears to attenuate the difference in outcome of patients with diabetes compared to nondiabetic patients. In the ARTS I study, there was no significant difference in survival between diabetic and nondiabetic patients who had surgical revascularization, and major adverse cardiac and cerebrovascular event rates were similar in surgically treated patients with or without diabetes. In contrast, in the percutaneous intervention group, diabetic patients had a significantly
higher mortality rate than nondiabetic patients (13% vs 7%), and death was attributed to a cardiac cause in 50% of cases. The difference in the composite endpoints (death, stroke, and myocardial infarction) favoring CABG surgery was driven primarily by a lower incidence of myocardial infarction in the surgical revascularization group.

Drug-eluting stents represent the next major advance in the evolution of percutaneous technology. In a subgroup analysis of the ART II trial, diabetes proved to be the strongest preprocedural predictor of major adverse events (odds ratio: 1.76, \( P = 0.012 \), and this was driven mainly by a greater need for repeat revascularization among diabetic vs nondiabetic patients (21% vs 12%).\(^{125}\) Major adverse cardiac events occurred in 44 of the 159 diabetic patients (27%), and 12 of 22 (55%) of the clinically driven repeat target lesion revascularizations were performed for definite stent thrombosis. The study demonstrated that diabetic patients had higher risks of failure of percutaneous drug-eluting stent interventions than nondiabetic patients.

Two recently published trials (SYNTAX and CARDia) have compared drug-eluting stents vs CABG surgery in patients with diabetes.\(^{122,123}\) Several themes previously established in studies comparing surgical revascularization against angioplasty and bare-metal stents repeat in these 2 studies. The SYNTAX trial reaffirmed previous trial outcomes showing a lower rate of complete revascularization in diabetic patients treated with percutaneous intervention (49%) compared with nondiabetic patients (59%). Surgical revascularization, however, demonstrated similar rates of complete revascularization for diabetic (61%) and nondiabetic (64%) patients.\(^{122}\)

Survival was also better in patients treated with surgical revascularization and was directly proportional to the extent of coronary artery disease. In the SYNTAX trial, patients with the most severe coronary artery disease (SYNTAX score \( \geq 33 \)) experienced significantly higher 1-year mortality rates following percutaneous treatment (13.5%) compared with CABG surgery (4.1%). In patients with extensive coronary disease, the rate of subsequent revascularization was also much higher following percutaneous intervention with drug-eluting stents (24.3% vs 5.4%). Importantly, even with the short follow-up reported in this trial (1 year), major adverse cardiac and cerebrovascular event rates were greater among diabetic patients treated with drug-eluting stents compared with surgery.

Rates of myocardial infarction in diabetic patients treated with drug-eluting stents have a major impact on survival. In the CARDia trial, the risk of late myocardial infarction occurring >7 days after the index
revascularization procedure was greater in the stent group than in surgical patients (5.5% vs 1.2%). In patients with 3-vessel coronary artery disease, the outcome of death/myocardial infarction/stroke was also higher in the stent group (15.2% vs 11%). Similar to the SYNTAX trial, the rate of repeat revascularization in the CARDia study was higher in the stent group (11.8 vs 2.0%), and this was true again after only 1 year of follow-up.

D. R. Holmes: A typical comment about randomized clinical trials is that they recruit only very selected patients with lower risk anatomy. That statement was clearly not operative in the SYNTAX trial, which included the highest risk patient group who has been randomized in a large trial.

Randomized studies, such as the SYNTAX trial often enroll less than 50% of screened patients and may not be representative of the larger pool of patients encountered in clinical practice. In this regard, registry studies may give a more realistic assessment of the outcome of percutaneous coronary intervention with drug-eluting stents in diabetics. In a study from Cedars-Sinai Medical Center by Lee and colleagues, patients treated with surgical revascularization had more complex coronary artery lesions than patients treated with stents, yet outcomes of surgical patients were superior with respect to major adverse events, myocardial infarction rates, and need for repeat revascularization. Importantly, in-stent stenosis was not a benign event as it accounted for over 60% of cases of repeat revascularization and posttreatment myocardial infarction.

D. R. Holmes: It must be remembered that because the overall SYNTAX trial was negative, any other observations must be considered hypothesis-generating only, that stroke rates at 1 year were increased in the surgical group.

Benefits of Coronary Artery Bypass Graft Surgery and Possible Mechanisms

Compared to medical therapy or percutaneous intervention, coronary artery bypass surgery improves survival of diabetic patients with severe coronary artery disease. The likely explanation is that the risk of death during the follow-up period is inversely proportional to the completeness of revascularization, and CABG surgery provides more complete revascularization, especially in patients with more extensive disease.
The pattern of coronary artery narrowing in diabetic patients is often complex with multiple lesions with diffuse artery involvement. Percutaneous techniques are limited primarily to the proximal and middle segments of the coronary arteries, which are the most common diseased portions of the vessel. Bypass grafts are not limited to the proximal diseased areas of the coronary arteries. The grafts routinely terminate in distal segments of the arteries, which are often beyond occlusions and more normal in nature. Thus, surgical revascularization is generally more complete with CABG surgery than percutaneous coronary intervention.

Additionally, need for subsequent revascularization is markedly less in surgically treated patients compared to those who undergo percutaneous coronary intervention. Multiple studies demonstrate high rates of repeat revascularization after percutaneous intervention, including 80% of patients having angioplasty in the BARI trial, 43% of patients receiving bare-metal stents in the ART I trial, and 21% of patients treated with drug-eluting stents in the ART II trial. Importantly, with only 1-year follow-up, the rates of repeat revascularization after intervention with drug-eluting stents were 20% in the SYNTAX trial and 12% in the CARDia trial.

Reported rates of repeat revascularization in surgical patients, however, are much less and range from 10% in the ART I trial with 5-year follow-up to 18% in the BARI trial with 10-year follow-up. Restenosis is an important endpoint because it is not always a benign event. Need for repeat revascularization following angioplasty does not appear to decrease subsequent survival but clinically driven repeat revascularization in patients with bare-metal or drug-eluting stents is often associated with death (30%) or myocardial infarction (60%). In contrast, bypass graft occlusion often results only in angina leading to revascularization.

A final consideration in the decision to proceed with revascularization in patients with diabetes is the clinical observation that many such patients have minimal or no angina despite the presence of significant myocardial ischemia. Indeed, in the Detection of Ischemia in Asymptomatic Diabetics study, 22% of asymptomatic diabetic patients had silent myocardial ischemia, and over one quarter of these patients had moderate or large ischemic territories. Assessment of medical treatment and detection of restenosis or stent narrowing may be difficult if patients do not have warning angina, and late myocardial infarction and cardiac death may be the first manifestation of recurrent ischemia.
Summary

Treatment strategies for diabetic patients with coronary atherosclerosis continue to be refined. Patients with limited disease burden can be treated safely with medical therapy and referred for invasive revascularization if ischemic symptoms persist or worsen, or if noninvasive studies demonstrate larger ischemic burden. For diabetic patients with severe, multivessel disease, CABG surgery remains the preferred strategy as it provides greater myocardial revascularization with less late myocardial infarction and associated mortality; in addition, CABG surgery provides more durable myocardial revascularization with less need for repeat revascularization. Continued developments with respect to new antiplatelet strategies and multiple arterial bypass graft strategies will undoubtedly improve our ability to treat such patients and will form the basis for future comparisons in treatment.

The Future

The basic technique of suturing the CABG anastomosis has not changed over the last 60 years. What continues to change, however, are the technologies that surround the anastomosis, including the introduction of the hybrid operating room suite and the ability for intraoperative coronary angiography, the use of less invasive techniques to perform the anastomosis, and methods to improve patency of bypass grafts. These new technologies will undoubtedly influence the method of surgical revascularization.

Hybrid Procedures. With the exception of CABG surgery, every major cardiovascular procedure—including percutaneous coronary intervention, heart valve surgery, and endovascular and traditional open vascular surgery—including completion imaging to assess results. At 1 heart center that routinely performs open-chest completion coronary graft angiography in the hybrid suite, angiographic defects were present in 12% of grafts. In addition to routine completion angiography, the hybrid suite also allows the surgeon and interventional cardiologist, in a collaborative environment, to offer patients traditional surgery and/or percutaneous coronary intervention during the same operative session. Some centers are evaluating a hybrid surgical approach with a left internal mammary artery bypass graft to the left anterior descending coronary artery combined with percutaneous drug-eluting stent placement in the other coronary arteries. Direct comparison of saphenous vein grafts against percutaneous coronary intervention with drug-eluting stents is lacking, but historically saphenous vein graft occlusion rate within 12-18 months may exceed the restenosis rate with drug-eluting stent.
Robotic CABG Surgery, Total Endoscopic Coronary Artery Bypass (TECAB), Off-Pump Total Endoscopic Coronary Artery Bypass (OPTECAB). Robotic technology facilitates total endoscopic coronary artery bypass grafting. Recent advances have allowed the expansion of this technique to include multivessel procedures. A limitation of the method is the longer times necessary to complete bypass graft anastomoses; however, total endoscopic double-vessel coronary artery bypass grafting of the arrested heart appears to be a reproducible and reasonably safe procedure.134

Inhibition of Atherosclerosis. The number of patients with coronary artery disease and type 2 diabetes will increase dramatically over the next decade and many of these patients will require CABG surgery. Diabetes causes accelerated atherosclerosis, which is associated with saphenous vein graft failure in approximately 50% of patients at 10-year follow-up. Rosiglitazone, a peroxisome proliferator-activated receptor-gamma agonist, improves multiple metabolic parameters in patients with type 2 diabetes and may have anti-atherosclerotic effects in post-CABG surgery patients. The vein-coronary atherosclerosis and rosiglitazone in bypass surgery trial randomly assigned patients with type 2 diabetes to rosiglitazone or placebo 1 to 10 years after CABG surgery. After a 12-month follow-up, there was no significant effect of rosiglitazone on vein graft atherosclerosis but glycemic control and cardiometabolic risk profile appeared improved by changes in subcutaneous adiposity.135 Similar studies with longer follow-up are in progress to better define the contribution of this class of drug in patients with type 2 diabetes.136

Gene and Cell Therapy. Conventional surgery for the treatment of ischemic heart disease has been advanced with biopharmaceutical-based therapy, such as protein, gene, and cell therapy that are promising approaches in inducing neovascularization and improving collateral blood flow in the ischemic heart. A variety of catheter or surgical approaches for in vivo cardiac gene transfer show encouraging results in animal and clinical studies. Transmyocardial laser revascularization may provide angiogenesis engendered by the laser–tissue interaction and, when combined with biopharmaceutical therapy, may enhance the angiogenic response which appear to be promising future endeavors.137,138

Conclusions

The history of CABG surgery is an amazing story through which continuous refinement of techniques has resulted in safe and effective methods of coronary artery revascularization. A better of understanding of the natural history of coronary atherosclerosis has identified patients
best served with the technique and today surgical revascularization is the treatment of choice for diabetic patients and others with complex coronary artery disease. The future will bring improved results with better graft patency and less operative insult and morbidity. CABG surgery is here to stay.

D. R. Holmes: The authors are to be commended on a superb surgical article. An important aspect not discussed but which is critical, nonetheless, is matching the specific procedure for the specific patient. Not all endpoints are the same—what for 1 patient is a major adverse outcome for another patient is an inconvenience. The optimal approach involves the formation of Heart Teams, popularized in the SYNTAX Trial, which meet, identify the risk–benefit ratio of each procedure for each patient, and then help the patient to reach the best decision of care.

REFERENCES

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