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REVIEW

Clinical update

Coronary artery bypass grafting: Part 1—the evolution over the first 50 years

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Surgical treatment for angina pectoris was first proposed in 1899. Decades of experimental surgery for coronary artery disease finally led to the introduction of coronary artery bypass grafting (CABG) in 1964. Now that we are approaching 50 years of CABG experience, it is appropriate to summarize the advancement of CABG into a procedure that is safe and efficient. This review provides a historical recapitulation of experimental surgery, the evolution of the surgical techniques and the utilization of CABG. Furthermore, data on contemporary clinical outcomes are discussed.

Keywords Coronary artery bypass grafting • Evolution • Graft Patency • Minimally invasive • Outcomes • Outcome prediction • Review

Introduction

In 1899, Francois Franck proffered the first surgical treatment for angina pectoris; he believed that ligation of sympathetic pain pathways would result in relief of angina.[1] Several decades later, a number of groups started performing surgical sympathectomy that indeed resulted in relief of angina, yet this was found to be inconsistent. Moreover, mortality remained high during follow-up, and although patients no longer experienced symptoms, the consequences of the underlying coronary artery disease (CAD) continued.

To specifically address reduced myocardial perfusion, several experimental surgical techniques were designed to supply external blood to the myocardium (*Figure 1*). Thorel in 1903 suggested that pericardial adhesions to the myocardium could provide blood to ischaemic areas,[2] which was confirmed in 1932 by Moritz et al.[3] Pericardial abrasion was performed either mechanically or with the use of irritants (e.g. beef bone, aleuronat, talc) to initiate formation of adhesions.[4,5] Simultaneously, numerous tissues were used as 'collaterals' and sutured to the ventricle:[1,6] in 1935, Beck used the pectoral muscle,[7] in 1936 O'Shaugnessy the great omentum,[8] in 1937 Lezius the lung,[9] and in 1954 Key used a pedicle of jejunum.[10]

The internal mammary artery (IMA) formed an area of interest early on, particularly after the report of Fieschi in 1939. He ligated the right IMA at the second intercostal space to increase blood flow to the coronary circuit through smaller anastomotic collaterals from the IMA bed.[4] Although angina was significantly reduced in up to 95% of patients,[11] a study with sham controls proved no benefit of ligating the IMA.[12] It was not until the work by Arthur Vineberg in 1946 that the use of the IMA was starting to show promising results.[13] He skeletonized the left IMA and tunneled the artery next to the left anterior descending (LAD) coronary artery—without using any anastomosis—in a tract in the ventricular wall he made with a tonsil-type instrument. Remarkably, in 71% of dogs with ischaemic heart disease spontaneous anastomosis developed;[14] probably because dogs have greater capacity to form collaterals.[15] Beck in 1946 moved away from the IMA and focused on the coronary sinus; in dogs he used a segment of the carotid artery as a graft between the descending aorta and coronary sinus creating a systemic-cardiac arteriovenous fistula,[16] which for obvious reasons failed to help patients. Prophetically, Murray in 1954 suggested that one would need direct anastomosis to the LAD to provide the best results, and like Beck he also favoured the carotid artery.[17] Thereafter, Goetz and colleagues in 1960 performed an IMA-right coronary artery anastomosis using a nonsuture technique with a tantalum ring as a connector device.[18]

One of the most crucial developments was that of coronary angiography by Mason Sones;[19] he demonstrated the formation of collaterals after the Vineberg operation, but, more importantly, was able to evaluate native coronary arteries and identify lesions that required

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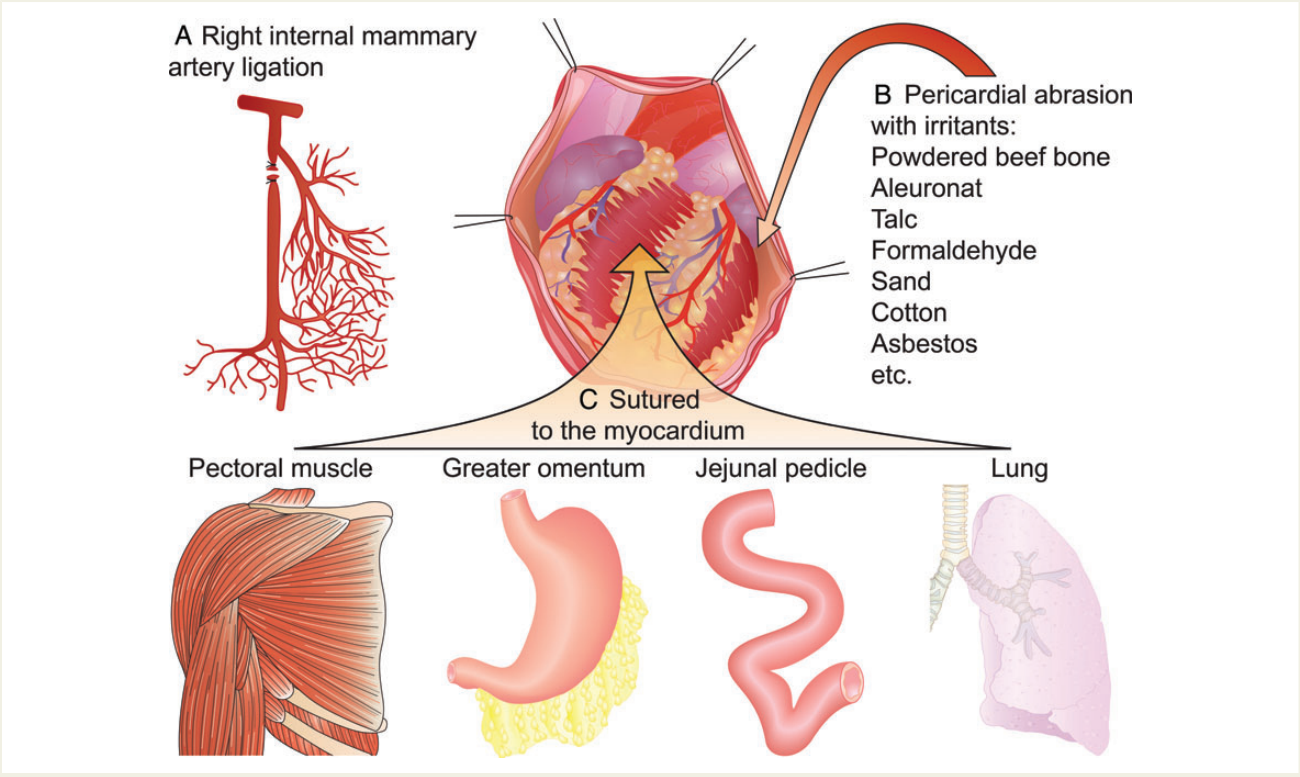

Figure 1 Experimental surgery for coronary artery disease that preceded the introduction of coronary artery bypass grafting. Different surgical methods have been applied: (*A*) ligation of the right internal mammary artery to increase blood flow to the coronary circuit through collaterals, (*B*) pericardial abrasion with the use of irritants to form adhesions, and (*C*) suturing different tissues to the myocardium as collaterals.

targeted therapy. Coronary angiography was quickly considered to be mandatory to select patients and plan the procedure. Its use during follow-up resulted in the recommendation to perform revascularization on coronary arteries with >75% stenosis to ensure good patency rates.[20]

These advancements finally led to the 'modern' coronary artery bypass grafting (CABG) procedure of the mid-1960s (*Figure 2A*). Vasilii Kolesov is believed to have been the first to perform a sutured anastomosis of an IMA to the LAD on February 25th, 1964.[21] Later that year, on November 23rd, a team led by Michael DeBakey performed a saphenous vein aorta-coronary bypass with a continuous suture technique.[22] Although not the first to perform this operation, René Favaloro was the first to systematically perform CABG with reproducible results.[23] He is considered the 'father' of bypass surgery and is acknowledged for his tremendous contribution in the field of surgical revascularization.[20,24]

From initial experiences to the standard of care

Quickly it became clear that given the limited possibilities of medical therapy at the time, surgical revascularization could be very beneficial for patients with CAD. In a review of >10 000 CABG procedures performed before 1971 at 16 selected centres, 70–95% of patients had improved their symptomatic status and 60–70% became asymptomatic.[25] However, operative mortality was as high as 10% in some large series.[20,25] Skepticism was additionally fueled by a perioperative myocardial infarction (MI) rate of 15%.[26] With growing experience, the rate of mortality and MI reduced significantly,[27] but still remained high in some all-comers series; respectively 7 and 14%.[28] Selection of patients appeared of paramount importance, as mortality was significantly higher in patients who suffered a recent MI with/without severe left ventricular dysfunction,[29,30] or who underwent concomitant procedures.[28]

The controversial early data unmasked the need for comparative effectiveness analyses of CABG and medical therapy in the form of randomized clinical trials. While it was unquestionable that surgery relieved angina, it remained unclear whether there would also be a benefit in reducing long-term mortality and preventing future MI, especially since the introduction of β-blockers had in the meantime optimized medical therapy. Several retrospective and prospective (randomized) studies were performed but were unable to show a significant survival benefit of CABG over optimal medical therapy in patients with stable angina,[31–34] with the exception of patients with left main disease.[35,36] However, these studies were heavily criticized for their (i) selection bias, (ii) use of historical controls, (iii) comparability of study groups and (iv) small sample size.[37] The results from three large trials formed the basis for clinical decision making: the Veterans Administration (VA) Cooperative Study ($n = 686$),[38] the European Coronary Surgery Study ($n = 767$)[39] and the Coronary Artery Surgery Study ($n = 780$) (CASS).[40] Although the individual trials did not consistently show superiority of CABG over medical therapy in terms of long-term survival, they provided much of the

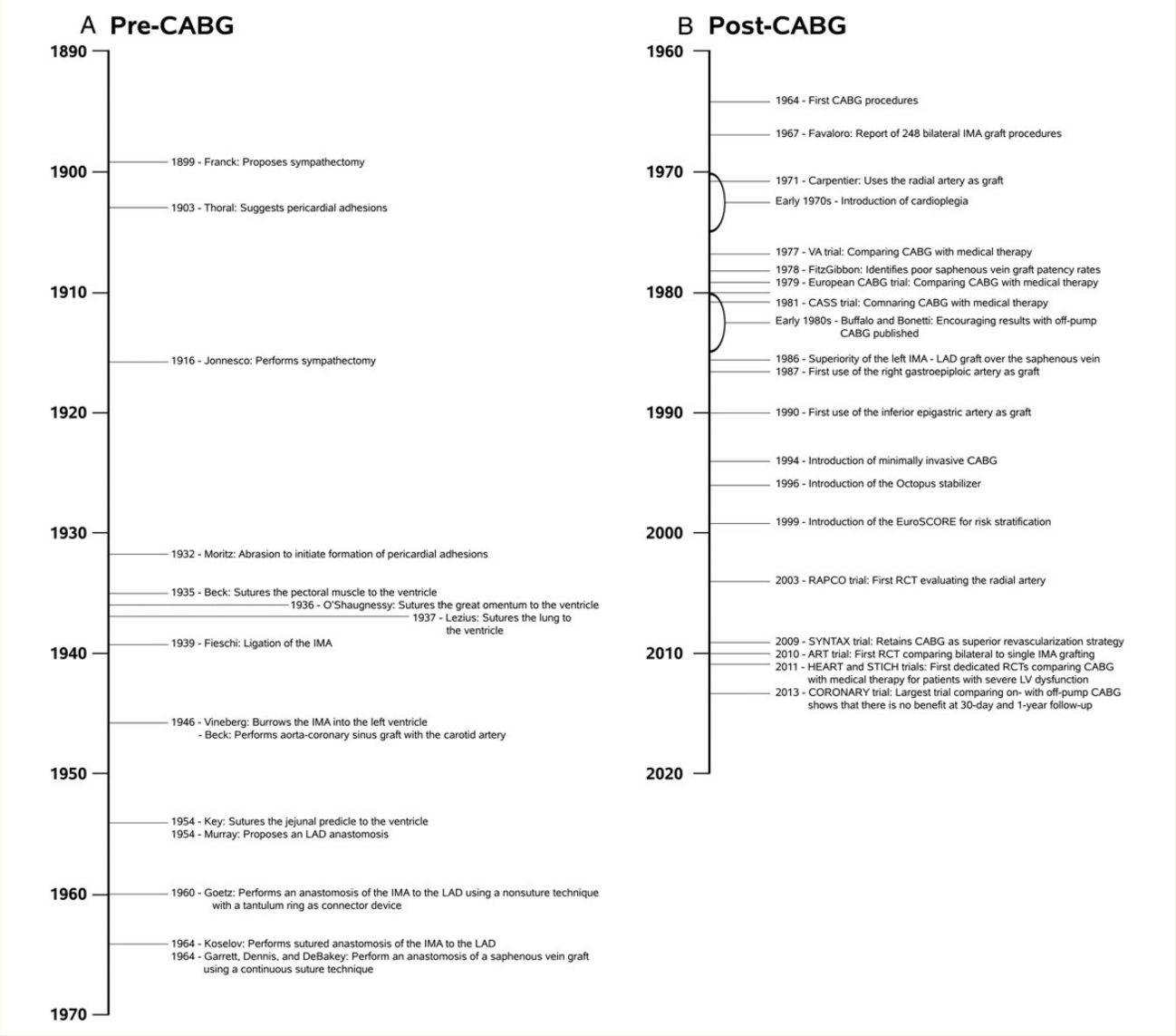

Figure 2 Timeline of developments that led to the first 'modern' coronary artery bypass grafting (*A*) and facilitated continuous improvements in surgical technique and outcomes during the first 50 years (*B*).

basis for a later meta-analysis of seven trials that reported a survival benefit with CABG at 5 (OR = 0.61, 95% CI 0.48–0.77), 7 (OR = 0.68, 95% CI 0.56–0.83) and 10 years (OR = 0.83, 95% CI 0.70–0.98) of follow-up.[41] Besides the relief of symptoms, the benefits of CABG now included an improved prognosis after which it evolved as the standard of care for the treatment of CAD on the grounds of evidence-based recommendations rather than expert opinion.

The costs involved with CABG procedures were criticized for its possible impact on health care budgets. However, apart from prolonging life, compared with medical therapy, CABG also significantly improves the quality of life for at least up to 5 years.[42,43] In the MASS-II trial, angina-free survival at 5-year follow-up was 54.8% for patients in the medical therapy group vs. 74.2% in the CABG group ($P < 0.001$).[44] Although initial hospitalization costs are indeed higher for patients undergoing CABG, these are counterbalanced by the long-term benefits of the treatment. Compared with other therapies, the benefit of CABG on quality-adjusted-life-years proved favourable.[45,46]

Utilization of coronary artery bypass grafting

After the successful introduction of CABG, the procedure remained in a state of relative experimental therapy outside of a few pioneering centres.[47–49] In the beginning of the 1970s, larger experiences were published which resulted in a growing interest in surgical revascularization. At one point, it was even anticipated to become the '*most frequently performed operation in America*'.[22]

In the 1960s, >35% of total deaths per 100 000 population in the USA were the result of ischaemic heart disease, which was somewhat lower in European countries (e.g. United Kingdom ~29% and the

Netherlands ~25%).[50] The option of surgical revascularization was a long awaited solution for patients with CAD, and like any disruptive technology was quickly adopted with widespread enthusiasm. The annual number of CABG procedures in the USA increased rapidly to 30 000–40 000 in 1974 and exceeded 60 000 in 1976.[34,51] By 1976, it was estimated that already more than 300 000 patients had undergone CABG.[34] The annual rate continued to grow to 114 000 procedures/year in the USA alone by 1979.[52]

Andreas Grüntzig introduced percutaneous coronary intervention (PCI) in 1978,[53] which provided an alternative treatment strategy for symptomatic CAD. Nevertheless, the annual CABG rate continued to grow to 191 000 CABG procedures/year in 1983 in the USA.[54] When the indications for PCI quickly developed first for acute MI[55] and later for stable single- and multivessel disease with the development of bare-metal stents, PCI rates started to grow exponentially and already by 1986 more than 133 000 PCIs were performed annually in the USA.[56] Continuous technical advancements of PCI (e.g. drug-eluting stents) and adjuvant medical therapy (e.g. $P2Y_{12}$ receptor antagonists) allowed a broader range of clinical scenarios to be treated percutaneously. As a result, CABG more and more became reserved for patients with complex lesions.

Despite the dramatic increase in PCI procedures during the 1990s,[57] there was also an expansion of the number of CABG programs thereby increasing the absolute rate of CABG per population.[58,59] In an analysis of European countries, the annual rate of CABG increased from 137 000 to 225 000 procedures/year between 1992 and 2000.[58] In the USA, there was also a constant increase in the number of CABG procedures, although the age- and gender-adjusted rate per 100 000 population finally leveled out at 100–150 procedures/year.[59,60] Approaching the turn of the millennium and a stage of market saturation, the utilization of CABG started to decline. Community-based studies in Olmsted and Washington State showed a significant shift in the PCI-to-CABG ratio; while the increase in the number of revascularizations stagnated, the number of PCIs continued to rise as the number of CABGs declined.[59,60] Through 2001–2008, the number of revascularization procedures in the USA have declined from 5569 to 4748 per 100 000 population due to a significant reduction of CABG (1742 to 1081; $P < 0.001$) but not PCI (3827–3667; $P = 0.74$).[61] This has been predominantly the result of the absence of a survival benefit with CABG in randomized trials performed during the 1990s and 2000s. Results from the BARI trial showed that 71.0 and 73.5% patients were alive 10 years after PCI and CABG, respectively ($P = 0.18$), and survival free of MI was comparable (63.9% vs. 63.6%, respectively; $P = 0.97$).[62] In larger pooled analyses with 5-year follow-up, there were also no differences in survival or the composite of death or MI.[63,64] More recent results from the SYNTAX trial and ASCERT study have contradicted these findings and may initiate another shift in the PCI-to-CABG ratios in favour of CABG.[65,66]

Over 50 years, the increase in the number of CABG procedures has shown significant inter-country variation. Between 1985 and 2006, there was a 6% increase in CABG procedures in the USA, while there was a staggering 915% increase in Germany (*Figure 3A*).[67,68] The average annual number of CABG procedures per 100 000 is 62.2 in contemporary Western practice, but differs significantly by country ranging from 29.3 to 135.4 procedures in Spain and Belgium, respectively (462% variation) (*Figure 3B*).[68] When considering age-standardized death rates from ischaemic heart disease, the ratio of CABG per death varies even more from 0.17 procedures/death in Hungary to 1.40 procedures/death in Germany (817% variation) (*Figure 3C*). This variation may be the result of a myriad of reasons, including, but not limited to: patient and/or physician preferences, the number of centres performing CABG, differences among private and public sectors, thresholds for revascularization and import/export of patients to best practices in more developed countries.

Research

A simple entry of '*CABG OR coronary bypass*' in PubMed yields 59 732 publications in peer-reviewed journals through 1964–2012 (*Figure 4*). Over the past 10 years, this search results in consistently ~2300–2500 publications annually. The body of evidence originating from this research has (i) produced a technical evolution of the procedure, (ii) focused on complications that are associated with CABG, (iii) provided an estimate of the incidence in which these complications occur and (iv) identified predictors of short-and long-term outcomes. These data have led to continuous quality improvements and have been incorporated in clinical decision-making and guideline-directed treatment recommendations.

An evolution of the technique

Myocardial protection

Initially, CABG was almost exclusively performed with the use of cardiopulmonary bypass (CPB) and the anastomoses were performed on the arrested heart. Myocardial protection during the period of induced ischaemia was found to be of utmost importance as operative myocardial injury was directly resulting in left ventricular dysfunction, thereby impacting prognosis.[69] The work by Follette, Buckberg and colleagues in the 1970s demonstrated the deleterious effects of induced ischaemia and reperfusion injury and triggered a whole new field of research.[70] Improved CPB techniques, advanced anaesthesia techniques, shorter-operating times and more refined suturing all contributed to reducing the amount of myocardial injury.[71] However, the introduction of myocardial protection is believed to be the single most important contribution to CABG.[71] Operative mortality and morbidity were significantly reduced in the early 1970s by using potassium cardioplegia to lower myocardial energy demands during the ischaemic period (*Figure 2B*).[72] In the 1980s, advanced myocardial protection methods aimed at providing oxygen, optimizing the metabolic rate, reducing calcium influx, reversing acidosis, avoiding edema and replenishing substrates.[70]

Over the years, two different types of cardioplegia have been extensively investigated; blood and crystalloid cardioplegia. Warm blood cardioplegia may have an advantage over crystalloid cardioplegia as it resembles the normal physiology, which could result in less myocardial injury and better clinical outcomes. However, administration of blood cardioplegia is more complex than for crystalloid cardioplegia: (i) it can be cold, normothermic, or warm, (ii) it can be administered antegrade or retrograde and (iii) should it be given continuous or intermittent, and at what interval between doses? Crystalloid cardioplegia is less expensive and provides better intraoperative visibility.[73] The most recent meta-analysis summarized data from 36

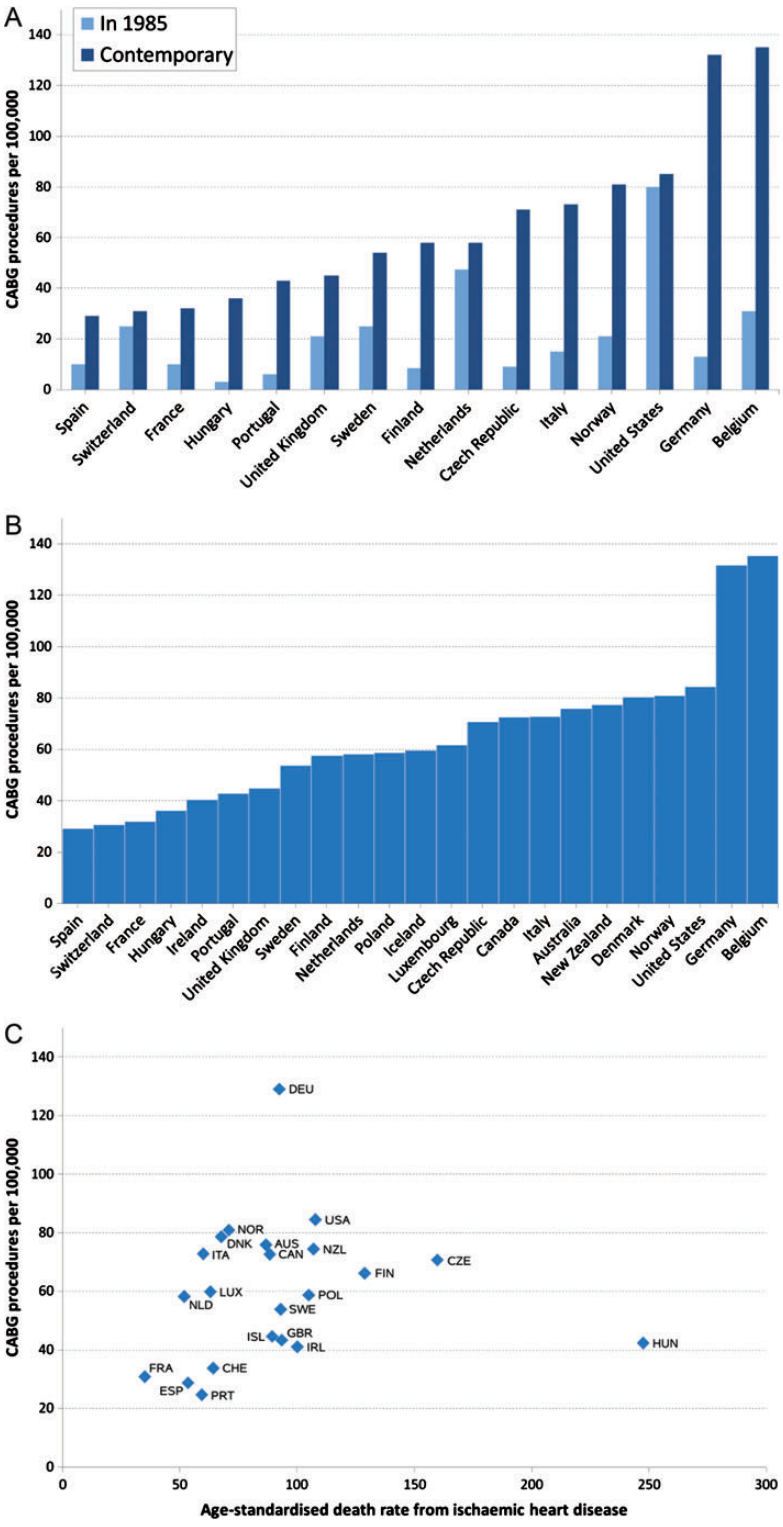

Figure 3 The utilization of coronary artery bypass grafting around the world. The increase in coronary artery bypass grafting procedures per 100 000 population has differed significantly between countries (*A*), as well as the number of coronary artery bypass grafting procedures that are performed in contemporary practice (2006) (*B*). These differences are independent of the prevalence of ischaemic heart disease (*C*). Data originated from the Organization for Economic Co-operation and Development[68] and from Rothlin.[67] AUS, Australia; CAN, Canada; CZE, Czech Republic; DNK, Denmark; FIN, Finland; FRA, France; DEU, Germany; HUN, Hungary; ISL, Iceland; IRL, Ireland; ITA, Italy; LUX, Luxembourg; NLD, Netherlands; NZL, New Zealand; NOR, Norway; POL, Poland; PRT, Portugal; ESP, Spain; SWE, Sweden; CHE, Switzerland; GBR, UK; USA, United States of America.

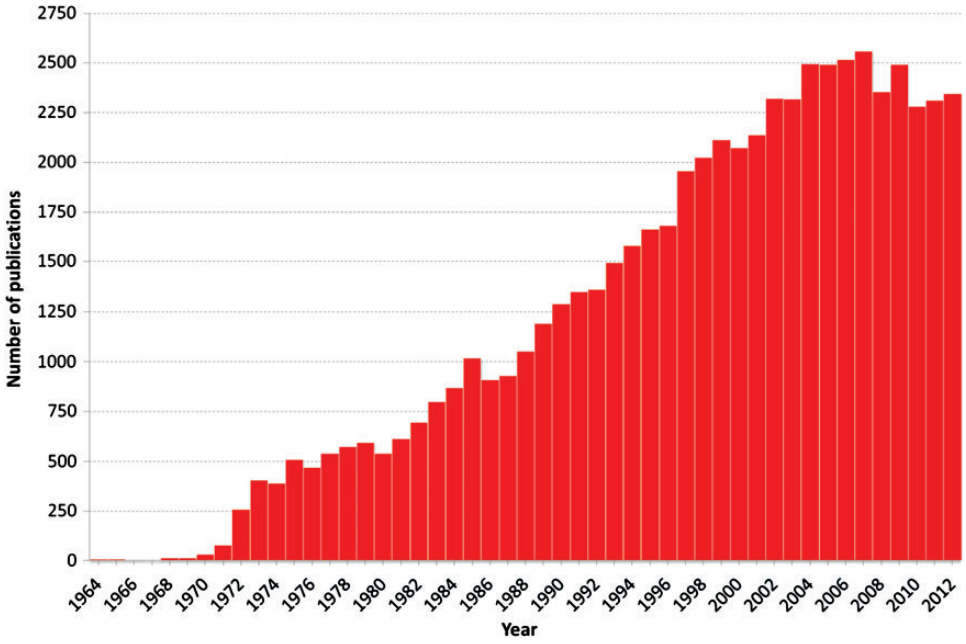

Figure 4 Peer-reviewed articles published since the introduction of coronary artery bypass grafting. The search was performed using an entry of '*CABG OR coronary bypass*' in PubMed.

randomized trials and was unable to identify a clear advantage of one cardioplegic over the other for endpoints of death (RR = 0.95, 95% CI 0.60–1.51), MI (RR = 0.80, 95% CI 0.55–1.19), or low cardiac output syndrome (RR = 0.69, 95% CI 0.48–1.04).[74] The debate continues and until large randomized trials show a particular benefit it appears that surgeons should continue using their own preferred strategy, in which they have experience and that allows proper myocardial protection in their cases.

The clinical impact of other measures of myocardial protection remain debated: whether CPB flow should be non-pulsatile or pulsatile to mimic the physiological blood flow,[75] whether direct and remote ischaemic preconditioning through a number of brief periods of ischaemia proves to have a clinical benefit by increasing the tolerance of the myocardium to sustain a large period of ischaemia,[76] as well as the use of prophylactic or adjunctive pharmacological agents to minimize ischaemia and/or reperfusion injury.[77,78]

Grafts

In the early years of coronary surgery, the saphenous vein graft (SVG) was used in the majority of cases;[28] in 1979 in the USA, it was used in 87% of CABG procedures.[52] However, in 1978 FitzGibbon *et al.*[79] demonstrated that venous bypass grafts fail early: 11% of 1400 vein grafts were occluded at 2–3 weeks postoperatively. At 1 year, failure rates of up to 20% have been reported,[80,81] and only 60% of SVGs are open at 10-year follow-up.[82,83] This failure rate is particularly influenced by graft thrombosis (early failure), intimal hyperplasia (late failure) and atherosclerosis (late failure).[84]

Although the first ever CABG was performed using an IMA graft, IMA grafting was only done in few centres. Favaloro *et al.* were particularly interested in this technique, and by the end of 1967 had already performed 248 bilateral IMA graft procedures.[20] Throughout the history of CABG, the Cleveland Clinic has provided seminal work demonstrating data in favour of IMA grafting. They reported excellent graft patency and significantly better survival in patients receiving an IMA graft to the LAD instead of SVGs only.[85] Second, they demonstrated for the first time that bilateral IMA grafting proved superior to single IMA grafting in reducing rates of reoperation and long-term mortality.[86,87] The excellent patency of the IMA graft triggered a search for additional arterial grafts to revascularize non-LAD myocardial territories. Experimental surgeries were performed using the splenic artery,[88] subscapular artery,[89] intercostal artery,[90] lateral femoral circumflex artery,[91] inferior mesenteric artery[92] and ulnar artery.[93] In 1978, the use of Gore-Tex grafts was suggested,[94] but because of the high thrombogenicity and disappointing patency rates this technique was quickly abandoned. The most promising arterial conduits besides the IMA were the right gastroepiploic artery (GEA),[95] inferior epigastric artery (IEA)[96] and radial artery.[97]

The GEA and IEA were introduced in 1987 and 1990, respectively, and showed good patency results in several studies.[98] However, their use has never been fully integrated into clinical practice because of a number of technical issues, including the need for an additional laparotomy, limited graft length, variation in size and small distal diameter. Differences in biological characteristics when compared with the IMA graft make them also less suitable.[99,100] Data from CABG procedures performed in 1992 in the UK showed that in only 3% of cases one of these grafts was used mainly when the IMA or SVGs were not available.[101]

The radial artery is the best and most commonly used arterial alternative (or addition) to the right IMA graft. Its use was first investigated by Carpentier in 1971,[97] but was discarded after high early graft occlusion rates of 30% were reported.[71] The unexpected finding of patent grafts after >15 years renewed the interest in the radial

artery during the early 1990s,[102] although concerns remained with regard to its susceptibility for spasm and intimal hyperplasia.[103,104] Refined operative techniques aim at minimizing endothelial damage and adjunctive medical therapy are applied to reduce vasoreactivity. As a result, 5-year patency rates of >90% have been reported,[105] but are strongly dependent on the graft territory and the degree of stenosis of the native coronary. The best results with the radial artery are achieved in high-grade stenosis (>90%), when the graft is harvested as a pedicle, when pharmacological dilatation is applied locally and when postoperative administration of vasodilator therapy is performed.[105–107]

Contemporary data on international use of grafts are available from the SYNTAX trial that included 1541 patients who underwent CABG at 85 sites in 18 countries between 2005 and 2007.[108] In 95.2% of patients, an arterial graft was anastomosed to the LAD, and in 97.1% at least one arterial graft was used. Bilateral IMA grafting was only performed in 22.7%. Complete arterial revascularization was performed in 15.6%. Abdominal arteries were not used at all, and the radial artery was used in 12.8% of patients.

Invasiveness

Since its introduction, CABG has been performed with and, to a lesser degree, without CPB, even though on-pump CABG is referred to 'conventional CABG'. The use of CPB and cardioplegic arrest provides a more stable and bloodless operative field, but are associated with a systematic inflammatory response, increased red cell damage and stroke from manipulation and clamping of the ascending aorta.[109] With the development of heparin-coated circuits in 1983,[110] CPB-associated systemic inflammation became less of an issue. Off-pump CABG (OPCAB) avoids the use of CPB altogether and, if performed in a no-touch technique, by avoiding aortic manipulation has the potential to reduce the risk of stroke. The benefit of OPCAB is, however, offset by a more challenging technical demand. Surgical series from the early 1980s reported excellent results,[111,112] which encouraged further implementation. The introduction of the Octopus stabilizer in 1996 marked a significant improvement in the operative technique and reduced the technical difficulty.[113] Furthermore, the use of distal anastomotic connector devices was investigated already in 1979 but interest was renewed with the advent of off-pump procedures, as it would omit difficult suturing on a beating heart.[114] Series reporting increased rates of repeat revascularization have hampered widespread use of distal connector devices,[115] although recent favourable results have been reported as well.[116] Off-pump coronary artery bypass grafting is performed particularly in developing countries to reduce the procedural costs. However, numerous large randomized trials have not proven an early or long-term clinical advantage ,and there appears to be no benefit of off-pump CABG with respect to quality of life.[117–120]

In 1994, a number of centres were performing LIMA-to-LAD minimally invasive CABG (MIDCAB) through a left mini thoracotomy using video-assisted LIMA harvesting.[121,122] Growing experiences have shown excellent results for the LIMA to LAD similar to CABG through a sternotomy. Reported early patency rates range from 94 to 99% and perioperative mortality is 0.8% for the largest series.[123,124] Survival at 5 and 7 years for all-comers populations are reported as 91.9% (95% CI 90.1–93.8%) and 89.4% (95% CI 86.7–92.1%), respectively.[123] Familiarity with video-assisted procedures furthermore reduced surgical trauma through robotic-assisted totally endoscopic CABG.[125] Initially, it was performed on-pump and patency results were inferior compared with those achieved with the standard MIDCAB technique; more recent results with advanced computer-assisted technology, better endoscopic stabilizers, and without the use of CPB have shown excellent results with up to 100% LIMA to LAD patency and very low conversion rates.[126]

The patient population

Disease specifics

The principal indication for CABG utilization was (chronic) stable angina,[41] whether by single-, double,- or three-vessel disease. The benefit of revascularization became more evident in patients with complex coronary disease as outcomes with medical therapy gradually worsened with increasing complexity, while outcomes after CABG were consistent.[41] In patients with left main disease the benefit of CABG was largest.

For many years CABG was the only revascularization strategy proven to be effective and has therefore been used for a number of clinical scenarios. In the 1960s and 1970s, patients with acute MI often did not survive to reach the hospital or died early thereafter.[127] Acute MI was therefore considered a contraindication for CABG.[128] In very selected cases, emergency CABG was performed and did show increasingly improved results when compared with medical therapy.[129] However, with the advent of fibrinolysis and PCI to acutely treat the culprit lesion,[130,131] early survival of patients with acute MI significantly improved. Since the early 1990s, PCI has been the treatment of choice while the need for CABG has been limited to a minority of acute MI cases with a disease pattern too complex for PCI. Patients requiring additional bypasses for non-culprit lesions do undergo subsequent elective CABG.

In the initial CABG trials, patients with severe left ventricular (LV) dysfunction were excluded. However, the dismal prognosis of such patients treated medically led to explore the impact of CABG on long-term survival in patients with severe LV dysfunction. A prognostic benefit was first confirmed by registry data.[132,133] Utilization of CABG for LV dysfunction subsequently increased but was limited principally to patients who would suffer from angina, with limited hypokinesia and with an expected improvement of ventricular function. Interestingly, the impact of CABG on improving LV dysfunction in patients with ischaemic heart failure has not been adequately addressed over the years and continues to remain under debate.[134] Guideline recommendations are similar to what they were half a century ago, although recent results from the randomized STICH trial shed new light on this discussion: in the intention-to-treat analysis there was no difference in the primary endpoint of all-cause mortality at 5-year follow-up (41 vs. 36% for medical therapy and CABG, respectively; $P = 0.12$).[135] CABG was associated with significantly reduced rates of the secondary endpoint of all-cause mortality or hospitalization (HR = 0.81, 95% CI 0.71–0.93; $P = 0.003$). Moreover, a per-protocol analysis excluding crossed-over patients showed that CABG was superior to medical therapy also for the primary endpoint (HR = 0.76, 95% CI 0.62–0.92; $P = 0.005$). It is crucial to assess the percentage of myocardial ischaemia as a trigger for revascularization, with a proposed cut-off of 12% ischaemia.[136]

Patient specifics

The early populations that underwent CABG included patients at a mean age of 50–55 years, the majority were males, smoking history was frequent[28,41,137,138] and diabetes and hypertension were present in ~10–30 and 20–50%, respectively.[138,139] Evaluation of patient subgroups who underwent coronary angiography demonstrated that male patients were more likely to undergo CABG than women and Caucasians more than blacks.[140] As expected from the worsening Western lifestyle that involves less exercise, amplified dietary intake, more stress and sleep deprivation, patients referred for CABG are becoming increasingly higher risk. Over the last two decades, the mean age of patients undergoing CABG has increased to about 60–65 years of age.[141,142] An ever increasing number of patients present with co-morbidities; between 2000 and 2009 in the USA, e.g. the rate of diabetes in the CABG population has grown from 33 to 40%, hypercholesterolemia from 60 to 84% and COPD from 17 to 23%. Other risk factors such as hypertension, renal failure requiring dialysis, previous stroke and prior PCI all have increased in prevalence.[141] Interestingly, it appears that CABG remains underutilized in black patients as well as in women.[143]

In those patients requiring revascularization, the trend of the first 50 years has led to utilization of CABG particularly in patients with stable angina, complex CAD, not too high risk and with an expected long-term benefit for IMA grafts.[144–146] Patients with concomitant moderate/severe aortic stenosis or mitral valve regurgitation require surgical intervention according to the current guidelines. However, advancements in percutaneous valvular therapies (transcatheter aortic[147,148] and mitral valve[149] techniques) may allow an increasing number of high-risk patients to be treated percutaneously by the Heart Team and consequently undergo PCI for concomitant CAD.[150]

Postoperative clinical outcomes

Outcomes

The periprocedural risk of elective CABG has constantly declined despite an ageing population. Owing to the invasiveness of CABG, several procedural risks require consideration (*Table 1*). Mortality is considered operation-related if it occurs within 30 days after surgery. Even though the patient population is becoming older and of higher operative risk,[193] mortality continues to decline in contemporary practice; currently, operative mortality for elective CABG is in the range of 1–3%. One of the most devastating complications is stroke.[194] Approximately 1–3% of patients suffer an intraprocedural or early postoperative stroke, which are predominantly ischaemic in nature.[195,196] Other important complications are postoperative MI or injury, renal failure, delirium, deep sternal wound infection, mediastinitis and atrial fibrillation. Re-exploration for bleeding is required in 2–6% of patients and increases the risk for these complications.[163,164]

Complications are associated with increased morbidity, longer postoperative stays, higher costs, and increase the risk of early or delayed mortality. The risk may be reduced by adopting (and considering early in the decision-making process) lesser-invasive surgical techniques and/or by applying intraoperative quality assessments.[197]

Determinants of short-term outcomes

Many of the procedural complications associated with CABG can be anticipated on the basis of the preoperative patient history, characteristics and demographics.[198] These factors can be divided into the categories of: factors with an impact on how well a patient tolerates the invasiveness of CABG (e.g. age, COPD, renal function), factors that identify the progression of disease (e.g. acute coronary syndrome, left ventricular function, NYHA and CCS classification), factors that impact procedural complexity (e.g. previous surgery, emergent surgery, the presence of acute ischaemic mitral regurgitation), and factors that influence postoperative recovery (e.g. diabetes, neurological impairment, reduced mobility). To provide an estimate of the operative risk based on these factors, several generic risk models have been developed.[199–202] These can be helpful tools during decision making;[203] in some instances, it may be more appropriate to refer patients to the interventional cardiologist for PCI[145] or continue with medical therapy only. The additive and logistic EuroSCORE have been used most frequently in Europe,[200,204] and have recently been updated to the EuroSCORE II (*Figure 5A*).[205] The Society of Thoracic Surgeons (STS) score is the standard risk model in the USA and its popularity is increasingly recognized in Europe as well (*Figure 5B*).[151,201] The existing risk models have been severely criticized over the recent years for a number of reasons,[198,206–208] including (i) models have become outdated because of dynamic trends in patient risk, (ii) (lack of) inclusion of risk factors, (iii) the majority of models have been developed to predict mortality but do not predict postoperative complications (e.g. stroke) and (iv) suboptimal methodology for model development. Therefore, risk estimation by such models should not be taken as gospel, but rather used as guidance and interpreted according to the individual patient.

Not only patient-related factors are essential in this regard. A great number of studies have been devoted to assess volume–mortality interactions, where the number of cases per surgeon and/or hospital influences CABG outcomes. As one would expect, the expertise of higher-volume surgeons would be beneficial to the quality of the procedure, particularly in complex and/or critical situations. Similarly, the quality of perioperative care in high-volume centres would likely be improved when compared with low-volume centres, thereby reducing the risk of adverse events. Although these assumptions have shown to be genuine in several large studies,[209,210] results have been challenged.[211–213] Compared with other major complex surgeries, the impact of volume on outcomes after CABG is limited.[214] More important than volume itself are quality measures and being a low-volume centre by itself does not necessarily preclude quality.[214–216] Other factors independent of the patient, operator, and/or hospital, have also shown to impact postoperative complications; for example the duration of red-cell storage in patients requiring blood transfusions.[217]

Long-term clinical outcomes

Outcomes

In the early randomized trials (patient inclusion 1972–1984) comparing CABG with medical therapy, long-term survival at 5 and 10 years of follow-up was 90 and 74%, respectively.[41] Remarkably, in later trials

Table 1 **Incidence and predictors of early clinical outcomes after coronary artery bypass surgery, with a focus on perioperative considerations to prevent complications**

Complication	Incidence	Specific predictors	Outcome	Considerations	References
Mortality	1–3%	A wide variety of predictors of mortality have been identified. These are generally factors that are associated with how well the patient tolerates the procedure, the progression of disease, the procedural complexity, and the postoperative recovery.	N/A	Reduce procedural invasiveness and adequately select patients for CABG by implementing multidisciplinary Heart Team meetings.	119,151–153
Stroke	1–3%	History of cerebrovascular disease, atrial fibrillation, peripheral vascular disease, hypertension, and severe atherosclerotic aorta.	Postoperative stroke has been found to increase the risk of 30-day mortality by five- to six-fold.[154,155] In an analysis of 469 444 patient-years of follow-up, long-term survival after 20 years was significantly reduced (12 vs. 35%, $P < 0.001$) even after propensity-matching (22 vs. 35%, $P < 0.001$).[154]	Off-pump CABG or anaortic surgery, and epiaortic scanning are measures that are associated with reduced rates of stroke in (selected) patients.	119,151–156
Myocardial infarction	2–10%	Causes include, although are not limited to, insufficient myocardial protection, air embolism, and regional and/or global ischaemia during the procedure. Other predictors are: urgency of procedure, recent MI, number of distal anastomoses, incomplete revascularization, longer cardiopulmonary bypass time.	Myocardial injury, as measured by CK-MB levels within 24 h after surgery, was the strongest predictor of 30-day mortality even after correction for baseline risk in a pooled analysis of 7 CABG trials that included >18 000 patients.[157]	Sufficient myocardial protection should be used, which includes cardioplegia and thermal regulation. Operative graft flow measurement may identify grafts that need revision.	119,152,158–162
Re-exploration for bleeding	2–6%	Body surface area or body mass index, urgency of operation, preoperative antiplatelet and/or anticoagulation use, complexity of coronary disease or number of distal grafts, previous cardiovascular interventions, immunosuppressive therapy, preoperative cardiogenic shock.	Re-exploration for bleeding increases the risk of stroke, MI, pneumonia, and deep sternal wound infection, but also significantly increases the use of blood products and prolongs postoperative hospital stay by about 2 days.[163,164]	Discontinuation of anti-platelet and/or anticoagulation therapy before surgery is crucial. Antifibrinolytic agents may reduce blood loss. The reduction in operative time should be weighed against increased rates of re-exploration.	119,162–166
Delirium	10–50%	Older age, preoperative renal function, cognitive function, prior cerebrovascular disease, duration of cardiopulmonary bypass.	Delirium is associated with increased morbidity and mortality, as well as prolonged hospital stay and increased hospitalization costs.	A multicomponent intervention for the management of cognitive impairment, sleep deprivation, immobility, visual and hearing impairment, and dehydration reduces number and duration of delirium episodes.[167]	168–173
Renal failure (requiring dialysis)	Highly variable depending on the definition: 5–50% (1% requires dialysis)	Preoperative renal function, diabetes, preoperative cardiogenic shock.	Renal failure is a significant predictor of short- and long-term mortality, even in patients with preoperative normal renal functions.[174,175]	Off-pump surgery has been found to reduce the rate of renal failure. Easy preventive strategies consist of: preoperative hydration, prevention and correction of hypotension, abandon the use of nephrotoxic drugs, and use of nonionic contrast during angiography.[176]	119,177,178

Mediastinitis	0.5–3%	Obesity, diabetes, hypertension, renal failure on dialysis, prior cardiac surgery, duration of cardiopulmonary bypass, bilateral IMA use, re-exploration for bleeding.	Postoperative sternal wound infections increase the postoperative process, stay are associated with incremental costs, and lead to a drastic increase in early or delayed mortality.	Prevention of mediastinitis through preoperative antiseptic showers, hair removal, and administration of perioperative antibiotics has been instated. Limiting the need for re-exploration for bleeding will furthermore reduce its rate.	[179–185]
Atrial fibrillation	15–30%	Older age, peripheral vascular disease, prior atrial fibrillation, obesity.	Often of transient nature due to early postoperative inflammatory responses and oxidative stress that are reduced over subsequent days post-surgery. Atrial fibrillation is a predictor of stroke and was found to significantly reduce long-term survival in a number of studies.[186,187]	Atrial pacing has shown to be beneficial, as well as a battery of drugs: anti-arrhythmics such as amiodarone or sotalol, anti-inflammatory corticosteroids, β-blockers, statins, antioxidant agents such as *N*-acetylcysteine, ACE inhibitors, and omega-3 fatty acids.	[186,188–192]

comparing CABG with PCI, the long-term survival did not significantly improve. The BARI trial included 1829 patients through 1988–1991 and reported 5- and 10-year survival rates nearly identical to earlier trials: 89 and 74%, respectively.[62] The most recent 5-year follow-up data originates from the SYNTAX and FREEDOM trials.[65,195] Again, survival was similar with 89% in SYNTAX and 89% in FREEDOM. It should, however, be noted that these trials included patients with impaired LV function and either complex left main and/or three-vessel disease (SYNTAX), or diabetics with complex disease (83% three-vessel disease, FREEDOM); compared with the first randomized trials where only 50% had three-vessel disease, impaired LV function was an exclusion criteria and patients were generally lower risk.[41] In large registries that include 'real-world' 'all-comers' data, 5-year survival has been estimated at 78–82%.[66,218,219] To summarize, it appears as if the improvements in patient care (pre-, operative, and post-operative) have kept an even pace with the increase in patient morbidity, resulting in similar rates of survival today as in previous years with lower risk patients.

Data from the PREVENT IV trial showed that the rate of SVG failure was a dramatic 25% at 1 year.[220] The high graft failure rate was associated with an increased risk of MI during follow-up, which in turn is associated with increased mortality, left ventricular dysfunction and reduced quality of life. In a pooled analysis of four randomized trials by Daemen *et al*., the risk of non-fatal MI at 5 years after CABG was 7.6%.[64] Even though SYNTAX and FREEDOM included more complex patients, the rates of MI were somewhat lower (3.8 and 6.0%, respectively), suggesting a continuous improvement in long-term outcomes after CABG. The occurrence of MI may require repeat revascularization; however, caution is advised when interpreting repeat revascularization rates because the decision to treat is a less well-defined, subjective endpoint.

After the perioperative phase, the risk of stroke after CABG remains constant at approximately 0.5–0.8% per year.[154] At 5-year follow-up, the rate of stroke is 2.5–5%.[65,195,221,222] Longest follow-up is available from the MASS II trial, where the 10-year stroke rate was 8.4%.[223] These data are consistent with a limited number of prospective observational studies.[224,225] There is little evidence regarding the severity of strokes, but results from the FREEDOM trial suggest that strokes were severely disabling in 55% of diabetic patients with a stroke at any time during follow-up.[195] In addition, results from the SYNTAX trial show that 68% of patients who suffered a stroke and survived had long-term residual deficits.[196]

Several observational studies[226,227] and randomized studies have shown that health-related quality of life is significantly improved with CABG. At 3 months after randomization in the VA Cooperative Study, subjective improvement was reported in 79.8% of patients who underwent CABG compared with only 58% of the medically managed patients ($P < 0.01$).[228] At longer follow-up of 5 years, it was found that more patients in the CABG group were free from chest pain (54.8% vs. 32.9%; $P < 0.01$). Data from the CASS trial support these findings, but showed that differences in freedom from angina and the activity level between surgery and medical therapy were less by 10-year follow-up because late surgery was performed in almost 40% of patients randomized to medical therapy.[43] With regard to psychobehavioural endpoints, specific attention has been given to depression during the perioperative period and long-term follow-up after CABG. Up to 47% of patients present with

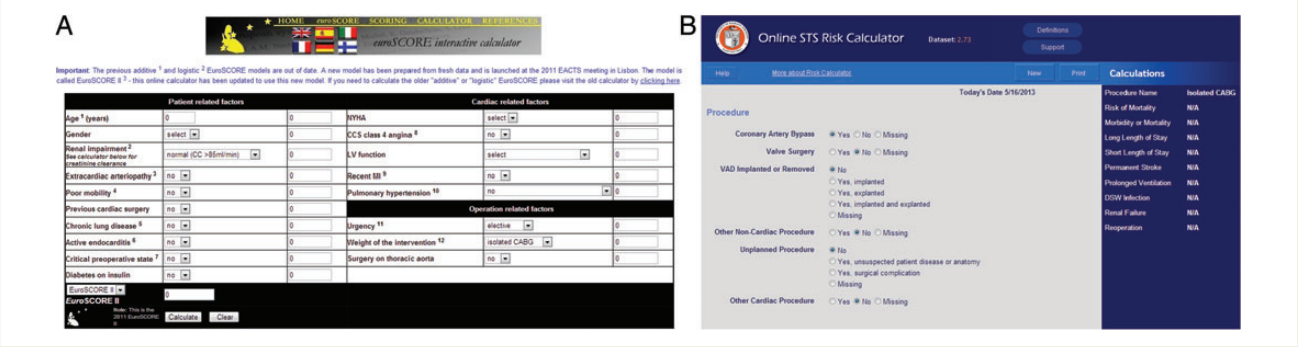

Figure 5 The most commonly used operative risk models. The EuroSCORE is most frequently used in Europe (*A*) and the Society of Thoracic Surgeon score in the USA (*B*).

depression at baseline, which has a significant impact on long-term freedom from cardiovascular events and death.[229–231]

Determinants of long-term outcomes

There are a number of factors that have a significant impact on long-term outcomes. Postoperative complications such as stroke,[156] renal failure,[174] atrial fibrillation,[186] and myocardial injury[232] diminish patient survival as well as quality of life. Procedural factors including graft patency and completeness of revascularization are critical to ensure reduction in angina pectoris and preservation of the left ventricle. The degree of periprocedural blood loss as measured by the need for (and number of) red blood cell transfusions has been found to be an independent predictor of long-term survival.[233] Furthermore, life expectancy is significantly reduced by non-coronary disease patient-related factors such as advanced age, the presence of co-morbidities and pshychobavioral deficits. Finally, life-long optimal medical therapy and other secondary prevention measures after CABG positively impact the incidence of late events after CABG, although secondary prevention including antiplatelet therapy has been underused after CABG.

The choice of graft is one of the most important procedural factors to consider. Grafting the LIMA to the LAD undoubtedly is the best treatment option to prolong survival,[85] but there are several grafts that can be used for other myocardial territories: the SVG, the right IMA and the radial artery. Bilateral IMA grafting with the left and right IMA produces the best long-term survival,[234] but may not always be feasible and/or safe; it increases the risk of sternal wound complications particularly in obese and diabetic patients. Recent evidence suggests that under such circumstances the radial artery provides better long-term patency and survival than the SVG.[105,235–239]

Complete revascularization is usually the goal of CABG, as incomplete revascularization may be associated with reduced survival during follow-up. However, results are not uniform; there is a difference in appropriateness of incomplete revascularization.[240] Where incomplete revascularization of distal lesions and/or small vessels with little myocardium at risk may be categorized as appropriate incomplete revascularization,[241] leaving a large area of viable myocardium in patients with more complex disease would result in inappropriate incomplete revascularization and subsequently lead to detrimental outcomes.

Procedure-specific risk models have been developed to predict long-term mortality based on preoperative patient characteristics.[218,242–244] Naturally, the procedural and post-procedural factors as discussed earlier will have a significant impact, but recognizing the impact of preoperative risk factors may be helpful in assessing the risk–benefit ratio of surgical revascularization. It is advised to use these during multidisciplinary Heart Team decision-making. Clearly, the life expectancy of older patients or patients with severe co-morbidities is limited, and CABG with several months of rehabilitation may not be the best treatment recommendation.

Conclusions

Surgical treatment for CAD has shown substantial improvements that finally led to the introduction of CABG. During the first 50 years of performing CABG, the technique has evolved into a refined, safe, and efficient procedure that even in contemporary practice shows a continuous reduction in postoperative complications. It has been an extensively investigated topic that has accumulated a body of evidence in favour of performing CABG for a wide range of clinical scenarios, and provided crucial data that is weighted during decision making and can be integrated in risk–benefit ratios to optimize treatment recommendations. However, there are still a number of procedural advancements that may be considered to improve short- and long-term outcomes. In an accompanying manuscript, we discuss in more detail off-pump CABG, clampless/anaortic CABG, minimally invasive CABG with or without extending to hybrid procedures, arterial revascularization, endoscopic vein harvesting, intraprocedural epiaortic scanning, graft flow assessment, and improved secondary prevention measures.

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