BUILDING A BETTER BYPASS WITH EMPHASIS ON BILATERAL INTERNAL MAMMARY GRAFTING

Teresa Mary Kieser

Pictures by Jean Prieur

Picture Captions

Cover: 'Three Sisters, Canmore Alberta'
Chapter 1: 'Erasmus'
Chapter 2: 'Boats in waiting'
Chapter 3: 'Take-off'
Chapter 4: 'View from Sulphur Mountain, Banff, Alberta'
Chapter 5: 'Hermit Crab'
Chapter 6: 'Florentine Fields'
Chapter 7: 'Stargazer Lilies'
Chapter 8: 'Flow…'
Chapter 9: 'Reflection'
Chapter 10: 'View from Piazzale San Michelangelo, Florence'
Chapter 11: 'Sunset over Brentwood Bay, Vancouver Island, British Columbia'
Chapter 12: 'Erasmus'
Chapter 13: 'Almaty, Kazakhstan'
Chapter 14: 'Lily pads, Lac Bataille, Gatineau, Quebec'
Chapter 15: 'Sunset, San Lucia'
Chapter 16: 'Jack Frost'
Chapter 17: 'Artwork, Erasmus Medical Centre'
Chapter 18: 'Lake Louise, Alberta'
Chapter 19: 'Charyn Canyon, Kazakhstan'
Chapter 20: 'Young elk grazing in the Rockies, Alberta'
Chapter 21: 'Tulips, close and far'
Chapter 22: 'Five Sails, San Lucia'
Chapter 23: 'Betwixt Heaven and Earth'

Layout and Printing: Optima Grafische Communicatie (www.ogc.nl)

BUILDING A BETTER BYPASS WITH EMPHASIS ON BILATERAL INTERNAL MAMMARY GRAFTING

Het optimaliseren van een bypass: nadruk op het gebruik van twee interne thoracale slagaderen

Thesis

To obtain the degree of Doctor from the
Erasmus University Rotterdam
By command of the
Rector Magnificus

Prof. Dr. H.A.P. Pols

And in accordance with the decision of the Doctorate Board

The public defense shall be held on
Thursday the 8th of October 2015 at 15:30am

By

Teresa Mary Kieser
Born the 29th of January 1952 in
London Ontario, Canada

Erasmus University Rotterdam

DOCTORAL COMMITTEE

Promotor:	Prof. dr. A.P. Kappetein
Other Members:	Prof. dr. A.J.J.C Bogers
	Prof. dr. F. Zijlstra
	Prof. dr. R.J. Klautz

TABLE OF CONTENTS

PART 1

INTRODUCTION

General Introduction

"I shall pass this way but once; any good that I can do or any kindness I can show to any human being; let me do it now. Let me not defer nor neglect it, for I shall not pass this way again."

Etienne de Grellet
Quaker Missionary

Chapter 1

General Introduction and General Philosophy

The coronary artery bypass graft (CABG) operation has been a mainstay for the treatment of coronary artery disease (CAD) for more than 50 years. It is hoped that this body of work presents evidence for and facilitates the use of the very best 'substitute' coronary arteries available – the internal mammary arteries – right and left.

Coronary artery disease is a chronic disease; it is not curable. The diagnosis of atherosclerosis is a life sentence. A chronic disease that causes only minor limitation of activities is compatible with a good and happy life but a disease which carries with it the possibility of sudden death is not. Damocles an envious courtier of King Dionysius II willingly accepted a change of place with his king, until he realized that above his head hung a huge sword, held by a single hair of a horse's tail. Cicero (3 Jan 106 BC – 7 December 43 BC) in his *Tusculanae Disputationes*, V. 62, asked: 'Satisne videtur declarasse Dionysius nihil esse ei beatum, cui semper aliqui terror impendeat?' or 'Does not Dionysius seem to have made it sufficiently clear that there can be nothing happy for the person over whom some fear always looms?' [1]

The spectre of CAD has plagued mankind for centuries. Just after William Harvey (1578-1657) discovered the circulation of blood, Professor Hoffman (1660-1742) at the University of Halle noted that CAD started in the 'reduced passage of the blood within the coronary arteries'. [2] As physicians and surgeons, all we can hope to do is to ameliorate, palliate or reduce the progression of this disease. The treatment has come a long way since the early diagnosis. However, as there is always room for improvement; it is the wish of this author to convince readers of the value and possibility of a way to remove the 'sword of Damocles' or at the very least - use more than one horse hair to secure it.

The surgical treatment of obstructive CAD, CABG involves the addition of 'new routes to Rome' in the form of either vein from the leg or arteries from the chest and/or arms. Although the preferred conduit in use for more than 50 years, the saphenous vein does not stand up to the test of time. At 12.5 years post-operatively, 60% of saphenous vein grafts are occluded or severely diseased [3], whereas 95% of internal mammary arteries (IMA) are well patent at 10 years. [4] The preferred use of the saphenous vein as a bypass conduit continues despite an ever increasing body of evidence that arterial grafting - especially with the IMA - confers not only longevity to the bypass, but also to the patient. It was in 1986 that Floyd Loop in the New England Journal of Medicine reported that use of just one internal mammary artery conferred not only increased patient survival, but also a better quality of cardiac-disease free life. ' After an adjustment for demographic and clinical differences by Cox multivariate analysis, he found that patients who had only vein grafts had a 1.61 times greater risk of death throughout the 10 years, as compared with those who received an internal mammary artery graft. In addition, patients who received only vein grafts had 1.41 times the risk of late myocardial infarction ($P<0.001$), 1.25 times the risk of hospitalization for cardiac events ($P<0.0001$), and 1.27 times the risk of all late cardiac events ($P<0.0001$), as compared with patients who received IMA grafts.'[5] Then in 1999, Bruce Lytle and colleagues produced convincing evidence that 'Two internal thoracic artery grafts are better than one.' He found that after reviewing 10,124 patients over a mean follow-up of 10 postoperative years that 'survival for the bilateral IMA group was 94%, 84% and 67%, while for the single IMA group it was only 92%, 79%, and 64% at 5, 10, and 15 postoperative years, respectively ($P < 0.001$).' [6]

We come now to the reason for this thesis: contemporary CABG is performed with bilateral IMA grafts in only 4% of patients in North America, 12% in Europe and 30% in Japan. Why is this? Reasons are many and varied; the basis of this thesis contains research intended to counteract rationale opposing more liberal use of bilateral internal mammary grafting.

'I will give thanks unto thee: for I am fearfully and wonderfully made: wonderful are thy works; and that my soul knoweth right well.' (English Revised Version of Psalm 139:14). We are wonderfully made indeed. Coronary artery bypass grafting is 'reconstructive' in nature, unlike 'ablative' surgery as in excision/removal of a left atrial myxoma. Reconstructive surgery requiring 'extra parts' is advantaged if these 'spare parts' are close-by. Internal mammary arteries or 'internal thoracic arteries' are situated in the thorax right next to the heart. They are so close that one end can even be 'left attached', thereby reducing the amount of effort for their use. They are also the only artery in the human body endowed with nitric oxide secreting properties, which protects them from the development of atherosclerosis. The Almighty is probably wondering why after His creation of such beautiful conduits situated right next to the heart, that all too often we go to the farthest corner of the human body – the ankle – to procure the inferior saphenous vein.

In the recent 2014 Guidelines for myocardial revascularization [7], it is recommended that 'Bilateral IMA grafting should be considered in patients <70 years of age'. If these guidelines were to be followed, so many lives could be improved. For example, if the average age of patients undergoing CABG is approximately 65 years of age [8], then performance of BIMA grafting in patients 70 years and younger would lead to more than 50% of patients undergoing CABG with BIMA grafting – more than 10 times the current rate in North America, and 5 times the rate in Europe.

Why then do we not as surgeons as part of our treatment of this most lethal disease, give patients the very best 'fresh start' that we are able? This body of work seeks to dispel every fear, remove every refutation against more frequent use of internal mammary arteries; it hopes to empower surgeons with the ability to do this confidently and safely in their practice.

REFERENCES:

1. Cicero 1-6-43 Tusculan disputations 5.62, (trans by Gavin Betts)
2. Colleen Story The History of Heart Disease Healthline April 10, 2012
3. Fitzgibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. *J Am Coll Cardiol* 1996;28(3):616-26.
4. Tatoulis J, Buxton BF, Fuller JA. The right internal thoracic artery: is it underutilized? *Curr Opin Cardiol* 2011;26(6):528-35
5. Loop FD, Lytle BW, Cosgrove DM, Stewart RW, Goormastic M, Williams GW, Golding LA, Gill CC, Taylor PC, Sheldon WC, et al. Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. *N Engl J Med* 1986;314(1):1-6
6. Lytle BW, Blackstone EH, Loop FD, Houghtaling PL, Arnold JH, Akhrass R, McCarthy PM, Cosgrove DM.Two internal thoracic artery grafts are better than one. *J Thorac Cardiovasc Surg* 1999;117(5):855-72
7. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI).Kolh P, Windecker S, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A; ESC Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol Ç, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S; EACTS Clinical Guidelines Committee, Sousa Uva M, Achenbach S, Pepper J, Anyanwu A, Badimon L, Bauersachs J, Baumbach A, Beygui F, Bonaros N, De Carlo M, Deaton C, Dobrev D, Dunning J, Eeckhout E, Gielen S, Hasdai D, Kirchhof P, Luckraz H, Mahrholdt H, Montalescot G, Paparella D, Rastan AJ, Sanmartin M, Sergeant P, Silber S, Tamargo J, ten Berg J, Thiele H, van Geuns RJ, Wagner HO, Wassmann S, Wendler O, Zamorano JL. *Eur J Cardiothorac Surg* 2014;46(4):517-92.
8. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Ståhle E, Colombo A, Mack MJ, Holmes DR Jr, Morel MA, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013;381(9867):629-38

Chapter 2

Aim and Outline

The goals for this thesis are 1) to encourage the use of bilateral internal mammary artery (BIMA) grafting more frequently so that many more patients receive the 'BIMA benefit' and 2) to ensure that an increase in bilateral IMA grafting is achieved with accuracy and no greater morbidity than that which is achieved with one IMA and the rest of bypasses with a saphenous vein.

Revascularization of diseased coronary arteries may be accomplished in one of two ways: by percutaneous coronary intervention (PCI) or by coronary artery bypass graft surgery (CABG). The principal difference between the two procedures involves the length of coronary artery needed to be addressed to improve blood flow to the heart. PCI with placement of stents must open all significantly obstructed areas along a coronary artery whereas in CABG, a surgeon needs only a 'postage-stamp' size of disease-free artery in order to perform an anastomosis. However as with everything in life, there are pros and cons to both approaches. PCI is quicker and requires no surgical incision from which a patient must recover. CABG is a major surgical procedure with all the inherent risks associated with a median sternotomy and the use of a heart-lung machine (or not, in the case of off-pump CABG). Patients are naturally drawn to the less invasive PCI but recent publications, most notably the recent 5 year SYNTAX trial results have clearly shown an advantage for CABG for the majority of patients needing revascularization [1]. 'Pay me now or pay me later' is a saying that comes to mind…

Coronary artery bypass grafting (CABG) has remained the cornerstone treatment for obstructive coronary artery disease for more than 50 years. **Chapters 3 and 4** outline the past and the present/future of the CABG procedure, respectively. **Chapters 5 and 6** are commentary articles on the benefit of bilateral IMA grafting. **Chapter 7** addresses the possibility of an age cut-off as to the survival benefit of BIMA use.

BIMA grafting is technically more challenging – all the more reason to use an intra-operative assessment of graft function to ensure bypasses are functioning to the best of a surgeon's ability *before* the patient leaves the operating room. **(Chapter 8)** Operative revascularization is more invasive compared to that with PCI but cementing a sternum solid within 24 hours of operation may possibly reduce the relative invasiveness of CABG, especially when the revascularization rate for CABG is so much lower than PCI. **(Chapter 9)**

BIMA grafting is definitely associated with an increase in deep sternal wound infection, one of the most dreaded complications of CABG surgery and commonest reason for not performing BIMA grafting. However if many preventive measures/procedures are used meticulously and consistently on every patient, the risk for this complication can be reduced to almost zero. **(Chapter 10)**

Complete revascularization has been found to improve the survival of patients undergoing CABG surgery; however it is not always possible to completely revascularize a patient. For example if coronary arteries are very small, diffusely diseased or are mostly in scar tissue it may not be possible or even advisable to perform bypasses to such arteries. We have shown that if total arterial grafting (with the majority of arterial grafts of internal mammary artery origin) is used, there is no difference in midterm survival if a patient is incompletely revascularized by inability to bypass one of three artery systems. This is a valuable point as there is only a finite amount of arterial conduit available and there may not be enough to perform all bypasses desired. **(Chapter 11 and 12)**

BIMA grafting does take increased operative time but harmonic ultrasound technology used to skeletonize IMAs helps shorten this time. **(Chapter 13 and 14) Chapter15** discusses sequential bypass grafts and the inherent risk of losing the second anastomosis in preference to the first, a serious problem if the second anastomosis is to the more important artery. **Chapter 16** presents a rare complication of CABG surgery but from this problem, an operative technique has been developed that is applicable to similar patients with prohibitively calcified coronary arteries.

To summarize: It is the author's wish to 1) refute every reason used as to why BIMA grafting is not performed more frequently and 2) to establish credible studies and guides to encourage their use.

REFERENCES:

1. Head SJ, Davierwala PM, Serruys PW, Redwood SR, Colombo A, Mack MJ, Morice MC, Holmes DR Jr, Feldman TE, Ståhle E, Underwood P, Dawkins KD, Kappetein AP, Mohr FW. Coronary artery bypass grafting vs. percutaneous coronary intervention for patients with three-vessel disease: final five-year follow-up of the SYNTAX trial. *Eur Heart J* 2014;35(40):2821-30

PART 2

RATIONALES FOR USE OF BILATERAL INTERNAL MAMMARY ARTERY GRAFTING IN THE MAJORITY OF CORONARY ARTERY BYPASS GRAFT PATIENTS

Chapter 3

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

Head SJ, Kieser TM, Falk V, Huysmans HA, Kappetein AP

Eur Heart J 2013;34:2862-2872

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

Stuart J. Head[1], Teresa M. Kieser[2], Volkmar Falk[3], Hans A. Huysmans[4], and A. Pieter Kappetein[1]*

[1]Department of cardiothoracic surgery, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Department of cardiac sciences, LIBIN Cardiovascular Institute of Alberta, University of Calgary, Calgary, AB, Canada; [3]Division of cardiovascular surgery, University Hospital Zurich, Zurich, Switzerland; and [4]Heart Center, Leiden University Medical Center, Leiden, The Netherlands

Received 15 April 2013; revised 19 June 2013; accepted 28 July 2013

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

* Corresponding author. Tel: +31 10 70 35784, Fax: +31 1070 33993, Email: a.kappetein@erasmusmc.nl

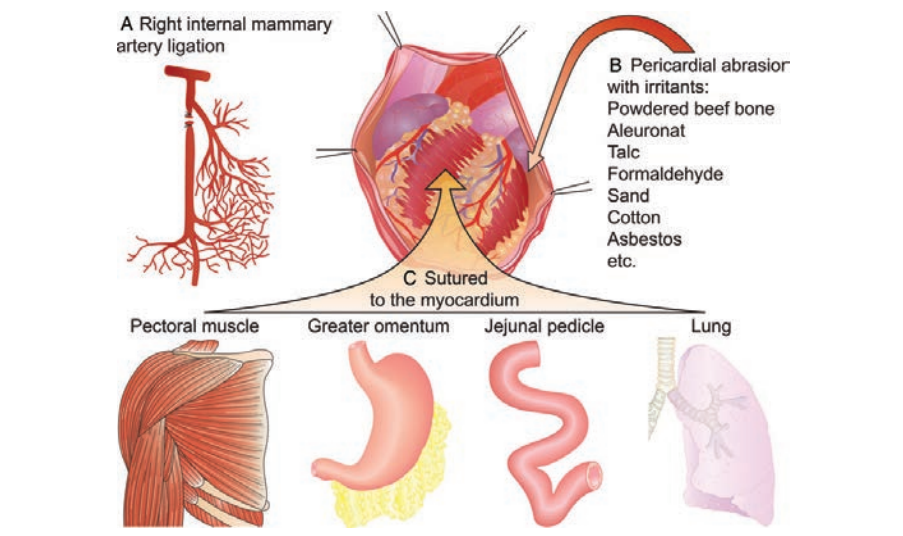

Figure 1 Experimental surgery for coronary artery disease that preceded the introduction of coronary artery bypass grafting. Different surgical methods have been applied: (*A*) ligation of the right internal mammary artery to increase blood flow to the coronary circuit through collaterals, (*B*) pericardial 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

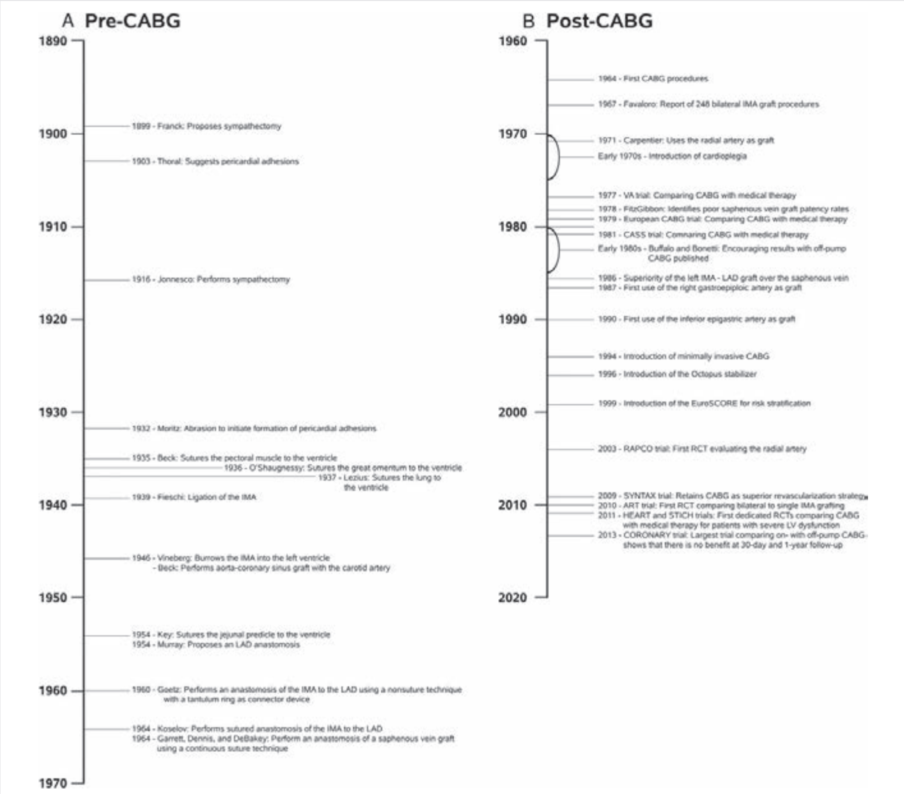

Figure 2 Timeline of developments that led to the first 'modern' coronary artery bypass grafting (*A*) and facilitated continuous improvements in surgical technique and outcomes during the first 50 years (*B*).

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

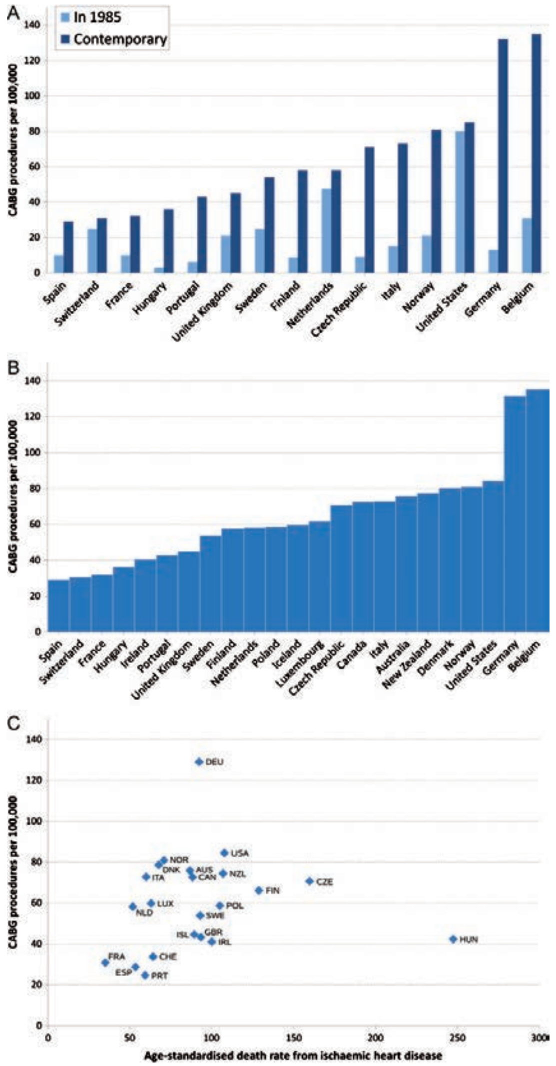

Figure 3 The utilization of coronary artery bypass grafting around the world. The increase in coronary artery bypass grafting procedures per 100 000 population has differed significantly between countries (*A*), as well as the number of coronary artery bypass grafting procedures that are performed in 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.

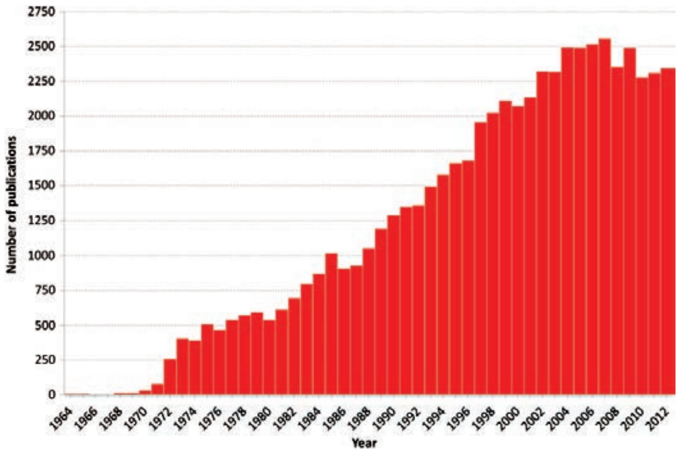

Figure 4 Peer-reviewed articles published since the introduction of coronary artery bypass grafting. The search was performed using an entry of '*CABG OR coronary bypass*' in PubMed.

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

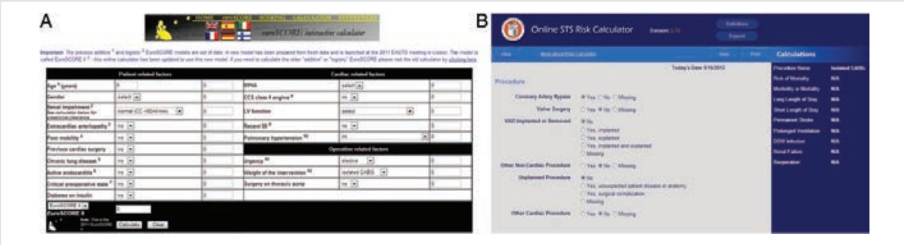

Figure 5 The most commonly used operative risk models. The EuroSCORE is most frequently used in Europe (*A*) and the Society of Thoracic Surgeon score in the USA (*B*).

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.

Conflicts of interest: none declared.

References

1. Harken DE, Black H, Dickson JF 3rd, Wilson HE 3rd. De-epicardialization: a simple, effective surgical treatment for angina pectoris. *Circulation* 1955;**12**:955–962.
2. Thorel CH. Pathologie der Kreislauforgane. *Ergebn Allg Path path Anat* 1903;**9**:559.
3. Moritz AR, Hudson CL, Orgain ES. Augmentation of the extracardiac anastomoses of the coronary arteries through pericardial adhesions. *J Exp Med* 1932;**56**: 927–931.
4. Case RB, Brachfeld N. Surgical therapy of coronary arterial disease with special reference to myocardial revascularization. *Am J Cardiol* 1962;**9**:425–438.

5. Schildt P, Stanton E, Beck CS. Communications between the coronary arteries produced by the application of inflammatory agents to the surface of the heart. *Ann Surg* 1943;**118**:34–45.
6. Glenn WW. Some reflections on the coronary bypass operation. *Circulation* 1972; **45**:869–877.
7. Beck CS. The development of a new blood supply to the heart by operation. *Ann Surg* 1935;**102**:801–813.
8. O'Shaughnessy L. An experimental method of providing collateral circulation to the heart. *Br J Surg* 1936;**23**:665–670.
9. Lezius A. Die anatomischen und funktionellen Grundlagen der kiinstlichen Blutversorgung des Herzmuskels dutch die Lungen bei Coronarterien Verschluss. *Arch F Klin Chir* 1938;**191**:101.
10. Key JA, Kergin FG, Martineau Y, Leckey RG. A method of supplementing the coronary circulation by a jejunal pedicle graft. *J Thorac Surg* 1954;**28**:320–330.
11. Battezzati M, Tagliaferro A, Cattaneo AD. Clinical evaluation of bilateral internal mammary artery ligation as treatment coronary heart disease. *Am J Cardiol* 1959; **4**:180–183.
12. Cobb LA, Thomas GI, Dillard DH, Merendino KA, Bruce RA. An evaluation of internal-mammary-artery ligation by a double-blind technic. *N Engl J Med* 1959; **260**:1115–1118.
13. Vineberg AM. Restoration of coronary circulation by anastomosis. *Can Med Assoc J* 1946;**55**:117–119.
14. Vineberg A, Munro DD, Cohen H, Buller W. Four years' clinical experience with internal mammary artery implantation in the treatment of human coronary artery insufficiency including additional experimental studies. *J Thorac Surg* 1955; **29**:1–32; discussion, 32–36.
15. Unger EF. Experimental evaluation of coronary collateral development. *Cardiovasc Res* 2001;**49**:497–506.
16. Beck CS, Stanton E, Batiuchok W, Leiter E. Revascularization of heart by graft of systemic artery into coronary sinus. *J Am Med Assoc* 1948;**137**:436–442.
17. Murray G, Porcheron R, Hilario J, Roschlau W. Anastomosis of systemic artery to the coronary. *Can Med Assoc J* 1954;**71**:594–597.
18. Goetz RH, Rohman M, Haller JD, Dee R, Rosenak SS. Internal mammary-coronary artery anastomosis. A nonsuture method employing tantalum rings. *J Thorac Cardiovasc Surg* 1961;**41**:378–386.
19. Sones FM Jr, Shirey EK. Cine coronary arteriography. *Mod Concepts Cardiovasc Dis* 1962;**31**:735–738.
20. Favaloro RG, Effler DB, Groves LK, Fergusson DJ, Lozada JS. Double internal mammary artery-myocardial implantation. Clinical evaluation of results in 150 patients. *Circulation* 1968;**37**:549–555.
21. Olearchyk AS, Vasilii IK. A pioneer of coronary revascularization by internal mammary-coronary artery grafting. *J Thorac Cardiovasc Surg* 1988;**96**:13–18.
22. Garrett HE, Dennis EW, DeBakey ME. Aortocoronary bypass with saphenous vein graft. Seven-year follow-up. *JAMA* 1973;**223**:792–794.
23. Cooley DA. In memoriam. Tribute to Rene Favaloro, pioneer of coronary bypass. *Tex Heart Inst J* 2000;**27**:231–232.
24. Favaloro RG. Saphenous vein autograft replacement of severe segmental coronary artery occlusion: operative technique. *Ann Thorac Surg* 1968;**5**:334–339.
25. Mundth ED, Austen WG. Surgical measures for coronary heart disease (first of three parts). *N Engl J Med* 1975;**293**:13–19.
26. Mundth ED, Gerald Austen W. Surgical measures for coronary heart disease (second of three parts). *N Engl J Med* 1975;**293**:75–80.
27. Chalmers TC. Randomization and coronary artery surgery. *Ann Thorac Surg* 1972; **14**:323–327.
28. Cooley DA, Dawson JT, Hallman GL, Sandiford FM, Wukasch DC, Garcia E, Hall RJ. Aortocoronary saphenous vein bypass. Results in 1492 patients, with particular reference to patients with complicating features. *Ann Thorac Surg* 1973;**16**:380–390.
29. Dawson JT, Hall RJ, Hallman GL, Cooley DA. Mortality in patients undergoing coronary artery bypass surgery after myocardial infarction. *Am J Cardiol* 1974;**33**: 483–486.
30. Kouchoukos NT, Kirklin JW, Oberman A, George C. Griffith lecture. An appraisal of coronary bypass grafting. *Circulation* 1974;**50**:11–16.
31. Kloster FE, Kremkau EL, Ritzmann LW, Rahimtoola SH, Rosch J, Kanarek PH. Coronary bypass for stable angina: a prospective randomized study. *N Engl J Med* 1979; **300**:149–157.
32. Mathur VS, Guinn GA, Anastassiades LC, Chahine RA, Korompai FL, Montero AC, Luchi RJ. Surgical treatment for stable angina pectoris. Prospective randomized study. *N Engl J Med* 1975;**292**:709–713.
33. Aronow WS, Stemmer EA. Bypass graft surgery versus medical therapy of angina pectoris. *Am J Cardiol* 1974;**33**:415–420.
34. McIntosh HD, Garcia JA. The first decade of aortocoronary bypass grafting, 1967–1977. A review. *Circulation* 1978;**57**:405–431.
35. Oberman A, Harrell RR, Russell RO Jr, Kouchoukos NT, Holt JH Jr, Rackley CE. Surgical versus medical treatment in disease of the left main coronary artery. *Lancet* 1976;**2**:591–594.
36. Talano JV, Scanlon PJ, Meadows WR, Kahn M, Pifarre R, Gunnar RM. Influence of surgery on survival in 145 patients with left main coronary artery disease. *Circulation* 1975;**52**:I105–I111.
37. Hurst JW, King SB 3rd, Logue RB, Hatcher CR Jr, Jones EL, Craver JM, Douglas JS Jr, Franch RH, Dorney ER, Cobbs BW Jr, Robinson PH, Clements SD Jr, Kaplan JA, Bradford JM. Value of coronary bypass surgery. Controversies in cardiology: part I. *Am J Cardiol* 1978;**42**:308–329.
38. Detre K, Murphy ML, Hultgren H. Effect of coronary bypass surgery on longevity in high and low risk patients. Report from the V.A. Cooperative Coronary Surgery Study. *Lancet* 1977;**2**:1243–1245.
39. Coronary-artery bypass surgery in stable angina pectoris: survival at two years. European Coronary Surgery Study Group. *Lancet* 1979;**1**:889–893.
40. National Heart, Lung, and Blood Institute Coronary Artery Surgery Study. A multicenter comparison of the effects of randomized medical and surgical treatment of mildly symptomatic patients with coronary artery disease, and a registry of consecutive patients undergoing coronary angiography. *Circulation* 1981;**63**:I1–I81.
41. Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, Davis K, Killip T, Passamani E, Norris R, Morris C, Mathur V, Varnauskas E, Chalmers TC. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994;**344**:563–570.
42. Peduzzi P, Hultgren H, Thomsen J, Detre K. Ten-year effect of medical and surgical therapy on quality of life: Veterans Administration Cooperative Study of coronary artery surgery. *Am J Cardiol* 1987;**59**:1017–1023.
43. Rogers WJ, Coggin CJ, Gersh BJ, Fisher LD, Myers WO, Oberman A, Sheffield LT. Ten-year follow-up of quality of life in patients randomized to receive medical therapy or coronary artery bypass graft surgery. The Coronary Artery Surgery Study (CASS). *Circulation* 1990;**82**:1647–1658.
44. Vieira RD, Hueb W, Hlatky M, Favarato D, Rezende PC, Garzillo CL, Lima EG, Soares PR, Hueb AC, Pereira AC, Ramires JA, Kalil Filho R. Cost-effectiveness analysis for surgical, angioplasty, or medical therapeutics for coronary artery disease: 5-year follow-up of medicine, angioplasty, or surgery study (MASS) II trial. *Circulation* 2012;**126**:S145–S150.
45. Weinstein MC, Stason WB. Cost-effectiveness of coronary artery bypass surgery. *Circulation* 1982;**66**:III56–III66.
46. Pliskin JS, Stason WB, Weinstein MC, Johnson RA, Cohn PF, McEnany MT, Braun P. Coronary artery bypass graft surgery: clinical decision making and cost-effectiveness analysis. *Med Decis Making* 1981;**1**:10–28.
47. Favaloro RG, Effler DB, Groves LK, Sheldon WC, Sones FM Jr. Direct myocardial revascularization by saphenous vein graft. Present operative technique and indications. *Ann Thorac Surg* 1970;**10**:97–111.
48. Loop FD, Spampinato N, Siegel W, Effler DB. Internal mammary artery grafts without optical assistance. Clinical and angiographic analysis of 175 consecutive cases. *Circulation* 1973;**48**:III162–III167.
49. Morris GC Jr, Howell JF, Crawford ES, Reul GJ, Chapman DW, Beazley HL, Winters WL, Peterson PK. The distal coronary bypass. *Ann Surg* 1970;**172**: 652–662.
50. Organisation for Economic Co-operation and Development. http://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_STAT (12 February 2013).
51. Braunwald E. Coronary artery bypass surgery—an assessment. *Postgrad Med J* 1976; **52**:733–738.
52. Miller DW Jr, Ivey TD, Bailey WW, Johnson DD, Hessel EA. The practice of coronary artery bypass surgery in 1980. *J Thorac Cardiovasc Surg* 1981;**81**:423–427.
53. Gruntzig A. Transluminal dilatation of coronary-artery stenosis. *Lancet* 1978;**1**:263.
54. Gillum RF. Coronary artery bypass surgery and coronary angiography in the United States, 1979–1983. *Am Heart J* 1987;**113**:1255–1260.
55. Faxon DP, Detre KM, McCabe CH, Fisher L, Holmes DR, Cowley MJ, Bourassa MG, Van Raden M, Ryan TJ. Role of percutaneous transluminal coronary angioplasty in the treatment of unstable angina. Report from the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty and Coronary Artery Surgery Study Registries. *Am J Cardiol* 1984;**53**:131C–135C.
56. Holmes DR Jr, Vlietstra RE. Balloon angioplasty in acute and chronic coronary artery disease. *JAMA* 1989;**261**:2109–2115.
57. Togni M, Balmer F, Pfiffner D, Maier W, Zeiher AM, Meier B, Working Group of Interventional Cardiology and Coronary Pathophysiology, European Society of Cardiology. Percutaneous coronary interventions in Europe 1992–2001. *Eur Heart J* 2004;**25**:1208–1213.
58. Balmer F, Rotter M, Togni M, Pfiffner D, Zeiher AM, Maier W, Meier B, Working Group Interventional Cardiology, Coronary Pathophysiology of the European Society of Cardiology. Percutaneous coronary interventions in Europe 2000. *Int J Cardiol* 2005;**101**:457–463.
59. Ulrich MR, Brock DM, Ziskind AA. Analysis of trends in coronary artery bypass grafting and percutaneous coronary intervention rates in Washington state from 1987 to 2001. *Am J Cardiol* 2003;**92**:836–839.

60. Gerber Y, Rihal CS, Sundt TM 3rd, Killian JM, Weston SA, Therneau TM, Roger VL. Coronary revascularization in the community. A population-based study, 1990 to 2004. *J Am Coll Cardiol* 2007;**50**:1223–1229.
61. Epstein AJ, Polsky D, Yang F, Yang L, Groeneveld PW. Coronary revascularization trends in the United States, 2001–2008. *JAMA* 2011;**305**:1769–1776.
62. The BARI Investigators. The final 10-year follow-up results from the BARI randomized trial. *J Am Coll Cardiol* 2007;**49**:1600–1606.
63. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, Carrie D, Clayton TC, Danchin N, Flather M, Hamm CW, Hueb WA, Kahler J, Kelsey SF, King SB, Kosinski AS, Lopes N, McDonald KM, Rodriguez A, Serruys P, Sigwart U, Stables RH, Owens DK, Pocock SJ. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet* 2009; **373**:1190–1197.
64. Daemen J, Boersma E, Flather M, Booth J, Stables R, Rodriguez A, Rodriguez-Granillo G, Hueb WA, Lemos PA, Serruys PW. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. *Circulation* 2008;**118**:1146–1154.
65. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR Jr, Morel MA, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013;**381**:629–638.
66. Weintraub WS, Grau-Sepulveda MV, Weiss JM, O'Brien SM, Peterson ED, Kolm P, Zhang Z, Klein LW, Shaw RE, McKay C, Ritzenthaler LL, Popma JJ, Messenger JC, Shahian DM, Grover FL, Mayer JE, Shewan CM, Garratt KN, Moussa ID, Dangas GD, Edwards FH. Comparative effectiveness of revascularization strategies. *N Engl J Med* 2012;**366**:1467–1476.
67. Rothlin ME. The need for coronary artery surgery: expand or restrict? A European view. *Eur Heart J* 1987;**8**:51–55.
68. Organisation for Economic Co-operation and Development. *Health at a Glance*. OECD Publishing; 2009.
69. Taber RE, Morales AR, Fine G. Myocardial necrosis and the postoperative low-cardiac-output syndrome. *Ann Thorac Surg* 1967;**4**:12–28.
70. Rosenkranz ER, Buckberg GD. Myocardial protection during surgical coronary reperfusion. *J Am Coll Cardiol* 1983;**1**:1235–1246.
71. Favaloro RG. Critical analysis of coronary artery bypass graft surgery: a 30-year journey. *J Am Coll Cardiol* 1998;**31**:1B–63B.
72. Gay WA Jr, Ebert PA. Functional, metabolic, and morphologic effects of potassium-induced cardioplegia. *Surgery* 1973;**74**:284–290.
73. Guru V, Omura J, Alghamdi AA, Weisel R, Fremes SE. Is blood superior to crystalloid cardioplegia? A meta-analysis of randomized clinical trials. *Circulation* 2006;**114**: I331–I338.
74. Sa MP, Rueda FG, Ferraz PE, Chalegre ST, Vasconcelos FP, Lima RC. Is there any difference between blood and crystalloid cardioplegia for myocardial protection during cardiac surgery? A meta-analysis of 5576 patients from 36 randomized trials. *Perfusion* 2012;**27**:535–546.
75. O'Neil MP, Fleming JC, Badhwar A, Guo LR. Pulsatile versus nonpulsatile flow during cardiopulmonary bypass: microcirculatory and systemic effects. *Ann Thorac Surg* 2012;**94**:2046–2053.
76. D'Ascenzo F, Cavallero E, Moretti C, Omede P, Sciuto F, Rahman IA, Bonser RS, Yunseok J, Wagner R, Freiberger T, Kunst G, Marber MS, Thielmann M, Ji B, Amr YM, Modena MG, Zoccai GB, Sheiban I, Gaita F. Remote ischaemic preconditioning in coronary artery bypass surgery: a meta-analysis. *Heart* 2012;**98**: 1267–1271.
77. Hausenloy DJ, Boston-Griffiths E, Yellon DM. Cardioprotection during cardiac surgery. *Cardiovasc Res* 2012;**94**:253–265.
78. Newman MF, Ferguson TB, White JA, Ambrosio G, Koglin J, Nussmeier NA, Pearl RG, Pitt B, Wechsler AS, Weisel RD, Reece TL, Lira A, Harrington RA, Committee R-CS, Investigators. Effect of adenosine-regulating agent acadesine on morbidity and mortality associated with coronary artery bypass grafting: the RED-CABG randomized controlled trial. *JAMA* 2012;**308**:157–164.
79. FitzGibbon GM, Burton JR, Leach AJ. Coronary bypass graft fate: angiographic grading of 1400 consecutive grafts early after operation and of 1132 after one year. *Circulation* 1978;**57**:1070–1074.
80. Desai ND, Miwa S, Kodama D, Koyama T, Cohen G, Pelletier MP, Cohen EA, Christakis GT, Goldman BS, Fremes SE. A randomized comparison of intraoperative indocyanine green angiography and transit-time flow measurement to detect technical errors in coronary bypass grafts. *J Thorac Cardiovasc Surg* 2006;**132**: 585–594.
81. Alexander JH, Hafley G, Harrington RA, Peterson ED, Ferguson TB Jr, Lorenz TJ, Goyal A, Gibson M, Mack MJ, Gennevois D, Califf RM, Kouchoukos NT, Investigators PI. Efficacy and safety of edifoligide, an E2F transcription factor decoy, for prevention of vein graft failure following coronary artery bypass graft surgery: PREVENT IV: a randomized controlled trial. *JAMA* 2005;**294**:2446–2454.
82. Motwani JG, Topol EJ. Aortocoronary saphenous vein graft disease: pathogenesis, predisposition, and prevention. *Circulation* 1998;**97**:916–931.
83. Fitzgibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5065 grafts related to survival and reoperation in 1388 patients during 25 years. *J Am Coll Cardiol* 1996;**28**:616–626.
84. Kulik A, Le May MR, Voisine P, Tardif JC, Delarochelliere R, Naidoo S, Wells GA, Mesana TG, Ruel M. Aspirin plus clopidogrel versus aspirin alone after coronary artery bypass grafting: the clopidogrel after surgery for coronary artery disease (CASCADE) trial. *Circulation* 2010;**122**:2680–2687.
85. Loop FD, Lytle BW, Cosgrove DM, Stewart RW, Goormastic M, Williams GW, Golding LA, Gill CC, Taylor PC, Sheldon WC, Proudfit WL. Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. *N Engl J Med* 1986;**314**:1–6.
86. Lytle BW, Blackstone EH, Loop FD, Houghtaling PL, Arnold JH, Akhrass R, McCarthy PM, Cosgrove DM. Two internal thoracic artery grafts are better than one. *J Thorac Cardiovasc Surg* 1999;**117**:855–872.
87. Lytle BW, Loop FD, Cosgrove DM, Ratliff NB, Easley K, Taylor PC. Long-term (5 to 12 years) serial studies of internal mammary artery and saphenous vein coronary bypass grafts. *J Thorac Cardiovasc Surg* 1985;**89**:248–258.
88. Edwards WS, Lewis CE, Blakeley WR, Napolitano L. Coronary artery bypass with internal mammary and splenic artery grafts. *Ann Thorac Surg* 1973;**15**:35–40.
89. Mills NL, Dupin CL, Everson CT, Leger CL. The subscapular artery: an alternative conduit for coronary bypass. *J Card Surg* 1993;**8**:66–71.
90. van Son JA, Smedts F, Korving J, Guyt A, de Kok LB. Intercostal artery: histomorphometric study to assess its suitability as a coronary bypass graft. *Ann Thorac Surg* 1993; **56**:1078–1081.
91. Tatsumi TO, Tanaka Y, Kondoh K, Minohara S, Sawada Y, Tsuchida T, Tajima S, Sasaki S. Descending branch of lateral femoral circumflex artery as a free graft for myocardial revascularization: a case report. *J Thorac Cardiovasc Surg* 1996;**112**: 546–547.
92. Shatapathy P, Aggarwal BK, Punnen J. Inferior mesenteric artery as a free arterial conduit for myocardial revascularization. *J Thorac Cardiovasc Surg* 1997;**113**: 210–211.
93. Buxton BF, Chan AT, Dixit AS, Eizenberg N, Marshall RD, Raman JS. Ulnar artery as a coronary bypass graft. *Ann Thorac Surg* 1998;**65**:1020–1024.
94. Molina JE, Carr M, Yarnoz MD. Coronary bypass with Gore-Tex graft. *J Thorac Cardiovasc Surg* 1978;**75**:769–771.
95. Pym J, Brown PM, Charrette EJ, Parker JO, West RO. Gastroepiploic-coronary anastomosis. A viable alternative bypass graft. *J Thorac Cardiovasc Surg* 1987;**94**: 256–259.
96. Puig LB, Ciongolli W, Cividanes GV, Dontos A, Kopel L, Bittencourt D, Assis RV, Jatene AD. Inferior epigastric artery as a free graft for myocardial revascularization. *J Thorac Cardiovasc Surg* 1990;**99**:251–255.
97. Carpentier A, Guermonprez JL, Deloche A, Frechette C, DuBost C. The aorta-to-coronary radial artery bypass graft. A technique avoiding pathological changes in grafts. *Ann Thorac Surg* 1973;**16**:111–121.
98. Manapat AE, McCarthy PM, Lytle BW, Taylor PC, Loop FD, Stewart RW, Rosenkranz ER, Sapp SK, Miller D, Cosgrove DM. Gastroepiploic and inferior epigastric arteries for coronary artery bypass. Early results and evolving applications. *Circulation* 1994;**90**:II144–II147.
99. He GW. Arterial grafts for coronary artery bypass grafting: biological characteristics, functional classification, and clinical choice. *Ann Thorac Surg* 1999;**67**:277–284.
100. Glineur D, Hanet C, Poncelet A, D'Hoore W, Funken JC, Rubay J, Astarci P, Lacroix V, Verhelst R, Etienne PY, Noirhomme P, El Khoury G. Comparison of saphenous vein graft versus right gastroepiploic artery to revascularize the right coronary artery: a prospective randomized clinical, functional, and angiographic midterm evaluation. *J Thorac Cardiovasc Surg* 2008;**136**:482–488.
101. Izzat MB, West RR, Bryan AJ, Angelini GD. Coronary artery bypass surgery: current practice in the United Kingdom. *Br Heart J* 1994;**71**:382–385.
102. Acar C, Jebara VA, Portoghese M, Beyssen B, Pagny JY, Grare P, Chachques JC, Fabiani JN, Deloche A, Guermonprez JL. Revival of the radial artery for coronary artery bypass grafting. *Ann Thorac Surg* 1992;**54**:652–659; discussion 659–660.
103. Fisk RL, Brooks CH, Callaghan JC, Dvorkin J. Experience with the radial artery graft for coronary artery bypass. *Ann Thorac Surg* 1976;**21**:513–518.
104. Chardigny C, Jebara VA, Acar C, Descombes JJ, Verbeuren TJ, Carpentier A, Fabiani JN. Vasoreactivity of the radial artery. Comparison with the internal mammary and gastroepiploic arteries with implications for coronary artery surgery. *Circulation* 1993;**88**:II115–II127.
105. Deb S, Cohen EA, Singh SK, Une D, Laupacis A, Fremes SE, RAPS Investigators. Radial artery and saphenous vein patency more than 5 years after coronary artery bypass surgery: results from RAPS (Radial Artery Patency Study). *J Am Coll Cardiol* 2012;**60**:28–35.

106. Tranbaugh RF, Dimitrova KR, Friedmann P, Geller CM, Harris LJ, Stelzer P, Cohen BM, Ko W, DeCastro H, Lucido D, Hoffman DM. Coronary artery bypass grafting using the radial artery: clinical outcomes, patency, and need for reintervention. *Circulation* 2012;**126**:S170–S175.
107. Cable DG, Caccitolo JA, Pearson PJ, O'Brien T, Mullany CJ, Daly RC, Orszulak TA, Schaff HV. New approaches to prevention and treatment of radial artery graft vasospasm. *Circulation* 1998;**98**:II15–II21; discussion II21–II22.
108. Mohr FW, Rastan AJ, Serruys PW, Kappetein AP, Holmes DR, Pomar JL, Westaby S, Leadley K, Dawkins KD, Mack MJ. Complex coronary anatomy in coronary artery bypass graft surgery: impact of complex coronary anatomy in modern bypass surgery? Lessons learned from the SYNTAX trial after two years. *J Thorac Cardiovasc Surg* 2011;**141**:130–140.
109. Kirklin JK, Westaby S, Blackstone EH, Kirklin JW, Chenoweth DE, Pacifico AD. Complement and the damaging effects of cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1983;**86**:845–857.
110. Larm O, Larsson R, Olsson P. A new non-thrombogenic surface prepared by selective covalent binding of heparin via a modified reducing terminal residue. *Biomater Med Devices Artif Organs* 1983;**11**:161–173.
111. Buffolo E, Andrade JC, Succi J, Leao LE, Gallucci C. Direct myocardial revascularization without cardiopulmonary bypass. *Thorac Cardiovasc Surg* 1985;**33**:26–29.
112. Benetti FJ. Direct coronary surgery with saphenous vein bypass without either cardiopulmonary bypass or cardiac arrest. *J Cardiovasc Surg (Torino)* 1985;**26**:217–222.
113. Borst C, Jansen EW, Tulleken CA, Grundeman PF, Mansvelt Beck HJ, van Dongen JW, Hodde KC, Bredee JJ. Coronary artery bypass grafting without cardiopulmonary bypass and without interruption of native coronary flow using a novel anastomosis site restraining device ('Octopus'). *J Am Coll Cardiol* 1996;**27**: 1356–1364.
114. Falk V, Walther T, Gummert JF. Anastomotic devices for coronary artery bypass grafting. *Expert Rev Med Devices* 2005;**2**:223–233.
115. Dewey TM, Crumrine K, Herbert MA, Leonard A, Prince SL, Worley C, Edgerton JR, Magee MJ, Mack MJ. First-year outcomes of beating heart coronary artery bypass grafting using proximal mechanical connectors. *Ann Thorac Surg* 2004;**77**:1542–1549.
116. Verberkmoes NJ, Wolters SL, Post JC, Soliman-Hamad MA, Ter Woorst JF, Berreklouw E. Distal anastomotic patency of the Cardica C-PORT(R) xA system vs the hand-sewn technique: a prospective randomized controlled study in patients undergoing coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2013; doi: 10.1093/ejcts/ezt079.
117. Diegeler A, Borgermann J, Kappert U, Breuer M, Boning A, Ursulescu A, Rastan A, Holzhey D, Treede H, Riess FC, Veeckmann P, Asfoor A, Reents W, Zacher M, Hilker M, The GOPCABE Study Group. Off-pump versus on-pump coronary-artery bypass grafting in elderly patients. *N Engl J Med* 2013;**368**: 1189–1198.
118. Lamy A, Devereaux PJ, Dorairaj P, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, Noiseux N, Padmanabhan C, Bahamondes JC, Novick RJ, Vaijyanath P, Reddy SK, Tao L, Olavegogeascoechea PA, Airan B, Sulling TA, Whitlock RP, Ou Y, Pogue J, Chrolavicius S, Yusuf S, CORONARY Investigators. Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. *N Engl J Med* 2013;**368**:1179–1188.
119. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, Noiseux N, Padmanabhan C, Bahamondes JC, Novick RJ, Vaijyanath P, Reddy S, Tao L, Olavegogeascoechea PA, Airan B, Sulling TA, Whitlock RP, Ou Y, Ng J, Chrolavicius S, Yusuf S, CORONARY Investigators. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *N Engl J Med* 2012;**366**:1489–1497.
120. Bishawi M, Shroyer AL, Rumsfeld JS, Spertus JA, Baltz JH, Collins JF, Quin JA, Almassi GH, Grover FL, Hattler B, VA #517 Randomized on/off Bypass Study Group. Changes in health-related quality of life in off-pump versus on-pump cardiac surgery: Veterans Affairs Randomized On/Off Bypass Trial. *Ann Thorac Surg* 2013;**95**:1946–1951.
121. Benetti FJ, Ballester C, Sani G, Doonstra P, Grandjean J. Video assisted coronary bypass surgery. *J Card Surg* 1995;**10**:620–625.
122. Subramanian VA, McCabe JC, Geller CM. Minimally invasive direct coronary artery bypass grafting: two-year clinical experience. *Ann Thorac Surg* 1997;**64**:1648–1653; discussion 1654–1655.
123. Holzhey DM, Jacobs S, Mochalski M, Walther T, Thiele H, Mohr FW, Falk V. Seven-year follow-up after minimally invasive direct coronary artery bypass: experience with more than 1300 patients. *Ann Thorac Surg* 2007;**83**:108–114.
124. Kettering K. Minimally invasive direct coronary artery bypass grafting: a meta-analysis. *J Cardiovasc Surg (Torino)* 2008;**49**:793–800.
125. Mack MJ, Acuff TE, Casimir-Ahn H, Lonn UJ, Jansen EW. Video-assisted coronary bypass grafting on the beating heart. *Ann Thorac Surg* 1997;**63**:S100–S103.
126. Srivastava S, Barrera R, Quismundo S. One hundred sixty-four consecutive beating heart totally endoscopic coronary artery bypass cases without intraoperative conversion. *Ann Thorac Surg* 2012;**94**:1463–1468.
127. Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. *N Engl J Med* 2012;**366**:54–63.
128. Mundth ED, Austen WG. Surgical measures for coronary heart disease (third of three parts). *N Engl J Med* 1975;**293**:124–130.
129. Berg R Jr, Kendall RW, Duvoisin GE, Ganji JH, Rudy LW, Everhart FJ. Acute myocardial infarction: a surgical emergency. *J Thorac Cardiovasc Surg* 1975;**70**:432–439.
130. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). *Lancet* 1986;**1**:397–402.
131. Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JH, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med* 1993;**328**:680–684.
132. Alderman EL, Fisher LD, Litwin P, Kaiser GC, Myers WO, Maynard C, Levine F, Schloss M. Results of coronary artery surgery in patients with poor left ventricular function (CASS). *Circulation* 1983;**68**:785–795.
133. Bounous EP, Mark DB, Pollock BG, Hlatky MA, Harrell FE Jr, Lee KL, Rankin JS, Wechsler AS, Pryor DB, Califf RM. Surgical survival benefits for coronary disease patients with left ventricular dysfunction. *Circulation* 1988;**78**:I151–I157.
134. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;**33**:1787–1847.
135. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, Ali IS, Pohost G, Gradinac S, Abraham WT, Yii M, Prabhakaran D, Szwed H, Ferrazzi P, Petrie MC, O'Connor CM, Panchavinnin P, She L, Bonow RO, Rankin GR, Jones RH, Rouleau JL, STICH Investigators. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med* 2011;**364**:1607–1616.
136. Hachamovitch R, Rozanski A, Hayes SW, Thomson LE, Germano G, Friedman JD, Cohen I, Berman DS. Predicting therapeutic benefit from myocardial revascularization procedures: are measurements of both resting left ventricular ejection fraction and stress-induced myocardial ischemia necessary? *J Nucl Cardiol* 2006;**13**: 768–778.
137. Morris GC Jr, Reul GJ, Howell JF, Crawford ES, Chapman DW, Beazley HL, Winters WL, Peterson PK, Lewis JM. Follow-up results of distal coronary artery bypass for ischemic heart disease. *Am J Cardiol* 1972;**29**:180–185.
138. Verska JJ, Walker WJ. Aortocoronary bypass in the diabetic patient. *Am J Cardiol* 1975;**35**:774–777.
139. Oldham HN Jr, Kong Y, Bartel AG, Morris JJ Jr, Behar VS, Peter RH, Rosati RA, Young WG Jr, Sabiston DC Jr. Risk factors in coronary artery bypass surgery. *Arch Surg* 1972;**105**:918–923.
140. Maynard C, Fisher LD, Passamani ER, Pullum T. Blacks in the coronary artery surgery study (CASS): race and clinical decision making. *Am J Public Health* 1986; **76**:1446–1448.
141. ElBardissi AW, Aranki SF, Sheng S, O'Brien SM, Greenberg CC, Gammie JS. Trends in isolated coronary artery bypass grafting: an analysis of the Society of Thoracic Surgeons adult cardiac surgery database. *J Thorac Cardiovasc Surg* 2012;**143**: 273–281.
142. Jones RH, Hannan EL, Hammermeister KE, Delong ER, O'Connor GT, Luepker RV, Parsonnet V, Pryor DB. Identification of preoperative variables needed for risk adjustment of short-term mortality after coronary artery bypass graft surgery. The Working Group Panel on the Cooperative CABG Database Project. *J Am Coll Cardiol* 1996;**28**:1478–1487.
143. Jha AK, Fisher ES, Li Z, Orav EJ, Epstein AM. Racial trends in the use of major procedures among the elderly. *N Engl J Med* 2005;**353**:683–691.
144. Head SJ, Osnabrugge RL, Kappetein AP. Long-term survival of young patients with coronary artery disease is best realized through surgical revascularization with mammary arteries. *J Am Coll Cardiol* 2013; doi: 10.1016/j.jacc.2012.11.078.
145. Head SJ, Holmes DR Jr, Mack MJ, Serruys PW, Mohr FW, Morice M, Colombo A, Kappetein AP. Risk profile and 3-year outcomes from the SYNTAX percutaneous coronary intervention and coronary artery bypass grafting nested registries. *JACC Cardiovasc Interv* 2012;**5**:618–625.
146. Kieser TM, Lewin AM, Graham MM, Martin BJ, Galbraith PD, Rabi DM, Norris CM, Faris PD, Knudtson ML, Ghali WA, Approach Investigators. Outcomes associated with bilateral internal thoracic artery grafting: the importance of age. *Ann Thorac Surg* 2011;**92**:1269–1275; discussion 1275–1276.
147. Genereux P, Head SJ, Wood DA, Kodali SK, Williams MR, Paradis JM, Spaziano M, Kappetein AP, Webb JG, Cribier A, Leon MB. Transcatheter aortic valve implantation: 10-year anniversary part II: clinical implications. *Eur Heart J* 2012;**33**: 2399–2402.

148. Genereux P, Head SJ, Wood DA, Kodali SK, Williams MR, Paradis JM, Spaziano M, Kappetein AP, Webb JG, Cribier A, Leon MB. Transcatheter aortic valve implantation 10-year anniversary: review of current evidence and clinical implications. *Eur Heart J* 2012;**33**:2388–2398.
149. Rogers JH, Franzen O. Percutaneous edge-to-edge MitraClip therapy in the management of mitral regurgitation. *Eur Heart J* 2011;**32**:2350–2357.
150. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M, Bax JJ, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Von Segesser L, Badano LP, Bunc M, Claeys MJ, Drinkovic N, Filippatos G, Habib G, Kappetein AP, Kassab R, Lip GY, Moat N, Nickenig G, Otto CM, Pepper J, Piazza N, Pieper PG, Rosenhek R, Shuka N, Schwammenthal E, Schwitter J, Mas PT, Trindade PT, Walther T. Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2012;**33**:2451–2496.
151. Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand SL, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP, Society of Thoracic Surgeons Quality Measurement Task Force. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1—coronary artery bypass grafting surgery. *Ann Thorac Surg* 2009;**88**:S2–S22.
152. Afilalo J, Rasti M, Ohayon SM, Shimony A, Eisenberg MJ. Off-pump vs. on-pump coronary artery bypass surgery: an updated meta-analysis and meta-regression of randomized trials. *Eur Heart J* 2012;**33**:1257–1267.
153. Newman MF, Ferguson TB, White JA, Ambrosio G, Koglin J, Nussmeier NA, Pearl RG, Pitt B, Wechsler AS, Weisel RD, Reece TL, Lira A, Harrington RA, RED-CABG Steering Committee Investigators. Effect of adenosine-regulating agent acadesine on morbidity and mortality associated with coronary artery bypass grafting: the RED-CABG randomized controlled trial. *JAMA* 2012;**308**: 157–164.
154. Tarakji KG, Sabik JF 3rd, Bhudia SK, Batizy LH, Blackstone EH. Temporal onset, risk factors, and outcomes associated with stroke after coronary artery bypass grafting. *JAMA* 2011;**305**:381–390.
155. Bucerius J, Gummert JF, Borger MA, Walther T, Doll N, Onnasch JF, Metz S, Falk V, Mohr FW. Stroke after cardiac surgery: a risk factor analysis of 16184 consecutive adult patients. *Ann Thorac Surg* 2003;**75**:472–478.
156. Filsoufi F, Rahmanian PB, Castillo JG, Bronster D, Adams DH. Incidence, topography, predictors and long-term survival after stroke in patients undergoing coronary artery bypass grafting. *Ann Thorac Surg* 2008;**85**:862–870.
157. Domanski MJ, Mahaffey K, Hasselblad V, Brener SJ, Smith PK, Hillis G, Engoren M, Alexander JH, Levy JH, Chaitman BR, Broderick S, Mack MJ, Pieper KS, Farkouh ME. Association of myocardial enzyme elevation and survival following coronary artery bypass graft surgery. *JAMA* 2011;**305**:585–591.
158. Alamanni F, Dainese L, Naliato M, Gregu S, Agrifoglio M, Polvani GL, Biglioli P, Parolari A, Monzino OPCAB Investigators. On- and off-pump coronary surgery and perioperative myocardial infarction: an issue between incomplete and extensive revascularization. *Eur J Cardiothorac Surg* 2008;**34**:118–126.
159. Jarvinen O, Julkunen J, Saarinen T, Laurikka J, Huhtala H, Tarkka MR. Perioperative myocardial infarction has negative impact on health-related quality of life following coronary artery bypass graft surgery. *Eur J Cardiothorac Surg* 2004;**26**:621–627.
160. Greaves SC, Rutherford JD, Aranki SF, Cohn LH, Couper GS, Adams DH, Rizzo RJ, Collins JJ Jr, Antman EM. Current incidence and determinants of perioperative myocardial infarction in coronary artery surgery. *Am Heart J* 1996;**132**:572–578.
161. Costa MA, Carere RG, Lichtenstein SV, Foley DP, de Valk V, Lindenboom W, Roose PC, van Geldorp TR, Macaya C, Castanon JL, Fernandez-Avilez F, Gonzales JH, Heyer G, Unger F, Serruys PW. Incidence, predictors, and significance of abnormal cardiac enzyme rise in patients treated with bypass surgery in the arterial revascularization therapies study (ARTS). *Circulation* 2001;**104**:2689–2693.
162. Sun JC, Whitlock R, Cheng J, Eikelboom JW, Thabane L, Crowther MA, Teoh KH. The effect of pre-operative aspirin on bleeding, transfusion, myocardial infarction, and mortality in coronary artery bypass surgery: a systematic review of randomized and observational studies. *Eur Heart J* 2008;**29**:1057–1071.
163. Mehta RH, Sheng S, O'Brien SM, Grover FL, Gammie JS, Ferguson TB, Peterson ED, Society of Thoracic Surgeons National Cardiac Surgery Database Investigators. Reoperation for bleeding in patients undergoing coronary artery bypass surgery: incidence, risk factors, time trends, and outcomes. *Circ Cardiovasc Qual Outcomes* 2009;**2**:583–590.
164. Choong CK, Gerrard C, Goldsmith KA, Dunningham H, Vuylsteke A. Delayed re-exploration for bleeding after coronary artery bypass surgery results in adverse outcomes. *Eur J Cardiothorac Surg* 2007;**31**:834–838.
165. Hu S, Zheng Z, Yuan X, Wang Y, Normand SL, Ross JS, Krumholz HM. Coronary artery bypass graft: contemporary heart surgery center performance in China. *Circ Cardiovasc Qual Outcomes* 2012;**5**:214–221.
166. Karthik S, Grayson AD, McCarron EE, Pullan DM, Desmond MJ. Reexploration for bleeding after coronary artery bypass surgery: risk factors, outcomes, and the effect of time delay. *Ann Thorac Surg* 2004;**78**:527–534; discussion 534.
167. Inouye SK, Bogardus ST Jr, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, Cooney LM Jr. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med* 1999;**340**:669–676.
168. Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, Jones RN. Cognitive trajectories after postoperative delirium. *N Engl J Med* 2012;**367**:30–39.
169. Santos FS, Velasco IT, Fraguas R Jr. Risk factors for delirium in the elderly after coronary artery bypass graft surgery. *Int Psychogeriatr* 2004;**16**:175–193.
170. Rolfson DB, McElhaney JE, Rockwood K, Finnegan BA, Entwistle LM, Wong JF, Suarez-Almazor ME. Incidence and risk factors for delirium and other adverse outcomes in older adults after coronary artery bypass graft surgery. *Can J Cardiol* 1999; **15**:771–776.
171. Bakker RC, Osse RJ, Tulen JH, Kappetein AP, Bogers AJ. Preoperative and operative predictors of delirium after cardiac surgery in elderly patients. *Eur J Cardiothorac Surg* 2012;**41**:544–549.
172. Arenson BG, Macdonald LA, Grocott HP, Hiebert BM, Arora RC. Effect of intensive care unit environment on in-hospital delirium after cardiac surgery. *J Thorac Cardiovasc Surg* 2013; doi: 10.1016/j.jtcvs.2012.12.042.
173. Bucerius J, Gummert JF, Borger MA, Walther T, Doll N, Falk V, Schmitt DV, Mohr FW. Predictors of delirium after cardiac surgery delirium: effect of beating-heart (off-pump) surgery. *J Thorac Cardiovasc Surg* 2004;**127**:57–64.
174. Chalmers J, Mediratta N, McShane J, Shaw M, Pullan M, Poullis M. The long-term effects of developing renal failure post-coronary artery bypass surgery, in patients with normal preoperative renal function. *Eur J Cardiothorac Surg* 2013;**43**:555–559.
175. Brown JR, Cochran RP, Dacey LJ, Ross CS, Kunzelman KS, Dunton RF, Braxton JH, Charlesworth DC, Clough RA, Helm RE, Leavitt BJ, Mackenzie TA, O'Connor GT, Northern New England Cardiovascular Disease Study Group. Perioperative increases in serum creatinine are predictive of increased 90-day mortality after coronary artery bypass graft surgery. *Circulation* 2006;**114**:I409–I413.
176. Nally JV Jr. Acute renal failure in hospitalized patients. *Cleve Clin J Med* 2002;**69**: 569–574.
177. Brown JR, Cochran RP, Leavitt BJ, Dacey LJ, Ross CS, MacKenzie TA, Kunzelman KS, Kramer RS, Hernandez F Jr, Helm RE, Westbrook BM, Dunton RF, Malenka DJ, O'Connor GT, Northern New England Cardiovascular Disease Study Group. Multivariable prediction of renal insufficiency developing after cardiac surgery. *Circulation* 2007;**116**:I139–I143.
178. Mehta RH, Grab JD, O'Brien SM, Bridges CR, Gammie JS, Haan CK, Ferguson TB, Peterson ED, Society of Thoracic Surgeons National Cardiac Surgery Database Investigators. Bedside tool for predicting the risk of postoperative dialysis in patients undergoing cardiac surgery. *Circulation* 2006;**114**:2208–2216.
179. Taggart DP, Altman DG, Gray AM, Lees B, Nugara F, Yu LM, Campbell H, Flather M, ART Investigators. Randomized trial to compare bilateral vs. single internal mammary coronary artery bypass grafting: 1-year results of the arterial revascularisation trial (ART). *Eur Heart J* 2010;**31**:2470–2481.
180. Gorlitzer M, Wagner F, Pfeiffer S, Folkmann S, Meinhart J, Fischlein T, Reichenspurner H, Grabenwoger M. A prospective randomized multicenter trial shows improvement of sternum related complications in cardiac surgery with the Posthorax support vest. *Interact Cardiovasc Thorac Surg* 2010;**10**:714–718.
181. Salehi Omran A, Karimi A, Ahmadi SH, Davoodi S, Marzban M, Movahedi N, Abbasi K, Boroumand MA, Davoodi S, Moshtaghi N. Superficial and deep sternal wound infection after more than 9000 coronary artery bypass graft (CABG): incidence, risk factors and mortality. *BMC Infect Dis* 2007;**7**:112.
182. Deo SV, Shah IK, Dunlay SM, Erwin PJ, Locker C, Altarabsheh SE, Boilson BA, Park SJ, Joyce LD. Bilateral internal thoracic artery harvest and deep sternal wound infection in diabetic patients. *Ann Thorac Surg* 2013;**95**:862–869.
183. Milano CA, Kesler K, Archibald N, Sexton DJ, Jones RH. Mediastinitis after coronary artery bypass graft surgery. Risk factors and long-term survival. *Circulation* 1995;**92**: 2245–2251.
184. Fowler VG Jr, O'Brien SM, Muhlbaier LH, Corey GR, Ferguson TB, Peterson ED. Clinical predictors of major infections after cardiac surgery. *Circulation* 2005;**112**: I358–I365.
185. Ridderstolpe L, Gill H, Granfeldt H, Ahlfeldt H, Rutberg H. Superficial and deep sternal wound complications: incidence, risk factors and mortality. *Eur J Cardiothorac Surg* 2001;**20**:1168–1175.
186. Filardo G, Hamilton C, Hebeler RF Jr, Hamman B, Grayburn P. New-onset postoperative atrial fibrillation after isolated coronary artery bypass graft surgery and long-term survival. *Circ Cardiovasc Qual Outcomes* 2009;**2**:164–169.
187. El-Chami MF, Kilgo P, Thourani V, Lattouf OM, Delurgio DB, Guyton RA, Leon AR, Puskas JD. New-onset atrial fibrillation predicts long-term mortality after coronary artery bypass graft. *J Am Coll Cardiol* 2010;**55**:1370–1376.

188. Calo L, Bianconi L, Colivicchi F, Lamberti F, Loricchio ML, de Ruvo E, Meo A, Pandozi C, Staibano M, Santini M. N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. *J Am Coll Cardiol* 2005;**45**:1723–1728.
189. Moller CH, Penninga L, Wetterslev J, Steinbruchel DA, Gluud C. Clinical outcomes in randomized trials of off- vs. on-pump coronary artery bypass surgery: systematic review with meta-analyses and trial sequential analyses. *Eur Heart J* 2008;**29**: 2601–2616.
190. Amar D, Shi W, Hogue CW Jr, Zhang H, Passman RS, Thomas B, Bach PB, Damiano R, Thaler HT. Clinical prediction rule for atrial fibrillation after coronary artery bypass grafting. *J Am Coll Cardiol* 2004;**44**:1248–1253.
191. El-Chami MF, Kilgo PD, Elfstrom KM, Halkos M, Thourani V, Lattouf OM, Delurgio DB, Guyton RA, Leon AR, Puskas JD. Prediction of new onset atrial fibrillation after cardiac revascularization surgery. *Am J Cardiol* 2012;**110**:649–654.
192. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, Barash PG, Hsu PH, Mangano DT, Investigators of the Ischemia Research and Education Foundation, Multicenter Study of Perioperative Ischemia Research Group. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA* 2004;**291**:1720–1729.
193. Head SJ, Howell NJ, Osnabrugge RL, Bridgewater B, Keogh BE, Kinsman R, Walton P, Gummert JF, Pagano D, Kappetein AP. The European Association for Cardio-Thoracic Surgery (EACTS) database: an introduction. *Eur J Cardiothorac Surg* 2013; doi: 10.1093/ejcts/ezt303.
194. Palmerini T, Biondi-Zoccai G, Reggiani LB, Sangiorgi D, Alessi L, De Servi S, Branzi A, Stone GW. Risk of stroke with coronary artery bypass graft surgery compared with percutaneous coronary intervention. *J Am Coll Cardiol* 2012;**60**:798–805.
195. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S 3rd, Bertrand M, Fuster V, Investigators FT. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012;**367**:2375–2384.
196. Mack MJ, Head SJ, Holmes DR Jr, Stahle E, Feldman TE, Colombo A, Morice MC, Unger F, Erglis A, Stoler R, Dawkins KD, Serruys PW, Mohr FW, Kappetein AP. Analysis of stroke occurring in the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial comparing coronary artery bypass surgery and percutaneous coronary intervention in the treatment of complex coronary artery disease. *JACC Cardiovasc Interv* 2013;**6**:344–354.
197. Head SJ, Börgermann J, Osnabrugge RL, Kieser TM, Valk F, Taggart DP, Puskas JD, Gummert JF, Kappetein AP. Coronary artery bypass surgery: Part 2—optimizing outcomes and future directions. *Eur Heart J* 2013; 10.1093/eurheartj/eht284.
198. Head SJ, Osnabrugge RL, Howell NJ, Freemantle N, Bridgewater B, Pagano D, Kappetein AP. A systematic review of risk prediction in adult cardiac surgery: considerations for future model development. *Eur J Cardiothorac Surg* 2013;**43**: e121–e129.
199. Higgins TL, Estafanous FG, Loop FD, Beck GJ, Blum JM, Paranandi L. Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients. A clinical severity score. *JAMA* 1992;**267**:2344–2348.
200. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999;**16**:9–13.
201. Shroyer AL, Coombs LP, Peterson ED, Eiken MC, DeLong ER, Chen A, Ferguson TB Jr, Grover FL, Edwards FH, Society of Thoracic Surgeons. The Society of Thoracic Surgeons: 30-day operative mortality and morbidity risk models. *Ann Thorac Surg* 2003;**75**:1856–1864; discussion 1864–1865.
202. Geissler HJ, Holzl P, Marohl S, Kuhn-Regnier F, Mehlhorn U, Sudkamp M, de Vivie ER. Risk stratification in heart surgery: comparison of six score systems. *Eur J Cardiothorac Surg* 2000;**17**:400–406.
203. Head SJ, Kaul S, Mack MJ, Serruys PW, Taggart DP, Holmes Jr DR, Leon MB, Marco J, Bogers AJ, Kappetein AP. The rationale for heart team decision-making for patients with stable, complex coronary artery disease. *Eur Heart J* 2013; doi: 10.1093/eurheartj/eht059.
204. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. *Eur Heart J* 2003;**24**:881–882.
205. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U. EuroSCORE II. *Eur J Cardiothorac Surg* 2012;**41**:734–744; discussion 744–745.
206. Hickey GL, Grant SW, Murphy GJ, Bhabra M, Pagano D, McAllister K, Buchan I, Bridgewater B. Dynamic trends in cardiac surgery: why the logistic EuroSCORE is no longer suitable for contemporary cardiac surgery and implications for future risk models. *Eur J Cardiothorac Surg* 2013;**43**:1146–1152.
207. Kappetein AP, Head SJ. Predicting prognosis in cardiac surgery: a prophecy? *Eur J Cardiothorac Surg* 2012;**41**:732–733.
208. Afilalo J, Mottillo S, Eisenberg MJ, Alexander KP, Noiseux N, Perrault LP, Morin JF, Langlois Y, Ohayon SM, Monette J, Boivin JF, Shahian DM, Bergman H. Addition of frailty and disability to cardiac surgery risk scores identifies elderly patients at high risk of mortality or major morbidity. *Circ Cardiovasc Qual Outcomes* 2012;**5**: 222–228.
209. Hannan EL, Wu C, Ryan TJ, Bennett E, Culliford AT, Gold JP, Hartman A, Isom OW, Jones RH, McNeil B, Rose EA, Subramanian VA. Do hospitals and surgeons with higher coronary artery bypass graft surgery volumes still have lower risk-adjusted mortality rates? *Circulation* 2003;**108**:795–801.
210. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med* 2003; **349**:2117–2127.
211. Plomondon ME, Casebeer AW, Schooley LM, Wagner BD, Grunwald GK, McDonald GO, Grover FL, Shroyer AL. Exploring the volume-outcome relationship for off-pump coronary artery bypass graft procedures. *Ann Thorac Surg* 2006; **81**:547–553.
212. Welke KF, Barnett MJ, Sarrazin MS, Rosenthal GE. Limitations of hospital volume as a measure of quality of care for coronary artery bypass graft surgery. *Ann Thorac Surg* 2005;**80**:2114–2119.
213. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. *N Engl J Med* 2011;**364**:2128–2137.
214. Shahian DM, O'Brien SM, Normand SL, Peterson ED, Edwards FH. Association of hospital coronary artery bypass volume with processes of care, mortality, morbidity, and the Society of Thoracic Surgeons composite quality score. *J Thorac Cardiovasc Surg* 2010;**139**:273–282.
215. Auerbach AD, Hilton JF, Maselli J, Pekow PS, Rothberg MB, Lindenauer PK. Shop for quality or volume? Volume, quality, and outcomes of coronary artery bypass surgery. *Ann Intern Med* 2009;**150**:696–704.
216. Kurlansky PA, Argenziano M, Dunton R, Lancey R, Nast E, Stewart A, Williams T, Zapolanski A, Chang H, Tingley J, Smith CR. Quality, not volume, determines outcome of coronary artery bypass surgery in a university-based community hospital network. *J Thorac Cardiovasc Surg* 2012;**143**:287–293.
217. Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, Blackstone EH. Duration of red-cell storage and complications after cardiac surgery. *N Engl J Med* 2008;**358**:1229–1239.
218. Wu C, Camacho FT, Wechsler AS, Lahey S, Culliford AT, Jordan D, Gold JP, Higgins RS, Smith CR, Hannan EL. Risk score for predicting long-term mortality after coronary artery bypass graft surgery. *Circulation* 2012;**125**:2423–2430.
219. Williams JB, Peterson ED, Brennan JM, Sedrakyan A, Tavris D, Alexander JH, Lopes RD, Dokholyan RS, Zhao Y, O'Brien SM, Michler RE, Thourani VH, Edwards FH, Duggirala H, Gross T, Marinac-Dabic D, Smith PK. Association between endoscopic vs open vein-graft harvesting and mortality, wound complications, and cardiovascular events in patients undergoing CABG surgery. *JAMA* 2012; **308**:475–484.
220. Magee MJ, Alexander JH, Hafley G, Ferguson TB Jr, Gibson CM, Harrington RA, Peterson ED, Califf RM, Kouchoukos NT, Herbert MA, Mack MJ, Prevent IV Investigators. Coronary artery bypass graft failure after on-pump and off-pump coronary artery bypass: findings from PREVENT IV. *Ann Thorac Surg* 2008;**85**:494–499; discussion 499–500.
221. Serruys PW, Ong ATL, van Herwerden LA, Sousa JE, Jatene A, Bonnier JJRM, Schönberger JPMA, Buller N, Bonser R, Disco C, Backx B, Hugenholtz PG, Firth BG, Unger F. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol* 2005;**46**:575–581.
222. van Dijk D, Spoor M, Hijman R, Nathoe HM, Borst C, Jansen EW, Grobbee DE, de Jaegere PP, Kalkman CJ, OCTOPUS Study Group. Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. *JAMA* 2007; **297**:701–708.
223. Hueb W, Lopes N, Gersh BJ, Soares PR, Ribeiro EE, Pereira AC, Favarato D, Rocha AS, Hueb AC, Ramires JA. Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation* 2010; **122**:949–957.
224. Schachner T, Zimmer A, Nagele G, Laufer G, Bonatti J. Risk factors for late stroke after coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2005;**130**:485–490.
225. Kaarisalo MM, Immonen-Raiha P, Marttila RJ, Salomaa V, Torppa J, Tuomilehto J, FINMONICA MI and Stroke Registry Teams. The risk of stroke following coronary revascularization—a population-based long-term follow-up study. *Scand Cardiovasc J* 2002;**36**:231–236.
226. Graham MM, Norris CM, Galbraith PD, Knudtson ML, Ghali WA, Investigators A. Quality of life after coronary revascularization in the elderly. *Eur Heart J* 2006;**27**: 1690–1698.
227. Caine N, Sharples LD, Wallwork J. Prospective study of health related quality of life before and after coronary artery bypass grafting: outcome at five years. *Heart* 1999; **81**:347–351.

228. Booth DC, Deupree RH, Hultgren HN, DeMaria AN, Scott SM, Luchi RJ. Quality of life after bypass surgery for unstable angina. 5-year follow-up results of a Veterans Affairs Cooperative Study. *Circulation* 1991;**83**:87–95.
229. Pignay-Demaria V, Lesperance F, Demaria RG, Frasure-Smith N, Perrault LP. Depression and anxiety and outcomes of coronary artery bypass surgery. *Ann Thorac Surg* 2003;**75**:314–321.
230. Connerney I, Shapiro PA, McLaughlin JS, Bagiella E, Sloan RP. Relation between depression after coronary artery bypass surgery and 12-month outcome: a prospective study. *Lancet* 2001;**358**:1766–1771.
231. Blumenthal JA, Lett HS, Babyak MA, White W, Smith PK, Mark DB, Jones R, Mathew JP, Newman MF, NORG Investigators. Depression as a risk factor for mortality after coronary artery bypass surgery. *Lancet* 2003;**362**:604–609.
232. Steuer J, Horte LG, Lindahl B, Stahle E. Impact of perioperative myocardial injury on early and long-term outcome after coronary artery bypass grafting. *Eur Heart J* 2002; **23**:1219–1227.
233. Koch CG, Li L, Duncan AI, Mihaljevic T, Loop FD, Starr NJ, Blackstone EH. Transfusion in coronary artery bypass grafting is associated with reduced long-term survival. *Ann Thorac Surg* 2006;**81**:1650–1657.
234. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. *Lancet* 2001;**358**:870–875.
235. Desai ND, Cohen EA, Naylor CD, Fremes SE, Radial Artery Patency Study Investigators. A randomized comparison of radial-artery and saphenous-vein coronary bypass grafts. *N Engl J Med* 2004;**351**:2302–2309.
236. Collins P, Webb CM, Chong CF, Moat NE, Radial Artery Versus Saphenous Vein Patency Trial Investigators. Radial artery versus saphenous vein patency randomized trial: five-year angiographic follow-up. *Circulation* 2008;**117**:2859–2864.
237. Goldman S, Sethi GK, Holman W, Thai H, McFalls E, Ward HB, Kelly RF, Rhenman B, Tobler GH, Bakaeen FG, Huh J, Soltero E, Moursi M, Haime M, Crittenden M, Kasirajan V, Ratliff M, Pett S, Irimpen A, Gunnar W, Thomas D, Fremes S, Moritz T, Reda D, Harrison L, Wagner TH, Wang Y, Planting L, Miller M, Rodriguez Y, Juneman E, Morrison D, Pierce MK, Kreamer S, Shih MC, Lee K. Radial artery grafts vs saphenous vein grafts in coronary artery bypass surgery: a randomized trial. *JAMA* 2011;**305**:167–174.
238. Locker C, Schaff HV, Dearani JA, Joyce LD, Park SJ, Burkhart HM, Suri RM, Greason KL, Stulak JM, Li Z, Daly RC. Multiple arterial grafts improve late survival of patients undergoing coronary artery bypass graft surgery: analysis of 8622 patients with multivessel disease. *Circulation* 2012;**126**:1023–1030.
239. Schwann TA, Al-Shaar L, Engoren M, Habib RH. Late effects of radial artery vs saphenous vein grafting for multivessel coronary bypass surgery in diabetics: a propensity-matched analysis. *Eur J Cardiothorac Surg* 2013; doi: 10.1093/ejcts/ezt061.
240. Taggart DP. Incomplete revascularization: appropriate and inappropriate. *Eur J Cardiothorac Surg* 2012;**41**:542–543.
241. Head SJ, Mack MJ, Holmes DR Jr, Mohr FW, Morice MC, Serruys PW, Kappetein AP. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. *Eur J Cardiothorac Surg* 2012;**41**:535–541.
242. Farooq V, Serruys PW, Bourantas C, Vranckx P, Diletti R, Garcia Garcia HM, Holmes DR, Kappetein AP, Mack M, Feldman T, Morice MC, Colombo A, Morel MA, de Vries T, van Es GA, Steyerberg EW, Dawkins KD, Mohr FW, James S, Stahle E. Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial. *Eur Heart J* 2012;**33**:3105–3113.
243. Shahian DM, O'Brien SM, Sheng S, Grover FL, Mayer JE, Jacobs JP, Weiss JM, Delong ER, Peterson ED, Weintraub WS, Grau-Sepulveda MV, Klein LW, Shaw RE, Garratt KN, Moussa ID, Shewan CM, Dangas GD, Edwards FH. Predictors of long-term survival after coronary artery bypass grafting surgery: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database (the ASCERT study). *Circulation* 2012;**125**:1491–1500.
244. van Domburg RT, Kappetein AP, Bogers AJ. The clinical outcome after coronary bypass surgery: a 30-year follow-up study. *Eur Heart J* 2009;**30**:453–458.

Chapter 4

Coronary artery bypass grafting: Part 2 – optimizing outcomes and future prospects

Head SJ, Börgermann J, Osnabrugge RLJ, Kieser TM, Falk V,
Taggart DP, Puskas JD, Grummert JF, Kappetein AP

Eur Heart J 2013;34:2873-2886

Coronary artery bypass grafting: Part 2—optimizing outcomes and future prospects

Stuart J. Head[1], Jochen Börgermann[2], Ruben L.J. Osnabrugge[1], Teresa M. Kieser[3], Volkmar Falk[4], David P. Taggart[5], John D. Puskas[6], Jan F. Gummert[2], and Arie Pieter Kappetein[1]*

[1]Department of Cardiothoracic Surgery, Erasmus University Medical Centre, PO Box 2040, 3000 CA Rotterdam, The Netherlands; [2]Department of Cardiothoracic Surgery, Heart and Diabetes Centre North-Rhine Westphalia, Ruhr-University Bochum, Bad Oeynhausen, Germany; [3]Department of Cardiac Sciences, LIBIN Cardiovascular Institute of Alberta, University of Calgary, Calgary, Alberta, Canada; [4]Division of Cardiovascular Surgery, University Hospital Zurich, Zurich, Switzerland; [5]Department of Cardiovascular Surgery, John Radcliffe Hospital, Oxford University Hospitals NHS Trust, Oxford, UK; and [6]Division of Cardiothoracic Surgery, Emory University School of Medicine, Atlanta, GA, USA

Received 15 April 2013; revised 28 May 2013; accepted 27 June 2013

Since first introduced in the mid-1960s, coronary artery bypass grafting (CABG) has become the standard of care for patients with coronary artery disease. Surprisingly, the fundamental surgical technique itself did not change much over time. Nevertheless, outcomes after CABG have dramatically improved over the first 50 years. Randomized trials comparing percutaneous coronary intervention (PCI) to CABG have shown converging outcomes for select patient populations, providing more evidence for wider use of PCI. It is increasingly important to focus on the optimization of the short- and long-term outcomes of CABG and to reduce the level of invasiveness of this procedure. This review provides an overview on how new techniques and widespread consideration of evolving strategies have the potential to optimize outcomes after CABG. Such developments include 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. In addition, this review represents a framework for future studies by summarizing the areas that need more rigorous clinical (randomized) evaluation.

Keywords Coronary artery bypass grafting • Off-pump • Anaortic • Minimally invasive • Hybrid revascularization • Arterial grafting • Endoscopic vein harvesting • Epiaortic scanning • Graft flow measurement • Secondary prevention • Guidelines • Heart team

Introduction

Coronary artery bypass grafting (CABG) was first introduced in the mid-1960s and evolved rapidly as the standard of care for patients with extensive coronary artery disease.[1] However, the introduction of percutaneous coronary intervention (PCI) led to a reconsideration of therapeutic strategies.[2] Improvements in stent design, adjuvant medical therapy and technical skills quickly turned PCI into a very attractive alternative treatment option for patients with acute coronary syndromes and less complex coronary disease.[3–7] The broader use of PCI is reflected by declining CABG rates over the last decades,[8] even though recent long-term results from the SYNTAX,[9] ASCERT,[10] and FREEDOM[11] trials showed significantly better survival rates after CABG than after PCI. Despite converging outcomes between the two treatments in select patient populations, coronary surgery currently remains the standard of care for most elective patients, including those with diabetes and/or complex left main or three-vessel disease.[9,12]

Although short-term outcomes have dramatically improved over the first 50 years, surprisingly, technical aspects of the CABG procedure did not change significantly. Particularly in an era of increasing and sometimes overuse of PCI, several aspects of CABG should be improved to further optimize short- and long-term outcomes, while at the same time improving the appeal of CABG which is regarded as an overly invasive attractive treatment option by some. A number of advancements have been proposed, but adoption rates for these techniques are low.

This review provides a summary of how CABG outcomes can be optimized by adoption of new developments. These developments include off-pump, clampless/anaortic, and minimally invasive CABG

*Corresponding author. Tel: +31 (0)10 70 35784, Fax: +31 (0)10 70 33993, Email: a.kappetein@erasmusmc.nl

with or without extending to hybrid procedures, arterial revascularization, endoscopic vein harvesting, intraprocedural epiaortic scanning and graft flow assessment and improved secondary prevention measures. Furthermore, this review represents a framework for future studies by summarizing the areas that need more rigorous clinical evaluation.

Operative techniques

Off-pump surgery

In 2001, ~25% of CABG procedures were performed off-pump.[13] In the Western world, the contemporary rate of off-pump CABG procedures is ~20%, while in Asia the majority of procedures is performed off-pump.[14] Theoretically off-pump CABG could reduce morbidity—particularly stroke—and even mortality by avoiding cardiopulmonary bypass that is associated with formation of microemboli, an increased blood–brain barrier permeability and aortic manipulation during cross-clamping and cannulation.[15]

Numerous risk-adjusted studies have found that the off-pump technique appears favourable in terms of both hard and surrogate endpoints.[16,17] A meta-analysis of propensity score-adjusted studies that included >120 000 patients demonstrated the superiority of the off-pump technique with respect to 11 selected short-term outcomes, particularly for mortality as the most important one (OR = 0.69; 95% CI: 0.60–0.75; $P < 0.0001$) and for stroke (OR = 0.42; 95% CI: 0.33–0.54; $P < 0.0001$).[18] In addition, the most recent meta-analysis of 59 randomized trials on a total of 8961 patients comparing on-pump with off-pump CABG demonstrated a 30% (95% CI: 1–51%) relative risk reduction for stroke.[13] However, some studies have shown increased rates of mortality and repeat revascularization during the follow-up;[19,20] probably caused by reduced graft patency after off-pump vs. on-pump CABG.[21,22] Although single-centre prospective angiographic studies have shown similar excellent graft patency rates with off-pump and on-pump CABG,[23] the 1-year results from the ROOBY trial showed a 27% higher risk of graft occlusion in the off-pump group (95% CI: 9–48%); graft patency was 87.8% in the on-pump and 82.6% in the off-pump patients ($P < 0.001$).[24] These results were criticized for the lack of sufficient experience that contributing surgeons had with off-pump procedures.[25] However, several other trials involving highly experienced surgeons and a meta-analysis pointed in a similar direction as the findings from the ROOBY trial.[25–27] Off-pump CABG has also been associated with increased rates of incomplete revascularization, and could result in reduced long-term survival.[28]

The CORONARY trial showed no benefit of off-pump CABG over on-pump CABG at 30 days or 1 year in 4752 randomized patients.[29,30] Although there appears to be a significant benefit of off-pump over on-pump CABG in patients at high-operative risk[31] and in patients with atherosclerotic aortas,[32] the hypothesis that off-pump CABG is beneficial for 'all-comers' may be too optimistic.[33] Despite the encouragement to a general use of off-pump techniques, it has been recommended specifically for high-risk patients.[34] However, even this recommendation was recently challenged by the results of the GOPCABE trial, which did include elderly higher-risk patients ($n = 2539$) but was still unable to confirm superiority of the off-pump over the on-pump approach in this subset of patients.[35] Patient selection is critical, since the majority of patients can safely and efficiently undergo on-pump CABG without the risk of increased 30-day repeat revascularization rates associated with off-pump procedures in the latest trials.[29,30,35] It may therefore be cumbersome for trainees to gain experience in a procedure with a steep learning curve that is infrequently performed only in selected patients.

It is worth noting that although evidence for a survival benefit of off-pump CABG is inconsistent across the peer-reviewed literature, a preponderance of evidence suggests that it is associated with significant reductions in transfusion requirements, prolonged ventilation, ICU and hospital length of stay, new renal failure, stroke/neurocognitive decline and other clinical endpoints.[36]

Clampless/anaortic off-pump surgery

If off-pump CABG is performed, the degree of aortic manipulation should be reduced to a minimum. The benefit of off-pump CABG may be limited unless partial clamping of the aorta is avoided. Aortic clamping produces a significantly higher number of solid microemboli on transcranial Doppler than clampless surgery and can therefore lead to procedural stroke.[37] It is to note that in most trials, including the major randomized trials, off-pump CABG was not performed using an anaortic technique, the major driver for reducing stroke.

The number of studies that compared clampless CABG to 'regular' CABG with clamping is limited (*Table 1*). In the absence of a large randomized comparison, Börgermann *et al.*[38] used propensity matching to compare mortality and stroke rates between patients who underwent clampless off-pump or conventional CABG. In the propensity-matched cohort of 395 pairs, clampless off-pump CABG reduced rates of death (OR = 0.25, 95% CI: 0.05–1.18; $P = 0.080$) and stroke (OR = 0.36, 95% CI: 0.13–0.99; $P = 0.048$). More specifically, one of the largest studies to date found significantly lower stroke rates after off-pump than on-pump CABG, if an all-arterial 'no touch' technique was applied or when the proximal vein-graft anastomoses were performed clampless using the HeartString device (Guidant, Indianapolis, USA).[39] This evidence is complemented by a meta-analysis including 11 398 patients that showed that the absence of aortic manipulation was associated with a significant reduction of neurological complications (OR = 0.46, 95% CI: 0.29–0.72; $P = 0.0008$).[40]

Minimally invasive coronary artery bypass grafting/hybrid revascularization

One of the drawbacks of CABG remains its invasiveness, even without the use of cardiopulmonary bypass. Quality of life scores at 30 days and patient treatment satisfaction surveys throughout the first 6 months are significantly higher after PCI than after CABG.[41] Moreover, CABG is sometimes referred to as a procedure where 'the chest is cracked open', which from a patient's perspective presents a frightening prospect of postoperative pain and extended rehabilitation. As a result, patients often prefer PCI to CABG because of 'temporal discounting', i.e. disproportionally emphasize short-term results even though CABG has been shown to be superior to PCI with respect to long-term survival and angina relief.[10,41–44]

Table 1 Studies comparing clampless or 'aortic no touch' off-pump coronary artery bypass grafting with conventional off-pump or on-pump surgery

Author (year)	Inclusion	Design	No. of patients	Use of devices	Unadjusted 30-day outcomes			Comment
					Mortality	Stroke	Perioperative MI	
Clampless								
Lev-Ran (2004)	2000–02	Retrospective	103 vs. 57 with clamp	No	2.9 vs. 7%	0 vs. 5.3%	3 vs. 5%	Side clamping an independent predictor of stroke or mortality: OR = 6.28, 95% CI: 1.39–28.4; $P = 0.017$
Kempfert (2008)	2003–05	RCT	51 vs. 48 with clamp	Connector: PAS-Port	0 vs. 2.1%	—	—	
Manabe (2009)	2004–07	Retrospective	109 vs. 185 no touch vs. 241 with clamp	HeartString ($n = 81$) Enclose II ($n = 28$)	1.8 vs. 1.1 vs. 1.2%	2.8 vs. 0.5 vs. 0.8%	—	
El Zayat (2012)	2009	RCT	29 vs. 28 with clamp	HeartString	0 vs. 0%	0 vs. 6.9%	—	
Emmert (2012)	1999–2009	Prospective	507 vs. 524 with clamp	HeartString	1.8 vs. 2.5%	0.4 vs. 2.9%	1.5 vs. 3.1%	Clampless off-pump CABG was a significant predictor of reduced stroke in a propensity-score-adjusted analysis: OR = 0.04, 95% CI: 0.003–0.48
Börgermann (2012)	2009–10	Prospective	395 vs. 887 with clamp	Connector: PAS-Port ($n = 310$)	3.3 vs. 7.6%	—	—	In a propensity-matched cohort of 395 pairs, clampless off-pump CABG was a predictor of less death (OR = 0.25, 95% CI: 0.05–1.18; $P = 0.080$) and stroke (OR = 0.36, 95% CI: 0.13–0.99; $P = 0.048$)
Aortic no touch								
Patel (2002)	1997–2001	Prospective	597 vs. 520 off-pump with manipulation vs. 1210 on-pump	No	1.5 vs. 1.0 vs. 2.5%	0.5 vs. 0.4 vs. 1.6%	—	Aortic manipulation was not a significant predictor of neurological outcome in off-pump patients
Calafiore (2002)	1998–2000	Retrospective	1533 vs. 3290 any manipulation (on- or off-pump)	No	—	0.2 vs. 1.4%	—	In multivariable stepwise logistic regression, any aortic manipulation was associated with an OR of 8.4 (95% CI: 2.4–28.9; $P = 0.0008$) for stroke
Kim (2002)	1998–2001	Prospective	222 vs. 123 'regular' off-pump vs. 76 on-pump	No	0.9 vs. 2.4 vs. 2.6%	0 vs. 0.8 vs. 3.9%	1.4 vs. 5.7 vs. 6.6%	
Leacche (2003)	1996–2001	Retrospective	84 vs. 556 'regular' off-pump	No	1.6 vs. 1.7%	0 vs. 1%	1.3 vs. 1.8%	
Kapetanakis (2004)	1998–2002	Retrospective	476 vs. 2527 moderate vs. 4269 extensive aortic manipulation off-pump	No	1.5 vs. 1.9 vs. 2.1%	0.8 vs. 1.6 vs. 2.2%	1.1 vs. 0.7 vs. 0.5%	No touch surgery was independently associated with reduced stroke when compared with extensive (OR = 1.7, 95% CI: 1.11–2.48; $P < 0.01$) and even moderate aortic manipulation (OR = 1.8, 95% CI: 1.15–2.74; $P < 0.01$). Propensity-matched analysis failed to show similar findings
Lev-Ran (2005)	2000–03	Retrospective	471 vs. 229 off-pump with side-clamp	No	2.1 vs. 2.6%	0.2 vs. 2.2%	1.4 vs. 1.5%	The use of side-clamping was an independent predictor of stroke: OR = 28.5, 95% CI: 2.27–333.3; $P = 0.009$
Bolotin (2007)	2000–01	Prospective	110 vs. 216 on-pump CABG	No	2.7 vs. 1.9%	0 vs. 2.3%	0.9 vs. 1.4%	

Continued

Table 1 *Continued*

Author (year)	Inclusion	Design	No. of patients	Use of devices	Unadjusted 30-day outcomes Mortality	Stroke	Perioperative MI	Comment
Vallely (2008)	2002–06	Prospective	1201 vs. 557 off-pump with aortic manipulation	No	1.4 vs. 1.3%	0.3 vs. 1.1%	0.6 vs. 0.4%	No touch surgery was an independent predictor of reduced rates of neurological events: OR = 0.23, 95% CI: 0.06–0.92; $P = 0.037$
Misfeld (2010)	2002–07	Retrospective	1346 vs. 600 'regular' off-pump vs. 1753 on-pump	No	1.0 vs. 1.0 vs. 2.3%	0.1 vs. 0.5 vs. 0.9%	0.5 vs. 0.5 vs. 0.6%	Compared to no touch off-pump CABG, on-pump CABG (OR = 12.3, 95% CI: 2.9–52.2; $P = 0.0006$) and 'regular' off-pump CABG (OR = 7.0, 95% CI: 1.4–35.0; $P = 0.018$) were independent predictors of neurological complications
Emmert (2011)	2004–09	Prospective	1365 vs. 567 off-pump with clamp	HeartString	1.8 vs. 1.6%	0.7 vs 2.3%	0.9 vs. 1.9%	No touch clampless off-pump CABG was a significant predictor of reduced stroke in a propensity score-adjusted analysis: OR = 0.39, 95% CI: 0.16–0.90; $P = 0.04$

CABG, coronary artery bypass grafting; MI, myocardial infarction; OR, odds ratio.

Less invasive surgical techniques may present an attractive alternative; minimally invasive direct coronary artery bypass (MIDCAB) does not require sternotomy and is therefore more acceptable to patients than conventional CABG.[45] The left minithoracotomy incision is smaller, the risk of scarring is less, and risks of deep sternal wound infection and problems with sternum healing are omitted. Although MIDCAB may be associated with slightly increased pain postoperatively due to spreading of the ribs, the length of stay is markedly reduced and there is an early postoperative quality of life benefit over conventional CABG.[46–48] MIDCAB was shown to be as safe and efficient as off-pump CABG, while reducing the recovery time.[49] Holzhey *et al.*[50] recently reported long-term results from their single-centre experience on 1768 patients. Five- and 10-year survival was 88.3 and 76.6%, respectively. The rates of freedom from major adverse cardiac or cerebrovascular events and angina were of 85.3 and 70.9%, respectively.

Exposure during MIDCAB is largely limited to the left anterior descending (LAD) artery and eventually diagonal branches, and therefore almost exclusively performed in patients with isolated LAD stenosis or occlusion. An open left internal mammary artery (IMA) graft to the LAD is without doubt the single most important conduit that offers a prognostic benefit based on its proven long-term patency and improved survival. Patients with multivessel disease—especially at younger age—also derive a survival benefit from total arterial grafting with bilateral IMA (BIMA) grafts.[51] The added benefit of a second arterial graft in older patients is less well documented;[52] however, the rate of early vein-graft failure, especially to distal targets and severely diseased small vessels, is high and ranges from 10 to 26% between 12 and 18 months after surgery.[21,53] In some patients, a hybrid procedure can combine the benefits of an MIDCAB—providing a left IMA (LIMA) graft to the LAD—and stenting of the circumflex and/or the right coronary artery. This type of management may yield results similar to those of a full CABG procedure,[54] but randomized trials are still lacking (*Table 2*). The hospitalization costs of hybrid revascularization are similar to the costs of off-pump CABG, but the time to return to work is shorter and patient satisfaction higher.[55] Halkos *et al.*[56,57] showed that survival after hybrid revascularization at 5-year follow-up was comparable with off-pump CABG in patients with left main disease (88.6 vs. 83.4%, respectively; $P = 0.55$) and in patients with multivessel disease (86.8 vs. 84.3%, respectively; $P = 0.61$) (*Figure 1*).

Complete revascularization in patients with multivessel disease by minimally invasive CABG can also be achieved via a totally endoscopic coronary artery bypass (TECAB) procedure,[58] by combining an endoscopic with an open approach,[59] or by a hybrid endoscopic and percutaneous procedure.[60] Such procedures are only performed in selected patients at specialized centres and require extensive operating times. Earlier series reported unsatisfactory patency results, but with the evolution of better endoscopic stabilizers the results from these highly experienced centres are similar to conventional CABG with a reported mortality rate of 1–2% [58–61] and a 5-year survival in the range of 85–95%.[60–62]

Adoption of minimally invasive CABG procedures has been slow. For MIDCAB, this may be explained in part by the low incidence of isolated proximal LAD stenosis[63] and also by the high technical demands of this procedure. Hybrid revascularization for multivessel disease, theoretically, has a much larger target population. However, a systematic search of the literature shows that the accumulated evidence is based on small non-randomized studies comprising just over 1000 patients in total (*Table 3*). Between October 2003 and April 2010, only 174 patients underwent hybrid revascularization in the USA.[56,57] Apart from technical issues, the low-adoption rate is partly due to logistic reasons; the staging of two procedures in a (hybrid) operating rooms, and/or catheterization laboratory, and the administration or discontinuation of antiplatelet therapy. A survey performed in 2002 indicated that 80% of US surgeons perform less than five MIDCAB procedures annually.[64] When asked about hybrid procedures, only 10% of surgeons were in favour. In contrast, 50% of 180 cardiologists were in favour of hybrid revascularization. Yet, only two cardiologists (1.1%) had referred patients for MIDCAB (with or without PCI). Stronger evidence to support a recommendation for hybrid revascularization is expected from a number of currently on-going registries, the largest of which is the Hybrid Revascularization Observational Study (NCT01121263) that includes patients throughout the USA and is sponsored by the National Heart, Lung, and Blood Institute (NHLBI).

Table 2 Reasoning supporting hybrid revascularization

Patients with double vessel disease and chronic total occlusion of the LAD
Patients with multivessel disease and an indication for CABG requiring complete revascularization in whom a full sternotomy is contraindicated or not desired
Patients with multivessel disease with a dominant LAD or complex proximal LAD lesion morphology and poor surgical targets in the distal CX or RCA territory amenable for PCI
Patients with multivessel disease with an indication for PCI (SYNTAX score <22) or in clinical trials comparing hybrid revascularization with PCI or CABG (SYNTAX score >23)
Patients with multivessel disease undergoing emergent PCI of a culprit lesion of a CX or RCA lesion (in the setting of STEMI, non-STEMI, or ACS) with a staged surgical revascularization of the LAD

Arterial grafting

The use of one IMA graft, most often the left IMA anastomosed to the LAD combined with venous conduits represents the standard therapy for patients undergoing CABG.[65,66] However, venous bypass grafts tend to fail: a recent study by Kim *et al.*[67] found that 11.8% of saphenous vein grafts failed within 7 days, which is similar to the failure rate reported by FitzGibbon *et al.*[68] Therefore, BIMA grafting should be strongly considered in patients with multivessel coronary disease, because BIMA grafting is associated with reduced mortality during the first year post-surgery and during the long-term follow-up.[69] A meta-analysis of seven pooled studies with 11 269 single and 4693 bilateral IMA grafts demonstrated that BIMA was associated with a reduced risk for death: HR = 0.81 (95% CI: 0.70–0.94).[51]

In the Arterial Revascularization Trial (ART), the only randomized trial to date comparing BIMA and single IMA (SIMA), 3102 patients were randomized in 28 centres in 7 countries.[70] Mortality rates at 30 days were 1.2% in both groups, and 2.3 vs. 2.5% at 1-year for SIMA and BIMA groups, respectively. There were also no differences in the incidence of stroke, MI, and repeat revascularization. While the use of a second IMA graft added 23 min to the operative procedure which in itself took 3–4 h, the trial clearly demonstrated that BIMA grafting was as safe as SIMA grafting, even though the risk of a need for later sternal reconstruction was increased: relative risk 3.24 (95% CI: 1.54–6.83). An extended follow-up (for up to 10 years) is expected for this study and will hopefully determine whether survival with BIMA grafts is indeed superior. The trial, however, also

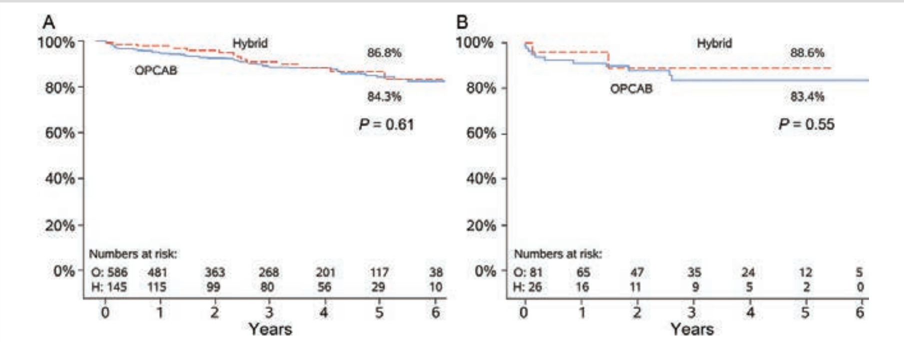

Figure 1 Long-term survival of hybrid revascularization in comparison with off-pump coronary artery bypass grafting. A comparison between treatment strategies shows no differences in 5-year survival in patients with multivessel disease (*A*), nor in patients with left main disease (*B*). Adapted with permission from Halkos *et al.*[56,57]

Table 3 Systematic review of studies evaluating hybrid revascularization

Author (year)	Inclusion	Design	No. of patients	Type of lesions	Strategy	30-day outcomes			Long-term outcomes		
						Conversion	Death	Revascularization	Mean follow-up	Mortality	Revascularization
Lloyd (1999)	1996–98	Prospective	18	Multivessel	Simultaneous, $n = 4$ PCI following MIDCAB, $n = 14$	0	0	5.6%	At 18 months	0	5.6%
Zenati (1999)	1996–98	Retrospective	31	Multivessel	Staged	0	0	3.2%	11 months	0	9.6%
Wittwer (2000)	1996–99	—	35	Multivessel	PCI following MIDCAB	0	0	0	11 ± 8 months	0	6.5% (of 31 patients)
de Canniere (2001)	1997–97	Retrospective	20	Two-vessel	MIDCAB following PCI, $n = 9$ PCI following MIDCAB, $n = 11$	0	0	0	At 2 years	0	15%
Cisowski (2002)	1999–2001	Retrospective	50	Two-vessel	PCI following MIDCAB	0	0	0	—	0	12.7%
Riess (2002)	1997–2001	Retrospective	57	Multivessel	PCI following MIDCAB	0	0	0	101 ± 38 weeks	1.8%	—
Stahl (2002)	—	Retrospective	54	Multivessel	PCI following MIDCAB, $n = 35$ MIDCAB following PCI, $n = 19$	0	0	0	12 months	0	—
Davidavicius (2005)	2001–03	Prospective	20	Multivessel	MIDCAB following PCI, $n = 14$ PCI following MIDCAB, $n = 6$	0	0	0	19 ± 10 months	0	0
Katz (2006)	—	Prospective	27	Two-vessel	Simultaneous, $n = 4$ PCI following MIDCAB, $n = 12$ MIDCAB following PCI, $n = 11$	0	0	0	At 3 months	0	18.5%
Us (2006)	2002–04	Prospective	17	Multivessel	MIDCAB following PCI	0	0	0	21 ± 7 months	0	17.6%
Gilard (2007)	2000–…	Prospective	70	Multivessel	MIDCAB following PCI	0	1.4%	2.9%	33 months	1.4%	0
Holzhey (2008)	1996–2007	Retrospective	117	Multivessel	Simultaneous, $n = 5$ PCI following MIDCAB, $n = 59$ MIDCAB following PCI, $n = 53$	0	1.9%	1.9%	208 patient-years	92.5% at 1 year 84.8% at 5 years	—
Kiaii (2008)	2004–07	Prospective	58	Two-vessel	Simultaneous	1.7%	0	0	20 months	0	—
Kon (2008)	2005–06	Prospective	15	Multivessel	Simultaneous	0	0	0	At 1 year	0	6.7%
Gao (2009)	2007–08	Prospective	10	Multivessel	PCI following MIDCAB	0	0	0	5 months	0	0
Vassiliades (2009)	2003–07	Prospective	91	Multivessel	Staged	2.0%	0	0	—	94% at 3 years	5.5% at 1 year
Zhao (2009)	2005–07	Retrospective	112	Multivessel	Simultaneous	N/A	2.6%	0	—	—	—
Delhaye (2010)	2006–08	Prospective	18	Multivessel	PCI following MIDCAB	0	0	0	At 1 year	0	5.6% (TVR)
Halkos (2011)	2003–10	Retrospective	27	LM	PCI following MIDCAB	0	0	0	Median 3.2 years	88.6% at 5 years	7.4%
Halkos (2011)	2003–10	Retrospective	147	Multivessel	Simultaneous $n < 10$ Staged for the remaining	0	0.7%	0	Median 3.2 years	86.8% at 5 years	12.2% 8.8% (TVR)
Hu (2011)	2007–09	Retrospective	104	Multivessel	Simultaneous	1.0%	0	0	18 months	0	1.9%
Rab (2012)	2003–…	Retrospective	22	LM	PCI following MIDCAB	0	0	0	39 ± 23	4.5%	0

The PubMed database was searched from its inception through June 2012, which yielded the included studies.
CABG, coronary artery bypass grafting; MIDCAB, minimally invasive coronary artery bypass; N/A, not applicable; LM, left main; PCI, percutaneous coronary intervention; TVR, target vessel revascularization.

highlighted the difficulties with BIMA grafting; 16.4% of patients randomized to BIMA did not receive the allocated treatment compared with 3.3% patients not receiving SIMA grafting.[71]

The proportion of procedures that are performed with IMA grafts is increasing, but a large inter-hospital variance remains. The use of at least one IMA can be as low as 45–65% in some centres, failing to provide optimal care to patients.[72] It is disconcerting that in the USA the use of BIMA grafts was only 4.0% among 541 368 patients.[72] The respective figures are 12% in Europe and 30% in Japan.[73] Among 1541 procedures performed in the SYNTAX trial and registry, 97.1% included a single arterial conduit while 22.7% received a second IMA graft. Owing to the technically more challenging and time-consuming nature of BIMA grafting, the fear of higher morbidity (i.e. sternal wound complications) and mortality, and the absence of clear randomized data showing a survival benefit, some surgeons may be reluctant to use BIMA grafts. Nevertheless, in order to improve CABG outcomes, the use of both IMA grafts should be considered more frequently.

When unilateral IMA grafting is performed, the saphenous vein is the most frequently chosen conduit for additional graft(s). Because of high failure rates of venous grafts, the radial artery has been investigated as an alternative. The long-term results from the RSVP trial ($n = 142$) suggested favourable radial artery graft patency rates.[74] More recent 5-year results from the larger randomized RAPS trial ($n = 510$) showed that, compared with the saphenous vein grafts, the radial artery had lower rates of functional graft occlusion (12.0 vs. 19.7%, respectively; $P = 0.03$) and complete occlusion (8.9 vs. 18.6%, respectively; $P = 0.002$), although the string sign was observed more frequently in radial artery grafts (3.4 vs. 0%, $P = 0.01$).[75] Several large observational studies have confirmed excellent graft patency and have even reported superior long-term survival rates,[76,77] also after applying propensity matching.[78–80] However, widespread utilization of the radial artery has been hampered by concerns regarding vessel spasm, graft atherosclerosis, and unfavourable results from a number of studies. The largest trial ($n = 733$) to date found no differences in graft patency at 1-year follow-up;[81] similar results have been reported from a number of observational studies.[79,82] At least one study has shown radial artery graft patency to be significantly worse than right IMA graft patency.[83] To ensure good graft patency, the radial artery should be used preferably in high-grade lesions.[84] Data from the STS database suggest that only 9% of CABG procedures are performed with the radial artery.[85]

A higher rate of disease progression to total occlusion in native coronaries has been reported after CABG than after PCI.[86] Patent arterial grafts, by virtue of their nitric oxide secreting properties, may protect against future atherosclerotic lesions. Therefore, arterial grafting can be viewed as a preventive measure that goes beyond pure treatment.[87,88]

Endoscopic vein harvesting

Traditional open saphenous vein-graft harvesting requires a large incision, resulting in a large scar and a risk of postoperative wound complications. Endoscopic vein harvesting was introduced in the mid-1990s as an alternative.[89] This method has the advantages of reduced scarring, less pain, decreased postoperative complications, and shorter length of stay.[90]

Several randomized studies and meta-analyses have shown that endoscopic harvesting significantly reduces rates of wound infection, wound dehiscence, and overall complications.[91] However, subgroup analyses from the PREVENT IV and ROOBY randomized trials suggested that endoscopic vein harvesting resulted in reduced graft patency during the follow-up.[92,93] In PREVENT IV, there even were significantly higher rates of death. Although this is of potential concern, long-term follow-up analyses from large observational studies have not been able to confirm that clinical outcomes are worse in patients that underwent endoscopic vein harvesting.[94,95] A recent study that included 235 394 patients with 3-year follow-up showed no increased risk of mortality [adjusted HR = 1.00 (95% CI: 0.97–1.04) $P < 0.99$] or the composite of mortality, myocardial infarction, and repeat revascularization [adjusted HR = 1.00 (95% CI: 0.98–1.05) $P = 0.34$].[95]

Current data indicate a paradigm shift towards endoscopic harvesting as opposed to open vein graft harvesting. Between 2003 and 2008, 52% of grafts were harvested endoscopically at 989 sites in the USA; in 2008, the rate was already 70%.[95] Trainees in the USA now almost exclusively learn how to perform endoscopic harvesting.[90] It is important to start using this technique at an early stage, especially because inexperienced surgeons are known to cause significantly more vein injury.[96] The International Society of Minimally Invasive Cardiothoracic Surgery Consensus statement has given a Class IB recommendation for endoscopic vein harvesting.[97] Still, endoscopic harvesting is performed in only a minority of cases in Europe. A recent single-centre study showed that only 12.4% of veins were harvested endoscopically between 2008 and 2010.[98] Unfortunately, large-scale real-world data from European centres are scarce.

Intra-operative assessments

Epiaortic scanning

Atherosclerosis of the ascending aorta is present in >50% of patients undergoing CABG.[99] Aortic atherosclerosis was found to be a significant predictor of postoperative neurological events and renal failure, both caused by atheroembolism.[100,101] Palpation of the aorta is frequently employed prior to cannulation and/or aortic manipulation, but the sensitivity of this technique is very limited.[102] Therefore, imaging is advocated to detect atherosclerosis if an anaortic technique cannot be applied. Depending on the findings, the operative technique can be modified as needed.[103] Both transoesophageal echocardiography and epiaortic ultrasonography were introduced as methods for detecting severe atherosclerosis. While transoesophageal echocardiography severely underestimates the degree of atherosclerosis, epiaortic scanning is an easy, safe and efficient procedure and is preferred.[104]

Epiaortic scanning is not routinely used probably because of the cost of the machine (>€100 000) and the fact that there have been no direct randomized comparisons between CABG with and without epiaortic scanning that demonstrate a benefit. Such a study would be problematic because of the large sample size required. However, although one small study indicated no reduction in transcranial Doppler-detected cerebral emboli,[105] several studies have suggested that early postoperative stroke is significantly reduced when the operative technique is modified in accordance with results of epiaortic scanning.[106–109] Wareing *et al.*[110] reported that in 14% of elderly patients undergoing cardiac procedures (CABG in 89%), the site of aortic cannulation and/or clamping, the sites for attaching vein grafts, and/or the sites for instillation of cardioplegic solution were altered. The precise rates of such modifications provided in the literature vary, between 4 and 31%.[99] A recent study by Daniel *et al.*[111] showed that epiaortic scanning was increasingly performed from 2002 to 2009 (45 and 90%, respectively) and coincided with less frequent aortic clamping (98 and 73%, respectively).

Graft flow measurement

Data from the PREVENT IV trial showed a suboptimal rate of saphenous vein-graft failure after on- and off-pump CABG at 1 year;[112] a meta-analysis reported a failure rate of ~5 and 25% at 3 and 12 months, respectively.[113] Several mechanisms of graft failure have been described. Early graft failure can occur as a result of anastomotic problems, limited outflow, graft kinking upon chest closure, and thrombosis. Late failure is the result of thrombosis and processes of intimal hyperplasia and atherosclerosis. Intra-operative graft assessment has been introduced to evaluate grafts and identify anastomotic problems and limited outflow. Disturbingly, Balacumaraswami *et al.*[114] demonstrated that intra-operative graft assessment identified 9% of grafts with inadequate flow in 25% of CABG patients, which led to revision in 3% of grafts and 8% of patients. Multiple techniques for intra-operative graft assessment have been proposed: coronary angiography, transit time flow measurement (TTFM), high-frequency epicardial echocardiography, thermal coronary angiography and intra-operative fluorescence imaging (IFI).[115] Although angiography is thought to be the best and most reliable method for assessing flow,[116] the infrastructure required for coronary angiography is rarely available in standard operating rooms. Wider implementation of hybrid operating rooms could potentially facilitate the use of coronary angiography. Currently, intra-operative graft assessment is most frequently performed by TTFM or IFI.

Both TTFM and IFI have strengths and weaknesses and have been criticized for their inability to identify grafts with minor abnormalities that present a risk for failure. Furthermore, inconsistent and variable measurements may lead to unnecessary graft revisions.[114] Two parameters, graft function and anatomy, are required for the complete assessment of bypass grafts. Transit time flow measurement assesses function and can very accurately detect truly poor and truly good grafts (true positives, true negatives), but there is an issue with respect to detecting poor grafts with a low pulsatility index (PI) (false negatives). False positives (good graft, high PI) rarely occur. Intra-operative fluorescence imaging evaluates anatomy but is associated with more inter-observer error than standard angiography. Comparisons between TTFM and IFI suggest that IFI is more sensitive.[113,114,117] Transit time flow measurement combined with epicardial ultrasonic scanning is a recently introduced approach that may provide both a functional as well as anatomic assessment.

Despite issues, the clinical value of TTFM has been demonstrated in studies that found that TTFM predicted graft failure at 3, 6, and/or 12 months post-CABG.[118–120] Inadequate graft flow as defined by PI >5 on TTFM was found to be an independent predictor of major adverse cardiac events, operative death in particular.[121] No studies have yet explored the impact of IFI measurements on clinical outcomes during the follow-up. In general, randomized comparisons between CABG with and without graft flow measurement remain absent. Such studies would be required to evaluate the true benefit their routine intra-operative use would have on early and late rates of reintervention, myocardial infarction and death. One issue that remains, however, is that long-term graft failure would still occur as caused by other mechanisms than those controlled by intra-operative graft assessment. This could be one of the reasons why surgeons doubt its clinical impact and consequently why routine use has been limited.

Secondary prevention

Apart from technical and procedural considerations, further optimization of long-term outcomes after CABG can be achieved through a strict medical regimen. Progression of atherosclerosis in the native coronary arteries continues after CABG and is associated with deterioration of left ventricular function. However, this can be prevented by the administration of antiplatelet agents,[122] β-blockers,[123] angiotensin-converting enzyme inhibitors (ACE-I),[124] statins[125,126] and fatty acids,[127] all of which have been identified as independent predictors of survival after CABG. The PREVENT IV trial found that secondary prevention medications were associated with significantly reduced rates of death or myocardial infarction after CABG.[128] Moreover, data suggest that graft patency may be better in patients taking statins,[129] fatty acids,[130] aspirin,[65] and possibly dual antiplatelet therapy.[131] Administration of secondary prevention medications has increased remarkably,[132,133] and differences between PCI and CABG have shown to converge (*Table 4*). Nevertheless, some data have shown that differences between PCI and CABG still remain and again stressed the need for further progress (*Figure 2*).[134–136]

Furthermore, the effect of lifestyle interventions on outcomes may be underestimated. A plethora of data exists on the impact of lifestyle intervention on outcomes after CABG. Van Domburg *et al.*,[137] for example, reported that patients who quit smoking had significantly improved 30-year survival when compared with persistent smokers after CABG [HR = 0.60 (95% CI: 0.48–0.72)]. Education and counselling on eliminating risk factors, healthy food choices, stress relief and exercise provide substantial benefit for patients.[138] A meta-analysis that combined 63 randomized clinical trials with follow-up data on 21 295 patients found that implementation of secondary prevention programmes significantly reduced all-cause mortality [risk ratio (RR) = 0.85 (95% CI: 0.77–0.94)] and myocardial infarction [RR = 0.83 (95% CI: 0.74–0.94)].[139] Notably, specific patient subgroups may benefit most from rigorous behavioural modifications: young (age <60 years) or old (age ≥ 75 years) patients, patients with a sedentary lifestyle and/or a smoking habit, patients with a low Mediterranean diet score and those who live alone.[140] However, data from three EUROASPIRE surveys showed that there was a clear need for more effective lifestyle management among patients with previous coronary revascularization.[141] The authors rightfully stated that treatment of coronary artery disease 'without addressing the underlying causes of the disease is futile; we need to invest in prevention'.

Initiatives should be undertaken to increase the rate of prescribing appropriate discharge medications and to emphasize the need for long-term medication compliance and lifestyle changes. In particular, home-based programmes may be efficient and more acceptable to

Table 4 Trends in the use of secondary preventive medication and the difference between coronary artery bypass grafting and percutaneous coronary intervention

	EUROASPIRE I 1995–96, $n = 9$ countries	EUROASPIRE II 1999–2000, $n = 15$ countries	EUROASPIRE III 2006–07, $n = 22$ countries
Antiplatelets (%)			
CABG	87.9	86.8	92.9
PCI	89.4	90.0	94.9
Δ	−1.5	−3.2	−2.0
Beta-blockers (%)			
CABG	56.5	68.0	90.7
PCI	61.7	73.6	84.4
Δ	−5.2	−5.6	+6.3
Blood pressure-lowering drugs (%)			
CABG	86.2	90.1	98.7
PCI	87.4	91.3	95.9
Δ	−1.2	−1.2	+2.8
Lipid-lowering drugs (%)			
CABG	36.7	67.6	90.5
PCI	42.2	69.9	89.4
Δ	−5.5	−2.3	+1.1

Data from Kotseva *et al.*[133]
CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

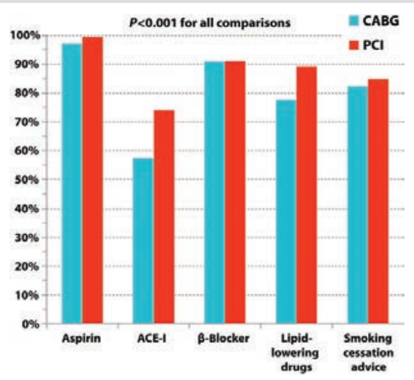

Figure 2 Difference in secondary prevention measures after percutaneous coronary intervention and coronary artery bypass grafting. Data from Hiratzka *et al.* [134] ACE-I, angiotensin-converting enzyme inhibitor; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

patients—with the additional benefit of lower costs.[142] Such quality improvement programmes can be easily instated and could potentially improve patient care significantly.

Decision-making

Despite the potential for further optimization of CABG outcomes, PCI will remain an excellent alternative in specific patients. Evidence suggests that there is overuse, underuse and inappropriate selection of revascularization strategies.[143] Inappropriate use and underuse may partly explain the preferences expressed by patients,[144] who prefer less invasive techniques with minimized pain over the long-term prospect of improved survival. In that respect, MIDCAB or hybrid procedures may present an alternative, but often patients are not even informed about the survival advantage with CABG.[145] Naturally, if two treatments are considered to produce similar results, patients will opt for the least invasive.

Reflecting on the current revascularization guidelines, recent trial results and weighting risk–benefit ratios of (new) developments, *Figure 3* provides a proposal for a decision-tree for revascularization. The myriad of treatment options emphasize the need for targeted patient selection, and the mix of surgical and interventional therapies provides rationale for multidisciplinary Heart Team decision-making to discuss all potential treatment options and obtain informed consent. Clinical cardiologists, interventional cardiologists and cardiovascular surgeons should convene on a regular basis to recommend the most appropriate treatment strategy for individual patients.[143,146] The importance of a Heart Team was once more stressed in the SYNTAX trial[147] and was subsequently included in the European and American guidelines.[3,148] Practice may be different across centres and countries, and a local protocol should be established to define patient populations that are candidates for certain

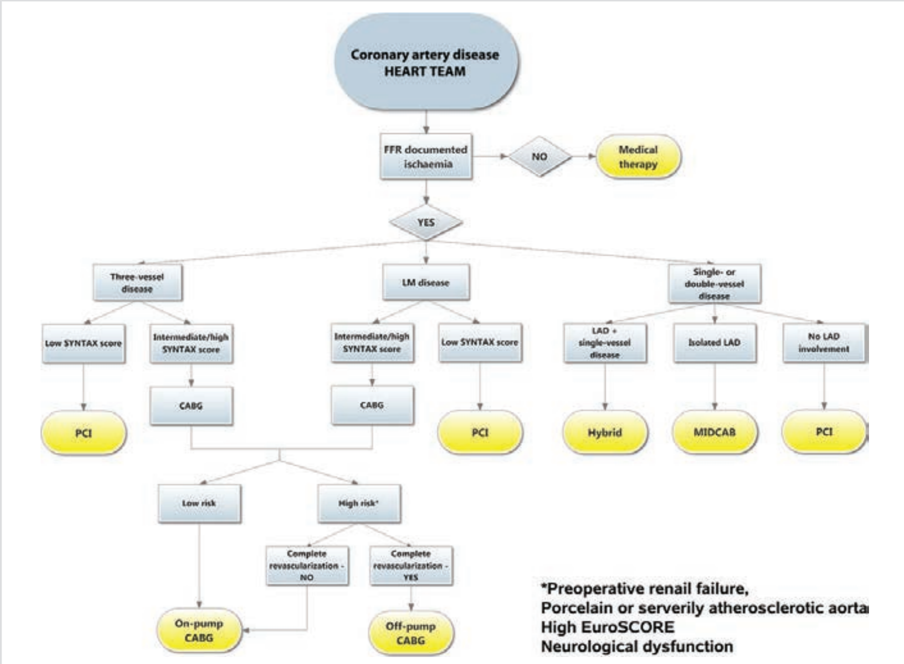

Figure 3 Proposal for a decision-tree for revascularization. Some of these recommendations have not yet been validated and still require randomized evaluation. CABG, coronary artery bypass grafting; LAD, left anterior descending; LM, left main; MIDCAB, minimally invasive coronary artery bypass; PCI, percutaneous coronary intervention.

therapies. The various pros and cons of surgical revascularization strategies should then be considered by the Heart Team (*Table 5*).

Future studies

Rigorous evaluation of potential advancements remains crucial before they are introduced on a wide scale. Even an extensive body of evidence supporting some interventions is not necessarily sufficient to provide evidence-based recommendations. This is exemplified by the >60 randomized trials comparing off-pump with on-pump surgery:[13,30,35] a benefit of off-pump CABG has been suggested in many studies that included different patient populations. Nevertheless, the two latest and largest randomized trials that included low- and high-risk patients found no difference between the two treatment options.[30,35]

In contrast, data on some new therapeutic strategies remain scarce, but the existing data may demonstrate excellent safety and efficacy. Such results often represent outcomes from highly selected patients treated by experienced surgeons in high-volume centres. This introduces a bias; the generalizability of such results is limited and caution is advised. An example of this is the evaluation of TECAB procedures.

Percutaneous coronary intervention vs. coronary artery bypass grafting studies

Continuous evaluation of PCI vs. CABG calls for a specific focus on new developments in both interventions. For PCI patients, new stents will become available and the use of fractional flow reserve to assess the need and completeness of revascularization is emphasized.[149,150] Equivalent data on FFR-guided CABG are scarce.[151] Future studies should explore the use and differences of FFR-guided revascularization between PCI and CABG.[152] The impact of the degree of ischaemia and viability on the outcomes of both CABG and PCI in patients with stable angina is still under debate. Whether image-guided revascularization that is based on a combination of functional and anatomical imaging—for example, position emission tomography computed tomography (*Figure 4*)—can improve the outcomes as compared with the traditional occulostenotic approach warrants further trials.

Table 5 Pros and cons of different surgical revascularization techniques

	Conventional CABG	Off-pump CABG	MIDCAB	TECAB	Hybrid revascularization
Lesions	Multivessel disease (+)	Multivessel disease (+)	Isolated LAD stenosis (+/−)	Multivessel disease (+)	Multivessel disease (+)
Technical difficulty	None (+)	Moderate (+/−)	Moderate (+/−)	Difficult (−)	Moderate (+/−)
Incision	Sternotomy (−)	Sternotomy (−)	J-incision (+/−)	Endoscopic (+)	J-incision (+/−)
Cardiopulmonary bypass	Yes (−)	No (+)	No (+)	No (+)	No (+)
Procedure time	Short (+)	Prolonged (+/−)	Long (−)	Long (−)	Long (−)
Blood products	Many (−)	Less (+/−)	Few (+)	Few (+)	Few (+)
Completeness of revascularization	Complete (+)	Complete (+) or incomplete (+/−)	Complete (+) or incomplete (+/−)	Complete (+) or incomplete (+/−)	Complete (+)
Postoperative length of stay	Long (−)	Prolonged (+/−)	Short (+)	Short (+)	Short (+)
Postoperative pain	Yes (−)	Yes (−)	Yes (−)	Less (+/−)	Yes (−)
Recovery time	Long (−)	Long (−)	Short (+)	Short (+)	Short (+)
Rate of stroke	High (−)	Less (+/−)	Less (+/−)	Less (+/−)	Less (+/−)
Rate of repeat revascularization	Good (+)	Moderate (+/−)	Good (+)	Moderate (+/−)	Moderate (+/−)

The various features are scored as following: in favour of the technique (+), reasonable in favour (+/−), detrimental for the technique (−).
CABG, coronary artery bypass grafting; LAD, left anterior descending; MIDCAB, minimally invasive coronary artery bypass.

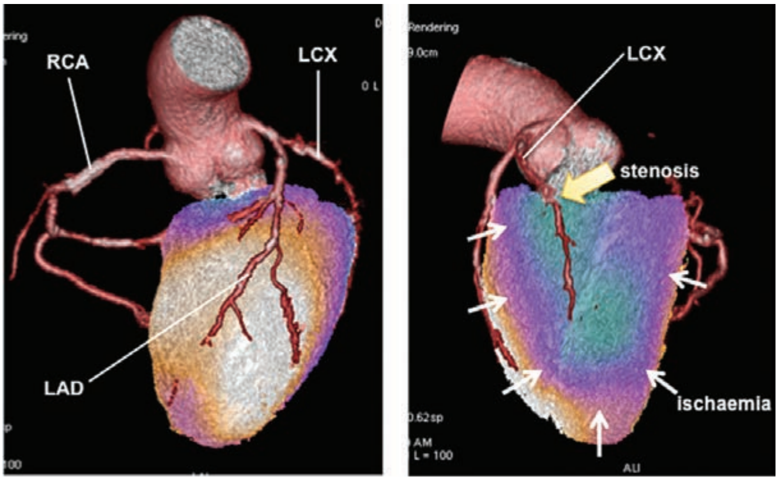

Figure 4 Functional and anatomical imaging using position emission tomography computed tomography. Case: 70-year-old male had atypical symptoms of three-vessel coronary artery disease for which he underwent stenting of the right coronary artery in 2012. Scan is positive for inferolateral wall ischaemia (purple). LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Traditionally, trials are limited to their internal validity, i.e. the results are only applicable to the included patient cohort; large 'real-world' registries are required to demonstrate whether trial results are also applicable to the general population.[10] Alternatively, an 'all-comers' trial design with none to limited patient exclusion criteria increases external validation, and presents a more balanced trade-off

Table 6 American and European guideline recommendations

	Guidelines	
	American	**European**
Off-pump CABG	'In patients with preoperative renal dysfunction (creatinine clearance <60 mL/min), off-pump CABG may be reasonable to reduce the risk of acute kidney injury' **IIb B** 'It is reasonable to consider off-pump CABG to reduce perioperative bleeding and allogeneic blood transfusion' **IIa A**	'Off-pump CABG may be considered, rather than on-pump CABG for patients with mild-to-moderate chronic kidney disease' **IIb B**
MIDCAB	No recommendation	No recommendation
Hybrid revascularization	'Hybrid coronary revascularisation is reasonable in patients with 1 or more of the following: limitations to traditional CABG, such as heavily calcified proximal aorta or poor target vessels for CABG (but amenable to PCI); lack of suitable graft conduits; unfavourable LAD artery for PCI (i.e. excessive vessel tortuosity or chronic total occlusion)' **IIa B** 'Hybrid coronary revascularization may be reasonable as an alternative to multivessel PCI or CABG in an attempt to improve the overall risk–benefit ratio of the procedures' **IIb C**	'Hybrid procedure, defined as consecutive or combined surgical and interventional revascularization may be considered in specific patient subsets at experienced centres' **IIb B**
Clampless/'no touch'	'Patients with extensive disease of the ascending aorta pose a special challenge for on-pump CABG; for these patients, cannulation or cross-clamping of the aorta may create an unacceptably high risk of stroke. In such individuals, off-pump CABG in conjunction with avoidance of manipulation of the ascending aorta (including placement of proximal anastomoses) may be beneficial' (**no formal recommendation, no level of evidence**)	No recommendation
Endoscopic vein harvesting	No recommendation	'Endoscopic vein-graft harvesting cannot be recommended at present as it has been associated with vein-graft failure and adverse clinical outcomes' (**no formal recommendation, no level of evidence**)
Epiaortic scanning	'Routine epiaortic ultrasound scanning is reasonable to evaluate the presence, location, and severity of plaque in the ascending aorta to reduce the incidence of atheroembolic complications' **IIa B**	No recommendation
Graft flow assessment	No recommendation	'Graft evaluation is recommended before leaving the operating theatre' **I C**
Arterial revascularization	'If possible, the LIMA should be used to bypass the LAD artery when bypass of the LAD artery is indicated' **I B** 'When anatomically and clinically suitable, use of a second IMA to graft the left circumflex or right coronary artery (when critically stenosed and perusing LV myocardium) is reasonable to improve the likelihood of survival and to decrease reintervention' **IIa B** 'Complete arterial revascularization may be reasonable in patients ≤ 60 years of age with few or no comorbidities' **IIb C**	'Arterial grafting to the LAD system is indicated' **I A** 'Complete revascularization with arterial grafting to non-LAD coronary systems is indicated in patients with reasonable life expectancy' **I A**

Secondary prevention	'All smokers should receive in-hospital educational counselling and be offered smoking cessation therapy during CABG hospitalization' **I A** '[Aspirin] should be initiated within 6 h postoperatively and then continued indefinitely to reduce the occurrence of SVG closure and adverse cardiovascular events' **I A** 'All patients undergoing CABG should receive statin therapy, unless contraindicated' **I A** 'β-blockers should be prescribed to all CABG patients without contraindications at the time of hospital discharge' **I C** 'ACE inhibitors and ARBs should be initiated postoperatively and continued indefinitely in CABG patients who were not receiving them preoperatively, who are stable, and who have an LVEF ≤40%, hypertension, diabetes mellitus, or CKD, unless contraindicated' **I A**	In general, an 'ABCDE' approach is proposed: 'A' for antiplatelet therapy, anticoagulation, ACE inhibition, or angiotensin receptor blockade; 'B' for beta-blockade and blood pressure control; 'C' for cholesterol treatment and cigarette smoking cessation; 'D' for diabetes management and diet; and 'E' for exercise. Several recommendations are provided with regard to lifestyle and risk factor management (e.g. counselling on physical activity and exercise training, **I A**; diet and weight control management, **I B**; smoking cessation, **I B**). 'Secondary prevention demands lifelong antiplatelet therapy with 75-325 mg acetylsalicylic acid daily' 'ACE inhibitors should be started and continued indefinitely in all patients with LVEF ≤40% and for those with hypertension, diabetes, or CKD, unless contraindicated' **I A** 'It is indicated to start and continue β-blocker therapy in all patients after MI or ACS or left ventricular dysfunction, unless contraindicated' **I A** 'High-dose lipid lowering drugs are indicated in all patients regardless of lipid levels, unless contraindicated' **I A** 'Fibrates and omega-3 fatty acids (1 g/day) should be considered in combination with statins and in patients intolerant of statins' **IIb B**

The level of evidence is shown in bold. ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; LAD, left anterior descending; LVEF, left ventricular ejection fraction; (L) IMA, (left) internal mammary artery; MI, myocardial infarction; PCI, percutaneous coronary intervention.

between internal and external validation.[153] Furthermore, reporting the experience of centres and operators will also contribute to the internal and external validity of trial results: superior outcomes in experienced centres as opposed to inexperienced centres unveils limited external validity and should restrict one from over-extrapolating trial results to real-world clinical settings.

In the SYNTAX trial a new angiographic score was validated—the SYNTAX score—for grading the complexity of coronary artery disease.[154] This score appears to be a very promising tool for deciding if PCI or CABG would be preferable. Use of the score is therefore recommended for decision-making. Recently, the SYNTAX II score was introduced and showed an improvement in guiding decision-making.[155] Yet, further validation of these hypothesis-generating data is needed and future studies should provide a larger body of evidence about the SYNTAX (II) score.

Pharmacological management of patients after PCI and CABG differs significantly and has an impact on long-term results. It would be interesting to see the results of PCI and CABG if the pharmacological management and treatment adherence after PCI and CABG would be identical.

Discussion

Broadening indications for and increasing use of PCI calls for more focus on the optimization of short- and long-term outcomes after CABG. Expanding the use of lesser invasive techniques may persuade patients to accept surgery as the preferable treatment option. Particularly studies comparing PCI with CABG require the most optimal surgical revascularization strategy to show superiority over PCI. Arterial revascularization with minimized aortic manipulation and intra-operative graft flow measurement is a relatively easy way to improve outcomes.

Adoption rates of new techniques have been low, despite all advances. This may be due to: (i) the familiarity that surgeons have with existing techniques, a reluctance to change and the willingness to go through the learning curve typical for a new technique, (ii) the more demanding nature of some technical advances, (iii) complications related to the use of a new technique and/or device, (iv) time-consuming steps that may have to be carried out during the procedure, and (v) logistic reasons with regard to the need for additional equipment, planning and sterility. Particularly when the presumed benefits with new techniques are not yet clearly proven, these factors play a major role in maintaining existing protocols. However, the benefit of advancements will often become evident when overcoming the learning curve. On the other hand, some techniques will always be time-consuming and reserved for highly specialized centres.

Guidelines

One explanation for the underuse of new techniques and secondary prevention measures may be the lack of data supporting their benefit. This calls for large registries and randomized trials to provide additional rigorous evaluation of, in particular, MIDCAB, hybrid revascularization, epiaortic scanning and graft flow measurement. Another reason for lack of widespread implementation and geographic variations may be the differing recommendations of the American and European guidelines concerning their use (*Table 6*). This is illustrated

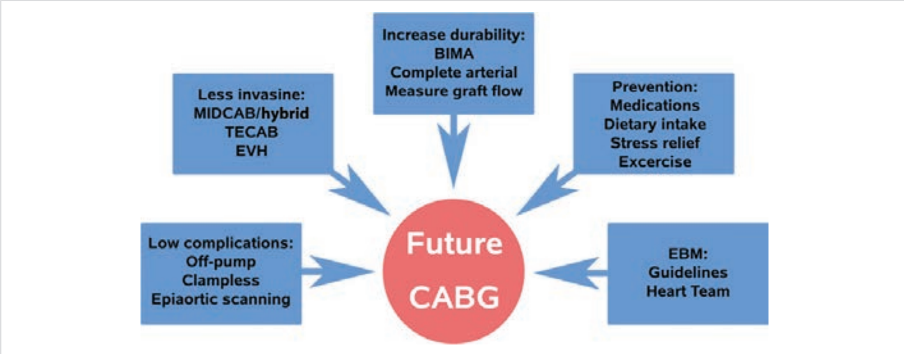

Figure 5 Summary of developments to optimize short- and long-term results after coronary artery bypass grafting. BIMA, bilateral internal mammary artery; CABG, coronary artery bypass grafting; EBM, evidence-based medicine; EVH, endoscopic vein harvesting; MIDCAB, minimally invasive coronary artery bypass; TECAB, totally endoscopic coronary artery bypass.

by recommendations for epiaortic scanning and graft flow assessment. The current European ESC/EACTS revascularization guidelines include a class 1C recommendation for intra-operative graft flow assessment [3] and the American guidelines state that 'epiaortic ultrasound is reasonable to evaluate…', which translates to a class IIa B recommendation.[148] However, the American guidelines do not include a recommendation for graft flow assessment, while the European guidelines lack a recommendation for epiaortic scanning.

Patient, cost, and market considerations

Adoption of minimally invasive techniques that result in lower post-operative complications and reduced length of stay will significantly improve patient satisfaction, and raise patients' willingness to undergo CABG as opposed to PCI. On the background of the issue of rising healthcare expenditures, these improvements may also help reduce overall costs.

Continued optimization of short- and long-term outcomes of CABG will reduce costs for health insurance providers who may therefore favour adoption of new techniques associated with shorter initial in-hospital stays, reduced complication rates and fewer repeat revascularizations. In addition, pay for performance is increasingly instated.[156] This system provides additional incentives to innovate and improve outcomes.

Containing costs to both health insurance providers and societies may in some healthcare systems require a reduction of the number of centres performing CABG. Innovation and integrating technological advances into everyday clinical practice may be rewarded by certification as a centre of excellence, by continued issuance of a practice licence and by more patient referrals. Implementation of the Heart Team decision-making process may furthermore strengthen the position of a centre. This approach highlights the centre's collaborative environment between specialties, which is appreciated by patients.[143] There may also be major cost implications by eradicating suboptimal treatment: healthcare costs will be contained as rates of adverse events requiring rehospitalization and additional procedures are reduced.

Conclusion

Outcomes after surgical revascularization have the potential to improve beyond the level achieved during recent decades (*Figure 5*). However, to facilitate these improvements, surgeons need to be willing to adopt new techniques that increase procedural safety, patient satisfaction, and long-term survival. To achieve these goals, guidelines should be conclusive about recommending certain techniques and provide guidance for their use. Future trials will need to provide sufficient evidence for such recommendations by focussing on specific areas where optimal therapy has yet to be substantiated.

Conflict of interest: none declared.

References

1. Head SJ, Kieser TM, Valk F, Huysmans HA, Kappetein AP. Coronary artery bypass grafting: part 1—the evolution over the first 50 years. *Eur Heart J* 2013.
2. Gruntzig A. Transluminal dilatation of coronary-artery stenosis. *Lancet* 1978;**1**:263.
3. Kolh P, Wijns W, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. *Eur J Cardiothorac Surg* 2010;**38**(Suppl):S1–S52.
4. Stefanini GG, Kalesan B, Serruys PW, Heg D, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, Di Mario C, Corti R, Antoni D, Sohn HY, Eerdmans P, van Es GA, Meier B, Windecker S, Juni P. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents vs. durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. *Lancet* 2011;**378**:1940–1948.
5. Palmerini T, Biondi-Zoccai G, Della Riva D, Stettler C, Sangiorgi D, D'Ascenzo F, Kimura T, Briguori C, Sabate M, Kim HS, De Waha A, Kedhi E, Smits PC, Kaiser C, Sardella G, Marullo A, Kirtane AJ, Leon MB, Stone GW. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet* 2012;**379**:1393–1402.

6. Onuma Y, Serruys PW, Ormiston JA, Regar E, Webster M, Thuesen L, Dudek D, Veldhof S, Rapoza R. Three-year results of clinical follow-up after a bioresorbable everolimus-eluting scaffold in patients with de novo coronary artery disease: the ABSORB trial. *EuroIntervention* 2010;**6**:447–453.
7. Serruys PW, Garcia-Garcia HM, Onuma Y. From metallic cages to transient bioresorbable scaffolds: change in paradigm of coronary revascularization in the upcoming decade? *Eur Heart J* 2012;**33**:16–25b.
8. Epstein AJ, Polsky D, Yang F, Yang L, Groeneveld PW. Coronary revascularization trends in the United States, 2001–2008. *JAMA* 2011;**305**:1769–1776.
9. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR Jr, Morel MA, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery vs. percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013;**381**:629–638.
10. Weintraub WS, Grau-Sepulveda MV, Weiss JM, O'Brien SM, Peterson ED, Kolm P, Zhang Z, Klein LW, Shaw RE, McKay C, Ritzenthaler LL, Popma JJ, Messenger JC, Shahian DM, Grover FL, Mayer JE, Shewan CM, Garratt KN, Moussa ID, Dangas GD, Edwards FH. Comparative effectiveness of revascularization strategies. *N Engl J Med* 2012;**366**:1467–1476.
11. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S III, Bertrand M, Fuster V. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012;**367**:2375–2384.
12. Kappetein AP, Head SJ, Morice MC, Banning AP, Serruys PW, Mohr FW, Dawkins KD, Mack MJ, SYNTAX Investigators. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. *Eur J Cardiothorac Surg* 2013;**45**:1006–1013.
13. Afilalo J, Rasti M, Ohayon SM, Shimony A, Eisenberg MJ. Off-pump vs. on-pump coronary artery bypass surgery: an updated meta-analysis and meta-regression of randomized trials. *Eur Heart J* 2012;**33**:1257–1267.
14. Abu-Omar Y, Taggart DP. The present status of off-pump coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2009;**36**:312–321.
15. Van Dijk D, Jansen EW, Hijman R, Nierich AP, Diephuis JC, Moons KG, Lahpor JR, Borst C, Keizer AM, Nathoe HM, Grobbee DE, De Jaegere PP, Kalkman CJ, Octopus Study G. Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery: a randomized trial. *JAMA* 2002;**287**:1405–1412.
16. Mack MJ, Pfister A, Bachand D, Emery R, Magee MJ, Connolly M, Subramanian V. Comparison of coronary bypass surgery with and without cardiopulmonary bypass in patients with multivessel disease. *J Thorac Cardiovasc Surg* 2004;**127**:167–173.
17. Racz MJ, Hannan EL, Isom OW, Subramanian VA, Jones RH, Gold JP, Ryan TJ, Hartman A, Culliford AT, Bennett E, Lancey RA, Rose EA. A comparison of short- and long-term outcomes after off-pump and on-pump coronary artery bypass graft surgery with sternotomy. *J Am Coll Cardiol* 2004;**43**:557–564.
18. Kuss O, von Salviati B, Börgermann J. Off-pump versus on-pump coronary artery bypass grafting: a systematic review and meta-analysis of propensity score analyses. *J Thorac Cardiovasc Surg* 2010;**140**:829–835.
19. Williams ML, Muhlbaier LH, Schroder JN, Hata JA, Peterson ED, Smith PK, Landolfo KP, Messier RH, Davis RD, Milano CA. Risk-adjusted short- and long-term outcomes for on-pump vs. off-pump coronary artery bypass surgery. *Circulation* 2005;**112**:I366–I370.
20. Filardo G, Grayburn PA, Hamilton C, Hebeler RF Jr, Cooksey WB, Hamman B. Comparing long-term survival between patients undergoing off-pump and on-pump coronary artery bypass graft operations. *Ann Thorac Surg* 2011;**92**:571–577. discussion 577–578.
21. Hattler B, Messenger JC, Shroyer AL, Collins JF, Haugen SJ, Garcia JA, Baltz JH, Cleveland JC Jr, Novitzky D, Grover FL, Veterans Affairs Randomized On/Off Bypass Study Group. Off-Pump coronary artery bypass surgery is associated with worse arterial and saphenous vein graft patency and less effective revascularization: results from the Veterans Affairs Randomized On/Off Bypass (ROOBY) trial. *Circulation* 2012;**125**:2827–2835.
22. Widimsky P, Straka Z, Stros P, Jirasek K, Dvorak J, Votava J, Lisa L, Budesinsky T, Kolesar M, Vanek T, Brucek P. One-year coronary bypass graft patency: a randomized comparison between off-pump and on-pump surgery angiographic results of the PRAGUE-4 trial. *Circulation* 2004;**110**:3418–3423.
23. Puskas JD, Williams WH, Mahoney EM, Huber PR, Block PC, Duke PG, Staples JR, Glas KE, Marshall JJ, Leimbach ME, McCall SA, Petersen RJ, Bailey DE, Weintraub WS, Guyton RA. Off-pump vs. conventional coronary artery bypass grafting: early and 1-year graft patency, cost, and quality-of-life outcomes: a randomized trial. *JAMA* 2004;**291**:1841–1849.
24. Shroyer AL, Grover FL, Hattler B, Collins JF, McDonald GO, Kozora E, Lucke JC, Baltz JH, Novitzky D, Veterans Affairs Randomized On/Off Bypass Study Group. On-pump versus off-pump coronary-artery bypass surgery. *N Engl J Med* 2009;**361**:1827–1837.
25. Puskas JD, Mack MJ, Smith CR. On-pump versus off-pump CABG. *N Engl J Med* 2010;**362**:851. author reply 853–854.
26. Sousa Uva M, Cavaco S, Oliveira AG, Matias F, Silva C, Mesquita A, Aguiar P, Bau J, Pedro A, Magalhaes MP. Early graft patency after off-pump and on-pump coronary bypass surgery: a prospective randomized study. *Eur Heart J* 2010;**31**:2492–2499.
27. Takagi H, Matsui M, Umemoto T. Lower graft patency after off-pump than on-pump coronary artery bypass grafting: an updated meta-analysis of randomized trials. *J Thorac Cardiovasc Surg* 2010;**140**:e45–e47.
28. Synnergren MJ, Ekroth R, Oden A, Rexius H, Wiklund L. Incomplete revascularization reduces survival benefit of coronary artery bypass grafting: role of off-pump surgery. *J Thorac Cardiovasc Surg* 2008;**136**:29–36.
29. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, Noiseux N, Padmanabhan C, Bahamondes JC, Novick RJ, Vaijyanath P, Reddy S, Tao L, Olavegogeascoechea PA, Airan B, Sulling TA, Whitlock RP, Ou Y, Ng J, Chrolavicius S, Yusuf S, CORONARY Investigators. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *N Engl J Med* 2012;**366**:1489–1497.
30. Lamy A, Devereaux PJ, Dorairaj P, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, Noiseux N, Padmanabhan C, Bahamondes JC, Novick RJ, Vaijyanath P, Reddy SK, Tao L, Olavegogeascoechea PA, Airan B, Sulling TA, Whitlock RP, Ou Y, Pogue J, Chrolavicius S, Yusuf S, CORONARY Investigators. Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. *N Engl J Med* 2013;**368**:1179–1188.
31. Puskas JD, Thourani VH, Kilgo P, Cooper W, Vassiliades T, Vega JD, Morris C, Chen E, Schmotzer BJ, Guyton RA, Lattouf OM. Off-pump coronary artery bypass disproportionately benefits high-risk patients. *Ann Thorac Surg* 2009;**88**:1142–1147.
32. Sharony R, Bizekis CS, Kanchuger M, Galloway AC, Saunders PC, Applebaum R, Schwartz CF, Ribakove GH, Culliford AT, Baumann FG, Kronzon I, Colvin SB, Grossi EA. Off-pump coronary artery bypass grafting reduces mortality and stroke in patients with atheromatous aortas: a case control study. *Circulation* 2003;**108**(Suppl 1):II15–II20.
33. Head SJ, Kappetein AP. Off-pump or on-pump coronary-artery bypass grafting. *N Engl J Med* 2012;**367**:577–578.
34. Magee MJ, Coombs LP, Peterson ED, Mack MJ. Patient selection and current practice strategy for off-pump coronary artery bypass surgery. *Circulation* 2003;**108**(Suppl. 1):II9–II14.
35. Diegeler A, Borgermann J, Kappert U, Breuer M, Boning A, Ursulescu A, Rastan A, Holzhey D, Treede H, Riess FC, Veeckmann P, Asfoor A, Reents W, Zacher M, Hilker M, The GOPCABE Study Group. Off-pump versus on-pump coronary-artery bypass grafting in elderly patients. *N Engl J Med* 2013;**368**:1189–1198.
36. Puskas JD, Edwards FH, Pappas PA, O'Brien S, Peterson ED, Kilgo P, Ferguson TB Jr. Off-pump techniques benefit men and women and narrow the disparity in mortality after coronary bypass grafting. *Ann Thorac Surg* 2007;**84**:1447–1454. discussion 1454–1456.
37. Guerrieri Wolf L, Abu-Omar Y, Choudhary BP, Pigott D, Taggart DP. Gaseous and solid cerebral microembolization during proximal aortic anastomoses in off-pump coronary surgery: the effect of an aortic side-biting clamp and two clampless devices. *J Thorac Cardiovasc Surg* 2007;**133**:485–493.
38. Börgermann J, Hakim K, Renner A, Parsa A, Aboud A, Becker T, Masshoff M, Zittermann A, Gummert JF, Kuss O. Clampless off-pump versus conventional coronary artery revascularization: a propensity score analysis of 788 patients. *Circulation* 2012;**126**:S176–S182.
39. Emmert MY, Seifert B, Wilhelm M, Grunenfelder J, Falk V, Salzberg SP. Aortic no-touch technique makes the difference in off-pump coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2011;**142**:1499–1506.
40. Misfeld M, Brereton RJ, Sweetman EA, Doig GS. Neurologic complications after off-pump coronary artery bypass grafting with and without aortic manipulation: meta-analysis of 11,398 cases from 8 studies. *J Thorac Cardiovasc Surg* 2011;**142**:e11–e17.
41. Cohen DJ, Van Hout B, Serruys PW, Mohr FW, Macaya C, den Heijer P, Vrakking MM, Wang K, Mahoney EM, Audi S, Leadley K, Dawkins KD, Kappetein AP, SYNTAX Investigators. Quality of life after PCI with drug-eluting stents or coronary-artery bypass surgery. *N Engl J Med* 2011;**364**:1016–1026.
42. Serruys P, Morice M, Kappetein A, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand MJ, Bass E, van Dyck N, Leadley K, Dawkins KD, Mohr FW, SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;**360**:961–972.
43. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, Carrie D, Clayton TC, Danchin N, Flather M, Hamm CW, Hueb WA, Kahler J, Kelsey SF, King SB, Kosinski AS, Lopes N, McDonald KM, Rodriguez A, Serruys P,

Sigwart U, Stables RH, Owens DK, Pocock SJ. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet* 2009; **373**:1190–1197.

44. Hannan EL, Wu C, Walford G, Culliford AT, Gold JP, Smith CR, Higgins RS, Carlson RE, Jones RH. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. *N Engl J Med* 2008;**358**:331–341.
45. Acuff TE, Landreneau RJ, Griffith BP, Mack MJ. Minimally invasive coronary artery bypass grafting. *Ann Thorac Surg* 1996;**61**:135–137.
46. Groh MA, Sutherland SE, Burton HG III, Johnson AM, Ely SW. Port-access coronary artery bypass grafting: technique and comparative results. *Ann Thorac Surg* 1999;**68**: 1506–1508.
47. Diegeler A, Walther T, Metz S, Falk V, Krakor R, Autschbach R, Mohr FW. Comparison of MIDCAP vs. conventional CABG surgery regarding pain and quality of life. *Heart Surg Forum* 1999;**2**:290–295. discussion 295–296.
48. Martens TP, Argenziano M, Oz MC. New technology for surgical coronary revascularization. *Circulation* 2006;**114**:606–614.
49. Lapierre H, Chan V, Sohmer B, Mesana TG, Ruel M. Minimally invasive coronary artery bypass grafting via a small thoracotomy versus off-pump: a case-matched study. *Eur J Cardiothorac Surg* 2011;**40**:804–810.
50. Holzhey DM, Cornely JP, Rastan AJ, Davierwala P, Mohr FW. Review of a 13-year single-center experience with minimally invasive direct coronary artery bypass as the primary surgical treatment of coronary artery disease. *Heart Surg Forum* 2012;**15**:E61–E68.
51. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. *Lancet* 2001;**358**:870–875.
52. Kieser TM, Lewin AM, Graham MM, Martin BJ, Galbraith PD, Rabi DM, Norris CM, Faris PD, Knudtson ML, Ghali WA, Approach Investigators. Outcomes associated with bilateral internal thoracic artery grafting: the importance of age. *Ann Thorac Surg* 2011;**92**:1269–1275. discussion 1275–1276.
53. Alexander JH, Hafley G, Harrington RA, Peterson ED, Ferguson TB Jr, Lorenz TJ, Goyal A, Gibson M, Mack MJ, Gennevois D, Califf RM, Kouchoukos NT, Prevent IV Investigators. Efficacy and safety of edifoligide, an E2F transcription factor decoy, for prevention of vein graft failure following coronary artery bypass graft surgery: PREVENT IV: a randomized controlled trial. *JAMA* 2005;**294**:2446–2454.
54. Friedrich GJ, Bonatti J, Dapunt OE. Preliminary experience with minimally invasive coronary-artery bypass surgery combined with coronary angioplasty. *N Engl J Med* 1997;**336**:1454–1455.
55. Kon ZN, Brown EN, Tran R, Joshi A, Reicher B, Grant MC, Kallam S, Burris N, Connerney I, Zimrin D, Poston RS. Simultaneous hybrid coronary revascularization reduces postoperative morbidity compared with results from conventional off-pump coronary artery bypass. *J Thorac Cardiovasc Surg* 2008;**135**:367–375.
56. Halkos ME, Rab ST, Vassiliades TA, Morris DC, Douglas JS, Kilgo PD, Liberman HA, Guyton RA, Thourani VH, Puskas JD. Hybrid coronary revascularization versus off-pump coronary artery bypass for the treatment of left main coronary stenosis. *Ann Thorac Surg* 2011;**92**:2155–2160.
57. Halkos ME, Vassiliades TA, Douglas JS, Morris DC, Rab ST, Liberman HA, Samady H, Kilgo PD, Guyton RA, Puskas JD. Hybrid coronary revascularization versus off-pump coronary artery bypass grafting for the treatment of multivessel coronary artery disease. *Ann Thorac Surg* 2011;**92**:1695–1701. discussion 1701–1702.
58. Bonaros N, Schachner T, Lehr E, Kofler M, Wiedemann D, Hong P, Wehman B, Zimrin D, Vesely MK, Friedrich G, Bonatti J. Five hundred cases of robotic totally endoscopic coronary artery bypass grafting: predictors of success and safety. *Ann Thorac Surg* 2013;**95**:803–812.
59. McGinn JT Jr, Usman S, Lapierre H, Pothula VR, Mesana TG, Ruel M. Minimally invasive coronary artery bypass grafting: dual-center experience in 450 consecutive patients. *Circulation* 2009;**120**:S78–S84.
60. Bonatti JO, Zimrin D, Lehr EJ, Vesely M, Kon ZN, Wehman B, de Biasi AR, Hofauer B, Weidinger F, Schachner T, Bonaros N, Friedrich G. Hybrid coronary revascularization using robotic totally endoscopic surgery: perioperative outcomes and 5-year results. *Ann Thorac Surg* 2012;**94**:1920–1926. discussion 1926.
61. Holzhey DM, Jacobs S, Mochalski M, Merk D, Walther T, Mohr FW, Falk V. Minimally invasive hybrid coronary artery revascularization. *Ann Thorac Surg* 2008;**86**: 1856–1860.
62. Bonatti J, Schachner T, Bonaros N, Lehr EJ, Zimrin D, Griffith B. Robotically assisted totally endoscopic coronary bypass surgery. *Circulation* 2011;**124**:236–244.
63. Thiele H, Neumann-Schniedewind P, Jacobs S, Boudriot E, Walther T, Mohr FW, Schuler G, Falk V. Randomized comparison of minimally invasive direct coronary artery bypass surgery versus sirolimus-eluting stenting in isolated proximal left anterior descending coronary artery stenosis. *J Am Coll Cardiol* 2009;**53**:2324–2331.
64. D'Ancona G, Vassiliades TA, Boyd WD, Donias HW, Stahl KD, Karamanoukian H. Is hybrid coronary revascularization favored by cardiologists or cardiac surgeons? *Heart Surg Forum* 2002;**5**:393–395.
65. Goldman S, Zadina K, Moritz T, Ovitt T, Sethi G, Copeland JG, Thottapurathu L, Krasnicka B, Ellis N, Anderson RJ, Henderson W, V. A. Cooperative Study Group. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study. *J Am Coll Cardiol* 2004;**44**:2149–2156.
66. Hayward PA, Buxton BF. Contemporary coronary graft patency: 5-year observational data from a randomized trial of conduits. *Ann Thorac Surg* 2007;**84**:795–799.
67. Kim KB, Kim JS, Kang HJ, Koo BK, Kim HS, Oh BH, Park YB. Ten-year experience with off-pump coronary artery bypass grafting: lessons learned from early postoperative angiography. *J Thorac Cardiovasc Surg* 2010;**139**:256–262.
68. FitzGibbon GM, Burton JR, Leach AJ. Coronary bypass graft fate: angiographic grading of 1400 consecutive grafts early after operation and of 1132 after one year. *Circulation* 1978;**57**:1070–1074.
69. Lytle BW, Blackstone EH, Loop FD, Houghtaling PL, Arnold JH, Akhrass R, McCarthy PM, Cosgrove DM. Two internal thoracic artery grafts are better than one. *J Thorac Cardiovasc Surg* 1999;**117**:855–872.
70. Taggart DP, Altman DG, Gray AM, Lees B, Nugara F, Yu LM, Campbell H, Flather M, ART Investigators. Randomized trial to compare bilateral vs. single internal mammary coronary artery bypass grafting: 1-year results of the Arterial Revascularisation Trial (ART). *Eur Heart J* 2010;**31**:2470–2481.
71. Kappetein AP. Bilateral mammary artery vs. single mammary artery grafting: promising early results: but will the match finish with enough players?. *Eur Heart J* 2010;**31**: 2444–2446.
72. Tabata M, Grab JD, Khalpey Z, Edwards FH, O'Brien SM, Cohn LH, Bolman RM III. Prevalence and variability of internal mammary artery graft use in contemporary multivessel coronary artery bypass graft surgery: analysis of the Society of Thoracic Surgeons National Cardiac Database. *Circulation* 2009;**120**:935–940.
73. Kinoshita T, Asai T. Bilateral internal thoracic artery grafting: current state of the art. *Innovations (Phila)* 2011;**6**:77–83.
74. Collins P, Webb CM, Chong CF, Moat NE, Radial Artery Versus Saphenous Vein Patency Trial Investigators. Radial artery versus saphenous vein patency randomized trial: five-year angiographic follow-up. *Circulation* 2008;**117**:2859–2864.
75. Deb S, Cohen EA, Singh SK, Une D, Laupacis A, Fremes SE, RAPS Investigators. Radial artery and saphenous vein patency more than 5 years after coronary artery bypass surgery: results from RAPS (Radial Artery Patency Study). *J Am Coll Cardiol* 2012;**60**:28–35.
76. Tranbaugh RF, Dimitrova KR, Friedmann P, Geller CM, Harris LJ, Stelzer P, Cohen BM, Ko W, DeCastro H, Lucido D, Hoffman DM. Coronary artery bypass grafting using the radial artery: clinical outcomes, patency, and need for reintervention. *Circulation* 2012;**126**:S170–S175.
77. Achouh P, Isselmou KO, Boutekadjirt R, D'Alessandro C, Pagny JY, Fouquet R, Fabiani JN, Acar C. Reappraisal of a 20-year experience with the radial artery as a conduit for coronary bypass grafting. *Eur J Cardiothorac Surg* 2012;**41**:87–92.
78. Schwann TA, Al-Shaar L, Engoren M, Habib RH. Late effects of radial artery vs. saphenous vein grafting for multivessel coronary bypass surgery in diabetics: a propensity-matched analysis. *Eur J Cardiothorac Surg*; doi: 10.1093/ejcts/ezt061. Published online ahead of print 21 February 2013.
79. Zacharias A, Habib RH, Schwann TA, Riordan CJ, Durham SJ, Shah A. Improved survival with radial artery versus vein conduits in coronary bypass surgery with left internal thoracic artery to left anterior descending artery grafting. *Circulation* 2004; **109**:1489–1496.
80. Locker C, Schaff HV, Dearani JA, Joyce LD, Park SJ, Burkhart HM, Suri RM, Greason KL, Stulak JM, Li Z, Daly RC. Multiple arterial grafts improve late survival of patients undergoing coronary artery bypass graft surgery: analysis of 8622 patients with multivessel disease. *Circulation* 2012;**126**:1023–1030.
81. Goldman S, Sethi GK, Holman W, Thai H, McFalls E, Ward HB, Kelly RF, Rhenman B, Tobler GH, Bakaeen FG, Huh J, Soltero E, Moursi M, Haime M, Crittenden M, Kasirajan V, Ratliff M, Pett S, Irimpen A, Gunnar W, Thomas D, Fremes S, Moritz T, Reda D, Harrison L, Wagner TH, Wang Y, Planting L, Miller M, Rodriguez Y, Juneman E, Morrison D, Pierce MK, Kreamer S, Shih MC, Lee K. Radial artery grafts vs. saphenous vein grafts in coronary artery bypass surgery: a randomized trial. *JAMA* 2011;**305**:167–174.
82. Khot UN, Friedman DT, Pettersson G, Smedira NG, Li J, Ellis SG. Radial artery bypass grafts have an increased occurrence of angiographically severe stenosis and occlusion compared with left internal mammary arteries and saphenous vein grafts. *Circulation* 2004;**109**:2086–2091.
83. Ruttmann E, Fischler N, Sakic A, Chevtchik O, Alber H, Schistek R, Ulmer H, Grimm M. Second internal thoracic artery versus radial artery in coronary artery bypass grafting: a long-term, propensity score-matched follow-up study. *Circulation* 2011;**124**:1321–1329.
84. Desai ND, Cohen EA, Naylor CD, Fremes SE, Radial Artery Patency Study Investigators. A randomized comparison of radial-artery and saphenous-vein coronary bypass grafts. *N Engl J Med* 2004;**351**:2302–2309.

85. Tranbaugh RF, Dimitrova KR, Friedmann P, Geller CM, Harris LJ, Stelzer P, Cohen B, Hoffman DM. Radial artery conduits improve long-term survival after coronary artery bypass grafting. *Ann Thorac Surg* 2010;**90**:1165–1172.
86. Rupprecht HJ, Hamm C, Ischinger T, Dietz U, Reimers J, Meyer J. Angiographic follow-up results of a randomized study on angioplasty versus bypass surgery (GABI trial). GABI Study Group. *Eur Heart J* 1996;**17**:1192–1198.
87. Alfieri O, Maisano F, Benussi S, Toracca L, Castiglioni A. Drug-eluting stents or drug-eluting conduits for multivessel disease?. *J Cardiovasc Med (Hagerstown)* 2007;**8**:359–361.
88. Dimitrova KR, Hoffman DM, Geller CM, Dincheva G, Ko W, Tranbaugh RF. Arterial grafts protect the native coronary vessels from atherosclerotic disease progression. *Ann Thorac Surg* 2012;**94**:475–481.
89. Lumsden AB, Eaves FF III, Ofenloch JC, Jordan WD. Subcutaneous, video-assisted saphenous vein harvest: report of the first 30 cases. *Cardiovasc Surg* 1996;**4**: 771–776.
90. Dacey LJ. Endoscopic vein-graft harvest is safe for CABG surgery. *JAMA* 2012;**308**: 512–513.
91. Cadwallader RA, Walsh SR, Cooper DG, Tang TY, Sadat U, Boyle JR. Great saphenous vein harvesting: a systematic review and meta-analysis of open versus endoscopic techniques. *Vasc Endovascular Surg* 2009;**43**:561–566.
92. Lopes RD, Hafley GE, Allen KB, Ferguson TB, Peterson ED, Harrington RA, Mehta RH, Gibson CM, Mack MJ, Kouchoukos NT, Califf RM, Alexander JH. Endoscopic versus open vein-graft harvesting in coronary-artery bypass surgery. *N Engl J Med* 2009;**361**:235–244.
93. Zenati MA, Shroyer AL, Collins JF, Hattler B, Ota T, Almassi GH, Amidi M, Novitzky D, Grover FL, Sonel AF. Impact of endoscopic versus open saphenous vein harvest technique on late coronary artery bypass grafting patient outcomes in the ROOBY (Randomized On/Off Bypass) Trial. *J Thorac Cardiovasc Surg* 2011; **141**:338–344.
94. Dacey LJ, Braxton JH Jr, Kramer RS, Schmoker JD, Charlesworth DC, Helm RE, Frumiento C, Sardella GL, Clough RA, Jones SR, Malenka DJ, Olmstead EM, Ross CS, O'Connor GT, Likosky DS, Northern New England Cardiovascular Disease Study Group. Long-term outcomes of endoscopic vein harvesting after coronary artery bypass grafting. *Circulation* 2011;**123**:147–153.
95. Williams JB, Peterson ED, Brennan JM, Sedrakyan A, Tavris D, Alexander JH, Lopes RD, Dokholyan RS, Zhao Y, O'Brien SM, Michler RE, Thourani VH, Edwards FH, Duggirala H, Gross T, Marinac-Dabic D, Smith PK. Association between endoscopic vs. open vein-graft harvesting and mortality, wound complications, and cardiovascular events in patients undergoing CABG surgery. *JAMA* 2012; **308**:475–484.
96. Desai P, Kiani S, Thiruvanthan N, Henkin S, Kurian D, Ziu P, Brown A, Patel N, Poston R. Impact of the learning curve for endoscopic vein harvest on conduit quality and early graft patency. *Ann Thorac Surg* 2011;**91**:1385–1391. discussion 1391–1392.
97. Allen K, Cheng D, Cohn W, Connolly M, Edgerton J, Falk V, Martin J, Ohtsuka T, Vitali R. Endoscopic vascular harvest in coronary artery bypass grafting surgery: a consensus statement of the International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) 2005. *Innovations (Phila)* 2005;**1**:51–60.
98. Grant SW, Grayson AD, Zacharias J, Dalrymple-Hay MJ, Waterworth PD, Bridgewater B. What is the impact of endoscopic vein harvesting on clinical outcomes following coronary artery bypass graft surgery? *Heart* 2012;**98**:60–64.
99. Whitley WS, Glas KE. An argument for routine ultrasound screening of the thoracic aorta in the cardiac surgery population. *Semin Cardiothorac Vasc Anesth* 2008;**12**: 290–297.
100. Davila-Roman VG, Barzilai B, Wareing TH, Murphy SF, Schechtman KB, Kouchoukos NT. Atherosclerosis of the ascending aorta. Prevalence and role as an independent predictor of cerebrovascular events in cardiac patients. *Stroke* 1994;**25**:2010–2016.
101. Davila-Roman VG, Kouchoukos NT, Schechtman KB, Barzilai B. Atherosclerosis of the ascending aorta is a predictor of renal dysfunction after cardiac operations. *J Thorac Cardiovasc Surg* 1999;**117**:111–116.
102. Van Zaane B, Zuithoff NP, Reitsma JB, Bax L, Nierich AP, Moons KG. Meta-analysis of the diagnostic accuracy of transesophageal echocardiography for assessment of atherosclerosis in the ascending aorta in patients undergoing cardiac surgery. *Acta Anaesthesiol Scand* 2008;**52**:1179–1187.
103. Davila-Roman VG, Barzilai B, Wareing TH, Murphy SF, Kouchoukos NT. Intraoperative ultrasonographic evaluation of the ascending aorta in 100 consecutive patients undergoing cardiac surgery. *Circulation* 1991;**84**:III47–III53.
104. Royse C, Royse A, Blake D, Grigg L. Screening the thoracic aorta for atheroma: a comparison of manual palpation, transesophageal and epiaortic ultrasonography. *Ann Thorac Cardiovasc Surg* 1998;**4**:347–350.
105. Djaiani G, Ali M, Borger MA, Woo A, Carroll J, Feindel C, Fedorko L, Karski J, Rakowski H. Epiaortic scanning modifies planned intraoperative surgical management but not cerebral embolic load during coronary artery bypass surgery. *Anesth Analg* 2008;**106**:1611–1618.
106. Lyons JM, Thourani VH, Puskas JD, Kilgo PD, Baio KT, Guyton RA, Lattouf OM. Intraoperative epiaortic ultrasound scanning guides operative strategies and identifies patients at high risk during coronary artery bypass grafting. *Innovations (Phila)* 2009;**4**:99–105.
107. Zingone B, Rauber E, Gatti G, Pappalardo A, Benussi B, Dreas L, Lattuada L. The impact of epiaortic ultrasonographic scanning on the risk of perioperative stroke. *Eur J Cardiothorac Surg* 2006;**29**:720–728.
108. Rosenberger P, Shernan SK, Loffler M, Shekar PS, Fox JA, Tuli JK, Nowak M, Eltzschig HK. The influence of epiaortic ultrasonography on intraoperative surgical management in 6051 cardiac surgical patients. *Ann Thorac Surg* 2008;**85**:548–553.
109. Hangler HB, Nagele G, Danzmayr M, Mueller L, Ruttmann E, Laufer G, Bonatti J. Modification of surgical technique for ascending aortic atherosclerosis: impact on stroke reduction in coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2003;**126**:391–400.
110. Wareing TH, Davila-Roman VG, Barzilai B, Murphy SF, Kouchoukos NT. Management of the severely atherosclerotic ascending aorta during cardiac operations. A strategy for detection and treatment. *J Thorac Cardiovasc Surg* 1992;**103**:453–462.
111. Daniel WT III, Kilgo P, Puskas JD, Thourani VH, Lattouf OM, Guyton RA, Halkos ME. Trends in aortic clamp use during coronary artery bypass surgery: effect of aortic clamping strategies on neurologic outcomes. *J Thorac Cardiovasc Surg*; doi: 10.1016/j.jtcvs.2013.02.021. Published online ahead of print 8 March 2013.
112. Magee MJ, Alexander JH, Hafley G, Ferguson TB Jr, Gibson CM, Harrington RA, Peterson ED, Califf RM, Kouchoukos NT, Herbert MA, Mack MJ, Prevent IV Investigators. Coronary artery bypass graft failure after on-pump and off-pump coronary artery bypass: findings from PREVENT IV. *Ann Thorac Surg* 2008;**85**:494–499. discussion 499–500.
113. Balacumaraswami L, Taggart DP. Intraoperative imaging techniques to assess coronary artery bypass graft patency. *Ann Thorac Surg* 2007;**83**:2251–2257.
114. Balacumaraswami L, Abu-Omar Y, Choudhary B, Pigott D, Taggart DP. A comparison of transit-time flowmetry and intraoperative fluorescence imaging for assessing coronary artery bypass graft patency. *J Thorac Cardiovasc Surg* 2005;**130**:315–320.
115. Mack MJ. Intraoperative coronary graft assessment. *Curr Opin Cardiol* 2008;**23**: 568–572.
116. Desai ND, Miwa S, Kodama D, Koyama T, Cohen G, Pelletier MP, Cohen EA, Christakis GT, Goldman BS, Fremes SE. A randomized comparison of intraoperative indocyanine green angiography and transit-time flow measurement to detect technical errors in coronary bypass grafts. *J Thorac Cardiovasc Surg* 2006;**132**: 585–594.
117. Waseda K, Ako J, Hasegawa T, Shimada Y, Ikeno F, Ishikawa T, Demura Y, Hatada K, Yock PG, Honda Y, Fitzgerald PJ, Takahashi M. Intraoperative fluorescence imaging system for on-site assessment of off-pump coronary artery bypass graft. *JACC Cardiovasc Imaging* 2009;**2**:604–612.
118. Jokinen JJ, Werkkala K, Vainikka T, Perakyla T, Simpanen J, Ihlberg L. Clinical value of intra-operative transit-time flow measurement for coronary artery bypass grafting: a prospective angiography-controlled study. *Eur J Cardiothorac Surg* 2011;**39**: 918–923.
119. Di Giammarco G, Pano M, Cirmeni S, Pelini P, Vitolla G, Di Mauro M. Predictive value of intraoperative transit-time flow measurement for short-term graft patency in coronary surgery. *J Thorac Cardiovasc Surg* 2006;**132**:468–474.
120. Tokuda Y, Song MH, Ueda Y, Usui A, Akita T. Predicting early coronary artery bypass graft failure by intraoperative transit time flow measurement. *Ann Thorac Surg* 2007;**84**:1928–1933.
121. Kieser TM, Rose S, Kowalewski R, Belenkie I. Transit-time flow predicts outcomes in coronary artery bypass graft patients: a series of 1000 consecutive arterial grafts. *Eur J Cardiothorac Surg* 2010;**38**:155–162.
122. Mangano DT, Multicenter Study of Perioperative Ischemia Research Group. Aspirin and mortality from coronary bypass surgery. *N Engl J Med* 2002;**347**: 1309–1317.
123. Chan AY, McAlister FA, Norris CM, Johnstone D, Bakal JA, Ross DB, Alberta Provincial Program for Outcome Assessment in Coronary Heart Disease Investigators. Effect of beta-blocker use on outcomes after discharge in patients who underwent cardiac surgery. *J Thorac Cardiovasc Surg* 2010;**140**:182–187.
124. Kjoller-Hansen L, Steffensen R, Grande P. The Angiotensin-converting Enzyme Inhibition Post Revascularization Study (APRES). *J Am Coll Cardiol* 2000;**35**:881–888.
125. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. The Post Coronary Artery Bypass Graft Trial Investigators. *N Engl J Med* 1997;**336**:153–162.
126. Shah SJ, Waters DD, Barter P, Kastelein JJ, Shepherd J, Wenger NK, DeMicco DA, Breazna A, LaRosa JC. Intensive lipid-lowering with atorvastatin for secondary prevention in patients after coronary artery bypass surgery. *J Am Coll Cardiol* 2008;**51**: 1938–1943.
127. Benedetto U, Melina G, di Bartolomeo R, Angeloni E, Sansone D, Falaschi G, Capuano F, Comito C, Roscitano A, Sinatra R. n-3 polyunsaturated fatty acids after coronary artery bypass grafting. *Ann Thorac Surg* 2011;**91**:1169–1175.

128. Goyal A, Alexander JH, Hafley GE, Graham SH, Mehta RH, Mack MJ, Wolf RK, Cohn LH, Kouchoukos NT, Harrington RA, Gennevois D, Gibson CM, Califf RM, Ferguson TB Jr, Peterson ED, Prevent IV Investigators. Outcomes associated with the use of secondary prevention medications after coronary artery bypass graft surgery. *Ann Thorac Surg* 2007;**83**:993–1001.
129. Kulik A, Voisine P, Mathieu P, Masters RG, Mesana TG, Le May MR, Ruel M. Statin therapy and saphenous vein graft disease after coronary bypass surgery: analysis from the CASCADE randomized trial. *Ann Thorac Surg* 2011;**92**:1284–1290. discussion 1290–1291.
130. Eritsland J, Arnesen H, Gronseth K, Fjeld NB, Abdelnoor M. Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. *Am J Cardiol* 1996;**77**:31–36.
131. de Leon N, Jackevicius CA. Use of aspirin and clopidogrel after coronary artery bypass graft surgery. *Ann Pharmacother* 2012;**46**:678–687.
132. Martin TN, Irving RJ, Sutherland M, Sutherland K, Bloomfield P. Improving secondary prevention in coronary bypass patients: closing the audit loop. *Heart* 2005;**91**: 456–459.
133. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyorala K, Keil U, Group ES. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. *Lancet* 2009;**373**:929–940.
134. Hiratzka LF, Eagle KA, Liang L, Fonarow GC, LaBresh KA, Peterson ED, Get With the Guidelines Steering Committee. Atherosclerosis secondary prevention performance measures after coronary bypass graft surgery compared with percutaneous catheter intervention and nonintervention patients in the Get With the guidelines database. *Circulation* 2007;**116**:I207–I212.
135. Kappetein AP, Feldman TE, Mack MJ, Morice MC, Holmes DR, Stahle E, Dawkins KD, Mohr FW, Serruys PW, Colombo A. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *Eur Heart J* 2011;**32**: 2125–2134.
136. Turley AJ, Roberts AP, Morley R, Thornley AR, Owens WA, de Belder MA. Secondary prevention following coronary artery bypass grafting has improved but remains sub-optimal: the need for targeted follow-up. *Interact Cardiovasc Thorac Surg* 2008;**7**: 231–234.
137. van Domburg RT, op Reimer WS, Hoeks SE, Kappetein AP, Bogers AJ. Three life-years gained from smoking cessation after coronary artery bypass surgery: a 30-year follow-up study. *Am Heart J* 2008;**156**:473–476.
138. Opie LH, Commerford PJ, Gersh BJ. Controversies in stable coronary artery disease. *Lancet* 2006;**367**:69–78.
139. Clark AM, Hartling L, Vandermeer B, McAlister FA. Meta-analysis: secondary prevention programs for patients with coronary artery disease. *Ann Intern Med* 2005; **143**:659–672.
140. Griffo R, Ambrosetti M, Tramarin R, Fattirolli F, Temporelli PL, Vestri AR, De Feo S, Tavazzi L, ICAROS Investigators. Effective secondary prevention through cardiac rehabilitation after coronary revascularization and predictors of poor adherence to lifestyle modification and medication. Results of the ICAROS Survey. *Int J Cardiol*; doi.org/10.1016/j.ijcard.2012.04.069. Published online 10 May 2012.
141. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyorala K, Keil U, EUROASPIRE Study Group. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. *Lancet* 2009;**373**: 929–940.
142. Clark AM, Haykowsky M, Kryworuchko J, MacClure T, Scott J, DesMeules M, Luo W, Liang Y, McAlister FA. A meta-analysis of randomized control trials of home-based secondary prevention programs for coronary artery disease. *Eur J Cardiovasc Prev Rehabil* 2010;**17**:261–270.
143. Head SJ, Kaul S, Mack MJ, Serruys PW, Taggart DP, Holmes Jr DR, Leon MB, Marco J, Bogers AJ, Kappetein AP. The rationale for Heart Team decision-making for patients with stable complex coronary artery disease. *Eur Heart J*; doi: 10.1093/eurheartj/eht059. Published online ahead of print 26 February 2013.
144. Marso SP, Teirstein PS, Kereiakes DJ, Moses J, Lasala J, Grantham JA. Percutaneous coronary intervention use in the United States: defining measures of appropriateness. *JACC Cardiovasc Interv* 2012;**5**:229–235.
145. Chandrasekharan DP, Taggart DP. Informed consent for interventions in stable coronary artery disease: problems, etiologies, and solutions. *Eur J Cardiothorac Surg* 2011;**39**:912–917.
146. Head SJ, Bogers AJ, Serruys PW, Takkenberg JJ, Kappetein AP. A crucial factor in shared decision making: the team approach. *Lancet* 2011;**377**:1836.
147. Head SJ, Holmes Jr DR, Mack MJ, Serruys PW, Mohr FW, Morice M, Colombo A, Kappetein AP. Risk profile and 3-year outcomes from the SYNTAX percutaneous coronary intervention and coronary artery bypass grafting nested registries. *JACC Cardiovasc Interv* 2012;**5**:618–625.
148. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, Cigarroa JE, Disesa VJ, Hiratzka LF, Hutter AM Jr, Jessen ME, Keeley EC, Lahey SJ, Lange RA, London MJ, Mack MJ, Patel MR, Puskas JD, Sabik JF, Selnes O, Shahian DM, Trost JC, Winniford MD, American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, Society of Thoracic Surgeons. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2011;**58**:e123–e210.
149. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;**360**:213–224.
150. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Juni P, Fearon WF. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;**367**:991–1001.
151. Botman CJ, Schonberger J, Koolen S, Penn O, Botman H, Dib N, Eeckhout E, Pijls N. Does stenosis severity of native vessels influence bypass graft patency? A prospective fractional flow reserve-guided study. *Ann Thorac Surg* 2007;**83**:2093–2097.
152. Kim YH, Ahn JM, Park DW, Song HG, Lee JY, Kim WJ, Yun SC, Kang SJ, Lee SW, Lee CW, Moon DH, Chung CH, Lee JW, Park SW, Park SJ. Impact of ischemia-guided revascularization with myocardial perfusion imaging for patients with multivessel coronary disease. *J Am Coll Cardiol* 2012;**60**:181–190.
153. de Boer SP, Lenzen MJ, Oemrawsingh RM, Simsek C, Duckers HJ, van der Giessen WJ, Serruys PW, Boersma E. Evaluating the 'all-comers' design: a comparison of participants in two 'all-comers' PCI trials with non-participants. *Eur Heart J* 2011;**32**:2161–2167.
154. Head SJ, Farooq V, Serruys PW, Kappetein AP. The SYNTAX Score and its clinical implications. *Heart*; doi:10.1136/heartjnl-2012-302482. Published online ahead of print 28 March 2013.
155. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR Jr, Mack M, Feldman T, Morice MC, Stahle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 2013;**381**:639–650.
156. Sutton M, Nikolova S, Boaden R, Lester H, McDonald R, Roland M. Reduced mortality with hospital pay for performance in England. *N Engl J Med* 2012;**367**: 1821–1828.

Chapter 5

The radial artery: neither gold, nor silver, but bronze?

Kieser TM

J Thorac Cardiovasc Surg 2004;127:607-608

TO THE EDITOR:

I greatly appreciated reading Dr Lylte's insightful comments in his editorial on the radial artery (RA) versus the right internal thoracic artery (RITA) as a secondary arterial conduit for coronary surgery.[1] All that he says is true: the RITA graft, when considering its historical older brother the left internal thoracic artery (LITA) graft, should have the same long-term potential but technically poses a bigger challenge. Hence surgeons opt for a more user-friendly arterial conduit, the RA. I would like to suggest a different comparison/substitute: the RA for the vein graft. Dr Lylte's comment in his editorial, "n my judgment, the RA graft is less predictable than the RITA graft in regard to patency," intrigued me. Over the past 15 years as a practicing cardio- thoracic surgeon, I have become profoundly aware of the inadequacy of veins, and since my recent attendance at the enlightening and energy-invoking symposium "Arterial Conduits for Myocardial Revascularization" in Rome by Dr G. F. Possatti and Dr A. M. Calafiore, I believe the thrust should be to continue to use double ITA grafts whenever possible (especially in the young) but to substitute the RA for the vein graft. Since my return from this symposium, I have tried to do this; perhaps I did not see (or did not want to see) before, but many patients have serious venous disease of their legs precluding use of the saphenous vein. I think one of the turning points for me was when I recently (July 24, 2003) had to reoperate on an 83-year-old woman, on whom I had placed 2 grafts at age 81. Her LITA had gone down, I believe because I placed the graft inadvertently above a stenosis and her vein graft to a marginal artery occluded. If her vein graft had stayed open, she probably would not have needed reoperation at age 83. I used a sequential RA graft to the left anterior descending coronary artery and the marginal branch on- pump, and postoperatively she woke up stating that this was easier than her first operation. (Obviously this time both grafts were working!)

A second reason to substitute the vein for the RA graft could be the anticipated longer-lasting results of the drug-eluting stents used by interventional cardiologists. I know we are all interested in the same end—stamping out coronary artery disease effects—but it can be a little dis- concerting for many surgeons currently in practice to see their favored coronary artery bypass grafts (LITA plus 2 veins) going the way of the dodo bird. I want to be so bold as to predict that the drug- eluting stents will rival our saphenous vein grafts (that is, by the time they figure out which drug, from which drug family, how much eluting, over what period of time, and so on, works; it might take 20 years). Although we should never be competitive with our interventional colleagues because we have the same end point in common, we must as surgeons find something ancillary to their work. I believe total arterial grafting (be it bilateral IT A, LIT A/RA, RIT A, bilateral ITA/ gastroepiploic artery) may well be the answer. As Dr Lytle most wisely stated at the 2003 meeting of The American Association for Thoracic Surgery in Boston (and I quote him often in this): “Did you think you were going to be doing the same operation for 100 years!?” Dr Lytle continues to be a driving force leading all our quests for the best coronary artery bypass conduit.

REFERENCE:

1. Lytle BW. Radial versus right internal thoracic artery as a second arterial conduit for coronary surgery: early and midterm outcomes. J Thorac Cardiovasc Surg 2003;126:5-6.

Chapter 6

Bilateral internal mammary artery grafting in CABG surgery: an extra 20 minutes for an extra 20 years…

Kieser TM

EuroIntervention 2013;9:899-901

Bilateral internal mammary artery grafting in CABG surgery: an extra 20 minutes for an extra 20 years…

Teresa M. Kieser*, MD, FRCS(C), FACS

Department of Cardiac Sciences, Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, Alberta, Canada

Bilateral internal mammary artery (BIMA) grafting has been the operation of the future for 25 years - it must now arrive! One cannot talk about BIMA grafting without first discussing why venous bypass grafts are no longer best practice.

Why are vein grafts so bad?

Because veins were never meant to be arteries. It is true that some vein grafts last 30 years but the majority don't. The blood pressure in veins is 25-30 mmHg; the pressure in arteries is 120/80 mmHg. So when a vein is expected to do the job of an artery, it all too often fails. In 1996, FitzGibbon[1] studied 5,065 bypass grafts from 1969 to 1994: early graft patency (<3 weeks) was 88%. In 2010, the results for early patency were still exactly the same: 88.2% patency in 322 venous grafts at ≤7 days in a study by Kim[2] versus 98.9% (3,495/3,535) in arterial grafts. In a 2008 study meant to determine if edifoligide would prevent vein graft failure due to neointimal hyperplasia, the one-year venous graft patency was 74.3%[3]. In FitzGibbon's study, "A" vein graft patency at one year was 76%. Despite improvements in every area of medicine and surgery over decades, vein graft patency has remained the same: unacceptable. As time goes on, vein graft patency worsens: at 10 years, 48% are "A" grafts and at ≥15 years 40% are patent[1].

Why are BIMA grafts so good?

Because God made them that way. The literature is replete with the benefits of BIMA grafting: decreased risk of death, reoperation and angioplasty[4], improved in-hospital mortality[5], increased long-term survival[6-9]. BIMA is also better in certain subgroups of patients, e.g., those with reduced ejection fraction[10] and patients with diabetes[11,12]. Use of BIMA has been shown to have better five-year reintervention-free survival compared with drug-eluting stents in diabetic patients[13]. Most recently, Kurlansky[14] demonstrated that use of BIMA reverses the influence of gender on CABG outcomes short and long-term, ameliorating both the increased perioperative mortality in female patients and the reduced long-term survival of male patients. The cut-off age for benefit of BIMA grafting ranges from 65 to 74 years of age[8,15-17]. The low incidence of BIMA grafting is no longer justifiable with the evidence to date.

Why do surgeons use veins?

Because this is how they were taught, immediate results are good, it's easier, inertia (it is hard to leave one's "comfort zone" and perform more technically demanding procedures with the requisite learning curve). BIMA grafting devascularises the sternum more than single mammary harvest and predisposes to deep sternal

*Corresponding author: Foothills Medical Centre, Room C 814, 1403 29th St NW, Calgary, Alberta, T2N 2T9, Canada.
E-mail: t.kieserprieur@ucalgary.ca

wound infection. In the United States, the centres for Medicare and Medicaid Services no longer reimburse for the extra care necessary for treatment of deep sternal wound infection as this is deemed a “never event”[18]. World-famous chefs do not use “freezer-burned chicken” and “one-week-old lettuce” to create a culinary masterpiece; they use the very best ingredients. Then why do we as surgeons use a vein? Fast-food mentality?

Why do surgeons not use BIMA?

Because BIMA harvest is more time-consuming, surgeons like to be “slick”. In some respects, we surgeons have not evolved much from the early days of barber-shop surgery. We now have general anaesthesia, so we do not have to be so “quick”. It may take an extra 20 minutes in a three- to four-hour operation to use the second mammary (principally the harvest time). What a payback for patients – an extra 20 minutes for an extra 20 years….

In a survey of 101 of 147 Canadian surgeons by Mastrobuoni et al[19], the main factors influencing BIMA use by surgeons were: risk of sternal wound infection for 35% of surgeons, the reluctance to believe in the superiority of the right internal mammary artery (RIMA) over the saphenous vein for long-term outcome for 30% of surgeons, limited length of the RIMA for 28% of surgeons, and increased operative time or bleeding for 6% of surgeons.

One famous surgeon (I am not sure who) said “I think that maybe what we should be doing is just put two internal mammaries on the heart somewhere and leave it at that”. This is a worthy thought: two IMAs on the two biggest territories (LAD, CIRC, or RCA) would leave the patient with single-vessel disease which (if symptomatic) could (if amenable) be addressed with PCI; this would perhaps be a more meaningful “hybrid” procedure than just the LIMA-LAD and the other two territories with DES stents.

The team effort

There is a common theme emerging from cardiologists all over the world – they “yearn for BIMA grafting”. Why is this? Venous graft disease is almost impossible to deal with for two reasons: 1) patients with serious venous graft disease often have a patent LIMA to LAD on which most surgeons will be reluctant to perform reoperation for fear of damage to the IMA upon chest re-entry; 2) PCI is fraught with the danger of embolisation causing serious myocardial damage, and the atherosclerosis that develops in vein grafts is the biggest challenge for any type of stent. Drug-eluting stents are somewhat better[20], but nothing fully corrects the problem of vein graft atherosclerosis, except not using veins to begin with. Please do not misunderstand – there is a place for using the vein. It has saved many a patient’s life, but its use should be the exception rather than the rule.

Cardiologists refer business to surgeons: as cardiac surgeons we are heartened when we see beautiful BIMA grafts studied years after CABG surgery. We rise to the occasion when the following is proposed: “If you would do a left internal mammary artery (LIMA) to the LAD and a RIMA to the RCA (or CIRC), we can do PCI for the third if the patient suffers angina”. And then there is tough love – what if cardiologists didn’t send surgeons CABG cases unless surgeons do BIMA(!)? Detailed discussion of cases between surgeons and cardiologists are often enlightening for both. We should learn to talk to each other - patients can only benefit…

Conflict of interest statement

T. Kieser is a consultant for Medistim ASA, Medistim USA and Ethicon Endosurgery.

References

1. Fitzgibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. *J Am Coll Cardiol.* 1996;28:616-26.

2. Kim KB, Kim JS, Kang HJ, Koo BK, Kim HS, Oh BH, Park YB. Ten-year experience with off-pump coronary artery bypass grafting: lessons learned from early postoperative angiography. *J Thorac Cardiovasc Surg.* 2010;139:256-62.

3. Magee MJ, Alexander JH, Hafley G, Ferguson TB Jr, Gibson CM, Harrington RA, Peterson ED, Califf RM, Kouchoukos NT, Herbert MA, Mack MJ; PREVENT IV Investigators. Coronary artery bypass graft failure after on-pump and off-pump coronary artery bypass: findings from PREVENT IV. *Ann Thorac Surg.* 2008;85:494-9; discussion 499-500.

4. Lytle BW, Blackstone EH, Loop FD, Houghtaling PL, Arnold JH, Akhrass R, McCarthy PM, Cosgrove DM. Two internal thoracic artery grafts are better than one. *J Thorac Cardiovasc Surg.* 1999;117:855-72.

5. Itagaki S, Cavallaro P, Adams DH, Chikwe J. Bilateral internal mammary artery grafts, mortality and morbidity: an analysis of 1,526,360 coronary bypass operations. *Heart.* 2013;99:849-53.

6. Taggart DP, D’Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. *Lancet.* 2001;358:870-5.

7. Grau JB, Ferrari G, Mak AW, Shaw RE, Brizzio ME, Mindich BP, Strobeck J, Zapolanski A. Propensity matched analysis of bilateral internal mammary artery versus single left internal mammary artery grafting at 17-year follow-up: validation of a contemporary surgical experience. *Eur J Cardiothorac Surg.* 2012;41:770-5; discussion 776.

8. Popovic B, Voillot D, Maureira P, Vanhuyse F, Agrinier N, Aliot E, Folliguet T, Villemot JP. BIMA bypass grafting: long-term clinical benefits in a series of 1000 patients. *Heart.* 2013;99:854-9.

9. Kelly R, Buth KJ, Légaré JF. Bilateral internal thoracic artery grafting is superior to other forms of multiple arterial grafting in providing survival benefit after coronary bypass surgery. *J Thorac Cardiovasc Surg.* 2012;144:1408-15.

10. Galbut DL, Kurlansky PA, Traad EA, Dorman MJ, Zucker M, Ebra G. Bilateral internal thoracic artery grafting improves long-term survival in patients with reduced ejection fraction: a propensity-matched study with 30-year follow-up. *J Thorac Cardiovasc Surg.* 2012;143:844-853.e4.

11. Dorman MJ, Kurlansky PA, Traad EA, Galbut DL, Zucker M, Ebra G. Bilateral internal mammary artery grafting enhances survival in diabetic patients: a 30-year follow-up of propensity score-matched cohorts. *Circulation*. 2012;126:2935-42.

12. Puskas JD, Sadiq A, Vassiliades TA, Kilgo PD, Lattouf OM. Bilateral internal thoracic artery grafting is associated with significantly improved long-term survival, even among diabetic patients. *Ann Thorac Surg.* 2012;94:710-5; discussion 715-6.

13. Moshkovitz Y, Mohr R, Medalion B, Hyam E, Herz I, Deitch I, Uretzky G, Pevni D. Drug-eluting stents compared with bilateral internal thoracic artery grafts for diabetic patients. *Ann Thorac Surg.* 2012;94:1455-62.

14. Kurlansky PA, Traad EA, Dorman MJ, Galbut DL, Zucker M, Ebra G. Bilateral internal mammary artery grafting reverses the negative influence of gender on outcomes of coronary artery bypass grafting surgery. *Eur J Cardiothorac Surg.* 2013;44:54-63.

15. Mohammadi S, Dagenais F, Doyle D, Mathieu P, Baillot R, Charbonneaul E, Perron J, Voisine P. Age cut-off for the loss of benefit from bilateral internal thoracic artery grafting. *Eur J Cardiothorac Surg.* 2008;33:977-82.

16. Kieser TM, Lewin AM, Graham MM, Martin BJ, Galbraith PD, Rabi DM, Norris CM, Faris PD, Knudtson ML, Ghali WA; APPROACH Investigators. Outcomes associated with bilateral internal thoracic artery grafting: the importance of age. *Ann Thorac Surg.* 2011;92:1269-75; discussion 1275-6.

17. Elmistekawy EM, Gawad N, Bourke M, Mesana T, Boodhwani M, Rubens FD. Is bilateral internal thoracic artery use safe in the elderly? *J Card Surg.* 2012;27:1-5.

18. Puskas JD. Why did you not use both internal thoracic arteries? *Circulation*. 2012;126:2915-7.

19. Mastrobuoni S, Gawad N, Price J, Chan V, Ruel M, Mesana TG, Rubens FD. Use of bilateral internal thoracic artery during coronary artery bypass graft surgery in Canada: The bilateral internal thoracic artery survey. *J Thorac Cardiovasc Surg.* 2012;144:874-9.

20. Nauta ST, Van Mieghem NM, Magro M, Deckers JW, Simsek C, Van Geuns RJ, Van Der Giessen WJ, De Jaegere P, Regar E, Van Domburg RT, Serruys PW. Seven-year safety and efficacy of the unrestricted use of drug-eluting stents in saphenous vein bypass grafts. *Catheter Cardiovasc Interv.* 2012;79:912-8.

PART 3

PATIENT'S AGE OF BENEFIT FOR BILATERAL INTERNAL MAMMARY ARTERY GRAFTING

Chapter 7

Outcomes associated with bilateral internal thoracic artery grafting: the importance of age

Kieser TM, Lewin AM, Graham MM, Martin BJ, Galbraith PD,
Rabi DM, Norris CM, Faris PD, Knudtson ML, Ghali WA

Ann Thorac Surg 2011;92:1269-76

Outcomes Associated With Bilateral Internal Thoracic Artery Grafting: The Importance of Age

Teresa M. Kieser, MD, Adriane M. Lewin, MS, Michelle M. Graham, MD, Billie-Jean Martin, MD, P. Diane Galbraith, BN, MS, Doreen M. Rabi, MD, MS, Colleen M. Norris, PhD, Peter D. Faris, PhD, Merril L. Knudtson, MD, and William A. Ghali, MD, MPH, for the "APPROACH" Investigators

Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary; Calgary Institute of Population and Public Health, Faculty of Medicine, University of Calgary, Calgary; Department of Medicine and Community Health Sciences, University of Calgary, Calgary; Department of Medicine, Division of Cardiology, University of Alberta, Edmonton; and Research Portfolio, Alberta Health Services, Calgary, Alberta, Canada

Background. **Although bilateral internal thoracic artery (BITA) grafting in coronary artery bypass grafting (CABG) is associated with low morbidity and good long-term results, controversy exists about the age after which BITA grafting is no longer beneficial. We sought to determine if such an age cutoff point exists.**

Methods. **The study cohort consisted of 5,601 consecutive patients from a cardiac surgery registry who underwent isolated CABG (1,038 [19%] BITA grafts, 4,029 [72%] single internal thoracic artery [SITA] grafts, 534 [10%] vein-only grafts) between 1995 and 2008. A Cox model was used to compare survival by use of bilateral, single, or no internal thoracic artery (ITA) grafts, adjusting for baseline clinical and demographic characteristics.**

Results. **Mean follow-up was 7.1 years. Patients undergoing BITA grafting had the lowest 1-year mortality (2.4% versus 4.3% SITA grafting and 8.2% vein-only grafting; $p < 0.0001$). Relative to SITA grafting, a crude survival benefit of 54% existed for BITA grafting (hazard ratio [HR] 0.46; 95% confidence interval [CI], 0.37 to 0.57; $p < 0.0001$) with worse survival for vein-only grafts (HR, 1.16; 95% CI, 0.99 to 1.37; $p = 0.07$). After adjustment, the benefit of BITA grafting was no longer statistically significant (HR, 0.87; 95% CI, 0.69 to 1.08; $p = 0.2$). However age may be an effect modifier: a spline analysis plotting HR (BITA grafting versus SITA grafting) against age suggested a potential survival advantage associated with BITA grafting in patients younger than 69.9 years.**

Conclusions. **Bilateral internal thoracic artery grafting is a reasonable revascularization strategy in suitable patients up to age 70 years. As benefits of arterial grafting become more obvious over time, a longer period of follow-up will be needed to confirm the advantage of a BITA grafting strategy. In the meantime the BITA grafting advantage for patients older than 70 years is not clear.**

(Ann Thorac Surg 2011;92:1269–76)

Approximately 1 million patients worldwide undergo coronary artery bypass grafting (CABG) every year [1]; the current standard of care is to use 1 internal thoracic artery (ITA) and saphenous vein for the remaining bypasses, the full benefit of arterial conduits becoming most obvious after 5 years or longer. Advantages of bilateral internal thoracic artery (BITA) conduits have been known since 1999 [2, 3]; however use of BITA grafting has not been widely adopted. In North America 4% of patients who undergo CABG receive BITA grafting [4] and in Europe the proportion is 12% [5]. Reasons for these low rates include longer operation times, technical demands, risk to the patients related to sternal healing, and lower flow to the myocardium in the early hours after surgery, especially if inotropic drugs are required.

Accepted for publication May 18, 2011.

Presented at the Forty-seventh Annual Meeting of The Society of Thoracic Surgeons, San Diego, CA, Jan 31–Feb 2, 2011.

Address correspondence to Dr Kieser, Foothills Medical Centre, Rm C816 1403 29th St NW, Calgary, Alberta, Canada T2N 2T9; e-mail: t.kieserprieur@ucalgary.ca.

Coronary artery bypass grafting with BITA grafting has traditionally been reserved for the young patient. The point at which "young" becomes "old" is in transition and may continue to advance as improved public health and lifestyle changes cause people to live longer. Currently there are no age guidelines for performance of CABG with BITA grafting. The aim of this study was to determine the role advancing age might play in the decision to perform CABG with BITA grafting.

Patients and Methods

Data Sources and Study Cohort

A cohort of consecutive patients who underwent isolated primary CABG between April 1, 1995 and March 31, 2008 was identified using a local cardiac surgery database. This cohort was then linked to a second data source, the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) database, an ongoing prospective clinical data collection initiative that captures detailed clinical information on all patients

Published by Elsevier Inc

0003-4975/$36.00
doi:10.1016/j.athoracsur.2011.05.083

undergoing cardiac catheterization and subsequent interventions in the Province of Alberta, Canada since 1995 [6]. After data collection from the APPROACH database, a data enhancement process verifies patient comorbidities and maximizes data completeness [7, 8]. Follow-up mortality for all patients is ascertained through quarterly linkage to the Alberta Bureau of Vital Statistics. Excluded from this study were patients undergoing repeated CABG or CABG with concomitant valve or other operations, non-Alberta residents, and patients with incomplete surgical or comorbidity data. This study was approved by the Health Research Ethics Boards of the University of Calgary.

Clinical and Outcome Variables

APPROACH contains detailed clinical information, including patient demographics, risk factors, comorbidities, diagnosis, and the Duke Jeopardy Score. The Duke Jeopardy score, included as an index of severity of coronary artery disease, encompasses both the percentage of stenosis in a coronary lesion and the volume of myocardium subtended by the stenosis—ie, the myocardium at risk. It has been validated in the APPROACH population and has been shown to provide independent prognostic information in patients with ischemic heart disease [9, 10]. Information retrieved from the local cardiac surgery database included the number and type of grafts used. Patients were followed until March 31, 2009 for determination of all-cause mortality (including operative mortality), the primary outcome. Secondary outcomes included repeated cardiac catheterization, the need for further revascularization by percutaneous coronary intervention or repeated CABG, and death within 1 year of CABG.

Statistical Analysis

Coronary artery bypass graft patients were divided into 3 groups: those with saphenous vein-only grafts, those with SITA grafts, and those with BITA grafts. Between-group comparisons were conducted using χ^2 or analysis of variance tests as appropriate. Kaplan-Meier survival curves were produced by graft type. A Cox proportional hazards analysis was used to compare survival by graft type. Adjustment variables included demographic information, comorbidities, the cardiac catheterization indication, left ventricular ejection fraction, and Duke Jeopardy Score. A second analysis was performed using the EuroSCORE as the sole adjustment variable [11]. These different adjustment methods were undertaken as a sensitivity analysis and account for differing dimensions of risk (ie, anatomic versus comorbidity risk).

Time was calculated from the date of CABG to the date on which the patient was censored (the end of follow-up March 30, 2009) or the date that an outcome event occurred. Risk-adjusted survival curves were plotted from the proportional hazards model using the corrected group prognosis method [12]. The proportional hazards assumption was evaluated and satisfied for these multivariable survival analyses by examining plots of the log-negative-log within-group survivorship functions versus log-time and also by examining Schoenfeld residuals. A spline analysis by age was conducted to determine whether there is evidence for an age cutoff for benefit of BITA grafting relative to SITA grafting. Statistical analyses were performed with SAS version 9.2 (SAS Institute Inc, Cary, NC). Outcomes at 1 year were compared using χ^2 tests; a multivariable-adjusted unconditional logistic regression model was used to calculate the odds ratio for death at 1 year.

Results

Study Population

A total of 5,601 patients underwent primary isolated CABG from April 1, 1995 through March 31, 2008. Among this group, 10% of patients (n = 534) had CABG using saphenous vein-only grafts, 72% (4,029) had SITA grafts, and 19% (1,038) had BITA grafts. A total of 105 patients with BITA grafts (10.1%), 1,853 (46%) of patients with SITA grafts, and 225 (42.1%) patients with vein-only grafts were 70 years or older ($p < 0.0001$).

Baseline Clinical Characteristics

Baseline clinical characteristics of the study patients are shown in Table 1. Patients who received BITA grafts were younger, more often men, and had less comorbidity (except hyperlipidemia) than those receiving SITA or vein grafts, factors reflected in the lower EuroSCOREs seen in the BITA graft group. Patients with BITA grafts had higher baseline left ventricular ejection fractions and more often underwent cardiac catheterization for stable angina. Although the Duke Jeopardy Score was similarly distributed across the 3 groups, a greater proportion of patients with BITA grafts were high risk. The mean follow-up for all patients was 7.0 years (range, 0 to 13.9 years); the mean follow-up for patients with vein grafts was 7.9 years, for patients with SITA grafts it was 7.1 years, and for patients with BITA grafts it was 6.4 years.

Survival and Postoperative Revascularization

A total of 1,233 deaths (22.0%) occurred by the end of the follow-up period. A Kaplan-Meier curve showed that crude mortality was significantly lower in patients with BITA grafts than in patients with SITA grafts and this survival difference continued to increase over prolonged follow-up (Fig 1A): (HR, 0.46; 95% CI, 0.37 to 0.57) (Table 2). After multivariable adjustment controlling for age, sex, diagnosis, comorbidities, extent of coronary disease, and left ventricular ejection fraction, the BITA advantage was no longer statistically significant (Fig 1B) (adjusted HR for mortality, 0.87; 95% CI, 0.69 to 1.09; $p = 0.22$) in a survival analysis extending to 13.9 years of follow-up. Patients with vein-only grafts fared worse than those with SITA grafts in both crude (HR, 1.16; 95% CI, 0.99 to 1.37; $p = 0.07$) and adjusted (HR, 1.14; 95% CI, 0.94 to 1.38; $p = 0.18$) analyses, but again the relationships were not statistically significant. An additional sensitivity analysis adjusting for EuroSCORE rather than APPROACH comorbidity variables yielded similar results (Table 2). To

Table 1. Characteristics of the Study Population

Variable	Vein Graft N = 534	SITA Graft N = 4,029	BITA Graft N = 1,038	*p* Value
Mean EuroSCORE (SD)	5.3 (3.1)	4.9 (2.8)	3.0 (2.3)	<0.0001
Demographics				
Mean age (SD)	66.9 (10.2)	67.6 (9.5)	58.0 (9.1)	<0.0001
Age ≥ 70	225 (42.1)	1,853 (46.0)	105 (10.1)	<0.0001
Mean follow-up (years)	7.9 (4.1)	7.1 (3.4)	6.4 (3.2)	<0.0001
Comorbidities				
Cerebrovascular disease	52 (9.7)	366 (9.1)	47 (4.5)	<0.0001
Pulmonary disease	81 (15.2)	578 (14.4)	122 (11.8)	0.07
Congestive heart failure	91 (17.0)	594 (14.7)	97 (9.3)	<0.0001
Liver/gastrointestinal disease	31 (5.8)	291 (7.2)	74 (7.1)	0.48
Peripheral artery disease	81 (15.2)	441 (11.0)	77 (7.4)	<0.0001
Renal disease (Creatinine level > 200 mol/L)	33 (6.2)	137 (3.4)	32 (3.1)	0.003
Malignancy	38 (7.1)	219 (5.4)	36 (3.5)	0.005
Hypertension	335 (62.7)	2,629 (65.3)	678 (65.3)	0.51
Hyperlipidemia	339 (63.5)	2,652 (65.8)	828 (79.8)	<0.0001
Dialysis	10 (1.9)	48 (1.2)	16 (1.5)	0.34
Diabetes	146 (27.3)	1,057 (26.2)	289 (27.8)	0.54
Former smoker	208 (39.0)	1,847 (45.8)	433 (41.7)	0.002
Thrombolysis	36 (6.7)	235 (5.8)	68 (6.6)	0.54
Cardiac history				
Previous myocardial infarction	306 (57.3)	2,097 (52.1)	435 (41.9)	<0.0001
Previous coronary artery bypass grafting	6 (1.1)	48 (1.2)	12 (1.2)	0.98
Previous percutaneous coronary intervention	63 (11.8)	429 (10.7)	79 (7.6)	0.007
Indication for catheterization				<0.0001
Stable angina	147 (27.5)	1,369 (34.0)	390 (37.6)	
Myocardial infarction	161 (30.2)	1,265 (31.4)	340 (32.8)	
Unstable angina	207 (38.8)	1,228 (30.5)	279 (26.9)	
Other	19 (3.6)	167 (4.1)	29 (2.8)	
Left ventricular ejection fraction				0.0004
> 50%	338 (63.3)	2,681 (66.5)	737 (71.0)	
35%–50%	108 (20.2)	896 (22.2)	213 (20.5)	
20%–34%	37 (6.9)	216 (5.4)	35 (3.4)	
<20%	1 (0.2)	14 (0.4)	4 (0.4)	
Not done	37 (6.9)	165 (4.1)	41 (4.0)	
Unknown	13 (2.4)	57 (1.4)	8 (0.8)	
Jeopardy score				
0/12	5 (0.9)	22 (0.6)	6 (0.6)	0.98
2/12	23 (4.3)	133 (3.3)	33 (3.2)	
4/12	51 (9.6)	368 (9.1)	100 (9.6)	
6/12	97 (18.2)	764 (19.0)	189 (18.2)	
8/12	101 (18.9)	767 (19.0)	200 (19.3)	
10/12	103 (19.3)	795 (19.7)	220 (21.2)	
12/12	154 (28.8)	1,180 (29.3)	290 (27.9)	
Duke index				0.02
Low risk[a]	73 (13.4)	548 (13.6)	105 (10.1)	
High risk[b]	297 (55.6)	2,335 (58.0)	654 (63.0)	
Left main[c]	164 (30.7)	1,141 (28.3)	278 (26.8)	
Missing/not entered	0	5 (0.1)	1 (0.1)	

[a] Duke index 1–6 (1 VD 50-75%, 1 VD 95%, 2 VD, 2 VD both 95%, 1 VD 95% PLAD, 2 VD 95% PLAD). [b] Duke index 7–11 (2 VD 95%, PLAD, 3 VD, 3 VD 1 95%, 3VD PLAD, 3VD 95% PLAD). [c] Duke index 12 or 13 (Left main, severe left main).

BITA = bilateral internal thoracic artery; EuroSCORE = European System for Cardiac Operative Risk Evaluation; PLAD = proximal left anterior descending artery; SITA = single internal thoracic artery; VD = vessel disease.

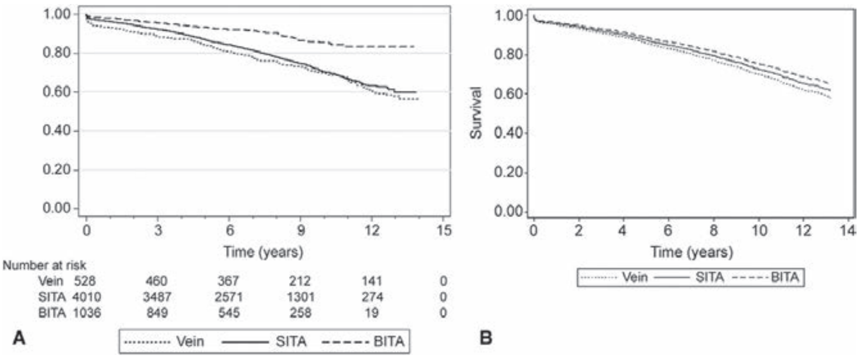

Fig 1. (A) Kaplan-Meier survival curve by conduit used (vein only, single or bilateral internal thoracic artery). (B) Multivariable Cox-adjusted survival by conduit used (vein only, single or bilateral internal thoracic artery).

specifically assess the impact of age on outcome with BITA grafts, we performed a spline analysis, which suggested that age might be an important effect modifier (Fig 2). BITA grafting appeared to be associated with improved outcomes for patients up to the age of 70 years and possibly reduced survival after age 70 years.

For the secondary outcomes, within the first year after surgery only crude mortality at 1 year was significantly lower in patients with BITA grafts (2.4%) than in patients with SITA grafts (4.3%) or in patients with vein grafts (8.2%) ($p < 0.0001$) (Table 3). A logistic regression model for mortality at 1 year gave an odds ratio (relative to SITA grafting) of 2.4 (95% CI, 1.58 to 3.66; $p < 0.001$) for vein grafts and 1.04 (95% CI, 0.64 to 1.70; $p = 0.9$) for BITA grafts.

Comment

In this population of consecutive isolated patients who underwent CABG, our work suggests that the use of BITA grafting was associated with a survival advantage in patients up to the age of 70 years that continued to increase with time, although this advantage lost statistical significance after clinical feature adjustment. These findings align with studies that suggest better outcomes with BITA grafting relative to SITA grafting.

Long-term patient outcome is directly related to coronary artery bypass durability [13]. Additionally, atherosclerosis of the ITA is quite rare [14] and patency rates of more than 90% have been demonstrated at 10 to 12 years [15–18]. As a result, the full effect of BITA grafting would be expected to continue to accumulate well beyond the relatively short 7-year follow-up period used in this analysis.

There is some support in the literature for an improved survival with BITA grafting [19, 20]. Most recently Kurlansky and colleagues [19] reported that BITA grafting offers a long-term survival at a mean follow-up of 11.5 years with an advantage over SITA grafting in propensity-matched groups. However this advantage appears to decline in the elderly, and the age at which this advantage is lost has been debated (cutoff ages of 60 to 69 have been suggested) [20, 21]. In contrast, a study of 716 patients with BITA grafts and 662 patients with SITA grafts with a mean age of 69.2 and 71.0, respectively, found mortality rates at 5.3 years of 5.2% for BITA grafts and 9.1% for SITA grafts [22]. In a large cohort study, Mohammadi and colleagues [20] found an advantage of BITA grafting over SITA grafting up to age 60 years, with a favorable trend extending to the age of 67 years (HR, 0.74; $p = 0.05$). Our results are qualitatively in agreement with those of Mohammadi and colleagues, with a signal

Table 2. Unadjusted and Adjusted Hazard Ratios by Vessel

Vessel Used	Crude Hazard Ratio (95% Confidence Interval)	Adjusted[a] Hazard Ratio (95% Confidence Interval)	EuroSCORE Adjusted[b] Hazard Ratio (95% Confidence Interval)
Vein	1.16 (0.99–1.37)	1.14 (0.94–1.38)	1.08 (0.91–1.27)
SITA	1.00	1.00	1.00
BITA	0.46 (0.37–0.57)	0.87 (0.69–1.09)	0.76 (0.61–0.94)

[a] Adjusted for age, sex, comorbidities, diagnosis, Duke Jeopardy Score and ejection fraction. [b] Adjusted for EuroSCORE only.

BITA = bilateral internal thoracic artery; EuroSCORE = European System for Cardiac Operative Risk Evaluation; SITA = single internal thoracic artery.

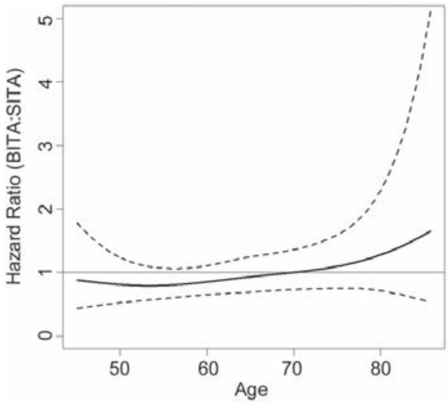

Fig 2. Relationship of hazard ratio for bilateral internal thoracic artery (BITA) relative to single internal thoracic artery (SITA) across age. The solid line is the hazard ratio and the dotted lines are the 95% confidence interval around the hazard ratio. A hazard ratio less than 1 suggests decreased mortality with BITA grafting relative to SITA grafting, as seen in this figure up to age 70 years.

of diminished relative benefit of BITA grafting becoming evident beyond the age of 70 years, suggesting extra caution when considering BITA grafting for patients older than this.

There are limitations to this study. It is observational, and we acknowledge that revascularization strategies occurred in a nonrandom fashion. We used a dataset rich in clinical detail, and although we had the ability to control for important potential confounding variables, it is possible that other factors (eg, patient fitness) are associated with both selection of BITA grafting and outcome not accounted for in our analysis. This is a single-center study; important differences may be seen across regions. In addition, BITA grafting was performed by surgeons most comfortable with the procedure and not uniformly performed by all. Weighing against these limitations are the notable study strengths of robust outcome data from an unselected regional CABG population and the rich clinical risk adjustment that we were able to undertake using various risk measurement methods that capture differing dimensions of risk (EuroSCORE, Duke Jeopardy Score, and Duke Index).

Mortality was the principal end point used in this analysis, but this is not the only or even the most important outcome of relevance to the elderly. Improvement in quality of life was previously demonstrated by our group in elderly patients receiving CABG [23]. Berreklouw and colleagues [24] reported that 47.5% of patients with BITA grafts versus 35.4% of patients with SITA grafts had an ischemic event–free existence after 13 years ($p < 0.001$). Muneretto and colleagues [25] also found better ischemia-free survival at 1 year in a prospective randomized group of 188 patients older than 70 years randomized to either total arterial grafting or SITA grafting. Recurrent angina occurred in 11.1% of the left ITA/vein group versus 2.1% of the total arterial group. Follow-up symptom status was not available for our study cohort.

Reasons why BITA grafting may be problematic in older patients include increased tissue fragility, especially in women, technical challenges with attaching the right ITA to its target arteries, and operator inexperience in performing BITA grafting in this age group. Also, BITA CABG is most likely performed in elderly patients when no adequate venous conduits exist. In addition some think that the ITA, being smaller than the saphenous vein, is not capable of supplying adequate flow to the myocardium, creating a “conduit-coronary mismatch.” Finally, concern has been expressed that BITA grafting adversely affects sternal blood flow, predisposing the patient to infection, especially in patients with diabetes [26], even though there is evidence to the contrary in patients with a broad range of comorbidities [27–36]. To date Taggart and colleagues [36] are responsible for the only study randomizing to BITA grafting or SITA grafting—a study design that reliably addresses the potential improved survival with BITA grafting. One-year results showed that BITA grafting is feasible on a routine basis; the 10-year results will determine if BITA grafting confers better survival and decreased repeated intervention.

In conclusion, 7-year observation of 5,601 patients

Table 3. Reintervention and Death Within 1 Year of Coronary Artery Bypass Grafting

	N = 5,601			
Intervention	Vein N = 534 (%)	SITA N = 4,029 (%)	BITA N = 1,038 (%)	*p* Value
Catheterization	31 (5.8)	258 (6.4)	66 (6.4)	0.87
Percutaneous coronary intervention	12 (2.3)	67 (1.7)	24 (2.3)	0.29
Repeated CABG	3 (0.6)	18 (0.5)	8 (0.8)	0.43
Revascularization (percutaneous coronary intervention or CABG)	15 (2.8)	82 (2.0)	31 (3.0)	0.13
Death	44 (8.2)	174 (4.3)	25 (2.4)	<0.0001

BITA = bilateral internal thoracic artery; CABG = coronary artery bypass grafting; SITA = single internal thoracic artery.

undergoing isolated primary CABG suggests that there is no basis for undue caution with respect to liberal and routine use of BITA grafting, at least up to age 70 years. However a trend to greater adverse outcomes after BITA grafting in patients older than age 70 years demands that caution be exercised when using this technique in older patients until further studies can clarify the nature of an adverse outcome versus age relationship in BITA grafting.

APPROACH was initially funded with a grant from the W. Garfield Weston Foundation. Ongoing operation is funded by the Provincial Wide Services Committee of Alberta Health and Wellness and the following industry sponsors: Merck Frosst Canada Inc, Roche Canada, Eli Lilly Canada Inc, Bristol-Myers Squibb, and Philips Medical Systems Canada. We appreciate support from Alberta Health Services (Calgary Area, Edmonton Area), Libin Cardiovascular Institute of Alberta, and Mazankowski Alberta Heart Institute. We gratefully acknowledge the cardiac personnel for their diligent data collection and entry. Dr Knudtson receives partial support from the Libin Trust Fund. Dr Ghali is supported by a Government of Canada Research Chair in Health Services Research and a Health Scholar award from the Alberta Heritage Foundation for Medical Research. Dr Martin is funded by Alberta Heritage Foundation for Medical Research (Alberta Innovates–Health Solution, Edmonton, AB) with a Clinical Research Fellowship. The project was also supported by funding from the Canadian Cardiovascular Outcomes Research Team (CCORT), a team grant supported by the Canadian Institutes of Health Research.

We also thank the members of the APPROACH Clinical Steering Committee. Edmonton: Drs Ross Tsuyuki (chair), Blair O'Neill, Wayne Tymchak, Michelle Graham, David Ross, Neil Brass. Calgary: Drs Michael Curtis, William A. Ghali, Merril L Knudtson, Andrew Maitland, L. Brent Mitchell, Mouhieddin Traboulsi.

Finally we would to like to acknowledge and thank the cardiac surgeons of the Calgary zone whose patients are included in this study: Drs Jehangir Appoo, Alexander Bayes, John Burgess, Paul Fedak, William Kidd, Teresa Kieser, Andrew Maitland, and Gregory Prystai.

References

1. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularization on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. Lancet 2001;358:870–5.
2. Lytle BW, Blackstone EH, Loop FD, et al. Two internal thoracic artery grafts are better than one. J Thorac Cardiovasc Surg 1999;117:855–72.
3. Loop FD, Lytle BW, Cosgrove DM, et al. Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. N Engl J Med 1986;314:1–6.
4. Tabata M, Grab JD, Khalpey Z, et al. Prevalence and variability of internal mammary artery graft use in contemporary multivessel coronary artery bypass graft surgery: analysis of the Society of Thoracic Surgeons National Cardiac Database. Circulation 2009;120:935–40.
5. Kappetein AP. Bilateral mammary artery versus single mammary artery grafting: promising early results: but will the match finish with enough players? Eur Heart J 2010;31: 2444–6.
6. Ghali WA, Knudtson ML. Overview of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease. On behalf of the APPROACH investigators. Can J Cardiol 2000;16:1225–30.
7. Norris CM, Ghali WA, Knudtson ML, Naylor CD, Saunders LD. Dealing with missing data in observational health care outcome analyses. J Clin Epidemiol 2000;53:377–83.
8. Faris PD, Ghali WA, Brant R, Norris CM, Galbraith PD, Knudtson ML. Multiple imputation versus data enhancement for dealing with missing data in observational health care outcome analyses. J Clin Epidemiol 2002;184–18355:
9. Califf RM, Phillips HR, III, Hindman MC, et al. Prognostic value of a coronary artery jeopardy score. J Am Coll Cardiol 1985;5:1055–63.
10. Graham MM, Faris PD, Ghali WA, et al. Validation of three myocardial jeopardy scores in a population-based cardiac catheterization cohort. Am Heart J 2001;142:254–61.
11. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16: 9–13.
12. Ghali WA, Quan H, Brant R, et al. Comparison of 2 methods for calculating adjusted survival curves from proportional hazards models. JAMA 2001;286:1494–7.
13. FitzGibbon GM, Kafka HP, et al. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1388 patients during 25 years. J Am Coll Cardiol 1996;28:616–26.
14. Sisto T, Isola J. Incidence of atherosclerosis in the internal mammary artery. Ann Thorac Surg 1989;47:884–6.
15. Lytle BW, Loop FD, Cosgrove DM, Ratliff NB, Easley K, Taylor PC. Long-term (5 to 12 years) serial studies of internal mammary artery and saphenous vein coronary bypass grafts. J Thorac Cardiovasc Surg 1985;89:248–58.
16. Sabik JF III, Lytle BW, Blackstone EH, Houghtaling PL, Cosgrove DM. Comparison of saphenous vein and internal thoracic artery graft patency by coronary system. Ann Thorac Surg 2005;79:544–51.
17. Cameron A, Kemp HG Jr, Green GE. Bypass surgery with the internal mammary artery graft: 15 year follow-up. Circulation 1986;74(5 Pt 2):III30–36.
18. Stevens LM, Carrier M, Perrault LP, et al. Single versus bilateral internal thoracic artery grafts with concomitant saphenous vein grafts for multivessel coronary artery bypass grafting: effects on mortality and event-free survival. J Thorac Cardiovasc Surg 2004;127:1408–15.
19. Kurlansky PA, Traad EA, Dorman MJ, Galbut DL, Zucker M, Ebra G. Thirty-year follow-up defines survival benefit for second internal mammary artery in propensity-matched groups. Ann Thorac Surg 2010;90:101–8.
20. Mohammadi S, Dagenais F, Doyle D, et al. Age cut-off for the loss of benefit from bilateral internal thoracic artery grafting. Eur J Cardiothorac Surg 2008;33:977–82.
21. Toumpoulis IK, Anagnostopoulos CE, Balaram S, Swistel DG, Ashton RC Jr, DeRose JJ Jr. Does bilateral internal thoracic artery grafting increase long-term survival of diabetic patients? Ann Thorac Surg 2006;81:599–606.
22. Gansera B, Loef A, Angelis I, Gillrath G, Schmidtler F, Kemkes BM. Double thoracic artery—halved mid-term mortality? A 5-year follow-up of 716 patients receiving bilateral ITA versus 662 patients with single ITA. Z Kardiol 2004;93: 878–83.
23. Graham M, Norris C, Galbraith P, Knudtson M, Ghali W; APPROACH Investigators. Quality of life after coronary revascularization in the elderly. Eur Heart J 2006;27:1690–8.
24. Berreklouw E, Rademakers PP, Koster JM, van Leur L, van der Wielen BJ, Westers P. Better ischemic event-free survival after two internal thoracic artery grafts: 13 years of follow-up. Ann Thorac Surg 2001;72:1535–41.
25. Muneretto C, Negri A, Bisleri G, et al. Is total arterial myocardial revascularization with composite grafts a safe and useful procedure in the elderly? Eur J Cardiothorac Surg 2003;23:657–64.

26. Kouchoukos NT, Wareing TH, Murphy SF, Pelate C, Marshall WG Jr. Risks of bilateral internal mammary artery bypass grafting. Ann Thorac Surg 1990;49:210–7.
27. Barner HB, Sundt TM III, Bailey M, Zang Y. Midterm results of complete arterial revascularization in more than 1,000 patients using an internal thoracic artery/radial artery T graft. Ann Surg 2001;234:447–52.
28. Sergeant P, Blackstone E, Meyns B. Validation and interdependence with patient-variables of the influence of procedural variables on early and late survival after CABG. K.U.Leuven Coronary Surgery Program. Eur J Cardiothorac Surg 1997;12:1–19.
29. Gansera B, Schmidtler F, Gillrath G, et al. Does bilateral ITA grafting increase perioperative complications? Outcome of 4462 patients with bilateral versus 4204 patients with single ITA bypass. Eur J Cardiothorac Surg 2006;30:318–23.
30. Hirotani T, Kameda T, Kumamoto T, Shirota S, Yamano M. Should arterial grafts be used for urgent coronary artery bypass surgery? [in Japanese] Kyobu Geka 2000;53:69–73.
31. Bonacchi M, Maiani M, Prifti E, Di EG, Di EM, Leacche M. Urgent/emergent surgical revascularization in unstable angina: influence of different type of conduits. J Cardiovasc Surg (Torino) 2006;47:201–10.
32. Kinoshita T, Asai T, Hosoba S, et al. Does off-pump bilateral internal thoracic artery grafting increase operative risk in dialysis patients? Heart Surg Forum 2010;13(2):E74–9.
33. Lev-Ran O, Mohr R, Amir K, et al. Bilateral internal thoracic artery grafting in insulin-treated diabetics: should it be avoided? Ann Thorac Surg 2003;75:1872–7.
34. Momin AU, Deshpande R, Potts J, et al. Incidence of sternal infection in diabetic patients undergoing bilateral internal thoracic artery grafting. Ann Thorac Surg 2005;80:1765–72.
35. Pevni D, Uretzky G, Mohr A, et al. Routine use of bilateral skeletonized internal thoracic artery grafting: long-term results. Circulation 2008;118:705–12.
36. Taggart D, Altman D, Gray A, et al. Randomized trial to compare bilateral versus single internal mammary coronary artery bypass grafting: 1-year results of the Arterial Revascularisation Trial (ART). Eur Heart J 2010;31:2470–81.

DISCUSSION

DR JENNIFER L. ELLIS (Washington, DC): A great talk. Thank you very much. Can you talk about where you put that second arterial graft and whether or not you think that is important to put it on the right side versus the left side?

DR KIESER: Thank you for your question Dr Ellis. I can't speak for all of my colleagues, but I believe most of the time we tend to put it on the circumflex system through the transverse sinus, although Dr Sabik has a paper out in *Circulation* that said there wasn't much difference whether you put it on the right or the left. I can speak for my own practice: two thirds went to the circumflex system and about one third most often to the PDA, because the right is often not negotiable for bypass.

DR JOSEPH F. SABIK (Cleveland, OH): From this morning's discussion there was a lot of talk about who we should use, and I think everyone kind of agrees about the age cutoff. At one time it used to be 60; now we are seeing it is probably closer to 70. Do you have any insight into other things that might be important? People talked about size, in particular, BMI greater than 40, or diabetes.

DR KIESER: Thank you Dr Sabik. I think certainly one of the biggest risks that deter people from doing a bilateral internal thoracic artery procedure is the risk for infection. I just know from a bit of work that I have done on my own that the one subgroup of diabetics that I do not do double mammaries in are obese women. They do, in my experience, have a higher risk of infection. I think with the elderly, you can have trouble with fragility of tissues and that is why we are putting a note of caution in this paper. If you look at the number of patients who are under the age of 70, if you think our average age is 65 to 66 years, maybe 66% to 70% of patients are under the age of 70. So if we just did 50% of patients under the age of 70, we would be doing 34% mammaries, and if we did 80%, you can't do bilateral mammaries on everybody, but if you did 80%, you would be doing double mammaries in 55%, which is a far cry from 4% and 12%.

One part of me didn't want to talk about the downside, but if you look at the upside, it really increased the number. For the spline diagram, I just want to say one thing; it is analogous to something I believe we see in our everyday life, the milk cartons. What is written on our milk cartons is "it is 'best before'"; it does not say "bad after."

DR SUDHIR P. SRIVASTAVA (Atlanta, GA): I think I agree exactly. One comment and a question. The comment is that I think this age cutoff obviously is being discussed in light of the sternotomy cases where there are certain concerns, but I think we have seen that in less invasive approaches or nonsternotomy approaches we have used bilateral IMAs without any concern, elderly patients in their 80s and all that, and we would love not to give them leg incisions, because those are the patients that often will get into healing issues and so on. So could you comment on that?

DR KIESER: Thank you. I couldn't agree more. I think the same, though, you could say for off pump versus on pump. I think the ideal operation for an 82-year-old is a double mammary off pump; they do very, very well, And just because they're 82, if I can do a no-touch aorta off pump, I think that's the best. I don't have any experience in minimally invasive, not yet. I'm not sure I will, to be quite honest. But thank you for your comments. I agree.

DR WALTER E. MCGREGOR (Pittsburgh, PA): A significant limitation of the right internal mammary artery is that it is just not as versatile as a vein graft. Can you please comment on what techniques you use in the operating room to increase this conduit's utility, ie, gaining length, proximal anastomosis, just overall grafting strategy?

DR KIESER: Thank you. That is very, very good. Honestly, I think to do 2 internal thoracic—well, the left, you're okay, but the right, skeletonization is a big, big plus. By the time you go to use the right mammary, if you have wrapped it in a papaverine sponge, it has grown longer. If I am putting the RITA to the RCA system, I can get 80% of my RITAs to the PDA. Sometimes there are a few little tricks. When I bring the RITA to the right, if I bring it to the main right, I bring it through an incision in the pericardium just above the superior vena cava, and if I am bringing it to the PDA, I bring it outside the pericardium through an incision just opposite, just above the inferior vena cava, so it comes directly as the crow flies, and it always, almost always, reaches. Less than 5% of double mammaries in my hands are attached to the aorta. Skeletonization I think is the biggest, biggest plus.

DR JAMES TATOULIS (Parkville, Victoria, Australia): I enjoyed your talk and obviously I am a believer. To follow on from the previous question, do you have much experience in and can you comment about the use of free internal thoracic artery grafts, particularly the free RITA, and techniques to handle it and make it more versatile and more comfortable to use?

DR KIESER: Thank you very much Dr Tatoulis. Certainly it is excellent to do an ITA where you can, but an in situ ITA has only 1 man-made anastomosis, and the fewer man-made, the more God-made anastomoses, the longer your conduit will last. This is just a personal bias that I have. I certainly have used what I call creative arterial grafting where you take bits of radial artery to make it reach an ITA and RITA to a huge heart. It is all within the spectrum of arterial grafting, because you can't just go and get more ITA, you can't just go and get more radial artery like you can vein, so it is difficult sometimes.

DR RAVISHANKAR RAMAN (Philadelphia, PA): I enjoyed your presentation, and I am glad this generated a good discussion about bilateral internal mammary arteries. In our center, we harvest bilateral internal mammary arteries in 75% of cases, including valvular heart surgery. I entirely agree with your comment, the older the patient, the better it is to use bilateral internal mammary arteries, as stroke incidence is significantly lower with a no-touch technique.

Thank you.

DR KIESER: Thank you very much.

Notice From the American Board of Thoracic Surgery Regarding Trainees and Candidates for Certification Who Are Called to Military Service Related to the War on Terrorism

The Board appreciates the concern of those who have received emergency calls to military service. They may be assured that the Board will exercise the same sympathetic consideration as was given to candidates in recognition of their special contributions to their country during the Vietnam conflict and the Persian Gulf conflict with regard to applications, examinations, and interruption of training. If you have any questions about how this might affect you, please call the Board office at (312) 202-5900.

Valerie W. Rusch, MD
Chair
The American Board of Thoracic Surgery

PART 4

REDUCING THE RISKS ASSOCIATED WITH BILATERAL INTERNAL MAMMARY ARTERY GRAFTING

Chapter 8

Transit-time flow predicts outcomes in coronary artery bypass graft patients: a series of 1000 consecutive arterial grafts

Kieser TM, Rose S, Kowalewski R, Belenkie I

Eur J Cardiothorac Surg 2010;38:155-162

Transit-time flow predicts outcomes in coronary artery bypass graft patients: a series of 1000 consecutive arterial grafts☆

Teresa Mary Kieser *, Sarah Rose, Ryszard Kowalewski, Israel Belenkie

Department of Cardiac Sciences, LIBIN Cardiovascular Institute of Alberta, University of Calgary, Calgary, Alberta, Canada

Received 30 September 2009; received in revised form 8 January 2010; accepted 14 January 2010; Available online 21 February 2010

Abstract

Objective: This study was undertaken to evaluate transit-time flow (TTF) as a tool to detect technical errors in arterial bypass grafts intra-operatively and predict outcomes. **Methods:** TTF's three parameters, pulsatility index (PI, index of resistance), flow (cc min^{-1}) and diastolic filling (DF, proportion of diastole with coronary flow), were measured in 990/1000 (99%) of arterial grafts in 336 consecutive patients, prospectively enrolled in a database. Grafts were revised when TTF findings supported the otherwise suspected graft malfunction. If no other signs/suspicion of graft malfunction existed (normal electrocardiogram (EKG), stable haemodynamics and unchanged ventricular function on trans-oesophageal echocardiography (TEE)), and the PI was >5, grafts were not revised. Major adverse cardiac events (MACEs: recurrent angina, perioperative myocardial infarction, postoperative angioplasty, re-operation and/or perioperative death) were related to TTF measurements. **Results:** The average number of grafts per patient was 3.02, of which 99% were arterial. Satisfactory grafts were achieved in 916/990 (93%) of the grafts, with flows from 34 to 61 cc min^{-1}, PI $\leq$5 and DF of 62—85%. Fourteen conduits, 20 grafts (2%) suspected to be problematic, were revised. Patients were divided into two groups: 277 (82%) with at least one graft with PI $\leq$5 and 59 (18%) with a PI >5. MACE occurred in 25 (7.4%) patients — 15/277 patients with a PI $\leq$5 (5.4%) and 10/59 with a PI >5 (17%, p = 0.005). Mortality following non-emergent surgery was significantly higher in patients with a PI >5 (5/54, 9%) than in patients with a PI $\leq$5 (5/250, 2%, p = 0.02). Flow and DF were not predictive of outcomes. **Conclusion:** A high PI predicts technically inadequate arterial grafts during surgery — even if all other intra-operative assessments indicate good grafts; it also predicts outcomes, particularly mortality.

Keywords: Transit-time flow; Coronary artery bypass surgery; Arterial grafts; Outcomes

1. Introduction

Early postoperative graft failure following coronary artery bypass graft (CABG) surgery is associated with high morbidity and mortality [1—4]. Surgeons generally rely on finger palpation assessment of the pulse in the bypass graft; recent data suggest that only 20% of cardiac surgeons in North America use transit-time flow (TTF) measurement to assess grafts.[1] It is well established that arterial grafting with internal thoracic arteries confers long-term benefit [5—7]; a reliable method to assess graft function before completing the operation could potentially improve outcomes. There are no published studies of this size evaluating TTF in a pure series of arterial grafts.

In the present study, we used TTF in 336 consecutive patients to assess the value of this method in predicting postoperative major adverse cardiac events (MACEs). Our findings suggest that the pulsatility index (PI), one of three TTF measurements, is highly predictive of outcomes.

2. Materials and methods

This study is a retrospective analysis of data from consecutive patients of a single surgeon in whom TTF was first used in our institution for bypass graft assessment intra-operatively. Beginning April 2004, TTF was used in all but three patients (with 10 grafts for whom the equipment was either in use or not functioning) until the number of 1000 consecutive arterial grafts were reached (April 2007). This study was submitted to our institutional Research Ethics Board and individual patient consent was waived.

2.1. Surgical details

Intermittent antegrade warm blood for myocardial protection and systemic hypothermia at 32 °C were used. Internal thoracic conduits were harvested in a skeletonised

☆ Presented at the 23rd Annual Meeting of the European Association for Cardio-thoracic Surgery, Vienna, Austria, October 18—21, 2009.

* Corresponding author. Address: Foothills Medical Centre, Rm C 816, 1403 29th St. NW, Calgary, Alberta, Canada T2N 2T9. Tel.: +1 403 944 8449; fax: +1 403 944 4895.

E-mail address: t.kieserprieur@ucalgary.ca (T.M. Kieser).

[1] Milstein H. Introductory Letter Graft Patency.com.

1010-7940/$ — see front matter © 2010 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.ejcts.2010.01.026

manner using a harmonic scalpel. Radial artery conduits were harvested in a non-skeletonised manner, also with a harmonic scalpel. High spinal anaesthesia (local anaesthetic and opioid) supplemented by light general anaesthesia was used; intra-operative trans-oesophageal echocardiography (TEE) was also used except where contraindicated. Patients with radial artery conduits received long-acting nitrates for 6 weeks to prevent arterial spasm.

2.2. TTF assessment

TTF measurement provides three parameters: PI, mean flow and diastolic filling (DF). Abnormal values for bypass grafts for these three parameters used in this study were as follows: PI >5, flow <15 cc min^{-1} and DF <25. A PI value ≤5, as recommended by the manufacturer (MediStim Oslo, Norway),[2] was chosen as the principal measure of graft adequacy. The cut-off value for flow has not yet been defined in the literature and was defined as <15 cc min^{-1} to be consistent with that used in several previous studies [9—12]. Similarly for DF, an optimal cut-point has not been clarified and, therefore, after consultation with MediStim personnel, it was defined as <25,[3] a value well below the accepted range of 45—80 recommended by the manufacturer.[4]

The measurements were performed three times for each graft — after removal of the cross-clamp with a beating heart, off-pump before protamine and then off-pump after protamine administration. Only the post-protamine value was used for the present analysis. Probe sizes were selected to match the largest arterial conduit, skeletonising a small portion of the radial artery when necessary. Grafts were revised if a poorly functioning graft was suspected employing usual clinical criteria (electrocardiogram (EKG) changes, haemodynamic instability and new regional wall motion abnormalities on TEE). For the most part, if the TTF values alone indicated a poor graft, the grafts were not revised. Occasionally, a graft was revised if the TTF value was surprisingly abnormal or corroborated the suspicion of a poor graft. Individual graft measurement for sequential grafts was done whenever possible by measuring the whole graft and the 'in-between segment'. This was usually only possible for grafts on the anterior surface of the heart (left anterior descending coronary artery (LAD) region) because the necessary displacement of the heart (causing blood pressure (BP) drop) precluded measurement of this segment in sequential grafts to the posterior and inferior regions of the left ventricle. Perioperative mortality was defined as death within 30 days of surgery or during the same hospitalisation if it was longer.

2.3. Data collection

All patients were entered at the time of initial cardiac catheterisation into a provincial database (APPROACH: Alberta Provincial Program for Outcome Assessment in Coronary Heart disease) [8]. APPROACH is an ongoing prospective data collection initiative in the province of Alberta in which patients are followed up long term to assess outcomes. Patients were seen 6—8 weeks postoperatively by the operating surgeon and the mean follow-up was 3 years.

2.4. Statistical analysis

Continuous variables are expressed using the median and interquartile range since the distributions were highly skewed. Exact binomial 95% confidence intervals (CIs) were calculated for proportions. The data of two independent groups were compared by Fisher's exact test (FET). Initially, a univariate logistic regression analysis was done for each of the potential predictor variables of MACE. Variables that were significant at $p < 0.10$ were also included in a multivariate regression model. Statistical analyses were performed using Stata.8.0 (StataCorp, College Station, TX, USA). A p value of <0.05 was considered to be statistically significant.

3. Results

3.1. TTF measurements

Demographics of the patient population are shown in Table 1. A total of 336 consecutive patients had 1015 grafts, of which 1000 were arterial. TTF was used to measure flow in 990 (99%) of the grafts, which included single (grafts with only one distal anastomoses), sequential (grafts with one or more side-to side and one end-to-side anastomoses) and composite (grafts with two separate conduits joined to make 'Y' or 'T' graft) left internal thoracic arteries (LITAs), single and sequential right internal thoracic arteries (RITAs), single and sequential radial arteries and single inferior epigastric arteries (Table 2). Fifteen primary vein grafts were used and five arterial grafts were replaced with saphenous veins at a second emergent operation in four patients (one of the five arterial grafts had a PI >5). Sequential grafts comprised 111/323 (34%) of LITA conduits and 66/239 (28%) of radials. Of the 1000 arterial grafts, 693 (69%) were internal thoracic arteries, and 234/336 patients (70%) of the patients had bilateral internal thoracic artery (BITA) grafts. Almost all the operations were on-pump (95%); off-pump was done either

Table 1
Patient demographics.

Average age (range)	64 years (36—86 years)
Male	79%
Out-patient	42%
In-patient[a]	49%
Emergent	10%
Diabetes	35%
Hypertension	65%
Hyperlipidemia	68%
Active smoker	24%
Past smoker	58%
Never smoked	18%
Ejection fraction <30%	7.4%

[a] In-patient — patient considered too unstable to be discharged home before undergoing surgery.

[2] Karamanoukian HL, Donias HW. Seeing is Believing Intraoperative Graft Assessment During on- and Off-Pump Coronary Bypass Surgery; Product Monograph MediStim.

[3] Personal communication with MediStim representative Andreas Koop.

[4] Personal communication with Medi-Stim representative Clemens Kuhn-Neureuther.

Table 2
Conduit type and number of grafts for each type of conduit.

Conduit type	Number of conduits	Number of grafts
Single LITA	189	189
Sequential LITA	111	222
Composite LITA	23	29[a]
Single RITA	236	236
Sequential RITA	8	17[b]
Radial	173	173
Sequential radial	66	132
IEA	2	2
Vein	13	15
Total	821	1015

IEA, inferior epigastric artery; LITA, left internal thoracic artery; RITA, right internal thoracic artery.
[a] Includes six composite LITA's made with only LITA.
[b] Includes one triple sequential RITA.

for single grafts or in patients with a calcified ascending aorta.

Satisfactory grafts were those grafts with a PI $\leq$5. Suboptimal grafts were those grafts with a PI of $>$5. As many as 916 of the 990 grafts assessed (93%) were deemed satisfactory (a PI value $\leq$5). The remaining 74 grafts (7%) with a PI value $>$5 occurred in 59 of the 336 patients (18%). None of the patients in the latter group showed any other signs of graft malfunction, such as EKG changes, regional wall motion abnormalities on TEE or haemodynamic compromise. Table 3 shows the TTF values for the grafts deemed satisfactory and Table 4 shows the values for the grafts deemed suboptimal.

As seen in Table 3 (satisfactory grafts), the mean PI values for the individual conduits ranged from 1.7 to 3.1 and the DF values from 62% to 73%. Median flow in the major single conduits (LITA, RITA and radial) was 39, 32 and 34 cc min^{-1}, respectively (average 35 cc min^{-1}). In the sequential grafts (LITA, RITA and radial), the median flow was 43, 45.5 and 42 cc min^{-1}, respectively (average 43.5 cc min^{-1}), and the composite grafts had the highest median flow (54 cc min^{-1}). We found that sequential grafts had greater flow than single conduits and when these 'in-between segments' were in a technically easy accessible location to measure, the individual components could be evaluated. Flow in the sequential grafts was 1.24 times higher, and flow in the composite grafts was 1.5 times higher than flow in single conduits. For the measured sequential LITA grafts, one coronary artery territory was served by the majority of the sequential conduits (107/110, 97%), whereas two coronary artery territories were served by composite grafts in the majority of cases (21/23 grafts, 91%).

Table 4 shows the TTF parameters for the suboptimal grafts: for all types of grafts, the median PI was higher ranging from 5.8 for the sequential radial grafts to 8.8 for the single radial grafts. The single RITA group had the highest number of grafts with a PI $>$5. (14.2% compared with 3.7% single LITAs, 5.5% sequential LITAs, 4.3% composite LITAs, 0% sequential RITAs, 7.7% single radial grafts, 4.6% sequential radial grafts and one of two IEAs (Inferior Epigastric Arteries)). Fig. 1(a) and (b) shows examples of TTF values of a good and suboptimal graft, respectively.

Table 3
TTF values of satisfactory grafts.

Conduit	*n* (%)	PI	Flow	DF
LITA-single	180/187 (96)	2.3 (1.8–2.8)	39 (26–55)	72 (64–77)
LITA-Seq	104/110 (95)	2.3 (1.9–2.9)	43 (29–62)	73 (67–80)
LITA-Comp	22/23 (96) (27grafts)	1.7 (1.3–2.7)	54 (29–95.5)	69 (66.5–73)
RITA-single	199/232 (86)	2.5 (1.9–3.3)	32 (22–47)	68 (60–74)
RITA-Seq	8/8 (100) (17 grafts)	3.0 (2.0–3.4)	45.5 (32.3–71.3)	64.5 (53–71)
Radial-single	155/168 (92)	1.9 (1.4–2.7)	34 (19–53)	62 (56–68)
Radial-Seq	62/65 (95)	1.9 (1.6–2.7)	42 (23.3–60)	67 (62.3–73)
IEA	1/2 (50)	3.1	4	71
Vein	15/15 (100)	2.4 (1.1–3.6)	38.5 (28–80)	64 (63–66)
Total	926			

Values are median and interquartile ranges. LITA, left internal thoracic artery; RITA, right internal thoracic artery; IEA, inferior epigastric artery; PI, pulsatility index; DF, diastolic filling; Seq, sequential; Comp, composite.

Table 4
TTF values of suboptimal grafts.

Conduit	*n* (%)	PI	Flow	DF
LITA-single	7/187 (3.7)	7.8 (7.2–12.3)	16 (6–24)	62.5 (46.5–92)
LITA-Seq	6/110 (5.5)	6.0 (5.2–6.1)	21 (9–25)	87 (46–98)
LITA-Comp	1/23 (4.3) (2 grafts)	6.1	21	44
RITA-single	33/232 (14.2)	7.5 (6.2–9.7)	11 (7–17)	49 (36–66.5)
RITA-Seq	0			
Radial-single	13/168 (7.7)	8.8 (6.3–10.5)	10 (5–12)	54 (41.5–60)
Radial-Seq	3/65 (4.6%)	5.8 (5.6–8.2)	9 (5.5–13)	81 (72.5–89.5)
IEA	1/2 (50%)	6.2	5	100
Vein	0			
Total	74 (7.4%)			

Values are median and interquartile ranges. DF, diastolic filling; IEA, inferior epigastric artery; LITA, left internal thoracic artery; PI, pulsatility index; RITA, right internal thoracic artery; Seq, sequential; Comp, composite.

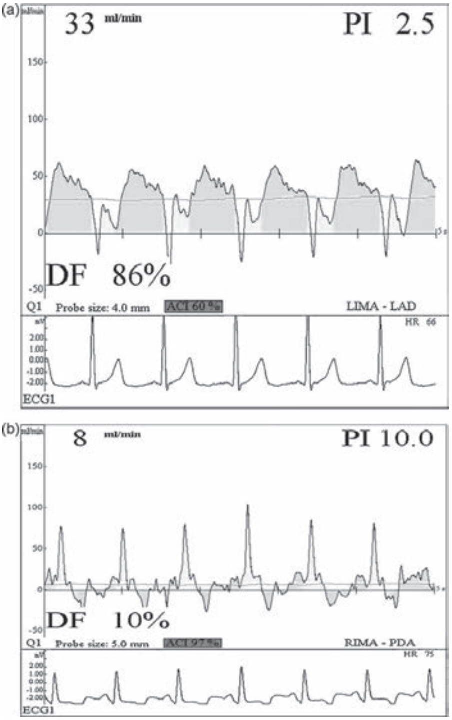

Fig. 1. (a) Example of TTF flow curve and TTF parameters in patent bypass. (b) Example of TTF trace of suboptimal graft.

3.2. Intra-operative revisions

Fifteen conduits in 14 patients, responsible for 20 grafts (2%), were revised. Simple corrections were required in five grafts (four conduits) by preventing twisting of the graft or tendency to flip, by incision of an obstructing pericardial edge or by correcting spasm. Ten conduits responsible for 15 grafts required major revisions: redo distal anastomosis (four conduits, five grafts), direct attachment of conduit to aorta or another conduit (seven conduits, nine grafts), endarterectomy (one conduit, one graft) or replace with a vein (one conduit, two grafts). (Some patients required more than one type of revision.) Most of the revisions (19/20) were performed before protamine administration: five grafts after the first TTF measurements (on-pump, cross-clamp off), 14 grafts when a problem was noticed off-pump and one revision was required after protamine administration. The decision was made to revise when other signs of graft malfunction occurred (abnormal wall motion on TEE in two patients and ventricular fibrillation in one patient), when all three TTF parameters suggested an unanticipated poorly functioning graft (eight patients) or when there was a high index of suspicion that the graft was not good and was associated with poor TTF parameters (three patients). After revision, PI improved in 17 of the 20 grafts and 16 of the 17 grafts had an improved PI to a value <5. The TTF values listed were for the revised grafts.

Table 5
Relations between TTF and MACE.

	MACE			Mortality			Deaths excluding 32 emergency patients		
	Patients (*N*)	%	*p* value	Patients (*N*)	%	*p* value	Patients (*N*)	%	*p* value
PI									
>5	10/59	17%	0.005	7/59	12%	0.011	5/54	9%	0.020
≤ 5	15/277	5%		9/277	3%		5/250	2%	
Flow									
<15	8/73	11%	0.209	4/73	5%	0.757	3/69	4%	0.700
≥ 15	17/263	6%		12/263	5%		7/235	3%	
DF[a]									
<45	6/43	6%	0.124	4/43	9%	0.256	4/40	10%	0.043
≥ 45	18/263	14%		12/263	5%		6/234	3%	

Flow (cc min^{-1}). PI, pulsatility index; DF, diastolic filling.
[a] DF recorded in 306/336 patients (91%) (DF is dependent on the EKG trace, which was not always acceptable).

3.3. Major adverse cardiac events

Twenty-five (7.4%) patients suffered 41 (95% CI 4.9—1.8%) MACEs postoperatively — recurrent angina: 6/336 (1.8%), perioperative myocardial infarction: 9/336 (2.7%), percutaneous coronary intervention (PCI): 6/336 (1.8%), early re-operation (no late re-operations): 4/336 (1.2%) and/or perioperative death: 16/336 (4.8%). Excluding emergency operations (patients requiring surgery within 24 h of known requirement for surgery), operative mortality was 3.3%. MACE occurred in 10/59 (17%) of those patients with at least one bypass graft with a PI value >5, and in 15/277 (5.4%) of those with a PI ≤ 5 for all bypasses ($p = 0.005$). Excluding 32 emergency operations from these two groups (two deaths out of the five with a high PI, and four deaths out of the 27 with a low PI), there were still significantly more deaths in the high PI group: 5/54 (11%; 95% CI 4.4—23.4) compared to 5/250 (2%; 95% CI 0.4—4.0 patients in the low PI group ($p = 0.02$).

A flow value <15 cc min^{-1} and a DF value of <45 did not predict MACE, including cardiac death, with the possible exception of a mortality difference using DF to assess graft function only after emergency cases were excluded (Table 5).

The variables PI >5, age (per 10 years) and admission status were all significant predictor variables of MACE at $p < 0.05$. No other variable was significant at $p < 0.10$ and, therefore, no other variables were included in the multivariate regression analysis. All three variables were independent significant predictors of MACE in the multivariate regression model. Note that although the variables were significant, the CIs are wide due to the small number of MACE. The multivariate logistic regression model showed that PI >5 was a significant predictor of MACE (odds ratio (OR) = 4.23, 95% CI 1.7—10.6, $p = 0.002$) after controlling for admission status, that is, for a given admission status and age, the risk of MACE was 4.2 times higher when the PI >5 (Table 6).

Table 6
Logistic regression analysis predicting MACE.

Univariate

Variable	Odds ratio	95% CI	p value
Significant at $p < 0.05$			
PI >5	3.56	1.51, 8.39	0.004
Age (per 10 years)	1.57	1.04, 2.37	0.033
Admission			
Out-patient	1		
In-patient	4.6	1.3, 16.23	0.018
Emergent	12.79	3.1, 52.8	<0.001
Non-significant at $p < 0.10$			
Male	0.54	0.22, 1.31	0.172
Diabetes	0.7	0.28, 1.73	0.440
Hypertension	1.15	0.48, 2.74	0.758
Hyperlipidemia	1.55	0.6, 3.99	0.368
Smoking status			
None	1		
Current	1.01	0.22, 4.71	0.987
past	1.16	0.29, 4.64	0.837
Ejection fraction	0.5	0.06, 3.83	0.502
On-pump	0.35	0.09, 1.29	0.115

Multivariate

Variable	Odds ratio	95% CI	p value
PI >5	4.23	1.69, 10.59	0.002
Age (per 10 years)	1.67	1.08, 2.57	0.022
Admission			
Out-patient	1.00		
In-patient	4.61	1.28, 16.58	0.019
Emergent	15.29	3.52, 66.37	<0.001

We examined in detail the 10 patients with high PI values in at least one graft that also suffered MACEs and related the territory of the high PI graft to the territory causing angina, PCI and myocardial infarction. In seven of these 10 patients, there was a direct correlation: three with angina (one went on to have PCI) had verification to the same territory with regular angiography (1), computed tomography (CT) angio (1) and thallium (1). In four patients with perioperative myocardial infarction, one of whom needed emergency re-operation (all four died), the infarct was in the territory supplied by the artery with the high PI, verified by the EKG changes (2), echo changes (1) and re-operative findings (1). In the three remaining patients, although the PI was high (5.2, 6.3 and 6.9) the flows were reasonable or good (17, 42 and 64 cc min^{-1}), and the cause of death was non-cardiac (sepsis and cerebrovascular accident (CVA) (1), autopsy-documented CVA with patent bypasses (1) and intra-abdominal catastrophe (1)).

4. Discussion

In this study of 336 consecutive patients who had CABG surgery with almost exclusively arterial grafts, we have shown that the PI obtained by TTF measurement is a strong predictor of clinical outcomes, whereas flow and DF measurements were not. Thus, those patients with at least one graft with a PI value >5 were more than four times more likely to suffer an MACE postoperatively. In addition, if the operation was non-emergent, the mortality was four times higher if the PI >5. Thus, our study directly links MACEs, including operative mortality with grafts predicted, to be malfunctioning by TTF.

Several authors have also correlated adverse events with abnormal intra-operative TTF measurements. Herman et al. [13], in a study of 985 cardiac surgery patients with both arterial and venous conduits, found abnormal grafts (PI > 5) in 19% of patients; this group suffered significantly more events compared with the normal PI group (31% vs 17%, $p < 0.0001$). However, in-hospital mortality did not correlate with abnormal grafts. Becit et al. [14] compared 100 patients with 40% arterial and 60% venous grafts, before starting to use TTF with a subsequent 100 patients in whom TTF was first used; there were more adverse events in the pre-TTF patient group. Poorly functioning bypass grafts are known to be associated with postoperative morbidity and mortality. Weman et al. [4] reported that 54.7% of 223 patients who died early after CABG surgery had gross technical problems in the bypasses (unrecognised twisted conduits, stenotic anastomoses and dissections).

Using the PI to assess intra-operative graft function is simple and takes little time. This is especially important in on-pump surgery where at least three measurements are optimal; with serial measurements, a surgeon can be alerted to the presence of a poorly functioning graft before the more complex-to-reverse steps in an operation, such as coming off-pump or administering protamine.

The cut-off value of 5 for an optimal graft is suggested by the manufacturer; some authors have chosen a PI <3 as an indicator of a good graft [9,10]. Grafts with a PI value between 3 and 5 may not necessarily indicate poor graft function because parameters such as competitive flow or diffuse disease of the grafted artery can also increase resistance. Competitive flow can be assessed by snaring the native coronary proximal to the anastomosis. If neither significant competitive flow nor diffuse disease exists and the PI is suboptimal (3—5), the graft may require revision. In this study, 93% of grafts had a PI ≤5; 78% (775/990) had a PI of <3.0. The authors devised an algorithm for decision making based on our experience and that of others (Fig. 2). However, we do not suggest that every graft with a PI of ≥5 must be revised. Rather, a high PI should serve as an indicator that the graft should be re-assessed and that revision may be appropriate. Sometimes a minor twist or an obstructing pericardial edge is easily reparable and improvement can be confirmed with a quick second TTF measurement. Competitive flow, for example, may cause an elevated PI value of 6—7; however, in this case, usually the flow is good (>15 cc min^{-1}). This could possibly be the case in the three patients with high PI and non-cardiac cause of death discussed in the previous paragraph.

A PI value may be elevated in very long arterial conduits because resistance to blood flow is determined by, among other factors, vessel length. This may not indicate poor graft function. In this study, the *in situ* RITA group, mostly going through the transverse sinus to a marginal artery (67% of the RITAs went to circumflex system), had the highest number of grafts with a high PI (14.2% vs 5.5% average for the single, sequential, composite LITA, single and sequential radial) —

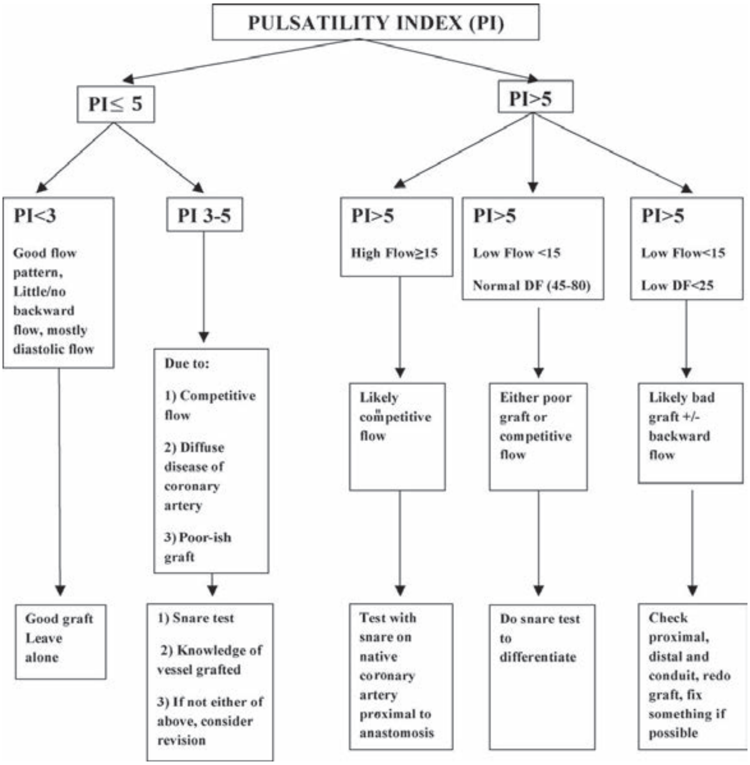

Fig. 2. Transit-time flow algorithm.

we suspect that the necessarily greater length of conduits may explain higher PI values in this group.

Several authors have commented on the difficulty in assessing TTF in sequential grafts and have not included them in their studies [10,11]. However, sequential grafting is an important feature of total arterial grafting — in this study 37% (371/1000 grafts) were sequential. We found that if one could measure the 'in-between-segment', the flow is almost always less and the PI higher when compared with total graft flow. In this manner, the individual components of a sequential graft can be assessed.

Flow did not prove to be a good indicator of graft function. It is dependent on many factors, including size, length and quality of conduit and native artery, run-off quality of coronary bed, mean arterial pressure, heart rate, competitive flow, viscosity of the blood and quality of distal ± prox-proximal anastomoses. Some authors have controlled one factor, such as mean BP, with inotropic agents when measuring flow [10—12]. As flow is affected by so many variables, we chose not to standardise mean BP, which in our patients ranged from 60 to 70 mmHg. Several authors [9—12] have suggested that a flow of <15 cc min^{-1} may signal a poor graft. In this study, a flow of <15 cc min^{-1} did not correlate with either postoperative death or MACE. Moreover, in those patients who underwent angiography, many with clinical indications, initial low flow values recorded at the time of surgery, did not appear to predict patent ($n = 7$, mean flow of 10.6 cc min^{-1}) or occluded or compromised grafts ($n = 5$, mean flow of 9 cc min^{-1}). Others have had similar findings: Shin et al. [15] observed that in LITA grafts, decreased graft flow with an acceptable PI correlated with vasospasm and not anastomotic problems. Hirotani et al. [16] found that mean flow in ITA grafts was greater than that in saphenous vein grafts and correlated significantly with the size of the territory being supplied by the graft.

As can be seen in Table 5, DF appears to be a significant predictor of MACE in the non-emergency group of patients. Although it is possible that this finding is significant, we are concerned that, for several reasons, this may be just incidental — there were multiple comparisons; the significant *p* value was achieved only when emergency patients were excluded and this is the least well-defined cut-point of all three TTF parameters. (This value was recommended by the manufacturers; there is no research data to support this cut-point). Furthermore, the DF data are incomplete (9% missing) because the EKG trace (on which the DF depends) was not always satisfactory. This remains an open question, and should be addressed in further studies.

5. Conclusions

The PI, obtained by TTF measurement, is a valuable tool to assess adequacy of arterial grafts and predict outcomes. Postoperative adverse events, especially operative mortality, are significantly higher in patients with grafts with a high PI. Such grafts should be carefully assessed even when there is no other indicator of a suboptimal graft function clinically, by either EKG or echocardiography. The authors suggest that intra-operative use of TTF measurement of arterial aortocoronary bypass grafts should become the standard of care.

References

[1] Tan ES, Jessurun G, Deurholt W, van der Vleuten P, van der Heuvel A, Ebels T, Zijlstra F, Tio R. Differences between early, intermediate, and late angioplasty after coronary artery bypass grafting. Crit Pathw Cardiol 2008;7(4):239—44.

[2] Levine S, Mendoza CE, Virani SS, Barquet G, Purow J, Katariya K, Salerno T. Rescue percutaneous coronar y intervention for graft failure immediately after coronary artery bypass grafting: case report and review of literature. J Card Surg 2008;23(6):709—12.

[3] Thielmann M, Massoudy P, Jaeger BR, Neuhäuser M, Marggraf G, Sack S, Erbel R, Jakob H. Emergency re-revascularization with percutaneous coronary intervention, reoperation, or conservative treatment in patients with acute perioperative graft failure following coronary artery bypass surgery. Eur J Cardiothorac Surg 2006;30(1):117—25.

[4] Weman SM, Salminen US, Penthilä A, Männikkö A, Karhunen PJ. Postmortem cast angiography in the diagnostics of graft complications in patients with fatal outcome following coronary artery bypass grafting (CABG). Int J Legal Med 1999;112:107—14.

[5] Loop FD, Lytle BW, Cosgrove DM, Stewart RW, Goormastic M, Williams GW, Golding LA, Gill CC, Taylor PC, Sheldon WC, Proudfit WI. Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. N Eng J Med 1986;314(1):1—6.

[6] Lytle BW, Blackstone EH, Loop FD, Houghtaling PL, Arnold JH, Akhrass R, McCarthy PM, Cosgrove DM. Two internal thoracic artery grafts are better than one. J Thorac Cardiovasc Surg 1999;117(5):855—72.

[7] Acinapura AJ, Rose DM, Cunningham JN, Jacobowitz IJ, Kramer MD, Zisbrod Z. Internal mammary artery bypass: effect on longevity and recurrent angina pectoris in 2900 patients. Eur J Cardiothorac Surg 1989;3(4):321—5 [Discussion 325—6].

[8] Ghali WA, Knudtson ML. Overview of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease on behalf of the APPROACH investigators. Can J Cardiol 2000;16(10):1225—30.

[9] Tokuda Y, Song MH, Oshima H, Usui A, Ueda Y. Predicting midterm coronary artery bypass graft failure by intraoperative transit time flow measurement. Ann Thorac Surg 2008;86(2):532—6.

[10] Di Giammarco, Pano M, Cirmeni S, Peline P, Vitolla G, Di Mauro M. Predictive value of intraoperative transit-time flow measurement for short-term graft patency in coronary surgery. Thorac Cardiovasc Surg 2006;132(3):468—74.

[11] Kim KB, Kang CH, Lim C. Prediction of graft flow impairment by intraoperative transit time flow measurement in off-pump coronary artery bypass using arterial grafts. Ann Thorac Surg 2005;80(2):594—8.

[12] Leong D, Ashok V, Nishkantha A, Shan Y, Sim E. Transit-time flow measurement is essential in coronary artery bypass grafting. Ann Thorac Surg 2005;79(3):854—7 [Discussion 857—8].

[13] Herman CR, Sullivan JA, Buth KJ, Legare JF. Intraoperative graft flow measurements during coronary artery bypass surgery predict in-hospital outcomes. Interact Cardiovasc Thorac Surg 2008;7(4):582—5.

[14] Becit N, Erkut B, Ceviz M, Unlu Y, Colak A, Kocak H. The impact of intraoperative transit time flow measurement on the results of on-pump coronary surgery. Eur J Cardiothorac Surg 2007;32(2):313—8.

[15] Shin H, Yozu R, Mitsumaru A, Iino Y, Hashizume K, Matayoshi T, Kawada S. Intraoperative assessment of coronary artery bypass graft: transit-time flowmetry versus angiography. Ann Thorac Surg 2001;72(5):1562—5.

[16] Hirotani T, Kameda T, Shirota S, Nakao Y. An evaluation of the intraoperative transit time measurements of coronary bypass flow. Eur J Cardiothorac Surg 2001;19(6):848—52.

Appendix A. Conference discussion

Dr G. D'ancona (*Palermo, Italy*): Although I am a great promoter of intraoperative graft patency verification, I think that this paper doesn't answer the question of which are the bad grafts and which are the good grafts, because there is no angiographic control. But the issues are very important. Now, my question is, it is difficult on the basis of a sole univariate analysis to state that a PI more than 5 is a determinant of mortality and MACE. Did the author consider building a more structured, multivariate analysis model and maybe in this model to see which are the real determinants for MACE and mortality, including also morbidity data and data concerning the coronary anatomy and the coronary quality? If in such a model the PI result is a determinant of MACE and mortality, then it is possible with C analysis to see which is the real cut-off for a PI. This I think would be a great message. Have you considered doing that?

The second question is, on the basis of your experience, and if I followed your presentation and your paper correctly, you are now suggesting revision of any grafts that have a PI more than 5, but you just showed us an inferior epigastric artery with a normal angiogram, with a PI that was around 6. I have been using this technology for more than 10 years, and I can tell you it is very difficult to say a PI should be precisely 5, especially because coronary rheology differs. The right coronaries, for example, have flows both in systole and diastole and they have a higher PI; it is higher than 5. So, again, we don't have a real cut-off. So would you feel very confident in suggesting revision of any graft that has a PI more than 5? This is the second question.

The third question is for the floor. Actually allow me to ask this question: How many in the audience routinely use any means of intra-operative graft patency verification?

Dr Kieser: First of all, the multivariate analysis, no, we have not thought to do that. I will look at this, though. I am not sure if there are enough patients involved to do this with, but I did look at the two groups and there was no difference between the characteristics of the two groups. There were a few more diabetics in the high PI group, but it did not reach statistical significance. But that is a good point.

Dr D'ancona: What about the coronary artery, because I am afraid that the PI is a surrogate that tells you, well, there may be also something wrong with the peripheral condition of the coronaries, you know what I mean? Did you look at the type of lesions, did you look at the coronary anatomy, did you try analysing those variables as well?

Dr Kieser: Well, I do have all the data. I haven't actually looked at that specifically. I do have angiographic follow-up, but it is sporadic and it is only about 13% of the patients, anywhere from zero to three years, so it isn't going to correlate with what happened in the time of the operating room, unfortunately.

Your second question was, would I feel comfortable in revising a graft if the PI was high? No, that is not what I would recommend. I would recommend looking at that graft, addressing the high PI. Just a quick glance — if it is 6, 7, you look at the graft. If you know you just did a graft to a terribly diseased vessel, and you did the best you could, or you see maybe there is a kink in it. A high PI needs addressing, looking at it just to see, not necessarily to revise.

Dr D'ancona: So the 5 cut-off you agree is not realistic?

Dr Kieser: No, no, it is not, but it is the first level. If it is over 5, you really have to look at it, but if it is between 3 and 5, there are other reasons: competitive flow, a diffusely diseased vessel, poor run-off. But as long as you, I guess, address it, look to see if there is a problem, instead of just saying the machine is wrong, I know I did a good graft. It is just one way to check before you leave the operating room.

Dr D'ancona: I agree with you.

And so the last question. How many in this room routinely use any means of intra-operative graft patency verification?

Dr F. Beyersdorf (*Freiburg, Germany*): Nobody? No. So raise your arms, who is using this flow measurement?

(Show of hands).

Dr Beyersdorf: Thank you very much, and I just remind you that coronary artery bypass surgery is one of the only surgeries on vessels which is not controlled in the OR by angiography, for reasons we all know. So at least the flow measurement is one of the quality assurance measurements we can do, and therefore I am also a great proponent for using that even though there are, of course, many problems with the distal flow, the distal vascular bed and so on, but, still, it is something that we can check when we are doing the graft.

Chapter 9

Adhesive-enhanced sternal closure to improve postoperative functional recovery: a pilot, randomized controlled trial

Fedak PWM, Kieser TM, Maitland AM, Holland M,
Kasatkin A , LeBlanc P, Kim JK, King KM

Ann Thorac Surg 2011;92:1444-50

Adhesive-Enhanced Sternal Closure to Improve Postoperative Functional Recovery: A Pilot, Randomized Controlled Trial

Paul W. M. Fedak, MD, PhD, Teresa M. Kieser, MD, Andrew M. Maitland, MD, Margaret Holland, RN, Aleksey Kasatkin, MD, Pamela LeBlanc, Jae K. Kim, MD, PhD, and Kathryn M. King, RN, PhD

Division of Cardiac Surgery, Department of Cardiac Sciences, University of Calgary, Libin Cardiovascular Institute of Alberta; Faculty of Nursing, University of Calgary; and Department of Community Health Sciences, University of Calgary, Calgary, Alberta; and Thunder Bay Regional Research Institute, Thunder Bay, Ontario, Canada

Background. **We previously established a proof-of-concept in a human cadaveric model where conventional wire cerclage was augmented with a novel biocompatible bone adhesive that increased mechanical strength and early bone stability. We report the results of a single-center, pilot, randomized clinical trial of the effects of adhesive-enhanced closure of the sternum on functional postoperative recovery.**

Methods. **In 55 patients undergoing primary sternotomy, 26 patients underwent conventional wire closure and were compared with 29 patients who underwent adhesive-enhanced closure, which consisted of Kryptonite biocompatible adhesive (Doctors Research Group Inc, Southbury, CT) applied to each sternal edge in addition to conventional 7-wire cerclage. Patients were monitored postoperatively at 72 hours, weekly for 12 weeks, and then after 12 months for incisional pain, analgesic use, and maximal inspiratory capacity measured by spirometry. Standardized assessment tools measured postoperative physical disability and health-related quality of life.**

Results. **No adverse events or sternal complications from the adhesive were observed early or after 12 months. Incisional pain and narcotic analgesic use were reduced in adhesive-enhanced closure patients. Inspiratory capacity was significantly improved, postoperative health-related quality of life scores normalized more rapidly, and physical disability scores were reduced. Computed tomography imaging was suggestive of sternal healing.**

Conclusions. **Adhesive-enhanced closure is a safe and simple addition to conventional wire closure, with demonstrated benefits on functional recovery, respiratory capacity, incisional pain, and analgesic requirements. A large, multicenter, randomized controlled trial to examine the potential of the adhesive to prevent major sternal complications in higher risk patients is warranted.**

(Ann Thorac Surg 2011;92:1444–50)

Postoperative recovery after cardiac operations is influenced by early sternal bone stability. Small degrees of sternal motion can result in decreased patient mobility, compromised respiration, excessive incisional pain, and major complications, such as infection and sternal dehiscence. Wire cerclage closure of the sternotomy is the current standard of care but can result in pathologic sternal displacement (>2 mm) during physiologic distracting forces such as coughing [1, 2]. Traditional sternal closure techniques may not always provide optimal fixation [3]. Even in the absence of gross instability, imaging can discern sternal gaps and delayed healing after a routine uncomplicated sternotomy [4]. Sternal complications, including sternal malunion, infection, and dehiscence, are a growing concern due to the increasing risk profile of patients undergoing cardiac operations. Innovations in closure techniques, such as modified external fixation devices, may provide incremental benefit; however, no single technique has been widely adopted and a practical solution is needed [5–11].

Kryptonite bone adhesive (Doctors Research Group Inc, Southbury, CT) is a biocompatible polymer that can accomplish rigid bone fixation within 24 hours of application. The porous network within the product allows healing by osteointegration with the host bone over time, without fibrosis or inflammation [12]. We previously demonstrated in a human cadaveric model that Kryptonite bone adhesive, combined with a standard wire cerclage, enhanced mechanical strength and prevented pathologic sternal displacement [13]. Augmenting sternal closure with tech-

Accepted for publication May 3, 2011.

Address correspondence to Dr Fedak, C880, Foothills Medical Center, 1403-29 St NW, Calgary, AB T2N 2T9, Canada; e-mail: paul.fedak@gmail.com.

Dr Fedak discloses that he has a financial relationship with Doctors Research Group Inc.

niques to enhance early bone stability may accelerate functional recovery from cardiac operations and prevent major sternal complications. In this report we present the results of a single-center, single-blinded, pilot, randomized controlled trial of adhesive-enhanced sternal closure compared with conventional wire cerclage in patients undergoing routine cardiac operations.

Patients and Methods

Participants and Study Design

Eligible patients undergoing first-time cardiac operations through a median sternotomy between April 2009 and February 2010 at Foothills Medical Center, Calgary, Alberta were approached to participate in this study. Inclusion criteria mandated that adult patients underwent elective or semielective operations, resided within 1-hour driving distance from Calgary to enable close follow-up, as necessary, and were capable of informed consent. Exclusion criteria included patients who:

- were at high-risk of early postoperative bleeding requiring reopening of the chest; for example, taking clopidogrel within 5 days of the operation or intravenous antiplatelet medication within 24 hours of the operation;
- had received previous chest radiotherapy;
- did not speak and read the English language;
- presented in a clinical preoperative state that suggested a prolonged recovery; for example, other concurrent illness such as significant respiratory disease or renal failure requiring dialysis, residence in a long-term care facility, preoperative hospitalization exceeding 3 weeks in which physical decompensation occurred, or current substance abuse;
- were identified by physiotherapist in a preoperative assessment as requiring assistance with sternal precautions; or
- did not have telephone access.

Demographic data were collected, and all eligible patients were assessed for baseline parameters by specially trained research assistants. Study participants were randomized to conventional wire sternal closure (control) or adhesive-enhanced closure using Kryptonite bone adhesive with wire cerclage. All patients were treated with the same postoperative protocols; caregivers were blinded to the intervention. All patients were placed in routine “sternal precautions” according to the protocol at our institution. All data were collected by blinded research assistants and were maintained at a secure site at the University of Calgary. The protocol received institutional ethics approval. Written informed consent was obtained from each participant.

Surgical Technique

All patients underwent sternal closure using 7-wire interrupted cerclage with 12-gauge stainless steel. Use of bone wax or other hemostatic agents was prohibited. In adhesive-enhanced closure patients, trabecular bone was cleaned with a sterile brush and irrigated with saline solution. The Kryptonite bone adhesive was mixed for 4 minutes, and then 3 to 6 mL was applied as a thin layer to each hemisternum at the trabecular interface. Bone and soft-tissue approximation was identical in each patient.

Data Collection

Data were collected by site research assistants while patients were still in the hospital. Pain and discomfort scores, analgesic use, wound healing scores, incentive spirometry values (a measure of lung capacity using Voldyne incentive spirometry [Hudson RCI, Research Triangle Park, NC]), and standardized assessments of physical disability, as assessed by the Health Assessment Questionnaire and by the EQ-5D health-related quality of life instrument (EuroQol, Rotterdam, The Netherlands), were obtained. Data were collected for each patient preoperatively (baseline) and postoperatively at days 1, 3, 5, and 7, and at weeks 2, 4, 6, 8, and 12.

Pain and discomfort were measured using Likert-type 11-point numeric rating scales that were anchored with descriptors (0 = none, 10 = worst), as previously described [14]. Analgesic use data (generic name, dose, number of doses) for the preceding 24 hours were collected at each interval. Narcotic analgesics included codeine, morphine, hydromorphone, and fentanyl. Nonnarcotic medications included acetaminophen, ibuprofen, and ketorolac.

Sternal wound-healing data were collected using The Society of Thoracic Surgeons–based descriptors on ordinal scales for wound drainage (5-point scale: 0 = none, 5 = large amount requiring dressing changes > 2 per day), stability (3-point scale: 0 = stable, 3 = palpable movement without cough), and incision approximation (5-point scale: 0 = closed, 5 = gaping). Participants were successfully taught how to score their sternal wounds in this study, as previously described [14].

Clinical data were collected through a health record audit at the time of discharge. Once the patient was discharged, data were collected by telephone contact. Pain, discomfort, analgesic use, sternal wound-healing data, incentive spirometry values, physical disability, and health-related quality of life were collected at each contact. A final follow-up assessment was performed at a minimum of 12 months for all patients.

Statistical Analysis

All analyses were based on intention-to-treat principles. Wilcoxon tests, Student *t* tests, two-way analysis of variance, and χ^2 tests were used, as appropriate, to compare the demographic and clinical characteristics of participants assigned to the intervention and control groups. All data are expressed as mean ± standard deviation. Values of $p < 0.05$ were considered statistically significant.

Results

The study comprised 55 patients: 26 were randomized to conventional wire closure and 29 to adhesive-enhanced closure. Despite the small sample size, baseline demographics and other relevant clinical variables were not significantly different between groups (Table 1). Analysis of baseline demographics indicates that most of the population comprised low-risk patients who were free of multiple risk factors for sternal complications. Completeness of follow-up at 12 weeks was 98% (54 of 55 patients). One patient refused further follow-up after 1 week despite an uncomplicated recovery. Bleeding unrelated to the closure technique required 2 adhesive-enhanced closure patients to undergo reopening. The patients were closed secondarily without adhesive but were included in the intervention group according to the intention-to-treat protocol.

Early Outcomes

There were no differences between groups in conventional postoperative complications (Table 1). No major complications and no deaths were documented after 12 months of follow-up. No patients required hospital readmission for sternal malunion, infection, or dehiscence. Minor sternal instability was identified in 2 control patients and treated conservatively with regular follow-up and prolonged sternal precautions. Superficial sternal wound infection occurred in 2 control patients. Wound-healing scores were not significantly different between groups (Table 2).

Postoperative Pain

Pain was assessed at baseline and with trigger activities such as walking, deep breathing, changes in position while attempting to sleep, and with coughing. On the 11-point Likert scale, scores below 3 were considered minor discomfort [14, 15]. Incisional pain after sternotomy, as expected, was most severe early after sternotomy and declined significantly after 2 weeks in most patients (Table 3). The adhesive-enhanced closure patients had significantly less incisional pain after sternotomy ($p < 0.0001$), with mean scores below 3 of 10 at all time points (maximal mean incisional pain was 2.46 ± 1.71 at 72 hours postoperatively, Table 3). Pain scores between groups were not significantly different with triggers such as deep breathing, sleeping, or walking (data not shown).

However, coughing, a well-known pain trigger for patients after sternotomy, stimulated the most severe pain and incisional discomforts. The adhesive-enhanced closure patients reported significantly less pain with coughing than controls during the 12-week study period ($p < 0.0001$, Table 3). At 72 hours postoperatively, incisional pain during coughing was substantially diminished in the adhesive-enhanced closure patients (3.9 ± 2.4 vs 5.8 ± 2.3, $p = 0.004$). No patients in the control group reported scores of less than 2, and many scores exceeded 6 (Fig 1) compared with the adhesive-enhanced closure patients, where coughing pain was greatly reduced in a significant proportion.

Analgesic Usage

We used assessments of electronic nursing records to compare postoperative analgesic use between groups. Use of any analgesic medicine (yes/no) postoperatively was not significantly different between groups (data not shown). However, at days 3 and 5—when pain scores are highest—use of narcotic analgesics was significantly lower in the adhesive-enhanced closure

Table 1. Demographics and Outcomes of Study Participants

Variable[a]	CWC (n = 26)	AEC (n = 29)	*p* Value
Age	62.5 ± 9.8	62.0 ± 9.1	0.87
Body mass index, kg/m^2	30.8 ± 8.9	27.8 ± 4.4	0.11
Type of operation			
CABG	23 (88)	21 (72)	0.57
Aortic valve regurgitation	2 (8)	5 (18)	
Mitral valve regurgitation	1 (4)	2 (7)	
Myxoma	0 (0)	1 (3)	
History			
Diabetes	7 (27)	8 (28)	>0.99
COPD	3 (12)	2 (7)	0.66
Arthritis	4 (16)	4 (14)	>0.99
Stroke	1 (4)	2 (7)	>0.99
Postprocedural events			
Neurologic	0 (0)	0 (0)	>0.99
Pneumonia	0 (0)	0 (0)	>0.99
Atrial fibrillation	10 (38)	10 (34)	0.79
Return to ICU	2 (8)	4 (14)	0.67
Superficial sternal infection	2 (8)	0 (0)	0.22
Deep sternal infection	0 (0)	0 (0)	>0.99

[a] Continuous data are presented as mean ± standard deviation; categoric data as number (%).

AEC = adhesive-enhanced closure; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CWC = conventional wire closure; ICU = intensive care unit.

Table 2. Wound Scores by Type of Sternal Closure

Postop Time	Wound Score	CWC (n = 26) N (%)	AEC (n = 29) N (%)	*p* Value
Day 3	0	25 (96)	25 (89)	0.38
	1		2 (7)	
	2	1 (4)	1 (4)	
Day 7	0	20 (87)	29 (100)	0.13
	1	2 (9)		
	2	1 (4)		
Week 2	0	23 (89)	27 (96)	0.45
	1	1 (4)		
	2	2 (8)	1 (4)	
Week 4	0	23 (89)	27 (93)	0.34
	1	3 (11)	1 (3)	
	3		1 (3)	
Week 8	0	24 (100)	27 (93)	0.42
	4		1 (3)	
	5		1 (3)	
Week 12	0	25 (96)	28 (97)	1.00
	1	1 (4)	1 (3)	

AEC = adhesive-enhanced closure; CWC = conventional wire closure; Postop = postoperative.

Table 3. Effect on Treatment and Time on Outcome Scores by Sternal Closure[a]

Outcome Variable	CWC Mean ± SD	AEC Mean ± SD	p Value
Incisional pain at rest			
Treatment effect			<0.001
Time effect			<0.001
72 hours	4.00 ± 1.52	2.46 ± 1.71	0.001
1 week	2.23 ± 1.80	1.45 ± 1.62	0.097
2 weeks	1.46 ± 1.27	1.21 ± 1.57	0.472
4 weeks	1.19 ± 1.88	0.98 ± 1.39	0.643
8 weeks	0.56 ± 0.96	0.62 ± 0.82	0.83
12 weeks	0.69 ± 1.67	0.28 ± 0.59	0.245
Incisional pain with cough			
Treatment effect			<0.001
Time effect			<0.001
72 hours	5.81 ± 2.33	3.89 ± 2.36	0.004
1 week	4.27 ± 2.34	3.10 ± 2.18	0.062
2 weeks	4.54 ± 2.40	2.75 ± 2.22	0.007
4 weeks	3.00 ± 2.37	2.72 ± 1.89	0.637
8 weeks	1.32 ± 1.91	2.00 ± 2.10	0.258
12 weeks	1.00 ± 1.74	1.21 ± 1.71	0.713
Inspiratory capacity, mL			
Treatment effect			<0.001
Time effect			<0.001
72 hours	1109 ± 399	1405 ± 318	0.004
1 week	1604 ± 536	1995 ± 451	0.006
2 weeks	1990 ± 665	2330 ± 451	0.034
4 weeks	2228 ± 669	2601 ± 442	0.02
8 weeks	2546 ± 778	2928 ± 612	0.051
12 weeks	2625 ± 928	3059 ± 629	0.051
Physical disability, HAQ score			
Treatment effect			0.048
Time effect			0.001
Baseline (pre-op)	0.16 ± 0.27	0.15 ± 0.31	0.424
1 week	2.03 ± 0.51	1.76 ± 0.59	0.053
2 weeks	1.39 ± 0.70	1.09 ± 0.73	0.129
4 weeks	0.82 ± 0.67	0.57 ± 0.44	0.115
8 weeks	0.40 ± 0.40	0.30 ± 0.30	0.297
12 weeks	0.25 ± 0.32	0.15 ± 0.19	0.202
Recovery of HRQL	Patients, %	Patients, %	
2 weeks	7.1	26.7	0.12
4 weeks	21.4	46.7	0.34
8 weeks	71.4	73.3	0.83
12 weeks	85.7	100	0.89

[a] Data are not shown for 5 days, 3 weeks, 5 weeks, 6 weeks, 8 weeks, and 10 weeks.

AEC = adhesive-enhanced closure; CWC = conventional wire closure; HAQ = Health Assessment Questionnaire; HRQL = Health-Related Quality of Life; SD = standard deviation.

patients (Fig 2). Pain scores were also significantly lower. The proportion of narcotic pain medicine use was not significantly different between groups after 1 week (data not shown).

Inspiratory Capacity

The ability to deep breathe is compromised after sternotomy due to pain and altered chest mechanics. We assessed inspiratory capacity in all patients throughout the postoperative period. The adhesive-enhanced closure patients were observed to have a marked improvement in inspiratory capacity at all time points (Table III). Inspiratory capacity was significantly improved in the adhesive-enhanced closure patients after controlling for preoperative incentive spirometry values ($p = 0.05$), body mass index ($p = 0.01$), and patient age ($p = 0.005$). The adhesive-enhanced closure patients showed an earlier recovery to baseline preoperative values compared with controls. At postoperative day 3, when pain and deep breathing are most compromised, the adhesive-enhanced closure patients showed a similar distribution of scores but with a marked improvement in maximal inspiratory capacity compared with controls (Fig 3).

Physical Disability and Health-Related Quality of Life

We used the Health Assessment Questionnaire to evaluate physical disability postoperatively compared with baseline. All patients showed a similar and expected pattern of negligible baseline disability scores, with a steep rise in disability early after the operation and a steady recovery to baseline over 12 weeks (Table 3). The disability scores were significantly lower in the adhesive-enhanced closure patients, suggesting that the degree of physical disability was blunted in this group compared with controls.

In addition, we assessed health-related quality of life during the same intervals using the EQ-5D standardized tool. We compared 14 conventional wire closure patients and 15 adhesive-enhanced closure patients with equivalent baseline (preoperative) health-related quality of life scores. The adhesive-enhanced closure patients returned to baseline health-related quality of life more rapidly than the conventional wire closure patients, suggesting an accelerated postoperative recovery (46.7% vs 14.3% at 3 weeks, $p = 0.06$, Table 3).

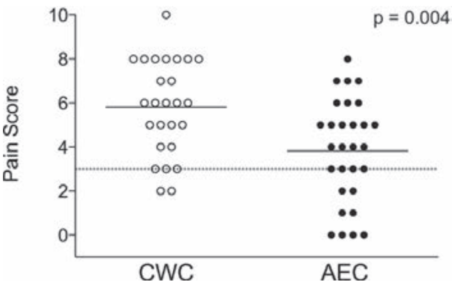

Fig 1. The distributions of individual pain scores with cough at postoperative day 3 are compared by adhesive-enhanced closure (AEC, black circles) and conventional wire closure (CWC, white circles). The horizontal bars indicate the group means. Scores of less than 3 are considered minor discomfort (dashed line).

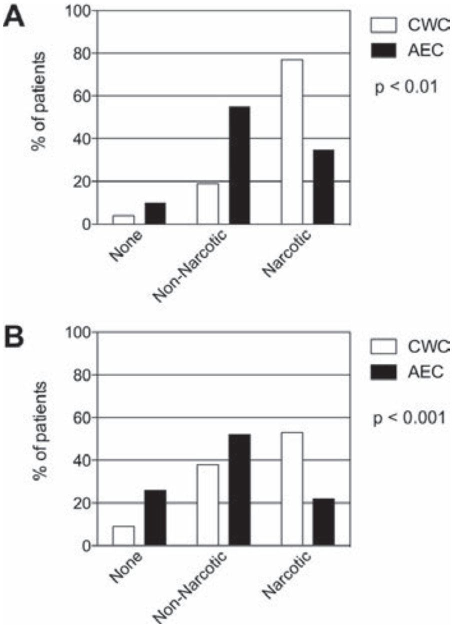

Fig 2. Analgesic use during a 24-hour period and its profile are compared between adhesive-enhanced closure (AEC, black bars) and conventional wire closure (CWC, white bars). Results are shown for (A) postoperative day 3 and (B) postoperative day 5.

Follow-Up at 1 Year

Follow-up after 12 months was complete for 54 of 55 patients (98%; 1 control patient was lost to follow-up). Mean follow-up was 16.4 $\pm$ 2.3 months. No major sternal complications were documented. No patients in the control group (n = 26) reported persistent incisional chest pain or discomfort. One patient in the adhesive-enhanced closure group (n = 29) reported significant residual incisional chest pain. An examination showed he had a stable and well-healed sternal incision. The patient localized pain over the internal mammary artery harvest site and was treated for neuropathic pain. A computed tomography (CT) scan ruled out nonunion or infection.

Two patients from each group were randomly selected for late CT imaging. All 4 patients showed evidence consistent with varying stages of sternal healing and bony union compared with postoperative CT scans 11 months earlier. A gradual interval increase in radiodensity between the sternal edges was observed, suggestive of new bone formation within the adhesive core (Fig 4).

Comment

More than 1 million sternotomies are performed every year worldwide. Patient recovery and return to normal activities after cardiac operations is often delayed by the 6 to 8 weeks required for osteosynthesis (solid bony union), necessitating use of sternal precautions for 6 to 8 weeks in most centers. These measures are designed to limit the distracting forces on the sternum until osteosynthesis is achieved. Sternal wires are placed under significant load during upper limb movement, deep breathing, and coughing before osteosynthesis occurs [16]. Bone instability can result in substantial patient discomfort and sometimes prevent healing.

Many novel techniques to improve the stability of sternal closure have been proposed, but no single method has gained widespread adoption [8]. Surgeons have developed minimal access approaches that are sometimes cumbersome, expensive, and risky. Although appropriate in selected cases, minimal access cardiac techniques have not had a significant impact in reducing the worldwide frequency of sternotomy. Accordingly, most patients receive sternal closure with techniques that have not changed substantially since the dawn of cardiac surgery more than 60 years earlier. Although sternotomy provides optimal exposure for most cardiac operations, efforts to accelerate postoperative wound healing and physical recovery are welcome.

Pain after sternotomy correlates with the stability and alignment of the sternal closure [17]. We observed significant reductions in postoperative pain and analgesic requirements with use of adhesive-enhanced closure. These benefits were observed within the first 2 postoperative weeks and have maximal benefit within the first week. Early pain after operations can result in poor mobility and shallow breathing (splinting) that may lead to complications, including deep vein thrombosis, pulmonary embolus, and pneumonia. The use of strong narcotic medication was significantly reduced; in elderly patients, these medications can have serious side effects such as hallucinations, confusion, and disabling falls [18]. Most patients with adhesive-enhanced closure did not reach significant levels of pain (pain score < 3), whereas the concomitant finding of reduced pain in the setting of reduced analgesic requirements also supports a significant effect of the therapy on pain and discomfort. Re-

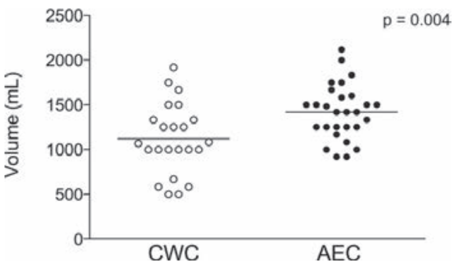

Fig 3. The distributions of individual inspiratory volumes at postoperative day 3 are compared by adhesive-enhanced closure (AEC, black circles) and conventional wire closure (CWC, white circles). The horizontal bars indicate the group means.

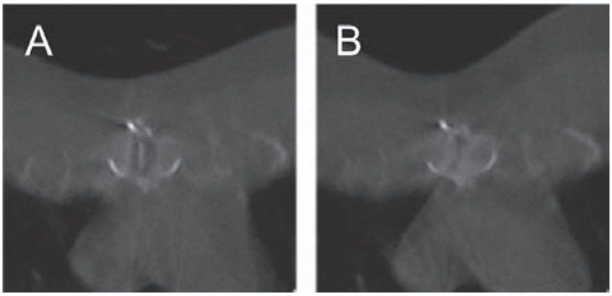

Fig 4. (A) An early computed tomography midsternal image of a patient who received adhesive-enhanced closure is shown for comparison with (B) a corresponding follow-up image taken 11 months later. Correspondence of location was made by the position and appearance of sternal wires. The initial postoperative lucency (adhesive) appeared less lucent over time, consistent with a process of sternal healing and bony in-growth.

duced postoperative pain can potentially result in decreased hospital length of stay and improved functional recovery [19].

Among the most frequent causes of postoperative morbidity and death after cardiac operations are respiratory dysfunction and pulmonary complications [20]. Sternotomy results in significant postoperative atelectasis and reduced pulmonary function for more than 8 weeks after the operation [21]. Pain may be partly responsible for this reduced pulmonary function because patients with adhesive-enhanced closure showed much earlier improvement to baseline in inspiratory capacity. Promoting deep breathing in the postoperative period is an important clinical target that is believed to reduce complications and accelerate recovery.

From the perspective of the contemporary cardiac surgical patient, an accelerated return to normal activities after the operation and rapid functional recovery are of great interest and importance [22]. Patients with adhesive-enhanced closure showed an accelerated recovery of heath-related quality of life and a reduction in overall physical disability in the postoperative period compared with control patients. Providing these patient-centered benefits while allowing for maximal surgical exposure for the operator through conventional full sternotomy may facilitate excellent clinical outcomes without the need for patient discomfort and prolonged recovery. Sternal precautions and other protocols that restrict patient activities until the sternotomy has fully healed may not be necessary after adhesive augmentation in low-risk patients. Further research will be required to assess the safety of this strategy. In addition, although not specifically addressed in this study, these benefits could result in a substantial cost-benefit to patients as well as to health care providers. Further economic analysis will be required to support these opinions.

We believe that improving conventional sternal closure can enhance and accelerate postoperative recovery. Improved early sternal stability may reduce postoperative pain, decrease the need for narcotic analgesics, improve breathing and chest wall mechanics, and stimulate early mobility with rapid hospital discharge. Kryptonite bone adhesive can rapidly provide internal bone fixation. We previously demonstrated in a cadaveric model that early sternal bone fixation is substantially improved with the addition of this bone adhesive. Wire cerclage is still needed for the first few hours postoperatively until the adhesive "bonds" with the sternal bone [13]. In addition, the adhesive has osteoconductive properties. Host osteoblasts can synthesize new bone within the porous network of the material without loss of structural support, fibrosis, or inflammation [12]. We show suggestive evidence of new bone formation and healing in the adhesive core after 12 months by CT scan.

Adhesive-enhanced closure improved early functional recovery after cardiac operations. No safety concerns or side effects were identified after 12 months of follow-up. No infections occurred. Given that deep sternal wound infection and dehiscence are rare complications, a much larger study will be required to confirm that infection is not increased in patients with adhesive-enhanced closure. However, the early stability provided by the adhesive could potentially reduce the incidence of deep sternal wound infection and dehiscence, which can only be assessed in a much larger patient population.

In summary, adhesive-enhanced closure is a safe and simple addition to conventional wire closure, with demonstrated benefits on functional recovery, respiratory function, incisional pain, and analgesic requirements. A large, multicenter, randomized controlled trial to examine the potential of the adhesive to prevent major sternal complications in higher risk patients is warranted.

Dr Fedak and Dr King are supported by Alberta Innovates Health Solutions, and Dr Fedak is supported by the Heart and Stroke Foundation of Alberta, NWT, and Nunavut. This pilot study was partly funded by Doctors Research Group Inc. Kryptonite adhesive was donated for the study. The authors had full control of the design of the study, methods used, outcome variables, analysis of data, and production of the written report.

References

1. McGregor WE, Trumble DR, Magovern JA. Mechanical analysis of midline sternotomy wound closure. J Thorac Cardiovasc Surg 1999;117:1144–50.

2. Losanoff JE, Jones JW, Richman BW. Primary closure of median sternotomy: techniques and principles. Cardiovasc Surg 2002;10:102–10.
3. Robicsek F, Fokin A, Cook J, Bhatia D. Sternal instability after midline sternotomy. Thorac Cardiovasc Surg 2000;48:1–8.
4. Li AE, Fishman EK. Evaluation of complications after sternotomy using single- and multidetector CT with three-dimensional volume rendering. Am J Roentgenol 2003;181:1065–70.
5. Dasika UK, Trumble DR, Magovern JA. Lower sternal reinforcement improves the stability of sternal closure. Ann Thorac Surg 2003;75:1618–21.
6. Losanoff JE, Richman BW, Jones JW. Lower sternal reinforcement to improve median sternotomy closure. Ann Thorac Surg 2004;77:2261.
7. McGregor WE, Payne M, Trumble DR, Farkas KM, Magovern JA. Improvement of sternal closure stability with reinforced steel wires. Ann Thorac Surg 2003;76:1631–4.
8. Robicsek F, Fokin AA. Search for a better mousetrap. The quest for an ideal method of sternal closure. Eur J Cardiothorac Surg 2008;33:767–8.
9. Song DH, Lohman RF, Renucci JD, Jeevanandam V, Raman J. Primary sternal plating in high-risk patients prevents mediastinitis. Eur J Cardiothorac Surg 2004;26:367–72.
10. Losanoff JE. Invited commentary. Ann Thorac Surg 2006;82:907–8.
11. Schimmer C, Reents W, Berneder S, et al. Prevention of sternal dehiscence and infection in high-risk patients: a prospective randomized multicenter trial. Ann Thorac Surg 2008;86:1897–904.
12. Jannetty J, Kolb E, Boxberger J, Deslauriers R, Ganey T. Guiding bone formation in a critical-sized defect and assessments. J Craniofac Surg 2010;21:1848–54.
13. Fedak PW, Kolb E, Borsato G, et al. Kryptonite bone cement prevents pathologic sternal displacement. Ann Thorac Surg 2010;90:979–85.
14. King KM, Tsuyuki R, Faris P, Currie G, Maitland A, Collins-Nakai R. The Women's Recovery from Sternotomy (WREST) study: design of a randomized trial of a novel undergarment for early use after sternotomy. Am Heart J 2005;149:761–7.
15. King KM, Tsuyuki R, Faris P, Currie G, Maitland A, Collins-Nakai RL. A randomized controlled trial of women's early use of a novel undergarment following sternotomy: the Women's Recovery from Sternotomy Trial (WREST). Am Heart J 2006;152:1187–93.
16. Casha AR, Yang L, Cooper GJ. Measurement of chest wall forces on coughing with the use of human cadavers. J Thorac Cardiovasc Surg 1999;118:1157.
17. Tamiya E, Asakawa M, Shibamoto M, et al. Correlation of wound pain following open heart surgery (median sternotomy) and sternum misalignment assessed using X-ray computed tomography. Int J Angiol 2000;9:159–63.
18. Solomon DH, Rassen JA, Glynn RJ, et al. The comparative safety of opioids for nonmalignant pain in older adults. Arch Intern Med 2010;170:1979–86.
19. Morrison RS, Magaziner J, McLaughlin MA. The impact of post-operative pain on outcomes following hip fracture. Pain 2003;103:303–11.
20. Freitas ER, Soares BG, Cardoso JR, Atallah AN. Incentive spirometry for preventing pulmonary complications after coronary artery bypass graft. Cochrane Database Syst Rev 2007:CD004466.
21. Johnson D, Hurst T, Thomson D, et al. Respiratory function after cardiac surgery. J Cardiothorac Vasc Anesth 1996;10: 571–7.
22. Parker RD, Adams J. Activity restrictions and recovery after open chest surgery: understanding the patient's perspective. Proc (Bayl Univ Med Cent) 2008;21:421–5.

Chapter 10

Toward zero: deep sternal wound infection after 1001 consecutive coronary artery bypass procedures using arterial grafts: implications for diabetic patients

Kieser TM, Rose MS, Aluthman U, Montgomery M, Louie T, Belenkie I

J Thorac Cardiovasc Surg 2014;148:1887-95

Toward zero: Deep sternal wound infection after 1001 consecutive coronary artery bypass procedures using arterial grafts: Implications for diabetic patients

Teresa M. Kieser, MD,[a] M. Sarah Rose, PhD,[b] Uthman Aluthman, MD,[a] Marlene Montgomery, RN,[c] Thomas Louie, MD,[d] and Israel Belenkie, MD[e]

Objective: Coronary artery bypass graft (CABG) surgery with arterial conduits is considered optimal. A deterrent to bilateral internal thoracic artery (BITA) grafting is the risk of deep sternal wound infection (DSWI). We introduced infection prevention measures sequentially, attempting to reduce DSWIs. The aim was to determine (1) if the absence of DSWIs in the last 469 of 1001 consecutive operations was significant; (2) which measures explained the change; and (3) the impact of diabetes.

Methods: The measures included internal thoracic artery (ITA) skeletonization, no bone wax, wound irrigation, 1 observer per case, harmonic scalpel harvest of ITAs, vancomycin paste on sternal marrow, iodine-impregnated skin drapes, chlorhexidine-alcohol skin preparation, no BITA grafts in obese, diabetic women, more off-pump procedures, aseptic wound care, and marrow irrigation before sternal approximation.

Results: Mean age was 65 ± 10.4 years, 78% were male, 34% had diabetes, and 34% were obese. The first 532 patients had 16 DSWIs (3%) and the subsequent 469 had none ($P < .001$). Analysis of the data suggested that the first 11 measures likely contributed to the absence of DSWI and less likely, the twelfth. Key measures were likely chlorhexidine-alcohol use and avoidance of BITAs in obese diabetic women who had a 10-fold higher DSWI rate than the other patients (21.4% vs 2.0%). Other diabetics, including obese men, had no increased risk of DSWI.

Conclusions: The measures applied caused a substantial reduction in DSWIs. Key measures included the use of chlorhexidine-alcohol and avoidance of BITA grafting in obese diabetic females. These measures reduced DSWIs after BITA grafting in most diabetics. (J Thorac Cardiovasc Surg 2014;148:1887-95)

See related commentary on pages 1896-8.

For more than 25 years, the standard of care for coronary artery bypass graft (CABG) conduits has been the use of 1 internal thoracic artery (ITA) and saphenous veins. However, the shorter life span of venous grafts limits the long-term benefits of the procedure. Use of bilateral ITAs (BITA), although known to improve results in all patient groups, is not common (4% in North America, 12% in Europe, and 30% in Japan).[1] Reasons for limited use of BITAs include longer operating times, technical challenges, perceived conduit−coronary perfusion mismatch, and risk of deep sternal wound infection (DSWI). The latter is considered a major deterrent to using BITA grafts.[2,3] If this risk could be reduced to that associated with single ITA grafts, BITA grafting might be considered more often.[4] Although mediastinitis is infrequent after CABG surgery (0.4%-4%), the associated mortality ranges from 10% to 47%.[5]

After sequential implementation of numerous changes designed to reduce infection rates associated with CABG, we analyzed our data to (1) verify that the perception of a reduced DSWI rate was indeed significant, (2) determine which prevention measures were responsible for the reduced rate, (3) assess the relative risk in diabetics, and (4) compare DSWI rates with those of our other surgeons who did not systematically use the same measures.

From the Departments of Cardiac Sciences and Surgery,[a] Libin Cardiovascular Institute of Alberta; Rho Sigma Scientific Consultants[b]; Infection Control and Prevention,[c] Alberta Health Services; Department of Internal Medicine,[d] University of Calgary; and Departments of Cardiac Sciences and Internal Medicine,[e] Libin Cardiovascular Institute of Alberta, Calgary, Alberta, Canada.

Disclosures: Teresa M. Kieser reports consulting fees and lecture from Medistim USA and Medistim ASA, and consulting fees from Ethicon Endosurgery. Thomas Louie reports consulting and lecture fees from Optima Pharma and grant support from Cubist and Actelion. All other authors have nothing to disclose with regard to commercial support.

Received for publication Oct 8, 2013; revisions received Jan 21, 2014; accepted for publication Feb 3, 2014; available ahead of print March 7, 2014.

Address for reprints: Teresa M. Kieser, MD, Foothills Medical Centre, Room C814, 1403, 29th St NW, Calgary, Alberta, Canada T2N 2T9 (E-mail: t.kieserprieur@ucalgary.ca).

0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2014.02.022

MATERIALS AND METHODS

From July 2003 to October 2012, total arterial grafting was performed where possible in all patients operated on by 1 surgeon, regardless of age, level of urgency, and comorbidities. There was continuous effort to mitigate infections by implementing sequential preventative measures. This retrospective analysis of prospectively collected data from consecutive patients was undertaken when it was noted that there were no DSWIs over 4 years, 7 months. For the first 532 patients, the DSWI rate was 3%. This study was approved by our institutional Research Ethics Board.

Surgical Details

All operations were performed with standard cardiopulmonary bypass or off-pump using high spinal and light general anesthesia. Intermittent

Abbreviations and Acronyms

BITA = bilateral internal thoracic artery
BMI = body mass index
CABG = coronary artery bypass graft
CI = confidence interval
COPD = chronic obstructive pulmonary disease
DSWI = deep sternal wound infection
IEI = interevent intervals
ITA = internal thoracic artery

antegrade blood cardioplegia and systemic hypothermia (32°C) were used for on-pump procedures; off-pump CABG was performed with the Octopus stabilizing device (Medtronic, Inc, Minneapolis, Minn). ITA conduits were harvested and skeletonized, most with an ultrasonic scalpel (Harmonic Scalpel; Ethicon Endo-Surgery, CVD, Cincinnati, Ohio). ITAs were used mostly as in situ grafts and wrapped in papaverine-soaked gauze. Negative air pressure was used in operating rooms. Antibiotic coverage (cephazolin 2 g 30 minutes before knife to skin, every 4 hours intraoperatively, and every 8 hours for 3 doses) was routine as was intraoperative glycemic control (4-9 mmol/L) by insulin infusion. Seven single horizontal sternal wires were used for a single ITA and 8 for BITA or when body surface area was greater than 2.0 m^2.

Deep Sternal Wound Infection

DSWI was defined as infection involving the sternum, pericardium, and/or mediastinum requiring 6 weeks of antibiotics with or without surgical debridement, rewiring, or muscle flap reconstruction.[6] In the infectious disease literature for all types of surgery, 3 categories of surgical site infection are defined: type 1, superficial incisional; type 2, deep incisional (muscle and fascia); type 3, deep organ space, bone, and/or mediastinum.[6] The DSWI definition used in this study is the same as type 3. Patients were followed for a minimum of 2 months at their postoperative clinic assessment; all DSWIs appeared before 4 weeks.

Infection Prevention Measures

Before 2003, 4 measures were in place: bone wax was not used on sternal edges and subcutaneous tissues were irrigated with a solution of bacitracin/saline before skin closure. From 1994, we limited observers to 1. Skeletonization of the ITAs began in 2000. From July 2003 onwards, 8 measures were added sequentially and continued subsequently. (1) Starting in November 2003, an ultrasonic scalpel was used to skeletonize ITAs (Harmonic Scalpel; Ethicon Endo-Surgery). Because a bloodless surgical field is required, less clot or charred tissue in the mammary bed reduces substrate for infection. (2) Starting in July 2005, vancomycin paste (2 g of vancomycin powder in 2 to 3 mL of saline) was applied to the sternal marrow before approximation.[7] (3) Beginning in January 2006, iodine-impregnated surgical adhesive drapes (Ioban 3M, St Paul, Minn) were applied on the chest area before incision and removed at skin closure. (4) DSWIs occurred in 15 of the first 500 patients in this study; 5 were in obese (body mass index [BMI] $\geq$30 kg/m^2) diabetic women. Thereafter (November 2007), only 1 ITA and radial arteries were used in this group with diabetes, either the left ITA as a Y with itself, or the radial divided into two-thirds/one-third with the one-third used as a Y graft with the left ITA and the two-thirds used as a separate graft. (5) Beginning in November 2007, operative skin preparation was changed to 2% chlorhexidine gluconate/70% isopropyl alcohol (Soluprep 2% to 70% tinted; Laval, Quebec) (instead of 10% povidone-iodine) which was applied for at least 30 seconds over potential incision sites. Also, the night before, patients underwent skin preparation with a 6-wipe package of chlorhexidine (Sage Products LLC, Cary, Ill). (6) Beginning in April 2008, off-pump CABG was performed in 75% of cases versus 6% before then. (7) In June 2008, wound care was changed to an aseptic technique (Figure 1). (8) Irrigating and manual cleansing of the sternal marrow before applying vancomycin paste began in September 2009, which was part of a protocol for a trial of Kryptonite bone cement[8] for approximation of the sternum (15 patients). Marrow cleansing was necessary before applying the cement; this was done in all subsequent patients.

Data Collection

Systematically collected data from consecutive patients were entered prospectively into a surgical database. DSWIs were recorded prospectively by the Infectious Disease Department of the hospital. For comparison with rates from other surgeons at the same hospital, data were retrieved from our APPROACH database[9] (prospectively collected data from patients enrolled at the time of cardiac catheterization and followed to assess outcomes).

Statistical Analysis

Objective 1. To determine whether there was a significant change in DSWI rate and, if so, when the change occurred. Because the surgeries were unevenly distributed over time, we used groups of 20 consecutive surgeries to model the infection rate, ensuring sufficient numbers in the denominator for adequate precision. To avoid the use of zero (for statistical reasons), the rate of successful surgeries (ie, those without a DSWI) was modeled instead of infection rates. In this case, time was considered as the sequential number representing each consecutive group of 20 surgeries. To determine our objective, a nonlinear 4-parameter logistic model was fitted to the successful surgery rate. One equation for this model is[10]

$$\text{rate} = \beta_0 + \beta_1/\{1+\exp[-\beta_2 \times (\text{time}-\beta_3)]\}$$

This describes a sigmoidal function that allows for an initial infection rate β_0 and a final infection rate β_1 and a gradual change over a period of time (midpoint β_3).

Objective 2. To determine which measure was key in reducing DSWIs, we considered that a change in the rate was most likely due to the measure implemented just before when the infection rate attains the right-hand asymptote (the new infection rate). This key intervention was considered necessary (but not necessarily sufficient) to reduce the rate, provided that the probability of observing a DSWI (after the last observed infection if the rate remained the same) was nonzero. Any of the measures implemented before this key intervention may also have contributed, but we were unable to determine this in this study. Similarly, it is possible that any measure implemented after this key intervention also contributed to a decreased rate, if the probability of a DSWI at this point after the last change point was nonzero.

To estimate the probability of a DSWI after the last observed infection as a function of the number of surgeries completed, we assumed that the DSWIs formed a stationary Poisson point process with mean λ. This required examination of the number of surgeries between each infection. To be considered a stationary point process, there should be no autocorrelation between the interevent intervals (IEI) and the cumulative distribution function should be exponential with rate $1/\lambda$ where λ is the mean of the IEI. After this assumption was checked, we calculated the probability of a DSWI for a given number of surgeries after the last infection using an exponential distribution with rate $1/\lambda$. To examine the assumptions, we calculated the autocorrelation function of the IEIs and used a survival-type analysis to determine the distribution function of the IEI.

Objective 3. We examined whether the proportion of patients in the subgroup of obese diabetic women significantly decreased after the change point and then examined the difference in DSWI rates between this subgroup and the remainder of the patients before the change point. In both cases, we used the Fisher exact test to compare the proportions.

Objective 4. To examine the change in DSWI rates in 2 other (overlapping) cohorts at our institution before and after the institution-wide change in operative skin preparation change to chlorhexidine-alcohol in November 2007 (several of the other measures were used by other surgeons, but not consistently) for: (1) all cardiac procedures performed by all surgeons for 3 years 4 months before the implementation of chlorhexidine-alcohol and for 8 months after, using a comparison of proportions; (2) isolated CABG surgeries performed by 8 other surgeons at this institution, over the same period as the study cohort. A Poisson regression model was used to estimate the incidence of DSWI for each surgeon and before and after the implementation of chlorhexidine-alcohol. The model included a categorical variable indicating surgeon and a binary variable indicating before/after chlorhexidine-alcohol implementation. The interaction between these 2 variables was examined to investigate whether the change in rates differed by surgeon. In the absence of a statistically significant interaction, and the absence of a statistically significant difference across surgeons, overall rates (with 95% confidence intervals [CI]) were estimated from the model from each time period.

Guiding Principles

- ✓ **Cardiac surgery patients are at high risk for developing surgical site infections**
- ✓ **A protective approach will be taken in regard to wound care**
- ✓ Wound care is done **OD** (once a day) and **prn after initial 48 hrs**
- ✓ **PRN means:** if oozing, if visibly soiled, if patient is incontinent, if wound edges are not well approximated.
- ✓ No soaps, lotions or skin creams to be used on the incision
- ✓ If present, keep pannus clean and dry – dry gauze or abd pad, change BID and prn

Definition: Aseptic technique is a set of specific practices and procedures performed under carefully controlled conditions with the goal of minimizing contamination by pathogens.

Aseptic Technique:

- ✓ Sterile dressing tray - sterile field
- ✓ Clean gloves – no touch technique
- ✓ Mask if wound is open or draining (if organisms and pus can get out, they can also get in!)
- ✓ Sterile normal saline

Leg and Arm Dressings

Encourage underwear and bra ASAP within 48 hours and when foley is out

Initial Post-Op Sterile Dressing

↓ ↓

If no oozing → leave dressing X 48 hours

↓

Change dressing using aseptic technique OD and PRN (See definitions)

After 48 hours

↓

Change dressing OD and PRN using aseptic technique if oozing

Steri-strip support guidelines

- apply steri-strips every 4cm when ordered

- if supporting a "gap" in the incision, apply steri-strips superior, and distal to the gap. Do not cover the open area, cover with a dressing

- change steri-strips when visibly soiled

D/C Wound Care and leave open to air when:

1. Wound is healed – no oozing
2. Pt is not incontinent

If wound is infected

↓

Follow wound care orders in computer Order-set

FIGURE 1. Cardiac surgery wound care algorithm. *BID*, Twice daily; *D/C*, discontinue; *Pt*, patient; *CT*, chest tubes; *d/c'd*, discontinued; *OD*, once a day; *PRN*, pro re nata [as needed]; *ASAP*, as soon as possible; *CV-ICU*, cardiovascular intensive care unit.

Sternal Dressing

Initial Post Op Sterile Dressing

↓ ↓

If no oozing → leave dressing x 48 hrs

↓

Change dressing using aseptic technique OD and PRN (See definitions)

After 48 hours

Change dressing OD using aseptic technique (even if not oozing)

Until CT, Telemetry are d/c'd (protection from contamination) – then leave open to air (see exceptions)

Exceptions

If trached
Intubated
Diagnosed with Ventilator Acquired Pneumonia,
Coughing and has +++ oral secretions (protection)

↓

Continue to dress sternal wound using aseptic technique OD and prn

If wound is infected

↓

Follow wound care orders in computer Order-set

↓

D/C Wound Care When:

1. All chest tubes and lines are out
2. Wound is healed – no oozing, edges will approximate
3. Exceptions as mentioned above are not present (i.e. not trached, intubated etc.)
4. Nurse will review sternal care with patient

Encourage underwear and bra ASAP within 48 hours and when foley is out

Pacer Wires

- **Cover insertion site** with OpSite and date
- use chlorhexidine swabs just like for a central line
- change q 7 days
- sterile procedure
- cover site after removal x 24 hours with a band aid
- **CV-ICU** – Don't cover pacer wires (only insertion site)
- **Post-op unit** – Cover pacer wires with a separate OpSite

FIGURE 1. (*Continued*).

RESULTS

Study Population

From July 18, 2003 to October 16, 2012, 1001 consecutive CABG operations (1 patient had a second procedure 8 years later for new disease) were performed with 98% (2928 of 2987) arterial grafts. Fifty-nine operations were for single-vessel disease; 73% (689 of 942) of the remaining operations were with BITA grafts. Graft conduits consisted of 70% ITAs, 28% radial arteries, 2% venous, and 4 inferior epigastric arteries (0.13%). The demographics of the patients are listed in Table 1. There was less chronic obstructive pulmonary disease (COPD) ($P = .022$), fewer active smokers ($P = .029$), and less insulin-dependent diabetics ($P = .003$). In 4 patients, 6 of 8 harvested ITAs could not be used because of damage and/or fragility. They were included in the analysis because they shared the presumed associated risk for infection. Twenty-six (2.7%) patients required reexploration for bleeding, none of whom developed DSWI.

TABLE 1. Patient characteristics: before and after the change point

	All patients (n = 1001)	Before change point (n = 532)	After change point (n = 469)	*P* value
Off-pump, n (%)	388 (39)	37 (7)	351 (75)	<.001
BITA rate excluding single-vessel disease	689/942 (73)	358/504 (71)	331/438 (76)	.122
Demographics				
Mean age, y (SD)	64.9 (10.4)	64.8 (10.6)	65.1 (10.2)	.671
Male, n (%)	780 (78)	409 (77)	371 (79)	.402
Outpatient, n (%)	435 (44)	227 (43)	208 (44)	.151
Inpatient, n (%)	455 (45)	254 (48)	201 (43)	
Emergency, n (%)	111 (11)	51 (10)	60 (13)	
Comorbidities				
Total diabetics, n (%)	345 (34)	180 (34)	165 (35)	.755
Type 1 diabetes, n (%)	58 (6)	42 (8)	16 (3)	.003
Type 2 diabetes, n (%)	287 (29)	138 (26)	149 (32)	.130
Hypertension, n (%)	691 (69)	361 (68)	330 (70)	.411
Hypercholesterolemia, n (%)	697 (70)	371 (70)	326 (70)	.973
Active smoker, n (%)	208 (21)	125 (24)	83 (18)	.029
Ejection fraction 30%-50%, n (%)	228 (23)	122 (23)	106 (23)	.739
Ejection fraction <30%, n (%)	66 (7)	32 (6)	34 (7)	
Obesity: BMI $\geq$35 kg/m^2, n (%)	113 (11)	61 (11)	52 (11)	.920
BMI $\geq$30 kg/m^2, n (%)	339 (34)	185 (35)	154 (33)	.547
COPD, n (%)	114 (11)	73 (14)	41 (9)	.016
Cerebrovascular disease, n (%)	101 (10)	59 (11)	42 (9)	.293
Peripheral vascular disease, n (%)	106 (11)	63 (12)	43 (9)	.182
Renal disease, creatinine >200 μmol/L, n (%)	36 (4)	19 (4)	19 (4)	1.0
EuroSCORE, median (IQR)	2.9 (1.5, 6.2)	3.0 (1.6, 6.2)	2.8 (1.5, 6.2)	.618

BITA, Bilateral internal thoracic artery; *SD*, standard deviation; *BMI*, body mass index; *COPD*, chronic obstructive pulmonary disease; *IQR*, interquartile range.

Operative mortality was 3.9% overall, 16% for emergency procedures, 4% for urgent operations, and 0.7% for elective procedures. Among the 16 patients with DSWIs, 6 (38%) died, 4 during the first admission and 2 after early readmission.

Deep Sternal Wound Infection

There were 16 DSWIs overall (1.6%; 95% CI, 0.9%-2.6%). Two occurred after single ITA grafting. Fourteen DSWIs occurred after BITA grafting, all in the first 316 of 686 patients with BITA grafts (14 of 316, 4.4%; 95% CI, 2.4%-7.3%). Of the 14 with BITA grafts, 9 were diabetic; 9 were male, 8 were obese including 4 with morbid obesity (BMI $\geq$40 kg/m^2) and 5 (36%) were obese diabetic women. Treatment included debridement $\pm$ rewiring in 6 (1 patient left open), sternal reconstruction with muscle flap in 2, pericardial window in 1, vacuum-assisted closure in 1, local wound dressing in 2, antibiotics only for 6 weeks in 3 without wound breakdown (purulent drainage, severe sternal pain, positive white blood cell scans), and no treatment in 1 of the 2 patients with a single ITA artery graft who died quickly with purulent pleuritis/mediastinitis; the other single ITA graft patient (the last) needed only dressing changes.

Detection of a Statistically Significant Change Point

The last DSWI was in patient number 532 on April 7, 2008. The estimated 4-parameter logistic model is shown in Figure 2, *A*. There was a statistically significant (P = .001) change in the DSWI rate from 3.1% to 0%. The midpoint of the inflection was the 513th operation on November 16, 2007, and for practical purposes, we consider surgery 532, when the last infection was observed, to be the change point of infection rates.

Which Infection Prevention Measures Contributed to the Decrease?

Measures implemented just before the decrease in infection rates (April 2008) were avoidance of BITA grafts in obese diabetic women on October 12, 2007 and change to chlorhexidine-alcohol on October 30, 2007. However 1 more infection occurred after this just at the sixth measure (change to off-pump and this patient had surgery performed off-pump). Overall, the mean number of surgeries between infections was 33.25 and the number of surgeries between infections fitted an exponential distribution (Figure 2, *B*). The probability of observing 17 surgeries without an infection at this incidence was high (P = .60) indicating that the wound care protocol may also have contributed to the decreased infection rates. The final measure listed (irrigation of bone marrow) was implemented on September 28, 2009, 155 surgeries after the last DSWI (P < .001) indicating that it is less likely to have contributed substantially to the decreased infection rate, but not impossible.

To decide whether the DSWIs had been eradicated (ie, P < .000001 [1E-06] of observing no DSWIs after

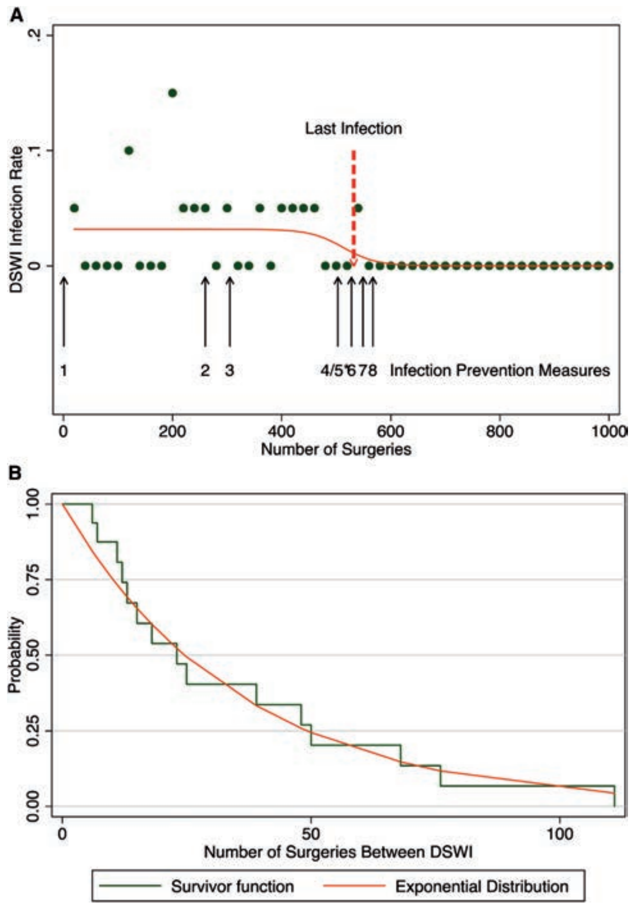

FIGURE 2. A, Infection rates per 20 consecutive surgeries (*dots*). The *dashed red arrow* indicates when the last deep sternal wound infection was observed. The *black arrows* indicate when each infection prevention measure (see later discussion) was implemented. *Indicates an institution-wide measure. Infection prevention measures: (1) Skeletonization of internal thoracic arteries with ultrasonic scalpel; (2) vancomycin paste applied to sternal halves; (3) use of iodine-impregnated surgical adhesive drapes; (4) avoidance of use of bilateral internal thoracic arteries in obese diabetic women; (5) preoperative skin preparation with chlorhexidine-alcohol; (6) off-pump coronary artery bypass graft was performed where feasible; (7) wound care was changed to an aseptic technique; (8) cleansing the sternal marrow before applying vancomycin paste. B, Distribution of the interinfection intervals for the first 523 surgeries: the Kaplan-Meier estimate (*green line*) is the estimated probability of remaining infection-free given the number of surgeries since the last infection. The *red line* indicates the fitted exponential distribution; ie, the probability of observing 50 surgeries or more between infections is high (about 25%). The probability of observing 100 surgeries or more is about 5% and the probability of observing 200 surgeries or more without infection is low at 0.2%. *DSWI*, Deep sternal wound infection.

the last 1 observed); we would have to follow an additional 460 patients after the last observed infection without another occurrence. A total of 469 surgeries were observed without infection (P = 7.48e-07 if the infection rate had not changed) indicating that the rate of DSWI in BITA patients had decreased (and potentially been eradicated) by the combination of measures.

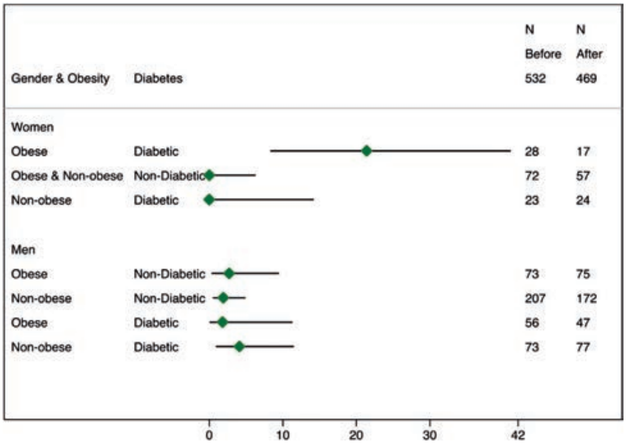

FIGURE 3. Comparison of deep sternal wound infection (DSWI) rates in men, women, diabetic and nondiabetic, obese and nonobese patients. *Diamonds*, DSWI rate in each subgroup before the change point. *Lines* indicate the confidence intervals (CI). CIs are one-sided (97.5%) when the estimates are zero and 95% when nonzero. There is no significant effect of obesity and diabetes in men ($P = .696$); the overall rate was 2.4% (1.2-4.4). However, obese diabetic women have a significantly higher risk of DSWI than other women ($P < .001$). Notably, the only DSWIs in women were observed in obese diabetics. The last 2 columns indicate the number of patients in each subgroup before and after the change point. There was no significant difference within women ($P = .547$) or men ($P = .512$).

DSWI Risk in Obese Diabetic Women

In Figure 3 shows the DSWI rate in the subgroups identified by sex, obesity, and diabetes. After October 2007, BITA grafting was avoided in obese diabetic women and therefore the proportion of such patients relative to the total population of BITA patients (N = 689) decreased from 5.3% (95% CI, 3.2%-8.2%) to 1.8% (95% CI, 0.7%-3.9%), $P = .015$. The DSWI rate in 28 obese diabetic women before April 2008 was 21.4% (95% CI, 8.3%-40.9%), which was 10-fold greater than that in all other patients in this first group of 532 patients combined (N = 504; DSWI rate = 2.0% [8 of 504]; 95% CI, 1.0%-3.6%). Reasons for performing BITA in 6 diabetic obese women after the changed strategy included ideal circumstances for just BITA, a BMI just more than 30 kg/m^2, ability to perform off-pump CABG and unawareness of a BMI of 35.5 kg/m^2 in 1 woman.

Comparison With All Other CABG Procedures in the Same Institution

Before the operative skin preparation was changed to chlorhexidine-alcohol (November 2007), the DSWI rate was 3.1% (139 of 4420) for all cardiac procedures for all surgeons over 3 years 4 months. Subsequently, the rate over 8 months decreased to 0.8% (6 of 818 procedures) ($P = .001$). There was no evidence of an interaction between surgeon and the before/after November 2007 variable ($P = .415$) or of a significant difference in rates across surgeons ($P = .127$). The overall after/before November 2007 incidence rate ratio was 0.46 (95% CI, 0.24-0.86) indicating that the overall rate of DSWI in isolated CABG was halved after the introduction of chlorhexidine-alcohol in November 2007, from 2.65% (95% CI, 1.74%-4.02%) to 1.21% (95% CI, 0.67%-2.17%) but not eliminated.

DISCUSSION

In this study of 1001 consecutive CABG operations by a single surgeon with near total arterial and 74% BITA grafting, we were able to achieve a significant reduction in the incidence of DSWIs after sequential introduction of multiple infection prevention measures. There were no DSWIs associated with the last 469 procedures, whereas the DSWI rate was 3.01% in the preceding 532 operations. To date, this is the lowest reported DSWI rate after bypass surgery. This is particularly important because of the substantial number of patients with BITA grafts. Also important is that among diabetic patients, only obese women seem to have a high risk of DSWI and that the risk in other diabetics, including obese men, is similar to the nondiabetic population.

Risk Associated With BITA Grafting

In 1990, Kouchoukos and colleagues[11] first documented the relationship between BITA grafting and DSWI (which occurred in 6.9% of patients with BITA conduits, 1.9% of patients with single ITA grafts, and 1.3% of patients with

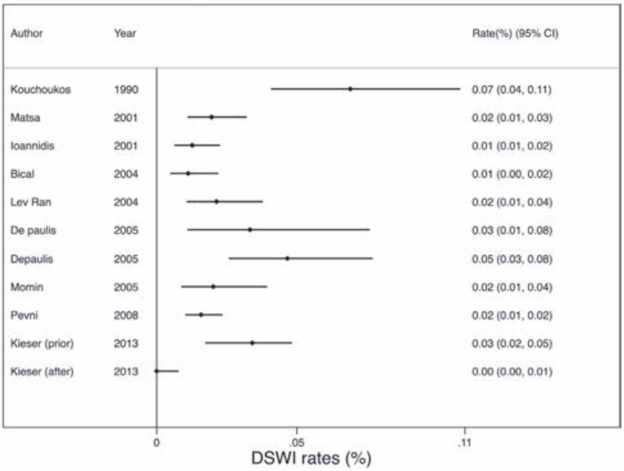

FIGURE 4. Comparison of the estimated deep sternal wound infection (*DSWI*) rate in this study (Kieser 2013) before and after the change point with other previously reported studies. The *diamonds* represent the infection rates and the *lines* indicate the 95% confidence intervals (*CI*) of the estimate. Because the number of infections for Kieser 2013 (after) was zero, a one-sided 95% confidence interval is presented.

vein-only grafts). They suggested that BITA grafting was not justified (unless other conduits were not available) until they were proven superior to single ITA grafts. Subsequently, in 1999 Lytle and colleagues[12] documented the long-term benefits of BITA grafting. However, there is still reluctance to use BITA grafts in diabetics even though many have verified the safety of BITA in such patients, especially if ITAs are skeletonized.[13-17] Our observations add credence to the safety of BITA grafting (with respect to DSWI) and demonstrate how the DSWI rate can be lowered even further. This is particularly important in the United States; the Centers for Medicare and Medicaid Services have deemed mediastinitis after cardiac surgery a "never event" and no longer reimburse for extra care if a DSWI occurs.[18]

Risk Associated With Diabetes

As previously reported by Matsa and colleagues[13] and stated by Lev-Ran and colleagues,[14] we found only 1 subgroup of patients with an increased risk of DSWI: obese diabetic women; they had a 10-fold greater incidence of DSWI than obese diabetic men. They represented 13% of the diabetics, but had 38% of the DSWIs (5 with BITA and 1 with single ITA). Thus, our results suggest that there is no increased risk of DSWI with BITA grafting in most diabetics in whom the DSWI rate was only 1.3% and that only obese diabetic women should not undergo BITA grafting. Because 2 measures (not using BITAs in obese diabetic women and the switch to chlorhexidine-alcohol) were implemented at approximately the same time; it remains possible that just the antiseptic change was sufficient. Although this raises the possibility that the current risk may be lower in obese diabetic women than our data suggest, the continued (but low) incidence in DSWIs in patients operated on by other surgeons who also use chlorhexidine-alcohol does not support that.

Key Infection Prevention Measures

The use of chlorhexidine-alcohol and avoidance of BITA grafting in obese diabetic women seem to be the key effective measures responsible for eliminating DSWIs in a substantial number of subsequent procedures. Certainly, all implemented measures may have contributed, but it was only after these 2 that the DSWI rate decreased dramatically. Even though the DSWI rate for our other surgeons was halved after the introduction of chlorhexidine-alcohol, it was not eliminated, which suggests that the introduction of chlorhexidine-alcohol in November 2007 was not solely responsible for the reduction in DSWIs in the authors' patients.

Chlorhexidine-alcohol is an effective infection prevention agent. The 2011 Guidelines for the Prevention of Intravascular Catheter-Related Infections, as a Category IA level of evidence, recommends skin preparation with greater than 0.5% chlorhexidine-alcohol for intravenous or arterial line insertions.[19] Several controlled trials[20-22] compare chlorhexidine-alcohol with povidone-iodine in surgical patients. For general surgical patients undergoing clean-contaminated surgery, chlorhexidine-alcohol was more protective against superficial and deep infections but inexplicably not against organ-space infections.[22]

BITA Grafting and DSWI

The incidence of DSWI using skeletonized BITA grafts varied from 1.1% to 3.3% in previous studies (Figure 4)[13,15,17,23,24] and was greater when ITAs were harvested in a pedicled fashion[16,23] in BITA grafting,[13,15-17,23-25] and lower after single ITA grafting.[11,23] In our series, although the DSWI rate after BITA grafting was 1.6% for the whole group, it was 3.0% for the first 532 patients and 0% in the last 469 patients (76% with BITA grafts).

Limitations

As is common in retrospective studies, it was not possible to control for all factors that may have changed outcomes in the 2 groups of patients. The non-DSWI group had slightly fewer active smokers, insulin-dependent diabetics, and patients with COPD; the small number of patients with these characteristics should not have affected the results. Also, general improvements over time in surgery, anesthesia, and knowledge of infection may also have helped to reduce infections. The strategy of not using BITA grafts in obese diabetic women, and the switch to chlorhexidine-alcohol were key measures. The strength of this study is that it is a consecutive all-comer population of patients in which most had BITA grafting, including most diabetics.

CONCLUSIONS

We have shown in a series of 1001 CABG procedures with near total arterial grafting, three-quarters BITA grafts and one-third diabetics, that the risk of DSWIs can be reduced to close to zero through multiple infection prevention measures. We cannot predict a zero rate; the risk will certainly not disappear. We suggest that just as DSWI may be caused by the transgression of several barriers to infection, the incidence of DSWI may be reduced by the addition of layers of prevention. We cannot point to a single measure as being critical and speculate that multiple barrier techniques are likely necessary to optimize outcomes. DSWIs still occur in our unit at a low rate, but not in patients in whom all the measures have been implemented. It is important to emphasize that the risk was reduced in all subgroups except for obese diabetic women. Our data support the avoidance of BITA grafting in obese diabetic women; however, most diabetics may benefit from BITA grafting without increased risk of DSWI.

The authors greatly appreciate the support of the APPROACH cardiac and catheterization personnel.

References

1. Kinoshita T, Asai T. Bilateral internal thoracic artery grafting current state of the art. *Innovations (Phila)*. 2011;6:77-83.
2. Dorman MJ, Kurlansky PA, Traad EA, Galbut DL, Zucker M, Ebra G. Bilateral internal mammary artery grafting enhances survival in diabetic patients. A 30 year follow-up of propensity score-matched cohorts. *Circulation*. 2012;126:2935-42.
3. Tatoulis J, Buxton BF, Fuller JA. The right internal thoracic artery: the forgotten conduit–5,766 patients and 991 angiograms. *Ann Thorac Surg*. 2011;92:9-15; discussion 15-17.
4. Toumpoulis IK, Theakos N, Dunning J. Does bilateral internal thoracic artery harvest increase the risk of mediastinitis? *Interact Cardiovasc Thorac Surg*. 2007;6:787-91.
5. Risnes I, Abdelnoor M, Almdahl SM, Svennevig JL. Mediastinitis after coronary artery bypass grafting. Risk factors and long-term survival. *Ann Thorac Surg*. 2010;89:1502-9.
6. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection 1999. *Infect Control Hosp Epidemiol*. 1999;20: 247-80.
7. Arruda MVF, Braile DM, Joaquim MR, Suzuki FA, Alves RH. The use of the vancomycin paste for sternal hemostasis and mediastinitis prophylaxis. *Rev Bras Cir Cardiovasc*. 2008;23:35-9.
8. Fedak PW, Kieser TM, Maitland AM, Holland M, Kasatkin A, Leblanc P, et al. Adhesive-enhanced sternal closure to improve postoperative functional recovery: a pilot, randomized controlled trial. *Ann Thorac Surg*. 2011;92:1444-50.
9. Ghali WA, Kundtson ML. Overview of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease on behalf of the APPROACH investigators. *Can J Cardiol*. 2000;16:1225-30.
10. Reeve R, Turner JR. Pharmacodynamic models: parameterizing the Hill equation, Michaelis-Menten, the logistic curve, and the relationship between these models. *J Biopharm Stat*. 2013;23:648-61.
11. Kouchoukos NT, Wareing TH, Murphy SF, Pelate C, Marshall WG Jr. Risks of bilateral internal mammary artery bypass grafting. *Ann Thorac Surg*. 1990;49: 210-7; discussion 217-19.
12. Lytle BW, Blackstone EH, Loop FD, Houghtaling PL, Arnold JH, Akhrass R, et al. Two internal thoracic artery grafts are better than one. *J Thorac Cardiovasc Surg*. 1999;117:855-72.
13. Matsa M, Paz Y, Gurevitch J, Shapira I, Kramer A, Pevny D, et al. Bilateral skeletonized internal thoracic artery grafts in patients with diabetes mellitus. *J Thorac Cardiovasc Surg*. 2001;121:668-74.
14. Lev-Ran O, Mohr R, Amir K, Matsa M, Nehser N, Locker C, et al. Bilateral internal thoracic artery grafting in insulin-treated diabetics: should it be avoided? *Ann Thorac Surg*. 2003;75:1872-7.
15. Bical OM, Khoury W, Fromes Y, Fischer M, Sousa Uva M, Boccara G, et al. Routine use of bilateral skeletonized internal thoracic artery grafts in middle-aged diabetic patients. *Ann Thorac Surg*. 2004;78:2050-3.
16. Momin AU, Deshpande R, Potts J, El-Gamel A, Marrinan MT, Omigie J, et al. Incidence of sternal infection in diabetic patients undergoing bilateral internal thoracic artery grafting. *Ann Thorac Surg*. 2005;80:1765-72; discussion 1772.
17. Pevni D, Uretzky G, Mohr A, Braunstein R, Kramer A, Paz Y, et al. Routine use of bilateral skeletonized internal thoracic artery grafting: long-term results. *Circulation*. 2008;118:705-12.
18. Puskas JD. Why did you not use both internal thoracic arteries? *Circulation*. 2012;126:2915-7.
19. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al., Healthcare Infection Control Practices Advisory Committee. Guidelines for the prevention of intravascular catheter-related infections. *Am J Infect Control*. 2011; 39(4 Suppl 1):S1-34.
20. Culligan PJ, Kubik K, Murphy M, Blackwell L, Snyder J. A randomized trial that compared povidone iodine and chlorhexidine as antiseptics for vaginal hysterectomy. *Am J Obstet Gynecol*. 2005;192:422-5.
21. Ostrander RV, Botte MJ, Brage ME. Efficacy of surgical preparation solutions in foot an ankle surgery. *J Bone Joint Surg Am*. 2005;87:980-5.
22. Darouiche RO, Wall MJ Jr, Itani KM, Otterson MF, Webb AL, Carrick MM, et al. Chlorhexidine-alcohol versus povidone-iodine for surgical-site antisepsis. *N Engl J Med*. 2010;362:18-26.
23. De Paulis R, de Notaris S, Scaffa R, Nardella S, Zeitani J, Del Giudice C, et al. The effect of bilateral internal thoracic artery harvesting on superficial and deep sternal infection: the role of skeletonization. *J Thorac Cardiovasc Surg*. 2005;129:536-43.
24. Lev-Ran O, Mohr R, Pevni D, Nesher N, Weissman Y, Loberman D, et al. Bilateral internal thoracic artery grafting in diabetic patients: short-term and long-term results of a 515-patient series. *J Thorac Cardiovasc Surg*. 2004;127:1145-50.
25. Ioannidis JP, Galanos O, Katritsis D, Connery CP, Drossos GE, Swistel DG, et al. Early mortality and morbidity of bilateral versus single internal thoracic artery revascularization: propensity and risk modeling. *J Am Coll Cardiol*. 2001;37: 521-8.

PART 5

COMPLETENESS OF REVASCULARIZATION AND BILATERAL INTERNAL MAMMARY ARTERY GRAFTING

Chapter 11

Arterial grafts balance survival between incomplete and complete revascularization: a series of 1000 consecutive coronary artery bypass graft patients with 98% arterial grafts

Kieser TM, Curran HJ, Rose MS, Norris CM, Graham MM

J Thorac Cardiovasc Surg 2014;147:75-84

Arterial grafts balance survival between incomplete and complete revascularization: A series of 1000 consecutive coronary artery bypass graft patients with 98% arterial grafts

Teresa M. Kieser, MD,[a] Helen J. Curran, MD,[b] M. Sarah Rose, PhD,[a] Colleen M. Norris, PhD,[c] and Michelle M. Graham, MD[c]

Objective: Coronary artery bypass grafting (CABG) with incomplete revascularization (ICR) is thought to decrease survival. We studied the survival of patients with ICR undergoing total arterial grafting.

Methods: In a consecutive series of all-comer 1000 patients with isolated CABG, operative and midterm survival were assessed for patients undergoing complete versus ICR, with odds ratios and hazard ratios, adjusted for European System for Cardiac Operative Risk Evaluation category, CABG urgency, age, and comorbidities.

Results: In this series of 1000 patients with 98% arterial grafts (2922 arterial, 59 vein grafts), 73% of patients with multivessel disease received bilateral internal mammary artery grafts. ICR occurred in 140 patients (14%). Operative mortality was 3.8% overall, 8.6% for patients with ICR, and 3.2% for patients with complete revascularization ($P = .008$). For operative mortality using multivariable logistic regression, after controlling for European System for Cardiac Operative Risk Evaluation category ($P < .001$) and CABG urgency ($P = .03$), there was no evidence of a statistically significant increased risk of death due to ICR (odds ratio, 1.73; 95% confidence interval, 0.80-3.77). For midterm follow-up (median, 54 months [interquartile range, 27-85 months]), after controlling for European System for Cardiac Operative Risk Evaluation category ($P < .001$) and comorbidities ($P = .017$) there was a significant interaction between age $\geq$ 80 years and ICR ($P = .017$) in predicting mortality. The adjusted hazard ratio associated with ICR for patients older than age 80 years was 5.7 (95% confidence interval, 1.8-18.0) versus 1.2 (95% confidence interval, 0.7-2.1) for younger patients.

Conclusions: This is the first study to suggest that ICR in patients with mostly arterial grafts is not associated with decreased survival perioperatively and at midterm in patients younger than age 80 years. Arterial grafting, because of longevity, may balance survival between complete revascularization and ICR. (J Thorac Cardiovasc Surg 2014;147:75-84)

The concept of complete revascularization (CR) in coronary artery bypass graft (CABG) surgery portending to improved patient outcomes was first espoused by McNeer and colleagues in 1974.[1] This gold standard may not be applicable today because data suggesting the benefits of CR included young, stable patients, first-time procedures, and predominantly vein grafting.[1] Newer studies are needed to evaluate contemporary CABG surgery, including use of total arterial grafting; off-pump CABG; and revascularization procedures in older, sicker patients. The goal of our study was to determine if there was a survival advantage of completely revascularized patients compared with ICR in a patient cohort with predominantly (98%) arterial grafting. We hypothesized that the long-term advantage of arterial grafts would potentially counteract the reduced survival of ICR in an all-comer group of CABG patients.

METHODS

From July 2003, to October 2012, total arterial grafting was performed where possible in all patients by 1 surgeon at a high volume academic tertiary care center. Patients were divided into 2 groups: Those in whom revascularization was complete and those in whom it was not.

All patients were entered into the Alberta Provincial Program for Outcome Assessment in Coronary Heart Disease study,[2] a prospective data collection initiative in the province of Alberta, Canada, since 1995. Patients are enrolled at initial cardiac catheterization and are followed to assess long-term survival and repeat revascularization with percutaneous coronary intervention (PCI) or CABG. Mortality is verified by linkage to Alberta Vital Statistics. All study patients were also entered into a prospective surgical database, recording patient demographics and relevant surgical data. This study was approved by our institution's research ethics board.

Angiogram and operative reports, and office charts of each patient were independently reviewed by both an interventional cardiologist and a cardiac surgeon to determine completeness of the revascularization. Revascularization was considered complete when all diseased arterial territories in

From the Libin Cardiovascular Institute of Alberta,[a] University of Calgary, Calgary, Alberta, Canada; Dalhousie University,[b] Halifax, Nova Scotia, Canada; and Mazankowski Alberta Heart Institute,[c] University of Alberta, Edmonton, Alberta, Canada.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Read at the 93rd Annual Meeting of The American Association for Thoracic Surgery, Minneapolis, Minnesota, May 4-8, 2013.

Received for publication May 11, 2013; revisions received July 2, 2013; accepted for publication Aug 9, 2013; available ahead of print Sept 30, 2013.

Address for reprints: Teresa M. Kieser, MD, FRCSC, FACS, Department of Cardiac Sciences, Calgary Health Region Foothills Medical Centre, 1403 29th St NW, Calgary, Alberta, T2N2T9, Canada (E-mail: t.kieserprieur@ucalgary.ca).

0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2013.08.003

Abbreviations and Acronyms

CABG	= coronary artery bypass graft
CIRC	= circumflex artery
CR	= complete revascularization
EuroSCORE	= European System for Cardiac Operative Risk Evaluation
FFR	= fractional-flow reserve
ICR	= incomplete revascularization
IMA	= internal mammary artery
LAD	= left anterior descending
PCI	= percutaneous coronary intervention
RCA	= right coronary artery

left anterior descending (LAD) artery, circumflex artery (CIRC), and right coronary artery (RCA) regions, with ≥70% stenosis—or ≥50% in the left main artery—received at least 1 bypass graft for coronary arteries measuring >1 mm in diameter. Left main revascularization was considered complete if grafts were placed to the LAD and CIRC.

Five categories of reasons for incomplete revascularization (ICR) were obtained from operative reports: small vessel (<1 mm diameter), diffuse disease precluding healthy anastomosis, coronary artery inaccessible for grafting (location in the atrioventricular groove), infarcted territory (akinetic wall, thinned segment, or nonviable myocardium), technical problems (adhesions in reoperative surgery, high-risk or porcelain aorta needing off-pump procedure).

Surgery Details

All operations were performed off- or on-pump. For on-pump procedures, we used intermittent antegrade blood cardioplegia and systemic hypothermia to 32°C. Off-pump CABG was performed with the Octopus stabilizing device (Medtronic, Inc, Minneapolis, Minn). Internal mammary artery (IMA) conduits were harvested in a skeletonized manner, with the left IMA anastomosed to the LAD and the right IMA to either the CIRC or RCA. IMAs were used mostly as in-situ grafts and were wrapped in papaverine-soaked gauze after harvesting. High spinal anesthesia (local anesthetic and opioid) supplemented by light general anesthesia was used. Intraoperative transesophageal echocardiography was used except where contraindicated. Long-acting nitrates were used postoperatively for 6 weeks in only patients with radial artery grafts.

Statistical Analysis Methods

Descriptive analysis. Descriptive statistics (Table 1) for categorical variables and the means ± standard deviation for normally distributed continuous variables and the median and interquartile range (IQR) for non-normally distributed variables were provided for all patients. Comparisons of baseline variables were made between patients who experienced ICR and those who did not, only in patients with multivessel disease (single-vessel disease patients by virtue of their inability to be incompletely revascularized were excluded) (Table 2). Comparisons were made using the Fisher exact test for categorical variables and the *t* test (for normally distributed) or Wilcoxon signed rank tests (for non-normally distributed) continuous variables.

Regression modeling strategy for both logistic and proportional hazards regression. Initially we used individual regression models for each variable in Table 1 to examine if they were significant predictors of outcome. The functional form for continuous variables was examined using residuals analysis and if nonlinearity was detected, suitable transformations were used or the variable was categorized using appropriate cut-points to aid interpretation of the model. Next we entered each variable in Table 1 into a regression model, including the ICR variable to assess for confounding. In the event of evidence of confounding we examined the possibility of an interaction between ICR and that variable. All variables significant at $P < .2$ in the individual regression, interactions significant at $P < .20$ and variables that appeared to be confounding were entered into a multivariable logistic regression model. The possibility of collinearity was examined between predictor variables; the inclusion of highly correlated predictor variables that might cause instability of the model was avoided. To avoid overfitting, we reduced the model by excluding nonsignificant variables (starting with the largest *P* value), provided that this did not change the estimate of the primary predictor variable, ICR (ie, the excluded variable did not contribute to confounding). This process continued until the appropriate number of degrees of freedom in the model was retained (n/10) where n is the number deaths in each model.

Logistic regression was used to assess operative mortality, with the effect of univariate predictors presented as odds ratios (ORs) with 95% confidence intervals (CIs) and estimates of 30-day mortality for each level of the variable. The multivariable model was presented as ORs and adjusted 30-day morality rates were estimated using predictive margins.

Midterm survival was estimated in the operative-survivor patient population, using proportional hazards regression. Out-of-province patients not available for follow-up were excluded. The assumption for proportional hazards was examined using Schoenfeld residuals.[3]

RESULTS

Study Population

From July 18, 2003, to February 2, 2013, 1000 consecutive patients underwent CABG surgery with 98% (2922 out of 2981) arterial grafts. Excluding 59 patients (6%) with single vessel coronary artery disease, 73% (686 out of 941) of patients had bilateral IMA grafts. The majority of patients had triple vessel disease (60%; 600 out of 1000) and 34% had double vessel disease (341 out of 1000). Graft conduits consisted of 70% IMAs, 28% radial arteries, 2% venous grafts, and 4 grafts were inferior-epigastric arteries. Eighty-six percent of the ICR group (120 out of 140 patients) had triple vessel disease. Demographics of the patient groups are shown in Table 1. Patients with ICR were older, had higher European System for Cardiac Operative Risk Evaluation (EuroSCORE) category, experienced more reoperative CABG, underwent off-pump procedures, and were less likely to have normal ejection fraction.

ICR Versus CR

CR was achieved in 801 out of 941 patients (85%) with multivessel disease and ICR occurred in 140 patients (15%). Significant predictors of ICR are presented in Table 2. The ICR group had less bilateral IMA grafting, more off-pump procedures, higher logistic EuroSCORE category, was more likely to have collaterals, was older, more patients with ejection fraction <30%, fewer outpatients, and more likely to undergo reoperative surgery. The numbers for very low ejection fraction and reoperation were small in both groups. No other cardiac risk factors or comorbidities were associated with ICR.

TABLE 1. Baseline characteristics of the study population of 1000 patients; 801 with complete revascularization 140 with incomplete revascularization and 59 with single vessel disease

	All patients (N = 1000)*	CR (n = 801)	ICR (n = 140)	*P* value†
Bilateral internal mammary artery grafts	686 (68.6)	626 (78.2)	60 (42.9)	<.001
Off-pump coronary artery bypass graft	387 (38.7)	283 (35.3)	64 (45.7)	.023
EuroSCORE (median [IQR])	2.9 (1.5-6.2)	2.7 (1.5-5.9)	5.0 (2.7-10.2)	<.001
Collaterals	628 (62.9)	489 (61.2)	116 (82.9)	<.001
Demographics				
Age, mean ± standard deviation‡	64.9 ± 10.4	64.4 ± 10.3	68.9 ± 9.4	<.001
Male	779 (77.9)	624 (77.9)	112 (80.0)	.657
Outpatient	435 (43.5)	370 (46.2)	44 (31.4)	.004
Inpatient	454 (45.4)	345 (43.1)	76 (54.3)	.138
Emergent	111 (11.1)	86 (10.7)	20 (14.3)	.279
Comorbidities				
Hypertension	690 (69.0)	549 (68.5)	102 (72.9)	.323
Hypercholesterolemia	697 (69.7)	555 (69.3)	102 (72.9)	.426
Diabetes	344 (34.4)	279 (34.8)	53 (37.9)	.503
Ever smoked	587 (58.7)	470 (58.7)	87 (62.1)	.457
Active smoker	208 (20.8)	171 (21.3)	31 (22.1)	.824
Ejection fraction >50%	66 (6.6)	45 (5.6)	21 (15.0)	<.001
Ejection fraction 30%-50%	228 (22.8)	182 (22.7)	37 (26.4)	.455
Ejection fraction <30%	706 (70.6)	574 (71.7)	82 (58.6)	.177
Body mass index ≥30	338 (33.8)	275 (34.3)	45 (32.1)	.630
Chronic obstructive pulmonary disorder	131 (13.1)	103 (12.9)	24 (17.1)	.180
Cerebrovascular disease	101 (10.1)	79 (9.9)	18 (12.9)	.292
Peripheral vascular disease	105 (10.5)	87 (10.9)	17 (12.1)	.661
Renal disease§	35 (3.5)	27 (3.4)	7 (5.0)	.328
Reoperative coronary artery bypass graft	37 (3.7)	23 (2.9)	10 (7.1)	.021

Data are presented as n (%) unless otherwise indicated. *CR*, Complete revascularization; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation; *IQR*, interquartile range; *ICR*, incomplete revascularization. *Includes 59 single vessel disease patients. †Comparing ICR patients (n = 140) to CR patients (n = 801). ‡Range (29-96 years). §Creatinine >200 mg/dL.

Operative Mortality

Overall operative mortality was 3.8%. In ICR patients, 30-day mortality was 8.6% compared with 3.2% in patients with complete revascularization ($P = .008$).

Examination of the continuous variables age and logistic EuroSCORE categories revealed substantial nonlinearity in the prediction of mortality. Although log transformation of the logistic EuroSCORE category and a quadratic form for age described this nonlinearity well, we decided to categorize the variables to ease interpretation. Age categories were <65 years, 65 to 80 years, and ≥80 years. For EuroSCORE, there was substantial heterogeneity in the highest risk category (EuroSCORE >6); therefore we subdivided this category into 6 to 9.99, 10 to 19.99, and ≥20.

Baseline factors associated with 30-day mortality are shown in Table 3. Most were also confounders of the relationship between ICR and operative mortality and were considered eligible for entry into the multivariate logistic regression model. Off-pump procedure history and sex were potential confounding variables and were therefore entered into the multivariable model.

In this full model, the effect of ICR was not significant (OR, 1.82; 95% CI, 0.78-4.22; $P = .168$). In the reduced model (Table 3), containing only ICR, EuroSCORE category, and urgency, the estimated OR was 1.73 (95% CI, 0.80-3.77; $P = .166$). Adjusted operative mortality was 5.6% (95% CI, 2.7-8.5) for ICR patients and 3.6% (95% CI, 2.3-4.6; $P = .166$) for CR patients, indicating that after controlling for EuroSCORE category and urgency the effect of ICR on 30-day mortality, although higher than that for CR patients, was not significantly different. For the 65 octogenarians (1 patient aged 96 years), there was no difference in operative mortality due to ICR (for ICR: 9.5%; 95% CI, 1.2-30.3 and for CR: 6.8%; 95% CI, 1.4-18.6; $P = .655$), even though the 37 octogenarians with off-pump CABG history had a significantly higher rate of ICR compared with the non-octogenarians. (48.7% for age ≥80 years; 95% CI, 31.9-65.6 compared with 10.7% for age <80 years; 95% CI, 2.3-28.2; $P < .001$).

Midterm Follow-up

Thirty-eight patients who died during the 30-day postoperative period and 62 patients who were out-of-province were excluded from the midterm follow-up, leaving a total of 841 patients for follow-up (723 with CR and 118 with ICR). The median follow-up time was 56 months. ICR was a significant predictor of midterm mortality (hazard

TABLE 2. Significant predictors (P < .15) of incomplete revascularization

Variable	% ICR (95% CI)	P value
Overall	14.9 (12.7-17.3)	
Off-pump		.023
Yes	18.4 (14.5-22.9)	
No	12.8 (10.2-15.8)	
Bilateral internal mammary artery grafts		<.001
Yes	8.8 (6.7-11.1)	
No	31.4 (25.7-37.5)	
EuroSCORE		<.001
0-2.99	8.7 (6.3-11.6)	
3-5.99	18.6 (13.6-24.5)	
≥6	23.4 (18.3-29.1)	
Age		<.001
<65	10.6 (7.8-14.0)	
65-79	16.5 (13.1-20.3)	
≥80	32.3 (21.1-45.1)	
Urgency		.004
Elective	10.6 (7.8-14.0)	
Urgent in	18.1 (14.5-22.1)	
Emergency	18.9 (11.9-27.6)	
Ejection fraction		<.001
<30	31.8 (20.9-44.4)	
30-50	16.9 (12.2-22.5)	
>50	12.5 (10.1-15.3)	
Collaterals		<.001
Yes	19.2 (16.1-22.5)	
No	7.2 (4.7-10.6)	
Reoperative CABG		.021
Yes	30.3 (15.6-48.7)	
No	14.3 (12.2-16.8)	

CI, Confidence interval; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation; *CABG*, coronary artery bypass graft; *ICR*, incomplete revascularization.

ratio [HR], 2.0; 95% CI, 1.3-3.3). Unadjusted overall survival curves are presented in Figure 1, *A*. Examination of the linearity continuous variables revealed that different cut-points were more appropriate when predicting midterm mortality. Thus age had 2 categories (<80 and ≥80 years) and EuroSCORE had 3 categories (0-2.99, 3-5.99, and ≥6). (see Table 4.) There was evidence against the proportional hazards assumption for urgency; therefore, this variable was not included in the model, but used for stratification. Only 2 variables were confounding factors: age >80 years and EuroSCORE. Interactions between these 2 variables and ICR were examined and the interaction with EuroSCORE was not significant (P = .240), whereas the interaction with age was significant (P = .072). The unadjusted HR was 4.7 (95% CI, 1.5-14.4) for patients older than age 80 years and 1.5 (95% CI, 0.9-2.7) for patients younger than age 80 years in a model that contained only the interaction between age and ICR. Therefore the age × ICR interaction along with the predictors significant at P < .2 were entered into the multivariable proportional hazards model, stratified by urgency due to the nonproportional hazards for this variable. Chronic obstructive pulmonary disease, renal disease, cerebrovascular disease, peripheral vascular disease, and diabetes were all combined into a single variable of a comorbid condition. The final model (Table 5) included the age × ICR interaction (P = .017), comorbid conditions (P = .017), the 3 category EuroSCORE (P < .001), and sex (P = .25) because this was a confounding factor. The adjusted HR associated with ICR for patients aged ≥80 years was 5.7 (95% CI, 1.8-17.7) indicating a higher risk of mortality due to ICR in older patients. The estimated adjusted HR for patients younger than age 80 years was 1.2 (95% CI, 0.7-2.1). The unadjusted 5-year survival rate for patients younger than age 80 years was 90.9% for CR patients and 86.0% and for ICR patients. For patients aged ≥80 years the 5-year survival rate was 77.7% for CR patients and 56.4% for ICR patients. (Figure 1, *B*). Three factors significantly predicted decreased long-term survival in the octogenarians and older patients: ICR (P = .006), higher logistic EuroSCORE category (P = .006), and male sex (P = .029). When included in the same regression model all 3 variables were simultaneously significant (P = .029 for EuroSCORE, P = .032 for ICR, and P = .021 for men.) This indicates that even controlling for fragility using EuroSCORE category, the HR for ICR was 2.9 (95% CI, 1.1-7.7) and HR for male sex was 4.4 (95% CI, 1.2-15.4).

Examination of these unadjusted survivor functions indicates that midterm survival in ICR patients younger than age 80 years was not statistically significantly different from CR patients, either before (P = .141) or after adjusting for other predictive factors (P = .544).

Other Outcomes

There was no difference between ICR and CR patients for recurrence of angina (6.4%; P = .99), myocardial infarction (1.8%; P = 1.0), and postoperative angiography either for any reason (15.5%; P = .787) or symptom-directed (13.3%; P = 1.00). Repeat revascularization procedures with either PCI or CABG were also similar (0.7%; P = .267).

Reasons for ICR

Reasons for ICR in 140 patients included small vessel <1 mm in 64% (n = 92), diffuse disease in 17% (n = 24), inaccessible location in 14% (n = 20), infarct territory in 22% (n = 31), technical reasons in 9% (n = 13), and multiple reasons in 25% (n = 36). The RCA was the most common artery not bypassed (52%), with 48% for the CIRC. A diseased LAD territory was bypassed in all patients at this or at a previous surgery. The most common reasons for not bypassing the CIRC was small vessel and location, whereas reasons for not grafting the RCA were small vessel and diffuse disease. For 138 of 140 patients (99%) 1 territory of 3 was not bypassed; in 2 patients

TABLE 3. Predictors of operative mortality

	Single predictor variable analysis			Multivariable model	
Variable	**% Operative mortality (95% CI)**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value***
Constant				0.002 (0.00-0.01)	<.001
Incomplete revascularization			.008	1.73 (0.80-3.77)	.166
Yes	3.2 (2.0-4.5)	2.8 (1.4-5.7)			
No	8.6 (3.9-13.2)	1			
EuroSCORE†			<.001	1	<.001
<3	0.4 (0.05-1.5)	1			
3-5.99	3.3 (0.9-5.6)	7.9 (1.6-38.6)		5.4 (1.1-27.1)	
6-9.99	6.8 (2.3-11.4)	17.3 (3.6-82.7)		10.2 (2.0-50.6)	
10-19.99	7.8 (3.1-15.4)	19.9 (4.1-97.5)		8.9 (1.7-47.8)	
≥20	31.1 (17.6-44.6)	106 (23.2-490)		42.2 (8.0-223.5)	
Urgency†			<.001	1	.03
Elective	0.7 (0.0-1.5)	1			
Urgent in	4.0 (2.2-5.9)	5.8 (1.7-19.8)		3.2 (0.88-11.4)	
Emergency	17.0 (9.8-24.1)	28.0 (8.1-97.2)		5.6 (1.4-21.9)	
Bilateral internal mammary artery grafts†			.017		
Yes	6.7 (3.6-9.7)	0.44 (0.23-0.85)			
No	3.1 (1.8-4.4)	1			
Age†, y			.061		
<65	2.5 (1.1-4.0)	1			
65-80	5.0 (2.9-7.0)	2.0 (1.0-4.2)			
>80	7.7 (1.2-14.2)	3.2 (1.1-9.5)			
Hypertension			.03		
Yes	4.9 (3.3-6.6)	2.4 (1.0-5.9)			
No	2.1 (0.1-3.7)				
Ejection fraction†			.021		
<30	10.6 (3.2-18.0)	1			
<30-50	4.6 (1.8-7.3)	0.4 (0.2-1.1)			
>50	3.2 (1.9-4.5)	0.3 (0.1-0.7)			
Cerebrovascular disease			.013		
Yes	8.2 (2.7-13.7)	2.4 (1.1-5.5)			
No	3.6 (2.3-4.8)				
Peripheral vascular disease			.145		
Yes	6.7 (1.9-11.5)	1.9 (0.8-4.4)			
No	3.7 (2.4-5.0)				
Renal disease					
Yes	14.6 (2.8-26.6)	4.6 (1.7-12.6)	.003		
No	3.6 (2.4-4.9)				
Reoperative CABG†					
Yes	15.2 (2.9-27.4)	4.7 (1.7-13.0)	.003		
No	3.6 (2.4-4.9)				

CI, Confidence interval; *OR*, odds ratio; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation; *CABG*, coronary artery bypass graft. *Likelihood ratio statistic. †Significant predictors of incomplete revascularization.

both RCA and CIRC territory were not grafted because coronary arteries were too small in 1 patient and both diffusely diseased and small in the second.

DISCUSSION

In this large contemporary series of 1000 CABG patients with 98% arterial grafts, we have shown that after adjusting for factors affecting operative mortality and midterm survival, there is no evidence that ICR decreases survival perioperatively in all patients and at midterm in patients younger than age 80 years. Ours is the first study to evaluate outcomes from ICR in a cohort of patients with extensive (98%) arterial grafting. Midterm follow-up analysis yielded a dichotomous result: for patients younger than age 80 years ICR did not affect survival before or after adjusting for 11 significant predictors, even though 1 of these (EuroSCORE) was a confounding variable. There was, however, a significant effect of lCR on reduced midterm survival in patients aged ≥80 years (7% of the overall cohort). Other studies have shown age conundrums: Girerd and colleagues[4] found that patients aged <60 years had increased mortality with ICR but not in patients aged >60 years. Three articles

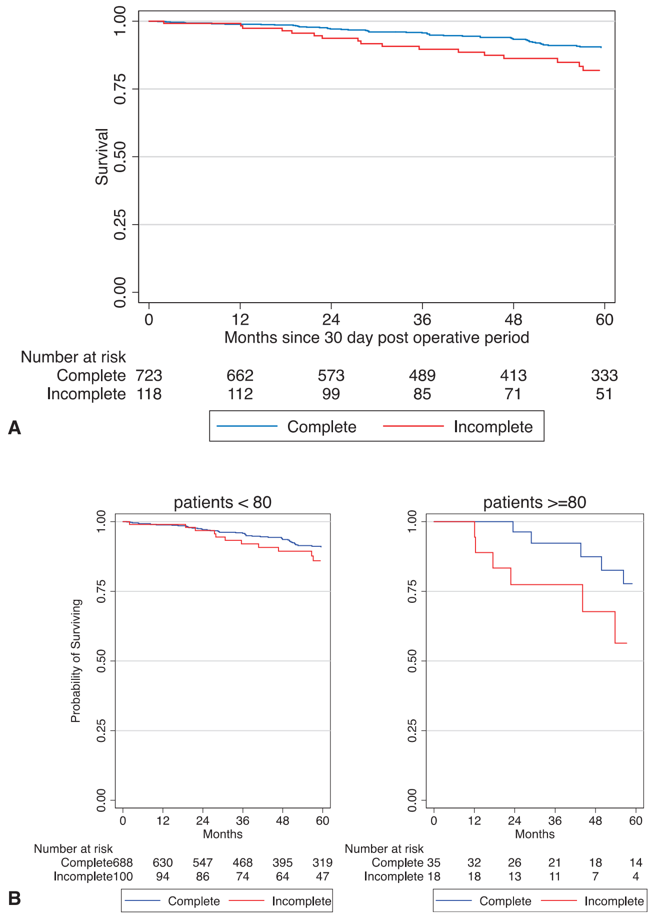

FIGURE 1. A, Unadjusted overall survival rates by complete and incomplete revasculariztion. B, Unadjusted Kaplan-Meier survival curves stratified by age <80 years (n = 788) and age ≥80 years (n = 53).

studying octogenarians have opposing views: Mohammadi and colleagues[5] found no difference in survival in octogenarians with ICR whereas Aziz and colleagues[6] found 18% decline and Kozower and colleagues[7] found 10% reduced 8-year survival in octogenarians with ICR. For the 53 patients aged ≥80 years in this series who survived the operation, ICR carries an almost 6-fold risk of dying but this may be sample-specific. This finding of reduced survival in octogenarians with ICR is not explainable within the data/scope of our study but deserves careful consideration regarding its validity and/or meaningfulness. Given that operative survival was not affected by ICR in this age group, surgeons may wisely opt for early survival rather than subject frail elderly patients to a CR operation of greater risk; for example a difficult-to-graft lateral wall target performed off-pump. Although well-selected elderly patients undergoing CABG have good outcomes, an objective assessment of frailty has been found to be associated with increased risk for morbidity and mortality after cardiac surgery.[8,9]

TABLE 4. Individual predictors of midterm mortality, single predictor variable analysis

Variable	Hazard ratio	*P* value	95% CI
Incomplete revascularization	2.0	.003	1.3-3.3
Off-pump	1.4	.151	0.9-2.4
Male	0.5	.004	0.4-0.8
Chronic obstructive pulmonary disease	2.0	.006	1.2-3.2
Renal disease	3.8	<.001	1.9-7.6
Peripheral vascular disease	2.5	<.001	1.6-4.2
Re-do coronary artery bypass graft	2.0	.090	0.9-4.2
Cardiovascular disease	2.2	.002	1.3-3.7
Diabetes mellitus	1.5	.049	1.0-2.3
Bilateral internal mammary artery grafts	0.8	.176	0.5-1.1
Age >80 y*	2.8	.001	1.6-5.0
EuroSCORE*			
3-5.99	1.9	<.001	1.1-3.3
≥6	4.0		2.5-6.4

CI, Confidence interval; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation. *Variable was also a confounding factor. Estimates for urgency were not included because there was evidence against the proportional hazards assumption for urgency.

Previous studies suggesting superiority of CR over ICR have included patients in which the majority of grafts were venous. Poorer outcomes with ICR in such populations may not be due to the ICR in and of itself but rather due to relatively early occlusion of venous conduits. Early postoperative vein graft occlusion has not changed in 4 decades: at <3 weeks postoperatively in the study by FitzGibbon and colleagues[10] of 5065 venous grafts performed from 1969 to 1994, vein graft occlusion was 12%, similar to the more contemporary study from Kim and colleagues[11] wherein 7-day vein graft occlusion was 11.8%. One-year graft occlusion rates have also stayed the same since the study by FitzGibbons and colleagues[10]: 24% compared with the 1-year vein graft occlusion in the Prevent IV trial[12] of 25.7%. This rapid attrition of vein grafts would convert a patient with single vessel disease (1 territory not bypassed) at the time of CABG to double vessel disease in 12% of patients at early postoperation and in 24% to 26% of patients at 1 year and could well explain the poorer survival of patients with ICR. The use of more arterial conduit known to last longer could therefore mitigate the effect of ICR.

TABLE 5. Multivariable proportional hazards regression model predicting midterm survival in patients who survived the postoperative period, stratified by urgency

Variable	Hazard ratio	*P* value	95% CI
Incomplete revascularization			
Age >80 y	5.7	.003	1.8-17.7
Age <80 y	1.2	.544	0.7-2.1
Comorbid condition	1.74	.017	1.10-2.73
EuroSCORE		<.001	
3-5.99	1.71		0.96-3.04
≥6	3.25		1.84-5.73
Male	0.71	.125	0.46-1.10

CI, Confidence interval; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation.

Other Studies of CR and Arterial Grafting

The literature on ICR is difficult to interpret due to lack of a universal definition; varying lengths of follow-up; differing amounts of arterial and venous grafting; studies including just PCI, just patients undergoing CABG, or a combination of both; and studies including only specific subgroups such as patients with diabetes and octogenarians. Hence there is no consistent negative correlation between ICR and survival; studies showing reduced survival with ICR include the 10-year follow-up of the Medicine, Angioplasty, or Surgery Study for Patients Undergoing PCI (MASS II),[13] the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial in persons with diabetes,[14] the 4-year SYNTAX trial results (including both randomized and registry patients),[15] patients younger than age 60 years by Girerd and colleagues,[4] studies in octogenarians,[6,7] a study by Synnergren and colleagues[16] in patients with 2 of 3 territories missed, and a 5-year follow-up study by Kleisli and colleagues.[17] Studies showing the opposing view—no difference in survival between ICR and CR groups—include as many studies and some even in similar patient subgroups: the 10-year follow-up of the MASS II trial for patients undergoing CABG[11]; a study of octogenarians by Mohammadi and colleagues[5]; a study with left internal thoracic artery to LAD in only 75% to 77% of patients by Kim and colleagues[11]; McNeer and colleagues' 1974 study[1] of patients with all vein grafts; a study of patients older than age 60 years by Girerd and colleagues[4]; a study by Sarno and colleagues,[18] including patients undergoing PCI with less complex disease; a study by Rastan and colleagues[19] with no difference at 1 and 5 years follow-up; the SYNTAX trial (randomized patients) at 1 year[20]; a study by Synnergren and colleagues[16] for no difference if 1 of 3 territories missed; and the Bypass Angioplasty Revascularization Investigation trial, which also noticed that multiple grafting resulted in worse survival.[21]

Other investigators have assessed the effects of ICR in patients with multiple arterial grafts, and similar to our own findings, found no difference in survival between CR and ICR: MASS II with 1 IMA in 92%, 1 IMA with radial artery grafts in 36% and epigastric artery grafts in 10%.[13] Rastan and colleagues' study[19] with 21.9% total arterial grafting in the CR group and 32.2% in the ICR group found that arterial revascularization was protective for decreased mortality, and Kleisli and colleagues' study[17] showed that use of the right IMA (22.6%) and radial artery (58.7%) correlated with improved survival at a mean of 5 years (HR, 0.51 for right IMA use and 0.49 for radial artery use). Hayward and colleagues[22] showed that use of arterial grafts for lesions (largely severe) in the right circulation were protective against progression of native vessel disease whereas bypassed moderate lesions with saphenous vein caused greater native lesion progression to severe 40% versus 14% of the time if not bypassed. Arterial grafting especially with IMAs prevents native disease progression.[23] Because a randomized controlled trial comparing patients with CR versus ICR is not possible, evidence for rationale of the CR dogma is dependent on retrospective observational studies. Our study of almost pure arterial grafting eliminates 1 important variable: The venous graft.

Early theories of what were appropriate revascularizations and hence the definition of ICR must by necessity, change. Before the advent of angioplasty,[24] coronary arteries with 50% stenosis were routinely bypassed to avoid reoperation for disease progression. Venous conduits offer almost no resistance to flow whereas competitive flow is a significant factor when using arterial conduits.[25] Also, use of fractional-flow reserve (FFR) has demonstrated that many lesions[26] are not hemodynamically significant. In the ongoing Evaluation of Xience Prime Everolimus Eluting Stent System (EECSS) or Xience V EECSS Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial[27] randomizing low SYNTAX score patients with left main stenosis to PCI or CABG, CR for the PCI arm favors addressing 70% narrowed coronary arteries, whereas for the CABG arm it is 50% stenosis. Opinion as to the level of significant stenosis appears to be changing, but should change similarly for both PCI and CABG. Gössl and colleagues[28] proposed a new definition for both PCI and CABG: CR complete anatomic (>50% stenosis; >1.5 mm coronary arteries), ICR anatomic but functionally adequate (FFR >70%), and ICR anatomical and functionally inadequate (FFR ≤70). This third category is probably significant for survival; the authors state: ''…CR based on anatomic criteria alone may soon become obsolete, emphasizing physiology driven coronary interventions.''[28] There is even evidence to show that ''overgrafting'' may be detrimental.[21] However unless FFR testing becomes routine for pre-revascularization assessment at coronary angiography, perhaps what is simplest is best: the definition of CR used in our study is the same as the very first used by McNeer and colleagues[1] in 1974: a revascularization by ''territory''; that is, 1 bypass for each territory that has a 70% stenosis in a major branch.

Limitations

Limitations of our study include the relatively small number of the ICR group, the small number of octogenarians (and older) and the number of factors found to significantly influence survival. This real-world, single-center study evaluating total arterial grafting performed by a single operator may be advantageous because it provides consistent techniques, skills, and decision making but at the same time may not be applicable to other centers. Ongoing use of evidence-based medications for secondary prevention, which is known to affect outcome, was not evaluated in this study. Finally, we evaluated outcomes out to 4.5 years but longer follow-up may be required to better evaluate the consequences of ICR, especially because the advantage of arterial grafts may last decades.

CONCLUSIONS

Contrary to current beliefs regarding completeness of revascularization, we have demonstrated that ICR in this unique series of all-comer CABG with 98% arterial grafts is not associated with decreased survival perioperatively and at midterm in patients younger than age 80 years. However many factors affect survival and may act synergistically or independently. Use of arterial grafts minimizes the adverse effects of not grafting the third region.

The authors thank the Alberta Provincial Program for Outcome Assessment in Coronary Heart disease study for providing support and thank the cardiac catheterization personnel for performing data entry.

References

1. McNeer JF, Conley MJ, Starmer CF, Behar VS, Kong Y, Peter RH, et al. Complete and incomplete revascularization at aortocoronary bypass surgery: experience with 392 consecutive patients. *Am Heart J*. 1974;88:176-82.
2. Ghali WA, Kundtson ML. Overview of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease on behalf of the APPROACH investigators. *Can J Cardiol*. 2000;16:1225-30.
3. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika*. 1982;69:239-41.
4. Girerd N, Magne J, Rabilloud M, Charbonneau E, Mohamadi S, Pibarot P, et al. The impact of complete revascularization on long-term survival is strongly dependent on age. *Ann Thorac Surg*. 2012;94:1166-72.
5. Mohammadi S, Kalavrouziotis D, Dagenais F, Voisine P, Charbonneau E. Completeness of revascularization and survival among octogenarians with triple-vessel disease. *Ann Thorac Surg*. 2012;93:1432-7.
6. Aziz A, Lee AM, Pasque MK, Lawton JS, Moazami N, Damiano RJ Jr. Evaluation of revascularization subtypes in octogenarians undergoing coronary artery bypass grafting. *Circulation*. 2009;120(11 Suppl):S65-9.
7. Kozower BD, Moon MR, Barner HB, Moazami N, Lawton JS, Pasque MK, et al. Impact of complete revascularization on long-term survival after coronary artery bypass grafting in octogenarians. *Ann Thorac Surg*. 2005;80:112-6; discussion 116-7.
8. Graham MM, Ghali WA, Faris PD, Galbraith PD, Norris CM, Knudtson ML. Survival after coronary revascularization in the elderly. *Circulation*. 2002;105: 2378-84.
9. Lee DH, Buth KJ, Martin BJ, Yip AM, Hirsch GM. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. *Circulation*. 2010;121:973-8.
10. FitzGibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. *J Am Coll Cardiol*. 1996;28:616-26.
11. Kim KB, Kim JS, Kang HJ, Koo BK, Kim HS, Oh BH, et al. Ten-year experience with off-pump coronary artery bypass grafting: lessons learned from early postoperative angiography. *J Thorac Cardiovasc Surg*. 2010; 139:256-62.
12. Magee MJ, Alexander JH, Hafley G, Ferguson TB Jr, Gibson CM, Harrington RA, et al. Coronary artery bypass graft failure after on-pump and off-pump coronary artery bypass: findings from PREVENT IV. *Ann Thorac Surg*. 2008;85:494-9; discussion 499-500.

13. Vieira RD, Hueb W, Gersh BJ, Lima EG, Pereira AC, Rezende PC, et al. Effect of complete revascularization on 10-year survival of patients with stable multivessel coronary artery disease: MASS II trial. *Circulation*. 2012;126(11 Suppl 1):S158-63.
14. Schwartz L, Bertolet M, Feit F, Fuentes F, Sako EY, Toosi MS, et al. Impact of completeness of revascularization on long-term cardiovascular outcomes in patients with type 2 diabetes mellitus: results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D). *Circ Cardiovasc Interv*. 2012;5:166-73.
15. Farooq V, Serruys PW, Garcia-Garcia HM, Zhang Y, Bourantas CV, Holmes DR, et al. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. *J Am Coll Cardiol*. 2013;61:282-94.
16. Synnergren MJ, Ekroth R, Odén A, Rexius H, Wiklund L. Incomplete revascularization reduces survival benefit of coronary artery bypass grafting: role of off-pump surgery. *J Thorac Cardiovasc Surg*. 2008;136:29-36.
17. Kleisli T, Cheng W, Jacobs MJ, Mirocha J, Derobertis MA, Kass RM, et al. In the current era, complete revascularization improves survival after coronary artery bypass surgery. *J Thorac Cardiovasc Surg*. 2005;129:1283-91.
18. Sarno G, Garg S, Onuma Y, Gutiérrez-Chico JL, van den Brand MJ, Rensing BJ, et al. Impact of completeness of revascularization on the five-year outcome in percutaneous coronary intervention and coronary artery bypass graft patients (from the ARTS-II study). *Am J Cardiol*. 2010;106:1369-75.
19. Rastan AJ, Walther T, Falk V, Kempfert J, Merk D, Lehmann S, et al. Does reasonable incomplete surgical revascularization affect early or long-term survival in patients with multivessel coronary artery disease receiving left internal mammary artery bypass to left anterior descending artery? *Circulation*. 2009; 120(11 Suppl):S70-7.
20. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961-72.
21. Vander Salm TJ, Kip KE, Jones RH, Schaff HV, Shemin RJ, Aldea GS, et al. What constitutes optimal surgical revascularization? Answers from the Bypass Angioplasty Revascularization Investigation (BARI). *J Am Coll Cardiol*. 2002; 39:565-72.
22. Hayward PA, Zhu YY, Nguyen TT, Hare DL, Buxton BF. Should all moderate coronary lesions be grafted during primary coronary bypass surgery? An analysis of progression of native vessel disease during a randomized trial of conduits. *J Thorac Cardiovasc Surg*. 2013;145:140-8; discussion 148-9.
23. Dimitrova KR, Hoffman DM, Geller CM, Dincheva G, Ko W, Tranbaugh RF. Arterial grafts protect the native coronary vessels from atherosclerotic disease progression. *Ann Thorac Surg*. 2012;94:475-81.
24. Gruentzig A. Results from coronary angioplasty and implications for the future. *Am Heart J*. 1982;103(4 Pt 2):779-83.
25. Glineur D, Hanet C. Competitive flow in coronary bypass surgery: is it a problem? *Curr Opin Cardiol*. 2012;27:620-8.
26. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol*. 2010;55:2816-21.
27. Stone GW, Serruys PW, Sabik J, Kappetein AP. Evaluation of Xience Prime Everolimus Eluting Stent System (EECSS) or Xience V EECSS Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization. ClinicalTrials.gov identifier: NCT01205776.
28. Gössl M, Faxon DP, Bell MR, Holmes DR, Gersh BJ. Complete versus incomplete revascularization with coronary artery bypass graft or percutaneous intervention in stable coronary artery disease. *Circ Cardiovasc Interv*. 2012;5: 597-604.

Discussion

Dr Philip A. Hayward *(Melbourne, Australia)*. I'd like to thank the American Association for Thoracic Surgery Committee for the invitation to discuss this work and also thank Dr Kieser for supplying me with a draft of the manuscript in a timely fashion.

Dr Kieser, you are to be congratulated on an important study. You've done a sophisticated analysis of your own coronary practice, and your commitment to arterial grafting and to completeness of revascularization is impressive.

You state as a limitation that this is a single-surgeon experience, but in this context this may be 1 of the merits of the study because it allows us to really tease out the effect of incomplete revascularization. Other series published can be pools of patients done by different surgeons, with varying thresholds for grafting small or poor targets, and it is difficult to tease out the effect of incomplete revascularization when there have been 2 different revascularization strategies and thresholds. You have a uniformity of your threshold for revascularization—the same eyes, the same hands, the same threshold—I think that's why your study is unique.

Fractional-flow reserve (FFR) is redefining what we think needs revascularization now. It's all about physiology, not anatomy, we know that from percutaneous intervention and the Fractional Flow Reserve versus Angiography for Multivessel Evaluation study. FFR depends on the volume of distal antegrade flow, not just the stenosis. Vessels that are small or running into scar or that are well collateralized do not have significant FFR. About 87% of the vessels you left fall into this category. I suggest that really your ''incomplete revascularization'' group was in fact functionally completely revascularized for the most part, and the vessels that you left alone really were functionally insignificant. And that's probably why you've not shown any effect on survival from your ''incomplete revascularization'' and that's reflected in the lack of a difference in angina, myocardial infarction, or percutaneous coronary intervention thereafter.

You say that your findings differ from other authors because you used arterial grafts rather than vein grafts and that you therefore avoided early vein graft failure. But, of course, you also avoid the progression of native vessel disease that's seen primarily after vein grafts, and it is this progression that can damage the collateralization that had been providing protection from the effects of incomplete revascularization. An all-arterial graft population has been shown to produce less native vessel disease progression, so perhaps the collaterals are better preserved and hence your different findings.

I would like to pose 2 questions: The surprise finding clearly is the difference in the long-term outcome in the octogenarians who had incomplete revascularization. Do you really think this is a different effect of incomplete coronary revascularization in older people, or is there another factor here—a frailty factor—where really this was a different pool of frail elderly people where you lowered your threshold for leaving targets alone, such that really their poorer survival comes from their frailty rather than the fact that you decided to leave 1 target?

The second question follows from that. You told us that incomplete revascularization didn't affect in-hospital mortality overall, but was that also true for the octogenarians whose long-term outcome you say is poorer with incomplete revascularization? Perhaps their long-term outcome is just a reflection of a turbulent perioperative period. I think that shorter-term outcome data might influence most surgeons' practice more than the long-term survival, because many of us faced with frail octogenarians are really focused on getting them out of the hospital intact and we tend to lower our horizons. If I'm faced with that frail octogenarian patient and I want to get him or her safely through, does complete or incomplete revascularization matter in the short term, irrespective of if it matters in the long term?

Dr Teresa Kieser *(Calgary, Alberta, Canada)*. Your point regarding FFR is very well taken. Rastan and Fred Mohr had an article in *Circulation* in 2009 that spoke to this. They didn't say the reason was FFR, but they spoke about vessels that were within scar, for example. So it didn't matter if you didn't completely revascularize them. I think your reason is correct, the FFR would be insignificant. However, being the bilateral internal mammary artery graft fanatic that I am, I would still like to invoke the untimely demise of the vein graft as a mechanism.

With respect to poorer survival coming from surgical frailty or not wanting to put an older patient through the stress of surgery, I think the reasons are 2-fold: Operating on frail people does cause a surgeon to possibly scale down the operative procedure. But experience has taught me that when you operate on an 80-year old, everything has to go correctly. They cannot tolerate the slightest complication the way a younger patient would. The wheels easily fall off the wagon.

Incomplete revascularization in an octogenarian patient perioperatively, you are right, we probably should have included this. There were only 70 patients older than age 80 years, 53 were incompletely revascularized, so that's 76%.

The operative mortality was not different. There were 2 out of 23 incompletely revascularized patients who died, and 3 out of 47 of the completely revascularized patients died—a *P* value that was insignificant. We looked at the cause of death of these 5 patients: 1 died from fulminant sepsis at another hospital, very quickly; another had a massive stroke; another died of necrotic bowel because he had embolized from a calcified aorta (we had had to perform the procedure on him off-pump and he was a redo). The deaths of 2 patients of the 5 were probably due to graftability issues or graft failure. Incomplete revascularization did not make a difference in these patients. So the answer is if you can get a patient—an 80-year-old—out of hospital alive and intact with incomplete revascularization this is better.

Dr Hayward. That's a great relief. Thank you.

Chapter 12

Arterial grafting and complete revascularization: challenge or compromise?

Kieser TM, Head SJ, Kappetein AP

Curr Opin Cardiol 2013;28:1-8

Arterial grafting and complete revascularization: challenge or compromise?

Teresa M. Kieser[a], Stuart J. Head[b], and A. Pieter Kappetein[b]

Purpose of review
Arterial grafting is superior to venous grafting in coronary artery bypass graft surgery with respect to graft patency and long-term patient outcome, but it may be difficult to achieve complete arterial revascularization.

Recent findings
Use of arterial grafts, especially bilateral internal mammary artery grafts, is not common, whereas there are clear indications that it may increase survival. Definitions of complete revascularization are varied and confusing, making study comparisons difficult. Technical challenges in complete revascularization with arterial grafts can be minimized by surgical techniques. Competitive flow in moderately stenosed coronary arteries grafted with arterial conduits may result in reduced patency. While internal mammary arteries may be used in arteries with at least 60% stenosis, radial artery and gastroepiploic grafts are best placed onto coronaries with severe stenosis. Moderate lesions in the left coronary circulation should be bypassed, but right coronary artery lesions can be left untouched as there is minimal progression over time. Complete revascularization may not be necessary or possible in every patient because of technical challenges.

Conclusion
Complete revascularization with arterial grafts presents both technical and physiological challenges. However, with techniques to maximize length of arterial conduits, knowledge of competitive flow and which moderate lesions should be addressed, complete revascularization with arterial grafts can be accomplished in the majority of patients, notwithstanding it may not be possible or even indicated for every patient.

Keywords
arterial grafts, CABG, complete revascularization

INTRODUCTION

As stated by a 29-year-old woman after total arterial coronary artery bypass graft (CABG) surgery (‘Doctors always question the scar on my wrist and are astounded to hear that you used an artery in my heart; it makes only sense’), arterial grafts for CABG are intuitively the correct conduit. Just the pressure difference alone between veins (25–30 mmHg) and arteries (mean pressure 70 mmHg) should be evidence enough of arterial superiority. Why then do only 4% of patients in North America [1] and 10% in Europe [2] receive bilateral internal mammary artery (BIMA) grafting? The reasons are complex and many: non-belief of the evidence to date, technical and time demands of use of arterial grafts, fear of deep sternal wound infection [3], lack of benefit beyond a certain patient age, perceived mismatch between arterial graft flow and myocardial demand, and inertia to change. In addition, surgeons find it difficult to completely revascularize patients using only arterial grafts because of technical (limited length of arterial graft available) and physiologic factors (competitive flow when moderately stenosed coronary arteries are grafted).

EVIDENCE FOR IMPROVED SURVIVAL AND GRAFT PATENCY WITH ARTERIAL GRAFTING

As a result of advancements in operative techniques and myocardial protection, operative mortality of

[a]Department of Cardiac Sciences, LIBIN Cardiovascular Institute of Alberta, University of Calgary, Calgary, Alberta, Canada and [b]Department of Cardiothoracic Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands

Correspondence to Teresa M. Kieser, Foothills Medical Centre, Room C814, 1403 29th St NW Calgary, Alberta T2N 2T9, Canada. Tel: +1 403 944 8449; e-mail: t.kieserprieur@ucalgary.ca

Curr Opin Cardiol 2013, 28:000–000
DOI:10.1097/HCO.0000000000000001

KEY POINTS

- Arterial bypasses, especially BIMA grafting, portend long-lasting graft patency and improved survival compared with CABG with predominantly venous grafts. Multiple definitions of complete revascularization abound and need careful scrutiny to compare studies.
- Surgical techniques exist to maximize arterial conduit length to facilitate complete revascularization with the finite amount of arterial conduit.
- Arterial conduits to moderately stenosed coronary arteries may suffer from the effects of competitive flow: guides exist for minimizing this problem.
- The moderately stenosed coronary artery behaves differently depending whether it is in the left or right coronary circulation: right-sided lesions do not progress and hence may be left not bypassed, whereas left-sided lesions do progress over time and should be addressed.
- Incomplete revascularization in some patients may be ‘reasonable’ or ‘appropriate’.

CABG has reduced significantly (1% in planned cases) [4] and is no longer in question, but the longevity of the procedure is. As stated by Barner [5], ‘Only continued patency of a graft or stent provides benefit.’ Long-term venous graft patency is disappointing and has not changed for 44 years: Fitzgibbon *et al.* [6] reported in 1996 a series of 5065 grafts from 1969 to 1994 (25 years’ span) with venous graft patency of 50% for at least 15 years, and Tatoulis *et al.* [7] reported in 2011 3238 venous grafts from 1986 to 2008 (22 years’ span) with a patency of 50.7% at 15 years.

Use of the internal mammary artery (IMA) began 66 years ago as a myocardial implant by Vineberg and Jewett [8] in 1947. Evidence for superior long-term survival for arterial grafting was reported by multiple authors in the past years. Kelly *et al.*, in a study of 8264 patients (13% BIMA), found that risk-adjusted survival at 10 years was 71% [hazard ratio 0.8; 95% confidence interval (CI) 0.67–1.00] for BIMA grafts, 66% for single IMA grafts (reference group) and 58% (hazard ratio 1.42; 95% CI 1.2–1.7) for no IMA graft. Only the right IMA (no other arterial grafts) conferred benefit [9▪]. In another study with 8622 Mayo clinic patients (overall 12% BIMA), use of multiple arterial grafts compared with left IMA/vein was a strong predictor of survival at 10 (83 vs. 70%) and 15 (80 vs. 60%) years in matched groups ($P = 0.0025$) [10]. Kurlansky *et al.* [11] have reported the longest follow-up to date in a propensity-matched analysis of 4584 patients who underwent CABG through 1972–1994. Survival at 25 years of follow-up was significantly improved in BIMA graft patients as opposed to those receiving only one IMA (29 vs. 16%, respectively; $P < 0.001$) [11].

Bilateral internal mammary artery grafting in diabetic patients has gained little traction because the risk of deep sternal wound complications is particularly high in this subgroup of patients. However, use of two IMA grafts in diabetic patients has been recently shown to also increase late survival, similar to non-diabetic individuals. Puskas *et al.* [12▪] reviewed 3527 patients operated between 2002 and 2010, and showed that there were no increased propensity score-adjusted rates of 30-day mortality and sternal wound complications between the use of BIMA and single IMA grafts in diabetic patients; however, 8-year survival was 87.4% vs. only 60.6% in BIMA and single IMA patients, respectively ($P < 0.001$). Furthermore, Dorman *et al.* [13▪], in a cohort of 1107 consecutive patients with diabetes, showed that median survival of 646 single IMA patients was 9.8 years compared with 13.1 years of propensity-matched patients with BIMA grafts ($P = 0.001$).

Also for diabetic patients with complex disease in the SYNergy between Percutaneous Coronary intervention with TAXus and Cardiac Surgery (SYNTAX) trial, CABG is preferred over percutaneous coronary intervention (PCI) because of fewer major adverse cardiac or cerebrovascular events and less repeat revascularization, in keeping with findings from the Freedom trial [14▪,15].

Radial artery grafts, easier to harvest and use than the right IMA (RIMA), have some attrition beyond the first postoperative year, but remain stable thereafter up to 20 years: at 1.0, 5.4, 8.3 and 13.1 years, respectively, radial artery graft patency is 86.2, 81.9, 81.4 and 81.6% [16]. Because of the susceptibility of radial grafts to the effects of competitive flow (see below), radial grafts should only be constructed in areas of severe stenosis. As stated by Alfieri *et al.* [17] in their paper entitled ‘Drug-eluting stents or drug-eluting conduits for multivessel disease’, mammary arteries are the very best conduits. Tatoulis *et al.* [7], in a series of 5766 patients with BIMA, reported a 15-year patency of 91.1% for the left IMA, 79% for the RIMA and 50.7% for saphenous vein; 10-year patency for radial artery grafts was 78%. It is important to note that the patency of the right and left IMA is identical when used to the same vessels [7]. Yet, there are still those who remain to be convinced ... The Arterial Revascularisation Trial (ART) trial randomizing 3102 patients to either single IMA or BIMA will be the deciding vote [18].

DEFINITIONS OF COMPLETE REVASCULARIZATION

Incomplete revascularization (ICR) varies from 9 to 39% from study to study [19]. One of the difficulties interpreting the literature on this topic is the many and varied definitions of complete revascularization (Table 1) [20–27]. The 'traditional' definition defines complete revascularization as placement of at least one bypass in all diseased arterial systems and is basically a 'territorial' definition. 'Functional' complete revascularization most often refers to the bypassing of all diseased primary coronary segments, irrespective of size and territory. However, the term 'functional' has also been used to indicate bypasses into all territories except to those infarct areas without viable myocardium [22]. This has led to completely opposite definitions in some papers, in which traditional is called functional [28]. The amount of 'disease' (50% [20] or 70% stenosis [21]) varies among studies as well.

The definitions 'conditional' or 'unconditional' reflect revascularizing vessels of a certain size [>1.5 mm for CABG and PCI in the the Bypass Angioplasty Revascularization Investigation trial and >2.75 mm for PCI in the Arterial Revascularization Therapy Study (ARTS) trial] or location (main or branch) [22]. The definition 'numeric' refers to whether the number of distal anastomoses is either less than, equal to or greater than the number of diseased coronary segments [24]. One definition may be labelled the 'left anterior descending (LAD) artery definition': patients are grouped by whether they have at least two bypasses to both LAD and non-LAD system, at least two bypasses to the LAD, at least two bypasses to non-LAD system or whether no arterial system had multiple bypasses [24]. For the definition 'Index of Completeness of Revascularization (ICOR)', complete revascularization is a ratio of the number performed bypasses divided by the number of preoperatively planned bypasses and should be at least 1 [25]. This definition – because of the necessity of forethought – cannot be retrospectively applied to observational studies. However, to circumvent this, the definition has been extrapolated to be: the total number of distal anastomoses performed divided by the number of diseased coronary vessels defined on preoperative angiography [26,27]. Finally, complete revascularization can be measured by weighting stenoses in different vessels (extent of disease is a continuous variable) and may be 'anatomic' (irrespective of viable myocardium) or 'functional' (using the Jeopardy score to calculate the myocardium at risk after revascularization) [22]. Because of the different techniques by which PCI and CABG achieve complete revascularization, it is

Table 1. Definitions of incomplete vs. complete revascularization

Principal definitions	Description
Traditional	'Territorial' all territories diseased receive at least one graft/PCI (stenosis ≥50% [20] or ≥70%) [21]
Functional	'Territorial' without requirement for non-viable myocardium to be perfused [22]
Functional	Also called 'anatomic', all primary coronary segments irrespective of size or territory (SYNTAX trial is an example of this definition) [23]
Numeric	Number of stenotic vessels = number of distals [24]
'LAD definition'	≥2 distal sites to LAD + another artery
(Number of distal anastomoses to the LAD or other coronary arteries)	≥2 distal sites to LAD
	≥2 distal sites to an artery other than LAD
	<2 distal sites to all arteries [24]
ICOR (Index of Completeness of Revascularization)	Number of bypasses performed/number of bypasses preoperatively planned (should be >1) [25]
	Also, number of bypasses performed/number of stenotic arteries [26,27]
Weighted scoring (continuous variable)	Scoring of stenoses in different vessels at different locations with weighting, disease extent is a continuous variable, treatment is another variable; post treatment score determines completeness of revascularization [22]
Anatomic	Irrespective of viable myocardium [22]
Functional	Post-treatment score based on amount of viable myocardium still at risk by Jeopardy score [22]
Conditional	Conditions include specified vessel diameter or location (main or branch), can apply to any of above definitions [22]

LAD, left anterior descending; PCI, percutaneous coronary intervention.

questionable whether one definition for both PCI and CABG is possible or even advisable. Hopefully, one day, we will reach the utopian goal of no longer needing comparison of PCI and CABG because the role for each will be defined; for example, patients with diabetes [14▪,15], patients with a SYNTAX score above and below 33 and so on [29]. This multiplicity of definitions needs addressing, without which comparison from study to study is difficult and may not be meaningful. Forethought and decision beforehand of vessels potentially treatable by both the cardiologist and cardiac surgeon of the Heart Team (as used in the SYNTAX trial) [14▪], and then comparing with what was done, may be the best way to decide completeness of revascularization.

The residual SYNTAX score is a recently proposed definition to grade the degree of completeness of revascularization, adding more detail to previous dichotomous definitions. It is promising as a predictor of mortality during follow-up after PCI [30▪,31,32▪], but has not yet been validated in a CABG cohort. It will be interesting to see how it performs, particularly since the original core SYNTAX score lacks prognostic accuracy [33].

TECHNICAL CHALLENGES IN ARTERIAL GRAFTING FOR CORONARY ARTERY BYPASS GRAFT SURGERY

When using venous grafts, one can always ‘go and get more vein’, whereas with arterial grafts there is only so much conduit available. A large heart may require ‘creative arterial grafting’ in which various segments of arterial conduit are attached to each other to form a composite graft and reach their target. Technical tricks include the following:

(1) Skeletonization of the IMAs [34] adds considerable length and also facilitates sequential grafting because the correct ‘lie’ of the conduit can be judged accurately when the whole circumference of the IMA is seen (when performing the side-to-side anastomosis of a sequential graft).
(2) The length of an arterial graft is maximized if placed ‘as the crow flies’, that is, as direct a route as possible to the target. For example, for either the left or right IMA to reach the LAD, one can bring the conduit through a hole in the pericardium (or make a slit) instead of going ‘up and over’ the pericardial reflection. First pleural tissue is swept away to avoid entering the pleural cavity, then cautery is used to make a small hole in the pericardium, enough to admit two fingers. In order for the RIMA to reach the right coronary artery (RCA) system, pericardial holes are made in different locations depending on the location of the target: for a RIMA graft to the main RCA or postero-lateral branch of the RCA, the pericardial hole is made adjacent to the ‘superior vena cava’, and to graft the posterior descending artery (PDA), the hole is made near the ‘inferior vena cava’ (personal communication from Dr Pascal Berdat of Berne, Switzerland, July 2003). This route to the PDA is extrapericardial (may facilitate re-operation if needed); the IMA seems longer with this route, usually reaches the PDA and allows the ‘turnpoint’ of the IMA to be tethered by the pericardial edge, ensuring a correct lie of the distal segment of the RIMA. This allows no twisting at the heel.

In the authors’ experience of almost 10 years of 1047 patients with 98% arterial grafts, by using this technique, the RIMA–PDA was used as a free graft 13% of the time (26/194 RIMA to PDA). For this same group of 1047 patients, a total of 748 RIMA conduits included 309 (41%) RIMA conduits to RCA system and 439 (59%) to left coronary artery (LCA) system. For the RIMA to the circumflex system, the most direct route is usually through a hole in the pericardium just above the superior vena cava and through the transverse sinus to reach the marginal branches. A skeletonized IMA beating against an occluding clip or bulldog wrapped in a vasodilator solution usually lengthens enough to reach most branches of the circumflex system *in situ*. In the authors’ experience, for this same group of 1047 patients, the RIMA–LCA system was used as a free graft only 9% of the time (40/439 RIMA-to-LCA system). Although it may be twice as difficult to use the RIMA as the left internal mammary artery (LIMA), patients get close to twice as many grafts at 15 years (90 vs. 50% patent grafts). The radial artery is almost as easy to use as a saphenous vein and in fact may be ‘the new saphenous vein’. One must just be cognizant of the native coronary stenosis and use the radial when appropriate (in coronary arteries with 90% stenosis or higher, see below).

COMPETITIVE FLOW AND ARTERIAL GRAFTING

Venous grafts have virtually no resistance (the pressure at the distal anastomosis is nearly equal to the aortic pressure) and hence are less susceptible to the adverse effects of competitive flow [35▪▪]. Arterial grafts ‘auto-regulate in response to demand’ [36]; flow in an arterial graft will rise and fall as is needed. Arterial grafts have one Achilles heel – competitive flow if grafted into coronary arteries with moderate stenosis. The most severe form of ‘non-requirement’ results in a 'string sign' – on angiography, the graft looks like an atretic thread attached to the coronary artery. Conversely, arterial grafts increase their diameter over time [35••] and, in particular, left IMAs have been known to revascularize the whole of the LCA circulation in cases of isolated/predominant left main stenosis (Fig. 1). IMAs are the arterial conduit least affected by competitive flow; generally there is no critical level of stenosis below which graft flow is compromised [5]. Sabik *et al.* [37] studied 2121 IMAs from 1972 to 1999, and found that, although IMA patency diminished as the degree of coronary stenosis decreased, at no particular degree of stenosis was there a sharp decline in patency. Glineur *et al.* [38] showed that composite 'Y' IMA grafting to both the RCA and LCA systems had a negative prognostic influence on graft function, with loss of the graft to the RCA system. Possibly the different diastolic filling of the right (50%) and left coronary arteries (66%) could explain this: the RCA segment fails because two disparate pressure systems are grafted with one inflow.

For the radial artery graft, Barner [5] was the first to identify the relation of native coronary stenosis and radial artery patency; he found that patency was worse in moderate stenosis ($\leq$70%) compared with critical stenosis ($\geq$90%). Shah's review showed radial artery graft patency to be significantly reduced from 90 to 60% when grafts were placed to fewer than 70% stenotic arteries [39]. In the Radial Artery Patency Study, Desai *et al.* [40] found that radial grafts to coronary arteries with stenosis of at least 90% as compared with those with stenosis of 70–89% were associated with a lower rate of occlusion (5.9 vs. 11.8%). Composite grafts using the radial and IMA to the left circulation therefore need to take this into account as well. The right gastroepiploic artery, similar to the radial artery, is recommended to be used only on severely stenotic coronary arteries [41]. Some of these guidelines are difficult to implement for arterial grafting in that the conduit that 'reaches' may not be the most appropriate conduit for that particular coronary [e.g. a long graft (radial) is needed for two branches on the RCA system, but the stenoses are only 70%].

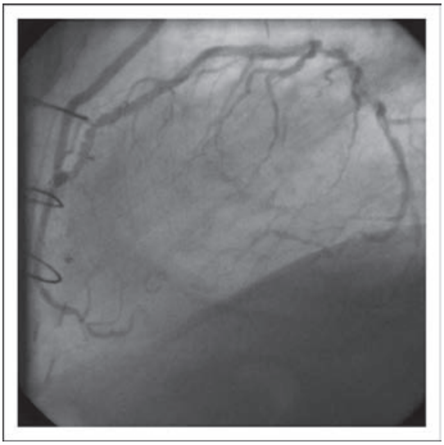

FIGURE 1. LIMA graft supplying all of LCA system in a patient with predominantly left main stenosis. LCA, left coronary artery; LIMA, left internal mammary artery.

WHAT ABOUT MODERATE STENOSIS?

If arterial grafts are better, but are subject to the vagaries of competitive flow, should moderate stenosis be left alone? Hayward *et al.* [42••] answered this when he studied 386 bypass grafts to moderately (40–69%) stenosed coronary arteries from the Radial Artery Patency and Clinical Outcomes trial. During a mean of 6.2 years follow-up in non-bypassed coronary arteries, moderate lesion progression differed according to location: only one in seven moderate lesions in the RCA showed significant progression (from moderate to severe) compared with one in two for left-sided coronary vessels. Conversely, however, when a moderately diseased coronary artery in the RCA system was bypassed, the native lesions progressed to severe 40% of the time vs. 14% of the time if not bypassed. Competitive flow from grafts seemed to cause greater disease progression in right-sided vessels than in left-sided vessels; as well, right-sided grafts tended to have inferior patency (73.3% at 7 years vs. 83.2% at 8 years; $P = 0.051$). He concluded that it is advisable to bypass moderate lesions of the left coronary system because of the likelihood of progression, but leave right-sided moderate lesions alone, given the low risk of progression if left undisturbed.

The use of fractional flow reserve has been shown to assist in deciding which lesions are best treated by angioplasty [43]; possibly the same may prove to be useful in deciding which moderate lesions should be grafted. With this new knowledge, that which constitutes 'completeness of revascularization' may need to be rethought.

IS COMPLETE REVASCULARIZATION ALWAYS NECESSARY?

Reduced survival after CABG is multifactorial and cannot be attributed solely to incompleteness

Table 2. Comparison of studies with differing amounts of arterial grafting

Grafts	Author, year	Number of patients	Length of follow-up (years)	Survival (ICR) (%)	Survival (CR) (%)	Comparison
Venous grafts only	McNeer *et al.*, 1974	392	2	75%	83	NS
IMA + vein	Mohammadi *et al.*, 2012	476	8	49	54	$P = 0.40$
	Kim *et al.*, 2011	514	5	90	87	$-P = 0.26$
	Sarno, 2010	567	5	91	93	$P = 0.48$
	Aziz, 2009	580	8	34	44	$P < 0.01$
	Lattouf *et al.*, 2008	12812	10	∼58[b]–	–∼68[b]	$P < 0.001$; HR = 0.85 (95% CI 0.77–0.93)
	Kozower, 2005	500	8	25	39	$P < 0.008$
Arterial (more than usual)	Farooq *et al.*, SYNTAX, 2013[a]	1541 (22.7% BIMA)	4	88	92	$P = 0.039$
	Vieira *et al.*, MASS II, 2012	198 (36% IMA+radial)	10	−88[b]	−91[b]	NS
	Girerd *et al.*, 2012	6539 (4.4–10.9% BIMA)	6	82	88	$P < 0.001$
	Head *et al.*, SYNTAX, 2012[c]	870 (27.6% BIMA)	3	93	94	$P = 0.60$
	Rastan *et al.*, 2009	8806 (22–32% TAG)	5	54	61	$P = 0.77$
	Kleisli *et al.*, 2005	1034	5	53	82	$P < 0.001$

[a]In comparison with Head *et al.*, this group also includes patients both in the trial and in the CABG registry
[b]Estimate from survival graphs in paper
[c]Includes only trial patients
CABG,coronary artery bypass graft; CR, complete revascularization; HR, hazard ratio; ICR, incomplete revascularization; IMA, internal mammary artery; MASS II, Second Medicine, Angioplasty, or Surgery Study; NS, not significant.

of revascularization [4]. Also, not all studies have shown that incomplete revascularization in CABG results in impaired survival [19,21,44,46–48,51] Table 2 shows 13 studies [19,21,27,28,32▪,44–51] comparing completeness of revascularization at follow-up times ranging from 2 to 10 years relating to the amount of arterial grafting.' In the SYNTAX trial with 27.6% BIMA [23,51,52], in the CABG group, no difference in outcomes was seen between incomplete and complete revascularization groups. Incomplete revascularization was identified as an independent predictor of Major Adverse Cardiac and Cerebrovascular Event (MACCE) in PCI (hazard ratio 1.55, 95% CI 1.15–2.08, $P = 0.004$), but not CABG patients. Rastan *et al*. spoke about 'reasonable ICR', noting that most often the territory not bypassed involves either the RCA or circumflex territory, which may or may not portend worse outcomes, especially if, as in their study, arterial grafting was more frequent [19]. Taggart [53▪] discussed the 'appropriateness' of ICR, noting that inability to completely revascularize often is a marker for more severe and diffuse disease. It is not 'appropriate' to place a bypass graft into an infarct area, or into a small target vessel, risking graft failure and possible infarct.

CONCLUSION

Arterial grafting is thought to be superior for graft longevity and patient survival, and we anxiously await the results of the ART trial to confirm this [18]. The definitions of ICR are as varied as is the incidence of ICR in the literature. Although technically challenging, it is possible to achieve complete revascularization with arterial grafts, especially if one skeletonizes the IMAs and as much as possible follows guidelines correlating the conduit type to level of stenosis in order to avoid competitive flow. Moderate lesions on the RCA system should probably be left alone as they do not progress (one in seven), whereas those in the left coronary system should be bypassed because of their progression over time (one in two). Finally, 'the enemy of good is perfect', and it may not be necessary to achieve completeness of revascularization each and every time.

Acknowledgements

The authors extend their thanks to all patients who entrust cardiac specialists to perform revascularization, and all those patients who through studies have contributed to our knowledge on this topic today.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
■ of special interest
■■ of outstanding interest

1. Tabata M, Grab JD, Khalpey Z, *et al.* Prevalence and variability of internal mammary artery graft use in contemporary multivessel coronary artery bypass graft surgery: analysis of the Society of Thoracic Surgeons National Cardiac Database. Circulation 2009; 120:935–940.
2. Bridgewater B, Kinsman R, Walton P, Keogh B. Demonstrating quality: the sixth National Adult Cardiac Surgery database report. Dendrite Clinical Systems Ltd; 2009 ; ISBN 1-903968-23-2. 2009. http://www.scts.org/documents/PDF/Sixth_NACSD_report_2008_with_c.pdf [Accessed 20 May 2013]
3. Mastrobuoni S, Gawad N, Price J, *et al.* Use of bilateral internal thoracic artery during coronary artery bypasses graft surgery in Canada: the bilateral internal thoracic artery survey. J Thorac Cardiovasc Surg 2012; 144:874–879.
4. Head SJ, Kieser TM, Falk V, *et al.* Coronary artery bypass grafting: part 1: an evolution over the first 50 years. Eur Heart J . (in press).
5. Barner HB. Conduits for coronary bypass: internal thoracic artery. Korean J Thorac Cardiovasc Surg 2012; 45:351–367.
6. Fitzgibbon GM, Kafka HP, Leach AJ, *et al.* Coronary bypass graft fate and patient outcome: angiographic follow-up of 5065 grafts related to survival and reoperation in 1388 patients during 25 years. J Am Coll Cardiol 1996; 28:616–626.
7. Tatoulis J, Buxton BF, Fuller JA. The right internal thoracic artery: the forgotten conduit: 5766 patients and 991 angiograms. Ann Thorac Surg 2011; 92:9–15; discussion 15–17.
8. Vineberg AM, Jewett BL. Development of an anastomosis between the coronary vessels and a transplanted internal mammary artery. Can Med Assoc J 1947; 56:609–614.
9. ■ Kelly R, Buth KJ, Légaré JF. Bilateral internal thoracic artery grafting is superior to other forms of multiple arterial grafting in providing survival benefit after coronary bypass surgery. J Thorac Cardiovasc Surg 2012; 144:1408–1415.

Over a 12-year period, 1079 BIMA patients were compared with 6554 single IMA patients: survival at 10 years was 71% for patients with BIMA grafts compared with 66% for patients with single IMA and 58% for patients with no IMA graft.

10. Locker C, Schaff HV, Dearani JA, *et al.* Multiple arterial grafts improve late survival of patients undergoing coronary artery bypass graft surgery: analysis of 8622 patients with multivessel disease. Circulation 2012; 126:1023–1030.
11. Kurlansky PA, Traad EA, Dorman MJ, *et al.* Thirty-year follow-up defines survival benefit for second internal mammary artery in propensity-matched groups. Ann Thorac Surg 2010; 90:101–108.
12. ■ Puskas JD, Sadiq A, Vassiliades TA, *et al.* Bilateral internal thoracic artery grafting is associated with significantly improved long-term survival, even among diabetic patients. J Thorac Cardiovasc Surg 2012; 94:710–716.

In a study of 3527 CABG operations (812 BIMA, 2715 single IMA), BIMA grafting conferred a 35% reduction (95% CI 12–52%, $P = 0.006$) in the long-term hazard of death equally for non-diabetic and diabetic patients ($P = 0.93$).

13. ■ Dorman MJ, Kurlansky PA, Traad EA, *et al.* Bilateral internal mammary artery grafting enhances survival in diabetic patients: a 30-year follow-up of propensity score-matched cohorts. Circulation 2012; 126:2935–2942.

In a 30-year follow-up study of 1107 consecutive diabetic patients with either single IMA ($n = 646$) or BIMA ($n = 461$), use of BIMA was found to be associated with enhanced late survival ($P = 0.003$) without any increase in peri-operative morbidity for sternal wound infection ($P = 0.179$) or mortality ($P = 0.279$).

14. ■ Kappetein AP, Head SJ, Morice MC, *et al.,* SYNTAX Investigators. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. Eur J Cardiothorac Surg 2013; 43:1006–1013.

Five-year outcomes of the SYNTAX trial in which 1800 patients with left main and/or 3VD were randomized to receive either PCI with TAXUS drug eluting stent or CABG showed significantly higher rates of MACCE in PCI vs. CABG in both diabetic (PCI 46.5% vs. CABG 29.0%; $P < 0.001$) and non-diabetic patients (PCI: 34.1% vs. CABG 26.3%; $P = 0.002$).

15. Bansilal S, Farkouh ME, Hueb W, *et al.* The Future REvascularization Evaluation in patients with Diabetes mellitus: optimal management of Multivessel disease (FREEDOM) trial: clinical and angiographic profile at study entry. Am Heart J 2012; 164:591–599.
16. Achouh P, Isselmou KO, Boutekadjirt R, *et al.* Reappraisal of a 20-year experience with the radial artery as a conduit for coronary bypass grafting. Eur J Cardiothorac Surg 2012; 41:87–92.
17. Alfieri O, Maisano F, Benussi S, *et al.* Drug-eluting stents or drug-eluting conduits for multivessel disease. J Cardiovasc Med (Hagerstown) 2007; 8:359–361.
18. Taggart DP, Altman DG, Gray AM, *et al.,* ART Investigators. Randomized trial to compare bilateral vs. single internal mammary coronary artery bypass grafting: 1-year results of the Arterial Revascularisation Trial (ART). Eur Heart J 2010; 31:2470–2481.
19. Rastan AJ, Walther T, Falk V, *et al.* Does reasonable incomplete surgical revascularization affect early or long-term survival in patients with multivessel coronary artery disease receiving left internal mammary artery bypass to left anterior descending artery? Circulation 2009; 120 (11 Suppl):S70–S77.
20. Lamy A, Devereaux PJ, Prabhakaran D, *et al.,* CORONARY Investigators. Off-pump or on-pump coronary-artery bypass grafting at 30 days. N Engl J Med 2012; 366:1489–1497.
21. McNeer JF, Conley MJ, Starmer CF, *et al.* Complete and incomplete revascularization at aortocoronary bypass surgery: experience with 392 consecutive patients. Am Heart J 1974; 88:176–182.
22. Ong AT, Serruys PW. Complete revascularization: coronary artery bypass graft surgery versus percutaneous coronary intervention. Circulation 2006; 114:249–255.
23. Mohr FW, Rastan AJ, Serruys PW, *et al.* Complex coronary anatomy in coronary artery bypass graft surgery: impact of complex coronary anatomy in modern bypass surgery? Lessons learned from the SYNTAX trial after two years. J Thorac Cardiovasc Surg 2011; 141:130–140.
24. Vander Salm TJ, Kip KE, Jones RH, *et al.* What constitutes optimal surgical revascularization? Answers from the Bypass Angioplasty Revascularization Investigation (BARI). J Am Coll Cardiol 2002; 39:565–572.
25. Puskas JD, Williams WH, Duke PG, *et al.* Off-pump coronary artery bypass grafting provides complete revascularization with reduced myocardial injury, transfusion requirements, and length of stay: a prospective randomized comparison of two hundred unselected patients undergoing off-pump versus conventional coronary artery bypass grafting. J Thorac Cardiovasc Surg 2003; 125:797–808.
26. Emmert MY, Salzberg SP, Cetina Biefer HR, *et al.* Total arterial off-pump surgery provides excellent outcomes and does not compromise complete revascularization. Eur J Cardiothorac Surg 2012; 41:e25–e31.
27. Lattouf OM, Thourani VH, Kilgo PD, *et al.* Influence of on-pump versus off-pump techniques and completeness of revascularization on long-term survival after coronary artery bypass. Ann Thorac Surg 2008; 86:797–805.
28. Kleisli T, Cheng W, Jacobs MJ, *et al.* In the current era, complete revascularization improves survival after coronary artery bypass surgery. J Thorac Cardiovasc Surg 2005; 129:1283–1291.
29. Mohr FW, Morice MC, Kappetein AP, *et al.* Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013; 381:629–638.
30. ■ Genereux P, Palmerini T, Caixeta A, *et al.* Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score. J Am Coll Cardiol 2012; 59:2165–2174.

The residual SYNTAX Score (rSS) (SYNTAX Score after revascularization) was studied in the PCI group of the SYNTAX trial: 40% had complete revascularization (rSS = 0), and, by multivariable analysis, a rSS was a strong independent predictor of all ischemic outcomes at 1 year including all-cause mortality (hazard ratio 1.05, 95% CI 1.02–1.09, $P = 0.006$).

31. Capodanno D, Chisari A, Giacoppo D, *et al.* Objectifying the impact of incomplete revascularization by repeat angiographic risk assessment with the residual SYNTAX score after left main coronary artery percutaneous coronary intervention. Catheter Cardiovasc Interv 2013; 82:333–340.
32. ■ Farooq V, Serruys PW, Bourantas CV, *et al.* Quantification of incomplete revascularisation and its association with five-year mortality in the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial: validation of the residual SYNTAX Score. Circulation 2013; 128:141–151.

The 'residual SYNTAX Score' (the burden of disease not removed) was calculated for PCI patients in the SYNTAX trial: patients with complete revascularization or residual SYNTAX scores 8 or less had comparable 5-year mortality (8.5–11.4%; $P = 0.6$), but a residual SYNTAX score above 8 was associated with a 35.3% all-cause mortality at 5 years ($P < 0.001$).

33. Head SJ, Farooq V, Serruys PW, Kappetein AP. The SYNTAX score and its clinical implications. Heart 2013; doi: 10.1136/heartjnl-2012-302482. [Epub ahead of print]
34. Rubens FD, Boodhwani M. Skeletonization of the internal thoracic artery for coronary artery bypass grafting. Curr Opin Cardiol 2009; 24:559–566.
35. ■■ Glineur D, Hanet C. Competitive flow in coronary bypass surgery: is it a problem? Curr Opin Cardiol 2012; 27:620–628.

This very comprehensive review of competitive flow discusses all aspects from the physics of flow to the effects of competitive flow on the different arterial conduits (and vein) as well as graft configuration most affected by flow competition.

36. Buxton BF, Hayward PA, Newcomb AE, *et al.* Choice of conduits for coronary artery bypass grafting: craft or science? Eur J Cardiothorac Surg 2009; 35:658–670.
37. Sabik JF 3rd, Lytle BW, Blackstone EH, *et al.* Does competitive flow reduce internal thoracic artery graft patency? Ann Thorac Surg 2003; 76:1490–1496; discussion 1497.
38. Glineur D, Hanet C, D'hoore W, *et al.* Causes of nonfunctioning right internal mammary used in a Y-graft configuration: insight from a 6-month systematic angiographic trial. Eur J Cardiothorac Surg 2009; 36:129–135; discussion 135–136.
39. Shah PJ, Seevanayagam S, Rosalion A, *et al.* Patency of the radial artery graft: angiographic study in 209 symptomatic patients operated between 1995 and 2002 and review of the current literature. Heart Lung Circ 2004; 13:379–383.
40. Desai ND, Cohen EA, Naylor CD. Radial Artery Patency Study Investigators. A randomized comparison of radial-artery and saphenous-vein coronary bypass grafts. N Engl J Med 2004; 351:2302–2309.
41. Suma H, Isomura T, Horii T, Sato T. Late angiographic result of using the right gastroepiploic artery as a graft. J Thorac Cardiovasc Surg 2000; 120:496–498.
42. ■■ Hayward PA, Zhu YY, Nguyen TT, *et al.* Should all moderate coronary lesions be grafted during primary coronary bypass surgery? An analysis of progression of native vessel disease during a randomized trial of conduits. J Thorac Cardiovasc Surg 2013; 145:140–148; discussion 148–149.

This very important study discusses for the first time the progression of moderate (40–69%) stenosis with respect to location in either right or left sided coronary vessels: when not bypassed, lesions on the left coronary system progress 47% of the time and lesions in the right system only 13.8% of the time.

43. Tonino PA, De Bruyne B, Pijls NH, *et al.,* FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009; 360:213–224.
44. Vieira RD, Hueb W, Gersh BJ, *et al.* Effect of complete revascularization on 10-year survival of patients with stable multivessel coronary artery disease: MASS II trial. Circulation 2012; 126 (11 Suppl 1):S158–S163.
45. Girerd N, Magne J, Rabilloud M, *et al.* The impact of complete revascularization on long-term survival is strongly dependent on age. Ann Thorac Surg 2012; 94:1166–1172.
46. Mohammadi S, Kalavrouziotis D, Dagenais F, *et al.* Completeness of revascularization and survival among octogenarians with triple-vessel disease. Ann Thorac Surg 2012; 93:1432–1437.
47. Kim YH, Park DW, Lee JY, *et al.* Impact of angiographic complete revascularization after drug-eluting stent implantation or coronary artery bypass graft surgery for multivessel coronary artery disease. Circulation 2011; 123: 2373–2381.
48. Sarno G, Garg S, Onuma Y, *et al.,* ARTS-II Investigators. Impact of completeness of revascularization on the five-year outcome in percutaneous coronary intervention and coronary artery bypass graft patients (from the ARTS-II study). Am J Cardiol 2010; 106:1369–1375.
49. Aziz A, Lee AM, Pasque MK, *et al.* Evaluation of revascularization subtypes in octogenarians undergoing coronary artery bypass grafting. Circulation 2009; 120:S65–S69.
50. Kozower BD, Moon MR, Barner HB, *et al.* Impact of complete revascularization on long-term survival after coronary artery bypass grafting in octogenarians. Ann Thorac Surg 2005; 80:112–116; discussion 116–117.
51. Head SJ, Mack MJ, Holmes DR Jr, *et al.* Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. Eur J Cardiothorac Surg 2012; 41:535–541.
52. Farooq V, Serruys PW, Garcia-Garcia HM, *et al.* The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. J Am Coll Cardiol 2013; 61:282–294.
53. ■ Taggart DP. Incomplete revascularization: appropriate and inappropriate. Eur J Cardiothorac Surg 2012; 41:542–543.

Professor Taggart discusses the difference between incomplete revascularization in PCI and CABG patients with respect to appropriateness, in that it is the remaining burden of ischemia that is prognostic of survival.

PART 6

FACILITATING SURGICAL USE OF BILATERAL INTERNAL MAMMARY ARTERY GRAFTING

Chapter 13

Quicker yet safe: skeletonization of 1640 internal mammary arteries with harmonic technology in 965 patients

Kieser TM, Rose MS, Aluthman U, Narine K

Eur J Cardiothorac Surg 2014;45:142-50

Quicker yet safe: skeletonization of 1640 internal mammary arteries with harmonic technology in 965 patients†

Teresa M. Kieser[a,*], M. Sarah Rose[b], Uthman Aluthman[a] and Kishan Narine[a]

[a] Department of Cardiac Sciences, LIBIN Cardiovascular Institute of Alberta, University of Calgary, Calgary, Alberta, Canada
[b] Rho Sigma Scientific Consultants, Calgary, Alberta, Canada

* Corresponding author. Foothills Medical Centre, Rm C 816, 1403 29th St. NW, Calgary, Alberta T2N 2T9, Canada. Tel: +1-403-9448449; fax: 1-403-9444895; e-mail: t.kieserprieur@ucalgary (T.M. Kieser).

Received 19 September 2013; received in revised form 6 December 2013; accepted 26 December 2013

Abstract

OBJECTIVES: Skeletonization of the internal mammary artery (IMA) facilitates arterial grafting and has been shown to reduce deep sternal infection but is more time-consuming and tedious than pedicle harvest. We wished to determine if use of harmonic technology (HT) facilitates skeletonization of the IMA and is as safe as the conventional technique of skeletonization.

METHODS: In a consecutive series of 1057 patients with isolated coronary artery bypass graft (CABG) surgery from 2003 to 2013, adverse events and recorded harvest times were compared between harmonic (965 patients) and non-harmonic patients (86 patients).

RESULTS: HT was used to harvest 1640 IMAs in 965 (91%) of 1057 consecutive CABG patients and skeletonization with the traditional technique (use of an electrocautery tip as a dissector) was used to harvest 147 IMAs in 86 patients. Six patients had no IMA harvested with this surgery (4 patients had an IMA used from a previous CABG, 1 had no disease of the left anterior descending coronary artery and 1 patient was in cardiogenic shock precluding IMA use). Excluding patients with single-vessel disease, 730/987 (74%) of patients received bilateral IMAs. Demographics of patients with and without harmonic skeletonization, respectively, were the following: mean age: 64.7 vs 67.7 years; diabetes: 33 vs 34%; women: 21 vs 26% and median European System for Cardiac Operative Risk Evaluation: 2.9 vs 3.2. The mean harvest time for 77 non-harmonic skeletonized mammary arteries (49 surgeries) was 32.2 min (95% confidence interval (CI): 30.1, 34.3), for harmonic skeletonized arteries after 450 surgeries was 28.4 min, (95% CI: 27.8, 29.1) and in the last 100 IMAs harvested for the isolated harmonic device use/mammary was 15.4 min (95% CI: 14.0, 16.7). Major adverse events for patients with and without harmonic skeletonization, respectively, were: reoperation for bleeding: 2.7 vs 3.5% (difference = 0.8%, 95% CI: −3.2, 4.8); damaged mammaries: 0.4 vs 0.7% (difference = 0.3%, 95% CI: −1.0, 1.7); deep sternal infection: 1.6 vs 1.2% (difference = −0.4%, 95% CI: −2.8, 2.0) and perioperative infarction: 1.7 vs 2.3% (difference = 0.7%, 95% CI: −2.6, 4.0).

CONCLUSION: In this largest series to date of harmonic IMA skeletonization, this technique results in rare damage, is quicker and with a comparable adverse event rate compared with the non-harmonic method.

Keywords: Harmonic scalpel • Coronary artery bypass graft • Bilateral internal mammary

INTRODUCTION

The internal mammary artery (IMA) is increasingly being acknowledged as the best conduit for replacement of diseased coronary arteries in the coronary artery bypass graft (CABG) operation. Even though Lytle *et al.* [1] pointed out in 1999 that 'Two internal thoracic artery grafts are better than one', bilateral internal mammary arteries (BIMAs) continue to be used rarely in North America (4%) and infrequently in Europe (10%). The majority of patients are still treated with the knowledge that 'one IMA is better than none', a concept proposed 27 years ago by Loop *et al.* [2] in 1986. Failure to adopt the 'Two IMA' philosophy may be explained by a number of valid reasons. First, evidence for 'BIMA being better' is at best 'Level of Evidence C', which is 'consensus of opinion of the experts and/or small studies, retrospective studies, registries'. Moreover, the only randomized trial to date by Taggart *et al.* [3], the arterial revascularization trial, is awaiting 10-year follow-up results in December 2017. Secondly, because the IMA is the main blood supply of the sternum, bilateral IMA harvest predisposes patients to an increased risk of failure to heal and/or deep sternal wound infection. Thirdly, the age until which BIMA grafting is advantageous is also in question. The average age of patients for CABG in most reported series ranges from 64 to 66 years. As such, the benefit of performance of BIMA grafting after the age of 70 is lacking [4]. Finally, technical and time demands are greater with BIMA use. Nevertheless, there is a preponderance of data from many observational studies [5–7] and meta-analyses [8], suggesting a significant long-term benefit with the use of BIMA.

†Presented at the 27th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Vienna, Austria, 5–9 October 2013.

In this retrospective review, we studied IMA harvest in a skeletonized fashion with harmonic technology (HT). Skeletonization of IMAs allows for more length of a finite conduit and reduced risk of deep sternal wound infection and we hypothesized that use of HT allows for a faster, skeletonized harvest of the IMA with infrequent damage. The purpose of this study was to (i) compare major adverse cardiac events (MACEs) related to IMA grafting between non-harmonic scalpel (HS) and HS patients, and (ii) compare times of harvest between non-HS harvest and HS harvest.

MATERIALS AND METHODS

This study group comprised a consecutive group of isolated CABG patients from July 2003 to July 2013 in which total arterial grafting was performed where possible in all patients operated on by one surgeon, regardless of comorbidities including advanced age, diabetes, obesity, chronic obstructive pulmonary artery disease (COPD) and urgency. This retrospective analysis of prospectively collected data from consecutive patients was undertaken to compare harvest times of IMAs with and without the HS and also the following major adverse effects of the two techniques related to IMA harvest: reoperation for bleeding, deep sternal wound infection, perioperative myocardial infarction (MI), operative mortality, need for early reoperation for failed grafts, postoperative development of angina and need for postoperative percutaneous coronary intervention (PCI) or redo CABG. Mammary arteries damaged to the point of non-use were recorded prospectively. Harvest times were recorded by nurses as part of operative routine for 816 mammary artery harvests from 2003 to 2007 and then this routine recording of IMA harvest times stopped because it was deemed no longer necessary by operating theatre administration personnel. To have the most recent data, harvest times (with the harmonic hook blade) of the last 100 IMAs were recorded from December 2012 to August 2013; also we noted the number of clips on the IMA branches and the repair stitches needed.

Surgical details

All operations were performed either with standard cardiopulmonary bypass or off-pump using high spinal anaesthesia (local anaesthetic and opioid) and light general anaesthesia. For on-pump procedures, we used intermittent antegrade warm (initial) and cold blood cardioplegia for myocardial protection and systemic hypothermia at 32°C. Off-pump CABG was performed with the Octopus stabilizing device (Medtronic, Inc., Minneapolis, MN, USA).

IMA conduits were harvested in a skeletonized manner either with the traditional skeletonization technique (with use of the cautery tip without power as a dissector) or with an ultrasonic scalpel (Harmonic Scalpel; Ethicon Endo-Surgery, CVD, Cincinnati, OH, USA) (Fig. 1). The three stages of the harvest comprised: (i) exposing the IMA on the chest wall by sweeping away the lung visceral pleura (trying to maintain this visceral pleura intact), (ii) incising horizontally with Metzenbaum scissors in the crevice between the medial internal mammary vein and the IMA and (iii) use of the cautery tip or HS to isolate and free the IMA, from its distal bifurcation into the superior epigastric and musculophrenic branches to proximally above the first intercostal branch. In the traditional skeletonization technique, side branches were clipped and cut and, in the harmonic technique, branches were sealed using the blunt end of the harmonic device. For harmonic skeletonization, clips were used only if the side branch bled before/after sealing with the harmonic device.

The left IMA was anastomosed to the left anterior descending artery and the right IMA was anastomosed to either the left circumflex or right coronary arteries. IMAs were used mostly as *in situ* grafts and were wrapped in papaverine-soaked gauze after harvesting before use. Intraoperative transoesophageal echocardiography was used, except where contraindicated. Long-acting nitrates were prescribed postoperatively for 6 weeks in patients with radial artery grafts.

Data collection

Data from all patients were entered into a province-wide database (APPROACH: Alberta Provincial Program for Outcome Assessment in CORONARY Heart disease) [9], which is a prospective data collection initiative in which patients are first enrolled at the time of initial cardiac catheterization and are followed for life to assess outcomes. Data from the same patients were also entered prospectively into a surgical database to document demographics and relevant surgical data. This study was approved by our Institutional Research Ethics Board. Major adverse cardiac events considered were operative mortality, perioperative MI, deep sternal wound infection and reoperation for either bleeding or failed grafts. The primary outcome was a composite measure indicating that any one of these adverse events occurred. In addition, we considered the postoperative MACEs of angina, and need for revascularization with CABG or PCI.

Statistical analysis

Continuous variables were described as the mean and standard deviation (SD) when normally distributed and the median (25th percentile, 75th percentile) when not. Categorical variables were described using percentages. Differences between the HS patients and the non-HS patients were assessed using unpaired *t*-tests for normally distributed continuous variables and the Wilcoxon test for non-normally distributed variables. Differences in categorical variables were examined using Fisher's exact test (FET). Differences between the HS patients and the non-HS patients were also described using the standardized mean difference. The unadjusted risk of the composite adverse event and each individual MACE was described, using percentages. The unadjusted absolute risk difference between HS patients and non-HS patients was calculated with exact 95% confidence intervals (CIs). Since this difference may have been a result of an imbalance of covariates between the two groups, we performed a propensity analysis to assess the difference in the composite perioperative adverse event variable. A non-parsimonious logistic regression model was used to calculate the propensity score in the iterative manner suggested by Rosenbaum and Rubin [10]. All potential covariates were entered into the model if they were significant for HS use or for the composite outcome at $P < 0.5$. In addition, quadratic terms for the continuous variables and plausible interactions were included. The balance between the HS groups was examined both using boxplots comparing the distribution of the propensity between HS groups within each quintile of the propensity score distribution and by calculating the standardized mean difference of each covariate within quintiles of the propensity score. After

Figure 1: Harmonic hook blade and generator.

achieving balance between the groups (standardized differences < 10% within quintiles), we estimated the difference in the composite adverse event risk stratifying on the quintiles of the propensity score and then obtained estimates of the risk difference from the coefficients. Standard errors and hence CIs were estimated using the delta method.

Harvest times were summarized separately for non-HS patients (Patients 1–49) and the patients recruited since December 2012 using the mean, since, for these two groups, the harvest times were constant across time. There was evidence of a non-linear effect of the number of surgeries on harvest times after the HS was introduced. This non-linear relationship was estimated using linear regression in which a log transformation was applied to the number of surgeries and then the results back-transformed to arrive at the presented estimates. For both the means and the regression, standard errors of the estimates were calculated taking into account the intrasubject correlation between the left and the right IMA using a generalized estimating equation approach. All analyses were done using Stata version 13 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX, USA: StataCorp LP.)

RESULTS

Demographics and arterial graft anatomy

In 10 years from July 2003 to July 2013, 1057 consecutive patients received 3150 grafts of which 3083 (98%) were arterial in origin, 2205 grafts were of IMA origin [1421 left internal mammary artery (LIMA) (45%) and 784 right internal mammary artery (RIMA) (25%)]

and the remaining were as follows: 874 Radial (28%), 4 inferior epigastric artery and 67 (2%) vein grafts with an average of 2.98 grafts/patient. A total of 1640 mammary arteries in 965 patients [940 left IMAs (57%) and 700 right IMAs (43%)] were skeletonized with HT and in 86 patients 147 IMAs were skeletonized using the cautery tip as a dissector (no power; side branches were individually clipped and cut). Six patients of this consecutive series had no IMA harvested with this surgery because IMAs existed from a previous CABG (4 patients); there was no need of IMA because of non-left anterior descending artery (LAD) disease with inferior wall scar (1 patient), and prolonged cardiogenic shock precluding IMA use (1 patient). Figure 2 shows a flow chart of the study groups. Excluding patients with single-vessel disease, 74% of patients received bilateral IMAs. Baseline variables of patients with and without harmonic skeletonization are described in Table 1. HS patients were younger ($P = 0.009$), less likely to have hypercholesterolaemia ($P = 0.068$) and more likely to have an ejection fraction <30% ($P = 0.024$). No other significant differences were observed at $P < 0.20$.

The majority of right IMA conduits went to the right coronary artery (RCA) (42%) (322/758) and the circumflex (Cx) (54%) (408/758) territories; only 3.7% (28/758) went to the LAD/diagonal system. Seventy-two percent of the right IMA-to-RCA grafts were to the sub-branches: 64% to the posterior descending artery, 8% to the posterolateral branch of the RCA; 28% went to the main RCA. In the majority of right IMA grafts to the RCA and Cx systems, skeletonization allowed *in situ* use: direct anastomosis to the aorta was required in 11% of right IMAs to the RCA system and 9% to the Cx system.

Skeletonization with harmonic technology

The traditional skeletonization technique for IMA harvest was used during two time periods: from 18 July to 13 November 2003 on 49 patients and from 11 March to 3 August 2010 on 37 patients because the HT changed. The first skeletonization of an IMA with any harmonic device for a patient occurred on 24 November 2003; and although it is usually the surgeon's preference to continue a change in technique without breaks, when the first device was discontinued by the company in 2009, it took 5 months to discover an adequate replacement. For the first 673 (71%) patients the HC105 HS (with non-disposable handle and disposable blade tip) was used and when the nation-wide supply of the blade tip was exhausted by the first author, in March 2010, for 5 patients the Harmonic Synergy Curved Blade was trialled. This blade was 3 mm wide compared with the 2 mm width of the HC105 blade, was sharper and tended to damage the accompanying internal thoracic veins of the IMA. The resulting bleeding from these damaged veins frustrated attempts to seal the IMA branches because of the dry field required. This device was only used in 5 patients before its use for IMA harvest was abandoned. After this, for a period of almost 5 months the traditional skeletonization technique was used in 37 patients until the harmonic hook blade was discovered in August 2010. This device has been used for the last 269 (28%) patients and has become the authors' device of choice for delicate, accurate dissection and speed of harvest of the IMA.

Major adverse events related to internal mammary artery harvest

The unadjusted rates of the composite adverse events were 6/86 = 6.98% in non-HS patients and 78/965 = 8.08% in HS patients with an unadjusted absolute risk difference of −1.1% (95% CI: −6.76%, 4.55%), FET $P = 0.838$. We developed a propensity

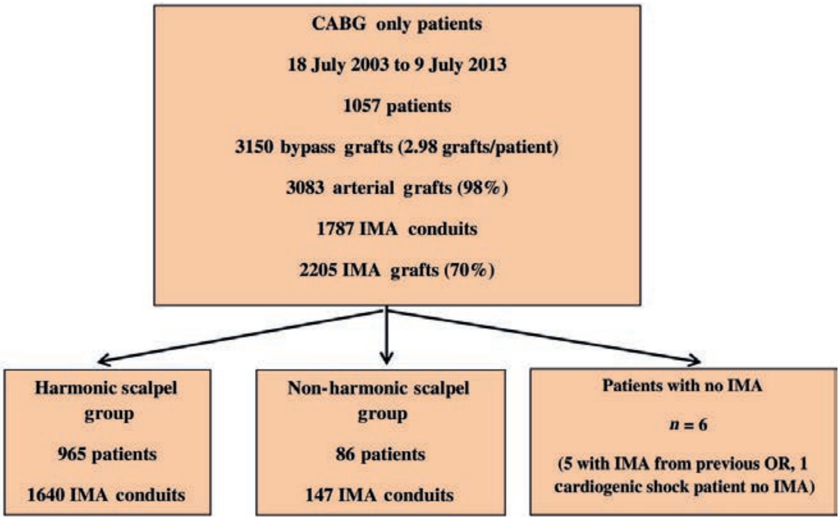

Figure 2: Flow chart of study patients, grafts, conduits, RIMAs and LIMAs of study groups. CABG: Coronary artery bypass graft; IMA: internal mammary artery; OR: operation.

Table 1: Baseline characteristics of the study population of 1057 patients: 86 patients with the conventional skeletonized harvest technique; 965 patients with harmonic skeletonization; 6 patients with no IMA graft

	All patients (n = 1057[a]) (%)	Harmonic patients (n = 965) (%)	Non-harmonic patients (n = 86) (%)	Standardized difference	*P*-value
Demographics					
Number of IMA conduits/patient	1787/1057 = 1.7	1640/965 = 1.7	147/86 = 1.7		0.999
SVD	64 (6.1)	57 (5.9)	7 (8.1)	−0.087	0.353
BIMA (excluding SVD)	730/987 (74%)	670/908 (74%)	60/79 (76%)	−0.050	0.789
Grafts/patient, mean (SD)	2.98 (0.94)	2.98 (0.93)	3.02 (1.07)	−0.039	0.685
Off-pump CABG	413 (39%)	377 (39%)	36 (42%)		0.645
Age, mean (SD)	64.9 (10.5)	64.7 (10.5)	67.7 (9.9)	−0.302	0.009
Female gender	229 (22%)	206 (21%)	22 (26%)	−0.100	0.343
Elective	459 (43%)	412 (43%)	43 (50%)	−0.147	0.447
Urgent-in	477 (45%)	441 (46%)	35 (41%)	0.101	
Emergency	121 (11%)	112 (12%)	8 (9%)	0.075	
EuroSCORE (median quartiles)	3.0 (1.6, 6.4)	2.9 (1.5, 6.3)	3.2 (2.0, 6.2)	0.057	0.262
Comorbidities					
Hypertension	729 (69%)	663 (69%)	63 (73%)	0.100	0.465
Hypercholesterolaemia	729 (69%)	658 (68%)	67 (78%)	−0.220	0.068
Diabetes mellitus	367 (35%)	316 (33%)	29 (34%)	−0.021	0.906
Ever smoked	622 (59%)	573 (59%)	45 (52%)	0.142	0.210
Ejection fraction[b] >50%	426 (55%)	380 (55%)	43 (64%)	−0.198	0.024
Ejection fraction 30–50%	267 (35%)	243 (35%)	23 (34%)	0.011	
Ejection fraction <30%	76 (10%)	74 (11%)	1 (1%)	0.390	
BMI ≥ 30	340 (32%)	312 (32%)	26 (30%)	0.045	0.720
COPD	133 (13%)	124 (13%)	9 (10%)	0.074	0.614
Cerebrovascular disease	112 (11%)	103 (11%)	9 (10%)	0.007	1.00
Peripheral vascular disease	117 (11%)	108 (11%)	8 (9%)	0.062	0.720
Renal disease Creatinine >200	40 (4%)	36 (4%)	3 (3%)	0.013	1.000
Reoperative CABG	38 (4%)	32 (3%)	2 (2%)	0.060	1.000

[a]Includes 6 patients with no IMA harvested/used with this surgery (4 reoperative CABG patients with IMA from previous surgery, 1 patient with no LAD disease (radial to diagonal and marginal) and 1 cardiogenic shock patient with no IMA).
[b]Ejection fraction known in 73% of 1057 patients.
IMA: internal mammary artery; SVD: single-vessel disease; BIMA: bilateral internal mammary artery; CABG: coronary artery bypass graft; EuroSCORE: European System for Cardiac Operative Risk Evalulation; BMI: body mass index; COPD: chronic obstructive pulmonary artery disease.

Table 2: Perioperative and mid-term outcomes of non-harmonic and harmonic patients

Outcomes	Harmonic patients (n = 965) (%)	Non-harmonic patients (n = 86) (%)	*P*-value
Composite perioperative adverse events	78 (8.1)	6 (7.0)	0.838
Reoperation for bleeding	26 (2.7)	3 (3.5)	0.726
Early reoperation for failed grafts	7 (0.7)	0 (0)	1.000
Deep sternal wound infection	15 (1.6)	1 (1.2)	1.000
Perioperative MI	16 (1.7)	2 (2.3)	0.653
Operative mortality total	36 (3.7)	2 (2.3)	0.763
Postoperative adverse events			
Angina	59 (6.1)	5 (5.8)	1.000
PCI	30 (3.1)	4 (4.7)	0.353
Late redo CABG	1 (0.1)	0 (0)	0.765

CI: confidence intervals; IMA: internal mammary artery; MI: myocardial infarction; PCI: percutaneous coronary intervention; LIMA: left internal mammary artery; Operative mortality: in-hospital mortality.

score that adequately balanced the covariates on the quintiles of the propensity and estimated the adjusted risk difference between non-HS patients and HS patients, which was −0.79% (95% CI: −6.73%, 5.14%, P = 0.793). The adjusted risk in the non-HS group was 7.26% (1.59%, 12.93%) and in the HS group 8.06% (95% CI: 6.34, 9.77%). Individual adverse event rates for patients with and without harmonic skeletonization, respectively, are seen in Table 2 and were not statistically different. Absolute risk differences are presented in Fig. 3. With respect to reoperation for bleeding, in the 10 years of use of the HS, the cause of bleeding was never from a reopened sealed IMA side branch. In 6 patients, 8 harvested IMAs could not be used due to arterial damage and/or fragility: 1/147 non-HS IMAs vs 7/1640 HS IMAs (difference = 0.3%, 95% CI: −1.0, 1.7).

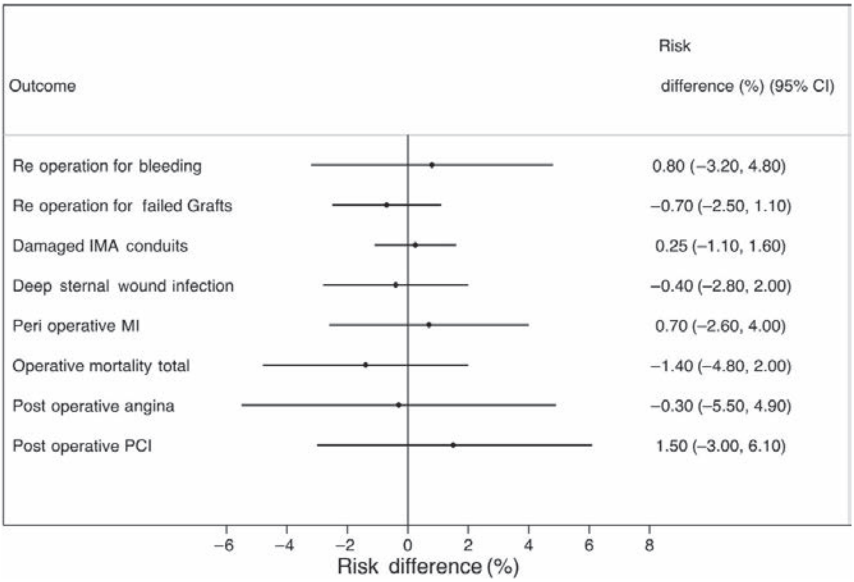

Figure 3: Absolute risk differences for major adverse events (actual risks by group are presented in Table 2) between non-harmonic patients and harmonic patients (with exact 95% CI for the risk differences) in which a positive value represents a beneficial effect of using a HS. This illustrates that there were no substantial differences in the risk of MACEs between HS patients and non-HS patients.

Operative time

The traditional technique of skeletonization, with use of the cautery tip as a dissector (no power) with clips and scissors, had been used for the previous 3½ years (June 2000 to November 2003). Hence the harvest of the first 77 non-harmonic skeletonized mammaries (49 surgeries) (mean time of 32.2 min) (95% CI: 30.1, 34.3) was done by a surgeon experienced in this technique. After introduction of the HS there was a significant non-linear decrease in harvest time ($P < 0.001$ controlling for intrasubject correlation between the left and the right IMA). Figure 4 illustrates the change in harvest times per IMA by the number of surgeries performed over time. Initially, for the 50 surgeries using the HS for the first time, the harvest time was 36.2 min (95% CI: 34.2, 38.2). After 100 surgeries the mean time was 33.7 min (95% CI: 32.3, 35.2) and after 450 surgeries the mean time was 28.4 min (95% CI: 27.8, 29.1). Times were further reduced with the addition of an easier-to-use mammary retractor (Bugge IMA retractor) and use of the harmonic hook blade. For the last 60 surgeries (100 IMAs harvested) from 29 December 2012 to 29 August 2013 the mean harvest time for use of the harmonic device per mammary was 15.4 min (95% CI: 14.0, 16.7) (16.7 min for the left IMA and 14.1 min for the right IMA). A total of 75 clips were used (0.75 clips/mammary), less than 1 clip/mammary. Seven repair stitches were needed to repair small needle holes or branches that were inadvertently transected flush with the IMA.

Postoperative events at mid-term follow-up

At a mean follow-up time of 5 years development of angina and requirement for revascularization (PCI or redo CABG) were no different for the non-harmonic and harmonic group of patients ($P = 1.00$, $P = 0.353$ and $P = 0.765$) (Table 2).

DISCUSSION

In this consecutive all-comer series of 1051 patients with 1787 skeletonized IMAs, we have shown that use of HT to skeletonize IMAs is safe and efficient with regard to harvest time. Major adverse events related to IMA use are no different when compared with patients whose IMAs were skeletonized with the conventional technique; time for IMA harvest with HT is half of that of harvest with the cautery tip as a dissector. Also the IMA is rarely damaged and in fact, in those rare instances that an IMA is not usable (7/1640 mammaries–0.43%), it is possible that the HS is able to harvest excessively fragile mammaries intact and this fragility comes to light only when one starts to work with the conduit in the performance of distal anastomoses.

Skeletonization technique for internal mammary artery harvest

This study also shows that skeletonization of the internal mammary artery allows for *in situ* right mammary grafts to reach

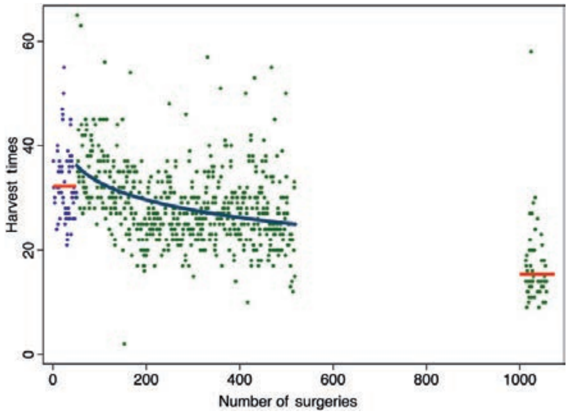

Figure 4: The change of harvest times per IMA by the number of surgeries performed over time. The blue dots represent the first 49 non-HS patients and the green dots represent HS patients. No time measurements were made between the 519th and 1012th surgeries. The red lines represent the mean values for the non-harmonic patients and the last 100 IMAs harvested (which do not change over time). There was a significant non-linear decrease in harvest time per IMA ($P < 0.001$), which is illustrated by the blue line. Multiple $R^2 = 0.1473$ for surgeries 50–518.

branches of the RCA and Cx the majority of the time. By comparison, the left IMA usually easily reaches the LAD and/or diagonal arteries. Use of the right IMA is largely responsible for the increased difficulty in use of double IMAs; right IMA *in situ* attachment to non-LAD territory arteries such as the distal branches of the RCA and Cx systems with the right IMA can be challenging. In our experience, skeletonization allows an easier 'reach' to distant distal targets. Although a benefit not easily quantifiable, a clip-less IMA is much easier to use especially in sequential grafting. In this series 35% (359/1021) of left IMAs were used in a sequential fashion and less frequently, 5.3% of right IMAs.

In 1946, Vineberg [11] was both the first surgeon to pioneer the use of the IMA in revascularization as an implanted artery into a tunnel in the myocardium and the first to harvest the IMA in a skeletonized fashion. None of Vineberg's early papers actually describe the technique, but Effler *et al.* [12] of the Cleveland Clinic, in a 1963 paper on 'Vineberg's Operation', outlined the technique in great detail. In 1962, in an attempt to promote collateral circulation in the heart muscle tunnel, Sewell, in animal experiments, first reported the use of a 'pedicle' of the IMA, which included IMA harvest with the veins and surrounding tissue. Hence, the most commonly used pedicle technique for IMA harvest today derives from research intended to improve the Vineberg operation [13]. In 1987 Keeley [14] introduced skeletonization again but harvested the IMA first as a pedicle, and then used bipolar cautery to skeletonize the IMA.

Studies have shown anatomical and physiological differences in skeletonized IMAs: skeletonization results in a longer conduit by as much as 4 cm compared with the pedicled conduit [15]. Also free flow is greater in the skeletonized mammary. In a review by Athanasiou *et al.* [16] Grade A evidence was found for 'skeletonization causing less sternal devascularization compared with pedicle harvest', and Grade B evidence was found for 'superior free flow for skeletonized IMAs', but all other parameters compared were Evidence Grade C, which included: 'damage to the harvested IMA', 'mortality/morbidity improvement with skeletonization', 'improved graft patency', 'reduction of postoperative respiratory complications', 'reduced postoperative blood loss and sternotomy-related pain', and 'reduction in the incidence of IMA hypoperfusion syndrome'.

Operative time

Lengthy preparation times with harvesting of bilateral IMAs for CABG surgery can be a deterrent to performance of bilateral IMA grafting. Shorter procedures are in everyone's best interest —the patient, the team, the surgeon and the hospital administration. Harvesting two IMAs by skeletonization may lengthen a 2½ h conventional procedure (one IMA and venous grafts) by at least 30–45 min for two reasons: first the skeletonization technique is more meticulous and time-consuming and also IMA harvest is metachronous by the primary surgeon and not synchronous as with simultaneous vein harvest by the assistant. We have shown that IMA harvest time can be reduced with use of HT and, although not as speedy as simultaneous vein harvest, is quicker than the conventional skeletonization technique. In principle, techniques that are less damaging usually take more time; not so with harmonic skeletonization—in this study in addition to being quicker, it is less damaging to the mammary artery.

Whereas it would be interesting to try and calculate a 'learning curve' for harmonic skeletonization, there have been too many variables introduced at different times over the 10-year period to allow scientific assessment. These variables include: use of three types of harmonic blades, use of two different mammary retractors and lack of time recordings for the entire series of IMA harvests. From the authors' personal experience in teaching this technique to junior and senior cardiac surgical residents as well as to surgeons already in practice, if one is familiar with the skeletonization technique, approximately 10 harvests with the HS gives one a comfort level with the technique and, if one is not experienced in skeletonization, approximately 20 harvests would be needed.

Arterial conduit harvest times recorded by other authors include Matsumoto's 20–25 min for the pedicle dissection of IMAs [17], Higami's 20–25 min for both pedicled and harmonic skeletonization of IMAs [15] and, in the early years of minimally invasive CABG, thoracoscopic harvest times were 65 min (range 35–95 min) for the left IMA and 37 min (range 25–45 min) for the right IMA [18]. Harvest times for other conduits were noted by Isomura: the gastro-epiploic harvest time was 9 min and that for the radial artery was 17 min, both with the HS. Use of the HS decreases harvest time and conduit spasm, and reduces the number of clips [19]. Prior to the authors' skeletonization experience (beginning in June 2000) the average time for pedicle harvest in the preceding 4 years was 19 min, making the current time of 15.4 min faster than that for the pedicle harvest. We believe that the extra time of 15.4 min to harvest the second IMA, with its potential to endure, is more than justified.

Physiological advantage of harmonic technology

HT in the form of the hook blade was first introduced in cardiac surgery by R.K. Wolf (with the first human harvest in 1994) and initially was used for thoracoscopic IMA harvest for minimally invasive CABG [20]. Wolf not only tested early prototypes of the HS for years in animal studies but also designed the hook blade specifically for IMA harvest, which is still used today. An ultrasonically activated scalpel seals vessels only by coaptive coagulation and not by tissue desiccation as with electrocautery. The blade tip vibrates longitudinally 55 500 times/s with an excursion of 50–100 μm. Energy propagates only in the direction in which force is applied—there is very little lateral distribution of energy. Vessels up to 5 mm in diameter are able to be sealed and without tissue desiccation or charring. The hook blade design (used in the latter 265 patients of this series) provides coaptive coagulation as well as haemostatic cutting.

Studies comparing electrocautery, lasers and ultrasonically activated (harmonic) scalpels have shown that with HT the zone of thermal injury is greatly reduced because of both decreased depth of penetration (coagulation) and lateral thermal spread [21]. With electrocautery a coagulation depth of 1 mm is reached almost instantly, whereas it takes 3 s for an ultrasonically activated scalpel to achieve the same depth. Similarly, lateral thermal spread after 1 s of contact by the HT is 0.1 mm compared with 1 mm by electrocautery (i.e. it takes 10 s of HT to cause the same thermal spread of 1 mm [22]. Thermal degeneration is limited to the depth of the connective tissue of the tunica externa [23]. Because of the decreased lateral thermal spread, wound repair is also superior and decreased postoperative adhesions are described by McCarus [21]

The HS has two cutting mechanisms: the primary is the cutting effect of the longitudinal vibrating sharp blade (vibrating 55 500 times/s over a distance of 50–100 μm), which incises high-density tissues such as muscle, and fibrous connective tissue. Cavitational fragmentation is the second cutting mechanism, which disrupts low-density tissues such as fat and parenchyma; tissue planes separate ahead of the blade tip quickly and easily. A dry field is advisable for the harmonic blade to function; therefore, blood vessels must be 'sealed' before they are cut. This is done by continuous pressure on the branch for about 1–2 s until the branch turns white or black. Harvesting IMAs in patients requiring ongoing intravenous heparin or who are on Clopidogrel can be challenging, but not impossible: more clips might be needed. 'Cauterization' of a bleeding vessel is possible but the bleeding cannot be brisk and, in the authors' experience, is most often only possible in actively smoking patients because of their hypercoagulability.

Histology/pharmacology of harmonic skeletonized internal mammary arteries

Use of HT does not damage the endothelium [24] but endothelial relaxation function may be compromised; Matsumoto *et al.* [17] found in a study of discarded distal ends of 50 skeletonized and 30 pedicled IMAs that whereas norepinephrine-mediated contraction was similar for skeletonized and pedicled IMAs, pedicled vessels showed greater relaxation responses to acetylcholine ($P < 0.05$). A topical vasodilator such as papaverine or nitroglycerin on the skeletonized IMA may therefore be important. Higami *et al.* [25] established the safe distance to seal IMA branches to be at least 1 mm distal to their origin from the IMA, using the power level 2 of a maximum level of 5. He also found that 92% of the sealed branches remained intact when subjected to burst pressures of 350 mmHg.

Limitations of this study

As with all observational retrospective reviews, it was not possible to control factors which may have changed outcomes in the two groups of patients. Also the numbers of the two groups are disparate but this is also in keeping with the nature of observational reviews. Even though some factors were different for the two groups, the major adverse events were no different, either before or after controlling for these factors, establishing that use of HT is safe and not inferior to the traditional technique of harvest. The strengths of this study lie in the fact that it is a real-world consecutive all-comer population of almost purely arterial grafting CABG patients.

CONCLUSIONS

In this study of 1051 consecutive all-comer patients with 2205 IMA grafts from 1787 IMA conduits, we have shown that use of HT to skeletonize IMAs facilitates the skeletonization technique by being faster and rarely damaging, needing less clips and having similar results with respect to reoperation for bleeding, deep sternal infection and peri- and postoperative MI compared with conventional IMA harvest by skeletonization. Simply put, use of HT is quicker than and just as safe as the conventional method of skeletonization; this easier technique may encourage use of bilateral IMAs. In turn, this may benefit patients in the long term with regard to improved survival and cardiac problem-free existence.

ACKNOWLEDGEMENT

The authors acknowledge the hundreds of hours spent by Randall K. Wolf in helping design and test the original HS in the early

1990's. The original device was very bulky, with a large cumbersome water-cooled jacket, which ultimately was redesigned with a hard sheath, eliminating the need for water cooling. R.K. Wolf remembers (fondly) 'If the tips weren't made precisely they would fly off from the body of the device and embed into the wall'. R.K. Wolf is thanked for his dedicated background work, which has given us a timeless device for IMA harvest.

Funding

Conflict of interest: Teresa M. Kieser is a paid consultant to teach the use of the harmonic scalpel for IMA harvest for Ethicon Endosurgery.

REFERENCES

[1] Lytle BW, Blackstone EH, Loop FD, Houghtaling PL, Arnold HH, Akhrass R *et al*. Two internal thoracic artery grafts are better than one. J Thorac Cardiovasc Surg 1999;117:855–72.

[2] Loop FD, Lytle BW, Cosgrove DM, Stewart RW, Goormastic M, Williams GW *et al*. Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. N Engl J Med 1986;314:1–6.

[3] Taggart D, Altman D, Gray A, Lees B, Nugara F, Yu LM *et al*. Randomized trial to compare bilateral vs. single internal mammary coronary artery bypass grafting: 1-year results of the Arterial Revascularisation Trial (ART). Eur Heart J 2010;31:2470–81.

[4] Kieser TM, Lewin AM, Graham MM, Martin BJ, Galbraith PD, Rabi DM *et al*. APPROACH Investigators. Outcomes associated with bilateral internal thoracic artery grafting: the importance of age. Ann Thorac Surg 2011;92: 1269–75. discussion 1275–6.

[5] Kurlansky PA, Traad EA, Dorman MJ, Galbut DL, Zucker M, Ebra G. Thirty-year follow-up defines survival benefit for second internal mammary artery in propensity-matched groups. Ann Thorac Surg 2010;90:101–8.

[6] Grau JB, Ferrari G, Mak AW, Shaw RE, Brizzio ME, Mindich BP *et al*. Propensity matched analysis of bilateral internal mammary artery versus single left internal mammary artery grafting at 17-year follow-up: validation of a contemporary surgical experience. Eur J Cardiothorac Surg 2012;41:770–5. discussion 776.

[7] Puskas JD, Sadiq A, Vassiliades TA, Kilgo PD, Lattouf OM. Bilateral internal thoracic artery grafting is associated with significantly improved long-term survival, even among diabetic patients. Ann Thorac Surg 2012;94:710–5. discussion 715–6.

[8] Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. Lancet 2001;358:870–5.

[9] Ghali WA, Kundtson ML. Overview of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease on behalf of the APPROACH investigators. Can J Cardiol 2000;16:1225–30.

[10] Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc 1984;79:516–24.

[11] Vineberg AM. Development of an anastomosis between the coronary vessels and a transplanted internal mammary artery. Can Med Assoc J 1946;55:117–9.

[12] Effler DB, Groves LK, Sones FM Jr, Shirey EK. Increased myocardial perfusion by internal mammary artery implant: Vineberg's operation. Ann Surg 1963;158:526–36.

[13] Sewell WH, Sealy WC. Coronary cinearteriography and pedicle operation in diagnosis and treatment of coronary insufficiency. Surgery 1964;55: 99–105.

[14] Keeley SB. The skeletonized internal mammary artery. Ann Thorac Surg 1987;44:324–5.

[15] Higami T, Kozawa S, Asada T, Shida T, Ogawa K. Skeletonization and harvest of the internal thoracic artery with an ultrasonic scalpel. Ann Thorac Surg 2000;70:307–8.

[16] Athanasiou T, Crossman MC, Asimakopoulos G, Cherian A, Weerasinghe AGlenville B *et al*. Should the internal thoracic artery be skeletonized?. Ann Thorac Surg 2004;77:2238–46.

[17] Matsumoto K, Tsuneyoshi I, Iguro Y, Kinjo T, Yotsumoto G, Ueno M *et al*. Effects of ultrasonic skeletonization on internal thoracic and gastroepiploic arteries for coronary artery bypass grafting. Eur J Cardiothorac Surg 2006; 30:592–6.

[18] Wolf RK, Ohtsuka T, Flege JB Jr. Early results of thoracoscopic internal mammary artery harvest using an ultrasonic scalpel. Eur J Cardiothorac Surg 1998;14 Suppl 1:S54–7.

[19] Isomura T, Suma H, Sato T, Horii T. Use of the harmonic scalpel for harvesting arterial conduits in coronary artery bypass. Eur J Cardiothorac Surg 1998;14:101–3.

[20] Ohtsuka T, Wolf RK, Hiratzka LF, Wurnig P, Flege JB Jr. Thoracoscopic internal mammary artery harvest for MICABG using the Harmonic Scalpel. Ann Thorac Surg 1997;63(6 Suppl):S107–9.

[21] McCarus SD. Physiologic mechanism of the ultrasonically activated scalpel. J Am Assoc Gynecol Laparosc 1996;3:601–8.

[22] Sutton PA, Awad S, Perkins AC, Lobo DN. Comparison of lateral thermal spread using monopolar and bipolar diathermy, the Harmonic Scalpel and the Ligasure. Br J Surg 2010;97:428–33.

[23] Fukata Y, Horike K, Kano M. Histological study on the influences of an ultrasonic scalpel on skeletonized vessel wall. Ann Thorac Cardiovasc Surg 2002;8:291–7.

[24] Yoshikai M, Ito T, Kamohara K, Yunoki J. Endothelial integrity of ultrasonically skeletonized internal thoracic artery: morphological analysis with scanning electron microscopy. Eur J Cardiothorac Surg 2004;25:208–11.

[25] Higami T, Maruo A, Yamashita T, Shida T, Ogawa K. Histologic and physiologic evaluation of skeletonized internal thoracic artery harvesting with an ultrasonic scalpel. J Thorac Cardiovasc Surg 2000;120:1142–7.

APPENDIX. CONFERENCE DISCUSSION

Dr M. Contino *(Milan, Italy)*: First of all, about the cost, can you do a comparison between the differences in cost of the two technologies, the Harmonic technology and the traditional technique?

And the second thing is about the learning curve, because during this study we see a significant speed-up in the harvesting time of the IMA, but I know that you also change the kind of instruments during this period. So in conclusion, how long can we consider the learning curve to be to achieve this very quick skeletonization time?

Dr Kieser: The cost. Okay. I do know that the disposable hook blade in Canadian dollars is $314. So clips don't cost that much, so it is expensive. The rest of the technology, the blue cord and the generator, often are already in your hospital because they're used by general surgeons, specifically thyroid surgeons. So the cost is $314 for the disposable handpiece.

Concerning the learning curve, if you already know how to skeletonize, it probably takes about 10 mammaries. And if you don't know how to skeletonize, or you're not familiar with the technique, about 20 mammaries. But I've taught several residents how to do this and they learn very quickly. And these are not residents who are experienced. We have young surgeons or young students coming out of medical school and I start them right away on the internal mammary harvest, because the way you start is the way you mean to continue. I don't want them learning vein, because that's what they'll do when they become staff. So I start them with internal mammary artery harvest right away with the Harmonic scalpel. Recently I was teaching a young surgeon in Varna, Bulgaria, and he was a qualified surgeon, he had been in practice for two years, and after he was harvesting for about 10 minutes, he turned to me and he said, "This is easy." And I said, "I know." So it's not so bad.

Dr T. Folliguet *(Nancy, France)*: I have just one short comment. I believe totally and I agree with you that I don't use clips, in our unit we don't use clips, but you can do the same thing without the Harmonic, you can do the same thing with the Bovie. You set up at 30 or 20 and you just go down. So I think on the question of cost, I mean I have no experience with Harmonic, but the regular Bovie does the job just the same way and you don't have to use clips. I think clips, as we see a lot of the time, are pinching, and you sometimes have a little bit of dimpling on the artery, and this technique allows you to have a smooth surface. The only thing we have to teach the residents is to be really far away from the mammary arteries in order not to cauterize, because otherwise you can get burn injury. Maybe that can be an advantage of the Harmonic, I don't know.

Dr Kieser: No, I agree, whatever works for you is a very, very good technique. The difference between the Harmonic and the cautery is that the lateral thermal spread is 10 to 1. The lateral thermal spread with electrocautery in one second is a millimetre, whereas it is 0.1 mm with the Harmonic. So if you're teaching it, you have a little more leeway. And if you're tired, if you're operating, you have a little more leeway. But no, the use of cautery is a very valid way.

Chapter 14

Skeletonization of the internal mammary artery with the harmonic hook blade

Kieser TM, Narine K

CTSNet Video published on July 12 2012 Website:
http://www.ctsnet.org/sections/videosection/videos/vg2012_KieserT_Harmonic

CTSNet a world- wide web site that can be joined by all cardiac surgeons in the world, currently has 52,000 members of which 35,000 are cardiac surgeons. When a surgical video is launched on CTSNet, it is viewed on average 1600 times in the first month. This video was viewed 4609 times in the first (approximately) 6 weeks.

This is the script of a video published on Cardio Thoracic Surgery network (CTSNet). It describes a method to harvest internal mammary arteries using high frequency ultrasound. There are two ways used to harvest internal mammary arteries: either by taking a swath of tissue surrounding the internal mammary artery including the accompanying veins and some muscle and endothoracic fascia (the pedicle method) or by dissecting just the internal mammary artery itself without any accompanying tissue (the skeletonization method). In turn, there are two techniques used to 'skeletonize' an IMA: by either using the cautery tip blade *without* power, just as a dissector, or with harmonic technology. The cautery tip used as a dissector 'drags' the surrounding tissue from an IMA and may damage a fragile artery. Some surgeons do use low dose cautery to harvest IMAs. Harmonic technology uses a device whose tip vibrates longitudinally 55,500 times/second. The advantage of this technique compared with cautery use is the comparative lack of thermal spread. With electrocautery a coagulation depth of 1 mm is reached almost instantly, whereas it takes 3 seconds for an ultrasonically activated scalpel to achieve the same depth. IMAs are usually 1-2 mm in diameter, therefore use of cautery with power could potentially obliterate the lumen of an IMA, precluding its use as a bypass.

"SKELETONIZATION OF THE INTERNAL MAMMARY ARTERY WITH THE HARMONIC HOOK BLADE"

As results of the SYNTAX trial comparing PCI and CABG surgery for treatment of de novo triple vessel and/or left main coronary artery disease are published, CABG surgery is enjoying renewed attention. <u>However</u> the preferred mammary artery grafts are avoided for many reasons among which include: their finite length, fear of sternal infection, increased technical and time demands, perceived inadequate flow for a specific coronary bed <u>or</u> lack of belief in the evidence to date, supporting the use of multiple mammary grafting. Many of these issues can be overcome, with use of the skeletonization harvest technique of the mammary artery; skeletonization produces longer conduits [1] and decreases the risk of DSWI by preserving three of the 6 types of collateral blood supply to the sternum.[2]

However, skeletonization <u>also</u> has issues: the procedure is more time-consuming than the standard pedicle technique and there is fear of <u>damage</u> to the mammary when harvested directly without its cushion of veins, fascia and muscle.

Use of the harmonic hook blade to skeletonize the mammary artery addresses these two factors: it is quicker than skeletonization with the cautery tip used as a dissector and much less damaging to the mammary artery; this video shows the technique of skeletonization of the mammary artery with the harmonic hook blade.

After clearing the pleura from the undersurface of the chest wall, without entering the thoracic cavity if possible, and insertion of the retractor of choice to harvest the mammary artery, the first step is to incise the fascia overlying the mammary artery with Metzenbaum scissors. This incision is made in the crevice between the medial mammary vein and the mammary itself, so that there will be no "over-hang" of tissue precluding complete view of the mammary, along its entire length during the course of the dissection.

The safest start point is the caudal end of the mammary near the level of the xiphisternum, but the mammary may not always be visible here, hidden by muscle or fascia. The mammary is usually easily seen about 1/3 of the distance up from the caudal end and if one draws an imaginary horizontal line from where the mammary is seen, to a point at the end of the sternum, incising over this imaginary line will expose the mammary artery more than 90% of the time; inadvertent damage at this level is usually inconsequential.

Before use, the harmonic hook blade should be positioned for ideal length and orientation: for going from right to left as in harvest of the left mammary, the hook part faces opposite to the direction of harvest. The hook part of the blade is very sharp and inadvertent movements can cut branches or even the mammary before intended.

The mammary artery is first bared over a small area without power to identify its borders. One can hold the mammary by the adventitia with delicate forceps, such as ringed forceps without fear of damage. Then using the harmonic hook blade on low power of 2 (of a possible 5), one "paints" the mammary artery in a sweeping motion with the non-hook side of the harmonic. The mammary artery can actually be "touched" briefly with this "painting" technique without fear of thermal damage (Figure 1). As long as one does not "dwell" on a part of the mammary, the tissues adherent to the mammary will part "like the red sea" and quickly expose the branches. Thermal dispersion of the harmonic is much less than that of traditional electrocautery; significant heat damage does not begin until after 3 seconds of harmonic blade contact.[3]

When coming to a branch, it is easiest if one isolates the branch on either side, so as to expose the exact width of the branch one is dealing with. Then using the forceps prongs on either side of the branch, and simultaneously depressing the mammary so

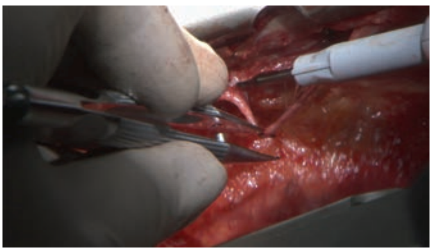

Figure 1. Harmonic hook blade separating (skeletonizing) IMA from chest wall

as to lengthen the branch, the blunt end of the harmonic hook is used to "sit on" the branch, at least 1 mm away from the mammary but at the same time not touching the mammary veins, until the branch turns white, or black and then breaks naturally with the gentle pressure of the blunt end of the hook. One quickly "learns" the tissues of a patient; sometimes only very gentle traction on the branch will result in tearing of the branch or an adventitial hematoma, but if one is still at the distal end of the mammary, no harm is usually done. I try to resist the temptation to go faster by using the hook to cut the branch when I feel it MUST be cooked, I am usually wrong and have to place a clip on an otherwise clipless mammary. This brings us to a question most frequently asked: do the harmonically sealed branches ever open up and make one take a patient back for bleeding? The answer is: in 8 years, for 815 patients with 1363 harmonically skeletonized mammary arteries - NO. If a branch is to bleed, it will have done so before the end of the case.

Additional advantages of using the harmonic to skeletonize the mammary artery render it relatively "clip-less". One can be absolutely sure that wherever one goes to perform a side-to-side anastomosis of a sequential graft, there will be a clip. Additionally, when the mammary artery dilates (when spasm from the handling is relieved), there are no "indents" in the mammary that one may see at a clip location.

Damage to a mammary artery when skeletonized with the harmonic rarely occurs (Figure 2): in this author's experience with the traditional skeletonization technique, an average of 1/20 arteries were damaged, whereas 0.4% representing 6 of 1363 (13 hundred 63) mammary arteries were damaged beyond the point of any use. It is the author's surmise that these mammaries were not actually damaged by the harmonic, but rather the harmonic does such a good job that these excessively fragile mammaries were taken down intact: their excessive fragility came to light, only when used to perform distal

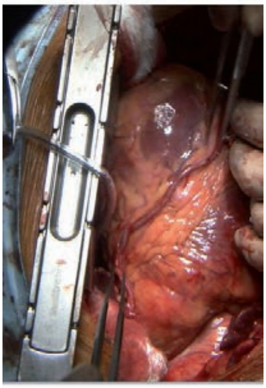

Figure 2. Harmonically skeletonized Left internal mammary artery graft to diagonal (left forceps tip) and left anterior descending artery (right forceps tip)

anastomoses. Possibly, the “dividing” of tissues by the harmonic rather than the “dragging” of tissues by the cautery tip contributes to decreased injury.

The “smoke” one sees in this video is in fact not smoke, but steam. This steam does not carry airborne particles that can be inhaled, as with smoke from traditional electrocautery- a very important factor when surgeons of other specialties operate on cancers.[4]

This technique of skeletonization with a little practice becomes quicker than the cautery tip method dissection – usually taking 15-18 minutes/mammary. If one has never skeletonized before, the learning curve reaches 80% comfort level after approximately 20 mammaries, if the technique of skeletonization is already known, probably 10 dissections will afford the same level of comfort.

There can be difficult dissections with the harmonic: in particular patients with a bleeding tendency due to Plavix or heparin on board, or fragile elderly tissues, mammary harvest can be tedious and frustrating. When bleeding occurs from a branch, the harmonic cannot “coagulate” this branch without damage to the mammary, necessitating the use of a clip.

Finally, when checking the mammary bed for bleeding at the end of the case, you will note the lack of “char”; in fact at times it will appear as if you were never there, the only sign is a missing mammary. Although not proven, this lack of burned, dead tissue, can only help toward minimization of infection.

To summarize, it is this author’s view: 1) Skeletonization of the mammary artery with the harmonic hook blade is a precise and efficient method to harvest the mammary artery. 2) Because fewer clips are needed, use of the harmonic facilitates arterial grafting and allows easier performance of sequential bypasses. And finally, skeletonization of the mammary artery with the harmonic hook blade rarely damages the artery and is the most atraumatic and refined way, to harvest this most important artery.

REFERENCES:

1. Gurevitch J, Kramer A, Locker C, Shapira I, Paz Y, Matsa M, Mohr R. Technical aspects of double-skeletonized internal mammary artery grafting. *Ann Thorac Surg* 2000;69:841-846
2. De Jesus RA, Acland RD. Anatomic study of the collateral blood supply of the sternum. *Ann Thorac Surg* 1995;59:163-8
3. McCarus SD Physiologic mechanism of the ultrasonically activated scalpel. *J Am Asso Gynecol Laparosc* 1996;3(4):601-8
4. Bigony L. Risks associated with exposure to surgical smoke plume: a review of the literature. *AORN J* 2007;86:1013-20

PART 7

SPECIAL TECHNIQUES IN THE USE OF ARTERIAL GRAFTING

Chapter 15

Sequential coronary bypass grafts

Kieser TM, FitzGibbon GM, Keon WJ

J Thorac Cardiovasc Surg 1986;91:767-772

Sequential coronary bypass grafts

Long-term follow-up

Sequential venous coronary bypass grafts have presented problems, mainly because of commonly reported differences between patency of side-to-side and end-to-side vein-coronary anastomoses. Better to define this, we have studied sequential anastomosis grafts done during a 13 year period. We concentrated specifically on 212 "double" grafts with 100% selective angiographic follow-up early, 90% at 1-year, and 44% at 5 years after operation. Four hundred twenty-four control single grafts were studied similarly. We found that patency rates of side-to-side anastomoses were much better than those of end-to-side anastomoses, whether of sequential or control single grafts. Considering specifically diagonal coronary artery–anterior descending coronary artery sequential grafts, the combined patency of all sequential anastomoses theoretically exceeds that of a comparable number of single grafts at all times of study, but the differences are small. Furthermore, there is definite danger of preserving proximal and perhaps limited bypass runoff at the cost of losing distal and perhaps more important myocardial perfusion. On balance, we believe that single vein grafts are to be preferred over sequential grafts unless shortage of conduit material or local aortic wall conditions dictate otherwise.

Teresa M. Kieser, M.D., Gerald M. FitzGibbon, L.R.C.P.&S.(Ireland), F.R.C.P.C., and Wilbert J. Keon, M.D., F.R.C.S.C., *Ottawa, Ontario, Canada*

Sequential venous coronary bypass grafts with distal outlets to coronary arteries supplying independently compromised myocardial perfusion territories were first described by Flemma, Johnson, and Lepley[1] and by Bartley, Bigelow, and Page.[2] Such conduits have also been called "snake,"[3,4] "bridge,"[5] "combination,"[6] "jump,"[7,8] and "circular"[9] grafts. Recently, McBride and Barner[10] and Tector and associates[11] have advocated using the internal mammary artery for sequential coronary bypass grafting. Sequential grafting has been controversial. A major problem has been the difference between patency rates of end-to-side (ESAs) and side-to-side anastomoses (SSAs) described in earlier years by Sewell and Sewell,[3,4] Grondin and Limet,[12] and FitzGibbon, Burton, and Leach.[13] We have now further studied our data, better to quantitate this difference by examining the long-term fate of sequential venous coronary bypass grafts.

From the Cardio-Pulmonary Unit, National Defence Medical Centre, and the University of Ottawa Heart Institute, Ottawa Civic Hospital, Ottawa, Ontario, Canada.

Received for publication April 23, 1985.

Accepted for publication June 4, 1985.

Address for reprints: Dr. G. M. FitzGibbon, National Defence Medical Centre, Ottawa, Ontario, Canada K1A OK6.

Methods

Total experience with coronary bypass in patients studied at and referred from the National Defence Medical Centre, Ottawa, to the University of Ottawa Heart Institute, Ottawa Civic Hospital, comprised 1,161 operations in 1,057 patients between Nov. 11, 1971, and Nov. 10, 1984. In 3,868 coronary bypass grafts, most of them venous conduits, 461 distal anastomoses (11.9%) arose from 224 veins. Eleven of these vein grafts led to three distal anastomoses and one to four. We present primarily our experience with the largest number of sequential grafts of the "double" variety, that is, one SSA and one ESA. A note on the 12 remaining grafts will be made separately. The 212 sequential "double" trunks were placed in 189 patients at 190 operations, 22 patients having two such sequential grafts per operation and one of these having two placed in each of two operations. Table I lists operations by year. The distribution of double sequential grafts by arteries involved is given in Table II. The largest number, 124, of these grafts bridged from a diagonal coronary artery to the anterior descending vessel. No patient having a sequential graft died during the operation hospital admission.

Four surgeons performed these operations but one fashioned 109 of the 212 grafts and another, 72. Femoral artery cannulation was used for early opera-

Table I. *Number of "double" sequential grafts by year*

Year	No.
1973	1
1974	32
1975	69
1976	39
1977	32
1978	16
1979	9
1980	3
1981	1
1982	2
1983	3
1984	5

Table II. *Coronary arteries grafted*

Arteries	No.
D-AD	124
M-M	28
R-R	22
AD-AD	19
D-D	13
M-D	2
D-M	2
M-AD	1
M-R	1
Total	212

Legend: D, Diagonal coronary artery. AD, Anterior descending coronary artery. M, Marginal coronary artery (branch of margino-circumflex trunk). R, Right coronary artery. First artery listed was grafted side to side.

tions and aortic cannulation for late ones. Direct left ventricular vents were placed early in the series. In later cases cold cardioplegia was added to anoxic cardiac arrest. Running sutures were used for proximal and distal anastomoses. Optical magnification was not used. The SSAs were fashioned with the most convenient lie for artery and vein and were not specifically of the "diamond" type described by Grow and Brantigan.[14]

Follow-up angiograms were made early (2 to 3 weeks), approximately 1 year (mean 1.01 years), and approximately 5 years (mean 5.19 years) after operation. The temporally closest "single" coronary bypass graft made by the same surgeon to an anatomically similar artery was assigned as a control for each anastomosis. Thus two controls, each with an artery-specific ESA, were selected for each double sequential graft. Early angiography was done in 100% of both the sequential and the control single grafts, in 90% of the sequential and control grafts at 1 year, and in 44% of the sequential and 51% of the control grafts at 5 years. These numbers represent percentages of grafts studied in surviving patients. All grafts were selectively opacified in at least four planes. Artery size was measured from angiograms by digital calipers (Mitutoyo 500). Statistical analyses were done by the chi square test.

Table III. *Patency of SSAs and ESAs of 212 sequential grafts*

Time	SSA	%	ESA	%	p Value
Early	202/212	95	181/212	85	<0.0005
1 yr	168/188	89	146/188	78	<0.001
5 yr	77/91	85	60/91	66	<0.005

Legend: SSA, Side-to-side anastomosis. ESA, End-to-side anastomosis.

Table IV. *Patency of 212 SSAs and 424 control single grafts*

Time	SSA	%	Control	%	p Value
Early	202/212	95	375/424	88	<0.005
1 yr	168/188	89	305/379	80	<0.005
5 yr	77/91	85	162/214	76	<0.05

Legend: SSA, Side-to-side anastomosis.

Results

Seven of 212 sequential grafts were totally occluded early, 17 of 188 at 1 year, and 14 of 91 grafts at 5 years after operation.

Tables III, IV, and V list the grading and patency rates of 212 double sequential grafts and of 424 control single grafts. SSAs clearly have the edge over ESAs. There were significant differences in patency between all SSAs and all ESAs early, 1 year, and 5 years after operation. Furthermore, significant differences in patency between all SSAs and all control single graft anastomoses were evident early, at 1 year, and at 5 years. The differences between patency rates of all ESAs and all control single graft anastomoses were not significantly early or at 1 year but were just significant in favor of single grafts at 5 years. There were no significant differences, early or at 1 year, between ESAs of control single grafts and ESAs of *all* double sequential grafts terminating in the anterior descending artery, which might be considered optimal for grafting. However, patency of control single grafts was significantly better at a 5 years ($p < 0.025$).

The largest group of sequential grafts involved SSAs with diagonal vessels and ESAs with anterior descending arteries. Considering these grafts only, the early patency of SSAs of diagonal vessels was just significantly better than that of SSAs of all other double sequential grafts; by contrast, there were no significant differences

Table V. *Patency of 212 ESAs and 424 control single grafts*

Time	ESA	%	Control	%	p Value
Early	181/212	85	375/424	88	NS
1 yr	146/188	78	305/379	80	NS
5 yr	60/91	66	162/214	76	<0.05

Legend: ESA, End-to-side anastomosis. NS, Not significant.

Table VI. *Patency of diagonal–anterior descending sequential and of all other sequential grafts*

Time	SSA D-AD	%	SSA others	%	p Value
Early	121/124	98	81/88	92	<0.05
1 yr	103/114	90	65/74	88	NS
5 yr	47/54	87	30/37	81	NS
Time	*ESA D-AD*	*%*	*ESA others*	*%*	*p Value*
Early	111/124	90	70/88	80	<0.025
1 yr	95/114	83	51/74	69	<0.01
5 yr	40/54	74	20/37	54	0.02

Legend: SSA, Side-to-side anastomosis. ESA, End-to-side anastomosis. AD, Anterior descending coronary artery. D, Diagonal coronary artery. NS, Not significant.

at 1 and 5 years. The patency of ESAs of diagonal–anterior descending artery grafts was significantly better than that of ESAs of all other sequential grafts early, at 1 year, and at 5 years (Table VI). When diagonal artery single control grafts were used for SSAs of these diagonal–anterior descending sequential grafts, the patency of the SSAs was significantly better early, at 1 year, and at 5 years. However, there was no significant difference between patency of control single anterior descending ESAs and sequential diagonal–anterior descending ESAs early, at 1 year, or at 5 years (Table VII).

Data have been analyzed for patency of SSA and ESA components of sequential grafts and of control single grafts for the surgeons undertaking the procedures. There were no significant patency differences with respect to specific anastomoses of sequential or control single grafts between the two surgeons who fashioned 85% of the "double" sequential grafts. Numbers for the three surgeons doing the other 15% of the total operations were too small for proper statistical analysis.

In an effort to determine whether the diameter of the distal grafted artery in relation to the diameter of the proximal was a major factor in determining ESA occlusion, as has been suggested by some authors,[7, 15] we measured the sizes of arteries grafted with SSAs and ESAs, which had patent grafts in the early study. We found that the distal artery was usually a little larger than the proximal, and we could determine no statistically significant differences in vessel size among those having ESAs that were patent early or became occluded at 1 or at 5 years.

As noted earlier, we did sequential coronary bypass grafts involving more than two distal anastomoses in 12 patients, three anastomoses in 11, and four in a single patient. The quadruple bypass trunk was found occluded at the early examination. Controls were selected as for the double sequential grafts. With 100% early, 91% 1 year, and 44% 5 year angiographic follow-up, 21 of 22 SSAs and nine of 11 ESAs were patent early, 15 of 20 SSAs and six of 10 ESAs at 1 year, and four of eight

Table VII. *Patency of diagonal–anterior descending sequential and of control single grafts*

Time	SSA D-AD	%	Control	%	p Value
Early	121/124	98	135/154	88	<0.001
1 yr	103/114	90	108/137	79	<0.01
5 yr	47/54	87	51/77	66	<0.005
Time	*ESA D-AD*	*%*	*Control*	*%*	*p Value*
Early	111/124	90	146/163	90	NS
1 yr	95/114	83	124/148	84	NS
5 yr	40/54	74	76/90	84	NS

Legend: AD, Anterior descending coronary artery. D, Diagonal coronary artery. NS, Not significant. Note: There were more diagonal and anterior descending grafts than there were diagonal–anterior descending sequential grafts.

SSAs and two of four ESAs at 5 years. Ten of 11 control grafts were patent early and at 1 year, and four of five were patent at 5 years. These numbers are too small to determine statistical significance, although the superiority of "single" grafts is suggested.

Discussion

Convinced judgments based on p values are not always easy to make. It is possible, however, to make a simple synthesis of the clear superiority of SSAs over ESAs and the questionable superiority of control single ESAs over sequential ESAs. Tables III to VII show patency rates for sequential and control single grafts for both SSAs and ESAs. Although the angiographic examination rate was only approximately 50% in the sequential and control single groups at 5 years, it was 90% at 1 year and 100% early.

We calculated the total number of SSAs and ESAs of sequential grafts that would be patent early, at 1 year, and at 5 years after operation by the known patency rates and the total numbers involved. Comparing these with similar numbers derived for patency rates of control single grafts and total numbers at similar times, we were able to determine, all other things being equal, whether there would have been more distal anastomoses open if single ESA grafts had been used instead of double-outlet SSA/ESA sequential grafts. Making this calculation for all 424 controls and all 212 sequential grafts (424 distal anastomoses), we found the sequential grafts would have a patency advantage of eight (1.9%) more grafts open early, 14 (3.3%) more open at 1 year, and two fewer sequential anastomoses than controls open at 5 years. However, if one applies similar calculations to the 124 diagonal–anterior descending sequential grafts that form the largest group, then the use of sequential rather than single grafts appears more advantageous. Early after operation, 11 (4.4%) more sequential than single graft anastomoses might have been patent. At 1 and similarly at 5 years after operation the figure is 13 (5.2%) grafts. In these diagonal–anterior descending grafts, the SSAs are clearly superior to the controls, with calculated excesses of patent anastomoses of 12, 14, and 26, early, at 1 year, and at 5 years after operation, respectively. However, the ESAs of these same diagonal–anterior descending grafts would be patent *less* often than the ESAs of control grafts to the anterior descending vessels; one less graft would be patent early and at 1 year, and 13 fewer grafts would be patent at 5 years after operation. Gains in one area are opposed by losses in another. Overall, nevertheless, there is a very small advantage in favor of total combined anastomotic patency of sequential grafts.

Sewell[3] reported 93% SSA and 87% ESA patency rates early after multiple sequential coronary bypass operations ($p < 0.05$) and, 2 years later,[4] 98% SSA and 88% ESA early patency rates. This difference did not deter him from doing "snake" grafts, because "improvement to 94% patency in our more recent single-graft procedures probably is the result of patient selection, since single grafts now are done only in patients who have large runoff beds distal to a single lesion." Sewell[16] still favored this type of graft 3 years later in 1979 but reported no new patency figures.

Cheanvechai and associates[5] described 250 patients having "bridge" grafts between two coronary branches, mostly on the left side. One hundred ten patients (44%) had angiography from 1 month to 2 years postoperatively; both anastomoses were patent in 83.6%, one was patent in 5.4%, and both were occluded in 10.9%; there was no breakdown by type of anastomosis. Bigelow and associates[17] reported postoperative angiography in 54 of 122 patients having multiple sequential coronary bypass grafts. One hundred four (72%) of 144 anastomoses were patent, but there was no discrimination between SSAs and ESAs. The late patency rate was 70% at least 2 years after operation. These patency rates were significantly better than for individual vein grafts. Seven of the 122 patients had all graft-coronary anastomoses occluded, this being discovered in three instances at autopsy. The authors nevertheless endorsed the sequential coronary bypass operation as increasing bypass patency and decreasing operating time.

Grondin and Limet[12] reported multiple bypass grafting in 140 patients; 40 were studied at 2 weeks and 27 of these at 1 year after operation. Thirty-nine of the grafts studied early had one SSA and one ESA, patency of the former being 97% and of the latter 82%. Twenty-five patients studied at 1 year had a single SSA in addition to the ESA. One of the ESAs had occluded but none of the SSAs. There was a higher occlusion rate in grafts having more than one SSA, but the numbers are too small for significance. One of 44 vein grafts studied early was totally occluded. The authors stated: "The fact that nearly 75% (11/15) of all occlusions occurred in the segment of graft located between the SSA and the distal ESA suggests a mechanical or a technical factor." This is interesting because Hutchins and Bulkley[8] indicated in autopsy studies that "jump" grafts "were susceptible to rolling or kinking of the graft, apparently as a result of torsion from placement of the side-to-side anastomosis"; they noted three examples of occlusion owing to this cause in eight grafts with two distal anastomoses each.

Grondin and associates[9] also described the "circular vein graft" with four or five coronary anastomoses in 22 patients. All grafts were studied by angiography early after operation, one at 3½ months. This last patient had occlusion of a graft beyond the first anastomosis but involving four more distal anastomoses. All other patients had all anastomoses patent (90/94, 95.7%). The terminal anastomosis was with the anterior descending coronary artery in all 22 cases and a diagonal branch was grafted in 19. The authors believed that the high early patency rate in their patients was attributable to high graft flow, termination of the graft in the anterior descending artery, use of the "diamond anastomosis,"[4] and "nearly equidistant anchoring at the site of the multiple anastomoses giving the graft a smooth, even contour."

Moreno-Cabral, Mamiya, and Dang[18] reported multiple coronary bypass grafting in 206 patients but had angiographic follow-up in only four, with complete graft closure in two. Yeh, Heidary, and Shelton[19] reported on "425 patients receiving Y-grafts, sequential grafts, or a combination of the two" but reported only 28 SSAs, of which 89% were patent at an unspecified time after operation. The report of Roth and co-workers[6] is unique: 100% of 25 ESAs were patent compared with only 76% of "continuity" graft SSAs ($p < 0.02$) in a study of factors influencing bypass graft patency. Eschenbruch and associates[7] described 243 patients having coronary bypass by the "jump-graft" technique. Patency of 361 SSAs and ESAs at angiographic follow-up was 87.8% compared with 82.2% for 248 single control grafts. Unfortunately, there was no breakdown by type of distal anastomosis. The authors emphasized that the "sequence of the jump-graft anastomoses should always have a major flow capacity in the most distal position."

Meurala and colleagues[20] reported at least one postoperative angiographic examination in 36 patients having sequential venous bypass grafting. Patency rate of SSAs early and late was 100%; that of ESAs was 93.9% early and 88.9% late. Patency rates for single control grafts were 86.9% early and 80.0% late. These authors measured blood flow in some of the grafts by a cineangiographic technique. Graft flow between the aorta and the SSA was higher than in SSA/ESA segments and also higher than flow in control single grafts. In all instances blood flow decreased between early and late examinations, but it decreased most rapidly in the SSA/ESA segments. From the same center, Harjola, Meurala, and Jarvinen,[21] measuring graft flow at operation, observed that, although this was higher in the proximal portion of the sequential vein trunk than in comparable single grafts, the total flow per heart was higher with multiple single rather than sequential grafts. In 36 sequential bypass and 40 single graft operations, they found no difference in total operating or cardiopulmonary bypass times, but there were significant differences, favoring single bypass grafting, in total ischemic cross-clamp time and in cross-clamp time per anastomosis.

McNamara and associates[22] measured blood flow in single and in double and triple sequential grafts. They found no difference in the total flow per graft in each of the categories, with lesser flows per anastomosis as the total number of these was increased. However, Minale and co-workers[23] demonstrated about a 25% greater myocardial flow in patients having two single grafts to diagonal and anterior descending arteries than in 14 with diagonal–anterior descending sequential grafts. The difference was attributable solely to the difference in anterior descending rather than diagonal flow. The authors believed that the anterior descending artery was more at risk with the diagonal–anterior descending sequential graft. O'Neill and associates[15] measured coronary blood flow at operation in 106 single and 35 double sequential grafts and found that flow velocity was higher in proximal segments of sequential grafts than in single grafts. They postulated that this phenomenon was responsible for the differences between SSA and ESA patency in sequential grafts, possibly by producing a greater shear stress at the vessel wall and decreasing the tendency for intimal proliferation. These authors recommended that the larger of two coronary arteries in a double sequential graft be used for the ESA. Minale and colleagues,[23] although cognizant of this study, concluded in 1984 that increasing the patency rate of an SSA with a small coronary artery and jeopardizing the larger vessel used for the ESA might not be wise. They recommended that since vessels of 1.5 mm diameter are suitable for single bypass grafting, the sequential coronary bypass technique should be abandoned for general use except in the case of insufficient vein or a very short or poor-quality ascending aorta.

Conclusion

Sequential venous coronary bypass grafting is perhaps somewhat less controversial than it previously was. In our follow-up study we have demonstrated a slight advantage in long-term patency for combined anastomoses of double sequential over single grafts, but only when total anastomoses are taken into account and when diagonal–anterior descending grafts are considered separately. Unquestionably the SSA of a double graft has a much better patency rate than an ESA. On the other hand, we have shown that control single grafts have a better 5 year patency rate than ESAs of sequential grafts. Our data for triple and quadruple sequential grafts suggest better patency of single rather than sequential grafts. Some of the data thus appear to favor the sequential graft, but only slightly and not in the long term. Furthermore, we know that ESAs are usually made with larger coronary arteries than SSAs; their loss thus jeopardizes more myocardium. Consequently, we recommend that a single venous bypass graft to each coronary artery requiring grafting is to be preferred unless shortage of venous conduit or local aortic conditions dictate otherwise.

We are grateful to Mrs. A. Brach for assistance with data collection.

REFERENCES

1 Flemma RJ, Johnson WD, Lepley D Jr: Triple aortocoronary vein bypass as treatment for coronary insufficiency. Arch Surg **103**:82-83, 1971

2 Bartley TD, Bigelow JC, Page US: Aortocoronary bypass grafting with multiple sequential anastomoses to a single vein. Arch Surg **105**:915-917, 1972

3 Sewell WH: Improved coronary vein graft patency rates with side-to-side anastomoses. Ann Thorac Surg **17**:538-544, 1974

4 Sewell WH, Sewell KV: Technique for the coronary snake graft operation. Ann Thorac Surg **22**:58-65, 1976

5 Cheanvechai C, Groves LK, Surakiatchanukul S, Tanaka N, Effler DB, Shirey EK, Sones FM Jr: Bridge saphenous vein graft. J Thorac Cardiovasc Surg **70**:63-68, 1975

6 Roth JA, Cukingnan RA, Brown BG, Gocka E, Carey JS: Factors influencing patency of saphenous vein grafts. Ann Thorac Surg **28**:176-181, 1979

7 Eschenbruch EM, Pabst F, Tollenaere P, Roskamm H, Schmuziger M: The significance of coronary topography for operative technique and tactics in multiple myocardial revascularization with jump-grafts. Thorac Cardiovasc Surg **29**:206-211, 1981

8 Hutchins GM, Bulkley BH: Mechanisms of occlusion of saphenous vein–coronary artery "jump" grafts. J Thorac Cardiovasc Surg **73**:660-667, 1977

9 Grondin CM, Vouché P, Bourassa MG, Lespérance J, Bouvier M, Campeau L: Optimal patency rates obtained in coronary artery grafting with circular vein grafts. J Thorac Cardiovasc Surg **75**:161-166, 1978

10 McBride LR, Barner HB: The left internal mammary artery as a sequential graft to the left anterior descending system. J Thorac Cardiovasc Surg **86**:703-705, 1983

11 Tector AJ, Schmahl TM, Canino VR, Kallies JR, Sanfilippo D: The role of the sequential internal mammary artery graft in coronary surgery. Circulation **70**:Suppl 1:222-225, 1984

12 Grondin CM, Limet R: Sequential anastomoses in coronary artery grafting. Technical aspects and early and late angiographic results. Ann Thorac Surg **23**:1-8, 1977

13 FitzGibbon GM, Burton JR, Leach AJ: Coronary bypass graft fate. Angiographic grading of 1400 consecutive grafts early after operation and of 1132 after one year. Circulation **57**:1070-1074, 1978

14 Grow JB, Brantigan CO: The diamond anastomosis. A technique for creating a right-angle side-to-side vascular anastomosis. J Thorac Cardiovasc Surg **69**:188-189, 1975

15 O'Neill MJ Jr, Wolf PD, O'Neill TK, Montesano RM, Waldhausen JA: A rationale for the use of sequential coronary artery bypass grafts. J Thorac Cardiovasc Surg **81**:686-690, 1981

16 Sewell WH: Should we do Y- and sequential grafts for coronary bypass? Ann Thorac Surg **27**:397-398, 1979

17 Bigelow JC, Bartley TD, Page US, Krause AH: Long-term follow-up of sequential aortocoronary venous grafts. Ann Thorac Surg **22**:507-513, 1976

18 Moreno-Cabral RJ, Mamiya RT, Dang CR: Multiple coronary artery bypass using sequential technic. Am J Surg **134**:64-68, 1977

19 Yeh TJ, Heidary D, Shelton L: Y-grafts and sequential grafts in coronary bypass surgery. A critical evaluation of patency rates. Ann Thorac Surg **27**:409-412, 1979

20 Meurala H, Valle M, Hekali P, Somer K, Frick MH, Harjola PT: Patency of sequential versus single vein grafts in coronary bypass surgery. Thorac Cardiovasc Surg **30**:147-151, 1982

21 Harjola PT, Meurala H, Jarvinen A: Sequential versus single aortocoronary saphenous vein bypass techniques. Ann Chir Gynaecol 70:191-196, 1981

22 McNamara JJ, Bjerke HS, Chung GKT, Dang CR: Blood flow in sequential vein grafts. Circulation **60**:Suppl 1:33-38, 1979

23 Minale C, Bourg NP, Bardos P, Messmer BJ: Flow characteristics in single and sequential aorto-coronary by-pass grafts. J Cardiovasc Surg **25**:12-15, 1984

Chapter 16

Iatrogenic Aortic Root and Left Main Dissection in CABG Surgery: An Unconventional Fix

Kieser TM, Spence FP, Kowalewski R

CTSNet Video published on Nov 3 2014 Website:
http://www.ctsnet.org/article/iatrogenic-aortic-root-and-left-main-dissection-cabg-surgery-unconventional-fix

This video was published on CTSNet on November 3 2014 and was viewed 1500 times in the first week it was aired, compared with the average of 1600 hits/month on CTSNet. It has also been nominated by the CTSNet Co-Editors Professors Joel Dunning and Mark Ferguson, as a 'Best of CTSNet' submission, for potential inclusion in *Interactive CardioVascular and Thoracic Surgery* because it earned 2,244 pageviews in its first 30 days of publication. Videos published in ICVTS in this way obtain MEDLINE indexing and a second avenue for promotion and distribution.

This is a video of a potentially lethal complication of coronary surgery which had a successful outcome due to the use of a novel surgical technique to escape disaster for a 74 year old patient. The complication was a dissection created by a bypass to a diffusely diseased marginal coronary artery which went retrograde from the marginal artery to include the aortic root and then went anterograde to include the entire LAD system (Figure 1). Transesophageal echocardiography before trying to come off pump showed an akinetic left ventricle. The dissection was reversed by pinning the dissection at a second site with another vein bypass on the mid LAD artery, but an oval of calcified coronary artery wall (including all three layers – intima, media and adventitia) had to be excised to do this (Figure 2). This patient is still alive at age 86 years of age.

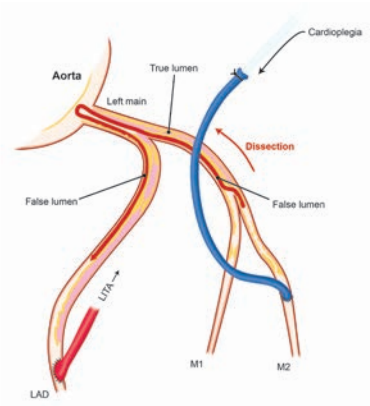

Figure 1. Suspected mechanism of dissection. The force from the cardioplegia flowing in the vein graft into the diseased coronary artery created a dissection plane, went retrograde to the left main, involving the aortic root and continued down the LAD to the apex of the heart (site of LIMA graft).

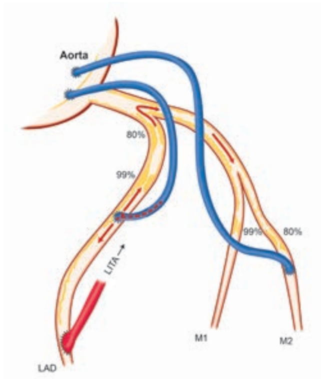

Figure 2. Final result

PART 8

GENERAL DISCUSSION AND CONCLUSIONS

SUMMARY

EPILOGUE

Chapter 17

General Discussion and Conclusions

Hunter S. Thompson, an American journalist and author (1937-2005) said: 'Anything worth doing is worth doing well'. In the case of coronary artery bypass grafting, the debatable point is: What is the definition of 'doing well?' Is it successfully getting the patient off the operating table alive, out of hospital alive, or is it giving them an operation that affords best long-term results? The mindset of doing *'just enough to afford patients operative survival'* possibly needs revamping to*: 'affording patients long-term survival or longest possible efficacy of that procedure'.*

Although the evidence of BIMA grafting being beneficial for increased patient longevity and improving quality of life is derived mainly from retrospective and objective studies, the volume of these studies is substantial. All too often human nature is such that rather than make a change, reasons are sought as to why *not* make that change.

Use of only one IMA and the rest of bypasses with saphenous vein is a comfortable operation and has been the 'norm' since since Cosgrove in 1985 and Loop in 1986 reported on the benefit of one IMA on patient longevity and quality of life. Is it time to move on? At the 83th annual meeting of the American Association of Thoracic Surgery in Boston 2003, one of the sessions was given by a cardiologist on drug eluting stents, which were just being introduced. Cardiac surgeons were worried about what seemed to be an inevitable decline of a principal part of their livelihood - the CABG procedure. Vividly remembered is Dr. Bruce Lytle of the Cleveland Clinic saying to the audience "Gentlemen, did you think you would be doing the same operation for 100 years?!" Is it not time to make an improvement on this operation, now 30 years later?

It is quite possible that surgeons indirectly have been responsible for the development of stents, drug-eluting stents (DES) in particular. Saphenous vein disease is very difficult to treat. As well, most surgeons prefer not to re-operate on patients with a patent mammary artery, for 2 other systems to which vein grafts have occluded. DES stents were hoped to be able to help to address vein graft disease, however this hope has not panned out. [1]

So if surgeons continue in the same vein (so to speak) of one IMA and rest of bypasses with saphenous vein, an opportunity will be missed to help thousands of coronary artery disease patients. As such, the stage is set for the revival of the CABG procedure.

Why is BIMA grafting not performed more often?

1. Surgeons do not believe the evidence to date.
2. More technically demanding.
3. More time consuming.
4. Fear of Deep Sternal Wound Infection (DSWI).
5. Little benefit beyond a certain age.
6. Right IMA won't reach far enough to branches of right coronary artery (RCA) or circumflex (Cx).

7. IMA flow thought to be not enough for certain situations: poor LV function, mis-match with native coronary arteries (i.e. small IMA on a coronary with large area of distribution) or spasm with inotropic agents.
8. Inertia.

RESPONSES TO THE ABOVE STATEMENTS ARE ADDRESSED IN THE CHAPTERS OF THIS BOOK:

1. Surgeons do not believe the evidence to date.

'Those who do not accept the truth do not accept the testament of the truth either. They go looking for its defects in order to justify their rejection of it with their conscience. Therefore always be careful to bear witness to God through a life that is blameless.' [2] There is much evidence to date: when a literature search of the key words of 'bilateral internal mammary artery and survival' is performed in PubMed, (http://www.ncbi.nlm.nih.gov/pubmed/?term=bilateral+internal+mammary+artery+and+survival 15197487) 349 articles appear which date from 1973 to 2015. However, all of this work is retrospective and/or observational in nature. There is only one randomized clinical trial by Taggart et al [3], in which patients were randomized to receive either one or two internal mammary arteries. The eagerly awaited 10 year results of this most important trial are due in December 2017.

2. More technically demanding.

It is well known that use of two internal mammary arteries is more technically demanding. Other factors also have increased the technical complexity of the CABG procedure over time: pre-morbid characteristics of patients have increased, and CAD is more diffuse especially in diabetic patients. Whereas use of the left IMA, performed in 90% of CABG procedures is mastered by most cardiac surgeons easily, use of the 2nd (right) IMA is not. Possibly the left-sided location of both the heart and the one IMA used to bypass the left anterior descending artery (the most important coronary artery) may have something to do with this. However there are 'tips' and tricks' on how to achieve bilateral mammary artery grafting safely and with relative ease. **Chapters 10** (Ways to reduce the incidence of deep sternal wound infection), **Chapters 13 and 14** (How to skeletonize the IMA with use of harmonic technology) are studies to help in this regard. But importantly, there is no substitute for practice: as Malcom Gladwell describes in his book 'Outliers': *'In fact, researchers have settled on what they believe is the magic number for true expertise: ten thousand hours.'* i.e. If you do anything for 10,000 hours, you get good at it. [4] '*Il faut le faire.*' - One just has to do it.

When a procedure is more technically demanding, the success of the procedure may be hindered due to the increased complexity. Up until recent years the CABG procedure was the only operation/procedure on arteries that did not have an 'intra-operative verification' of the procedure performed. For example as in the case of PCI, a cardiologist need only inject more radiopaque dye after a coronary stent is deployed to verify that there is relief of the coronary obstruction. **Chapter 8** is a study of the use and efficacy of one such intra-operative 'safety-check'- the use of transit-time flow measurement. This study has been appreciated internationally in that it has been quoted in three Guidelines. [5-7]

One method to maximize the finite length of arterial grafts, is to perform sequential grafting -the use of one arterial conduit for multiple coronary arteries. Because of the finite length of arterial conduits, knowledge of sequential grafting is essential. However a danger of sequential grafting is the loss of the second anastomosis in preference to the first, which is outlined in **Chapter 15** – a study of sequential vein grafts. This is a useful concept to be aware of when doing sequential arterial grafting.

Another aspect of arterial grafting was studied in **Chapter 11**. If one of the benefits of arterial grafting is the longevity of the arterial graft and one of the drawbacks of venous grafting is the early (venous) demise, possibly the accepted axiom that patients with incomplete revascularization do not fare as well may be in question. **Chapter 11** explored this concept – if a patient undergoing CABG has all arterial conduits, in the majority of patients we found that incomplete revascularization (with one of three territories not revascularized) did not reduce survival at midterm. The concept that incomplete revascularization being responsible for reduced mid or long-term survival, came from studies of patients with predominantly vein grafts (only one IMA). Given that vein grafts have reduced survival compared with arterial grafts, a patient with only 2 of 3 territories revascularized with one IMA and one vein graft would then progress to double vessel disease from single vessel disease if/when the vein graft would fail. As is known from many studies the occlusion rate of saphenous vein grafts is approximately 12% at early post op (3 weeks) and 25% at 1 year and 60 % at 12.5 years. It may be therefore reasonably concluded that patients with incomplete revascularization by way of one missed territory might become even more 'incompletely revascularized' with 2 missed territories when a saphenous vein graft would fail as soon as 3 weeks in 12% and 25% in 1 year. Two of three territories without blood supply would undoubtedly affect survival. Notwithstanding, complete revascularization may be more challenging in total arterial CABG – a concept explored in **Chapter 12**.

Chapter 16 outlines a novel technique of how to deal with arteries that have significant proximal stenosis, but are circumferentially calcified for most of their lengths but still have a good lumen.

3. More time consuming.

Use of a second IMA takes approximately an extra 20 minutes – principally the harvest time. However what is an extra 20 minutes to use the extra IMA, for maybe an extra 20 trouble free years for a patient? This is discussed in **Chapter 6**. In addition **Chapters 13**

and 14 describe an IMA harvest technique with harmonic technology that is not only quicker than the traditional method, but also safe for the patient and the IMA. The usual way to perform the skeletonization harvest technique of an IMA is by using the cautery tip (without power) as a dissector. However this technique takes often more than twice as long as the 'pedicle' technique. One of the deterrents to use of bilateral IMA grafting is the extra time taken for the operation: use of the harmonic scalpel to skeletonize as described in **Chapters 13** (manuscript format) and **Chapter 14** (video format) not only expedites IMA harvest, and damages the IMA infrequently.

4. Fear of Deep Sternal Wound Infection and Sternal Dehiscence

The internal mammary arteries are a major source of blood supply to the sternum. One real fear of bilateral IMA usage is devascularization of the sternum predisposing the patient to sternal instability/dehiscence and/or deep sternal wound infection (DSWI). **Chapter 10** outlines 12 sequentially added 'layers of protection' in the form of wound infection prevention techniques to reduce the incidence of DSWI to near zero all the while maintaining a high level of bilateral IMA grafting (73% in this group) in all patients. This manuscript was the subject of an editorial in the same issue of the Journal of Cardiovascular and Thoracic Surgery. Paul Kurlansky, author of this editorial commented: *'…the authors chose to chronicle their efforts to eliminate DSWI in the face of a dedicated and unusual commitment to bilateral internal thoracic artery (BITA) grafting, even in diabetic patients. …Kieser and colleagues were not satisfied to merely accept the risks of DSWI, but rather embarked on a journey to eliminate them, without compromising the integrity of the revascularization offered to the patient.'* The closing sentences of this editorial state: *'The true message of Kieser and colleagues – aside from the definitively actionable information related to minimizing the risk of DSWI while maintaining a commitment to arterial revascularization – is that it is ultimately the dedication to clinical improvement through rigorous self-examination and evidence-based programmatic adaptation that will drive surgical quality. Both her professional colleagues and her patients are the true beneficiaries'*. [8]

Another way to prevent sternal dehiscence is discussed in **Chapter 9**. This study describes a way to solidify the sternum in very short time (24 hours) with the use of biological glue.

5. No benefit beyond a certain age.

The 2014 ESC/ESCTS Guidelines on myocardial revascularization are the first guidelines to accumulate evidence pertaining to a possible age cut-off up to which use of bilateral internal mammary artery can be of benefit. One of the papers quoted in these guidelines is included in this thesis – **Chapter 7** on 'Outcomes associated with bilateral internal thoracic artery grafting: the importance of age'. From this and other papers, BIMA grafting is thought to be effective for increased survival up to age 70 years. If BIMA grafting was only performed in this ≤ 70 age group, more than 50% of patients would receive BIMA grafting – 10 times that which is performed now in North America.

6. Right IMA won't reach far enough to branches of RCA or Cx

One of the difficulties of using only arterial conduits for coronary surgery is their finite length, especially in the case of the mammary arteries. One cannot just 'go and get more artery' as one can do with saphenous vein. (The legs of patients are quite a bit longer than their sterna.) One way to maximize the length of IMAs is to skeletonize the artery. Most cardiac surgeons take a 'pedicle' of tissue with the IMA harvest believing that this technique has less risk of damage to the IMA. Although this may be true, the 'pedicled' IMA is quite a bit shorter than the 'skeletonized' IMA and is not as easy to use to reach far corners of the heart and especially harder to use for multiple grafts as in sequential grafting. Skeletonization of the IMA maximizes the use of IMA grafts and there is always the possibility of attaching the ITA directly to the aorta, to the LITA or another conduit. **Chapters 13 and 14** outline/demonstrate the skeletonization method of the IMA with harmonic technology.

7. IMA flow thought to be not enough for certain situations: poor LV function, mismatch with native coronary arteries (i.e. small IMA on a coronary with large area of distribution), or spasm with inotropic agents.

This is a subjective area and there is not much research on this topic, only some papers with IMA grafting on poor LV's, small ITA etc. The author has rarely seen "IMA-Coronary artery mismatch" in a series of 3333 arterial grafts (77% BIMA) in 1125 patients since 2003. A simple remedy to this problem, if it occurs, is use of the intra-aortic balloon pump. Though not needed often, (IABP in 2% of 1125 CABG) it may help release the spasm not only of the conduit but of the coronary bed. When mismatch is suspected, graft patency should first be verified. It is more likely that a suboptimal graft anastomosis or damaged conduit may be responsible for the inadequate graft flow; certainly a small IMA is more difficult to use. In addition, IMA flow rises dramatically within hours to meet the demand – one only has to measure graft flow in take-backs for bleeding to realize this. When flow is re-measured at this time using transit-time flow measurement, it is always much greater, rivaling that of vein grafts.

8. Inertia

Human Nature and change often do not mix. Understandably, it can be very difficult to leave the comfort zone of 'One-IMA-rest-vein-graft' CABG and go to a longer, more difficult procedure with increased risks. And as Bruce Lytle recently said '…cardiac surgeons are greatly incentivized to function extremely well in regard to short-term outcomes but do not practice the same scrutiny regarding long-term outcomes. The only advantages of a complex ITA grafting operation are improved long-term outcomes.' [9]

The very best way to counteract 'inertia' is to never let it take hold. If one remains a 'life-long learner', it is much easier to change. Failing this, another way is to start with the younger generation of cardiac surgeons and to never teach them how to use vein grafts…

However, this may not be practical. Perhaps the best way is to target young surgeons at the beginning of their training and perhaps teach them harvest of the IMA before they are taught how to harvest saphenous vein. One day when teaching a new first year resident in Cardiothoracic surgery how to skeletonize the IMA with the harmonic scalpel, (he had been a final year medical student two weeks before), a surgical colleague said: 'When I was at that level of training, I had to harvest a thousand miles of saphenous vein before I was allowed to touch a mammary artery.' Maybe this is part of the problem. My dear Mother always used to tell me: 'Start the way you mean to continue.' Perhaps if young cardiac surgeons-to-be started with IMA harvesting instead of vein conduits, maybe this would be the way they would continue? They would 'imprint' on internal mammary arteries as conduits instead of saphenous vein. This has already been seen with one of our now senior residents who when allowed to perform a case on his own, uses as much BIMA grafting as he is able.

To summarize this last paragraph: from Proverbs 22:6: 'Train up a child in the way he should go; even when he is old he will not depart from it.' comes the modern-day saying: "Get them young and train them right."

This Chapter will close with a favorite quote from the movie – 'Field of Dreams'. In this movie, a 1989 American fantasy-drama film based on the novel *Shoeless Joe* by W.P. Kinsella, Kevin Costner plays Ray Kinsella, a novice Iowa farmer who while walking through his cornfield one evening, hears a voice whispering, 'If you build it, he will come.' By building a baseball diamond in their failing cornfield and after many adventures and twists of fate, Ray fulfills his young daughter's prophecy of:

"Build it [a baseball diamond] and they [famous baseball players passed-on] will come"

Using this movie theme as an analogy in cardiac surgery, in cardiac surgery terms we can say:

"Do the optimal operation and patients will come for CABG"

or

"Use mammary arteries and they will come."

REFERENCES:

1. Harskamp RE, Lopes RD, Baisden CE, de Winter RJ, Alexander JH. Saphenous vein graft failure after coronary artery bypass surgery: pathophysiology, management, and future directions. *Ann Surg* 2013;257(5):824-33.
2. Quote from 'Minute Meditations for Each Day Oct 22 by Rev. Bede Naegele, Catholic Book Publishing Co. New York
3. Taggart DP, Altman DG, Gray AM, Lees B, Nugara F, Yu LM, Flather M; ART Investigators. Effects of on-pump and off-pump surgery in the Arterial Revascularization Trial. *Eur J Cardiothorac Surg* 2015;47(6):1059-65.
4. Malcolm Gladwell Nov 18 2008 Little, Brown and Co. Outliers the story of Success ISBN 978-0-316-01792-3
5. Guidelines on myocardial revascularization. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI), Kolh P, Wijns W, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. *Eur J Cardiothorac Surg* 2010;38 Suppl:S1-S52.
6. National Institute for Health and Clinical Excellence, Medical technology guidance: The VeriQ system for assessing graft flow during coronary artery bypass graft surgery Nov 2011
7. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI).Kolh P, Windecker S, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A; ESC Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol Ç, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S; EACTS Clinical Guidelines Committee, Sousa Uva M, Achenbach S, Pepper J, Anyanwu A, Badimon L, Bauersachs J, Baumbach A, Beygui F, Bonaros N, De Carlo M, Deaton C, Dobrev D, Dunning J, Eeckhout E, Gielen S, Hasdai D, Kirchhof P, Luckraz H, Mahrholdt H, Montalescot G, Paparella D, Rastan AJ, Sanmartin M, Sergeant P, Silber S, Tamargo J, ten Berg J, Thiele H, van Geuns RJ, Wagner HO, Wassmann S, Wendler O, Zamorano JL. *Eur J Cardiothorac Surg* 2014;46(4):517-92.
8. Kurlansky P. Arterial grafting and the risk of sternal infection: how we can learn from our experience. *J Thorac Cardiovasc Surg* 2014;148(5):1896-8
9. Lytle BW. Bilateral internal thoracic artery grafting. *Ann Cardiothorac Surg* 2013;2(4):485-492

Chapter 18

Summary English

PART 1: INTRODUCTION

Chapter 1 identifies the physical and psychological burden with which patients who have coronary artery disease must live. It also outlines the responsibility of health care professionals looking after these patients to help them to ameliorate their plight to the best of their ability especially with respect to the performance of mammary artery grafting CABG.

Chapter 2 explains the focus and goal of the subsequent chapters, which is to facilitate the use of mammary artery grafting and increase the safety for patients when mammary arteries are used more liberally. There are many obstacles both real and feared to the performance of BIMA grafting which with this thesis it is hoped that will promote a mindset of the necessity to overcome these obstacles and liberalize the use of BIMA grafting.

PART 2: RATIONALES FOR USE OF BILATERAL INTERNAL MAMMARY ARTERY GRAFTING IN THE MAJORITY OF CORONARY ARTERY BYPASS GRAFT PATIENTS

Chapter 3 describes the history and evolution of the coronary artery bypass graft procedure now 51 years of age, and also includes an overview of outcomes – post-operative, short and long-term and the determinants of these outcomes.

Chapter 4 describes contemporary CABG techniques, types of conduits used, and current methods of quality assurance that have come to make this procedure as safe as it is today.

Chapter 5 is a 'Letter to the Editor' about arterial grafting which poses the question as to whether the radial artery should supplant the vein graft as a superior conduit and be the 'third choice' conduit given that the best conduits are the left and right internal mammary arteries.

Chapter 6 is an editorial point of view regarding use of BIMA vs saphenous vein grafting and reasons are postulated as to why they are used or not.

PART 3: PATIENT'S AGE OF BENEFIT FOR BILATERAL INTERNAL MAMMARY ARTERY GRAFTING

Chapter 7 examined retrospectively three groups of patients receiving no, one or two internal mammary arteries with a view to defining an age cutoff at which BIMA grafting was not of benefit. The data finding of a statistical trend of the age cutoff of 70 years has been accepted by international experts in this field; this paper is referenced in the recent ESC and EACTS Guidelines of Myocardial Revascularization (Oct 2014).

PART 4: REDUCING THE RISKS ASSOCIATED WITH BILATERAL INTERNAL MAMMARY ARTERY GRAFTING

Chapter 8 retrospectively reviewed the use of intra-operative transit-time flow measurement (TTFM) to assess the function of bypass grafts in the first 336 patients and found that when only the TTFM was abnormal (no other signs of graft malfunction such as EKG changes, regional wall motion abnormalities on echo or hemodynamic compromise) and the graft was not revised, these patients had a significantly higher chance of morbidity and especially mortality. This study has been referenced in three guidelines for myocardial revascularization: in the ESCS/EACTS 2010 and 2014 Guidelines for Myocardial Revascularization and in the Medical Technology Guidance 'The VeriQ system for assessing graft flow during coronary artery bypass graft surgery' for the National Institute for Health and Clinical Excellence (NICE) for the National Health Service, UK in November 2011.

Chapter 9 describes a pilot study of a novel adhesive-enhanced closure of the sternum after cardiac surgery. Use of this biocompatible glue (Kryptonite) confers a solid sternum at 24 hours after application of the glue between the sternal halves at the time of surgery, instead of the 3 month requisite time to heal any broken bone.

Chapter 10 describes 12 sequentially added infection reduction techniques/procedures over several years in a group of 1001 consecutive CABG operations with the ultimate goal to reduce one of the most dreaded complications of CABG procedure, deep sternal wound infection to near zero. This study was also chosen as a topic for an editorial by Professor Paul Kurlansky in the same volume.

PART 5: COMPLETENESS OF REVASCULARIZATION AND BILATERAL INTERNAL MAMMARY ARTERY GRAFTING

Chapter 11 challenges the concept that incomplete revascularization in CABG surgery results in reduced survival. Midterm follow-up of 1000 patients with 98% arterial grafts, (if under the age of 80 years) showed similar survival whether they had incomplete or complete revascularization. We postulated that all previous studies showing the reduced survival of incompletely revascularized patients were in CABG patients with either only one or no arterial bypasses. Vein graft occlusion occurs in 12% of the bypasses early (3 weeks) 25% at 1 year. Between 5 and 10 years postoperatively, FitzGibbon et al reported an unexpected increase in vein graft abnormality, which they termed ‘the 7.5 year phenomenon’. [1] However 85-95% of arterial grafts are patent at 10 years. If a patient loses one of three bypass grafts – this patient essentially has single vessel disease; if they lose two, now with ‘double vessel disease’ their survival would be much more likely be affected than with just single vessel disease. To put this simply, because vein grafts occlude at a faster rate than arterial grafts, if patients start out with one (or two) less bypass grafts than they should have and then lose the vein graft(s), they are more than likely will suffer the consequences – myocardial infarction and reduced survival.

Chapter 12 is a review article exploring the challenge of complete revascularization when using arterial grafts. Factors hindering this include the finite length of arterial conduits, (the length of the sternum for mammary arteries and of the forearm for radial arteries), competitive coronary flow and technical challenges using arterial grafts.

PART 6: FACILITATING SURGICAL USE OF BILATERAL INTERNAL MAMMARY ARTERY GRAFTING

Chapter 13 examines the use of the harmonic scalpel to skeletonize 1640 internal mammary arteries in 965 patients. One drawback to performance of routine bilateral internal mammary artery grafting is increased operative time on two levels: 1) harvesting two IMAs doubles the conduit harvest time (saphenous vein harvest is simultaneous whereas double IMA harvesting is metachronous) and 2) skeletonization of the internal mammary artery (which facilitates arterial grafting,) also is more time intensive compared to the more common pedicle technique. We found that mean harvest skeletonization time of the IMA without harmonic technology was 32.2 minutes. When experienced with the use of the harmonic scalpel, the harvest times dropped to 15.4 minutes/IMA. This reduction in harvest time could therefore potentially reduce each operation by 30 minutes. As cardiac surgeons usually perform 2 procedures per day, this would reduce the whole day operative time by 1 hour; finishing a day at 18:00 hours instead of 19:00 hours has significant beneficial implications for the whole operative team. Use of harmonic technology is not only faster than the conventional method of skeletonization; damage to the mammary (to beyond its use as a conduit for bypass) occurs infrequently (7/1640 mammaries – 0.43%).

Chapter 14 is the script of a video published on Cardio Thoracic Surgery network (CTSNet) a world- wide web site. This 9 minute video shows the technique of skeletonizing internal mammary arteries using harmonic technology.

PART 7: SPECIAL TECHNIQUES IN THE USE OF ARTERIAL GRAFTING

Chapter 15 is a publication (1986) on the use of *sequential venous grafting*. This was a futuristically important paper because i) the study found that the second anastomosis of a sequential venous graft was more likely to occlude, ii) the second anastomosis was usually to the more important vessel – the left anterior descending artery (LAD) and iii) sequential grafts are a major technique used by arterial grafting surgeons because of the limited and finite length of arterial conduits. It will be very interesting to perform a similar study with arterial grafts to see if the second anastomosis loss occurs with arterial conduits as it does with venous grafts, giving one more reason for the reluctance to perform much arterial grafting.

This manuscript was co-authored with Dr. Gerald M. FitzGibbon who was an Irish cardiologist working in Canada for the Canadian Military. He is responsible for the 'A, B, O' classification of bypass graft patency that is still used today. I had the great fortune to work for 2 years with Dr. FitzGibbon at the military hospital, National Defense Medical Centre (NDMC) to fulfill my obligation to the Canadian Military for financially supporting me during medical school."

Chapter 16 is the script of a video published also on CTSNet and describes a rare complication of coronary artery surgery – dissection of the whole left coronary system and aortic root which originated from a bypass graft to the circumflex system. Usually lethal, disaster was averted by i) carving an oval opening in the calcified anterior LAD coronary artery wall which allowed ii) insertion of an additional graft placed to the true lumen of the dissected coronary artery (sutures placed through full wall thickness). This resulted in: i) closure of the dissection in the LAD at the graft site, ii) perfusion of the complete LAD system from the added graft and hence iii) reversal of the dissection in the left coronary and the aorta by obliteration of the false lumen. By closing the dissection locally at mid LAD level and with the forward flow in the new LAD graft, the dissection process was reversed restoring coronary flow to the left ventricle (LV) and hence function of the LV. The case by itself is dramatic, but the true importance of this report is that it has led to the incorporation of this technique of creating an oval opening for patients with densely calcified arteries. If such calcified coronary arteries have an acceptable lumen, this procedure will allow bypass grafting in patients that otherwise could not be done.

REFERENCES:

1. FitzGibbon GM, Leach AJ, Kafka HP, Keon WJ. Coronary bypass graft fate: long-term angiographic study. J Am Coll Cardiol 1991;17:1075-80

Chapter 19

Nederlandse Samenvatting
(summary Dutch)

DEEL 1: INLEIDING

Hoofdstuk 1 beschrijft de fysieke en psychologische belasting, waarmee patiënten met coronair arterie ziekte moeten leven. Het hoofdstuk omschrijft voorts de verantwoordelijkheid van de gezondheidszorg-beroepsgroep, die voor deze patiënten zorgdraagt, om hen naar beste vermogen te helpen deze last te verlichten met name met betrekking tot het uitvoeren van coronaire bypass chirurgie (CABG) met behulp van de arteriae mammariae internae (IMA).

Hoofdstuk 2: verklaart van de volgende hoofdstukken zowel het focus alsook het doel, namelijk het gebruik van IMA bypass-grafts te faciliteren en de veiligheid voor patiënten te vergroten wanneer IMA grafts meer vrijelijk gebruikt worden. Het gebruik van bilaterale IMA bypass-grafts (BIMA) ontmoet vele -zowel reële alsook vooral gevreesde- belemmeringen. Het is de hoop van de auteur dat dit proefschrift een 'mindset' van collegae zal bevorderen dat het nodig is deze belemmeringen te overkomen om BIMA-CABG frequenter toe te passen.

DEEL 2: REDENEN VOOR TOEPASSING VAN BIMA BYPASS-GRAFTS IN DE MEERDERHEID VAN CABG PATIËNTEN

Hoofdstuk 3: geeft een overzicht van geschiedenis en ontwikkeling van de nu 51 jaar oude CABG procedure met inbegrip van een overzicht van de resultaten I) direct postoperatief ii) op korte termijn en iii) op lange termijn alsook de bepalende factoren voor deze resultaten.

Hoofdstuk 4: beschrijft de hedendaagse CABG technieken, de aard van het gebruikte vat voor de bypassgraft, en de huidige methoden van kwaliteitsgarantie die deze procedure inmiddels zo veilig hebben gemaakt als hij heden ten dage is.

Hoofdstuk 5: is een 'Letter to the Editor' over arteriële grafts, die stelt dat de linker IMA en de rechter IMA de beste bypassvaten zijn en dat de Art. Radialis superieur is als bypass vat aan de Vena Saphena Magna. De 'Letter' stelt derhalve als vraag: 'dient de Art. Radialis de Vena Saphena Magna als derde keus voor bypassvat te vervangen?'.

Hoofdstuk 6: behelst een editorial standpunt betreffende BIMA versus Vena Saphena Magna bypassvaten en postuleert redenen waarom deze bypassvaten al dan niet gebruikt worden.

DEEL 3: DE LEEFTIJD VAN DE PATIENT WAARBIJ BIMA-CABG HET MEESTE BAAT HEEFT

Hoofdstuk 7: bestudeert in een retrospectieve studie drie patiëntengroepen, die i) geen ii) een of iii) twee IMA bypassvaten ontvangen hadden teneinde te bepalen of er een leeftijdsgrens is waarbij BIMA bypassvaten geen extra baat meer voor de patiënt oplevert. De gegevens toonden een statistische trend voor de leeftijdsgrens van 70 jaar; deze grens is nu geaccepteerd door internationale experts in het vakgebied en het artikel wordt gerefereerd in the recentelijk gepubliceerde ESC en EACTS Richtlijnen voor Revascularisatie van het Myocard (Oktober 2014).

DEEL 4: REDUCTIE VAN DE RISIKOS DIE SAMENHANGEN MET BIMA-CABG

Hoofdstuk 8: geeft een retrospectief overzicht van het gebruik van intra-operatieve meting van intravasculaire stroomsnelheid met behulp van de transit time techniek (TTFM) om de functie van bypassvaten te evalueren in de eerste 336 patiënten. De resultaten toonden aan, dat wanneer de TTFM abnormaal was -zonder andere tekenen van malfunctie van het bypassvat zoals ECG afwijkingen, regionale wandbewegings abnormaliteiten op het echocardiogram of gecompromitteerde hemodynamica- en het bypassvat niet gerevideerd werd, dat deze patiënten een significant grotere morbiditeit en mortaliteit hadden. Deze studie is gerefereerd in the drie gepubliceerde ESC en EACTS Richtlijnen voor Revascularisatie van het Myocard (2010 en 2014) en in de 'Medical Technology Guidance' getiteld:" The VeriQ system for assessing graft flow during coronary artery bypass graft surgery" voor the National Institute for Health and Clinical Excellence (NICE) voor the National Health Service, UK in November 2011.

Hoofdstuk 9: beschrijft een pilot studie van sluiten van het sternum met behulp van een adhesie-versterkte methode. Het gebruik van de bio-compatible lijm Kryptonite geeft een soliede sternum in 24 uur na het aanbrengen van de lijm tussen de helften van het sternum ten tijde van de operatie, in plaats van de verwachte 3 maanden voor het helen van willekeurig welk gebroken bot.

Hoofdstuk 10: beschrijft in detail 12 infectie reductie technieken/maatregelen die in een groep van 1001 achtereenvolgens uitgevoerde CABG operaties over de jaren werden toegevoegd met het uiteindelijke doel om de meest gevreesde complicatie van de CABG operatie –i.e. 'deep sternal wound infection'- te elimineren. Deze studie werd gekozen voor een editorial door Professor Paul Kurlansky (zie de appendix).

DEEL 5: VOLLEDIGHEID VAN REVASCULARISATIE MET BIMA BYPASSVATEN

Hoofdstuk 11: daagt het concept uit dat incomplete revascularisatie leidt tot verminderde postoperatieve overleving. Een 'midterm' vervolg studie van 1000 patiënten met 98 procent arteriële bypassvaten (indien zij minder dan 80 jaar oud waren) toonde gelijke overlevingspercentages onafhankelijk van de vraag of zij compleet of incompleet gerevasculariseerd waren. We veronderstelden dat in vroegere studies de lagere overlevingspercentage gevonden waren in incompleet gerevasculariseerde patiënten met een CABG zonder of met slechts één arterieel bypassvat. Occlusie van een veneus bypassvat treedt op in 12% van de bypasses in 3 weken en in 25% na een jaar. FitzGibbon et al. rapporteerden een onverwachte toename in veneuze bypass abnormaliteit na 5 tot 10 jaar en noemden dit het '7.5 jaar fenomeen' [1] Van de arteriële bypassvaten is daarentegen 85-95% open na 10 jaar. Als een patiënt één van drie bypassvaten verliest heeft de patiënt in essentie één-vat coronair ziekte. Als de patiënt twee vaten verliest heeft de patiënt twee-vaten coronair ziekte met als gevolg een beduidend ernstiger prognose dan één-vat coronair ziekte. Omdat veneuze bypasses sneller dan arteriële bypassvaten occluderen, staan patiënten met incomplete revascularisatie waarbij veneuze bypassvaten gebruikt worden simpelweg bloot aan een grotere kans op verlies van een bypassvat en lopen dus een groter risico van een hartinfarct en hebben een derhalve gereduceerde overlevingskans.

Hoofdstuk 12: is een review dat de uitdaging van de noodzaak to complete revascularisering middels arteriële bypassvaten evalueert. Factoren die de volledigheid van arteriële bypass procedure beperken zijn i) de lengte van het arteriële bypassvat (i.e. de lengte van het sternum voor de IMA en de lengte van de onderarm voor de Art Radialis bypass), ii) competitieve coronaire bloedstroom en iii) technische problemen bij het gebruik van arteriële bypassvaten.

DEEL 6: FACILITEREN VAN HET UITVOEREN VAN CABG MET BIMA BYPASS VATEN

Hoofdstuk 13: Onderzoekt het gebruik van de harmonic scalpel teneinde 1640 IMA's in 965 patiënten te skeletonizeren . Een nadeel van routinematig gebruik van BIMA grafts is de toegenomen operatietijd door twee oorzaken: 1) het oogsten van twee IMA vaten vergt tweemaal de tijd van de veneuze bypassoogst omdat de vene synchroon met de thoracale procedure plaatsvindt terwijl de IMA daar metachroon mee plaatsvindt; 2) skeletonizeren van de IMA vergemakkelijkt weliswaar de graft procedure aanzienlijk, maar is tijdrovender dan de meer gebruikelijke 'pedicle' techniek. De gemiddelde oogsttijd van één IMA, inclusief het skeletonizeren, zonder de harmonische scalpel technologie bleek hier 32.2 minuten te zijn. Het gebruik van het harmonisch scalpel in ervaren handen reduceerde de oogsttijd tot 15.4 minuten/IMA, hetgeen derhalve de totale operatieduur met een half uur kan reduceren. Aangezien hartchirurgen gewoonlijk twee procedures per dag verrichten maakt deze reductie het mogelijk een operatie dag om zes uur in plaats van om zeven uur in de namiddag te beëindigen met aanzienlijke voordelen voor het hele operatieve team. Voorts is het gebruik van de harmonische technologie niet alleen sneller dan de conventionele technologie van skeletonizeren maar ook vindt zodanige beschadiging van de IMA , dat geen enkel deel meer bruikbaar is als bypassvat, slechts sporadisch plaats (7/1640 IMAs ofwel 0.43%).

Hoofdstuk 14: is de tekst bij een video-opname (9min), die gepubliceerd is op het Cardio Thoracic Surgery netwerk (CTSNet). De video toont de techniek van het skeletonizeren van de IMA met het harmonisch scalpel.

DEEL 7: SPECIALE TECHNIEKEN GEBRUIKT BIJ ARTERIËLE BYPASSVATEN

Hoofdstuk 15 is een publicatie uit 1986 over het gebruik van *sequentiële veneuze bypasses*. Dit artikel was van futuristisch belang omdat: i) the studie beschreef dat de tweede anastomose van een sequentiële veneuze graft een grotere waarschijnlijkheid van occlusie vertoonde, terwijl ii) de tweede anastomose gewoonlijk een belangrijkere coronair arterie betrof -de Linker Art. Descendens Anterior (LAD) en iii) sequentiële grafts vaak worden als techniek gebruikt door coronair chirurgen als oplossing voor het probleem van de beperkte lengte van arteriële bypassvaten. Het is waarschijnlijk dat een soortgelijke studie van sequentiële arteriële grafts boeiende gegevens zal opleveren over de vraag of de tweede anastomose zal occluderen zoals gebeurde bij sequentiële veneuze grafts. Dit is van belang omdat vroegtijdige occlusie van de tweede sequentiële arteriële anastomose een extra reden zal vormen voor de -al bestaande- huiver voor het gebruik van arteriële grafts.

De co-auteur van dit manuscript was Dr. G.M. FitzGibbon, een Ierse cardioloog die in Canada voor het Canadese leger werkte. Hij is de auctor intellectualis van de 'A, B, O' classificatie voor de doorgankelijkheid van coronaire bypasses, die heden ten dage nog steeds in gebruik is. Ik had het grote voorrecht om twee jaar lang met Dr. FitzGibbon in het militaire ziekenhuis 'National Defense Medical Centre' te werken om mijn verplichtingen na te komen voor de financiële steun van het Canadese leger gedurende mijn medische studie.

Hoofdstuk 16: is de tekst van een video die ook op het CTSNet gepubliceerd is, die een ongebruikelijke complicatie van coronair chirurgie beschrijft: dissectie van het gehele linker coronair arteriële system inclusief de stam van de aorta uitgaande van de graft op een de Art. circumflex. Gewoonlijk is dit een lethale complicatie; in dit geval kon een ramp voorkomen worden door: i) een ovale opening uit de verkalkte anterieure wand van de LAD uit kerven en ii) daarna een additionele graft aan te sluiten met gebruik hechtingen die de gehele wand van de blootgelegde LAD passeerden. Als gevolg: i) werd de dissectie in de LAD lokaal afgesloten en ii) het linker coronair systeem werd nu geperfundeerd vanuit de toegevoegde graft iii) hetgeen de dissectie keerde in het linker coronair systeem en de aorta door obliteratie van het valse lumen. Hoewel de casus op zich dramatisch is, ligt het werkelijke belang in het principe van het 'kerven van een ovale opening' uit de coronair arterie wand ten behoeve van patiënten met zwaar verkalkte coronair arteriën -met niettegenstaande een goed lumen-, die anders ongeschikt lijken om bypass te accepteren.

REFERENCES:

1. FitzGibbon GM, Leach AJ, Kafka HP, Keon WJ. Coronary bypass graft fate: long-term angiographic study. J Am Coll Cardiol 1991;17:1075-80

Chapter 20

PhD Portfolio

PHD PORTFOLIO

Erasmus MC Department: Cardiothoracic Surgery
PhD period: 2009-2015
Promotor: Prof.dr. A.P.Kappetein

Conferences (41.7)	Year	ECTS
EACTS	2009-2014	8,1
AATS	2009-2015	9,45
STS	2011-2015	6,75
CCC (Canadian Cardiovascular Congress)	2009-2010	2,7
CSCS (Canadian Society of Cardiac Surgeons)	2009	0,6
ACC (American College of Cardiology 25th Ann CV Lake Louise)	2009	1,2
WTSA (Western Thoracic Surgical Association)	2009, 2013	1,8
ACS (Ass of Cardiac Surg XXVII Annual Meeting)	2011	1,2
ICCAD (International Congress on Coronary Artery Disease)	2011	1,2
Controversies and Advances in Rx of CV Disease	2009-2012	2,4
Dallas-Leipzig Valve Conference	2012	0,9
SCTS (Society for Cardiothoracic surgery in Great Britain and Ireland)	2011	1,5
ISMICS (International Society for Minimally Invasive Cardiothor. Surgery)	2011, 2013	2,4
IV Congress of Surgeons of Kazakhstan “New Technologies in Surgery	2013	1,5

Presentations (17.4)	Year	ECTS
Controversies and Advances in the Treatment of Cardiovascular Disease The Ninth in the Series, Cedars Sinai (Los Angeles)	2009	1,2
European Association for Cardio-thoracic Surgery (Vienna)	2009	0,6
Controversies and Advances in the Treatment of Cardiovascular Disease The Tenth in the Series, Cedars Sinai (Los Angeles)	2010	0,6
NNMC (National Medical Scientific Center) (Astana, Kazakhstan)	2010	0,6
Society of Thoracic Surgeons (San Diego)	2011	1,2
Society for Cardiothoracic Surgery in Great Britain and Ireland (London, England)	2011	1,2

American Association for Thoracic Surgery (Philadelphia)	2011	0,6
International Society for Minimally Invasive Cardiothoracic Surgery (Washington, DC)	2011	0,6
European Association for Cardio-thoracic Surgery (Lisbon)	2011	0,6
Controversies and Advances in the Treatment of Cardiovascular Disease The Eleventh in the Series (Los Angeles)	2011	1,2
International Congress on Coronary Artery Disease (ICCAD) (Venice)	2011	1,2
European Association for Cardio-thoracic Surgery (Barcelona)	2012	0,6
IV Congress of Surgeons of Kazakhstan (Almaty, Kazakhstan)	2013	0,6
American Association for Thoracic surgery (Minneapolis)	2013	1,2
International Society for Minimally Invasive Cardiothoracic Surgery (Prague)	2013	1,2
European Association for Cardio-thoracic Surgery (Vienna)	2013	1,8
European Association for Cardio-thoracic Surgery (Milan)	2014	2,4

<u>Teaching (13)</u>

Supervising Cardio-thoracic surgery residents	2008-2015	6
Royal Alexandra hospital, Edmonton Alberta	2009	0.25
Teaching Drs. Seryk Mendykulov, Dr. Timur Lesbekov and residents National Medical Scientific Center Astana, Kazakhstan	2010	0.75
Montreal Heart Institute, Montreal Quebec	2011	0.25
Albany Medical Centre, Albany, New York	2011	0.25
St. Boniface General Hospital, Winnipeg Manitoba	2012	0.25
Dr. Adil Aithmuhanov and residents, National Science Surgery Center Almaty Kazakhstan	2013	0.5
Dr. Plamen Panayotov and residents, St. Marina University Hospital,Varna, Bulgaria	2013	0.75
Cardiac Surgery Residents at Erasmus University, Rotterdam, The Netherlands	2013	0.25
European Association for Cardio-thoracic Surgery Academy Coronary Course Director (29 Jun-1July 2015)	2015	3.0
The 1st International Coronary Congress: State of the Art Surgical Coronary Revascularization New York	2015	0.75

<u>Other (11)</u>

Peer reviewer international scientific journals:		
European Journal of Cardio-Thoracic Surgery	2014	0.25
Annals of Thoracic Surgery	2015	0.75
Innovations	2014-2015	1.5
Cardiovascular Journal of Africa	2012	1.5
Grant Reviews:		
Medical Research Council of Canada	1992	0.25
Austrian Science Fund (FWF)	2012-2013	0.5
Invited Discussant:		
'Total arterial off-pump surgery does not compromise complete revascularization' Presented at 25th Meeting of EACTS Lisbon, Portugal, Oct 3 2011	2011	0.25
Abstract Reviewer:		
European Association for Cardio-thoracic Surgery	2013-2015	3
Canadian Cardiovascular Society	2006, 2015	2
Panel Member: International Society for Minimally Invasive Cardiothoracic Surgery 2013 Expert Consensus Panel for Off-pump CABG (OPCAB) vs Conventional CABG (CCAB), Dublin, Ireland May 26-27	2013	1

Chapter 21

List of Publications

PEER REVIEWED MANUSCRIPTS

1. **Kieser** TM, MacKenzie RL, Feld R, Leers N. Prophylactic metronidazole in appendectomy: a double-blind controlled trial. Surgery 1983;93:201-203.
2. Calvin JE, **Kieser** TM, Walley VM, McPhail NV, Barber GC, Scobie TK. Cardiac mortality and morbidity after vascular surgery. Canadian Journal of Surgery 1986;29(2):93-97.
3. **Kieser** TM, FitzGibbon GM, Keon WJ. Sequential coronary bypass grafts: long-term follow-up. Journal of Thoracic and Cardiovascular Surgery 1986 May;91(5):767-72.
4. **Kieser** TM, Walley VM, McPhail NV. Abdominal aortic ectasia due to distal traumatic arteriovenous fistulization. Journal of Vascular Surgery 1987 Jun; 5 (6) 882-6
5. Ball NJ, Urbanski SJ, Green FHY, **Kieser** TM. Pleural multicystic mesothelial proliferation. The American Journal of Surgical Pathology 1990;14(4):375-378.
6. Leitch J, Gillis AM, Wyse DG, Yee R, Klein G, Guiraudon G, Sheldon RS, Duff HJ, **Kieser TM,** Mitchell LB. Reduction in defibrillator shocks with an implantable device combining antitachycardia pacing and shock therapy. Journal of American College of Cardiology 1991;18(1).
7. Gillis AM, Rothschild JM, Hillier K, Fudge W, **Kieser TM,** Maitland A. A randomized comparison of a bipolar steroid-eluting electrode and a bipolar microporous platinum electrode: implications for long term programming. PACE 1993;16:964-970.
8. Daniels MCG, **Kieser TM,** ter Keurs HEDJ. Triggered propagated contractions in human atrial trabeculae. Cardiovascular Research 1993;27:1831-1835.
9. Wyse GD, Kavanagh KM, Gillis AM, Mitchell LB, Duff HJ, Sheldon R, **Kieser TM**, Maitland A, Flanagan P, Rothschild JM, Mehra R. Comparison of biphasic shocks for defibrillation using a nonthoracotomy system. The American Journal of Cardiology 1993;71:197-202.
10. Gillis AM, Rothschild JM, Hillier K, Fudge W, **Kieser TM,** Maitland A. A randomized comparison of a bipolar steroid-eluting electrode and a bipolar microporous platinum electrode: implications for long term programming. PACE 1993;16:964-970.
11. Daniels MCG, **Kieser TM,** ter Keurs HEDJ. Triggered propagated contractions in human atrial trabeculae. Cardiovascular Research 1993;27:1831-1835.
12. Platt RS, **Kieser TM,** Easton PA. Eliminating Ultrasonic Interference from respiratory muscle EMG. Respir Physiol. 1998 May; 112 (2): 203-13
13. Katagiri M, Young RN, Platt RS, **Kieser TM,** Easton PA. Respiratory muscle compensation for unilateral or bilateral hemidiaphragm paralysis in awake canines. Journal of Applied Physiology 1994 Oct; 77 (4):1972-1982.
14. Hamilton DR, Dani RS, Semlacher RA, Smith ER, **Kieser TM,** Tyberg JV. Right atrial and right ventricular transmural pressures in dogs and humans. Circulation 1994 Nov; 90 (5):2492-500.

15. Abe T, Tomita T, **Kieser TM,** Easton PA. Respiratory muscle activity during emesis in awake canines. Journal of Applied Physiology 1994Jun; 76 (6) 2552-2560.

16. Verma, S, Lovren F, Mather K, Maitland A, **Kieser, TM**, Triggle CR, Anderson TJ. Tetrahydrobiopterin improves endothelial function in human saphenous veins: a novel mechanism. J Thor Cardiovasc Surg, October 2000, Vol. 120, No. 4, 668-671.

17. Verma S, Lovren F, Dumont AS, Mather KJ, Maitland A, **Kieser TM**, Kidd W, McNeill JH, Steward DJ, Triggle CR, Anderson TJ. Endothelin receptor blockade improves endothelial function in human internal mammary arteries. Cardiovasc Res. 2001 Jan:49;(1): 146-51

18. Belenkie, I, **Kieser TM,** Sas R, Smith ER, Tyberg, JV. Evidence for left ventricular constraint during open heart surgery, Can J Cardiol.2002 Sep;18 (9) 951-959

19. **Kieser TM.** The radial artery: neither gold, nor silver, but bronze? J Thorac Cardiovasc Surg. 2004 Feb;127(2):607-8

20. Colangelo N, Moriggia S, **Kieser T,** De Simone F, Vescovo A, Palumbo L, Dent P, Guidotti A, Blasio A, Maisano F, Alfieri O. A cardioplegia circuit with versatility: the "ReVerse" system. How to do it. Perfusion. 2008 Jul;23(4):205-7

21. **Kieser TM** The Left ventricle: To Reconstruct or Not, Lessons from STICH Trial, J Thorac Cardiovasc Surg.2009 Sept, 138(3):784

22. **Kieser TM,** Rose MS, Kowalewski, Belenkie I "Transit-time Flow Predicts Outcomes in CABG patients: a series of 1000 consecutive Arterial Grafts. Eur J Cardiothorac Surg 2010 Aug;38(2):155-62. **Kieser TM**. On-pump versus off-pump CABG. N Eng J Med 2010 Mar 4;362(9):852; author reply 853-4

23. **Kieser TM**, Lewin AM, Graham MM, Martin BJ, Galbraith PD, Rabi DM, Norris CM, Faris PD, Knudtson ML, Ghali WA. Outcomes Associated with Bilateral Internal Thoracic Artery Grafting: The Importance of Age. Ann Thorac Surg 2011 Oct ;92:1269-76

24. Fedak PW, **Kieser TM,** Maitland AM, Holland M, Kasatkin A, LeBlanc P, Kim JK, King KM. Adhesive-enhanced sternal closure to improve post-operative functional recovery: A pilot randomized controlled trial. Ann Thorac Surg 2011 Oct;92:1444-50

25. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, Noiseux N, Padmanabhan C, Bahamondes JC, Novick RJ, Vaijyanath P, Reddy S, Tao L, Olavegogeascoechea PA, Airan B, Sulling TA, Whitlock RP, Ou Y, Ng J, Chrolavicius S, Yusuf S; **CORONARY Investigators**. Off-pump or on-pump coronary-artery bypass grafting at 30 days.N Engl J Med. 2012 Ap19;366(16):1489-97

26. Di Eusanio M, Patel HJ, Nienaber CA, Montgomery DM, Korach A, Sundt TM, Devincentiis C, Voehringer M, Peterson MD, Myrmel T, Folesani G, Larsen M, Desai ND, Bavaria JE, Appoo JJ, 26. **Kieser TM,** Fattori R, Eagle K, Di Bartolomeo R, Trimarchi S. Patients with type A acute aortic dissection presenting with major brain injury: should we operate on them? J Thorac Cardiovasc Surg. 2013 Mar;145(3 Suppl):S213-21.e1.

27. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, Noiseux N, Padmanabhan C, Bahamondes JC, Novick RJ, Vaijyanath P, Reddy SK, Tao L, Olavegogeascoechea PA, Airan B, Sulling TA, Whitlock RP, Ou Y, Pogue J, Chrolavicius S, Yusuf S, **CORONARY Investigators** Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. N Engl J Med. 2013 Mar 28;368(13):1179-1188

28. Head SJ, **Kieser TM**, Falk V, Kappetein AP. Coronary Artery Bypass Grafting: Part 1 — An Evolution Over the First 50 Years. Eur heart J. 2013 Oct:34(37):2862-72.

29. Head SJ, Börgermann, J, Osnabrugge RL, **Kieser TM**, Falk V, Taggart DP, Puskas JD; Gummert JF, Kappetein AP. Coronary Artery Bypass Grafting: Part 2 — Optimizing Outcomes and Future Directions. European Heart Journal 2013 Oct;34(37):2873-86.

30. **Kieser TM**. Bilateral Internal Mammary Artery Grafting in CABG Surgery: An Extra 20 Minutes for an Extra 20 Years…EuroIntervention. 2013 Dec 23;9(8):899-901.

31. **Kieser TM**, Curran H, Rose MS, Norris C, Graham MM. Arterial Grafts Balance Survival between Incomplete and Complete Revascularization: A series of 1000 Consecutive Coronary Artery Bypass Graft Patients with 98% Arterial Grafts. Journal of Cardio-Thoracic Surgery J Thorac Cardiovasc Surg 2014;147(1):75-83

32. Nagendran J, Norris CM, Graham MM, Ross DB, Macarthur RG, **Kieser TM**, Maitland AM, Southern D, Meyer SR; APPROACH Investigators. Coronary Revascularization for Patients With Severe Left Ventricular Dysfunction. Ann Thorac Surg. 2013 Dec;96(6):2038-44.

33. **Kieser TM,** Head SJ, Kappetein AP. Arterial grafting and complete revascularization: challenge or compromise? Curr Opin Cardiol. 2013 Nov;28(6):646-53.

34. Benussi S, **Kieser T**. Invited Commentary Ann Thorac Surg 2013 Dec;96(6):2060.

35. **Kieser TM**, Rose MS, Aluthman U, Narine K. Quicker yet safe: skeletonization of 1640 internal mammary arteries with harmonic technology in 965 patients. Eur J Cardiothorac Surg 2014 May;45(5):e142-50.

36. **Kieser TM**, Rose MS, Aluthman U, Montgomery M, Louie T, Belenkie I. Toward Zero: Deep Sternal Wound Infection Following1001 Consecutive Coronary Artery Bypass Procedures using Arterial Grafts: Implications for Diabetic Patients. J Thorac Cardiovasc Surg. 2014 Nov;148(5):1887-95.

PEER REVIEWED VIDEOS

1. **Kieser T,** Narine K. 'Skeletonization of the Internal Mammary Artery with the harmonic Hook Blade' Published on July 12, 2012 CTSNet Cardiac Videos
2. **Kieser T,** Spence F, Kowalewski R. 'Iatrogenic aortic root and left Main dissection in CABG surgery: An Unconventional Fix' Published on Nov 3 2014 CTSNet Cardiac Videos

NON-PEER REVIEWED MANUSCRIPTS

1. **Kieser TM**, Maitland A, Parsons L, Woodman RC, Verwendung des fibrinklebers tisseel bei 300 patienten in der offenen herzchirurgie. Fibrinklebun in der Herz-, Gefä- und Thoraxchirurgie 1993;85-95.
2. **Kieser TM,** Maitland A, Parsons L, Davison S, Woondman RC. Reduced postoperative bleeding following use of tisseel fibrin sealant in 300 patients undergoing open heart surgery. Update and Future Trends in Fibrin Sealing in Surgical and Non-Surgical Fields, Thoracic Surgery – Cardiovascular Surgery 1993;IV. Springer–Verlag – Berlin.
3. **Kieser TM**, Maitland A, Parsons L, Davison S, Woondman RC. Reduced postoperative bleeding following use of tisseel fibrin sealant in 300 patients undergoing open heart surgery. Cardiovascular Surgery/Thoracic Surgery 1995 (6):43-54.

BOOKS, CHAPTER

1. Keon WJ, **Kieser TM,** 1988(36):127-136 "Technical pitfalls of reoperation. Treatment of End State Coronary Artery Disease". Advances in Cardiology, 1988; 36: 127-37 Review. No abstract available.
2. Sheldon R, Rose S, Wilson **W, Kieser** T, Koshman: 1998 Utility of chamber pacing with automatic rate-drop sensing in the prevention of neutrally mediated syncope.
3. **Terry Kieser 2005** (8): 399-406 "Beginning of Cardiac Surgery at Foothills Hospital, Calgary" Heart Surgery In Canada 2005 (8): 399-406
4. **Terry Kieser** 2005 (13): 492-521 "Women in Cardiac Surgery in Canada" Heart Surgery in Canada 2005 (13): 492-521

Chapter 22

About the Author

Teresa Mary Kieser was born on 29 January 1952 and is a Consultant Cardiothoracic and Vascular Surgeon, Associate Professor at Foothills Medical Centre at the Libin Cardiovascular Institute of Alberta, University of Calgary. She was board certified in General Surgery in Canada and USA in 1985 and in Cardiovascular and Thoracic Surgery in 1986 in Canada. Dr. Kieser trained at the University of Ottawa (MD 1976), University of Toronto (General Surgery), at the University of Ottawa Heart Institute for Cardiovascular and Thoracic Surgery under Professor Wilbert J. Keon and at Barnes-Jewish Hospital, Washington University, St. Louis in arrhythmia surgery under Dr. James Cox.

Immediately upon completion of residency she started the Cardiac Surgery Program at Foothills Medical Centre, University of Calgary in Jan 1988 with performance of the first heart surgery on Sept 12, 1988. Her areas of interest include total arterial revascularization, predominantly with bilateral mammary arteries, skeletonization with harmonic technology, transit-time flow measurement (TTFM) for graft patency, bloodless cardiac surgery, tricuspid valve surgery and off-pump CABG.

Her publications focus on quality improvement for the CABG procedure and include completeness of revascularization using arterial grafting, the elimination of deep sternal wound infection, and intra-operative bypass graft patency assessment. Her 2010 EJCTS paper on TTFM is referenced in 3 Guidelines: the 2010 and 2014 ESC and EACTS Guidelines for Myocardial revascularization and the 2011 NHS NICE guidelines for the VeriQ device for TTFM.

Since 2009, she is Site Principal Investigator for 8 current/past trials, including CORONARY EXCEL and ISCHEMIA. She receives invitations to speak at international conferences as well as to operate – (Kazakhstan, Astana 2010 and Almaty 2013 and Varna, Bulgaria 2013) to demonstrate and teach BIMA grafting.

She has been married for 29 years to Jean Joseph Adrien Thomas Prieur and has two children: Alexandra Marguerite who at age 27 years is pursuing a career in International Relations and Adrienne Pasquale, born with phenylketonuria and after a 21 month battle with T-cell leukemia at the age of 5 went to pursue her career in heaven.

Chapter 23

Acknowledgements

As my dear husband of 29 years, Jean Prieur said to me: 'Nobody does one of these alone…'

To A. Pieter Kappetein, M.D., Ph.D., Professor: for your unwavering belief in me, and unconditional friendship and caring, I am forever in your debt.

To Stuart J. Head, M.D., Ph.D.: Were it not for your suggestion, I never would have dreamed of doing this, you are an open and generous giving mind.

MENTORS OF DAYS GONE BY:

To Dr. Gerald M. FitzGibbon, LRCP&S (Ireland), FACC: who taught me that vein grafts were fraught with difficulties, mostly for patients, and who finally believed that I really did want to be a surgeon and not a cardiologist!
To Dr. Wilbert J. Keon, MD, FACC: who taught me that arterial grafts were the future (said to me in 1983) and who encouraged and believed in me at a very early stage…

To My International Surgical Colleagues:
To Ottavio R. Alfieri, Professor, M.D.: who taught me the value of 'non-judgement' and open-mindedness. One of Professor Alfieri's common axioms is: 'There are many ways to do things…'
To Stefano Benussi, M.D., Ph.D.: whose genuine nature, care and astuteness have lifted me up time and time again…
To James L.Cox, M.D.: who taught me that thinking outside of the box, although sometimes potentially hazardous is well worth the effort.
To Ralph J. Damiano, Jr., M.D.: whose supportive friendship for so many years has taught me many things and especially how to ski safely!

To Erasmus Medical Centre, Rotterdam: One of my dreams was to one day study in Europe – you have made my dream come true….

CALGARY:

To M. Sarah Rose Ph.D., Senior Biostatistician at Alberta Health Services: by whose partnership and statistical brilliance in the major publications in this thesis have made realized the dreams of substantiating the usefulness of bilateral internal mammary grafting.

To My Surgical colleagues: thank you for putting up with me all of these years, although sometimes I have seemed distant, I have always been thankful to have such colleagues that have stimulated me to serve and learn and learn how to serve to the best that I am able.
To My Cardiology colleagues: for always supporting BIMA grafting by their encouragement, advice and referrals!
To Israel (Sonny) Belenkie, M.D.: For his long-time friendship and sage advice on everything from medicine, cardiology, surgery and life.
To Henk E.D.J.ter Keurs, Ph.D, M.D.: For his friendship and guidance over many years and especially this project.
To the Operating room staff: for tolerating the vision that BIMA grafting really is better for patients, even when it delays them so many times from being home with their families.
To the Nursing staff of the CVICU and Cardiac surgery ward: for their support of so many research endeavors always with smiles and cheery dispositions and outstanding patient care.
Admin assistants for 27 years: (Pamela Burns, Debbie Desrosiers, Joanna Gidluck, Tara Millions, Lynn Joki and Cristina Cabalce) for organizing my too complex life on many levels, enabling me to work efficiently and productively far beyond that which I could have done on my own, and for being such good 'protectors'.

FRIENDS:

To Janet Thompson: a dearest and life-long friend whose down-to-earth-advice (with incredible sarcastic wit) has countless times allowed me to pick myself up, again and again…
To Mrs. Karen and Dr. Alan Menkis M.D., FRCSC: who not only introduced me to me dear husband but have been supportive of both of us for so many years.

FAMILY:

To our daughters: Adrienne: for teaching us what is the real goal in life.
Alexandra: for giving us so much joy and pride in all of your accomplishments, hard earned, hard fought for and well deserved.
To my Father: I have your drive, your ability to persevere, and I got it by watching you.

To my Mother: I felt your drive and most importantly learned from you that wasted unused talent was the only regret one should avoid, and most importantly I learned from you it didn't matter that I was not a boy.

To Karen, my sister: you always knew the best way to say everything. You were the epitome of: 'Truth without love offends, love without truth deceives'.

To Liam Kieser Ph.D, my oldest brother: your unceasing energy and quest for knowledge has always been my inspiration. (But I can't keep up all the time!)

To John, my younger brother: your Irish and wonderful 'tongue-in-cheek' wit, make me never take myself too seriously, for which I thank you, this is vital to succeed.

To David, my youngest brother: your courage in life is un-paralleled and I am so proud of you and your family.

To Isabelle, my dear mother-in-law: although my own mother was the one to continually prod me into research so long ago, you have been the one to nurture and encourage me to do this project, so much so that I feel not like a daughter-in-law, but a daughter.

To Grandpa Johnny: you gave so much to us all, you left this life too early, but are always with us.

To Francois, my brother-in-law: your optimism and light-heartedness even when our family chips have been down, have always kept me going.

To Jean, my soul mate of 30 years: your selfless caring for me, your devotion to our family, your wisdom and guidance in all things medical, career direction, and your strength to withstand all, are all the things that have made me what I am today, because of you…

Financial support for the publication of this thesis was generously provided by:
Medistim ASA, Medistim USA, Medtronic Canada, and Ethicon Endosurgery”