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Improving Outcomes of Coronary Revascularization in Diabetic Patients: Can Real-world Data Provide Strategic Decision Support?



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Organization where work was conducted:
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September, 2019

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Declaration

I, Sajjad Raza, hereby grant powers of discretion to the University Librarian to allow the thesis to be copied in whole or in part without further reference to the author. This permission covers only single copies made for study purposes, subject to normal conditions of acknowledgement



PhD Supervisors & Examiners

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Abstract: Coronary artery disease (CAD) is the most common cause of death worldwide making it one of the most important public health issues. For the surgical treatment of CAD, a number of patients, 400,000 in US alone, undergo coronary artery bypass grafting (CABG) each year, making it one of the most widely performed surgeries in the world. During my research fellowship at the Cleveland Clinic, I undertook a series of studies that sought to identify strategies and techniques that improve the short and long-term outcomes of this important procedure. Most of my work was focused towards studying the outcomes of CABG in diabetic patients because patients with diabetes represent an important and growing population of patients undergoing CABG. Through my research work I showed that 1) the patients most likely to benefit from CABG, compared to PCI, are the ones with extensive CAD & comorbidities (like diabetic patients), 2) the proportion of patients undergoing CABG who have diabetes has increased over the last four decades and diabetes is an independent risk factor for worse long-term survival after CABG (20 year survival after CABG: 18% in diabetic patients vs. 42% in non-diabetic patients), 3) diabetes does not influence the long-term patency of coronary artery bypass grafts and, therefore, worse long-term survival after CABG in diabetic patients is likely not related to worse graft durability, 4) surgical revascularization techniques like bilateral internal thoracic artery (ITA) grafting compared to single ITA grafting and complete revascularization compared to incomplete revascularization are associated with better long-term survival in patients with diabetes undergoing CABG, and 5) bilateral ITA grafting and single ITA plus radial artery grafting are equally effective in terms of hospital outcomes and long-term survival for diabetic patients undergoing CABG. Through my research, I also demonstrated how real-world data could be used to provide insights into appropriate strategies for improving the outcomes of different health services and medical procedures.

Abbreviations for Commonly Used Terms

CAD: Coronary artery disease

IHD: Ischemic heart disease

CABG: Coronary artery bypass grafting

PCI: Percutaneous coronary intervention

ITA: Internal thoracic artery

SV: Saphenous vein

SITA: Single internal thoracic artery grafting

BITA: Bilateral internal thoracic grafting

RA: Radial artery

FREEDOM: Future Revascularization Evaluation in Patients with Diabetes

Mellitus: Optimal Management of Multivessel Disease

CVIR: Cardiovascular Information Registry

CASP: Critical Appraisal Skills Program

Chapter 1

Introduction

1.1 Motivation

Ischemic heart disease, also known as coronary artery disease (CAD), is the most common cause of death worldwide [1] making it an important public health issue. Diabetes is a major risk factor for development of CAD [2-4]. Therefore, compared to individuals without diabetes, those with diabetes have a higher prevalence of CAD [5] which can lead to myocardial infarction and death. Treatment options for CAD include medical management, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) surgery. For diabetic patients with complex multivessel CAD, CABG is the revascularization strategy of choice [6]. As the prevalence of diabetes has risen, CAD associated with it has also increased [3]. Today, diabetics represent an important and growing population of patients undergoing CABG [7]. It is, therefore, imperative to identify strategies that improve the outcomes of CABG in this important population so that the thousands of diabetic patients that undergo CABG each year could benefit from its improved outcomes.

1.2 Coronary Artery Disease

CAD refers to the buildup of plaque in the coronary arteries restricting blood flow to the heart. The impedance of blood flow to the heart can result in myocardial ischemia (causing chest pain also known as angina), myocardial infarction (also

known as heart attack) and death. According to the World Health Organization (WHO), CAD is the leading cause of death worldwide [1]. It is responsible for killing over 370,000 people in the US [8] and 73,000 people in the UK annually [9]. According to the American Heart Association (AHA) 2017 statistics, about 16.5 million American adults have CAD [10].

1.3 CABG: Statistics

CABG is one of the most commonly performed major surgical operations in the world, with about 400,000 procedures performed in the US [11] and about 20,000 performed in the UK annually [12].

1.4 CABG: The Procedure

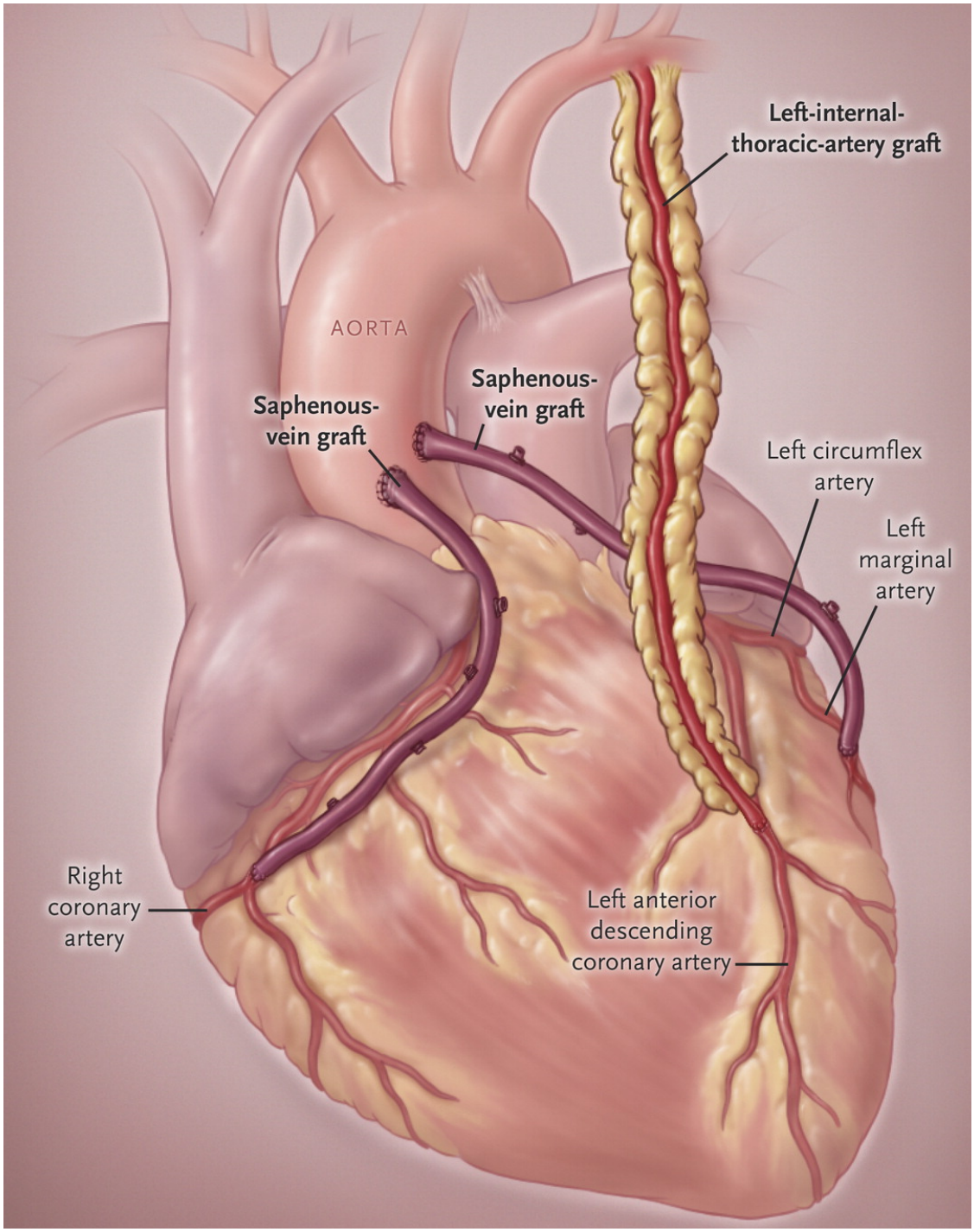
During CABG a healthy artery or vein is taken from elsewhere in the body and is grafted (attached) to a blocked coronary (heart) artery. This allows the grafted artery to “bypass” the blocked or narrowed coronary artery, restoring the blood flow to the heart.

The most commonly used conduits used for bypass grafting include internal thoracic artery (ITA), saphenous vein, and radial artery. The internal thoracic arteries, also known as the internal mammary arteries, are located in the chest wall, one on each side, and have the best patency rates compared to other grafts [13,14]. In a typical CABG operation, the left anterior descending coronary artery is grafted with the left ITA, whereas grafting of the circumflex and right

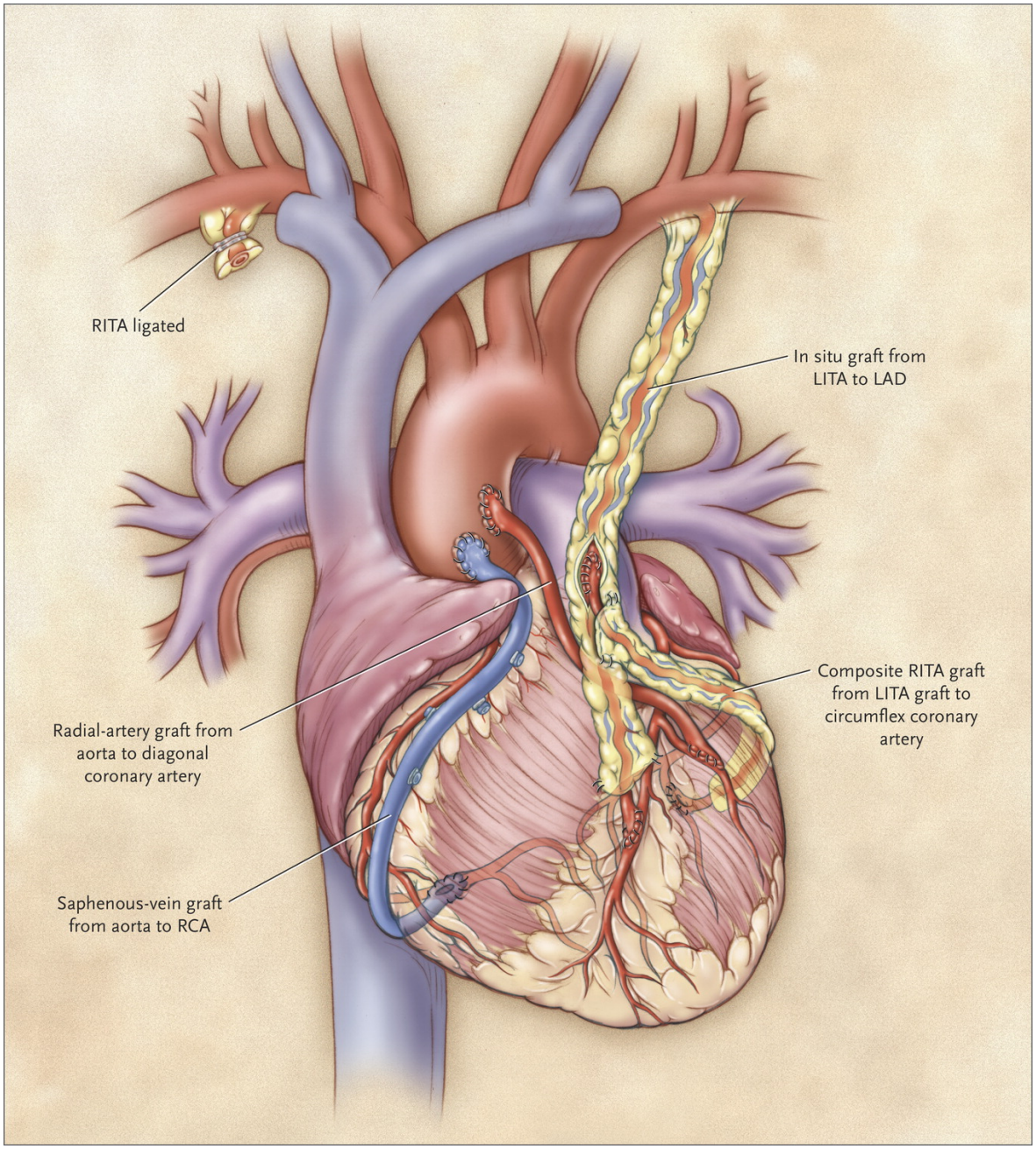
coronary artery systems is done using right ITA, radial or saphenous vein grafts (based on the degree of stenosis, importance of vessel and surgeon preference).

A surgeon can perform CABG operation with or without the help of a heart-lung machine. When a surgeon performs CABG on a non-beating/stopped heart with the help of a heart-lung machine it is referred to as on-pump surgery, whereas, when a surgeon performs CABG on a beating heart without the help of a heart-lung machine, it is referred to as off-pump surgery.

If a surgeon is able to graft all coronary arteries with ≥50% stenosis (i.e. ≥50% diameter narrowing based on visual angiographic assessment), it is referred to as complete revascularization, whereas, when a surgeon does not bypass all coronary arteries with ≥50% stenosis, it is referred to as incomplete revascularization (we used this definition of complete and incomplete revascularization in the paper described in chapter 5 below).



Coronary-Artery Bypass Grafting.
Shown are a left-internal-thoracic-artery graft to the left anterior descending coronary artery and saphenous-vein grafts to the left marginal and right coronary arteries. Reproduced with permission from Alexander JH, Smith PK. Coronary-Artery Bypass Grafting. N Engl J Med. 2016;374(20):1954-64, Copyright Massachusetts Medical Society.



Completed CABG Procedure.
The surgery depicted involves a saphenous-vein graft from the aorta to the right coronary artery (RCA), an in situ graft from the left internal thoracic artery (LITA) to the left anterior descending coronary artery (LAD), a composite right-internal-thoracic-artery (RITA) graft from the LITA graft to the circumflex coronary artery, and a radial-artery graft from the aorta to the diagonal coronary artery.
Reproduced with permission from Jones DS. CABG at 50 (or 107?) - The Complex Course of Therapeutic Innovation. N Engl J Med. 2017;376(19):1809-1811, Copyright Massachusetts Medical Society.

1.5 Diabetes & Coronary Artery Disease

Diabetes is a growing epidemic affecting over 400 million people worldwide [15]. In the US alone, 30.3 million people have diabetes and another 84 million have prediabetes—a condition that, if not treated, can progress to diabetes in only 5 years [16]. Moreover, the number of Americans with diabetes is projected to double or triple by 2060 [17].

There is a wealth of pathological and epidemiological data that shows that diabetes is a major risk factor for the development of various cardiovascular diseases including CAD, stroke, cardiomyopathy and renal disease [18]. CAD amongst these is of particular concern because it is the number 1 cause of death worldwide. The relative risk of myocardial infarction is 2- to 3-fold higher in diabetic patients compared to nondiabetics, independent of the presence of other known cardiovascular risk factors [19,20].

CAD is caused by atherosclerosis [21]. The process of atherosclerosis starts by the adhesion of monocytes to the endothelial cells of arteries. The monocytes then transmigrate into the subendothelial space. These monocytes differentiate into intimal macrophages, which take up lipids (forming foam cells) and accumulate in the artery wall, resulting in accelerated fatty streak formation and triggering the production of the extracellular matrix. This leads to the formation of fibrous plaques which may rupture resulting in the clinical manifestations of CAD [22].

Diabetes accelerates atherosclerosis [4]. Prolonged exposure to hyperglycemia and insulin resistance in combination with other risk factors such as obesity, dyslipidemia and hypertension play critical roles [20]. Insulin resistance in diabetic patients can alter lipid metabolism leading to the development of dyslipidemia which along with endothelial dysfunction (induced by aberrant insulin signaling) contribute to atherosclerotic plaque formation [23]. Hyperglycemia induces many alterations at the cellular level of vascular tissue that potentially accelerate the atherosclerotic process. These include: 1) non-enzymatic glycosylation of proteins and lipids, 2) oxidative stress, and 3) protein kinase C activation. Oxidative stress induced by hyperglycemia can foster the formation of advanced glycosylation end-products and the activation of protein kinase C [4]. Another mechanism by which hyperglycemia can contribute to the progression of atherosclerosis involves the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) [24,25]. This can lead to the expression of inflammatory genes like those of adhesion molecules that facilitate the adhesion of monocytes to arterial endothelial cells [24].

Studies have shown not only the increased prevalence of atherosclerotic plaques in diabetic patients but also the higher propensity of their rupture in these patients. A study based on angiographic data showed that among patients admitted to hospital with unstable angina, plaques were found to be ulcerated in 94% of diabetic patients compared to 60% of non-diabetic patients, and intracoronary thrombus formation was observed in 94% of diabetic patients compared to 55% of non-diabetic patients [26]. A postmortem study of coronary

atherectomy specimens in diabetic vs. non-diabetic patients found greater macrophage infiltration, thrombosis and lipid content in the atheromas of diabetic patients [27]. All these features increase the vulnerability of a plaque to rupture, and the increased thrombogenesis & platelet dysfunction seen in diabetic patients worsen the resulting clinical consequences [19, 28, 29].

A good share of our understanding of the pathophysiology of heart diseases come from the Framingham heart study [2,3]. It is considered a landmark study in cardiovascular sciences and is a long-term ongoing cardiovascular research on residents of the town of Framingham, Massachusetts, USA. This study started in 1948 with 5209 participants, and is now on its 3rd generation of adult subjects. This study also showed that risk of atherosclerotic disease is 2- to 3-fold higher in diabetic patients [2], with CAD as its main sequelae. Data from this study also suggests that duration of diabetes increases the risk of CAD and CAD-related death independent of coexisting risk factors [3].

The high prevalence of CAD in diabetic patients presents a significant burden of disease. The risk of death from CAD is higher in individuals with diabetes [3]. A patient with diabetes is not only at higher risk of developing CAD, but the disease accelerates much faster as compared to non-diabetic patients and the outcomes of treatments are not as good as those in non-diabetic patients [21,30]. Due to accelerated atherosclerosis, CAD in diabetic patients is also more diffused and advanced than that in non-diabetic patients [31,32]. Moreover,

ischemia in cardiac muscle due to CAD usually occurs without symptoms in patients with diabetes [33]. Therefore, multivessel CAD often is present before ischemic symptoms occur and before treatment is instituted. This delay further worsens the prognosis for survival for many diabetic patients [18]. As the prevalence of diabetes has risen, cardiovascular disease associated with it has also increased [3], making it an important area for current and future research efforts.

1.6 Coronary Revascularization in Diabetic Patients: CABG vs. PCI

With increasing diabetes prevalence, the proportion of patients undergoing coronary revascularization procedures who have diabetes has also increased [7, 30]. A number of studies have shown superiority of CABG over PCI for coronary revascularization in diabetics. Data from the Bypass Angioplasty Revascularization Investigation (BARI) trial showed that diabetic patients who underwent PCI had almost a doubled 5-year mortality compared to diabetics who underwent CABG [34]. The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study further showed that prompt revascularization by CABG significantly reduced major cardiovascular events in diabetic patients compared with intensive medical therapy alone [35]. The Coronary Artery Revascularization in Diabetes (CARDia) trial, which was the first randomized trial of coronary revascularization in patients with diabetes, failed to show superiority of CABG over PCI in diabetic patients. This trial, however, was underpowered to make this assertion [36]. In 2012, the landmark FREEDOM trial [11] (Future

Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) demonstrated that CABG, rather than PCI, is the revascularization strategy of choice for diabetic patients with multivessel CAD [6]. This was an RCT that compared CABG and PCI with drug-eluting stents in patients with diabetes & multivessel CAD and found that patients who underwent CABG had significantly lower rates of death and myocardial infarction. A subgroup analysis from Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) trial also showed survival benefit of CABG over PCI in patients with diabetes [37]. A meta-analysis from 8 trials, including 3,612 diabetic patients with multivessel stable CAD, showed that at 5-years of follow-up, patients undergoing CABG had lower all-cause mortality than those undergoing PCI [38].

The explanation for these contrasting findings between outcomes of PCI and CABG may lie in the fundamental differences between the revascularization achieved by these two techniques. PCI treats lesions as they exist at the time of the procedure, relying in the long term on the coronary artery to remain patent distal to the stent. We know that beyond 1 year after stenting, new events result almost exclusively from the progression of disease in segments other than the stented lesion [39]. Compared with PCI, CABG brings a second source of blood flow to the distal coronary artery that, if it remains patent, is independent of possible proximal plaque rupture that may occur with time. Therefore, PCI treats only existing lesions and provides no protection against future lesions, whereas CABG not only treats existing lesions, but also provides prophylactic benefit

against future lesions. Moreover, CABG results in more complete coronary revascularization than PCI, particularly in patients with advanced and complex multivessel CAD, which is often observed in patients with diabetes.

Today, diabetic patients represent nearly 50% of all patients undergoing CABG in the United States [7]. Though the outcomes of CABG in diabetic patients are better than those of PCI, they are worse compared to outcomes of CABG in non-diabetic patients. Therefore, it is important to identify strategies and techniques that improve the outcomes of CABG in this important population.

1.7 CABG in Diabetic Patients: Identifying Research Gaps

The long-term durability of surgical revascularization is one of the key advantages that CABG has over PCI. A number of studies are available looking into the outcomes of CABG in diabetic patients, but there is dearth of literature evaluating long-term data, particularly outcomes beyond 10 years. For example, there are limited studies available studying the long-term angiographic outcomes (graft patency) after CABG in diabetic vs. non-diabetic patients. As mentioned in the systematic review section of chapter 4, the three studies available on this topic only report less than 10-year patency of bypass grafts in diabetic vs. non-diabetic patients (also see section 10.3 in Appendix). No data is available regarding effect of diabetes on long-term (greater than 10 years) bypass graft patency. Similarly, studies reporting the long-term outcomes after different surgical techniques in diabetics, like off- vs. on-pump CABG, bilateral ITA (BITA) vs. single ITA (SITA) grafting, SITA plus RA vs. BITA grafting, and complete vs.

incomplete revascularization, are also limited (see sections 10.4 & 10.5 in Appendix). The studies included in the thesis attempt to fill these important gaps in the literature.

1.8 Venue of Research Work

All papers included in this thesis are based on the work that I did at the Cleveland Clinic during my research fellowship under the supervision of Dr. Joseph F. Sabik and Dr. Eugene H. Blackstone. Dr. Sabik was the Chairman of the Department of Thoracic & Cardiovascular Surgery from 2008 to 2016, and Dr. Blackstone is the Head of Clinical Investigations at the Heart & Vascular Institute of the Cleveland Clinic.

Cleveland Clinic is well known for heart surgery. Coronary angiography was developed in 1958 and CABG was pioneered in 1967 at the Cleveland Clinic. Since 1995, it is ranked number 1 in Cardiology and Cardiac Surgery according to U.S. News & World Report's Best Hospitals 2018-19.

1.8.1 HVI Clinical Investigations

Clinical Investigations for the Heart & Vascular Institute (HVI) of the Cleveland Clinic is a multidisciplinary environment, with activities divided into prospective clinical registries, investigator-initiated studies, statistical and informatics methodology research, and research education. It is divided into two wings, both with card-swipe access to ensure protection of data. It is easily accessible to faculty investigators and mentored medical students, residents, fellows, and NIH

scholars. It is organized according to its major emphases, which means that large portions follow a data-flow model.

Our registry activity currently employs 27 workers, including 12 nurses, an MD MBA quality coordinator, and an RN education coordinator. Their duties include prospective data collection on all adult cardiothoracic surgery cases, cardiac catheterizations, interventional cardiology procedures, and long-term follow-up of selected cohorts. Our medical students, residents, fellows, NIH scholars, and faculty make extensive use of these data for research. In addition, the data are used for quality of care initiatives and internal and external reporting, such as to the Society of Thoracic Surgeons and the American College of Cardiology National Databases. This reporting and research activity are supported entirely by Cleveland Clinic's institutional funds (approximately $4 million per year of operational expenses and $1 million infrastructure capital).

Our investigator-initiated project team is headed by a PhD Clinical Research Administrator, a project manager, a PhD-level database analyst, 1 full-time and 2 part-time statistical programmers, 4 full-time and 1 part-time MS-level statisticians and 1 full-time PhD-level statistician supervised by 2 Quantitative Health Sciences faculty members, and technical staff. These individuals work with the investigators through every stage of their research, from proposal development and refinement through presentation to the HVI Clinical Investigations Council, data analysis, and manuscript preparation.

1.8.2 Registries and Informatics

A group of nurses, research assistants, and a physician concentrate on clinical registry activities, abstracting more than 500 variables from cardiac and thoracic surgery patients' clinical records to form the core data elements for outcomes reporting, quality management, and investigator-initiated research. These data are entered into the Cardiovascular Information Registry (CVIR), a database that contains information on 250,000 patients and 125,000 cardiac operations. It is a prospective database updated concurrently with patient care. Founded in 1972, it is the largest and the longest continuous cardiovascular registry of its kind. Accuracy and availability of registry data are enhanced by the presence of a full-time nurse manager, nurse educator, research project manager, and database personnel. One hundred percent of the outcomes are audited, and a random 10% of cases are re-abstracted and data compared and adjudicated. The registry group also performs follow-up on 10,000 to 15,000 patients per year.

Our data abstractors are held to a 97% error-free rate at the time of their annual performance review to remain in a "fully meets" status. As of October 5, 2018, the last time we were chosen for STS Adult Cardiac audit was 2017, and our agreement rate with the auditor findings was 97.7%. Our nurse abstractors and quality facilitators have clinical backgrounds in the focus of the registries they oversee. Education is ongoing, particularly when there is a version change in the registry, after each national meeting (Society of Thoracic Surgeons Advances in Quality & Outcomes; STS AQO), and when any patterns of error or questions come up. For the past 5 years, we have held an annual abstraction

“boot camp” for our affiliated sites (now open to all, not just affiliated sites) to learn our best practices in abstraction and teach the registry definitions of key fields like risk factors, procedure details, and targeted outcomes.

1.9 Summary of Research Work

The papers presented in this thesis are interrelated and build together a coherent body of work. The thesis follows a narrative linking the papers to build a picture. There is also a temporal angle, going from the first paper to the last, as the findings of the first project led to the conduct and execution of the second project and so on. It is also important to mention that all these projects were collaborative in nature and were conducted with the support of a multidisciplinary research team. Therefore, in recognition of the work of my colleagues I will be using the term “we” to describe design and findings etc.

The initial projects that I worked on when I joined the Cleveland Clinic had been started and designed by others before me but left unfinished. Moving them forward needed consistent effort given their complexity. I chose to work on some of such projects that fit with my overall research objectives, identified the remaining work and analyses needed, worked with the statisticians to complete the analysis, interpreted the data, and drafted papers and followed them to publication under the supervision of my mentors. One such paper is “Survival Prediction Models for Coronary Intervention: Strategic Decision Support” [40]. I included this paper in my thesis (presented in Chapter 2) because appropriate procedure selection is crucial for improving outcomes in patients undergoing

coronary revascularization. Other such projects that I worked on and took to publication are not included in the thesis either because they are not directly related to the theme of my thesis or I am not the lead author on them. All other papers included in the thesis (presented in Chapters 3 through 6) resulted from my primary projects at the Cleveland Clinic that were initiated by me (see section 1.10 for details of my contribution to each paper).

The first research question that I attempt to answer in the thesis is: Which revascularization strategy, PCI or CABG, maximizes long-term survival for a given patient? The survival prediction model paper [40] mentioned in the preceding paragraph helps to answer this question. It shows that for patients with extensive CAD and comorbidities, like diabetic patients, CABG is associated with better long-term survival compared to PCI. This finding, and the findings of FREEDOM trial (described in section 1.6 above), made it imperative to look into the outcomes of CABG in diabetic patients in depth. The second paper (presented in Chapter 3) included in the thesis provides valuable data in this regard. In this paper we sought to determine the 4-decade (1972 to 2011) temporal trends in the prevalence of diabetes and cardiovascular risk factors among patients undergoing coronary surgery, and compare in-hospital outcomes and long-term survival after CABG in diabetic versus non-diabetic patients (see chapter 3) [41]. We found that the proportion of patients presenting for CABG who have diabetes increased each year during the past 4 decades, as did the proportion with cardiovascular risk factors. Moreover, in-hospital outcomes and

long-term survival after CABG were worse in diabetic patients compared to non-diabetic patients.

To investigate whether the worse outcomes of CABG in diabetic patients observed in previous study (presented in Chapter 3) were due to higher failure (occlusion) of bypass grafts in diabetic patients, we undertook a project to determine whether the occlusion of bypass grafts is higher in diabetic vs. non-diabetic patients (see chapter 4) [42]. We found that occlusion of bypass grafts was similar in diabetic and non-diabetic patients, suggesting that the worse outcomes of coronary surgery in diabetic patients are likely not related to worse graft patency and could be due in part to diabetic patients having more comorbidities, as well as a progressive disease that leads to many complications.

One of the most important finding of our previous study (presented in Chapter 4) was that ITA grafts have excellent long-term patency in both diabetic and non-diabetic patients even 20 years after CABG. Because the effectiveness of CABG is directly related to long-term graft patency, one can hypothesize that use of two ITA grafts (BITA grafting) compared to using one ITA graft (SITA grafting), would lead to better long-term survival after CABG in diabetic patients. Therefore, in our next project (presented in Chapter 5), we tested this hypothesis [43] and found that use of two ITA grafts vs. one was associated with better long-term survival but at the cost of increased risk of post-operative sternal wound infections. Therefore, we recommended in our paper that the use of two ITA grafts should be considered in all diabetic patients undergoing CABG whose risk of developing sternal wound infection after CABG is not high.

Because the use of two ITAs was associated with higher risk of sternal wound infections in our previous study (presented in Chapter 5), in our subsequent project (presented in Chapter 6) we sought to determine whether the use of one ITA plus a radial artery graft (SITA+RA grafting) yields outcomes similar to those of two ITA grafts (BITA grafting) in diabetic patients undergoing CABG [44]. We found that the long-term survival after CABG in diabetic patients was similar with these two arterial grafting strategies and concluded that in those diabetic patients whose risk of developing sternal wound infections is high, the use of one ITA plus a radial artery graft can be considered instead of using two ITA grafts, as both grafting strategies were associated with similar long-term survival.

It is important to note that CABG was pioneered at the Cleveland Clinic in 1967 [45]. The work presented in this thesis is mostly based on patients who underwent primary isolated CABG at the Cleveland Clinic from 1972 to 2011. The long period of studies enabled us to evaluate the effect on outcomes of different surgical techniques that required passage of time to reveal their advantages or disadvantages. However, a lot has changed in these years in terms of patient case-mix and advances in surgical and medical therapy of CAD that may negate our findings, and their applicability to contemporary patients could be questioned.

There have been several advancements in surgical techniques over the course of these years including the use of two ITA grafts vs. one ITA graft, radial artery grafts, off-pump (beating heart) surgery, and methods of myocardial

protection (some of these advancements are also the focus of the studies included in the thesis). There have been advancements in pre-operative and post-operative management like better understanding of risk factors of sternal wound infections, stroke and other post-operative complications leading to improvement in outcomes of CABG in recent years compared to earlier years. Of particular importance are the advances in medical therapy like the use of secondary preventive therapies after CABG. They play an important role in the management of patients recovering from CABG. These therapies slow the disease process and prevent adverse cardiac events both in the short and long term [46]. According to recent guideline statements [47,48], postoperative lipid-lowering agents like statins & antiplatelet therapies like aspirin continue to be mainstays of secondary prevention. Statins decrease the progression of native coronary artery atherosclerosis, slow the process of atherosclerosis in vein grafts, and lower adverse cardiac events after CABG [46,47,49]. Aspirin lowers the risk of stroke, myocardial infarction, and vascular death in patients with CAD. Therefore, all CABG patients are candidates for long-term aspirin therapy [46].

To account for patient factors and medical advancements that may have changed over time and affected our study outcomes, but could not be included in the analyses, we used date of operation as a surrogate. However, the medical and surgical advances after the study periods could not be taken into consideration, so caution should be used when drawing conclusions about implications for clinical practice today.

It is also important to note that in all studies presented in the thesis, ≥50% stenosis was considered significant or clinically important as traditionally the presence of a 50% diameter stenosis has been used as the threshold value for treatment [50]. In several landmark studies too like the Veterans Administration (VA) Cooperative Study [51], BARI trial [52] and SYNTAX trial [53], a stenosis of 50% was defined as significant or clinically important. However, it is important to note whether a stenosis is measured in terms of diameter or cross-sectional area because the two percentages do not correspond [54]. In our studies, and in the landmark studies mentioned above, a 50% stenosis that was considered significant refers to the ≥50% diameter narrowing of the coronary artery in question and this equates to a 75% cross-sectional area narrowing [54] because the 50% diameter narrowing and 75% cross-sectional area narrowing are related by the equation: cross sectional area = pi x square of radius. Compared to angiography, which provides a two dimensional luminal silhouette with little information about the vessel wall, intravascular ultrasound gives a cross-sectional, three-dimensional image of the full circumference of the coronary artery [55] and, therefore, can be used to clarify ambiguous angiographic findings. However, it is not generally used in clinical practice because of the need for an operator experienced in its use and its expense [55]. The stenosis data used in all studies presented in this thesis is based on coronary angiography which represents the real-world approach as clinical decision making is virtually always based on angiographic assessment of stenosis in coronary arteries.

1.10 My Contribution to Research Projects

Except for the first paper (basis of chapter 2), where my responsibilities were limited to step 6 and onwards, my responsibilities in all other papers included in the thesis were:

1) Conceiving and designing the study
2) Writing the proposal of each study
3) Working with statisticians on development of analysis plan
4) Working with database managers on the acquisition of data
5) Collection of data not available in existing registries through review of patients' charts
6) Collaborating with statisticians for statistical analyses
7) Interpreting the data
8) Drafting the manuscript and seeing it through submission
9) Presenting the study findings in scientific meetings
10) Working on reviewer's comments

Co-investigators who collaborated on the projects and met ICJME guidelines of authorship were included as co-authors on studies.

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Chapter 2

Research Question 1—Which Revascularization Strategy, PCI or CABG, Maximizes Long-term Survival for a Given Patient?

Based on Publication: Raza S, Sabik JF 3rd, Ellis SG, Houghtaling PL, Rodgers KC, Stockins A, Lytle BW, Blackstone EH. **Survival Prediction Models for Coronary Intervention: Strategic Decision Support.** Ann Thorac Surg. 2014;97(2):522-8.

2.1 Rationale

CABG vs. PCI has been a subject of debate among cardiologists and cardiac surgeons who treat patients with coronary artery disease (CAD) [1], and a number of studies compare these revascularization strategies [2-14]. Class 1 evidence suggests that CABG is recommended for improving survival in patients with significant (≥50% diameter) left main trunk stenosis; in those with significant (≥70% diameter) stenosis in three major coronary arteries, with or without proximal left anterior descending involvement; and in those with significant (≥70% diameter) stenosis in the proximal left anterior descending plus 1 other major coronary artery [15]. Contrary to these guidelines, a number of patients are revascularized with non-optimal strategies [16,17]. Furthermore, some patients are not typical candidates for either PCI or CABG. Decision-support tools are

needed as a cognitive aid to help identify the best revascularization strategy for these atypical patients.

A number of mathematical models are available to predict procedural or in-hospital mortality after PCI or CABG and to guide clinical practice [19-27]. However, there are very few risk models that can predict long-term survival after these procedures. Because the survival advantage of surgery becomes evident with time, it is important to have models capable of predicting which revascularization strategy—PCI or CABG—maximizes long-term survival for a given patient. Therefore, the first question that we sought to answer was to identify patients that would benefit more from CABG than PCI.

2.2 Summary of Study Design & Methods

From 1995 to 2007, 23,182 patients underwent primary isolated CABG (n=13,114) or first-time PCI with bare-metal stents (BMS; n=6,964) or drug-eluting stents (DES; n=3,104) at the Cleveland Clinic.

The study end point was time from intervention to all-cause mortality. Vital status after hospital discharge was obtained from routine anniversary follow-up and supplemented with data from the Social Security Death Master File. Using these data, we developed variable-rich models for predicting 10-year survival after CABG and PCI with BMS and 5-year survival after PCI with DES. The models contained factors (25 variables) ranging from demographics to symptomatology to cardiac and noncardiac comorbidities. We then used these models to develop a computerized tool able to show individualized survival

curves based on easily entered data to help physicians and surgeons make recommendations about interventional therapy for individual patients, and to inform patients of the survival risks and benefits of these therapies. We only studied long-term survival because other long-term outcomes data, such as quality of life and need of repeat revascularization after surgery vs. PCI, was not available for these patients.

2.3 Summary of Results

Using this tool, we found that many patients received therapy that was not optimal for their individual characteristics. We also found that patients most likely to experience a 5-year survival benefit from DES were those undergoing emergency revascularization for acute infarction, and patients most likely to benefit from CABG had extensive CAD and multiple comorbidities (like patients with diabetes; see Figure 4 and Table 2 of manuscript). We concluded that because treatment modalities for CAD are becoming more complementary than competitive, it is increasingly important to take a “heart team” approach to treatment to ensure that every patient receives the optimal therapy (heart team approach basically refers to the collaboration between cardiologists and cardiac surgeons to determine the best treatment plan for a given patient with heart disease). A variable-rich, programmed, decision-support tool based on detailed prediction models for prognosis after PCI and CABG would aid both cardiologists and cardiac surgeons in identifying the revascularization therapy that maximizes long-term survival in a given patient with CAD. Nevertheless, it is important to

remember that computers are not doctors, and it is both impossible and unwise to take the human element out of the decision tree. A decision-support tool can be used, however, to confirm that we are not making biased or wrong decisions, and that we are offering each of our patients the best available information to allow them to make more informed decisions about their own health care. One may ask why we should keep humans in the decision process if humans are more prone to error than computers, especially a computational model that takes all important variables into account. One counter argument to this is that our model is based on observational data, so only measured confounders are accounted for in the model. Unlike randomized controlled trial data, unmeasured confounders are not accounted for in observational data.

2.4 Findings Compared to Other Studies

In 2012, two separate models were developed to predict 3-year survival after PCI and CABG using the STS and ACC databases, respectively [28,29]. One limitation of these models is that they are applicable only to patients over age 65. Moreover, they can only predict 3-year survival whereas our model can predict survival for up to 10 years.

MacKenzie et al [30] developed and internally validated models that accurately predict long-term survival after CABG and PCI using routinely available variables. To do so, they linked CABG and PCI data from northern New England registries on 35,000 patients, with complete data on risk factors, to the National Death Index, ascertaining 7,000 deaths. These models predicted

survival for up to 8 years after coronary revascularization. However, a major limitation of these models was that they were developed using PCI data from 1992 to 2001 and thus do not account for advances in PCI, including use of drug eluting stents.

SYNTAX score is another available risk prediction tool. Although a high SYNTAX score suggests worse long-term outcomes after PCI, it does not influence surgical outcomes [31,32]. This is likely because it is based on coronary anatomy rather than patient characteristics such as age, diabetes, and renal failure, which are strong predictors of outcomes after CABG [31]. To address this, SYNTAX score II was developed which included important patient characteristics like age, ejection fraction, and creatinine clearance to predict survival up to 4 years [33]. Three things distinguish our model from SYNTAX score II. First, we have separately, although simultaneously, evaluated risk factors for death early after the procedure and later. The factors generally have different strengths in each of these eras, indicative of nonproportional hazards; SYNTAX score II assumes proportional hazards. Second, we have incorporated more clinical variables in our models, which tend to yield better predictions for patients with extremes of some variables, such as age, and combinations of variables (complex patients). Third, and a drawback of our model, is that SYNTAX score II includes the SYNTAX score itself, which is difficult to calculate retrospectively. This limitation is not so important for CABG, but is more important when considering PCI [31,32,34].

2.5 Addition to Literature in Light of Systematic Review

A systematic literature search was done to identify studies that already existed on this topic at the time of paper preparation/publication so that the addition to the literature that the study made could be effectively evaluated in the light of existing knowledge on the subject. Details of this systematic review are given in the Appendix (see section 10.1). Briefly, we searched the literature to identify prediction models that predict long-term survival after CABG vs. PCI to compare the strength and limitation of our risk model against those. Only models predicting long-term mortality/survival to at least 5 years after CABG and PCI were included. There was only one study identified that met the specified inclusion criteria. This study by MacKenzie and colleagues developed risk models for predicting short-term, mid-term, and long-term outcomes after PCI and CABG [30]. These models can predict survival after coronary revascularization out to 10 years. However, a major limitation is that they were developed using 1992–2001 data and thus do not account for advances in PCI, including use of DES. Our models can predict survival up to 10 years for CABG and BMS, and up to 5 years for DES and thus represent a valuable addition to the literature.

2.6 Critical Commentary

This appraisal was done using a modified version of PROBAST checklist [35].

2.6.1 Rationale: When developing a clinical prediction model (CPM), it is recommended to explain the clinical context and rationale with references to existing prediction models [36]. One of the reasons for this is to avoid creating many redundant similar CPMs for the same clinical problem.

We developed prognostic models using patients who underwent coronary revascularization procedures. In the introduction section, we argued for developing a new CPM for long term mortality because existing ones only addressed short term in-hospital mortality. However, in the discussion section we cited five CPMs that assessed 3- to 10-year outcomes (references 32-37 of the paper). A reader might wonder whether updating or validating these existing CPMs was considered before it was decided to make a completely new CPM. Regarding this concern, we provided details in discussion section contrasting each available long-term model with our risk prediction tool and the need for developing a new one. However, we could have been clearer about this by putting some information about existing long-term models, and the rationale of developing a new one, in the introduction of the paper.

2.6.2 Participant Selection: We used an appropriate data source, a good size (n = 23,183) cohort from our institution, for creating the CPM. We mentioned in the paper that patients undergoing PCI who had prior CABG were excluded but patients undergoing CABG who had prior PCI were included. We should have provided the rationale for doing so. The issue here was that patients increasingly

come to surgery after one or more PCI procedures, so keeping such patients in the study kept the decision tool closer to reality.

One of the limitations of this study was that it was based on observational data. To provide decision support and to inform patients about the comparative survival outlook of each therapy, a CPM based on data from a randomized controlled trial would have been ideal. However, randomized controlled trials are not always feasible for studying comparative effectiveness of surgical therapies because of lack of equipoise. Moreover, for predicting long-term survival after CABG and PCI, long-term follow-up data is needed which is often not feasible to obtain in clinical trials due to lack of resources and loss-to-follow-up due to various reasons.

2.6.3 Outcomes: The time from intervention to death was a sensible outcome. We mentioned that vital status was obtained from routine anniversary follow-up supplemented with data from the Social Security Death Master File. A reader might question whether the routine anniversary follow-up was used to verify outcomes of all patients and if this was not the case, were there outcomes that were only verified by Social Security Death Master File. This is a very important issue because incomplete or differential verifications can influence the results (verification bias). I think we could have provided more details of the follow-up in our study, particularly about the routine anniversary follow-up. Median follow-up was provided for long-term mortality along with mean follow-up as the distribution of survival data is usually (positively) skewed. Please see section 3.6.5 for details

regarding critical commentary on our follow-up.

2.6.4 Predictors: Reading our paper, a reader might think that little details were provided regarding the analysis and identification of predictors. How and when were the predictors assessed? What were the definitions of predictors? These are some of the crucial items needed to judge the validity of a derivation study. More details regarding variable selection and identification of risk factors would have been beneficial.

To identify risk factors for death, multivariable analyses were performed in the multi-phase hazard function domain for each of the three groups separately. Variables considered in the analysis were listed in the appendix of the paper. Variable selection utilized bootstrap bagging with resampling of 500 datasets, and identification of variables with automated forward selection and retention of variables in the models with $p \leq 0.05$. All variables with bootstrap reliability of 50% or greater were retained in the guided analysis. In addition to these reliable factors, at least one variable representing every cluster of variables was also added since these are predictive models and parsimony was not the goal. Three separate predictive survival models were created, one for CABG, a second for PCI with DES, and a third for PCI with BMS.

2.6.5 Sample Size: Sample size calculation was not done. This was a retrospective cohort study of patients who underwent primary isolated CABG and first time PCI at the Cleveland Clinic during a given time period. Therefore,

sample size calculation would not have affected the number of patients included. A common misconception is that the larger the study group, the larger the amount of information available for analysis of an event. For outcome events, the effective sample size is number of events, not total study size. Thus, sufficient data means a sufficient number of events associated with individual risk factors (37). Therefore, we should have provided more information regarding the number of predictors considered initially in the analysis and the number of patients with outcome events (i.e. death) to determine whether the sample size was adequate. Because all predictors mentioned in Appendix of the paper were considered initially, one could say that it is highly likely that the sample size was inadequate particularly for the DES model (n=3201). Based on empirical data, a general rule of thumb is 10 outcome events are needed for each continuous predictor variable and for each level of categorical variables initially considered (not only predictors in the final model) [38]. There were more than 60 predictors mentioned in the Appendix of the paper. If all of them were considered initially, we needed at least 600 outcome events. This can lead to overfitting of model. Usually, carefully justifying predictor variables likely to be associated with the outcome, using large enough sample size for the number of predictors tested, and conducting internal validation can prevent or reduce overfitting problem. Another disadvantage of "predictor-rich" models is that they are not necessarily user-friendly.

Table 1 of paper shows that there were some missing data. We could have provided more information regarding handling of missing data (for e.g. imputation, which was done).

2.6.6 Data Analysis: Throughout the paper, we drew causal inference based on observational data, which was not appropriate given the study design. Risk-adjustment in observational studies can control for measured factors but not unknown factors. For drawing causal inferences, data from an RCT should have been used.

Predictive performance was not reported (e.g. discrimination, calibration). Without the model specification and how to calculate the risk, it is not possible for these models to be externally validated or implemented in clinical practice.

It was also not mentioned whether imputation for missing values was performed. We did impute for missing values in the analysis.

It was not clearly stated why a multiphase hazard model was used instead of the usually applied Cox regression model. We used a multiphase hazard model instead of the Cox model because the Cox model is proportional in hazard, an assumption usually made, but often not realistic. We chose a multiphase hazard model because it non-arbitrarily decomposes hazard into time-overlapping temporal components based on the data and permits simultaneous assessment of risk factors (like diabetes and no diabetes) in discrete time-based phases. This method allows to assess non-proportional hazards, a feature that is common to interventional and surgical procedures (like CABG) that carry transiently high early risk that falls rapidly to a much lower level after a variable duration of recovery, and later rises.

Lastly, the rationale behind using 68% confidence limits instead of 95%

confidence limits was not provided. As nicely explained in the Chapter 6 of the Kirklin/Barratt-Boyes textbook, Cardiac surgery [39], the confidence limits are frequently used as scanning tools to help predictions and comparisons, either of proportions or time-related depictions. If only moderate certainty is desired that the evident difference is a true difference and would be found in larger samples, 50% confidence intervals might be chosen. However, if great certainty is required in the inference that there is a difference between two proportions of time- related depictions, 95% confidence intervals may be chosen for the comparisons. Most situations in cardiac surgery seem to lie somewhere between these extremes, so the use of 70% confidence limits for most comparisons is reasonable. Confidence limits of 70% (actually 68.3%) are equivalent to 1 standard deviation, and confidence limits of 95% to 2 standard deviations. For consistency, if other numeric estimates are presented to 1 standard deviation, 70% confidence limits should be used, and if 2 standard deviations are presented, 95% confidence limits should be used. We recommend consistency because we believe surgeons should become acquainted with using confidence limits as a scanning tool. To use a tool effectively, it is helpful to be consistent among all measures of uncertainty.

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2.8 Full-text of the Paper

ADULT CARDIAC

Survival Prediction Models for Coronary Intervention: Strategic Decision Support

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Background. For a given patient with coronary artery disease, it is uncertain which therapy, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), maximizes long-term survival. Hence, we developed survival models for CABG and PCI using bare-metal stents (BMS) or drug-eluting stents (DES), programmed a decision-support tool, and identified its potential usefulness.

Methods. From 1995 to 2007, 23,182 patients underwent primary isolated CABG (n = 13,114) or first-time PCI with BMS (n = 6,964) or DES (n = 3,104). Follow-up was 6.3 ± 3.9 years. Survival models were developed independently for each therapy, then all factors appearing in any of the three models were forced into a final model for each. These were programmed into a decision-support tool. Predicted differences in 5-year survival for the same patient among the three therapies were calculated.

Results. Unadjusted survival was 96%, 86%, and 68% at 1, 5, and 10 years after CABG, 94%, 83%, and 68% after BMS, and 95% and 84% (no 10-year estimate) after DES, respectively. Risk factors for early and mid-term mortality were identified, leading to variable-rich (25 variables) prediction models. Patients most likely to experience a 5-year survival benefit from DES were those undergoing emergency revascularization for acute infarction, and patients most likely to benefit from CABG had extensive coronary artery disease and numerous comorbidities.

Conclusions. Detailed prediction models for prognosis after PCI and CABG are useful for developing a clinically relevant, strategic decision-support tool that reveals who may experience a long-term survival benefit from each modality.

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A number of models are available for benchmarking in-hospital mortality after percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG) [1–9]. However, for a given patient with coronary artery disease, it is uncertain which therapy maximizes long-term survival. Therefore, we sought to develop models of long-term survival among patients with coronary artery disease after treatment by CABG or PCI with either bare-metal stents (BMS) or drug-eluting stents (DES) to provide decision support for cardiologists and cardiac surgeons making recommendations about interventional therapy, and to inform patients about the comparative survival outlook of each therapy.

Patients and Methods

From 1995 to 2007, 23,182 patients underwent primary isolated CABG (n = 13,114) and first-time BMS (n = 6,964) or DES (n = 3,104) at Cleveland Clinic.

Patients were identified and preoperative, procedure, and postprocedure morbidities retrieved from the Heart and Vascular Institute's prospective cardiovascular information and PCI registries (National Cardiovascular Disease Registry). These databases were approved for use in research by the Institutional Review Board, with patient consent waived. Patients undergoing PCI who had prior CABG were excluded. Patients undergoing CABG who had prior PCI were not excluded to keep the models closer to reality. Preintervention patient characteristics, including demography, noncardiac comorbidity, cardiac morbidity, and coronary anatomy, were harmonized between CABG and PCI registry variables.

Endpoint

Study endpoint was time from intervention to all-cause mortality. Vital status after hospital discharge was obtained

Dr Sabik discloses financial relationships with Abbott and Medtronic.

The Appendix can be viewed in the online version of this article [http://dx.doi.org/10.1016/j.athoracsur.2013.06.099] on http://www.annalsthoracicsurgery.org.

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from routine anniversary follow-up and supplemented with data from the Social Security Death Master File [10, 11], accessed on May 18, 2009; the closing date was January 18, 2009; 144,050 patient-years of follow-up data were available for analysis. Mean follow-up was 6.3 ± 3.9 years (median 6.8). Data on the first DES patients were available from 2001. Mean follow-up for this group was 3.6 ± 1.3 years (median 3.7; 15th and 85th percentiles, 2.4 and 5 years, respectively).

Data Analysis

OVERALL SURVIVAL. Overall and stratified nonparametric survival estimates were obtained using the Kaplan-Meier method. A parametric method was used to resolve number of phases of instantaneous risk of death (hazard function) and to estimate shaping parameters [12]. To make less biased overall survival comparisons, matched patient groups were formed based on patients' propensity to be in the DES versus CABG groups and BMS versus CABG groups [13]. Variables in the logistic propensity models are identified in the Appendix.

SURVIVAL MODELS AND DECISION-SUPPORT TOOL. To identify risk factors for death, multivariable analyses were performed in the multiphase hazard function domain, separately for each of the three groups. Variable selection used variables listed in the Appendix. We then amplified the three prediction models to include all variables identified in each model. Next, we used these models to develop a computerized tool able to show individualized survival curves and their confidence limits for each therapy based on entered data.

OPTIMAL VERSUS ACTUAL TREATMENT. By solving the three models for individual characteristics, three predicted survival curves were generated for every patient in the study. Difference in 5-year and 10-year survival for each patient, based on these three therapies, was calculated (5 years only for DES) using the assumption that all coronary anatomy was addressable by PCI.

PRESENTATION. Categorical variables are summarized by frequencies and percentages and continuous variables by mean ± SD. To consistently express degree of uncertainty and variation, medians are accompanied by 15th and 85th percentiles, equivalent to ± 1 SD, and survival estimates are enclosed within 68% asymmetrical confidence bands equivalent to ± 1 SE. For data analysis, SAS versions 8.2 to 9.1 (SAS Institute, Cary, NC) were used.

Results

Preprocedural Group Differences

Although age was similar across the three treatment groups, many patient characteristics differed substantially (Table 1). Left ventricular function was worst in the

Table 1. Patient Characteristics

Variable	CABG (Total n = 13,114)		DES (Total n = 3,104)		BMS (Total n = 6,964)		*p* Value
	n[a]	Count	n[a]	Count	n[a]	Count	
Demography							
Age, years	13,114	64 ± 11	3,104	65 ± 12	6,964	64 ± 12	<0.0001
Female	13,114	3,295 (25)	3,104	1,140 (37)	6,964	2,347 (34)	<0.0001
Body mass index, kg · m^{-2}	13,095	29 ± 5.4	3,104	30 ± 6.2	6,835	29 ± 7.4	<0.0001
Emergency status	13,114	262 (2.0)	3,104	349 (11)	6,963	823 (12)	<0.0001
Cardiac comorbidity							
Myocardial infarction	13,113	7,510 (57)	3,104	3,055 (98)	6,964	6,464 (93)	<0.0001
No. of systems diseased[b]	13,033		3,104		6,962		<0.0001
0		140 (1.1)		1 (0.03)		10 (0.14)	
1		1,114 (8.5)		1,218 (39)		3,330 (48)	
2		3,213 (25)		1,175 (38)		2,471 (35)	
3		8,566 (66)		710 (23)		1,151 (17)	
LMT diseased[b]	12,978	2,927 (23)	3,098	94 (3.0)	5,215	122 (2.3)	<0.0001
Heart failure	13,114	2,605 (20)	3,103	301 (9.7)	2,516	244 (9.7)	<0.0001
Unstable angina	13,114	4,422 (34)	3,104	1,000 (32)	6,964	3,726 (54)	<0.0001
Noncardiac comorbidity							
Treated diabetes mellitus	13,114	4,317 (33)	3,104	821 (26)	6,964	1,265 (18)	<0.0001
Hypertension	12,765	9,851 (77)	3,104	2,374 (76)	6,955	4,675 (67)	<0.0001
Smoking	12,974	8,375 (65)	3,104	2,032 (65)	6,964	4,469 (64)	0.5
COPD	10,451	2,401 (23)	3,104	398 (13)	6,963	712 (10)	<0.0001
History of renal disease	13,114	700 (5.3)	3,104	152 (4.9)	6,963	327 (4.7)	0.13
Creatinine, mg · dL^{-1}	12,160	0.8/1.0/1.4	3,070	0.7/0.90/1.3	4,286	0.8/1.0/1.4	<0.0001

[a] Patients with data available. [b] Stenosis 50% or more in left anterior descending coronary artery (LAD), left circumflex (LCx), or right coronary artery (RCA) systems (eg, 0-system disease was present in patients with left main trunk [LMT] disease).

Values are number and percent, mean ± SD, or 15th/50th/85th percentiles.

BMS = bare-metal stent; CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; DES = drug-eluting stent.

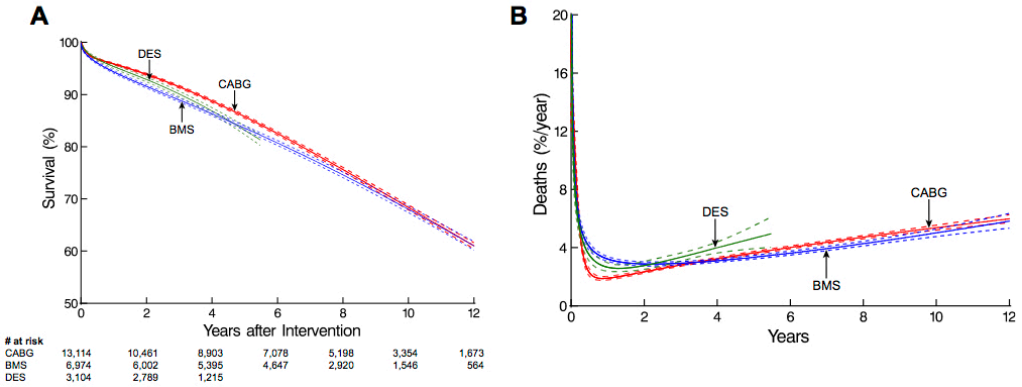


Fig 1. Unadjusted mortality after coronary intervention. (A) Survival according to type of intervention. Dashed lines represent 68% confidence bands equivalent to ± 1 SE. Numbers of patients remaining at risk are below horizontal axis. (B) Instantaneous risk of death. Depiction is as for (A). Note that all interventions are associated with an early rapidly declining phase of risk, a period of constant risk, and a rising phase of risk.

CABG group and best in the BMS group. Chronic obstructive pulmonary disease and diabetes mellitus were more common in the CABG group, whereas female sex, emergency treatment, and myocardial infarction were more common in both PCI groups. CABG tended to be performed for three-system disease and PCI for one-system and two-system disease.

Overall Survival

Unadjusted overall survival at 1, 5, and 10 years was 96%, 86%, and 68%, respectively, after CABG; 94%, 83%, and 68%, respectively, after BMS; and 95% and 84% (at 1 and 5 years) after DES (Fig 1A). The hazard function resolved to three phases, with an early rapidly declining phase of high risk in the first 6 months, a constant phase lasting about 5 years, and a late rising phase thereafter (Fig 1B). Early overall survival was similar between the CABG and DES groups, but patients with BMS had decreased survival compared with CABG patients in the early and constant hazard phases ($p < 0.008$), and similar survival in the late phase. Among propensity-matched patients, CABG offered an overall survival advantage over PCI with BMS ($p < 0.0001$ both early and late) or DES ($p = 0.3$ early, $p = 0.002$ late) that widened over time (Fig 2).

Risk Factors for Mortality

Twenty-five variables were identified in either early or late hazard phases as risk factors among the three therapies (Table 2). Of these, 16 were in common and in the same direction among all therapies, including older age, emergency status, more extensive coronary artery disease and left main trunk disease, impaired ventricular function, heart failure, and many comorbidities, the latter particularly in the late hazard phase. These 25 variables result in

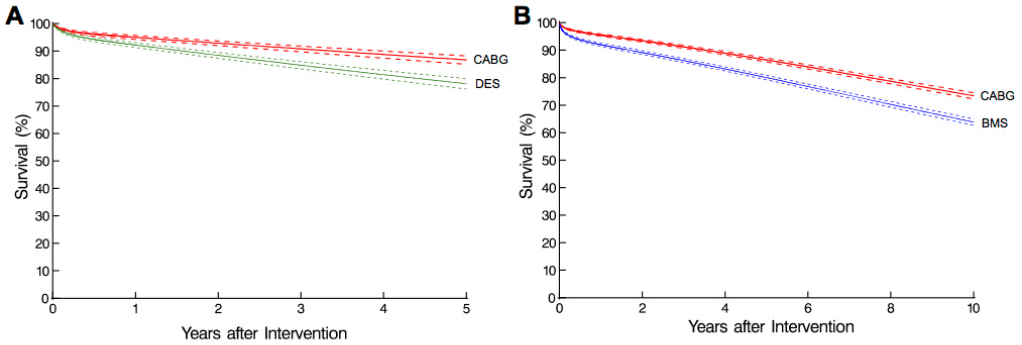


Fig 2. Death among propensity-matched patients after coronary intervention. Format is as for Figure 1A. (A) CABG versus DES patients to 5 years. (B) CABG versus BMS patients to 10 years. (BMS = bare-metal stent; CABG = coronary artery bypass graft surgery; DES = drug-eluting stent.)

Table 2. Incremental Risk Factors for Death

Factor	CABG (n = 13,114)	DES (n = 3,104)	BMS (n = 6,964)
Early phase			
Age	↑	↑	↑
Body mass index	↓↑	↑	—
Emergency status	↑	↑	↑
LV ejection fraction	↓	↓	↓
Mitral regurgitation severity	—	↑	—
Three-system CAD	—	↑	↑
Left main trunk stenosis	—	—	↑
Systolic blood pressure	—	↓	↓
Diastolic blood pressure	—	↑	—
Preoperative atrial fibrillation	↑	—	↑
Previous myocardial infarction	↑	—	—
Treated diabetes mellitus	↑	↑	↑
Heart failure	↑	—	—
Stroke	↑	—	—
COPD	↑	↑	↑
History of renal disease	↑	—	↑
Hematocrit	↓	—	—
Intervention to LAD	—	—	↑
Late phase			
Age	↑↓	↑	↑
Female	↑	—	—
Body mass index	↓	↓	↓
Weight	↑	—	—
LV ejection fraction	↓	—	↓
Mitral regurgitation severity	—	—	↑
Three-system CAD	↑	↑	↑
LMT stenosis ≥70%	↑	↑	↑
Preoperative atrial fibrillation	—	↑	—
History of malignancy	↑	↑	↑
Treated diabetes mellitus	↑	↑	↑
History of hypertension	—	—	↑
Heart failure	↑	↑	↑
Stroke	↑	↑	↑
COPD	↑	↑	↑
History of renal disease	↑	↑	↑
History of smoking	↑	↑	↑
Creatinine	↑	—	↑
Creatinine clearance	↓	↓	—

[↑] is associated with significant increase in risk with increased value of variable. [↓] is associated with significant decrease in risk with decreased value of variable. [↑↓] indicate nonlinear association with risk. BMS = bare-metal stent; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DES = drug-eluting stent; LAD = left anterior descending coronary artery; LMT = left main trunk; LV = left ventricular.

wide distributions of survival for each therapy that departed substantially from average overall survival (Fig 3).

Optimal Versus Actual Treatment

Of the 23,182 patients, 5-year survival was best after CABG in 17,436 (75%), DES in 5,658 (24%), and BMS in 88 (<1%). CABG was worse than DES for 5,690 (25%) and BMS for 393 (1.7%). However, 68% confidence limits of the survival estimate for CABG separated above those of DES in 11,989 instances (52%) and above those of BMS in 21,804 instances (94%). Similarly, these confidence limits separated below those of DES in 2,031 instances (8.8%) and below those of BMS in 109 (0.47%).

Decision-Support Tool

Figure 4 shows a screenshot of the decision-support tool derived from this study, depicting survival by each intervention in a 74-year-old diabetic man with 70% left main trunk disease and mild ischemic mitral regurgitation. Early procedure survival is similar among interventions, but after about 1 year, survival is predicted to diverge, with CABG the best long-term therapy.

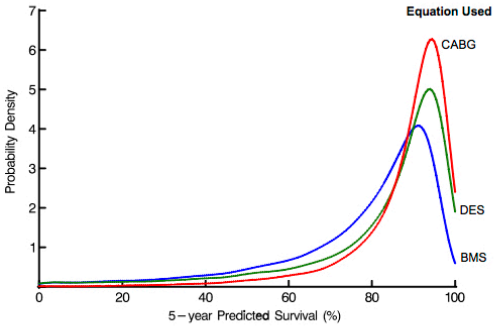


Fig 3. Distribution of predicted values for 5-year survival calculated by solving three multivariable equations for each patient receiving coronary artery bypass graft surgery (CABG), percutaneous coronary intervention (PCI) with drug-eluting stent (DES), or PCI with bare-metal stent (BMS).

Comment

Among cardiologists and cardiac surgeons treating patients with coronary artery disease, CABG versus PCI has long been a subject of debate [14], and a number of studies compare these revascularization strategies [15–28]. Class I recommendation with level of evidence A suggests that CABG is recommended for improving survival in patients with significant (>50% diameter) left main trunk stenosis; in patients with significant (>70% diameter) stenosis in three major coronary arteries, with or without proximal left anterior descending involvement; and in patients with significant (>70% diameter) stenosis in the proximal left anterior descending plus one other major coronary artery [29]. However, contrary to these guidelines, a number of patients are revascularized using a nonoptimal strategy [30, 31]. Furthermore, some patients are not typical candidates for either PCI or CABG. It is for these atypical patients that decision-support tools are needed as a cognitive aid to help identify the best revascularization strategy.

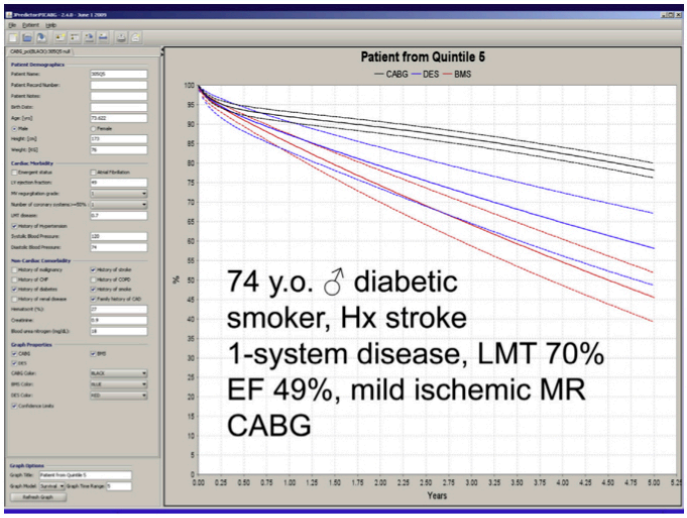
Several mathematical models are available to predict procedural or in-hospital mortality after PCI or CABG and to guide clinical practice [1–9]. However, few risk models predicting long-term survival are available to support clinical practice. Because the survival advantage of surgery becomes evident with time, it is important to have models capable of predicting which revascularization strategy—PCI or CABG—maximizes long-term survival for a given patient.

Principal Findings

We developed variable-rich models for predicting 10-year survival after CABG and PCI with BMS and 5-year survival after PCI with DES. They contained factors (25 variables) ranging from demographics to symptomatology to cardiac and noncardiac comorbidities. We then used these models to develop a computerized tool able to show individualized survival curves based on easily entered data to help physicians and surgeons make recommendations about interventional therapy for individual patients, and to inform patients of the survival risks and benefits of these therapies.

Using this tool, we found that many patients received therapy that was not optimal for their individual characteristics. Adjusted survival data showed that the advantage of CABG widened over time in patients who were neither typical CABG patients nor typical stent patients.

Fig 4. Screen shot of strategic decision-support tool. Values for variables are recorded on the left, and survival curves are obtained on the right. (CABG = coronary artery bypass graft surgery; EF = ejection fraction; Hx = history; LMT = left main trunk stenosis; MR = mitral regurgitation; y.o. = years old.)



This allowed us to be more patient-specific than would either a randomized clinical trial or a propensity-matched comparison. We believe that use of such a computerized tool will help inform both recommendations for treatment of coronary artery disease and patient decisions. If used in the concept of cooperative discussion between cardiologists and surgeons in a coronary artery disease–oriented heart team, it would promote optimal treatment of individual patients.

Recently, two separate models were developed to predict 3-year survival after PCI and CABG using The Society of Thoracic Surgeons and American College of Cardiology databases, respectively [32, 33]. A limitation is that these models are applicable only to patients aged more than 65 years.

MacKenzie and colleagues [34] developed risk models for predicting short-term, midterm, and long-term outcomes after PCI and CABG [34]. These models can predict survival after coronary revascularization out to 10 years. However, a major limitation is that they were developed using data from 1992 to 2001 and thus do not account for advances in PCI, including use of DES. Our models deal with and can predict survival up to 10 years for CABG and BMS and up to 5 years for DES.

The Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial score is another available risk prediction tool. Although a high SYNTAX score suggests worse long-term outcomes after PCI, surgical outcomes are not influenced by it [35, 36]. That is likely because it is based on coronary anatomy rather than patient characteristics like age, diabetes mellitus, and renal failure, which are strong predictors of outcomes after CABG [35]. To address this, SYNTAX score II was developed, including important patient characteristics like age, ejection fraction, and creatinine clearance to predict survival up to 4 years [37]. Three things distinguish our model from SYNTAX score II. First, we have separately, although simultaneously, evaluated risk factors for death early after the procedure and later. The factors generally have different strengths in each of these eras, indicative of nonproportional hazards; SYNTAX score II assumes proportional hazards. Second, we have incorporated more clinical variables in our models, which tend to yield better predictions for patients with extremes of some variables, such as age, and combinations of variables (complex patients). Third, and a drawback of our model, is that SYNTAX score II includes the SYNTAX score itself, which is difficult to calculate retrospectively. This limitation is not so important for CABG, but is more important when considering PCI [35, 36, 38].

Study Strengths and Limitations

This was not a randomized trial, but it has the advantage of a real-world comparative effectiveness approach. As such, there was selection bias in the types of patients being treated with stents versus CABG, and not all patients are equally eligible for one or the other treatment. In part this was addressed by propensity matching. Use of the decision-support tool requires that applicability of the various interventions be assessed independently. Although this is a single-institution study, it has the advantage of incorporating a large number of clinically relevant variables in the models—variables that may not be included in quality registries or administrative databases.

In conclusion, treatment modalities for coronary artery disease are becoming more complementary than competitive, and it is increasingly important to take a heart-team approach to treatment to ensure that every patient receives the optimal therapy. A variable-rich, programmed, decision-support tool based on detailed prediction models for prognosis after PCI and CABG would aid both cardiologists and cardiac surgeons in identifying the revascularization therapy that maximizes long-term survival in a given patient with CAD. Nevertheless, it is also important to remember that computers are not doctors, and it is both impossible and unwise to take the human element out of the decision tree. A decision-support tool can be used, however, to confirm that we are not making biased or wrong decisions, and are offering each of our patients the best available information to allow them to make more informed decisions about their own health care.

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INVITED COMMENTARY

Risk scores, such as The Society of Thoracic Surgeons (STS) Predicted Risk of Mortality (PROM) and the European System of Cardiac Operative Risk Evaluation (EuroSCORE), are important tools to better understand which variables play a role in predicting hospital outcome in patients undergoing cardiac surgery. However, these scores are inadequate to predict long-term outcome and unable to assess the negative consequences of a procedure. Risk-benefit analysis is particularly important when several treatment options are available. Myocardial

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Supplemental (Online-Only) Material

Appendix: Variables Considered in Multivariable Analyses

Demography

Age (years)*, sex*, race, height (cm), weight (kg), body surface area (m^2), body mass index ($kg \cdot m^{-2}$)*, diastolic blood pressure (mmHg)*, systolic blood pressure (mmHg)*, heart rate ($beats \cdot min^{-1}$)

Pre-procedure status

New York Heart Association functional class (I-IV), Canadian Angina class (I-IV), emergency operation*

Left ventricular function

LV dysfunction grade (none [EF≥60%], mild [EF 40%-50%], moderate [EF 25%-39%], severe EF <25%]), previous myocardial infarction*, ejection fraction (%)*, LV aneurysm

Pathology

MV regurgitation*, MV regurgitation severity (0, 1+, 2+, 3+, 4+), MV stenosis, AV regurgitation, AV regurgitation severity (0, 1+, 2+, 3+, 4+), AV stenosis

Cardiac comorbidity

Pre-procedure atrial fibrillation*, number of coronary systems with ≥50% stenosis*, LAD*, LMT*, RCA*, LCx* stenosis (≥50%, ≥70%, any), family history of coronary artery disease, ventricular arrhythmia, complete heart block, endocarditis, heart failure*, cardiogenic shock, previous cardiac operation, previous PCI , unstable angina*

Noncardiac comorbidity

Treated diabetes*, hypertension*, previous stroke*, chronic obstructive pulmonary disease*, history of renal failure*, history of smoking*, calculated preoperative glomerular filtration rate and pre-procedure creatinine clearance, history of malignancy*

Procedural

CABG, PCI (bare metal or drug-eluting stent), number of stents placed, number of internal thoracic artery grafts, LAD drug-eluting or bare metal stent, LCx drug-eluting or bare metal stent, RCA drug-eluting or bare metal stent, LMT drug-eluting or bare metal stent, graft to LAD, graft to diagonal, graft to LCx, graft to RCA

Pre-procedure laboratory data

Total cholesterol ($mg \cdot dL^{-1}$), high-density lipoprotein ($mg \cdot dL^{-1}$), low-density lipoprotein ($mg \cdot dL^{-1}$), triglycerides ($mg \cdot dL^{-1}$), blood urea nitrogen ($mg \cdot dL^{-1}$), creatinine ($mg \cdot dL^{-1}$), bilirubin ($mg \cdot dL^{-1}$), hematocrit (%)*, glucose (mg)

Experience

Date of intervention*, interventionalist

Outcomes

Death, time from intervention until death

Note: Asterisks indicate variables included in propensity scores.

Key: AV=aortic valve; CABG=coronary artery bypass grafting; ECG=echocardiogram; LAD=left anterior descending coronary artery; LCx=left circumflex coronary artery; EF=ejection fraction; LMT=left main trunk; LV=left ventricular; MV=mitral valve; PCI=percutaneous coronary intervention; RCA=right coronary artery.

Chapter 3

Research Question 2—What are the Outcomes of CABG in Diabetic Patients Compared to Non-diabetic Patients?

Based on Publication: Raza S, Sabik JF 3rd, Ainkaran P, Blackstone EH. **Coronary Artery Bypass Grafting in Diabetics: A Growing Health Care Cost Crisis.** J Thorac Cardiovasc Surg. 2015;150(2):304-2.e2.

3.1 Rationale

Diabetes is a growing epidemic affecting over 400 million people worldwide [1]. Because coronary artery disease (CAD) is common in diabetics [2], it is an important driver of diabetes-related healthcare costs [3]. As the prevalence of diabetes has risen, cardiovascular disease associated with it has also increased [4]. Today, diabetics represent an important subset of patients undergoing coronary artery bypass grafting (CABG), an expensive procedure. Therefore, the second question that we sought to answer was: What are the outcomes of CABG in diabetic patients compared to non-diabetic patients? For this, we determined the 4-decade temporal trends in prevalence of diabetes and cardiovascular risk factors for patients undergoing CABG, compared overall in-hospital adverse outcomes, hospital resource utilization & costs, and long-term survival after CABG in diabetics vs. non-

diabetics. We then compared these in diabetics vs. non-diabetics with a similar high-risk profile using propensity-matching.

3.2 Summary of Study Design and Methods

This study included 57,278 patients from January 1, 1972, to January 1, 2011, who underwent first-time isolated CABG at the Cleveland Clinic. Data on the presence or absence of pharmacologically treated diabetes mellitus (insulin or oral hypoglycemic agent) were available for 55,501 (97%) of these patients—45,139 non-diabetics and 10,362 diabetics. Patients were identified, and preoperative, operative, and postoperative variables (see Appendix E1 of the paper) were retrieved from the prospective Cardiovascular Information Registry (CVIR) of the Cleveland Clinic. This database is populated concurrently with patient care and has been approved for use in research by the Institutional Review Board, with patient consent waived.

The endpoints were in-hospital adverse events, resource utilization, and long-term survival. Actual direct technical cost data (not charge data), exclusive of physician professional salaries, were obtained from the Decision Support Services of the Cleveland Clinic. Data were available for patients only from 2003 onward (n=4,679: 1,776 diabetics and 2,903 non-diabetics). Costs were corrected to constant 2011 dollars.

Vital status after hospital discharge was obtained by routine anniversary follow-up questionnaires supplemented with data from the Social Security Death Master File.

3.3 Summary of Results

This study shows that the proportion of patients presenting for CABG who have diabetes increased each year over the last 4 decades, as did the proportion with cardiovascular risk factors (see Figure 1 of manuscript). Thus, compared with diabetics undergoing the operation in the 1970s, 1980s, and 1990s, those operated on more recently were more likely to be obese and present with more comorbidities and advanced CAD. CABG was more resource intensive and expensive in diabetics (see Figure 2 of manuscript), and in-hospital adverse events and long-term survival were worse for diabetics as well (see Figure 3 of manuscript). However, the increase in in-hospital resource utilization was not specific to diabetics, but was commensurate with that of patients coming to surgery with similar extent of comorbidities, but without diabetes. Unadjusted in-hospital and early mortality (1-year) were higher in diabetics than in non-diabetics, but similar for propensity-matched patients with a similar comorbidity profile. Long-term survival was worse in diabetics than in both non-diabetic patients and matched non-diabetic high-risk patients. Thus, diabetes is both a marker for high-risk, resource-intensive, and expensive care after CABG and an independent risk factor for reduced long-term survival.

3.4 Findings Compared to Other Studies

Other studies have also revealed worse hospital and long-term outcomes of CABG in diabetics [5,6]. The SYNTAX trial showed that at 3 years, diabetes had

little effect on outcomes of CABG, and diabetes control (as indicated by baseline hemoglobin A1c levels) was not predictive of major adverse cardiac and cerebrovascular events. In our study, overall postoperative prevalence of stroke and in-hospital death were higher in diabetics, and occurrence of myocardial infarction was higher in non-diabetics. However, after comparison with similar high-risk non-diabetic patients, occurrence of death and myocardial infarction was similar in the 2 groups, as was true in the SYNTAX trial, but stroke remained higher in diabetics [6].

Diabetic patients as a group had a higher early (1-year) risk of death after CABG than non-diabetic patients, as has been documented by others [5]. However, an interesting finding of our study is that among propensity-matched patients, early risk was similar to that of non-diabetic high-risk patients with a similar comorbidity profile. However, long-term survival was worse in diabetics compared with both non-diabetic patients and non-diabetic high-risk patients. Other studies have also demonstrated that diabetes is an independent risk factor for reduced long-term survival after CABG [5,8].

Other studies have also shown the association of diabetes with increased cost of CABG. These studies are discussed in the following section.

3.5 Addition to Literature in Light of Systematic Review

A systematic literature search was done to identify studies that already existed on this topic at the time of paper preparation/publication so that the addition to the literature made by our study could be effectively evaluated in the light of

existing knowledge on the subject. Details of this systematic review are given in the Appendix (see section 10.2). Briefly, we search the literature for studies reporting the cost of CABG in diabetic vs. non-diabetic patients. Studies only reporting the cost of CABG in either diabetic or non-diabetic patients, and not in both patient populations, were excluded. Only three studies [8-10] were identified which met the specified criteria.

All three studies reported higher cost of CABG in diabetic vs. non-diabetic patients similar to the results of our study. What distinguishes our study from these existing studies, and constitutes a valuable addition to existing literature, are the details of the components of total direct technical cost. Moreover, we had a much higher sample size compared to all three studies (55,501 patients vs. 312 in the study by Stewart et al [9], 605 in the study by Abizaid et al [10], and 9240 in the study by Zhang et al [8]. Apart from reporting the differences in total direct technical cost in diabetics vs. non-diabetics, we also reported the differences in the cost of its component parts which included the cost of anesthesia, surgery, cardiology, respiratory therapy, professional services, imaging, nursing, pharmacy, laboratory and miscellaneous. We found that the total cost of CABG was 9% greater (95% CI, 7%-11%) in diabetics. Most of this difference was due to higher costs of clinical and laboratory testing, diagnostic imaging, pharmacy services, and nursing care. As mentioned in the paper, greater severity of disease among diabetics necessitates preoperative admission and more extensive laboratory and diagnostic workup. Greater severity of disease among

diabetics necessitates preoperative admission and more extensive laboratory and diagnostic workup.

The study by Stewart et al (n=312; diabetic, 114) showed that hospital charges of CABG were higher in insulin-treated diabetics vs. non-diabetic but similar in non-insulin treated diabetics vs. non-diabetics. In their study, only the total hospital charges were reported which were calculated from the day of operation.

The study by Abizaid et al (n=605; diabetic, 96) showed that 1-year cost of CABG was higher in diabetic patients compared to non-diabetic patients. In their study only procedural, follow-up and total cost was reported.

The study by Zhang et al (n=9240; diabetic, 2682) showed that at 2 years after CABG, costs for diabetic patients were higher than for non-diabetic patients. In their study in-hospital costs were reported which included diagnostic, procedural, and postprocedural costs. Follow-up costs were limited to cardiovascular rehospitalizations and medication costs.

3.6 Critical Commentary

Help was taken from the Critical Appraisal Skills Program (CASP) checklist for Cohort Studies for critical commentary on this manuscript. Available at: http://www.casp-uk.net/casp-tools-checklists.

3.6.1 Rationale

The study rationale was clearly mentioned in the introduction section of the paper. However, our objective did not make it clear whether the study was trying to detect the beneficial or harmful effect of diabetes on outcomes of CABG.

3.6.2 Study Design

It is critical to determine whether the chosen study design is appropriate for the question under study. Generally, an RCT is regarded as the best form of epidemiological study. However, an RCT is not always possible. The strength of RCTs lies in the process of randomization and in certain cases randomization is not possible, like in the cases of diabetic and non-diabetic patients undergoing CABG—one cannot randomize patients to diabetes or non-diabetes groups. Therefore, to study the 4-decade temporal trends in prevalence of diabetes and cardiovascular risk factors for patients undergoing CABG, and the outcomes of CABG in diabetic and non-diabetic patients, a retrospective cohort study is appropriate. Moreover, studying long-term survival (>20 years) after CABG in diabetic and non-diabetic patients would require a very long follow-up period, which is challenging, if not impossible.

3.6.3 Participant Selection

We used data from CVIR, which is a well-regarded registry in cardiac surgery literature. This registry has been the basis of many landmark studies [11,12]. Both non-diabetic patients and diabetic patients were identified and extracted

from the same registry i.e. CVIR. Patients with unknown diabetic status were excluded. Patients were labelled as diabetic if they were on insulin or taking oral medications for diabetes, as mentioned in the paper. We chose patients undergoing first-time isolated CABG and excluded patients undergoing re-operative CABG. This was appropriate as the two patient populations are different. Patients undergoing reoperative CABG are older, sicker and have more comorbidities [13]. Patients undergoing CABG with other concomitant surgical procedures like CABG plus aortic valve replacement (AVR) were also excluded. This was appropriate as the primary objective of the study was just to study the outcomes of coronary surgery. One of the limitations of the study was that we were unable to discriminate between type I and type II diabetes. This maybe important as the long-term survival after CABG of type 1 diabetic patients is worse than the survival of type II diabetic patients. However, this was not mentioned in the limitations section of the paper.

It was also not mentioned in the paper whether this study required any additional data-collection, apart from the data retrieved from CVIR. No additional data was collected for this study.

3.6.4 Sample Size

Sample size calculation was not done. This was a retrospective cohort study of consecutive patients who underwent primary isolated CABG at the Cleveland Clinic during a given time period. Therefore, sample size calculation would not have affected the number of patients included. However, it is important to

determine whether the study was powered to detect a difference in outcomes, particularly long-term survival, after CABG in diabetic vs. non-diabetic patients, under the assumption that one exists. Our study showed that the 20-year survival after CABG was 20% for diabetic patients and 32% for non-diabetic patients. To detect this difference, our propensity-matched comparison was 100% powered, at a significance level of 5% (with 8926 patients in each group). Please note that some criticize the idea of retrospective power calculation. However, it was done just to provide an approximate idea regarding the statistical power of the study.

3.6.5 End-points

The studied end-points were defined clearly. These included in-hospital outcomes, resource utilization, and long-term mortality. Hospital outcomes were retrieved from CVIR. Please see 1.5.2 for details regarding data abstraction process for this registry and the accuracy of data collected—this information was not provided in the paper. The follow-up was long enough. Median follow-up was provided for long-term mortality as distribution of survival data is usually (positively) skewed. Although we mentioned in the paper that vital status was obtained by routine anniversary follow-up questionnaires supplemented with data from the Social Security Death Master File, we could have provided more information about the follow-up process. The following paragraph gives a detailed account of the follow-up in our studies.

CVIR systematic anniversary follow-up started in the early 1970s and included following the first 1000 consecutive cases per year of non-foreign non-

emergent patients undergoing primary isolated CABG. Follow-up information was obtained using standardized questionnaires by mail and telephone calls from trained personnel. The follow-up was performed at 5-year intervals for up to 25 years after CABG. This routine follow-up of CABG patients was eventually stopped. The last primary isolated CABG cohort to be followed included patients undergoing primary isolated CABG in 1997. One of the limitations was that the circumstances of each death, which may be different between diabetic and non-diabetic patients, were not reliably captured during the follow-up inquiries.

The follow-up information obtained through CVIR routine anniversary follow-up was supplemented with data from the US Social Security Administration's Death Master File (SSDMF), usually called the "Social Security Death Index" in medical literature. This used to be an important source of vital status for clinical researchers as it was sensitive, specific, inexpensive and up-to-date. However, it is no longer available for medical research since November 2011 and therefore could not be used for new projects [14]. The master file contains all deaths occurring in the United States or its territories (foreign or not). However, this file is only a file of deaths. Thus, if a person is not listed in the SSDMF, one assumes that person is alive. This creates errors on each side with approximately equal frequency. It amounts to about 2% error both ways. Furthermore, it provides only all-cause mortality—therefore, we do not know whether these deaths were cardiac or non-cardiac related.

3.6.6 Data Analysis

Use of Multiphase Model vs. Cox Model: Survival was assessed non-parametrically using the Kaplan-Meier method and parametrically using a multiphase hazard model. The latter involved resolving the number of hazard phases for instantaneous risk of death (hazard function) and estimating shaping parameters [15]. The details regarding the use of a multiphase hazard model vs. the Cox model are given in section 2.6.6 above.

Confounding: As mentioned in the paper, the patient characteristics significantly differed between the two groups, patients with and without diabetes. To adjust for the imbalances in measured characteristics and for fair comparison of outcomes, we performed matching based on propensity scores [16]. A number of variables (detailed in the appendix of the paper) were considered in this analysis ranging from demographic variables, to cardiac and non-cardiac comorbidities, and date of operation. However, any patient factors not included in the propensity model that importantly affect outcomes might have biased our findings.

Propensity Scores: Because patient characteristics differed between diabetic and non-diabetic groups, we attempted to fairly compare outcomes using propensity score matching. Propensity scores are the most commonly used balancing scores. They provide for each patient in the study an estimate of the propensity toward (probability of) belonging to one group versus another (group membership). Once the propensity score is calculated for each patient using

logistic regression or random forest classification method, it can be used in several ways for balancing. These include matching, inverse weighting, stratification and multivariable adjustment. We used matching because it eliminates a greater proportion of the systematic differences in baseline characteristics between the comparison groups of interest compared to stratification or multivariable adjustment. However, regarding the use of matching vs. inverse weighting, some studies show similar effectiveness and some show slight advantage of matching over inverse weighting [17]. A problem with inverse weighting is that at the tail ends of propensity score, patients are over-weighted, a well-known drawback of this method. Liang Li and colleagues [18] created a new weighting scheme that avoids the end-effects. Our statisticians did not use it for my studies, but are using it increasingly now and find that the resulting “virtual pairs” (obtained by analyzing fractional patients, just as in inverse weighting) tend to be even closer together than by traditional pairwise matching. Therefore, if I conduct a similar study again, I would use this technique instead of pairwise matching.

Variable Selection: As pointed out by Dr. David Naftel, different investigators sometimes produce different multivariable models from the same data [19]. In a 1983 Scientific American article, Diaconis and Efron [20] show that if one generates a new dataset by sampling with replacement from the original dataset (now called a bootstrap sample), repeats this many times, and then performs a multivariable analysis, the SAME investigator will get a different model every

time. Multivariable models are fragile and generally unreproducible. However, as explicitly found by Sauerbrei and colleagues [21], by “averaging” over the different models, one can obtain a stable model, separating signal from noise [22]. Thus, in constructing our multivariable models, we used automated stepwise variable selection on 250 to 1000 bootstrap samples (depending on the study), and selected those variables appearing in at least 50% of models at P<.05 (as suggested by Breiman [23] to balance Type I and Type II error).

Use of 68% Confidence Limits vs. 95% Confidence Limits: For explanation regarding use of 68% confidence limits, please see section 2.6.6 above.

3.6.7 Results & Discussion

The long-term survival was reported for up to 20 years. The results look precise given the range of the confidence intervals provided in the results and figures of the manuscript. However, measures like absolute risk reduction and hazard ratio were not reported in the manuscript. The results are believable because the study compared outcomes in a large number of diabetic and non-diabetic patients using data from a well-regarded registry and took appropriate measures to control for confounding.

The Discussion clearly mentioned the principal findings of the study, and in the section of “findings in context”, we discussed the existing knowledge on the topic and compared our findings with the results of other studies. The limitations of the study were clearly mentioned. This was a single-institution study, and

results may not be generalizable. Nevertheless, with the increasing proportion of patients with diabetes undergoing CABG, and with the widespread experience with CABG these days, our experience should be repeatable in other centers that see diabetic patients in need of CABG.

The conclusions of the paper were supported by the data presented and mentioned the clinical implications of the study instead of just summarizing the results again.

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3.8 Full-text of the Paper

Coronary artery bypass grafting in diabetics: A growing health care cost crisis

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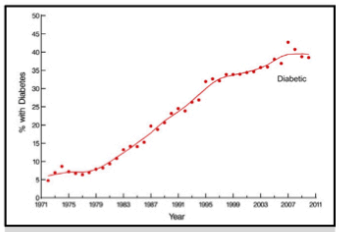
ABSTRACT

Objectives: To determine 4-decade temporal trends in the prevalence of diabetes and cardiovascular risk factors among patients undergoing coronary artery bypass grafting (CABG) and to compare in-hospital outcomes, resource utilization, and long-term survival after CABG in diabetics versus nondiabetics.

Methods: From January 1972 to January 2011, 10,362 pharmacologically treated diabetics and 45,139 nondiabetics underwent first-time CABG. Median follow-up was 12 years. Direct technical cost data were available from 2003 onward (n = 4679). Propensity matching by diabetes status was used for outcome comparisons. Endpoints were in-hospital adverse events, resource utilization, and long-term survival.

Results: Diabetics undergoing CABG increased from 7% in the 1970s to 37% in the 2000s. Their outcomes were worse, with more ($P < .05$) in-hospital deaths (2.0% vs 1.3%), deep sternal wound infections (2.3% vs 1.2%), strokes (2.2% vs 1.4%), renal failure (4.0% vs 1.3%), and prolonged postoperative hospital stay (9.6% vs 6.0%); and their hospital costs were 9% greater (95% confidence interval 7%-11%). Survival after CABG among diabetics versus nondiabetics at 1, 5, 10, and 20 years was also worse: 94% versus 94%, 80% versus 84%, 56% versus 66%, and 20% versus 32%, respectively. Propensity-matched patients incurred similar costs, but the prevalence of postoperative deep sternal wound infections and stroke, as well as long-term survival, remained worse in diabetics.

Conclusions: Diabetes is both a marker for high-risk, resource-intensive, and expensive care after CABG and an independent risk factor for reduced long-term survival. These issues, coupled with the increasing proportion of patients needing CABG who have diabetes, are a growing challenge in reining in health care costs. (J Thorac Cardiovasc Surg 2015;150:304-12)



Four-decade trend in prevalence of diabetes among patients undergoing primary isolated coronary artery bypass grafting. Each *circle* represents a yearly percentage, and the *solid line* is the locally estimated scatterplot smoother (loess) estimate.

Central Message

Increasingly, patients needing CABG have diabetes, a marker for high-risk, resource-intensive, expensive care after CABG, and an independent risk factor for reduced long-term survival, creating a growing challenge to health care cost reduction.

Perspective

The proportion of patients needing CABG who have diabetes has increased to nearly 40% of all patients undergoing CABG at our institution. The procedure is more resource intensive and expensive for diabetics than for nondiabetics, partly because of postoperative complications. However, when surgeons present the risks and benefits of CABG to diabetic patients, they should explain that CABG offers the best chance for long-term survival.

See Editorial Commentary page 313.

See Editorial page 284.

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Diabetes is an emerging worldwide epidemic that affects 382 million people,[1] including 25.8 million in the United States alone.[2] In 2013, global health expenditures resulting from diabetes were estimated at $548 billion and are expected to exceed $627 billion by 2035.[1] In the United States, the total economic burden of diabetes was $245 billion in 2012.[3] Because coronary artery disease is

Abbreviation and Acronym
CABG = coronary artery bypass grafting

common in diabetics,[4] it is an important driver of diabetes-related health care cost.[3]

As the prevalence of diabetes has risen, cardiovascular disease associated with it has increased as well.[5] Today, diabetics represent an important subset of patients undergoing coronary artery bypass grafting (CABG), an expensive procedure. Therefore, we sought to determine 4-decade temporal trends in the prevalence of diabetes and cardiovascular risk factors for patients undergoing CABG, compare overall in-hospital adverse outcomes, hospital resource utilization and costs, and long-term survival after CABG in diabetics versus nondiabetics, then compare these same factors in diabetics versus nondiabetics who have similar high-risk profiles using propensity matching.

METHODS

Patients

From January 1, 1972, to January 1, 2011, 57,278 patients underwent first-time isolated CABG at Cleveland Clinic. Data on the presence or absence of pharmacologically treated diabetes mellitus (insulin or oral hypoglycemic agent) were available for 55,501 (97%) of these patients: 45,139 nondiabetics and 10,362 diabetics.

Patients were identified, and preoperative, operative, and postoperative variables (Appendix E1) were retrieved from the prospective Cleveland Clinic Cardiovascular Information Registry. This database is populated concurrently with patient care and has been approved for use in research by the institutional review board, with the requirement for patient consent waived.

Variables and Definitions

A coronary artery system was considered meaningfully stenotic if it contained a ≥50%-diameter obstruction. Incomplete revascularization was defined as failure to graft any coronary system containing ≥50% stenosis, or both left anterior descending and circumflex coronary systems for ≥50% left main trunk stenosis. Left ventricular function was echocardiographically graded as normal (ejection fraction ≥60%), mild dysfunction (ejection fraction 40%-59%), moderate dysfunction (ejection fraction 25%-39%), or severe dysfunction (ejection fraction <25%).

Endpoints

Endpoints were: (1) in-hospital adverse outcomes defined as in the Society of Thoracic Surgeons national database (www.ctsnet.org/file/rptDataSpecifications252_1_ForVendorsPGS.pdf); (2) in-hospital direct technical costs (the sum of direct preoperative, operative, and postoperative costs), both total and broken down according to resource utilization areas; and (3) time-related mortality. Actual direct technical cost data (not charge data), exclusive of physician professional salaries, were obtained from Decision Support Services of Cleveland Clinic. Data were available for patients from only 2003 onward (n = 4679: 1776 diabetics and 2903 nondiabetics). Costs were corrected to constant 2011 dollars.[6] Indirect costs, including institutional costs and capital equipment costs used for all operations, could not be estimated on a per patient basis and are not included, but they were assumed to be distributed uniformly across groups.

Vital status after hospital discharge was obtained by routine anniversary follow-up questionnaires supplemented with data from the Social Security Death Master File,[7] accessed on October 27, 2011, with a closing date of April 27, 2011. A total of 714,709 patient-years of follow-up data were available for analyses. Median follow-up was 11.8 years, with 25% of survivors followed for >21 years, and 10% for >30 years.

For diabetic patients, 86,153 patient-years of follow-up data were available for analyses, with a median follow-up period of 7.5 years; 25% of survivors were followed for >12 years, and 10% for >18 years. For nondiabetic patients, 628,556 patient-years of follow-up data were available for analyses, with a median follow-up period of 13 years; 25% of survivors were followed for >24 years, and 10% for >31 years.

Statistical Analysis

Temporal trends. Four-decade temporal trends in the prevalence of diabetes and cardiovascular risk factors among patients undergoing CABG were assessed using plots of yearly percentages or averages over time. A nonparametric locally estimated scatterplot smoother, PROC LOESS (SAS Institute, Cary, NC), was used to smooth these temporal trends.

In-hospital adverse outcomes. Comparisons of outcomes after CABG between diabetics and nondiabetics, unmatched and propensity matched, were made using the χ^2 test for categoric endpoints.

Resource utilization and total direct technical cost. Hours in the intensive care unit and postoperative and total hospital lengths of stay had right-skewed distributions, so the Wilcoxon rank-sum test, and the median score test for continuous endpoints, were used for comparisons between diabetics and nondiabetics. To identify the relative difference in direct technical costs, we estimated the ratio of the median cost between the 2 groups. The percentile bootstrap confidence method[8] was used to estimate 95% confidence intervals. This procedure was applied to the overall and matched cohorts.

Long-term survival. Survival was assessed nonparametrically, using the Kaplan-Meier method, and parametrically, using a multiphase hazard model.[9] The latter involved resolving the number of hazard phases for instantaneous risk of death (hazard function), and estimating shaping parameters. (For details, see www.lerner.ccf.org/qhs/software/hazard.) Because the shape of time-varying risk of death may differ for diabetics versus nondiabetics, we constructed separate hazard models for each group.

Propensity-score matching. Although overall assessment of outcomes in diabetics compared with nondiabetics represents the realities of the real world, diabetics as a group present with a higher-than-average risk profile. We therefore treated diabetes as a "natural experiment,"[10] comparing outcomes of propensity-matched diabetics and nondiabetics.[11-13] This comparison was accomplished in 2 steps. First, a parsimonious multivariable logistic regression was used to identify differences in preoperative characteristics of diabetic versus nondiabetic patients, to obtain insight into these differences (see Appendix E1 for a list of variables analyzed). Bootstrap bagging for variable selection with automated analysis of 500 resampled datasets was used to accomplish this, followed by tabulation of the frequency of both single factors and closely related clusters of factors.[14] We retained factors that occurred in ≥50% of the bootstrap models (Table E1). The C-statistic for this parsimonious model was .83.

Second, the parsimonious model was augmented into a saturated propensity model by including patient characteristics that were not statistically significantly different between groups. These characteristics were demographic, cardiac, and noncardiac comorbidities not represented (see Appendix E1). The C-statistic for this model was .84.

A propensity score representing the probability of diabetes—group membership given the variables included in the propensity model, regardless of whether the patient had diabetes—was then calculated for each patient. A greedy matching strategy based on the propensity scores alone was used to match diabetic with nondiabetic patients, yielding 8926 well-matched pairs (86% of possible matches; Figure E1). Diabetes

cases with propensity scores that deviated >0.10 from those of nondiabetes cases were considered unmatched. Standardized differences demonstrated that covariable balance was achieved across nearly all variables (Figure E2).

Using a similar approach, separate propensity matching was done between the subset of diabetics and nondiabetics undergoing an operation in the period from 2003 to 2011, during which cost data were available. This yielded 1368 well-matched pairs (77% of possible matches).

Missing values. Several variables examined in multivariable analyses had missing values. We used fivefold multiple imputation[15] with a Markov chain Monte Carlo technique to impute missing values (SAS PROC MI; SAS Institute, Cary, NC). In multivariable modeling, for each imputed complete dataset, we estimated regression coefficients and their variance–covariance matrix. After this step, following Rubin,[15] we combined estimates from the 5 models (SAS PROC MIANALYZE; SAS Institute, Cary, NC) to yield final regression coefficient estimates, the variance–covariance matrix, and *P* values.

Presentation. Continuous variables are summarized by mean ± SD, or equivalent 15th, 50th (median), and 85th percentiles when the distribution of values is skewed. Analyses were performed using SAS statistical software, version 9.1 (SAS Institute, Cary, NC) and R (version 3.0.2). Uncertainty is expressed by confidence limits (CLs) equivalent to ±1 SE (68%).

RESULTS

Compared with nondiabetics, diabetic patients undergoing CABG were older and more likely to be overweight, and more likely to be women. In addition, they were more likely to have a history of heart failure, peripheral arterial disease, carotid disease, hypertension, renal failure, stroke, and advanced coronary artery disease (Table 1).

Temporal Trends

The proportion of patients presenting for CABG who have diabetes increased from 7% per year in the 1970s to 37% in the 2000s (Central Image). The cardiovascular risk factor profile also changed during this time, more so for diabetics than nondiabetics. Today, patients are likely to be older (Figure 1, *A*) and obese (Figure 1, *B*); to have had a stroke (Figure 1, *C*); and to have hypertension (Figure 1, *D*), peripheral arterial disease (Figure 1, *E*), lower total cholesterol (Figure 1, *F*), higher high-density lipoprotein cholesterol (Figure 1, *G*), lower triglycerides (Figure 1, *H*), and more-advanced coronary artery disease (Figure 1, *I*) (see Table E1).

Overall Outcomes

In-hospital adverse outcomes, and resource utilization and direct technical costs. Diabetics had higher in-hospital mortality and greater occurrence of deep sternal wound infection, stroke, atrial fibrillation, renal failure, and respiratory failure (Table 2). Hours spent in the intensive care unit and of length of stay >14 days were higher in diabetics than nondiabetics (Table 2). As a result, the total cost of CABG was 9% greater (95% CI, 7%-11%) in diabetics. Most of this difference was due to higher costs of clinical and laboratory testing, diagnostic imaging, pharmacy services, and nursing care (Figure 2).

Long-term survival. The instantaneous risk of death was high immediately after CABG, decreased over the ensuing 6 months, and then gradually increased for both diabetics and nondiabetics (Figure 3, *A*), resulting in early divergence of their survival curves (Figure 3, *B*). In addition, late hazard was elevated in diabetics; thus, ever-increasing divergence of survival was observed out to at least 20 years. Among diabetics, overall survival at 6 months, 1, 5, 10, 15, and 20 years after CABG was 95%, 94%, 80%, 54%, 31%, and 18%, respectively. In contrast, for nondiabetics, it was 97%, 97%, 90%, 76%, 59%, and 42%, respectively ($P < .0001$).

Comparison of Diabetics with Similar High-Risk Nondiabetics

In-hospital adverse outcomes, and resource utilization and direct technical costs. After matching, the incidence of deep sternal wound infection and stroke remained significantly higher among diabetics (Table 2). After propensity matching, no significant difference remained in total cost of CABG between diabetics and nondiabetics (Figure 2). Hours spent in the intensive care unit were similar, but length of stay >14 days remained higher for diabetics (Table 2).

Long-term survival. Among propensity-matched patients, instantaneous risk of death (hazard function) was similar for both diabetics and nondiabetics until 1 year after surgery, after which risk of death was greater for diabetics (Figure 3, *C*). Early survival was similar between the 2 groups, but late survival was worse for diabetics (Figure 3, *D*). Late survival continued to diverge as long as patients were followed, because of the substantial difference in late hazard for at least 20 years after CABG. Survival of diabetics at 6 months, 1, 5, 10, 15, and 20 years after operation was 96%, 94%, 80%, 56%, 35%, and 20%, respectively, versus 96%, 94%, 84%, 66%, 47%, and 32% for nondiabetics.

DISCUSSION

Principal Findings

This study shows that the proportion of patients presenting for CABG who have diabetes increased each year during the past 4 decades, as did the proportion with cardiovascular risk factors. Thus, compared with diabetics undergoing operation in the 1970s, 1980s, and 1990s, those operated on more recently were more likely to be obese and have more comorbidities and advanced coronary artery disease. For diabetics, CABG was more resource intensive and expensive, and in-hospital adverse events and long-term survival were worse. However, the increase in in-hospital resource utilization was not specific to diabetics, but rather commensurate with that of patients coming to surgery with

TABLE 1. Patient characteristics and revascularization details of nondiabetics and diabetics undergoing coronary artery bypass grafting

Characteristic	Nondiabetics (n = 45,139)		Diabetics (n = 10,362)		*P* value
	n	No. (%) or mean ± SD	n	No. (%) or mean ± SD	
Demographics					
Age (y)	45,139	60 ± 10	10,362	63 ± 9.7	<.001
Male	45,139	37,626 (83)	10,362	7249 (70)	<.001
Body mass index (kg/m^2)	27,739	28 ± 4.7	8883	30 ± 5.8	<.001
Symptoms and surgical priorities					
NYHA functional class	44,775		10,317		<.001
I		7645 (17)		1800 (17)	
II		16,533 (37)		3982 (39)	
III		4702 (11)		1468 (14)	
IV		15,895 (35)		3067 (30)	
Emergency operation	45,137	1242 (2.8)	10,362	248 (2.4)	.04
Cardiac comorbidity					
Myocardial infarction	45,139	22,916 (51)	10,362	5932 (57)	<.001
Left ventricular dysfunction	42,404		8996		<.001
None		37,013 (87)		6300 (70)	
Mild		2492 (5.9)		948 (11)	
Mild to moderate		514 (1.2)		238 (2.6)	
Moderate		1315 (3.1)		688 (7.6)	
Moderate to severe		492 (1.2)		384 (4.3)	
Severe		578 (1.4)		438 (4.9)	
Preoperative AF or flutter	36,357	411 (1.1)	8967	163 (1.8)	<.001
Heart failure	45,139	2219 (4.9)	10,362	1750 (17)	<.001
Coronary artery disease	35,015	20,687 (59)	7042	3446 (49)	<.001
No. of coronary systems diseased (stenosis ≥50%)	43,113		9908		<.001
0		366 (0.85)		69 (0.70)	
1		5310 (12)		615 (6.2)	
2		13,807 (32)		2332 (24)	
3		23,630 (55)		6892 (70)	
Left main disease (stenosis ≥50%)	41,909	6704 (16)	9277	1749 (19)	<.001
Noncardiac comorbidity					
Peripheral arterial disease	45,139	4551 (10)	10,362	1840 (18)	<.001
Carotid disease	45,139	3434 (7.6)	10,362	2278 (22)	<.001
Stroke	45,139	1515 (3.4)	10,362	880 (8.5)	<.001
Hypertension	29,346	17,615 (60)	9077	6966 (77)	<.001
COPD	14,360	1079 (7.5)	6639	584 (8.8)	<.001
Smoking	44,244	24,133 (55)	10,208	5319 (52)	<.001
Creatinine (mg/dL)	13,969	1.2 ± 0.83	6464	1.3 ± 1.2	.07
Blood urea nitrogen (mg/dL)	13,954	18 ± 9.0	6460	22 ± 12	<.001
Renal dialysis	7375	59 (0.80)	4060	98 (2.4)	<.001
Total cholesterol (mg/dL)	35,236	235 ± 56	7422	208 ± 60	<.001
HDL cholesterol (mg/dL)	14,734	40 ± 12	5283	39 ± 13	<.001
LDL cholesterol (mg/dL)	9616	128 ± 46	4309	113 ± 45	<.001
Triglycerides (mg/dL)	29,248	185 ± 116	6672	203 ± 173	.002
Bilirubin (mg/dL)	12,683	0.65 ± 0.50	5803	0.59 ± 0.51	<.001
Hematocrit (%)	13,037	40 ± 5.1	5993	38 ± 5.5	<.001
Experience					
January 1, 1972 to index operation	45,139	14 ± 9.5	10,362	21 ± 9.6	<.001
Revascularization details					
ITA grafts at index operation	45,139		10,362		<.001
None		14,888 (33)		2018 (19)	
Single		25,160 (56)		7570 (73)	
Bilateral		5091 (11)		774 (7.5)	
Complete revascularization*	45,139	40,405 (90)	10,362	9432 (91)	<.001
Cardiopulmonary bypass	45,139	43,761 (97)	10,362	9817 (95)	<.001

Values in "n" columns are numbers of patients with data available. *SD*, Standard deviation; *NYHA*, New York Heart Association; *AF*, atrial fibrillation; *COPD*, chronic obstructive pulmonary disease; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *ITA*, internal thoracic artery. *Incomplete revascularization was defined as failure to graft any system containing 50% stenosis or both the left anterior descending and circumflex coronary artery systems for 50% left main trunk stenosis.

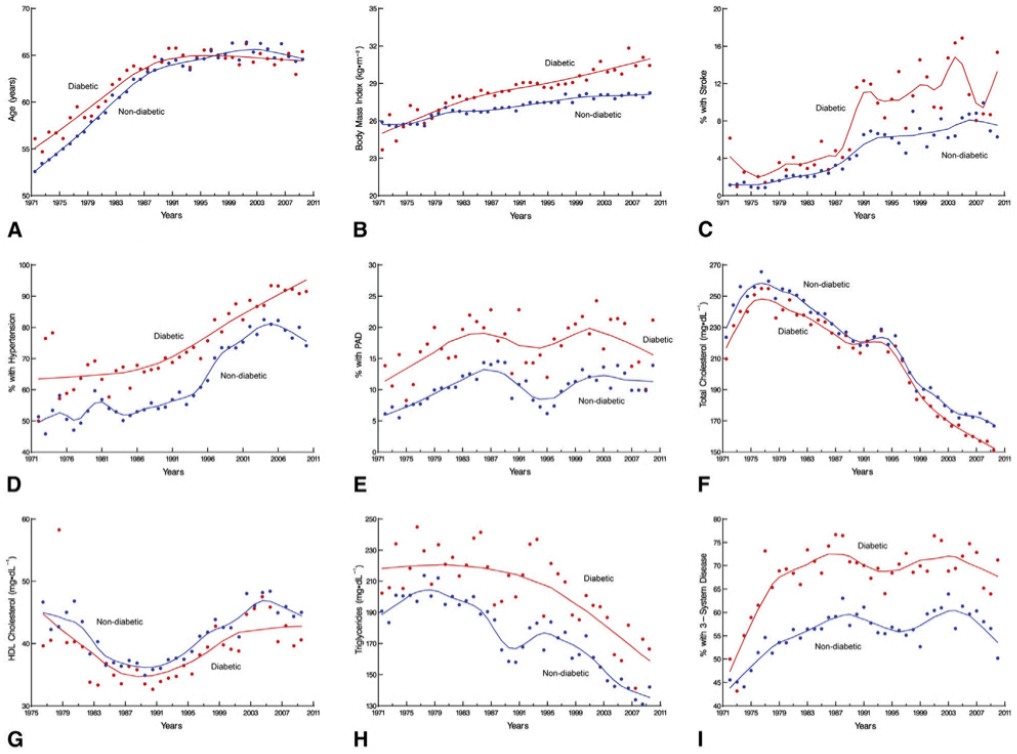


FIGURE 1. Four-decade trends in prevalence of diabetes and cardiovascular risk factors among patients undergoing primary isolated coronary artery bypass grafting. Each *circle* is a yearly percentage or mean value, and *solid lines* are loess estimates. The factors shown are: (A) age; (B) body mass index; (C) stroke; (D) hypertension; (E) PAD; (F) total cholesterol; (G) HDL cholesterol; (H) triglycerides; and (I) percentage with 3-system disease. *PAD*, Peripheral arterial disease; *HDL*, high-density lipoprotein.

a similar extent of comorbidities, but without diabetes. Unadjusted in-hospital and early mortality (1-year) were higher in diabetics than in nondiabetics, but similar for propensity-matched patients with a similar comorbidity profile. Long-term survival was worse in diabetics than in either nondiabetic patients or matched, nondiabetic, high-risk patients. Thus, diabetes is both a marker for high-risk, resource-intensive, and expensive care after CABG, and an independent risk factor for reduced long-term survival.

Trends

In 2010, nearly 40% of those undergoing CABG at our institution were diabetic, paralleling the rising prevalence of diabetes in the general population. However, the increasing use of percutaneous coronary intervention for revascularization, and the choice of CABG as the preferred revascularization strategy for diabetics, could also have been contributing factors.[16] Although cardiovascular disease–related morbidity and mortality has clearly been reduced in the United States over the past 50 years, the cardiovascular disease burden attributable to diabetes has increased.[5] Current estimates are that 18.8 million people in the United States have been diagnosed with diabetes, and 7 million remain undiagnosed.[2] In addition, nearly 79 million people aged ≥20 years have prediabetes,[2] a condition that places them at increased risk of developing diabetes and cardiovascular disease.[17]

We also observed a change in the cardiovascular risk-factor profile over time. Diabetics undergoing CABG in recent years are more likely to be obese and to have more-advanced coronary artery disease than those operated on in the 1970s, 1980s, and 1990s. In addition, they are more likely to have hypertension, one component of metabolic syndrome, together with diabetes, hyperlipidemia, and obesity—all risk factors for coronary artery disease.[18] Obesity is now considered a national epidemic and is of particular importance as a well-recognized contributor to

TABLE 2. In-hospital outcomes after coronary artery bypass grafting: overall and propensity matched

	Overall					Propensity matched				
	Nondiabetic (total n = 45,139)		Diabetic (total n = 10,362)			Nondiabetic (total n = 8926)		Diabetic (total n = 8926)		
Outcome	n	No. (%)	n	No. (%)	*P* value	n	No. (%)	n	No. (%)	*P* value
Hospital death	45,139	566 (1.3)	10,362	211 (2.0)	<.001	8926	152 (1.7)	8926	174 (1.9)	.2
Deep sternal wound infection	45,139	526 (1.2)	10,362	239 (2.3)	<.001	8926	116 (1.3)	8926	197 (2.2)	<.001
Septicemia	14,298	226 (1.6)	6633	151 (2.3)	.004	6393	139 (2.2)	5352	113 (2.1)	.8
Stroke	45,139	640 (1.4)	10,362	233 (2.2)	<.001	8926	134 (1.5)	8926	200 (2.2)	<.001
Perioperative MI	45,139	1023 (2.3)	10,362	135 (1.3)	<.001	8926	118 (1.3)	8926	123 (1.4)	.8
Bleeding or tamponade	45,139	1791 (4.0)	10,362	348 (3.4)	.004	8926	271 (3.0)	8926	314 (3.5)	.07
Atrial fibrillation	45,139	5148 (12)	10,362	1979 (19)	<.001	8926	1914 (21)	8926	1672 (19)	<.001
Renal failure	45,139	569 (1.3)	10,362	418 (4.0)	<.001	8926	258 (2.9)	8926	285 (3.2)	.2
Renal failure requiring dialysis	14,298	104 (0.73)	6633	86 (1.3)	<.001	6393	79 (1.2)	5352	60 (1.1)	.6
Prolonged ventilation (>24 h)	3492	320 (9.2)	2100	249 (12)	.001	1838	212 (12)	1563	160 (10)	.2
Length of stay*										
ICU (h)	14,296	24/24/72	631	24/26/95	<.001	6391	24/24/75	5351	24/24/76	<.001
Postoperative (d)	44,014	6.1/8.0/11	10,263	5.9/7.9/12	<.001	8864	5.2/7.0/11	8829	5.9/7.9/11	<.001
Hospital (d)	44,014	7/11/17	10,263	6.3/10/18	<.001	8864	6.3/9.3/16	8829	6.3/10/17	<.001
Prolonged (>14 d)	45,139	2688 (6.0)	10,362	995 (9.6)	<.001	8926	679 (7.6)	8926	785 (8.8)	.004

Values in "n" columns are numbers of patients with data available. *P* values are given for the median score test. *MI*, Myocardial infarction; *ICU*, intensive care unit. *15th/50th/85th percentiles. Median score test was used to compare medians and Wilcoxon rank-sum test to compare tails of distributions.

diabetes. More than one third of US adults are obese,[19] and in the next 20 years, obesity may play a contributing role in an estimated 6 million cases of diabetes.[20] On the other hand, diabetics undergoing CABG in recent years had lower total cholesterol, higher high-density lipoprotein cholesterol, and lower triglycerides than did patients operated on in earlier years; this difference may be attributable to better control of lipids in the statin era.

In-Hospital Adverse Outcomes

In-hospital adverse outcomes after CABG were more common in diabetics than nondiabetics. In part, this difference is attributable to diabetic patients being sicker and having more comorbidities than nondiabetics, because some of the differences, including hospital death, septicemia, renal failure, and respiratory failure, became statistically insignificant after comparison with similar high-risk nondiabetic patients through propensity matching. However, occurrence of deep sternal wound infection and stroke remained significantly higher in diabetics even after matching. Deep sternal wound infection results in prolonged postoperative length of stay and thus increases hospital resource utilization. Strokes may cause permanent disability, resulting in unemployment and thus increasing the indirect cost of diabetes through loss of productivity.

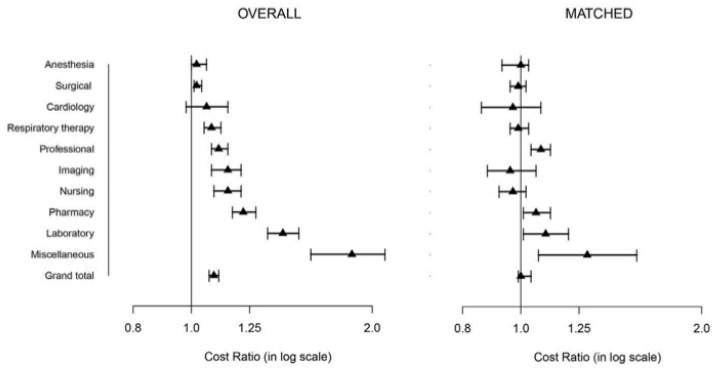


FIGURE 2. Median (*triangles*) ratio of total direct technical costs (overall and propensity matched) in diabetics versus nondiabetics. *Error bars* are 95% confidence intervals.

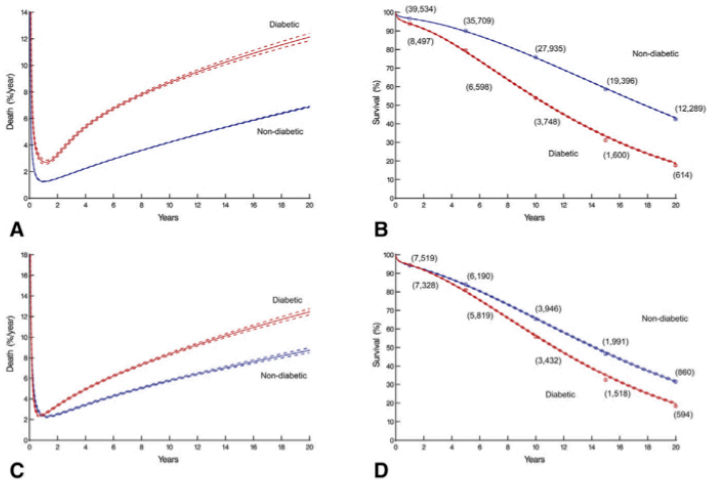


FIGURE 3. Time-related death after primary isolated coronary artery bypass grafting in diabetics and nondiabetics. *Solid lines* are parametric estimates enclosed within dashed 68% confidence bands equivalent to ±1 SE. The panels show: (A) instantaneous risk of death (overall); (B) survival (overall); (C) instantaneous risk of death (propensity-matched cohort); and (D) survival (propensity-matched cohort). Each *symbol* represents a death; *vertical bars* are confidence limits equivalent to ±1 SE; and values in parentheses are numbers of patients remaining at risk.

Other studies have also revealed worse hospital and long-term outcomes of CABG in diabetics.[21,22] The SYNTAX trial showed that at 3 years, diabetes had little effect on outcomes of CABG, and diabetes control (as indicated by baseline hemoglobin A1c levels) was not predictive of major adverse cardiac and cerebrovascular events. In our study, overall postoperative prevalence of stroke and in-hospital death was higher in diabetics, and occurrence of myocardial infarction was higher in nondiabetics. However, after comparison with similar, high-risk, nondiabetic patients, occurrence of death and myocardial infarction was similar in the 2 groups, as was true in the SYNTAX trial, but stroke remained higher in diabetics.[23]

Health Care Costs

Our study additionally shows that resource utilization and the actual direct technical cost of CABG were greater in diabetics, mainly because of longer intensive care unit and postoperative stays, and higher costs of clinical and laboratory testing, diagnostic imaging, pharmacy services, and nursing care. Greater severity of disease among diabetics necessitates preoperative admission and more-extensive laboratory and diagnostic workup. Furthermore, managing postoperative adverse events and the resulting increase in postoperative length of stay both lead to higher in-hospital costs.

After using propensity matching to compare similar high-risk, nondiabetic patients, no significant difference between the total cost of CABG in diabetics versus nondiabetics with a similar high-risk profile was observed, demonstrating that most of the increased cost was due to diabetics being sicker and having more comorbidities. In 2012, $176 billion was spent on direct health care for diabetics in the United States, with in-hospital care representing 43% of that amount.[3] Because heart disease is one of the leading causes of hospitalization in diabetics, a large share of in-hospital costs can be attributed to CABG and its postoperative complications.

Others have also demonstrated the association of diabetes with increased cost of CABG.[24,25] A study of 114 diabetics and 198 nondiabetics showed that insulin-treated diabetics have longer hospital stays and higher hospital charges than non–insulin-treated diabetics and nondiabetics.[24] A recently published study from China also showed that CABG was more costly, with worse long-term results, in diabetics than in nondiabetics.[26]

Survival

Diabetic patients as a group had a higher early (1-year) risk of death after CABG than nondiabetics, as has been documented by others.[21] However, an interesting finding of our study is that among propensity-matched patients, early risk was similar to that of nondiabetic high-risk patients with a similar comorbidity profile. Long-term survival, however, was worse in diabetics than in both nondiabetic patients and nondiabetic high-risk patients. Other studies have also demonstrated diabetes to be an independent risk factor for reduced long-term survival after

CABG.[21,26] Although long-term survival after CABG is worse in diabetics and high-risk nondiabetics, in general, high-risk patients reap the greatest survival benefit from CABG.[27] Moreover, using surgical techniques that are associated with better long-term survival after CABG in diabetics could further enhance this survival benefit.[28]

Diabetes: An Avoidable Economic Burden

Diabetes is a growing threat to the US economy. Diabetic patients' medical expenses are nearly 2.3 times higher than those of nondiabetics,[3] and this economic burden is expected to increase as the number of diabetes cases rises. Fortunately, however, this situation is largely preventable. In people with prediabetes, cost-effective lifestyle interventions have been shown to have a positive effect on preventing development of the disease.[29-31] In people with diagnosed diabetes, controlling blood sugar and cardiovascular disease risk factors, such as hypertension and hypercholesterolemia, has been shown to help reduce cardiovascular events.[32,33] With appropriate use of these approaches, we can help prevent development of diabetes and its complications, reducing the diabetes-related economic burden.

Strengths and Limitations

This study includes 4 decades of patients who underwent CABG at a single, high-volume academic medical center. An advantage of a long observation period is having a long follow-up period, but generalizing these late results to a contemporary patient population may not accurately reflect the changing patient case mix and advances in managing these patients over time. For adjusted comparison of outcomes, propensity-score matching was performed. Although the patient pairs were well matched, any patient factors that significantly affect outcomes after CABG but were not included in the propensity analysis might bias our adjusted results. In addition, circumstances of each death, which may differ among diabetic and nondiabetic patients, were not reliably captured during follow-up inquiries.

CONCLUSIONS

Diabetes is both a marker for high-risk, resource-intensive, and expensive care after CABG and an independent risk factor for reduced long-term survival. These issues, coupled with the annually increasing number of patients needing CABG who are diabetic, present a growing challenge to reining in health care costs, both in the United States and internationally. Diabetic patients, and those with a similar high-risk profile, set to undergo CABG should be made aware that their risks of postoperative complications are higher than average, and measures should be taken to reduce their postoperative complications. Moreover, trying to reverse the diabetes epidemic is important; if left uncontrolled, it will increase the prevalence of cardiovascular disease and add to the ever-increasing economic health care burden. Research and policies focused on reducing diabetes, and programs that raise awareness about preventive strategies, should be developed and implemented to check rising health care costs.

Conflict of Interest Statement

Dr Sabik is the North American principal investigator for the Abbott Laboratories–sponsored left main coronary disease randomized trial (EXCEL), is on the Society of Thoracic Surgeons Board of Directors, and is on the scientific advisory board of Medtronic. All other authors have nothing to disclose with regard to commercial support.

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Key Words: Coronary artery bypass grafting, diabetes, health care costs

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Thomas Gleason. Repair of Postinfarction Ventricular Septal Defect: Posterior Inferior Ventricular Septal Defect. *Oper Tech Thorac Cardiovasc Surg*. Spring 2014;19(1):115-126.

APPENDIX E1. VARIABLES CONSIDERED IN ANALYSES

Demographics

Age (y)*, sex*, race*, weight (kg), height (cm), weight/height ratio, body surface area (m^2), body mass index ($kg \cdot m^{-2}$)*

Symptoms and Surgical Priorities

New York Heart Association functional class (I-IV),* emergency surgery

Cardiac Comorbidity

Prior myocardial infarction,* atrial fibrillation or flutter,* complete heart block or pacer,* heart failure,* ventricular arrhythmia, left ventricular dysfunction (none, mild, mild to moderate, moderate, moderate to severe, severe)*

Noncardiac Comorbidity

Peripheral arterial disease,* carotid disease,* hypertension,* chronic obstructive pulmonary disease,* history of smoking,* prior stroke,* bilirubin ($mg \cdot dL^{-1}$),* total cholesterol ($mg \cdot dL^{-1}$),* high-density lipoprotein ($mg \cdot dL^{-1}$),* low-density lipoprotein ($mg \cdot dL^{-1}$), triglycerides ($mg \cdot dL^{-1}$),* creatinine ($mg \cdot dL^{-1}$),* blood urea nitrogen ($mg \cdot dL^{-1}$),* hematocrit (%)*

Coronary Anatomy

Number of systems diseased (≥50% stenosis),* left main trunk (LMT) disease, any LMT disease, LMT disease (≥70% stenosis),* LMT disease (≥50% stenosis),* left anterior descending coronary artery (LAD) system disease, any LAD system disease, LAD system disease (≥70% stenosis),* LAD system disease (≥50% stenosis),* left circumflex (LCx) coronary artery system disease, any LCx system disease, LCx system disease (≥70% stenosis),* LCx system disease (≥50% stenosis),* right coronary artery (RCA) system disease, any RCA system disease, RCA system disease (≥70% stenosis),* RCA system disease (≥50% stenosis)*

Experience

Date of operation (years since January 1, 1972)*

* Variables used in the saturated model to calculate propensity scores.

ACD

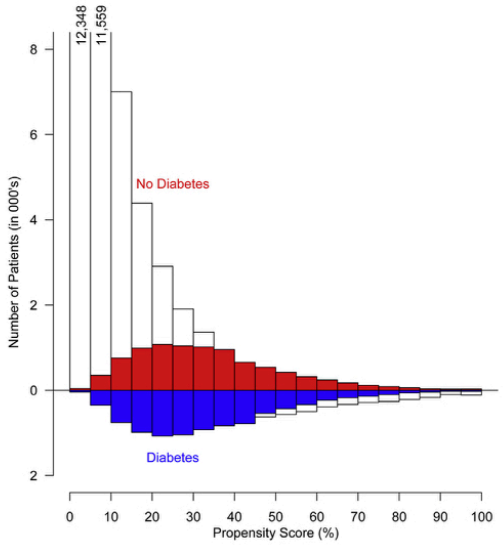


FIGURE E1. Mirrored histogram of distribution of propensity scores for diabetes and no diabetes (*shaded area* represents matched patient cohorts).

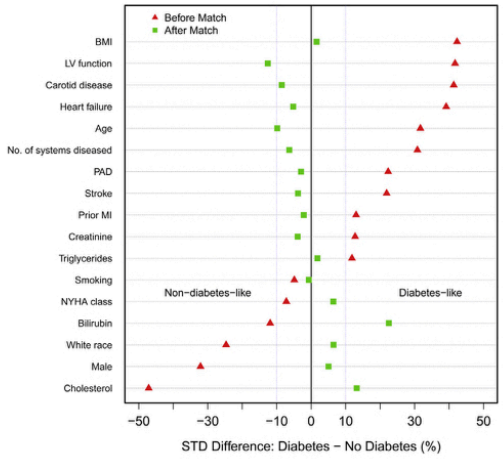


FIGURE E2. Covariable balance plot before and after propensity-score matching on selected covariables (Austin PC, Mamdani MM. A comparison of propensity score methods: a case study estimating the effectiveness of post-AMI statin use. Stat Med. 2006;25:2084-106.) Diabetes-like characteristics are on the right; non–diabetes-like characteristics are on the left. *BMI*, Body mass index; *LV*, left ventricular; *PAD*, peripheral arterial disease; *MI*, myocardial infarction; *NYHA*, New York Heart Association; *STD*, standardized.

TABLE E1. Factors associated with diabetes among patients undergoing coronary artery bypass grafting (parsimonious model)

Factor	Estimate ± SE	*P* value	Reliability (%)
More common in diabetics			
Higher body mass index*	2.09 ± 0.13	<.0001	100
NYHA functional class IV	0.063 ± 0.029	.03	67
Cardiac comorbidities			
Heart failure	0.37 ± 0.045	<.0001	99
More systems diseased†	0.30 ± 0.027	<.0001	100
LCx system disease‡	0.20 ± 0.038	<.0001	100
Worse left ventricular function	0.15 ± 0.011	<.0001	96
Noncardiac cormorbidities			
Peripheral arterial disease	0.40 ± 0.039	<.0001	100
Carotid disease	0.16 ± 0.040	<.0001	68
Hypertension	0.30 ± 0.036	<.0001	90
Stroke	0.25 ± 0.054	<.0001	88
Higher triglycerides§	0.10 ± 0.0036	<.0001	97
Lower bilirubin‖	0.49 ± 0.014	<.0001	75
More common in nondiabetics			
Black or other race¶	0.50 ± 0.041	<.0001	97
LMT system disease‡	−0.20 ± 0.055	.0009	100
Smoking	−0.37 ± 0.026	<.0001	96
Lower cholesterol#	−1.20 ± 0.07	<.0001	97
Lower hematocrit**	−1.29 ± 0.057	<.0001	87
Intercept	−2.28 ± 0.56	.001	

C-statistic = .83. The reliability indicates percentage of times the factor appeared in 500 bootstrap models. *SE*, Standard error; *NYHA*, New York Heart Association; *LCx*, left circumflex coronary artery; *LMT*, left main trunk. *Log(body mass index), logarithmic transformation. †≥50% stenosis. ‡≥70% stenosis. §(Triglycerides/180)^2, squared transformation. ‖(1/bilirubin), inverse transformation. ¶Black or other race compared with white race. #Log(cholesterol), logarithmic transformation). **(Hematocrit/40)^2, squared transformation.

Chapter 4

Research Question 3—What is the Influence of Diabetes on Long-term Patency of Bypass Grafts?

Based on Publication: Raza S, Blackstone EH, Houghtaling PL, Rajeswaran J, Riaz H, Bakaeen FG, Lincoff AM, Sabik JF 3rd. **Influence of Diabetes on Long-term Coronary Artery Bypass Graft Patency**. J Am Coll Cardiol. 2017;70(5):515-524.

4.1 Rationale

One of the findings of our previous study (presented in Chapter 3) was that long-term survival after CABG was worse in diabetic patients compared to non-diabetic patients. Therefore, we did this study to investigate whether worse long-term survival after CABG in diabetic vs. non-diabetic patients was due to higher failure (occlusion) of bypass grafts in diabetic patients. At the time of execution of this study, little was known about the long-term patency of bypass grafts in diabetic vs. non-diabetic patients and the few available studies showed conflicting results [3-8]. We hypothesized that because diabetic patients have more severe coronary artery stenosis [9,10], stenosis in their bypass grafts would also be more severe than in non-diabetic patients, resulting in lower graft patency. To test this hypothesis, we compared patency of the two most commonly used bypass grafts—internal thoracic arteries (ITA) and saphenous

veins (SV)—in diabetic vs. non-diabetic patients. Therefore, our third research question sought to answer: What is the influence of diabetes on patency of bypass grafts?

4.2 Summary of Study Design & Methods

This study included 1,372 pharmacologically treated diabetic patients and 10,147 non-diabetic patients who underwent primary isolated CABG at the Cleveland Clinic from 1972 to 2011 and had at least one postoperative angiogram available. Stenosis was quantified for 7,903 ITA grafts and 20,066 SV grafts. Grafts, particularly SV grafts, tended to be either completely patent or occluded (Figure 2). Therefore, for analysis of this bimodal distribution, a graft was defined as patent if it was not occluded on follow-up angiography. The status of graft patency across time was analyzed by longitudinal nonlinear mixed-effects modeling.

In order to explore the possible influence of cardiac death on longitudinal estimates of graft patency, we performed a pattern-mixture sensitivity analysis to estimate patency trends separately for patients who experienced a cardiac death and patients alive at the time of follow-up closing date.

The possibility of work-up bias affecting the estimates of graft patency was also assessed because diabetic patients tend to be clinically followed for their diabetes more closely than non-diabetic patients.

We did not know the indication for postoperative angiography on a case-by-case basis. We presumed it was most likely for recurrence of ischemic

symptoms. Therefore, it could be argued that the results of the study would be applicable only to patients with ischemic symptoms who undergo angiography and may not be generalizable to the entire CABG population. To account for this, we studied the influence of diabetes on the patency of bypass grafts in a subset of patients who underwent a single planned angiography 1 year after surgery. Moreover, using the multivariable model for graft occlusion for the overall study population, the predicted occlusion at 1 year was calculated for patients undergoing a single planned angiography and compared with the actual occlusion for this population.

4.3 Summary of Results

We studied 20,066 SV grafts and 7,903 ITA grafts and found no influence of diabetes on ITA or SV graft patency over more than 20 years, contrary to our hypothesis. ITA graft patency was stable over time and similar in diabetic and non-diabetic patients: at 1, 5, 10, and 20 years, 97%, 97%, 96%, and 96% in diabetic and 96%, 96%, 95%, and 93% in non-diabetic patients, respectively (early *P*=.2, late *P*=.3; see Figure 4 of manuscript). In contrast, SV graft patency declined over time, similarly in diabetic and non-diabetic patients: at 1, 5, 10, and 20 years, 78%, 70%, 57%, and 42% in diabetic and 82%, 72%, 58%, and 41% in non-diabetic patients, respectively (early *P*<.002, late *P*=.6; see Figure 4 of manuscript). The patient characteristics associated with worse graft patency included women vs. men, younger age, asymptomatic patients, and higher triglyceride levels. The grafting strategies associated with worse graft patency

included using an ITA to graft coronaries with a lesser degree of proximal stenosis, an ITA to graft the right coronary artery, and a SV to graft the circumflex. Despite similar long-term graft patency in diabetic and non-diabetic patients, long-term survival was worse in those with diabetes.

4.4. Findings Compared to Other Studies

Studies differ regarding the effect of diabetes on bypass graft patency. Supporting our observations, Schwartz and colleagues [3] found similar graft patency in patients with and without diabetes using angiographic data from the original BARI trial. ITA graft patency was 89% in diabetic patients vs. 85% in non-diabetic patients (*P*=.2), and SV graft patency was 71% vs. 75% (*P*=.4), respectively, at a mean follow-up of 3.9 years. Hwang and colleagues [4] found 5-year arterial graft patency of 95% in diabetic and 91% in non-diabetic patients. In their study, early, 1-, and 5-year follow-up angiograms were performed independently of patients' ischemic symptoms. Goldman and colleagues [8] studied long-term (10-year) patency of 457 ITA grafts and 1,074 SV grafts and identified risk factors for graft occlusion. Similar to our findings, they did not find diabetes to be a risk factor for graft occlusion.

Contrary to our findings, Deb and colleagues [5] found greater SV graft occlusion in diabetics; 25% in diabetic and 16% in non-diabetic patients at least 5 years after CABG (*P*=.06). Yilmaz and colleagues [7] also found diabetes to be associated with worse short-term (≤5 years) SV graft patency. Ayan and

colleagues [6] found similar arterial graft patency in matched diabetic and non-diabetic patients, but worse SV graft patency in diabetic patients.

4.5 Addition to Literature in Light of Systematic Review

A systematic literature search was done to identify studies that already existed on this topic at the time of paper preparation/publication so that the addition to the literature that the study made could be effectively evaluated in the light of existing knowledge on the subject. The details of this systematic review are given in the Appendix (see section 10.3). Briefly, we searched the literature for studies reporting mid- to long-term (at least 5 years) angiographic outcomes of ITA and SV grafts in diabetic vs. non-diabetic patients. Studies reporting only short-term patency (<5 years), or studies reporting influence of diabetes on overall patency of bypass grafts and not individually for ITA and SV grafts were excluded. Only three studies were identified which met the specified criteria. These included studies by Schwartz et al [3], Hwang et al [4], and Deb et al [5] discussed in the preceding section. The studies by Schwartz and colleagues and Hwang and colleagues supported our findings whereas the results of the study by Deb and colleagues were contrary to our findings. The fact that we studied 20,066 SV grafts and 7,903 ITA grafts in a total of 11,519 patients distinguishes our study from theirs. The study by Schwartz et al studied only 1093 SV grafts and 551 ITA grafts. Hwang et al studied the patency of bypass grafts in only 558 patients and Deb et al studied the patency of bypass grafts in only 269 patients. Furthermore, we reported >20 years patency of bypass grafts whereas studies by Schwartz et

al and Hwang et al reported patency for up to 5 years after CABG and Deb et al reported patency for up to about 10 years after CABG. Therefore, we believe that our study, by virtue of its large sample size, long follow-up, and distinctive statistical methodology, provides strong supporting evidence for our assertions and represents a valuable addition to the literature on this topic.

4.6 Critical Commentary

Help was taken from Critical Appraisal Skills Program (CASP) checklist for Cohort Studies for critical commentary on this manuscript. Available at: http://www.casp-uk.net/casp-tools-checklists.

4.6.1 Rationale

As mentioned in the introduction section of the paper, this study sought to answer a clearly focused question: Does diabetes influence long-term patency of coronary artery bypass grafts? The introduction section of the paper clearly presented the rationale of the study. Because diabetic patients represent an important and growing population of patients undergoing CABG and not much is known about the effect of diabetes on long-term graft patency, it is important to investigate the given research question. However, we could have also added that our previous study showed that long-term survival after CABG was worse in diabetic vs. non-diabetic patients and this could be due to worse long-term patency of bypass grafts in diabetic patients, making it imperative to study this question.

4.6.2 Study Design

This was a retrospective observational study. An RCT was not possible to study this question, as patients cannot be randomized into diabetes and no-diabetes categories. However, a prospective study with routine angiography at specified intervals would be the best method for determining graft patency. Although in some prospective studies high proportions of patients have undergone early angiography, by 5 years, patient dropout due to death, reoperation, and refusal to participate altered the characteristics of the remaining population in nonrandom ways [11-14]. Therefore, it is not easy to study long-term (>20 years) angiographic outcomes of CABG prospectively with routine angiograms at regular intervals.

4.6.3 Participant Selection

The cohort was recruited in an acceptable way. We used data from Cleveland Clinic's Cardiovascular Information Registry (CVIR) and identified patients who underwent primary isolated CABG at the Cleveland Clinic from 1972 to 2011. Both, non-diabetic patients and diabetic patients were identified and extracted from the same registry i.e. CVIR.

Patients with unknown diabetic status were excluded. Patients were considered diabetic if they were medically treated for diabetes (taking insulin or medications for diabetes), as mentioned in the paper. All of the subjects were classified into exposure groups using the same definition. Because the primary end-point of the study was an angiographic outcome i.e. graft patency, only

patients having at least one post-operative angiogram prior to any repeat coronary intervention i.e. PCI or CABG, were included. Data on graft patency was obtained through diagnostic catheterization data available in the CVIR and PCI registry. Patients with post-operative angiogram after a repeat coronary intervention were excluded because repeat coronary intervention could have influenced the primary outcome, graft patency. Patients with unknown diabetic status were excluded because it was not possible to study the influence of diabetes on graft patency of such patients.

It was not mentioned in the paper whether this study required any additional data-collection, apart from the data retrieved from the registries. As mentioned in section 8.3, this study required data collection of missing diagnostic catheterizations. I did this data-collection myself.

4.6.4 Sample Size

A sample size calculation was not done. This was a retrospective cohort study of patients who underwent primary isolated CABG at the Cleveland Clinic during a given time period. Therefore, a sample size calculation would not have affected the number of patients included. However, given that we studied 7,903 ITA grafts and 20,066 SV grafts, our study was adequately powered to detect a difference, under the assumption that one exists. For example, we studied 1132 ITA grafts in diabetic patients and 6771 ITA grafts in non-diabetic patients. The 20-year ITA graft patency in both patient populations was above 90%. To detect a difference of 5% in patency of grafts in diabetic and non-diabetic patients, our study was

>99% powered, at a significance level of 5%. Please note that some criticize the idea of retrospective power calculation. However, it was done just to provide an approximate idea regarding the statistical power of the study.

4.6.5 End-points

The primary end-point of the study was graft patency. A graft was considered patent if not occluded. This was because grafts tended to be either completely open (0% stenosed) or occluded (100% stenosed), as shown in Figure 3 of the manuscript. Therefore, for analysis of this bimodal distribution, a graft was defined as patent if not occluded on follow-up angiography. The follow-up was long enough (20-year patency estimate provided in the paper). One of the limitations of the study was that our stenosis data (from angiograms read by expert cardiologists) were based on qualitative angiography and not quantitative angiography, so inter-observer and intra-observer variability cannot be ruled out. Although quantitative coronary angiography is more reproducible, it is time-consuming and expensive. Given the number of patients in the study, retrospective quantitative analysis was not feasible. However, clinical decision-making is virtually always based on qualitative and not quantitative angiography. Therefore, qualitative angiography represents the real-world approach.

Long-term mortality was also studied in diabetic vs. non-diabetic patients undergoing CABG. Although we knew from our previous study that long-term mortality was higher in diabetic patients undergoing CABG, it was important to know whether this was true for a subset of patients who underwent post-op

angiography after CABG, presumed to be mainly due to ischemic symptoms. The median follow-up was provided for long-term mortality as distribution of survival data is usually (positively) skewed. Vital status was obtained by CVIR routine anniversary follow-up questionnaires supplemented with data from the Social Security Death Master File. Please see section 3.6.5 for in-depth critical commentary on our long-term mortality follow-up.

4.6.6 Data Analysis

Longitudinal Analysis: Because date of graft occlusion is rarely known, rendering time-to-event (Kaplan-Meier) analysis non-applicable, we used longitudinal data analysis to study bypass graft patency. The objective of this method was to estimate the ensemble average patency across time after CABG from multiple angiographic “snapshots” of the status of patients’ grafts, much as one would do for multiple blood pressure readings across time.

Marginal models and mixed effects models are two frequently used modeling approaches to analyze longitudinal data. A mixed effect modeling approach is preferable to a marginal modeling approach because, in practice, longitudinal data are often highly unbalanced in the sense that each subject has different number of longitudinal responses observed at non-fixed time points. In our study, the longitudinal binary measurement was unbalanced because the number and timing of binary measurements of graft occlusion could be different for different patients. Therefore, to account for the possible association between binary measurements in individual patients, we used a logistic mixed-effects

model. We knew from previous studies that the probability of patency may be nonlinear over time and that the influence of possible risk factors may also change over time. Therefore, a nonlinear multiphase logistic mixed-effects model [15] was used to resolve the number of time phases in the odds domain to form a temporal decomposition model and to estimate the shaping parameters at each phase.

Confounding: To control for confounding, the multivariable model for graft occlusion was adjusted for a number of risk factors. The variables considered and the details of this analysis are provided in the paper. This model was further adjusted for propensity score (propensity of having diabetes). However, any patient factors not included in the propensity model, or in the multivariable model for graft occlusion, that importantly affect outcomes might have biased our findings.

Applicability of Results to Other Patients: We did not know on a case-by-case basis the indication for postoperative angiography. We presumed it was most likely for recurrence of ischemic symptoms. Therefore, it could be argued that the results—that graft patency is similar among diabetic and non-diabetic patients—are applicable only to patients with ischemic symptoms who undergo angiography and may not be generalizable to the entire CABG population. To account for this, we studied the influence of diabetes on patency of bypass grafts in a subset of patients who underwent a single planned angiography 1 year after

surgery. The results of this analysis were similar to the overall results of our study and showed that diabetes was not associated with lower bypass graft patency.

Work-up Bias Evaluation: The possibility of work-up bias affecting estimates of graft patency cannot be ignored because diabetic patients tend to be clinically followed for their diabetes more closely than non-diabetic patients. Therefore, we assessed time to first post-CABG angiography and frequency of angiographic assessment as explained in the paper.

Long-term Mortality: Survival was assessed nonparametrically using the Kaplan-Meier method, and parametrically using a multiphase hazard model (please see section 2.6.6 above for details regarding this model*)*.

Influence of Cardiac Death on Patency: To explore the possible influence of cardiac death on longitudinal estimates of graft patency, we performed a pattern-mixture sensitivity analysis to estimate patency trends separately for patients who experienced a cardiac death and patients who were alive at the time of follow-up closing date. This analysis demonstrated that cardiac death did not substantially alter the results presented. In particular, it does not suggest that cardiac death caused us to overestimate graft patency.

4.6.7 Results & Discussion

The major finding of this study was that diabetes was not associated with lower graft patency. Given the range of confidence intervals, the results look precise.

These results were debated in the light of similar and contrary findings from other studies in the Discussion section of the paper. The limitations were also mentioned under the discussion section in detail.

The conclusions of the study were supported by the data presented and mentioned the implications of the results for clinical practice that use of ITA grafts should be maximized in all patients undergoing CABG as they have excellent patency even 20 years after CABG in both diabetic and non-diabetic patients.

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4.8 Full-text of the Paper

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ORIGINAL INVESTIGATIONS

Influence of Diabetes on Long-Term Coronary Artery Bypass Graft Patency

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ABSTRACT

BACKGROUND Nearly 50% of patients undergoing coronary artery bypass grafting have diabetes. However, little is known about the influence of diabetes on long-term patency of bypass grafts. Because patients with diabetes have more severe coronary artery stenosis, we hypothesized that graft patency is worse in patients with than without diabetes.

OBJECTIVES This study sought to examine the influence of diabetes on long-term patency of bypass grafts.

METHODS From 1972 to 2011, 57,961 patients underwent primary isolated coronary artery bypass grafting. Of these, 1,372 pharmacologically treated patients with diabetes and 10,147 patients without diabetes had 15,887 postoperative angiograms; stenosis was quantified for 7,903 internal thoracic artery (ITA) grafts and 20,066 saphenous vein grafts. Status of graft patency across time was analyzed by longitudinal nonlinear mixed-effects modeling.

RESULTS ITA graft patency was stable over time and similar in patients with and without diabetes: at 1, 5, 10, and 20 years, 97%, 97%, 96%, and 96% in patients with diabetes, and 96%, 96%, 95%, and 93% in patients without diabetes, respectively (early $p = 0.20$; late $p = 0.30$). In contrast, saphenous vein graft patency declined over time and similarly in patients with and without diabetes: at 1, 5, 10, and 20 years, 78%, 70%, 57%, and 42% in patients with diabetes, and 82%, 72%, 58%, and 41% in patients without diabetes, respectively (early $p < 0.002$; late $p = 0.60$). After adjusting for patient characteristics, diabetes was associated with higher early patency of ITA grafts (odds ratio: 0.63; 95% confidence limits: 0.43 to 0.91; $p = 0.013$), but late patency of ITA grafts was similar in patients with and without diabetes ($p = 0.80$). Early and late patency of saphenous vein grafts were similar in patients with and without diabetes (early $p = 0.90$; late $p = 0.80$).

CONCLUSIONS Contrary to our hypothesis, diabetes did not influence long-term patency of bypass grafts. Use of ITA grafts should be maximized in patients undergoing coronary artery bypass grafting because they have excellent patency in patients with and without diabetes even after 20 years. (J Am Coll Cardiol 2017;70:515–24) © 2017 by the American College of Cardiology Foundation.

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From the [a]Department of Thoracic and Cardiovascular Surgery, Cleveland Clinic, Cleveland, Ohio; [b]Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio; [c]Department of Internal Medicine, Cleveland Clinic, Cleveland, Ohio; and the [d]Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio. Funded in part by the Gus P. Karos Registry Fund; the Sheikh Hamdan bin Rashid Al Maktoum Distinguished Chair in Thoracic and Cardiovascular Surgery, held by Dr. Sabik; and the Kenneth Gee and Paula Show, PhD, Chair in Heart Research, held by Dr. Blackstone. Dr. Raza is a Clinical Research Scholar as part of the Cardiothoracic Surgical Trials Network, and his Master of Science in Management-Healthcare degree is being funded by National Institutes of Health/National Heart, Lung, and Blood Institute grant UM1HL088955. These individuals and funding organizations played no role in the collection of data or analysis and interpretation of the data and had no right to approve or disapprove publication of the finished manuscript. Dr. Sabik is the North American principal investigator for the Abbott Laboratories-sponsored left main coronary disease randomized trial (EXCEL); is on the Society for Thoracic Surgeons board of directors; is on the scientific advisory board of Medtronic; and has received consulting income from Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Presented at the American College of Cardiology Scientific Sessions 2016, Chicago, Illinois, April 2–4, 2016.

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

ITA = internal thoracic artery

LAD = left anterior descending coronary artery

SV = saphenous vein

The FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial demonstrated fewer deaths and myocardial infarctions in patients with diabetes and multivessel coronary artery disease after coronary artery bypass grafting (CABG) than after percutaneous coronary intervention (1). Today, nearly 50% of patients undergoing CABG have diabetes (2,3). However, little is known about bypass graft patency in patients with versus without diabetes (4–9). We hypothesized that because patients with diabetes have more severe coronary artery stenosis (10,11), stenosis in their bypass grafts would also be more severe than in patients without diabetes, resulting in lower graft patency. To test this hypothesis, we compared patency of the 2 most commonly used bypass grafts, internal thoracic arteries (ITA) and saphenous veins (SV), in patients with versus without diabetes.

SEE PAGE 525

METHODS

PATIENTS. From January 1, 1972, to January 1, 2011, a total of 57,961 patients underwent primary isolated CABG at Cleveland Clinic. Patients were included in this study if the following information was available: 1) knowledge of whether pharmacologically treated diabetes mellitus was present (treated with insulin or oral hypoglycemic agents); 2) detailed pre-operative angiographic data describing location and severity of native coronary system stenosis; 3) results of at least 1 post-operative angiogram before any repeat coronary intervention; and 4) quantitative information on degree of angiographic stenosis of bypass grafts. These criteria were met for 11,519 patients, 1,372 with pharmacologically treated diabetes and 10,147 without (**Figure 1**, Online Table 1). Pre-operative, operative, and post-operative variables (Online Appendix 1) were retrieved from the Cardiovascular Information Registry. Use of these data for research was approved by the Institutional Review Board, with patient consent waived. Compared with excluded patients, studied patients were younger, operated on in earlier years, had fewer comorbidities, fewer received bilateral ITA grafts, and more had incomplete revascularization (Online Table 2).

CORONARY ARTERY BYPASS GRAFTS. In the study group, 28,876 coronary artery bypasses were performed, 3,881 in patients with diabetes and 24,995 in patients without diabetes (Online Table 3). These included 8,124 ITA grafts and 20,376 SV grafts. Use of ITA grafting substantially increased in the 1980s (**Figure 2**). Most grafts were used as single conduits: 95.5% of ITA grafts in patients with diabetes and 96.5% in patients without diabetes, and 82% of SV grafts in patients with diabetes and 86% in patients without diabetes. Four general sites for graft anastomoses were defined: 1) left anterior descending (LAD); 2) diagonal; 3) left circumflex; and 4) right coronary artery.

POST-OPERATIVE ANGIOGRAPHY. Patients underwent post-operative coronary angiography for a variety of reasons. Early in the series, they underwent a single planned angiogram at 1 year after CABG; subsequently, we presume angiography was performed for suspected ischemic symptoms.

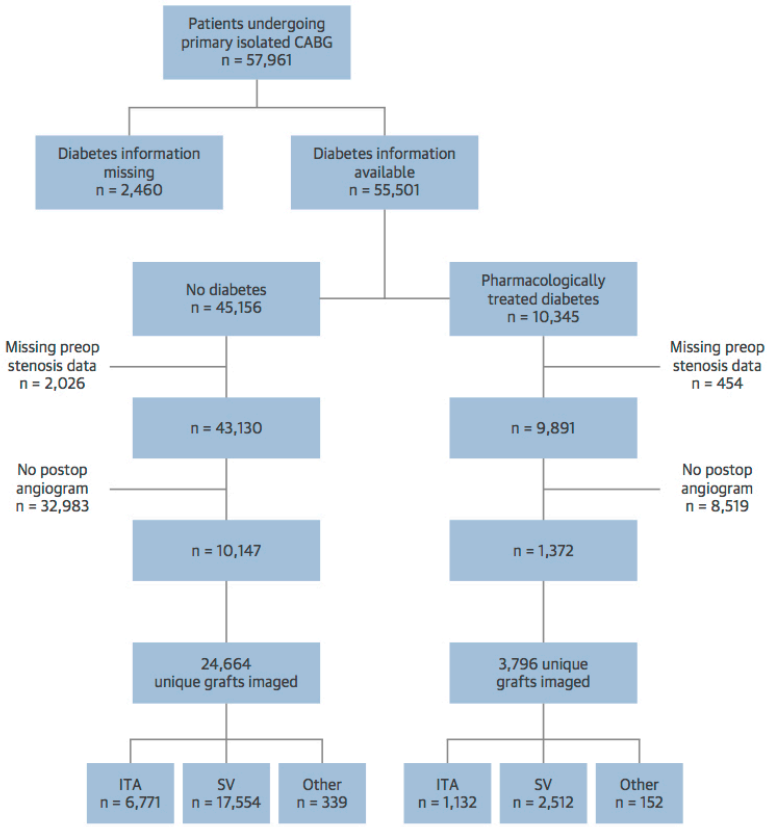
From 1972 to 2011, 15,887 post-operative angiograms were performed in the study group, with 38,753 individual graft observations (Online Figures 1 and 2, Online Table 4); 8,387 patients (73%) had 1 post-operative angiogram, 2,267 (20%) had 2 post-operative angiograms, 623 (5.4%) had 3 post-operative angiograms, and 242 (2.1%) had 4 or more. These angiograms recorded stenosis for 27,969 unique grafts: 7,903 ITA grafts (1,132 in patients with diabetes and 6,771 in patients without diabetes) and 20,066 SV grafts (2,512 in patients with diabetes and 17,554 in patients without diabetes). These 27,969 grafts were the unit of analysis, not the patient.

To investigate possible underestimation of graft patency caused by patients' reluctance to undergo angiography unless symptomatic, we studied a subgroup of 985 patients who underwent CABG from 1972 through 1975 and had a single planned angiogram at 1 year (11 to 13 months). These angiograms recorded stenosis for 1,883 unique grafts; 433 ITA grafts (27 in patients with diabetes and 406 in patients without diabetes), and 1,450 SV grafts (88 in patients with diabetes and 1,362 in patients without diabetes).

GRAFT PATENCY. Grafts, particularly SV grafts, tended to be either completely patent or occluded (**Figure 3**). Therefore, for analysis of this bimodal distribution, a graft was defined as patent if not occluded on follow-up angiography.

Because date of graft occlusion is rarely known, rendering time-to-event (Kaplan-Meier) analysis nonapplicable, we used longitudinal data analysis to study bypass graft patency. The objective of this method was to estimate ensemble average patency across time after CABG from multiple angiographic "snapshots" of the status of patients' grafts, much as one would do for multiple blood pressure readings across time. The patient was a random effect to

FIGURE 1 CONSORT-Style Diagram of Study Population



CABG = coronary artery bypass grafting; ITA = internal thoracic artery; postop = postoperative; preop = preoperative; SV = saphenous vein.

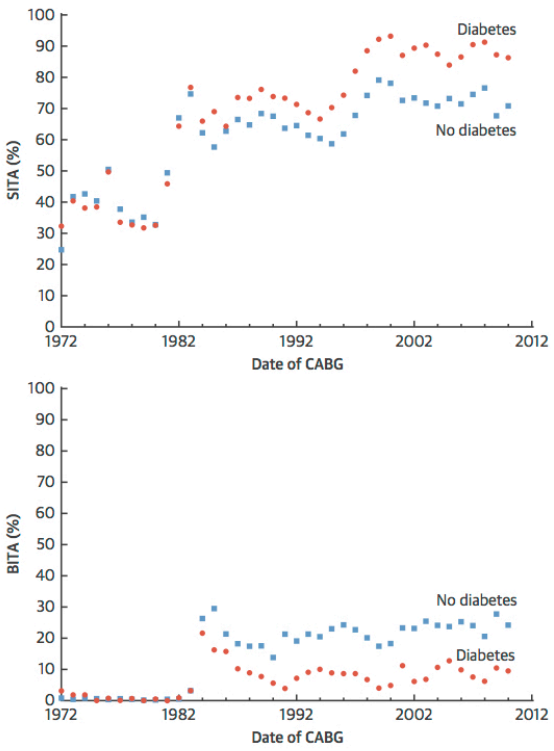
account for within-patient variability, because a patient generally had multiple grafts. Patency was compared for grafts in patients with and without diabetes and for type of graft, ITA or SV. Because the analysis identified both an early and late phase of graft occlusion, with the early phase lasting for about 1 year for ITA grafts and about 4 years for SV grafts, statistics for both phases are presented and arbitrarily designated as "early" and "late." Details of the analysis are given in Online Appendix 2 ("Patency Analysis").

RISK-ADJUSTED GRAFT PATENCY. Because we hypothesized that graft patency is adversely affected by secondary effects of diabetes, we developed a semi-saturated propensity score for having diabetes. Logistic regression was used, incorporating 30 clinical variables (C = 0.84). Effectiveness of the propensity score to match patients is displayed in Online Figure 3. This propensity score was used to adjust all models presented in this study ("Propensity Score Development" in Online Appendix 2).

For the 985 patients with a single planned angiogram available at 1 year, simple logistic regression for occlusion at 1 year (not time to event) was performed with adjustment done for sex, age, body mass index, degree of proximal stenosis, grafts to LAD, and propensity score.

RISK FACTORS FOR GRAFT OCCLUSION. Prevalence of graft occlusion across time was estimated by averaging patient-specific profiles. Therefore, we

FIGURE 2 Percentage of Patients With and Without Diabetes Undergoing Primary Isolated CABG Who Received Single or Bilateral ITA Grafts Per Year Over the Study Period



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

sought to identify variables besides diabetes and type of bypass graft that modulated this longitudinal prevalence. For this, we identified variables simultaneously in each phase of graft occlusion using variables in Online Appendix 1 ("Risk Factor Analysis" in Online Appendix 2).

WORK-UP BIAS. Because patients with diabetes tend to be clinically followed for their diabetes more closely than patients without diabetes, the possibility of work-up bias affecting estimates of graft patency cannot be ignored. Therefore, 3 complementary methods were used to assess time to first post-CABG angiogram and frequency of angiographic assessment: 1) crude comparison between patients with and without diabetes of time to first angiogram and number of angiograms performed per patient; 2) repeat of "1" for 1,328 propensity-matched patients (98% of all possible matches); and 3) New York Heart Association functional class at first angiogram ("Evaluation of Possible Work-up Bias" in Online Appendix 2).

SURVIVAL. The unanticipated results of this study made it imperative to re-examine this particular cohort of patients with diabetes who, by nature of the study, had to have survived to undergo at least 1 coronary angiogram ("Long-term Survival Analysis" in Online Appendix 2).

POSSIBLE INFLUENCE OF CARDIAC DEATH ON PATENCY. Although in longitudinal data analysis death merely terminates observation of graft stenosis, it is possible that increased risk of death in patients with diabetes may lead to overestimation of graft patency because it cannot account for cardiac deaths caused by graft occlusion. Formal statistical methods to quantify the effect of cardiac death on graft patency estimates do not yet exist, but methods do exist to discover if the pattern of graft patency in patients dying of cardiac causes diverges from that of patients still alive. The method is detailed in Online Appendix 2 ("Pattern Mixture Analysis").

STATISTICAL ANALYSIS. SAS version 9.4 (SAS Institute, Cary, North Carolina) was used for all analyses.

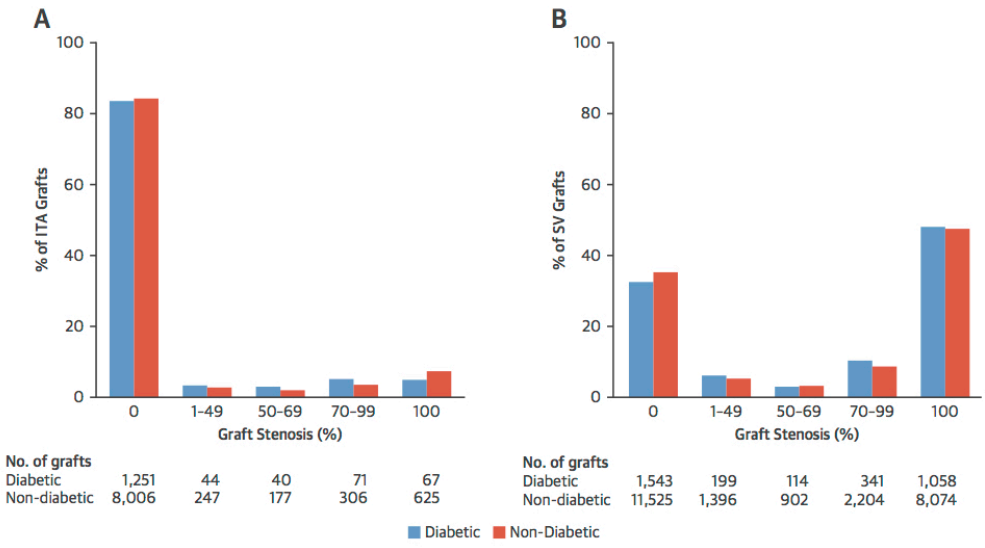
RESULTS

DIABETES AND BYPASS GRAFT PATENCY. In patients with diabetes, 85% of ITA grafts were free of any stenosis on follow-up angiograms, 10% had 1% to 99% stenosis, and 4.6% were occluded (**Figure 3A**). In patients without diabetes, 86% of ITA grafts were free of any stenosis, 7.8% had 1% to 99% stenosis, and 6.7% were occluded. Unadjusted ITA graft patency at 1, 5, 10, 15, and 20 years after surgery was 97%, 97%, 96%, 96%, and 96% in patients with diabetes and 96%, 96%, 95%, 94%, and 93% in patients without diabetes, respectively (early $p = 0.20$; late $p = 0.30$; **Figure 4**). Early and late patency of ITA grafts was similar in patients operated on in the 1970s, 1980s, and recent years (1990 to 2011; Online Figure 4A).

In the subgroup of patients with single planned angiograms, 1-year ITA graft patency was 93% in patients with diabetes and 96% in patients without diabetes ($p = 0.30$).

In patients with diabetes, 47% of SV grafts were free of any stenosis, 20% had 1% to 99% stenosis, and 32% were occluded (**Figure 3B**). In patients without diabetes, 48% of SV grafts were free of any stenosis, 19% had 1% to 99% stenosis, and 34% were occluded. Unadjusted SV graft patency at 1, 5, 10, 15, and

FIGURE 3 Frequency of Occurrence of Graft Stenosis (Percentage of Lumen Diameter)



(A) Internal thoracic artery grafts in patients with and without diabetes (number of observations for patients without diabetes = 9,361; number for patients with diabetes = 1,473). **(B)** Saphenous vein grafts in patients with and without diabetes (number of observations for patients without diabetes = 24,101; number for patients with diabetes = 3,255). Abbreviations as in Figure 1.

20 years after surgery was 78%, 70%, 57%, 49%, and 42% in patients with diabetes and 82%, 72%, 58%, 48%, and 41% in patients without diabetes (early $p < 0.002$; late $p = 0.60$) (Figure 4). Early patency of SV grafts was better in patients operated on in the 1970s (Online Figure 4B), but long-term patency was better in patients operated on in recent years (1990 to 2011).

In the subgroup of patients with single planned angiograms, 1-year SV graft patency was 80% in patients with diabetes and 86% in patients without diabetes ($p = 0.07$).

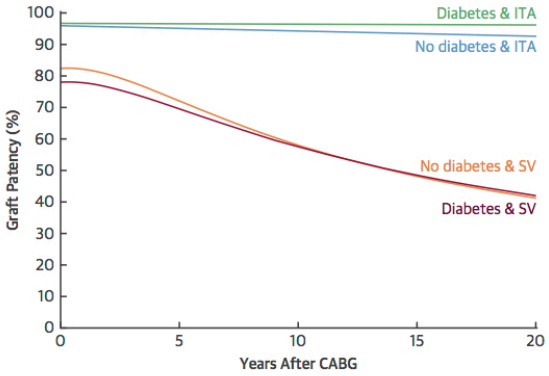
Risk-adjusted results. After adjusting for patient characteristics, patients with diabetes had higher, not lower, early patency of ITA grafts than those without diabetes (odds ratio: 0.63; 95% confidence limits: 0.43 to 0.91; $p = 0.013$), but late patency was similar ($p = 0.80$) (**Central Illustration, Figure 5A,** Online Figure 5, Online Table 5). Early and late patency of SV grafts was similar in patients with and without diabetes (early $p = 0.9$; late $p = 0.8$) (**Figure 5A,** Online Figure 5, Online Table 5).

In the subgroup of patients with single planned angiograms, adjusted 1-year patency was similar for both ITA grafts ($p = 0.60$) and SV grafts ($p = 0.40$) (**Figure 5B**) in patients with versus without diabetes. As a form of validation, predicted occlusion at 1 year from the multivariable graft occlusion model (Online Table 5) was similar to observed occlusion at 1 year for both ITA and SV grafts in patients with versus without diabetes (Online Table 6).

OTHER RISK FACTORS FOR GRAFT OCCLUSION. Other risk factors for early graft occlusion included: 1) female sex; 2) ITA grafts to right coronary artery; and 3) lesser degree of proximal coronary artery stenosis for ITA grafts (Online Table 5). Risk factors for late occlusion included: 1) younger age at time of CABG; 2) asymptomatic patients; 3) higher triglycerides; 4) SV grafts to left circumflex coronary artery; and 5) grafts to non-LAD coronary arteries (Online Table 5).

WORK-UP BIAS EVALUATION. Median time to first coronary angiography was shorter by about 7 months for patients with versus without diabetes ($p = 0.0009$), and 10 months among propensity-matched patients ($p = 0.0005$) (Online Table 7). However, median number of angiograms performed per patient was similar, 3 each for patients with and without diabetes, and for propensity-matched patients (Online Table 7). Time to first angiography

FIGURE 4 Temporal Pattern of Patency of ITA and SV Grafts in Patients With and Without Diabetes Undergoing CABG



Patency findings are based on angiographic "snapshots" of graft patency analyzed by a method that in essence creates for each patient a temporal profile of graft patency. These profiles are averaged across time for patients with and without diabetes. These curves, along with those in Online Figures 4 and 5, are not Kaplan-Meier curves depicting time-related events. Indeed, one does not know when a graft has occluded unless a catastrophic event occurs. Rather, what is depicted is the average state of graft patency across time for patients with and without diabetes. Abbreviations as in Figure 1.

was similar for patients with and without diabetes in the first year (overall $p = 0.09$; matched $p = 0.70$), but thereafter, shorter in patients with than without diabetes (overall $p < 0.0001$; matched $p < 0.0001$) (Online Figure 6).

More patients with diabetes (64%) were symptomatic than patients without diabetes (55%; $p < 0.0001$) at first angiogram overall, but results were similar for matched patients ($p = 0.14$) (Online Table 8).

LONG-TERM SURVIVAL. Among patients with diabetes, overall survival at 1, 5, 10, 15, and 20 years after CABG was 99.4%, 93%, 73%, 51%, and 35%, respectively; for patients without diabetes it was 99.8%, 98%, 88%, 74%, and 58%, respectively ($p < 0.0001$) (Online Figures 7A and 7B). Among patients with diabetes, mode of death was cardiac in 173 (45%), noncardiac in 102 (27%), and not known in 107 (28%). Among patients without diabetes, mode of death was cardiac in 1,266 (47%), noncardiac in 720 (26%), and not known in 737 (27%).

Among propensity-matched patients, survival for patients with diabetes at these same time points was 99.4%, 93%, 73%, 51%, and 35%, respectively; for patients without diabetes it was 99.6%, 96%, 83%, 69%, and 58%, respectively ($p < 0.0001$) (Online Figures 7C and 7D). Among propensity-matched patients with diabetes, mode of death was cardiac in 168 (45%), noncardiac in 101 (27%), and not known in 104 (28%). Among propensity-matched patients without diabetes, mode of death was cardiac in 103 (41%), noncardiac in 63 (25%), and not known in 85 (34%).

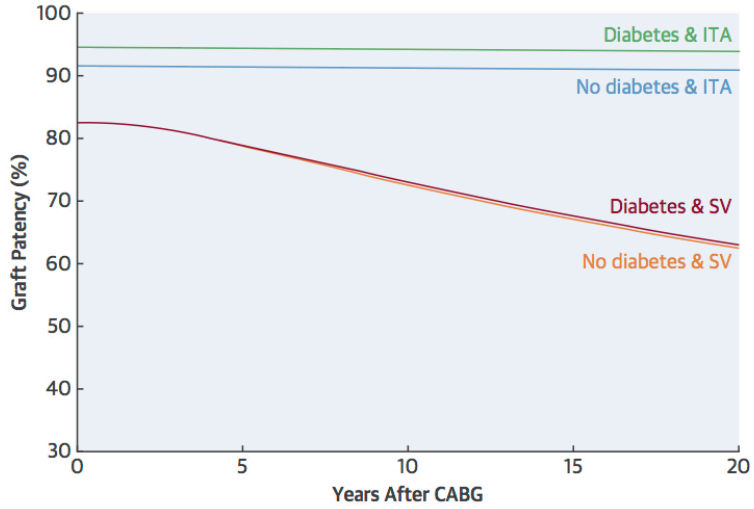
POSSIBLE INFLUENCE OF CARDIAC DEATH. For ITA grafts, there was no apparent difference in graft patency trend for patients with diabetes experiencing a cardiac death versus those who were alive. However, there was a slight difference in patients without diabetes: those experiencing a cardiac death had slightly higher patency (about 1%) than those who were alive (Online Figure 8A). In patients with diabetes receiving SV grafts, in every instance the longitudinal pattern of those experiencing a cardiac death was slightly lower within the first few years (by a maximum of 3%) and progressively higher/better beyond about 4 years (Online Figure 8B). In patients without diabetes receiving SV grafts, the pattern for those experiencing cardiac death was everywhere somewhat higher.

DISCUSSION

PRINCIPAL FINDINGS. We studied 20,066 SV grafts and 7,903 ITA grafts and found no influence of diabetes on ITA or SV graft patency over more than 20 years, contrary to our hypothesis. ITA graft patency remained stable over time, whereas SV graft patency declined progressively for patients with and without diabetes. Patient characteristics associated with worse graft patency included women versus men, younger age, asymptomatic patients, and higher triglyceride levels. Grafting strategies associated with worse graft patency included using an ITA to graft coronaries with a lesser degree of proximal stenosis, an ITA to graft the right coronary artery, and an SV to graft the left circumflex coronary artery. Despite similar long-term graft patency in patients with and without diabetes, long-term survival was worse in those with diabetes.

FINDINGS IN CONTEXT. Studies differ regarding the effect of diabetes on bypass graft patency. Supporting our observations, Schwartz et al. (4) found similar graft patency in patients with and without diabetes using angiographic data from the original BARI (Bypass Angioplasty Revascularization Investigation) trial. ITA graft patency was 89% in patients with diabetes versus 85% in patients without diabetes ($p = 0.20$), and SV graft patency was 71% versus 75% ($p = 0.40$), respectively, at a mean follow-up of 3.9 years. Hwang et al. (5) found 5-year arterial graft patency of 95% in patients with diabetes and 91% in patients without diabetes. In their study, early, 1-,

CENTRAL ILLUSTRATION **Diabetes and Bypass Graft Patency**



Raza, S. et al. J Am Coll Cardiol. 2017;70(5):515–24.

Temporal pattern of risk-adjusted patency of internal thoracic artery (ITA) and saphenous vein (SV) grafts in patients with and without diabetes undergoing coronary artery bypass grafting (CABG). In patients with and without diabetes, stable high patency of ITA grafts and decline of SV graft patency follow the same temporal pattern. Patency findings are based on angiographic "snapshots" of graft patency analyzed by a method that in essence creates for each patient a temporal profile of graft patency. These profiles are averaged across time for patients with and without diabetes.

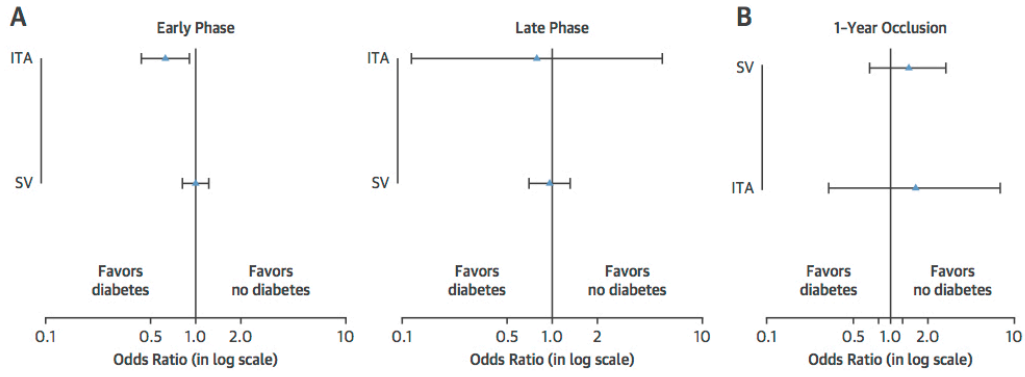
and 5-year follow-up angiograms were performed independently of patients' ischemic symptoms. Goldman et al. (9) studied long-term (10-year) patency of 457 ITA grafts and 1,074 SV grafts and identified risk factors for graft occlusion. Similar to our findings, they did not find diabetes to be a risk factor.

Contrary to our findings, Deb et al. (6) found greater SV graft occlusion by angiography at least 5 years after CABG, 25% in patients with diabetes and 16% in patients without diabetes ($p = 0.06$). Yilmaz et al. (8) also found diabetes to be associated with worse short-term (≤5 years) SV graft patency. Ayan et al. (7) found similar arterial graft patency in matched patients with and without diabetes, but worse SV graft patency in patients with diabetes. We believe that our study, by virtue of its large sample size, long follow-up, and distinctive statistical methodology, despite the unanticipated result, may reflect the truth.

Effectiveness of coronary artery bypass surgery is related to long-term graft patency. Because bypass grafts are equally durable in patients with and without diabetes, coronary surgery should be as effective in those with diabetes. Nevertheless, long-term survival after CABG in patients with diabetes is worse than for patients without diabetes. Why? The reason could be native-vessel disease progression and heart failure, or noncardiac modes of death. Patients with diabetes have more comorbid conditions than those without diabetes, including hypertension, chronic renal insufficiency, peripheral arterial disease, and higher body mass index (2,12). The BARI investigators (12) compared cause of death in patients with and without diabetes at 5 years after CABG and found similar cardiac mortality (5.8% in patients with diabetes and 4.7% in patients without diabetes), but 5-year noncardiac mortality was much higher in patients with diabetes (13% vs. 5.6%).

Similar to other reports, we found that bypass grafts to non-LAD coronary arteries (13–17) were associated with decreased graft patency. That non-LAD bypass grafts have lower patency than grafts to the LAD might be because it is easier technically to

FIGURE 5 Adjusted Risk of ITA and SV Graft Occlusion in Patients With and Without Diabetes



Symbols represent point estimates and **horizontal bars** 95% confidence limits. **(A)** Overall study population. **(B)** Patients undergoing a single planned angiogram 1 year after surgery. Abbreviations as in Figure 1.

graft anterior coronary arteries, and the amount of myocardium supplied by the LAD is greater than that supplied by other coronary arteries, resulting in a larger blood flow demand being placed on bypass grafts to the LAD.

Grafting a noncritically stenosed coronary artery with an ITA was another risk factor for graft occlusion. Unlike SV grafts, arterial grafts can autoregulate their size depending on flow requirements. When flow requirements are low, such as when ITA grafts are used to bypass coronary arteries with noncritical stenoses, grafts may close as a result of competitive blood flow in the native vessel (18-24). In our study, early ITA graft patency was better in patients with than without diabetes; this could be because patients with diabetes have more diffuse coronary artery disease than patients without diabetes, which may lead to decreased competitive flow in the native vessel. Maximum preoperative proximal coronary stenosis between the bypass graft anastomosis and aorta, the surrogate for competitive flow, could overestimate competitive flow in native vessels in patients with diabetes because the maximum proximal stenosis lesion could be longer due to the diffuse nature of coronary artery disease in these patients.

Progression of vein graft atherosclerosis causes bypass graft patency to decrease with time (25-27). Because ITA grafts are resistant to atherosclerosis, they are much more likely than SV grafts to remain patent in patients with and without diabetes (15,28-30).

Unadjusted early patency of SV grafts was better in patients who underwent surgery in the 1970s. This could be caused by the single planned angiogram at 1 year after CABG in the early 1970s. Unadjusted long-term patency of SV grafts was best in the recent cohort of patients, which could be due to statin use. The Post CABG trial showed that aggressive lowering of low-density lipoprotein cholesterol by statins reduces progression of atherosclerosis in SV grafts (31).

We have previously shown that bilateral ITA grafting maximizes long-term survival in patients with diabetes undergoing CABG (32). However, it is also associated with higher occurrence of deep sternal wound infections. Therefore, we recommend that bilateral ITA grafting be used in patients with diabetes (Figure 2) for whom risk of deep sternal wound infection is low; it might be best to avoid bilateral ITA grafting in obese women with diabetes and diffuse atherosclerotic burden, patients at the greatest risk of developing these infections (32).

METHODOLOGICAL CONSIDERATIONS AND STUDY LIMITATIONS. We do not know on a case-by-case basis the indication for postoperative angiography. We presume it most likely was for recurrence of ischemic symptoms. Therefore, it could be argued that the results (that graft patency is similar among patients with and without diabetes) are applicable only to patients with ischemic symptoms who undergo angiography and may not be generalizable to

the entire CABG population. To account for this, we studied the influence of diabetes on patency of bypass grafts in a subset of patients who underwent single planned angiography 1 year after surgery. The results of this analysis were similar to the overall results of our study and showed that diabetes was not associated with lower bypass graft patency. Moreover, using the multivariable model for graft occlusion for the overall study population, predicted occlusion at 1 year was calculated for patients undergoing single planned angiography and compared with the actual occlusion for this population. For patients with and without diabetes, and ITA and SV grafts, there was no significant difference between observed and predicted occlusion.

A prospective study with accurate, periodic noninvasive surveillance would be the best method for determining graft patency. Although in some prospective studies high proportions of patients have undergone early angiography, by 5 years, patient dropout because of death, reoperation, and refusal to participate altered the characteristics of the remaining population in nonrandom ways (13,33–35). Accurate, noninvasive advanced imaging with minimal radiation exposure is needed.

Patients with diabetes are less likely than those without diabetes to have symptoms from myocardial ischemia (36,37). Therefore, a patient with diabetes might have more coronary or bypass graft atherosclerotic disease before developing symptoms than would a patient without diabetes and be less likely to undergo angiography. Graft patency among patients with diabetes might be lower than our findings. In fact, contrary to this speculation, median time to first angiography was shorter for patients with diabetes. This could make their graft patency seem lower (earlier angiography, earlier detection of graft closure).

To explore the possible influence of cardiac death on longitudinal estimates of graft patency, we performed a pattern-mixture sensitivity analysis to estimate patency trends separately for patients who experienced a cardiac death and patients alive at the time of follow-up closing date. This analysis demonstrated that cardiac death did not substantially alter the results presented. In particular, it does not suggest that cardiac death caused us to overestimate graft patency.

We did not have long-term medical management data for patients in the study and therefore could not assess its influence on patency of grafts over time, except to observe better late graft patency in the most recent cohort.

CONCLUSIONS

Long-term patency of bypass grafts is similar in patients with and without diabetes. Therefore, worse long-term outcomes after CABG in patients with diabetes are likely not related to lower graft patency. Use of ITA grafts should be maximized in all patients undergoing surgical revascularization, because they have excellent patency in patients with and without diabetes even 20 years post-operatively.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Diabetes does not adversely influence the long-term patency of coronary artery bypass grafts. Worse survival after coronary surgery in patients with diabetes is not related to lower graft patency so much as to comorbidities, progressive atherosclerosis, and complications of diabetes.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Internal thoracic artery grafts should be used as much as possible in patients with and without diabetes undergoing coronary artery surgery because of their excellent patency even 20 years post-operatively.

TRANSLATIONAL OUTLOOK: Further studies are necessary to address the factors that compromise long-term survival of patients with diabetes after coronary bypass surgery and to assess the impact of diabetes on long-term patency of radial, gastroepiploic, and inferior epigastric artery grafts.

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KEY WORDS coronary artery bypass grafting, diabetes, graft occlusion, graft patency, internal thoracic artery grafts, saphenous vein grafts

APPENDIX For supplemental tables and figures, please see the online version of this article.

Supplemental (Online-Only) Material

Online Appendix 1: Variables Considered in Analyses

Demographics

Age* (y), sex*, race*, weight (kg), height (cm), weight/height ratio, body surface area (m^2), body mass index* ($kg \cdot m^{-2}$)

Symptoms and surgical priorities

New York Heart Association functional class* (I-IV), emergency surgery*

Cardiac comorbidity

Prior myocardial infarction*, atrial fibrillation or flutter*, complete heart block or pacer*, heart failure*, ventricular arrhythmia, left ventricular dysfunction* (none, mild, mild to moderate, moderate, moderate to severe, severe)

Noncardiac comorbidity

Pharmacologically treated diabetes, peripheral arterial disease*, carotid disease*, hypertension*, chronic obstructive pulmonary disease*, history of smoking*, prior stroke, bilirubin ($mg \cdot dL^{-1}$), total cholesterol* ($mg \cdot dL^{-1}$), high-density lipoprotein cholesterol* ($mg \cdot dL^{-1}$), low-density lipoprotein cholesterol ($mg \cdot dL^{-1}$), triglycerides* ($mg \cdot dL^{-1}$), creatinine* ($mg \cdot dL^{-1}$), blood urea nitrogen* ($mg \cdot dL^{-1}$), hematocrit (%)

Coronary anatomy

Number of systems diseased* (≥50% stenosis), left main trunk (LMT) disease, any LMT disease, LMT disease* (≥70% stenosis), LMT disease* (≥50% stenosis), left anterior descending coronary artery (LAD) system disease, any LAD system disease, LAD system disease* (≥70% stenosis), LAD system disease* (≥50% stenosis), left circumflex (LCx) coronary artery system disease, any LCx system disease, LCx system disease* (≥70% stenosis), LCx system disease* (≥50% stenosis), right coronary artery (RCA) system disease, any RCA

system disease, RCA system disease* (≥70% stenosis), RCA system disease* (≥50% stenosis), proximal stenosis in native coronary systems (%)

CABG details†

ITA graft, SV graft, graft to artery (LAD, LCx, RCA, diagonal), interaction: graft (ITA, SV) and diabetes status, interaction: graft (ITA, SV) and proximal stenosis in native coronary systems (%)

Experience:

Date of operation* (years since 1/1/1972)

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* Variables used in the saturated model to calculate propensity scores.
† CABG details are additionally considered in the multivariable longitudinal analysis.

Online Appendix 2: Details of Statistical Analyses

Patency Analysis

To assess the temporal trend of prevalence of graft occlusion over time after CABG, all postoperative coronary angiograms obtained on each patient were analyzed longitudinally to estimate patient-specific temporal profiles, and from these the ensemble average. Because the number and timing of binary measurements of graft occlusion were different for different patients, the longitudinal binary measurement is unbalanced. Therefore, to account for the association between binary measurements in individual patients, we used a logistic mixed-effects model. We knew from previous studies that the probability of patency was nonlinear over time and that the influence of risk factors changed over time,

i.e., different risk factors at different time phases or the same risk factor with varying influence at different time phases. Therefore, a nonlinear multiphase logistic mixed-effects model (1) was used to resolve the number of time phases in the odds domain to form a temporal decomposition model and to estimate the shaping parameters at each phase. SAS® PROC NLMIXED was used to implement the model for longitudinal binary measurements (2).

Propensity Score Development

Using multivariable logistic regression, we first identified preoperative variables (E-Appendix 1) associated with being diabetic (parsimonious model, Table E9). This was augmented with other preoperative patient factors to form a semi-saturated propensity model, as indicated in Appendix E1A. A propensity score for each patient was calculated and forced into the final model for risk adjustment, even if not statistically significant.

Risk-factor Analysis

Because of the limited capability of PROC NLMIXED to explore multivariable relations, we initially screened the variables (E-Appendix 1) using ordinary multivariable logistic regression (PROC LOGISTIC) and a computer-intensive machine learning "bagging" method (3), with the assumption of independence of observations and with entry criteria (.07) and stay criteria (.05). This analysis was performed simply to identify possible candidates for our repeated measurements multivariable model. Having identified these candidate variables and their transformations, if any, they were entered one by one until all variables remaining had a *P*-value of .05 or less.

Because diabetes and type of graft were the variables of interest, interaction (graft type x diabetes status) variables were kept in the model regardless of statistical significance. Note that the multivariable model was further adjusted for propensity score of having diabetes (described above), to adjust for a possible confounding effect.

Evaluation of Possible Work-up Bias

To assess for possible work-up bias, time to first angiography and number of angiograms performed per patient were compared between diabetic and non-diabetic patients. This was done in three ways. First, median times to first angiography and median number of angiograms performed per patient for all diabetic and non-diabetic patients were compared. Second, these same statistics were compiled in the propensity-matched pairs and compared. For this, greedy matching based on the calculated propensity scores was used to match diabetic with non-diabetic patients, yielding 1,328 matched pairs (97% of possible matches). A mirrored histogram of distribution of propensity scores for diabetic and non-diabetic patients showed that the matched cohort covered the complete spectrum of cases, and the standardized difference plot demonstrated that covariable balance was achieved across nearly all variables (Figure E9). Finally, the hazard functions for first angiography for the matched diabetic and non-diabetic patients were determined and compared.

To further investigate work-up bias, New York Heart Association functional class at first angiography was compared between diabetic and non-diabetic patients. Functional class at first angiography was available in 9,167 non-diabetic and 1,137 diabetic patients.

Long-term Survival Analysis

Vital status after hospital discharge was obtained by routine anniversary follow-up questionnaires and supplemented with data from the Social Security Death Master File, accessed on October 27, 2011, with a closing date of April 27, 2011. A total of 121,120 patient-years of follow-up data were available for analyses. Median follow-up was 10 years, with 25% of survivors followed for >18 years and 10% for >25 years. For diabetic patients, 9,660 patient-years of follow-up data were available for analyses, with a median follow-up of 6.1 years; 25% of survivors were followed for >11 years and 10% for >17 years. For non-diabetic patients, 111,460 patient-years of follow-up data were available for analyses, with a median follow-up of 11 years; 25% of survivors were followed for >20 years and 10% for >25 years.

For overall and matched patients, survival was assessed nonparametrically using the Kaplan-Meier method, and parametrically using a multiphase hazard model (6). The latter involved resolving the number of hazard phases for instantaneous risk of death (hazard function) and estimating shaping parameters. (For details, see www.lerner.ccf.org/qhs/software/hazard.)

Pattern Mixture Analysis

The nonlinear logistic mixed-effects model used in our analysis assumes there is no informative censoring. To assess for possible association between longitudinal binary occlusion data and cardiac death, and demonstrate that cardiac death is not informative of the longitudinal trend of graft patency, we performed a pattern mixture sensitivity analysis, where the objective was to see if

patients who experienced cardiac death exhibited a different pattern of temporal trend of patency than the pattern in patients who were alive at the end of the study follow-up. This sensitivity analysis was repeated for subgroups of patients with and without diabetes receiving ITA grafts, and those receiving SV grafts. The proper statistical approach for this problem is to jointly model the longitudinal binary response and time-to-event cardiac death outcome. There are numerous models that jointly model continuous longitudinal outcome and time-to-event outcomes. However, because of computational difficulties arising from the nonlinear link functions and possible nonlinearity in the longitudinal trend, there are few, if any, methods that jointly model binary longitudinal outcome and time-to-event outcome. Therefore, in the present state of lack of joint modeling methods for longitudinal binary data and time-to-event data, the pattern mixture approach to a sensitivity analysis was probably the best way to assess for possible association between longitudinal binary occlusion data and cardiac death.

Missing Values

For missing values we used multiple imputation (7) with the Markov chain Monte Carlo technique with the assumption of missing at random. We used 5-fold multiple imputation with PROC MI (SAS v9.1). In multivariable modeling, for each imputed complete dataset, we estimated the regression coefficients and their variance–covariance matrix. Then, following Rubin (7), we combined the estimates from the 5 models. This was implemented using PROC MIANALYZE.

Presentation

Graphical presentation of graft patency results is for mean effects, after considering the two sources of within-patient variability. Graphical solutions of the longitudinal equation were risk adjusted by holding values for variables in the model constant, as described in figure legends.

Continuous variables are summarized as mean ± standard deviation and as 15th, 50th (median), and 85th percentiles for skewed distributions; comparisons were made using the Wilcoxon rank-sum test. Categorical data are summarized as frequencies and percentages; comparisons were made using the chi-squared test or Fisher's exact test when frequency was less than 5. Uncertainty is expressed by confidence limits (CLs).

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Online Table 1. Patient characteristics (total n=11,519)

Characteristic	Diabetes (n=1,372) n[a]	Diabetes (n=1,372) No. (%) or Mean ± SD	No Diabetes (n=10,147) n[a]	No Diabetes (n=10,147) No. (%) or Mean ± SD	*P*
Demographics					
Age (y)	1,372	59 ± 9.0	10,147	56 ± 9.0	<.0001
Female	1,372	373 (27)	10,147	1,310 (13)	<.0001
Race					
Black	1,291	76 (5.9)	9,148	163 (1.8)	<.0001
White	1,291	1,166 (90)	9,148	8,757 (96)	<.0001
Body mass index ($kg \cdot m^{-2}$)	890	30 ± 5.2	4,094	27 ± 4.0	<.0001
Acuity					
NYHA functional class	1,367		10,083		.07
I		200 (15)		1,382 (14)	
II		469 (34)		3,454 (34)	
III		164 (12)		1,022 (10)	
IV		534 (39)		4,225 (42)	
Emergency operation	1,372	14 (1.0)	10,146	134 (1.3)	
Native coronary artery disease[b]					
Left main trunk	1,317	172 (13)	10,024	1,162 (12)	.12
Left anterior descending	1,369	1,263 (92)	10,140	9,126 (90)	.008
Circumflex	1,360	1,084 (80)	10,110	6,801 (67)	<.0001
Right coronary artery	1,365	1,161 (85)	10,112	8,018 (79)	<.0001
No. of coronary systems diseased	1,372		10,147		<.0001
0[c]		4 (0.29)		56 (0.55)	
1		103 (7.5)		1,417 (14)	
2		390 (28)		3,494 (34)	
3		875 (64)		5,180 (51)	
Cardiac comorbidity					
Prior MI	1,372	788 (57)	10,147	5,390 (53)	.003

Left ventricular dysfunction	1,294				<.0001
None		1,049 (81)	10,003	9,331 (93)	
Mild		96 (7.4)		356 (3.6)	
Mild to moderate		21 (1.6)		54 (0.54)	
Moderate		78 (6.0)		177 (1.8)	
Moderate to severe		27 (2.1)		42 (0.42)	
Severe		23 (1.8)		43 (0.43)	
Noncardiac comorbidity					
Peripheral arterial disease	1,372	183 (13)	10,147	748 (7.4)	<.0001
Carotid disease	1,372	166 (12)	10,147	252 (2.5)	<.0001
Hypertension	600	472 (79)	1,442	933 (65)	<.0001
Smoking	1,351	634 (47)	9,884	5,213 (53)	<.0001
Prior stroke	1,372	75 (5.5)	10,147	178 (1.8)	<.0001
Creatinine ($mg \cdot dL^{-1}$)[d]	576	0.8/1.1/1.4	1,365	0.8/1.1/1.4	.7
Cholesterol ($mg \cdot dL^{-1}$)					
Total	925	230 ± 56	7,619	248 ± 54	<.0001
HDL	470	36 ± 11	1,819	39 ± 12	<.0001
LDL	313	134 ± 46	827	142 ± 45	.003
Triglycerides ($mg \cdot dL^{-1}$)	805	226 ± 184	6,474	198 ± 117	.01

a. Patients with data available.

b. ≥50% stenosis.

c. These patients had left main trunk disease only. It was not anatomically coded as multisystem disease.

d. 15th/50th/85th percentiles.

Key: *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein; *MI,* myocardial infarction; *NYHA,* New York Heart Association; *SD,* standard deviation.

Online Table 2. Patient characteristics of angiographically studied (postoperative cath) and non-studied (no postoperative cath) populations

Characteristic	Postop Cath[a] (n=11,519) n[c]	Postop Cath[a] (n=11,519) No. (%) or Mean ± SD	No Postop Cath[b] (n=43,982) n[c]	No Postop Cath[b] (n=43,982) No. (%) or Mean ± SD
Diabetes	11,519		43,892	
Medically treated		1,372 (12)		8,973 (20)
Insulin		255 (19)		2,537 (28)
No insulin		344 (25)		3,483 (39)
Unknown		773 (56)		2,953 (33)
Demographics				
Age (y)	11,519	56 ± 9.0	43,982	61 ± 10
Female	11,519	1,683 (15)	43,982	8,943 (20)
White race	10,439	9,923 (95)	40,663	37,035 (91)
Body mass index ($kg \cdot m^{-2}$)	4,984	28 ± 4.4	27,719	28 ± 4.5
Acuity				
NYHA functional class	11,450		43,642	
I		1,582 (14)		7,862 (18)
II		3,923 (34)		16,589 (38)
III		1,186 (10)		4,988 (11)
IV		4,759 (42)		14,203 (33)
Native coronary artery disease[d]				
Left main trunk	11,341	1,334 (12)	39,845	7,119 (18)
Left anterior descending	11,509	10,389 (90)	41,404	38,315 (93)
Circumflex	11,470	7,885 (69)	41,094	30,140 (73)
Right coronary artery	11,477	9,179 (80)	41,140	33,862 (82)
Number of coronary systems diseased	11,519		41,502	
0		60 (0.52)		375 (0.90)
1		1,520 (13)		4,405 (11)
2		3,884 (34)		12,254 (30)
3		6,055 (53)		24,468 (59)

Cardiac comorbidity				
Prior MI	11,519	6,178 (54)	43,982	22,671 (52)
Heart failure	11,519	397 (3.4)	43,982	3,573 (8.1)
Noncardiac comorbidity				
Peripheral arterial disease	11,519	931 (8.1)	43,982	5,461 (12)
Carotid disease	11,519	418 (3.6)	43,982	5,294 (12)
Smoking	11,235	5,847 (52)	43,218	23,612 (55)
Prior stroke	11,519	253 (2.2)	43,982	2,142 (4.9)
Cholesterol ($mg \cdot dL^{-1}$)				
Total	8,544	246 ± 54	34,114	226 ± 58
HDL	2,289	38 ± 12	17,728	40 ± 13
LDL	1,140	140 ± 45	12,785	122 ± 46
Triglycerides ($mg \cdot dL^{-1}$)	7,279	201 ± 127	28,641	186 ± 129
CABG details				
ITA grafts at index operation	11,519		43,982	
0		4,468 (39)		12,438 (28)
1		6,256 (54)		26,474 (60)
2		795 (6.9)		5,070 (12)
Incomplete revasc.[d]	11,519	1,522 (13)	43,982	4,142 (9.4)
In-hospital outcomes	11,519		43,982	
Death		5 (0.043)		772 (1.8)
Permanent stroke		68 (0.59)		805 (1.8)
Perioperative MI		382 (3.3)		774 (1.8)
Surgery date				
1/1/1972 to index operation (y)	11,519	10 ± 7.7	43,982	17 ± 10

Note: All *P*-values <.0001.

a. Study cohort.
b. Not in study.
c. Patients with data available.
d. ≥50% stenosis.

Key: *CABG,* coronary artery bypass grafting; *HDL,* high-density lipoprotein; *ITA,* internal thoracic artery; *LDL,* low-density lipoprotein; *MI,* myocardial infarction; *NYHA,* New York Heart Association; *revasc.*, revascularization; *SD,* standard deviation.

Online Table 3. Number of coronary systems bypassed according to conduit type

Bypasses	Diabetes (n= 3,881)	No Diabetes (n=24,995)	Overall (n=28,876)
ITA to:	**1,173**	**6,951**	**8,124**
LAD	938	5,452	6,390
Diagonal	118	623	741
LCx	98	666	764
RCA	19	210	229
Saphenous vein to:	**2,573**	**17,803**	**20,376**
LAD	309	3,309	3,618
Diagonal	401	2,442	2,843
LCx	959	6,182	7,141
RCA	904	5,870	6,774
Other conduit to:	**135**	**241**	**376**
LAD	4	10	14
Diagonal	19	51	70
LCx	85	113	198
RCA	27	67	94

Key: *ITA,* internal thoracic artery; *LAD,* left anterior descending coronary artery; *LCx,* left circumflex coronary artery; *RCA,* right coronary artery.

Online Table 4. Number of postoperative angiographic studies by conduit type and coronary system grafted (n=38,753 observations)

Angiograms	Diabetes (n=4,903)	No Diabetes (n=33,850)	Overall (n=38,753)
ITA to:	1,473	9,361	10,834
LAD	1,183	7,421	8,604
Diagonal	137	800	937
LCx	130	872	1,002
RCA	23	268	291
Saphenous vein to:	3,255	24,101	27,356
LAD	379	4,466	4,845
Diagonal	516	3,281	3,797
LCx	1,216	8,359	9,575
RCA	1,144	7,995	9,139
Other conduit to:	175	388	563
LAD	24	62	86
Diagonal	33	85	118
LCx	86	153	239
RCA	32	88	120

Key: *ITA,* internal thoracic artery; *LAD,* left anterior descending coronary artery; *LCx,* left circumflex coronary artery; *RCA,* right coronary artery.

Online Table 5. Risk factors for graft occlusion

Factor	Estimate ± SE	*P*
Early constant phase		
Female	0.32 ± 0.075	<.0001
Graft to LAD		
ITA	-0.75 ± 0.18	<.0001
SV	-0.62 ± 0.087	<.0001
Graft to RCA		
ITA	1.2 ± 0.24	<.0001
SV (no effect)	-0.032 ± 0.061	.6
Preoperative stenosis and graft		
Lower stenosis and ITA	-1.2 ± 0.15	<.0001
Stenosis and SV (no effect)	0.0093 ± 0.085	.9
Diabetes and graft type (compared with no diabetes and ITA)		
Diabetes and ITA	-0.47 ± 0.19	.013
No diabetes and SV[a]	-0.44 ± 0.26	.09
Diabetes and SV[a]	-0.45 ± 0.27	.103
Propensity score[b]	0.12 ± 0.024	<.0001
Late increasing phase		
Younger age[c]	-2.2 ± 0.23	<.0001
NYHA functional class I	0.21 ± 0.096	.03
Higher triglycerides[d]	0.26 ± 0.102	.04
Graft to LAD		
ITA	-1.2 ± 1.1	.3
SV	-0.86 ± 0.099	<.0001
Graft to circumflex		
ITA	1.6 ± 0.87	.06
SV	0.22 ± 0.062	.0004
Diabetes and graft type (compared with no diabetes and ITA)		
Diabetes and ITA	-0.24 ± 0.98	.8
No diabetes and SV[a]	3.5 ± 0.89	<.0001

Diabetes and SV[a]	3.4 ± 0.90	.0001
Propensity score[b]	-0.036 ± 0.038	.3

a. Early and late patency was similar for SV grafts between diabetics and non-diabetics (early *P*=.9, late *P*=.8).

b. Log(propensity score/[1-propensity]), logistic transformation.

c. Log(age), logarithmic transformation.

d. Log(triglycerides), logarithmic transformation.

Key: *ITA*, internal thoracic artery; *LAD*, left anterior descending coronary artery; *NYHA*, New York Heart Association; *RCA*, right coronary artery; *SE*, standard error; *SV*, saphenous vein.

Online Table 6. Observed vs. predicted number of occluded grafts for patients undergoing a single planned angiogram at 1 year

Group	No. of Grafts	Predicted Occlusion	Actual Occlusion	*P*
Non-diabetic patients				
All	1,768	199	201	.9
ITA grafts	406	13	16	.4
SV grafts	1,362	186	185	>.9
Diabetic patients				
All	115	18	20	.6
ITA grafts	27	1	2	.3
SV grafts	88	17	18	.8

Key: *ITA,* internal thoracic artery; *SV*, saphenous vein.

Online Table 7. Time to first coronary angiography and number of angiograms per patient, stratified by diabetes

Variable	No Diabetes		Diabetes			
	No.	15th/50th/85th Percentiles	No.	15th/50th/85th Percentiles	*P*[a]	*P*[b]
Unadjusted						
Time to first angiogram	10,147	0.96/4.0/11	1,372	0.95/3.4/8.4	<.0001	.0009
No. of angiograms per patient	10,147	2/3/5	1,372	2/3/5	<.0001	<.0001
1	1,245	12%	96	7.0%		
2	3,063	30%	324	24%		
3	2,583	25%	459	33%		
4	1,630	16%	273	20%		
5	106	1.0%	26	1.9%		
6	827	8.1%	99	7.2%		
≥7	693	7.8%	95	7.0%		
Propensity matched						
Time to first angiogram	1,328	0.70/4.2/9.6	1,328	0.94/3.4/8.4	.003	.005
No. of angiograms per patient	1,328	2/3/6	1,328	2/3/5	.004	.006
1	65	4.9%	94	7.1%		
2	282	21%	319	24%		
3	448	34%	438	33%		
4	306	23%	264	20%		

5	24	1.8%	26	2.0%
6	93	7.0%	95	7.2%
≥7	110	8.3%	92	6.9%

a. Wilcoxon rank-sum test.

b. Median score test (number of points above overall median).

Online Table 8. Postoperative NYHA functional class at first coronary angiography, stratified by diabetes

	Diabetes		No Diabetes		
Variable	**n[a]**	**No. (%)**	**n[a]**	**No. (%)**	***P***
Unmatched					
NYHA functional class	1,137		9,167		<.0001
I		412 (36)		4,140 (45)	
II		335 (29)		2,394 (26)	
III		113 (9.9)		600 (6.5)	
IV		277 (24)		2,033 (22)	
Matched					
NYHA functional class	1,104		1,068		.14
I		400 (36)		338 (32)	
II		329 (30)		351 (33)	
III		109 (9.9)		113 (11)	
IV		266 (24)		266 (25)	

Key: *NYHA*, New York Heart Association.

Online Table 9. Factors associated with being diabetic

Variable	Estimate ± SE	*P*	Reliability (%)[a]
Demographics			
Female	0.82 ± 0.075	<.0001	100
Black or other race (vs. white)	0.75 ± 0.13	<.0001	56
Cardiac comorbidity			
Heart failure	0.60 ± 0.13	<.0001	77
Coronary system disease[b]			
LCx	0.49 ± 0.067	<.0001	74
RCA	0.22 ± 0.073	.003	68
Lower or higher LV function	0.31 ± 0.032	<.0001	86
Noncardiac comorbidity			
Peripheral arterial disease	0.42 ± 0.098	<.0001	96
Carotid disease	1.03 ± 0.12	<.0001	62
Smoking	-0.34 ± 0.062	<.0001	95
Higher triglycerides	0.0024 ± 0.00031	<.0001	98
Lower total cholesterol[c]	0.45 ± 0.070		97
Intercept	-2.19 ± 0.20	<.0001	

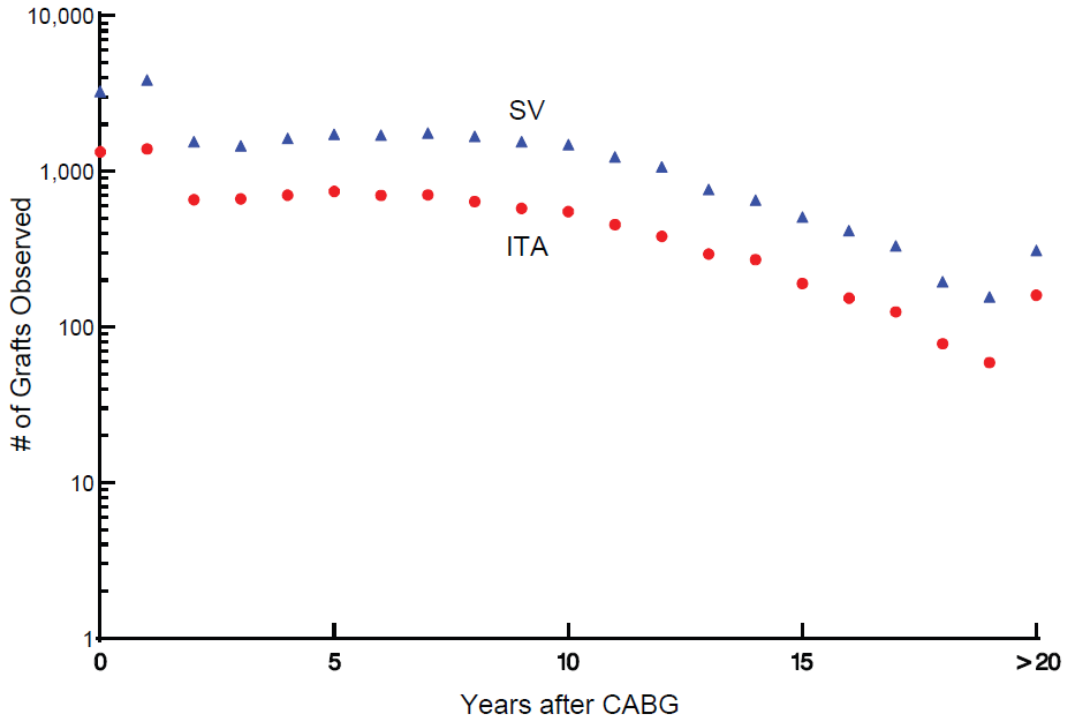
Note: C-statistic=0.73.

a. Percent of times factor appeared in 500 bootstrap models.

b. ≥70% stenosis.

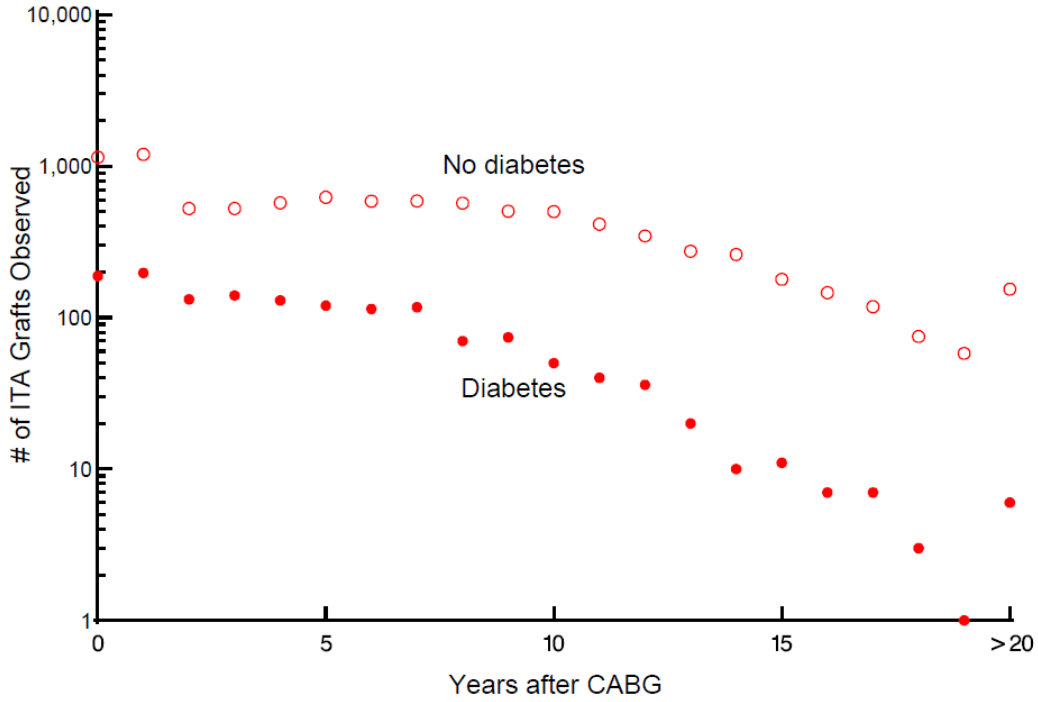
c. $(230/\text{total cholesterol})^2$, inverse squared transformation.

Key: *LCx*, left circumflex; *LV*, left ventricular; *RCA*, right coronary artery; *SE*, standard error.



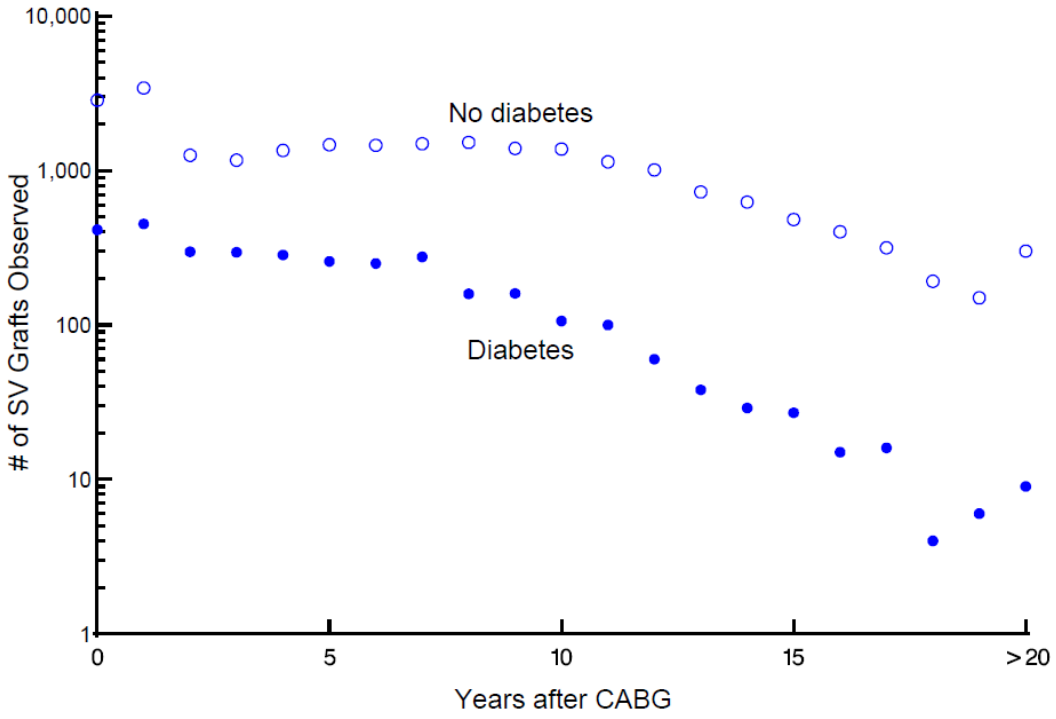
Online Figure 1. Number of internal thoracic artery (ITA) and saphenous vein (SV) bypass grafts studied by angiography each year after coronary artery bypass grafting (CABG). Note logarithmic vertical axis.

***A*,** ITA and SV grafts overall.



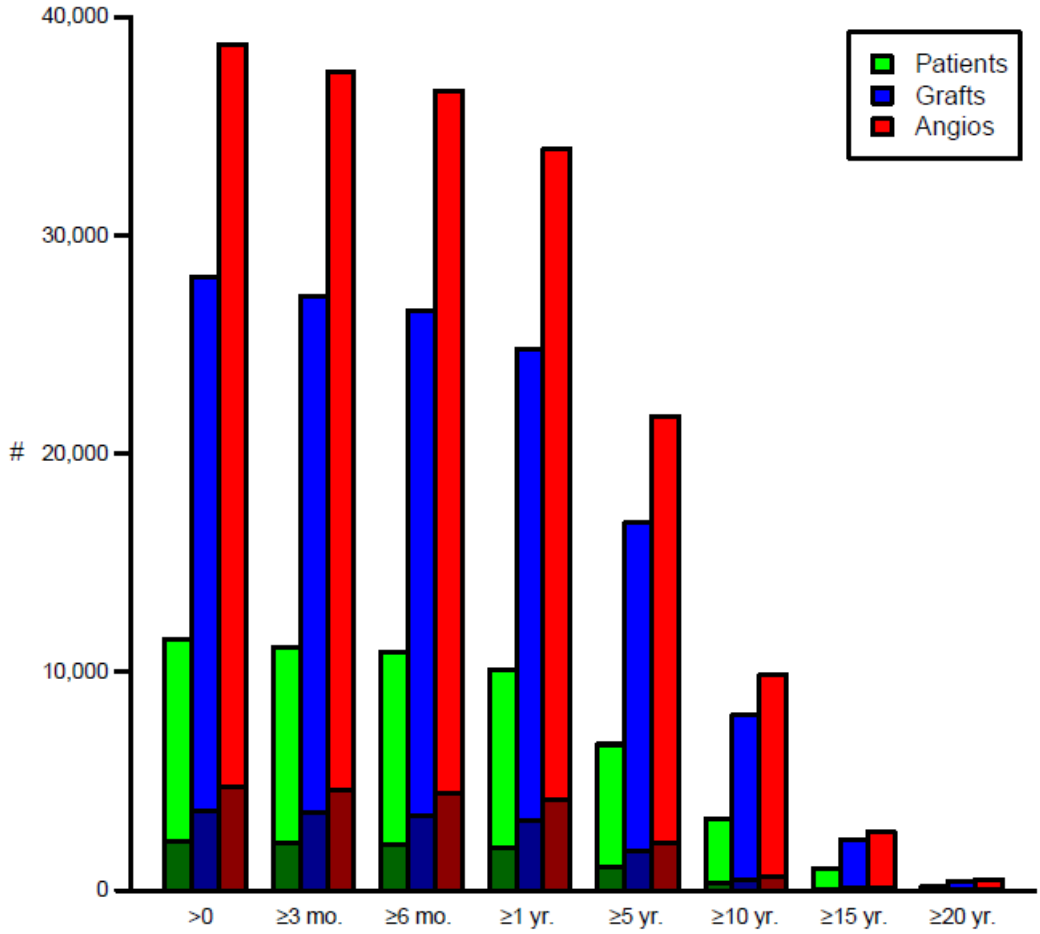
Online Figure 1. Number of internal thoracic artery (ITA) and saphenous vein (SV) bypass grafts studied by angiography each year after coronary artery bypass grafting (CABG). Note logarithmic vertical axis.

***B*,** ITA grafts stratified by presence of diabetes or no diabetes.



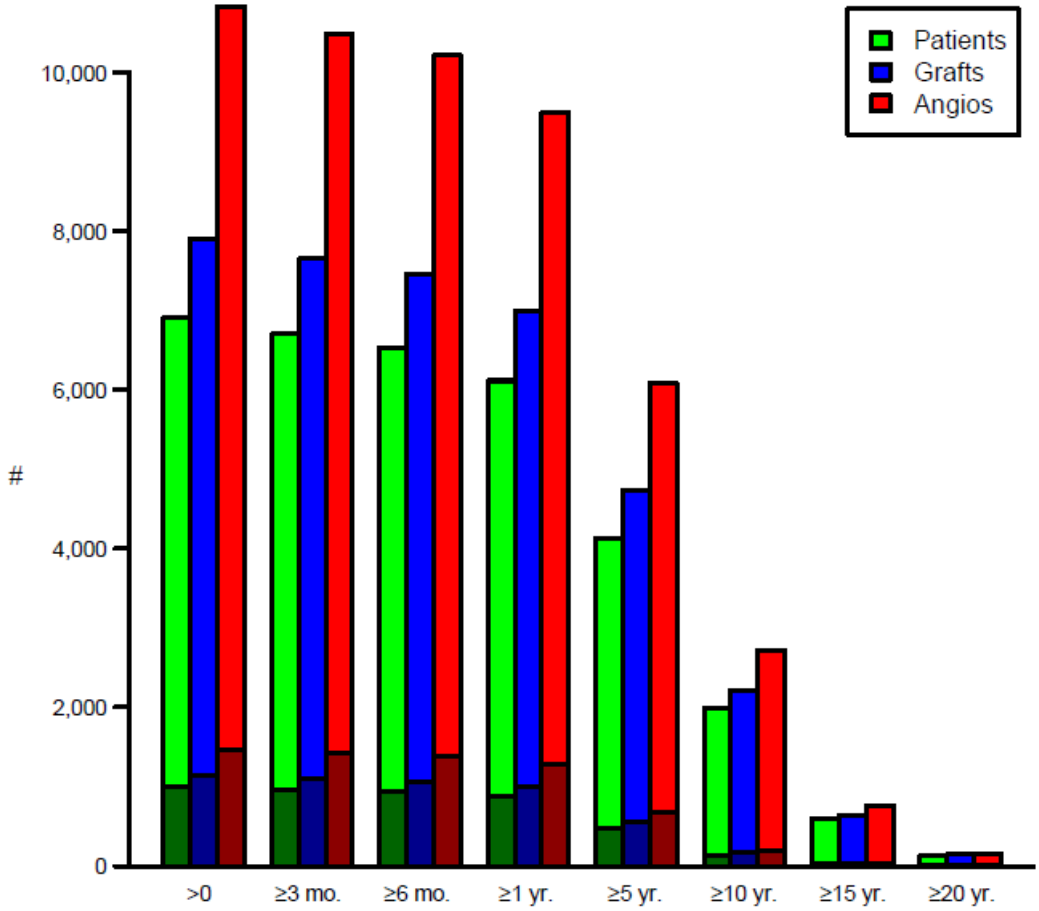
Online Figure 1. Number of internal thoracic artery (ITA) and saphenous vein (SV) bypass grafts studied by angiography each year after coronary artery bypass grafting (CABG). Note logarithmic vertical axis.

***C*,** SV grafts stratified by presence of diabetes or no diabetes.



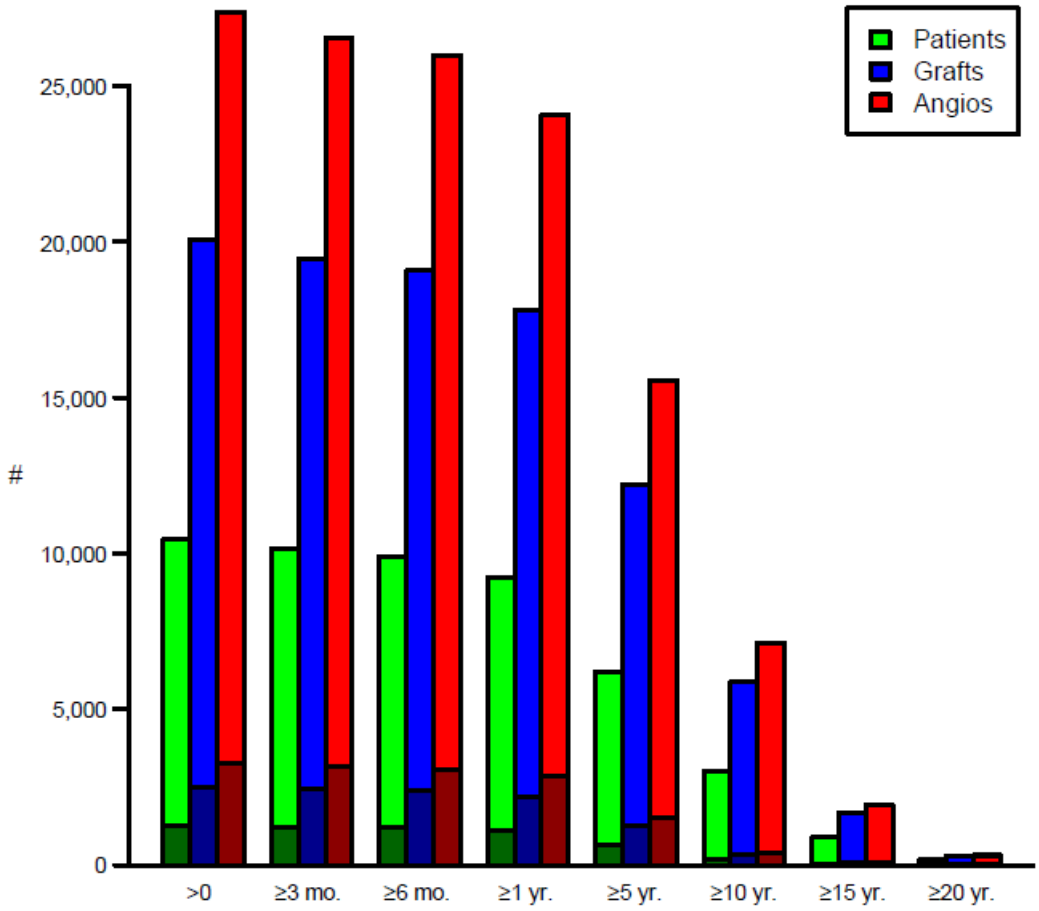
Online Figure 2. Number of patients and bypass grafts studied and postoperative angiograms available at and beyond each time point. Darker shaded portions represent diabetic patients. Key: *Angios,* angiograms.

A, Overall.



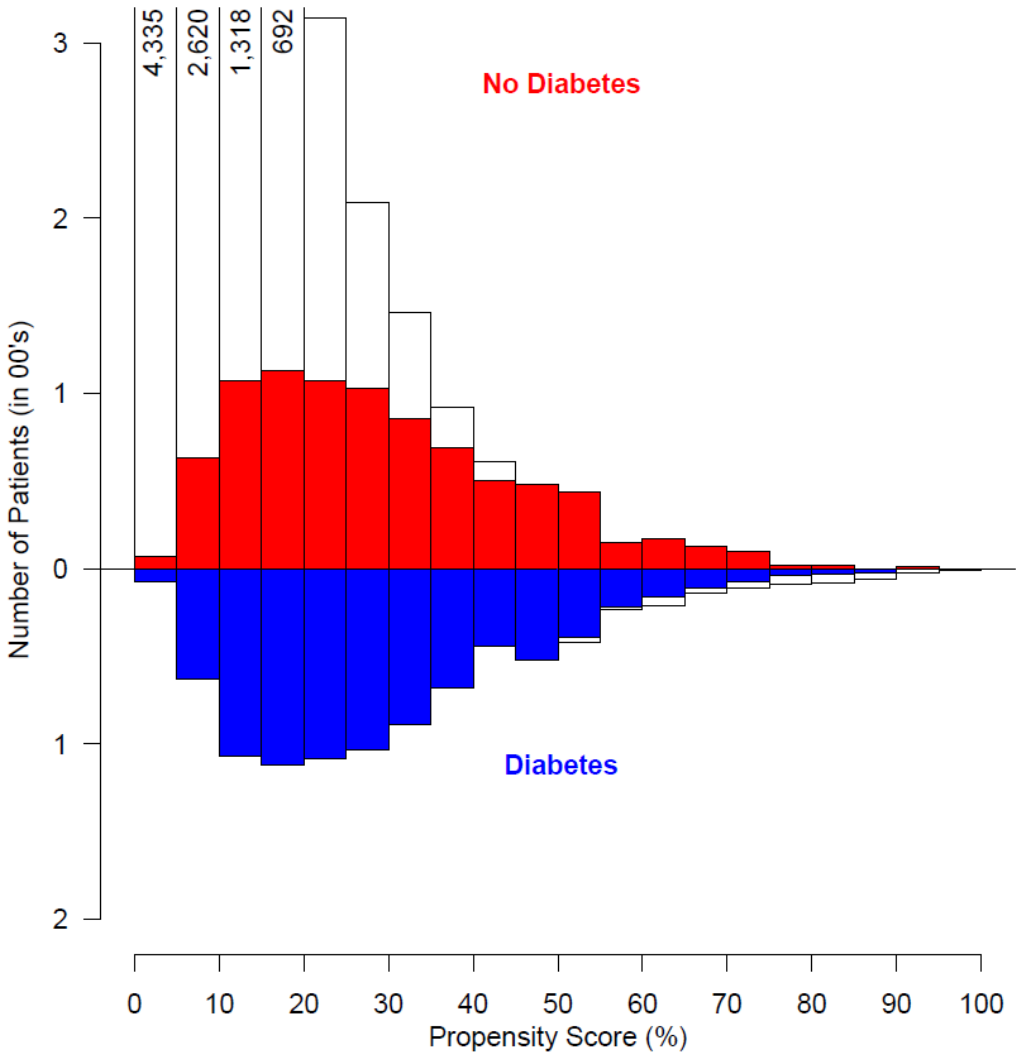
Online Figure 2. Number of patients and bypass grafts studied and postoperative angiograms available at and beyond each time point. Darker shaded portions represent diabetic patients. Key: *Angios,* angiograms.

B, Internal thoracic artery grafts.



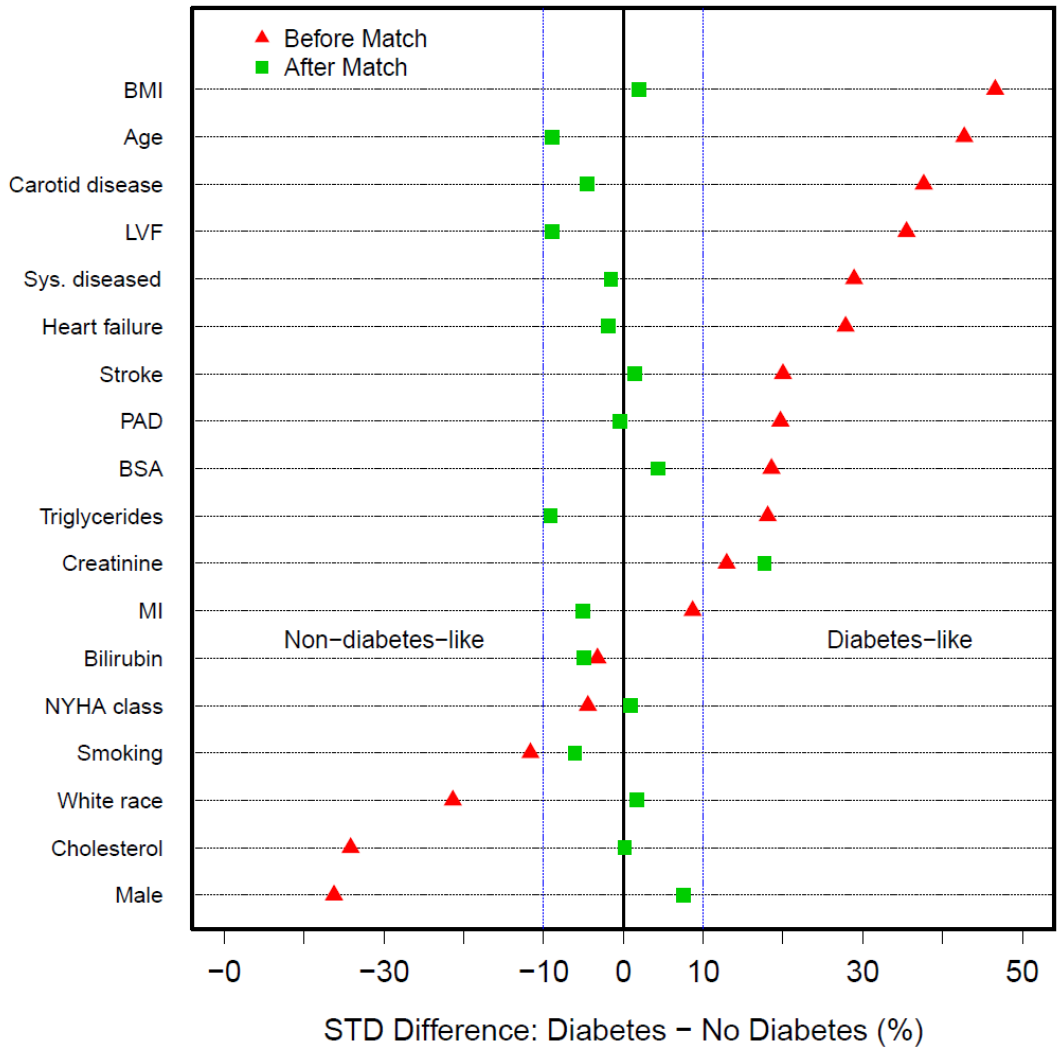
Online Figure 2. Number of patients and bypass grafts studied and postoperative angiograms available at and beyond each time point. Darker shaded portions represent diabetic patients. Key: *Angios,* angiograms.

C, Saphenous vein grafts.



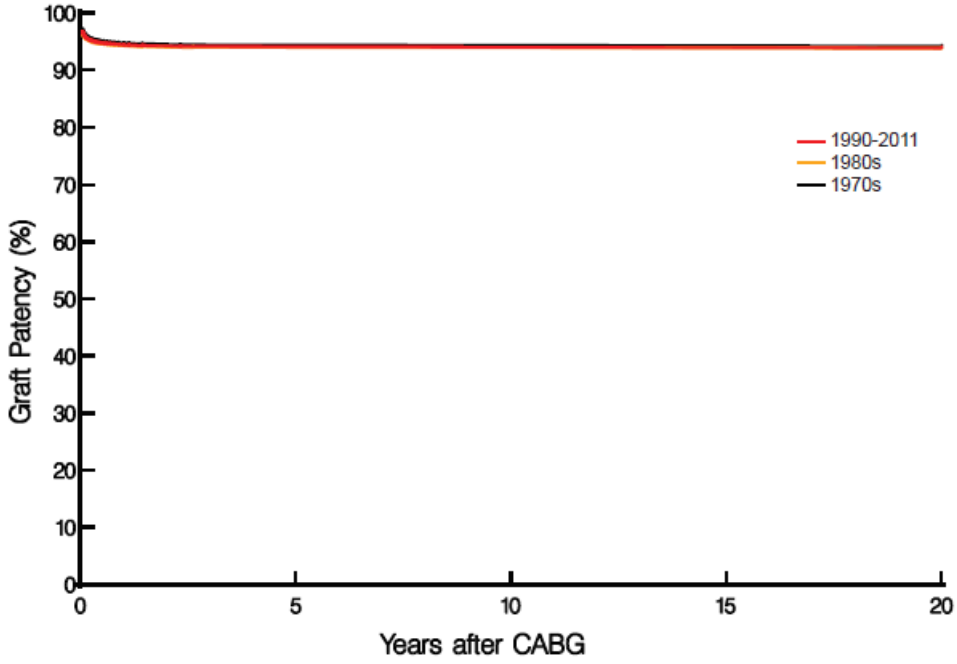
Online Figure 3. Quality of propensity matching of patients with and without diabetes.

A, Mirrored histogram of distribution of propensity scores between groups. Shaded areas represent matched patients.



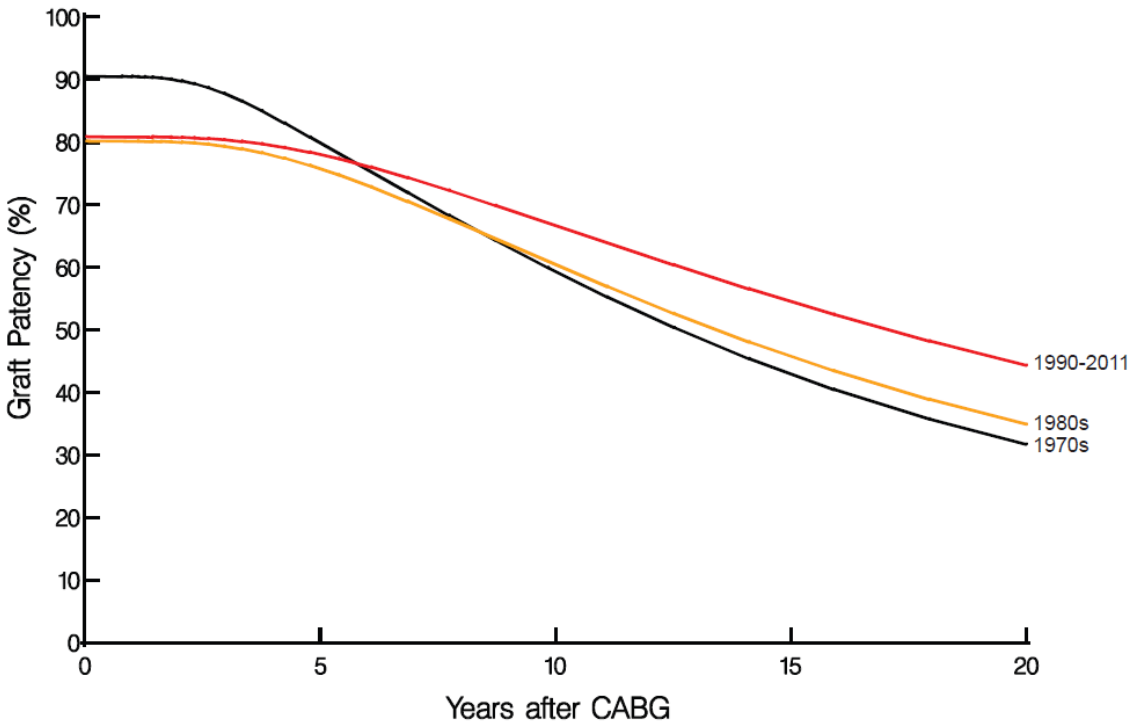
Online Figure 3. Quality of propensity matching of patients with and without diabetes.

B, Covariate balance plot before and after propensity-score matching on selected covariables. Key: *BMI*, body mass index *LVF*, left ventricular function, *Sys.,* systems; *PAD*, peripheral arterial disease; *BSA*, body surface area; *MI*, myocardial infarction; *NYHA*, New York Heart Association; *STD,* standardized.



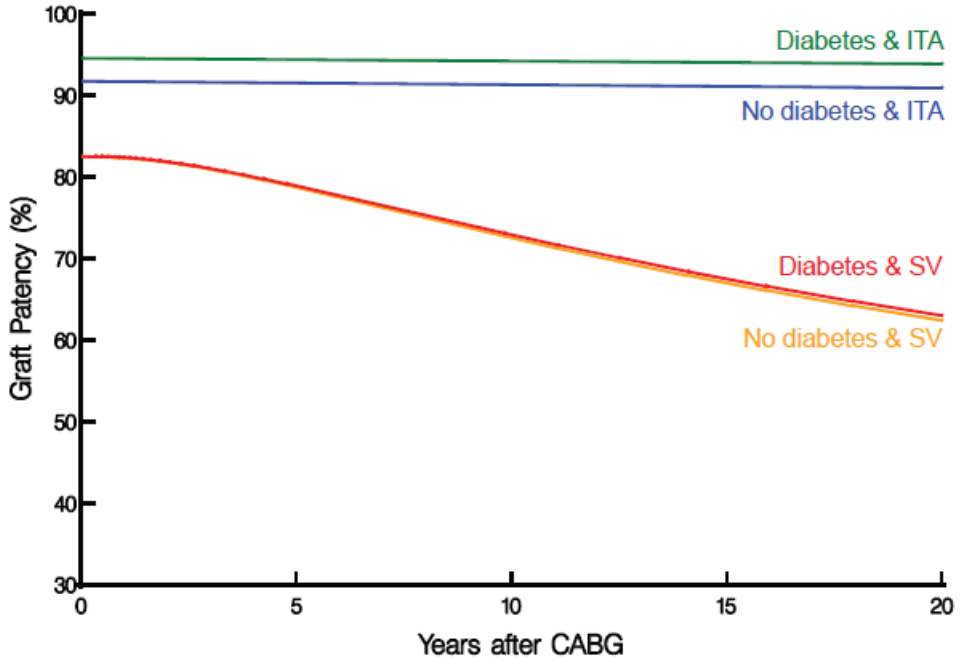
Online Figure 4. Temporal pattern of patency by decade of surgery.

***A*,** Internal thoracic artery grafts (all estimates overlap).



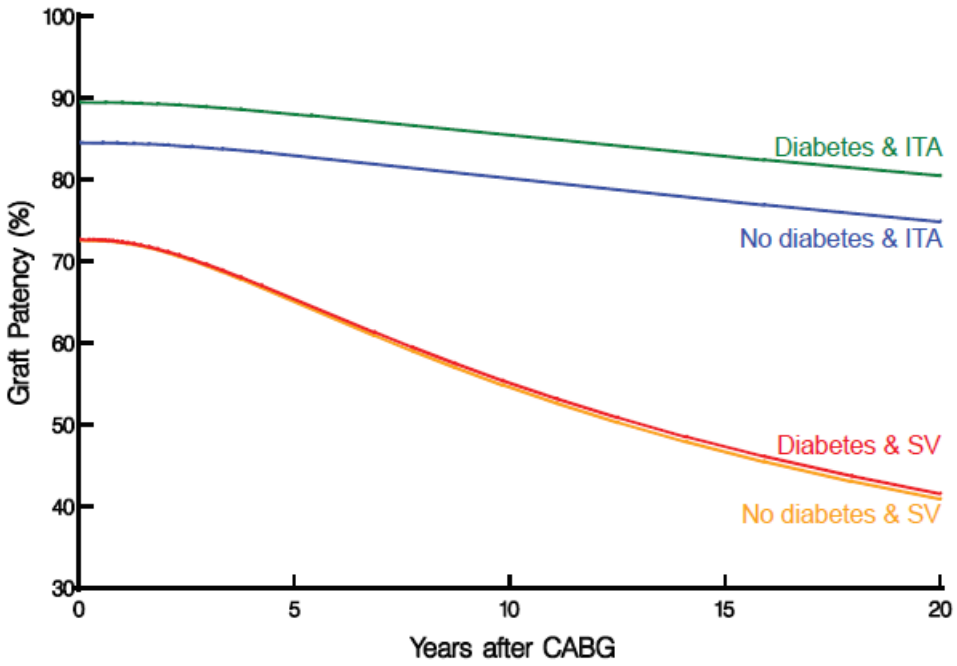
Online Figure 4. Temporal pattern of patency by decade of surgery.

***B*,** Saphenous vein grafts.



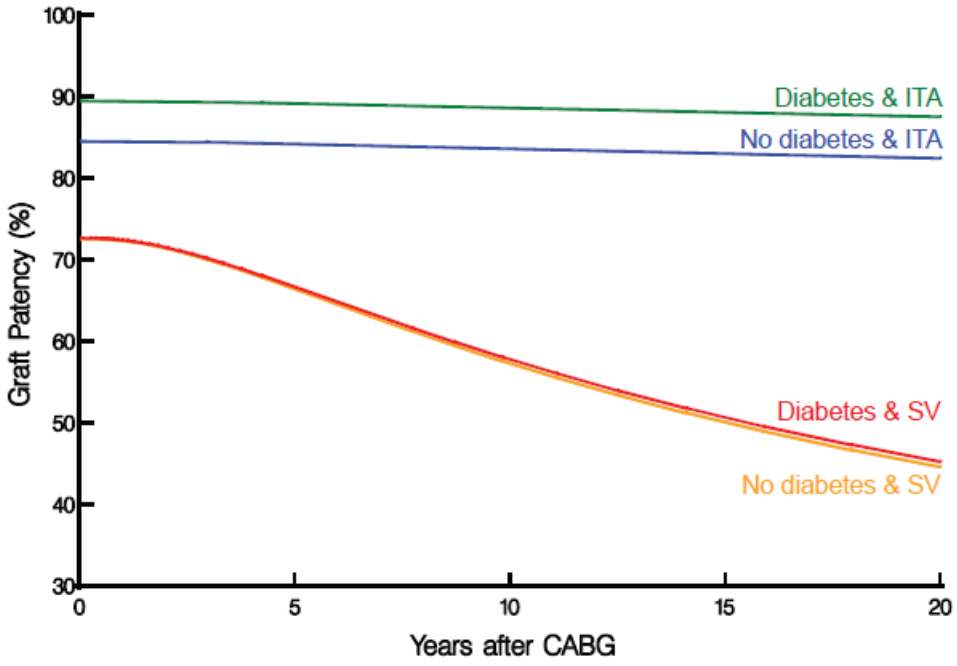
Online Figure 5. Nomograms of multivariable equation found in Table E5 depicting temporal pattern of risk-adjusted patency of internal thoracic artery (ITA) and saphenous vein (SV) grafts in diabetic and non-diabetic patients. Solid lines are parametric estimates of prevalence based on average of patient-specific profiles.

A, Grafts to left anterior descending (LAD) coronary artery. Except for the variables depicted in the figure, all other variables are fixed as follows: male, New York Heart Association functional class I, graft to LAD, propensity of having diabetes=.5, proximal stenosis=50%, triglycerides=175 mg/dL.



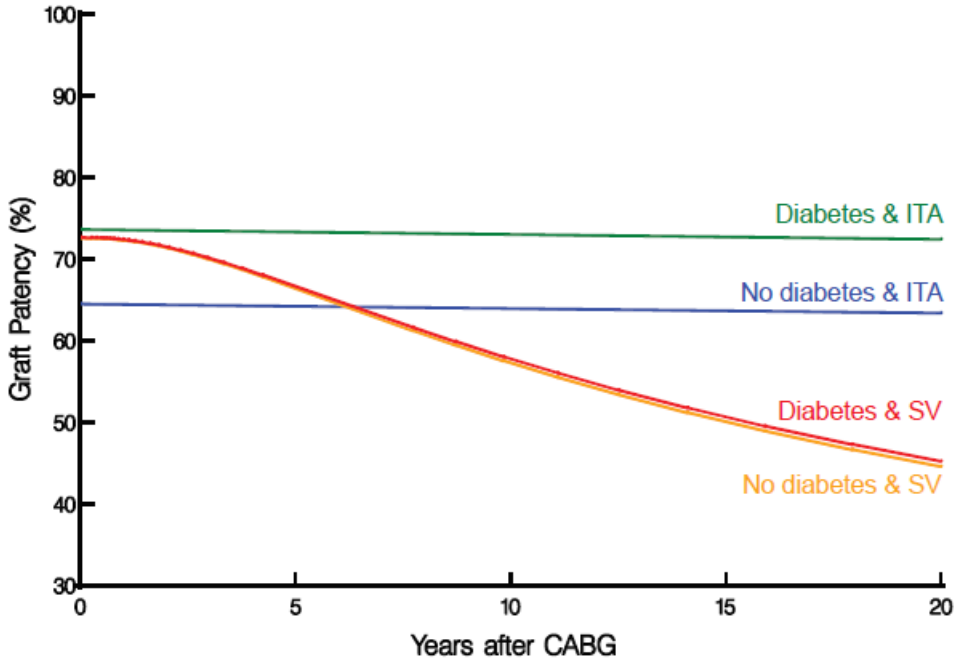
Online Figure 5. Nomograms of multivariable equation found in Table E5 depicting temporal pattern of risk-adjusted patency of internal thoracic artery (ITA) and saphenous vein (SV) grafts in diabetic and non-diabetic patients. Solid lines are parametric estimates of prevalence based on average of patient-specific profiles.

B, Grafts to circumflex coronary artery. Except for the variables depicted in the figure, all other variables are fixed as follows: male, New York Heart Association functional class I, graft to left circumflex coronary artery, propensity of having diabetes=.5, proximal stenosis=50%, triglycerides=175 mg/dL.



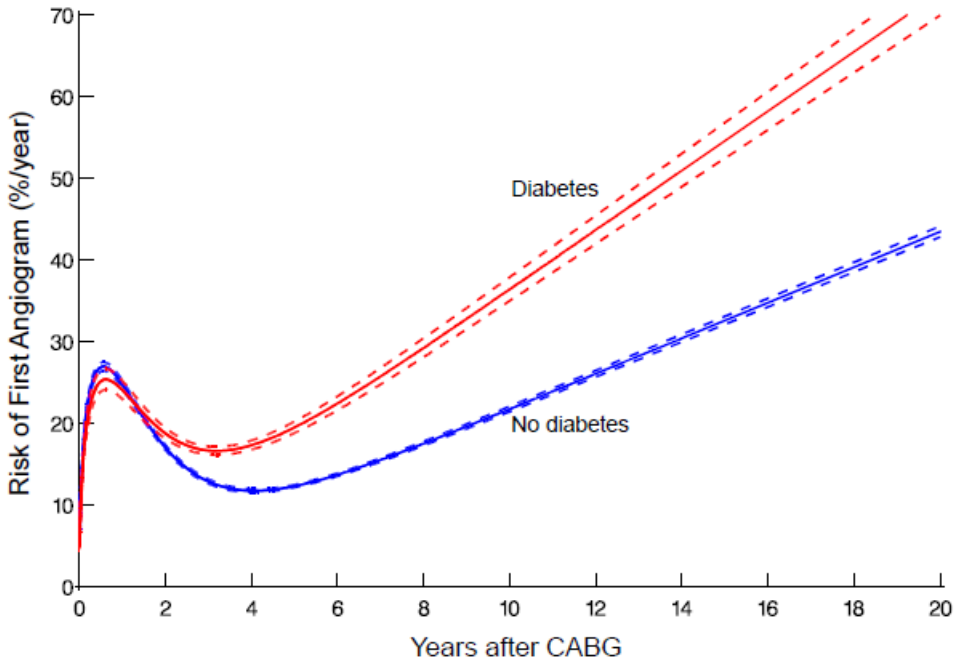
Online Figure 5. Nomograms of multivariable equation found in Table E5 depicting temporal pattern of risk-adjusted patency of internal thoracic artery (ITA) and saphenous vein (SV) grafts in diabetic and non-diabetic patients. Solid lines are parametric estimates of prevalence based on average of patient-specific profiles.

C, Grafts to diagonal coronary artery. Except for the variables depicted in the figure, all other variables are fixed as follows: male, New York Heart Association functional class I, graft to diagonal, propensity of having diabetes=.5, proximal stenosis=50%, triglycerides=175 mg/dL.



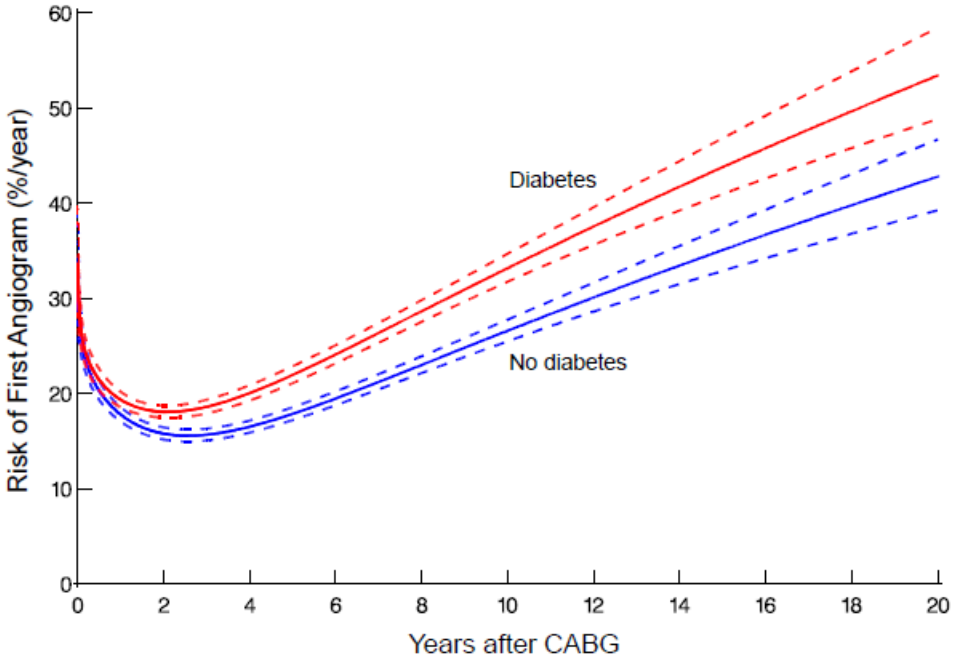
Online Figure 5. Nomograms of multivariable equation found in Table E5 depicting temporal pattern of risk-adjusted patency of internal thoracic artery (ITA) and saphenous vein (SV) grafts in diabetic and non-diabetic patients. Solid lines are parametric estimates of prevalence based on average of patient-specific profiles.

D, Grafts to right coronary artery. Except for the variables depicted in the figure, all other variables are fixed as follows: male, New York Heart Association class I, graft to right coronary artery, propensity of having diabetes=.5, proximal stenosis=50%, triglycerides=175 mg/dL.



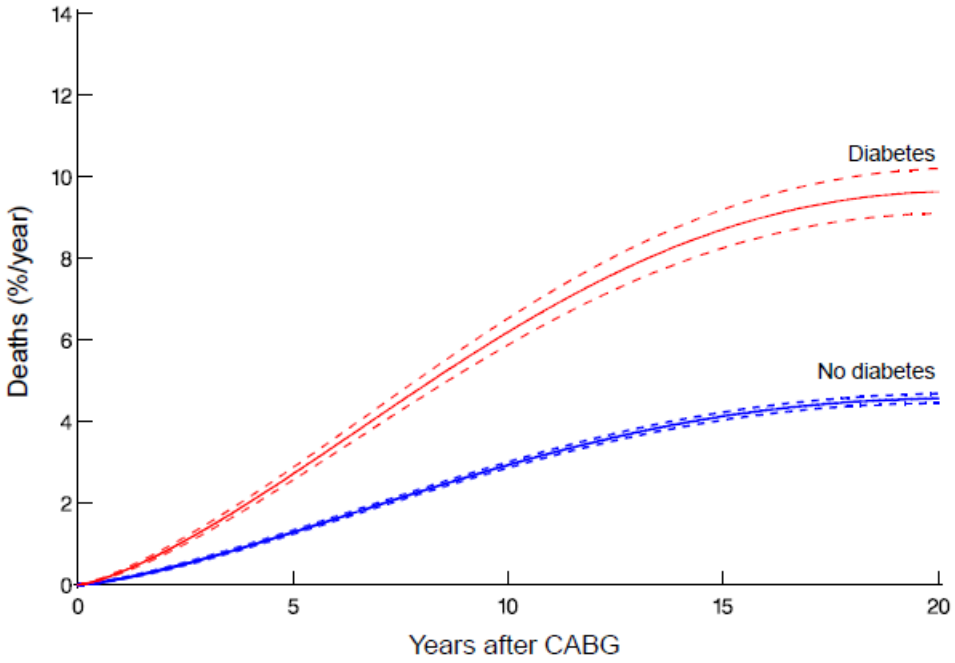
Online Figure 6. Instantaneous risk of first coronary angiography after coronary artery bypass grafting (CABG) in diabetic and non-diabetic groups. Solid lines represent parametric estimates enclosed within a 68% confidence interval, equivalent to ±1 standard error.

A, Overall.



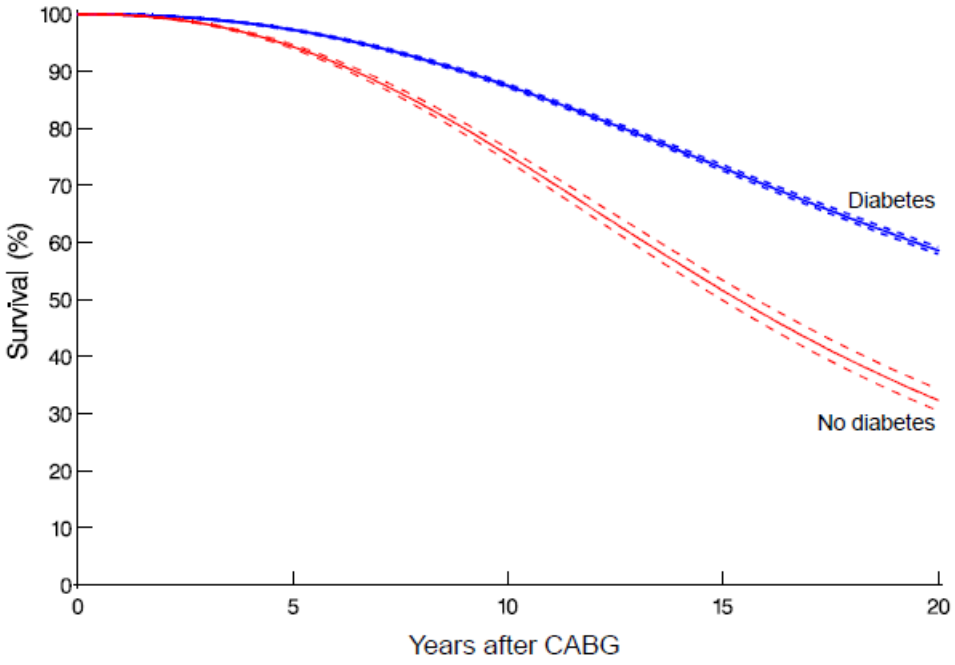
Online Figure 6. Instantaneous risk of first coronary angiography after coronary artery bypass grafting (CABG) in diabetic and non-diabetic groups. Solid lines represent parametric estimates enclosed with a 68% confidence interval, equivalent to ±1 standard error.

B, Matched cohort.



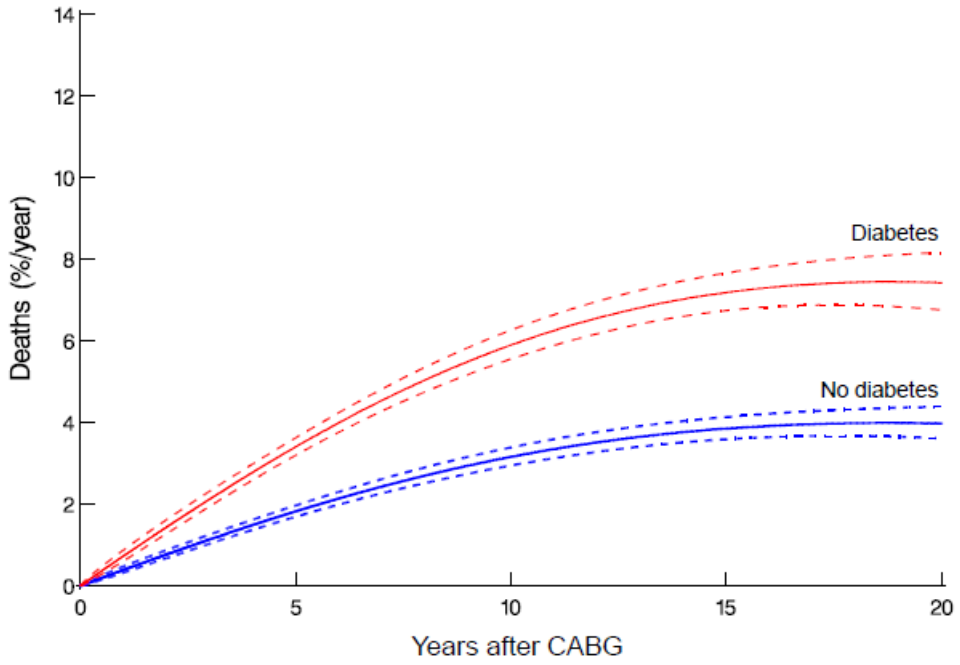
Online Figure 7. Time-related death after primary isolated coronary artery bypass grafting in diabetic and non-diabetic patients. Solid lines are parametric estimates enclosed within a dashed 68% confidence interval equivalent to ±1 standard error. Each symbol represents a death; vertical bars are confidence limits equivalent to ±1 standard error.

A, Instantaneous risk of death (overall).



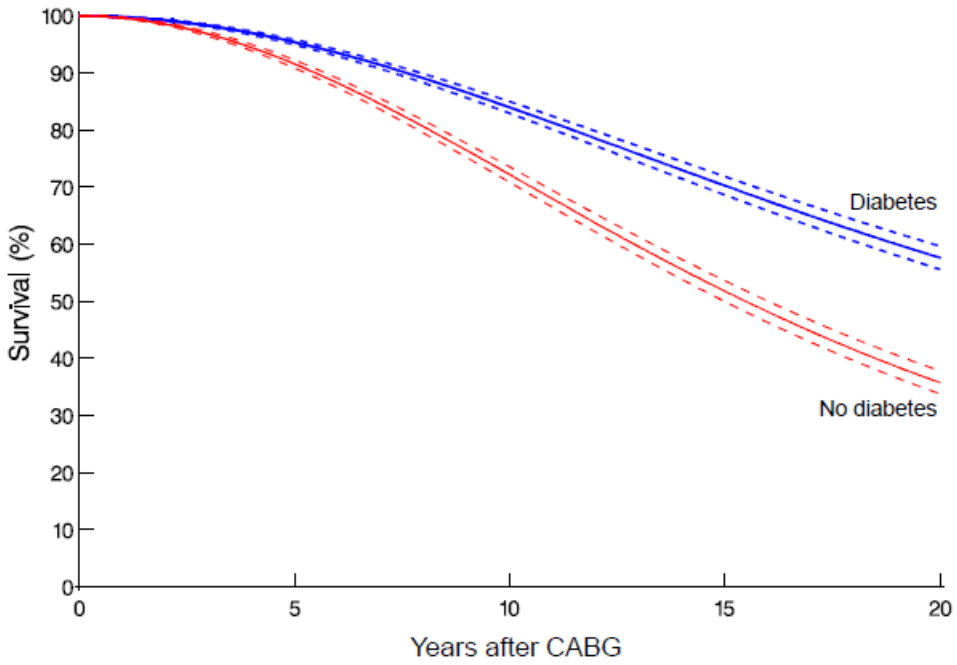
Online Figure 7. Time-related death after primary isolated coronary artery bypass grafting in diabetic and non-diabetic patients. Solid lines are parametric estimates enclosed within a dashed 68% confidence interval equivalent to ±1 standard error. Each symbol represents a death; vertical bars are confidence limits equivalent to ±1 standard error.

B, Survival (overall).



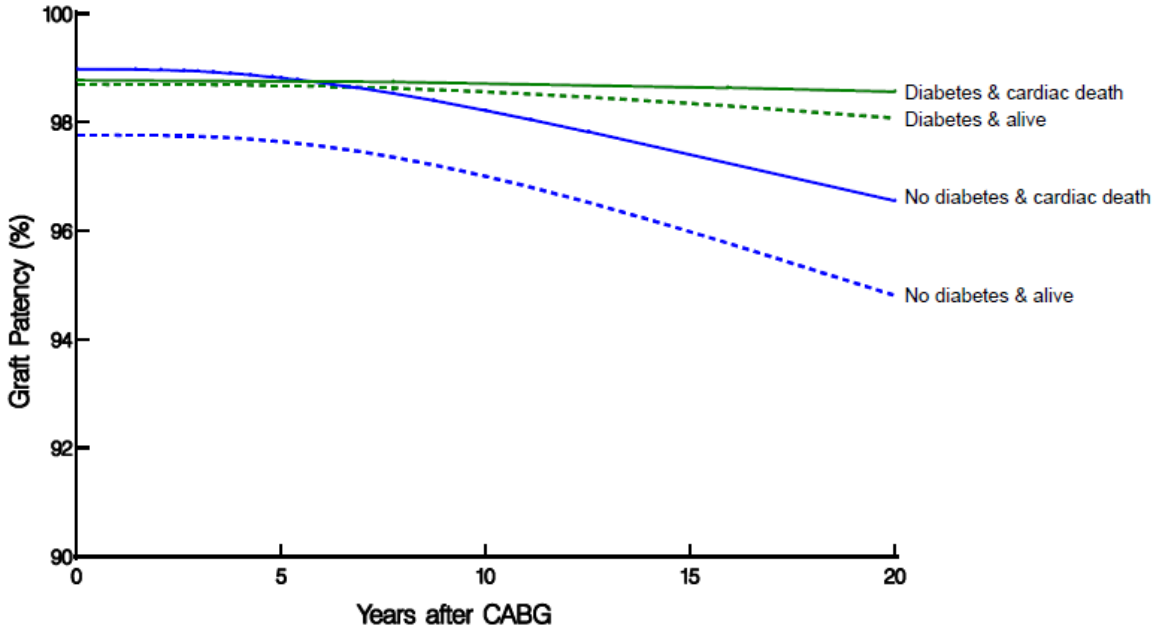
Online Figure 7. Time-related death after primary isolated coronary artery bypass grafting in diabetic and non-diabetic patients. Solid lines are parametric estimates enclosed within a dashed 68% confidence interval equivalent to ±1 standard error. Each symbol represents a death; vertical bars are confidence limits equivalent to ±1 standard error.

C, Instantaneous risk of death (propensity-matched cohort).



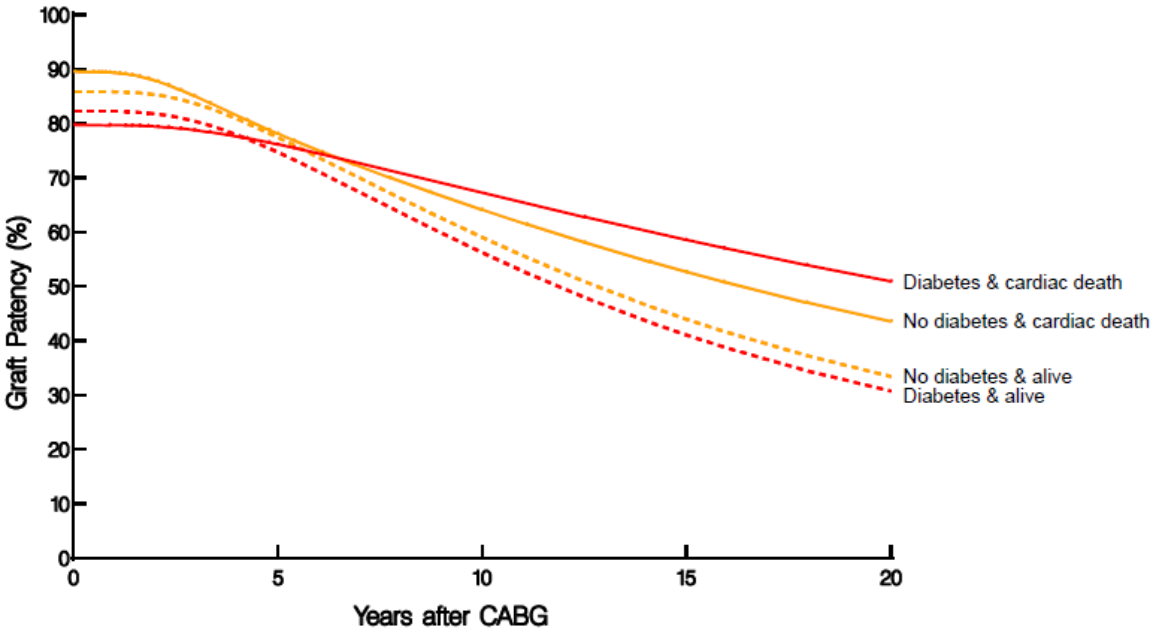
Online Figure 7. Time-related death after primary isolated coronary artery bypass grafting in diabetic and non-diabetic patients. Solid lines are parametric estimates enclosed within a dashed 68% confidence interval equivalent to ±1 standard error. Each symbol represents a death; vertical bars are confidence limits equivalent to ±1 standard error.

D, Survival (propensity-matched cohort).



Online Figure 8. Patterns of temporal trend of patency stratified by alive versus death due to cardiac causes. Key: *CABG,* coronary artery bypass grafting.

***A*,** Internal thoracic artery grafts in diabetic and non-diabetic patients.



Online Figure 8. Patterns of temporal trend of patency stratified by alive versus death due to cardiac causes. Key: *CABG,* coronary artery bypass grafting.

***B*,** Saphenous vein grafts in diabetic and non-diabetic patients.

Chapter 5

Research Question 4—Which Surgical Techniques Improve Outcomes of CABG in Diabetic Patients?

Based on Publication: Raza S, Sabik JF 3rd, Masabni K, Ainkaran P, Lytle BW, Blackstone EH. **Surgical Revascularization Techniques that Minimize Surgical Risk and Maximize Late Survival After Coronary Artery Bypass Grafting in Patients with Diabetes Mellitus.** J Thorac Cardiovasc Surg. 2014;148(4):1257-1264.

5.1 Rationale

The FREEDOM trial (Future Revascularization Evaluation in patients with Diabetes mellitus: Optimal Management of multivessel disease) showed that coronary artery bypass grafting (CABG) should be the preferred revascularization strategy for diabetics with multivessel coronary artery disease (CAD) [1]. This made it imperative to identify surgical techniques that optimize the outcomes of CABG in these patients. Our previous study (presented in Chapter 3) showed that diabetics make up nearly 40% of all patients undergoing surgical revascularization and represent an important & growing population of patients undergoing CABG today [2]. Therefore, the fourth research question that we sought to answer was: Which surgical techniques improve the outcomes of CABG in diabetic patients? In this regard, we evaluated the comparative effectiveness of (i) single internal thoracic artery (SITA) vs. bilateral internal

thoracic artery (BITA) grafting, (ii) complete vs. incomplete revascularization, and (iii) off-pump vs. on-pump CABG in diabetic patients undergoing CABG.

5.2 Summary of Study Design & Method

The study was based on 11,922 diabetic patients who underwent primary isolated CABG from January 1972 to January 2011, at the Cleveland Clinic. The type of diabetes management was known for 8,196 patients—2,743 insulin-treated diabetics, 3,766 non–insulin-treated diabetics, and 1,687 diet-controlled diabetics. The surgical revascularization techniques investigated included (i) SITA (n=8,466; 71%) and BITA (n=938; 7.9%) grafting with or without other grafts vs. saphenous vein grafting (SVG) alone (n=2,491; 21%), (ii) incomplete (n=2,109; 18%) vs. complete revascularization, and (iii) off- (n=602; 5.0%) vs. on-pump CABG. The end-points studied included hospital outcomes and long-term mortality. Multivariable analyses were performed to assess the effects of surgical techniques on outcomes. To identify the patients deriving the greatest survival benefit from an optimal surgical technique, the multivariable hazard model was solved for each patient in the study to produce 10-year predicted survival based on 12 possible surgical combinations (derived from 0 ITA, 1 ITA, 2 ITAs, incomplete revascularization, complete revascularization, off-pump CABG, and on-pump CABG).

5.3 Summary of Results

We found that BITA grafting was associated with 21% (68% CL, 16%-26%) and 33% (68% CL, 28%- 37%) lower long-term mortality compared to SITA grafting and saphenous vein grafting, respectively. However, BITA grafting was also associated with higher risk of deep sternal wound infections (DSWI) when compared to SITA grafting. We identified obese diabetic females with diffuse atherosclerotic burden as the patient population that is at the highest risk of developing sternal wound infections (see Figure 2 of manuscript). Complete vs. incomplete revascularization had similar hospital outcomes but incomplete revascularization was associated with 10% (68% CL, 6%-13%) higher long-term mortality. Off-pump vs. on-pump surgery had similar hospital outcomes and long-term mortality. We also found that the combination of BITA grafting with complete revascularization using off-pump technique was associated with the best long-term survival (see Figure 4 of manuscript). This survival benefit was mainly driven by BITA grafting followed by complete revascularization.

5.4 Findings Compared to Other Studies

Other studies support our findings of BITA vs. SITA comparison in diabetic patients. Studies by Lytle et al [3], Dorman et al [4], and Steven et al [5] showed that BITA grafting improves long-term survival in diabetic patients undergoing CABG. The study by Endo et al [6] showed that BIMA grafts are beneficial in coronary revascularization for diabetic patients with preserved ejection fraction,

but have limited survival benefit for those with reduced ejection fraction attributable to high cardiac mortality.

Despite evidence showing the association of BITA with better long-term survival, BITA grafting was performed in only 4.4% of CABG cases in the STS national database in 2011 [7,8]. This may be due to the fear of increased risk of DWSI [8,9], a trade-off with the long-term survival benefit. This increased risk is of particular concern in diabetics, because they are already at higher risk than non-diabetics of developing surgical site infections. Our data confirms this finding. However, we found that DSWI after BITA or SITA grafting minimally affected survival because of its rare occurrence. We identified women with large BMI, PAD, prior MI, and pharmacologically treated diabetes as patient characteristics associated with the highest risk of developing DSWI. In addition, we found that some of the risk factors associated with the greatest risk of developing DSWI after BITA grafting are also associated with deriving the greatest survival benefit from it. Thus, avoiding BITA grafting in patients at high risk for developing DSWI could lead to a decrease in the overall occurrence of DSWI at the expense of losing the long-term survival benefit gained from BITA grafting.

Recently, the results of the Arterial Revascularization Trial (ART) [10] were published in the New England Journal of Medicine (NEJM), and they showed no survival benefit of BITA grafts over SITA grafts at 10 years after surgery. I believe this trial failed to show the survival benefit of BITA grafts because of the following reasons. First, patients deriving the maximum survival

benefit from BITA grafting are sicker whereas ART-trial patients were relatively healthier. Second, the trial's statistical power to detect a 5% difference in 10-year survival between BITA vs. SITA patients had already been lowered by 45% because 16% of patients in BITA group didn't actually receive BITA grafts (with power lowered further by 5% lost to follow-up at 5 years), so it was expected that the trial might not be able to detect a difference in survival at 10 years, assuming one exists. Third, the observational data shows that the incremental survival benefit of BITA grafting over SITA grafting becomes evident in the second decade after surgery. The ART trial only followed patients up until 10 years after surgery. I wrote a letter-to-the-editor on the paper that presented five-year results of ART trial. The letter highlighted the important points mentioned here and was published by NEJM [11].

Early studies of CABG highlighted the survival advantage of complete over incomplete revascularization [12-14]. Since then, a number of studies have evaluated this effect, but literature specifically focusing on diabetics is sparse. Also, the definition of complete and incomplete revascularization has remained controversial, with different studies reporting different definitions [15]. We found that incomplete revascularization was associated with a higher risk of late death, highlighting the importance of completeness of revascularization for long-term survival benefit. Post-hoc analysis from the BARI 2D trial (Bypass Angioplasty Revascularization Investigation) also showed that less complete revascularization was associated with a higher risk of long-term cardiovascular events in diabetics [16].

Although a number of studies have compared the outcomes of off- vs. on-pump CABG [17-24], few have done so in diabetics [25-28]. Available studies show that in diabetic patients, off-pump CABG results in lower in-hospital morbidity and mortality and higher 1-year survival [25-27]. We found a small late survival benefit of off-pump CABG, similar in magnitude to complete vs. incomplete revascularization; however, the benefit could be due to chance, perhaps because of relatively small numbers. Both on- and off-pump strategies represent 2 skill sets which surgeons can use selectively. This is particularly relevant for patients at higher risk of developing complications from cardiopulmonary bypass or aortic manipulation, because they benefit the most from off-pump surgery.

5.5 Addition to Literature in Light of Systematic Review

A systematic literature search was done to identify studies that already existed on this topic at the time of paper preparation/publication so that the addition to the literature that the study made could be effectively evaluated in the light of existing knowledge on the subject. Details of this systematic review are given in the Appendix (see section 10.4). Briefly, we searched the literature for studies reporting the comparative effectiveness of (1) SITA versus BITA grafting, (2) complete versus incomplete revascularization, and (3) off-pump versus on-pump CABG in terms of long-term survival in diabetic patients undergoing CABG. Studies reporting the long-term survival (at least 10 years) with or without early outcomes of studied surgical techniques specifically in diabetic patients were

included. Studies reporting less than 10-year long-term survival were excluded. Four studies reporting the outcomes of BITA vs. SITA in diabetic patients [3-6] were found that met the specified inclusion criteria. One study reporting the outcomes of off-pump vs. on-pump surgery was found that met the inclusion criteria [29]. Regarding complete vs. incomplete revascularization in diabetic patients undergoing CABG, the search didn't yield any studies meeting the specified criteria.

Of the 4 studies reporting outcomes of BITA vs. SITA in diabetic patients, three [3-5] showed that BITA grafting improves long-term survival in diabetic patients undergoing CABG, similar to the results of our study. The study by Endo et al [6] showed that BIMA grafts are beneficial in coronary revascularization for diabetic patients with preserved ejection fraction but have limited survival benefit for those with reduced ejection fraction attributable to high cardiac mortality. In these 4 studies the number of patients receiving BITA grafts ranged from 190 to 461, and the number of patients receiving SITA graft ranged from 277 to 646, whereas we studied the outcomes of 938 patients receiving BITA grafts and 8466 patients receiving SITA grafts.

One study reporting the outcomes of off-pump vs. on-pump surgery by Hemo et al [29] showed that off-pump CABG was associated with better long-term survival than on-pump CABG in diabetic patients. However, this study only included patients receiving BITA grafts so the results are not generalizable to the vast majority of diabetic patients undergoing CABG who receive single ITA

grafts only. Moreover, this study included only 232 off-pump cases whereas we studied the outcomes of 602 off-pump CABG cases.

Though there were some studies available comparing long-term survival after CABG with BITA vs. SITA in diabetic patients, there was a dearth of studies comparing long-term outcomes of off-pump vs. on-pump surgery and complete vs. incomplete revascularization in diabetic patients undergoing CABG. Our study, therefore, added valuable evidence in these areas.

5.6 Critical Commentary

Help was taken from Critical Appraisal Skills Program (CASP) checklist for Cohort Studies for critical commentary on this manuscript. Available at: http://www.casp-uk.net/casp-tools-checklists.

5.6.1 Rationale

This study addresses a clearly focused issue of identifying surgical techniques that minimize the surgical risk and maximize the long-term survival after CABG in diabetic patients. Our previous study showed that the proportion of patients undergoing CABG who have diabetes increased from 7% in 1970s to about 40% in 2010 [2]. In 2012, the results of the landmark FREEDOM trial established CABG as the revascularization strategy of choice for diabetic patients with multivessel CAD [1]. These made it imperative to identify the techniques that improve the outcomes of CABG in diabetic patients.

5.6.2 Study Design

This was a retrospective cohort study. RCTs comparing the long-term outcomes of patients undergoing CABG with different surgical techniques like BITA vs. SITA grafting, and off- vs. on-pump CABG would have been ideal. However, demonstrating the survival benefit of surgical techniques like BITA grafting needs long-term follow-up (ideally greater than 10 years). This is because the observational data show that the survival benefit of the BITA grafting becomes evident in the second decade after CABG. Conducting an RCT with a follow-up of more than 10 years is challenging. Therefore, studying this research question in a retrospective fashion is reasonable, as an RCT with 15-20 years of follow-up would be expensive and challenging.

5.6.3 Participant Selection

The cohort was recruited in an acceptable way. Cleveland Clinic's Cardiovascular Information Registry (CVIR) was used to identify all diabetic patients who underwent primary isolated CABG at the Cleveland Clinic from 1972 through 2011. Of the 11,922 diabetic patients identified, diabetes management status was known for 8196 patients—2743 insulin-treated, 3766 non–insulin-treated, and 1687 diet-controlled. However, we were unable to discriminate between type I and type II diabetes. This maybe important as the long-term survival after CABG in type 1 diabetic patients is worse than the survival in type II diabetic patients. However, this was not mentioned in the imitations section of the paper.

The three main comparisons of interest in our study included (i) BITA vs. SITA grafting, (ii) complete vs. incomplete revascularization, and (iii) off- vs. on-pump CABG. Patients were reliably classified into respective groups as these details are clearly mentioned in operative reports.

It was not mentioned in the paper whether this study required any additional data-collection, apart from the data retrieved from CVIR. No additional data was collected for this study.

5.6.4 Sample Size

Our study showed that the 20-year survival after CABG in diabetic patients was 21% with SITA grafting and 37% with BITA grafting. To detect this difference, our study was 100% powered, at a significance level of 5%. The 20-year survival after CABG in diabetic patients was 18% with incomplete revascularization and 21% with complete revascularization. To detect this difference, our study was 88% powered, at a significance level of 5%. The 10-year survival after CABG in diabetic patients was 56% with off-pump surgery and 56% with on-pump surgery (a 20-year estimate was not available for this comparison). To detect a difference of 5% in survival between off-pump vs. on-pump CABG, assuming one existed, our study was only 68% powered, at a significance level of 5%. However, to detect a difference of 10%, assuming one existed, our study was >99% powered. Please note that some criticize the idea of retrospective power calculation. However, it was done to provide an approximate idea regarding statistical power of the study.

BITA grafting, incomplete revascularization, and off-pump CABG all represented small subsets of our study, which might have limited our ability to identify small incremental benefits within the 12 combinations of surgical strategies analyzed.

5.6.5 End-points

The end-points of the study included hospital outcomes and long-term mortality. Please see 3.6.5 for in-depth critical commentary on our long-term mortality follow-up.

5.6.6 Data Analysis

We used multivariate analyses for risk adjustment. A number of variables (detailed in the appendix of the paper) were considered in this analysis ranging from demographic variables, to cardiac and non-cardiac comorbidities, and date of operation. However, any patient factors not included in the propensity model that importantly affect outcomes may have biased our findings.

Alternatively, propensity matching could have been used for risk-adjustment. However, this would have required several separate propensity analyses to compare saphenous vein grafting vs. SITA grafting vs. BITA grafting, complete vs. incomplete revascularization, and off- vs. on-pump CABG. We used multivariable risk-adjustment because it is not realistic to see these surgical techniques in isolation of each other, as any single CABG procedure is actually a combination of these techniques. Moreover, of the 12 possible

realistic combinations of these 7 surgical techniques, multivariable analysis allowed us to identify the combination with best long-term survival.

Survival was assessed nonparametrically using the Kaplan-Meier method, and parametrically using a multiphase hazard model. Please see section 2.6.6 above for details regarding this model, and also for explanation regarding the use of 68% confidence interval in the paper.

5.6.7 Results & Discussion

The study showed that BITA versus SITA grafting was associated with 21% (68% CL, 16%-26%) lower late mortality in patients with multivessel disease. Incomplete revascularization was associated with 10% higher (68% CL, 6%-13%) late mortality. Off- pump CABG was associated with 10% lower late mortality than on-pump CABG, but the difference was not statistically significant.

Survival was reported for up to 20 years. The results look precise given the range of the confidence intervals provided in the results and figures of the manuscript. The results are believable because the study compared outcomes in a large number of patients using data from a well-regarded registry and took appropriate measures to control for confounding.

The discussion section clearly mentioned the principal findings of the study, and in the section of “findings in context”, we discussed the existing knowledge on the topic and compared our findings with the results of other studies.

The discussion section also mentioned the limitations of the paper, which included that fact that this was a single center study and findings may not be generalizable. Nevertheless, with the increasing proportion of patients with diabetes undergoing CABG, and the widespread experience with the use of ITA grafting and off-pump surgery, our experience should be repeatable in other centers that see diabetic patients in need of CABG.

The conclusions of the paper were supported by the data presented and mentioned the clinical implications of the study instead of just summarizing the results again.

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5.8 Full-text of the Paper

Surgical revascularization techniques that minimize surgical risk and maximize late survival after coronary artery bypass grafting in patients with diabetes mellitus

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Objective: To identify surgical revascularization techniques that minimize surgical risk and maximize late survival in patients with diabetes undergoing coronary artery bypass grafting (CABG).

Methods: From January 1972 to January 2011, 11,922 patients with diabetes underwent primary isolated CABG. The revascularization techniques investigated included bilateral internal thoracic artery (BITA) grafting (n = 938; 7.9%) versus single ITA (SITA) grafting, off-pump (n = 602; 5.0%) versus on-pump CABG, and incomplete (n = 2109; 18%) versus complete revascularization. The median follow-up was 7.8 years and total follow-up, 104,516 patient-years. Multivariable analyses were performed to assess the effects of surgical techniques on hospital outcomes and long-term mortality.

Results: After adjusting for patient characteristics, BITA versus SITA grafting was associated with a 21% lower late mortality (68% confidence limits, 16%-26%). However, BITA grafting was also associated with more deep sternal wound infections (DSWIs), but the considerable mortality from DSWI minimally affected overall survival because of its rare occurrence. The risk factors for DSWI were female sex (80% increased risk), higher body mass index (7% increased risk per kg/m^2), medically treated diabetes (73% increased risk), previous myocardial infarction (58% increased risk), and peripheral arterial disease (73% increased risk). Off-pump and on-pump CABG had similar results. Complete versus incomplete revascularization had similar hospital outcomes; however, complete revascularization was associated with 10% lower late mortality (68% confidence limits, 7.0%-13%).

Conclusions: BITA grafting with complete revascularization maximizes long-term survival and is recommended for patients with diabetes undergoing CABG. BITA grafting should be used in all patients with diabetes whose risk of DSWI is low. It might be best avoided in obese diabetic women with diffuse atherosclerotic burden—those at greatest risk of developing these infections. (J Thorac Cardiovasc Surg 2014;148:1257-66)

ACD

Supplemental material is available online.

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The FREEDOM trial (Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal Management of multivessel disease) showed that coronary artery bypass grafting (CABG) should be the preferred revascularization strategy for patients with diabetes mellitus with multivessel coronary artery disease (CAD).[1] However, it did not attempt to answer the important question of which surgical revascularization techniques will optimize the outcomes of CABG in these patients. Therefore, to identify the techniques that minimize surgical risk and maximize late survival, we studied the comparative effectiveness of (1) single internal thoracic artery (SITA) versus bilateral internal thoracic artery (BITA) grafting, (2) complete versus incomplete revascularization, and (3) off-pump versus on-pump CABG for diabetic patients undergoing CABG.

METHODS

From January 1972 to January 2011, 11,922 diabetic patients underwent primary isolated CABG at Cleveland Clinic (Table E1). The type of diabetes management was known for 8196 patients—2743 insulin-treated, 3766 non–insulin-treated, and 1687 diet-controlled. The surgical revascularization techniques investigated included (1) SITA (n = 8466; 71%) and BITA (n = 938; 7.9%) grafting with or without other grafts

Abbreviations and Acronyms

BITA = bilateral internal thoracic artery
BMI = body mass index
CABG = coronary artery bypass grafting
CAD = coronary artery disease
DSWI = deep sternal wound infection
ITA = internal thoracic artery
SITA = single internal thoracic artery
STS = Society of Thoracic Surgeons
SVG = saphenous vein grafting

versus saphenous vein grafting (SVG) alone (n = 2491; 21%). SITA versus BITA grafting was investigated in patients with multivessel CAD (n = 11,322, 95% of the total study cohort), (2) incomplete (n = 2109; 18%) versus complete revascularization, and (3) off-pump (n = 602; 5.0%) versus on-pump CABG. The patients were identified and the preoperative, operative, and postoperative variables retrieved from the prospective computerized Cardiovascular Information Registry of the Heart and Vascular Institute. The institutional review board approved this database for use in research, with patient consent waived.

Variables and Definitions

A coronary artery system was considered importantly stenotic if it contained a ≥50%-diameter obstruction. Incomplete revascularization was defined as failure to graft any system containing ≥50% stenosis or both the left anterior descending and circumflex coronary artery systems for ≥50% left main trunk stenosis.

Endpoints

The endpoints of the present study were (1) in-hospital outcomes with morbidities defined as for the Society of Thoracic Surgeons (STS) national database (available at: http://www.sts.org/sites/default/files/documents/word/STSAdultCVDataSpecificationsV2_73%20with%20correction.pdf), and (2) long-term all-cause mortality. Patients' vital status after hospital discharge was obtained from the Cardiovascular Information Registry routine anniversary follow-up information supplemented with data from the Social Security Death Master File[2,3] (accessed October 29, 2011); the closing date was set 6 months earlier (April 27, 2011). The median follow-up was 7.8 years, with 104,516 patient-years of data available for analysis. Twenty-five percent of the survivors had been followed up for >13 years and 10% for >19 years.

Statistical Analysis

In-hospital outcomes. Multivariable logistic regression (PROC LOGISTIC, SAS Institute, Inc, Cary, NC) was used to identify the factors associated with each postoperative in-hospital complication (ie, hospital death, deep sternal wound infection [DSWI], stroke, reoperation for bleeding, length of stay >14 days, renal failure, and prolonged ventilation [>24 hours]). Using only preoperative patient variables (Appendix E1), we first formed a risk factor (patient) model. For this, variable screening, with a *P* value criterion for retention of variables in the model of .05, used a computer-intensive machine-learning "bagging" method (bootstrap aggregation).[4,5] Variables with bootstrap reliability of ≥50% were included in the model. We then augmented the patient model with the surgical techniques and variables related to diabetes treatment, irrespective of their statistical significance. We also performed subgroup analyses for the patients with multivessel disease (n = 11,322, 95% of the total study cohort) to assess the effect of BITA versus SITA grafting.

Survival. Nonparametric survival estimates were obtained using the Kaplan-Meier method and parametric estimates using a multiphase nonproportional hazards model.[6] The parametric method was used to resolve the number of phases of instantaneous risk of death (hazard function). Multivariable analysis was performed in the hazard function domain, incorporating the risk factors simultaneously into all phases. Variable screening, formation of a patient and augmented model, and subgroup analyses for patients with multivessel disease were performed as described.

Missing values. A number of variables examined in the multivariable analyses had missing values. We used fivefold multiple imputation[7] by a Markov chain Monte Carlo technique (SAS PROC MI and SAS PROC MIANALYZE; SAS Institute, Inc).

Patients deriving maximum benefit from optimal strategy. To identify the patients deriving the greatest survival benefit from an optimal surgical technique, the multivariable hazard model was solved for each patient in the study to produce the 10-year predicted survival using 12 possible surgical combinations (derived from no ITA, 1 ITA, 2 ITAs, incomplete revascularization, complete revascularization, off-pump CABG, and on-pump CABG). Next, using cumulative distributions of 10-year predicted survival for each of the 12 possible surgical combinations, we identified the combinations with the best and worst 10-year predicted survival. The difference between the best and worst 10-year predicted survival was calculated for each patient. A logistic model was then fitted for the highest quintile group.

DSWI and mortality. The survival of patients after diagnosis of a postoperative DSWI was assessed nonparametrically using the Kaplan-Meier method. The effect of DSWI on time-related mortality for the BITA and SITA groups as a whole was assessed by comparing nonparametric survival with and without DSWI.

Presentation. Continuous variables are summarized as the mean ± standard deviation; comparisons were made using the Wilcoxon rank-sum (nonparametric) test. Categorical data are summarized as frequencies and percentages; comparisons were made using the chi-square test or Fisher's exact test, when the frequency was <5. Transformation of scale of the continuous variables was necessary to meet the statistical model assumptions; therefore, the results of the logistic and multiphase hazard models are presented with their coefficients rather than odds or hazard ratios. All analyses were performed using SAS, version 9.1, statistical software (SAS Institute, Inc). Uncertainty is expressed by confidence limits (CL) equivalent to ±1 standard error (68%). Graphics were constructed using either SAS software (SAS Institute, Inc) or the R package (R Project for Statistical Computing, Vienna, Austria).

RESULTS

Hospital Outcomes

Effect of BITA versus SITA. For patients undergoing BITA or SITA grafting, hospital mortality (0.75% vs 1.2%, $P = .11$) and the prevalence of stroke (0.96% vs 1.7%, $P = .10$) were similar. However, BITA grafting was associated with a higher occurrence of DSWI (3.4% vs 2.1%, $P = .01$) and reoperation for bleeding (4.4% vs 3%, $P = .04$). SITA grafting was associated with a higher occurrence of renal failure (4.1% vs 1.9%, $P = .002$), prolonged ventilation (11% vs 4%, $P = .001$), and postoperative length of stay >14 days (8.2% vs 6.0%, $P = .004$; Figure 1, Table E2). After multivariable risk

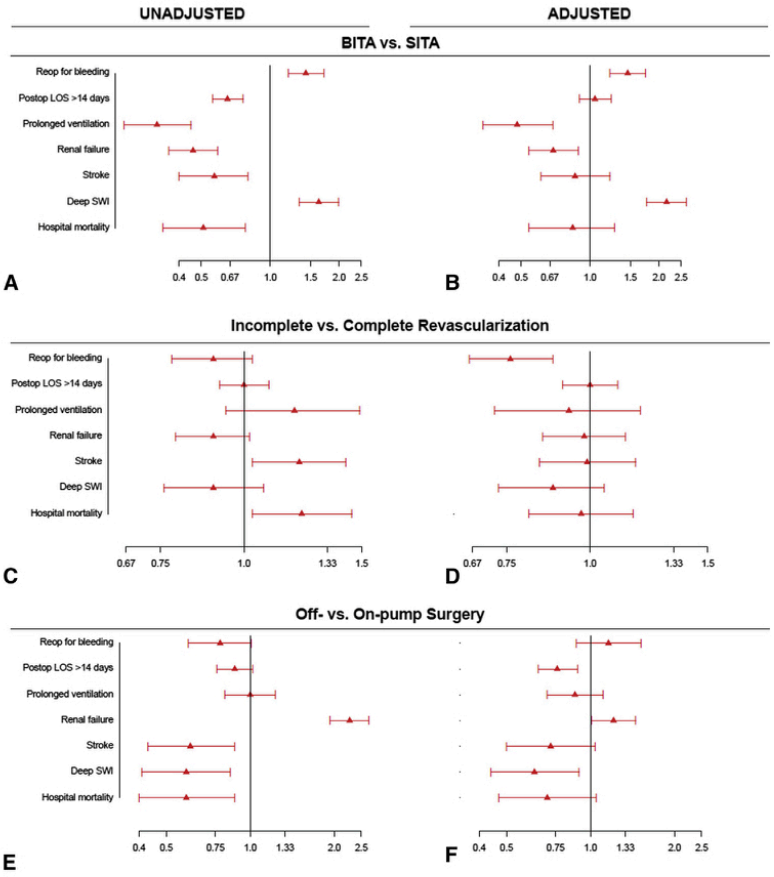


FIGURE 1. Comparative risk of developing complications after coronary artery bypass grafting in diabetic patients. An odds ratio of 1.0 indicates equal risk; odds ratios >1.0 indicate greater risk and those <1.0, lower risk. *Symbols* represent point estimates and *horizontal bars*, 68% confidence limits equivalent to ±1 standard error. A and B, Bilateral (*BITA*) versus single (*SITA*) internal thoracic artery grafting. C and D, Incomplete versus complete revascularization. E and F, Off- versus on-pump surgery. *Reop*, Reoperation; *Postop*, postoperative; *LOS*, length of stay; *SWI*, sternal wound infection.

adjustment, BITA was associated with a higher risk of DSWI ($P = .0002$) and reoperation for bleeding ($P = .03$), but with a lower risk of prolonged ventilation ($P = .04$; Figure 1, Table 1, Tables E3-E8).

Effect of complete versus incomplete revascularization. In patients undergoing complete versus incomplete revascularization, hospital mortality (1.8% vs 2.2%, $P = .2$), DSWI (2.2% vs 2.0%, $P = .6$), stroke (2.0% vs 2.5%, $P = .2$), renal failure (3.8% vs 3.4%, $P = .4$), reoperation for bleeding (3.4% vs 3.1%, $P = .4$), postoperative length of stay >14 days (9.1% vs 9.2%, $P > .9$), and prolonged ventilation (11% vs 13%, $P = .5$) were similar (Figure 1, Table E2). After adjustment, all hospital outcomes were similar, with the possible exception of a higher risk of reoperation for bleeding ($P = .06$) with complete revascularization (Figure 1, Table 1, Tables E3-E8).

Effect of off-pump versus on-pump CABG. In patients undergoing off- or on-pump surgery, hospital mortality (1.2% vs 1.9%, $P = .18$), DSWI (1.3% vs 2.2%, $P = .15$), stroke (1.3% vs 2.2%, $P = .17$), reoperation for bleeding (2.7% vs 3.4%, $P = .3$), postoperative length of stay >14 days (8.1% vs 9.2%, $P = .4$), and prolonged ventilation (11% vs 11%, $P > .9$) were similar. However, the occurrence of renal failure was greater with off-pump surgery (7.6% vs 3.5%, $P < .0001$; Figure 1, Table E2). After adjustment, all in-hospital outcomes were similar (Figure 1, Table 1, Tables E3-E8).

TABLE 1. Risk factors for deep sternal wound infection

Factor	Estimate ± SE	OR (68% CL)	*P* value	Reliability (%)*
Demographic data				
Female sex	0.59 ± 0.59	1.80 (1.64-1.99)	<.0001	88
BMI	0.057 ± 0.01†	—	<.0001	84
Cardiac comorbidity				
Previous MI	0.46 ± 0.13	1.58 (1.39-1.80)	.0006	89
Noncardiac comorbidity				
PAD	0.55 ± 0.15	1.73 (1.49-2.01)	.0003	83
Diabetes				83
Pharmacologically treated	0.55 ± 0.24	1.73 (1.36-2.20)	.02	
Insulin treated	−0.0094 ± 0.16	0.99 (0.84-1.16)	>.9	
Procedure				
ITA graft				95
Single (vs SVG only)	0.27 ± 0.19	1.31 (1.08-1.58)	.15	
Bilateral (vs SVG only)	1.01 ± 0.25	2.75 (2.14-3.53)	<.0001	
Bilateral vs single‡	0.74 ± 0.20	2.09 (1.72-2.56)	.0003	
Incomplete revascularization (vs complete)	−0.14 ± 0.18	0.87 (0.73-1.04)	.4	2§
Off-pump surgery (vs on-pump)	−0.44 ± 0.37	0.64 (0.54-0.77)	.2	28§
Earlier date of operation‖	−0.026 ± 0.0085†	—	.0025	35§

C-statistic = 0.67. *SE*, Standard error; *OR*, odds ratio; *CL*, confidence limits; *BMI*, body mass index; *MI*, myocardial infarction; *PAD*, peripheral arterial disease; *ITA*, internal thoracic artery; *SVG*, saphenous vein graft. *Percentage of times the factor appeared in 500 bootstrap models. †See Figure E1. ‡Estimate derived by running the model with the same variables for patients with multivessel coronary artery disease. §Variables were forced into model, even though the reliability was low. ‖Date of operation (years since January 1, 1972).

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Effect of diabetes management. After risk adjustment, pharmacologically treated diabetes was associated with a higher risk of DSWI, stroke, and prolonged length of stay (Table 1, Tables E3-E8). No statistically significant effect was found for pharmacologically treated diabetes on in-hospital death, renal failure, or reoperation for bleeding, nor was an effect found for insulin versus non–insulin-treated diabetes on in-hospital outcomes.

Patient factors associated with increased risk of DSWI. The risk factors for DSWI included female sex (80% increased risk), higher body mass index (BMI) (7% increased risk per kg/m^2; Figure E1, *A*), medically treated diabetes (73% increased risk compared with diet-controlled diabetes), previous myocardial infarction (58% increased risk), peripheral arterial disease (73% increased risk), and BITA versus SITA grafting (118% increased risk; Table 1). The risk of DWSI decreased steadily during the study period (Figure E1, *B*). For example, a diabetic man with a BMI of 40 kg/m^2 had a lower risk of developing DSWI than a diabetic woman with a BMI of 30 kg/m^2 (Figure 2, *A*). A female patient with a BMI > 30 kg/m^2, peripheral arterial disease, previous myocardial infarction, and pharmacologically treated diabetes had the greatest risk of developing a DSWI after BITA grafting (Figure 2, *B*). A medically treated diabetic patient undergoing BITA grafting had a greater risk of developing DSWI than a diet-controlled diabetic patient undergoing BITA grafting. The hemoglobin A1c level was not associated with DSWI occurrence (Table E9).

Early and Late Survival

Unadjusted. Survival at 30 days and 5, 10, and 20 years was 96%, 75%, 47%, and 15% after SVG alone, 98%, 82%, 58%, and 21% after SITA grafting with or without other grafts, and 99%, 91%, 76%, and 37% after BITA grafting with or without other grafts, respectively (*P[log-rank]* < .0001; Figure 3, *A*). At these same points, corresponding survival after incomplete revascularization was 97%, 78%, 52%, and 18% versus 98%, 82%, 57%, and 21% for complete revascularization (*P[log-rank]* = .0006; Figure 3, *B*) and 98%, 76%, and 56% (no 20-year estimate) after off-pump CABG versus 98%, 81%, 56%, and 20% (with 20-year estimate) after on-pump CABG (*P[log-rank]* = .4; Figure 3, *C*).

Adjusted. After adjustment for patient characteristics, SITA grafting with or without other grafts versus SVG alone was associated with 50% lower (68% CL, 44%-55%) early mortality and 16% lower (68% CL, 14%-19%) late mortality. BITA grafting with or without other grafts was associated with 68% lower (68% CL, 54%-77%) early mortality and 33% lower (68% CL, 28%-37%) late mortality (Figure 4, Table 2). BITA versus SITA grafting was associated with 21% (68% CL, 16%-26%) lower late mortality in patients with multisystem disease (Table E10). Incomplete revascularization was associated with 10% higher (68% CL, 6%-13%) late mortality. Off-pump CABG was associated with 10% lower late mortality than on-pump CABG, but the difference was not statistically significant (*P* = .2).

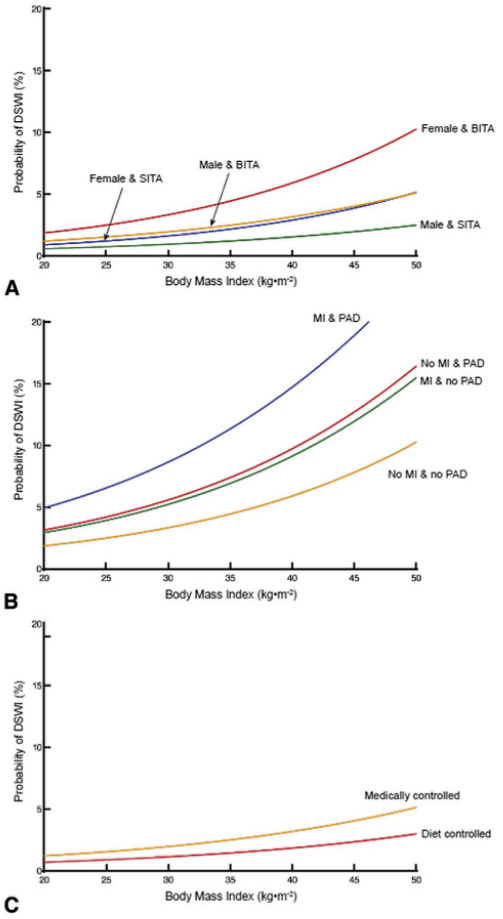


FIGURE 2. Effect of risk factors on probability of deep sternal wound infection (*DSWI*) across a range of body mass indexes. Simulations were based on the logistic regression model (Table 1) for a patient undergoing coronary artery bypass grafting with cardiopulmonary bypass, in the past decade, with complete revascularization. Other factors are listed for the individual depictions. A, Effect of female sex after bilateral (*BITA*) and single (*SITA*) internal thoracic artery grafting. Simulations are based on an insulin-treated patient with no history of peripheral arterial disease (*PAD*) or myocardial infarction (*MI*). B, Effect of PAD and MI after BITA grafting. Simulations are based on an insulin-treated woman. C, Effect of diet-controlled versus medically treated diabetes. Simulations are based on a man with no history of PAD or MI undergoing CABG with BITA grafting.

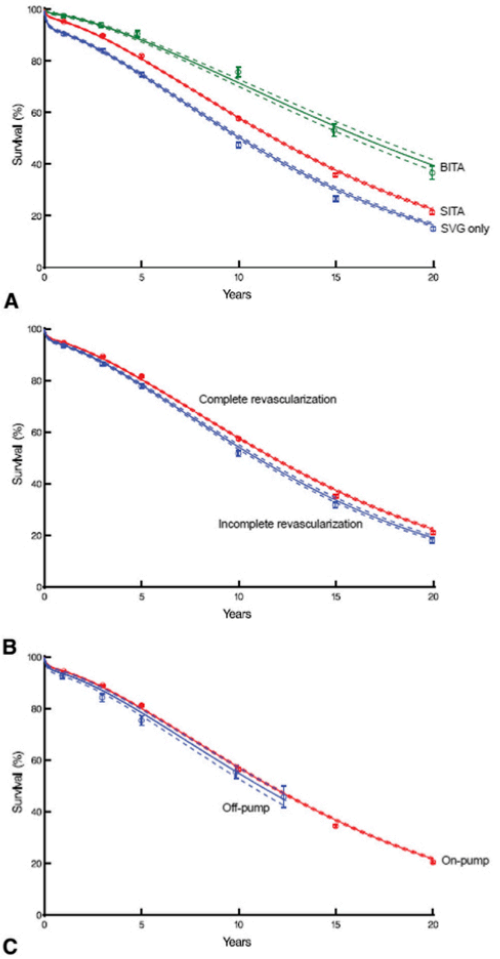


FIGURE 3. Unadjusted survival after coronary artery bypass grafting. Each *symbol* represents a death at selected points (1, 3, 5, 10, 15, and 20 years after surgery) from Kaplan-Meier estimation; *vertical bars* are confidence limits equivalent to ±1 standard error (SE). *Solid lines* are parametric estimates enclosed within dashed confidence bands equivalent to ±1 SE. A, Stratified by bilateral and single internal thoracic artery grafting and saphenous vein grafting only. B, Stratified by incomplete versus complete revascularization. C, Stratified by off- versus on-pump coronary artery bypass grafting. *BITA*, Bilateral internal thoracic artery; *SITA*, single internal thoracic artery; *SVG*, saphenous vein grafting.

Effect of diabetes management on survival. Risk-adjusted analyses showed that pharmacologically (insulin or non-insulin) treated diabetes compared with diet-controlled diabetes was associated with a higher risk of late death (Table 2). The early and late risk of death was similar for insulin- and non–insulin-treated diabetes.

Effect of occurrence of DSWI on survival. DSWI was associated with a high risk of death within the first year, irrespective of the type of grafting used (Figure E2, *A*).

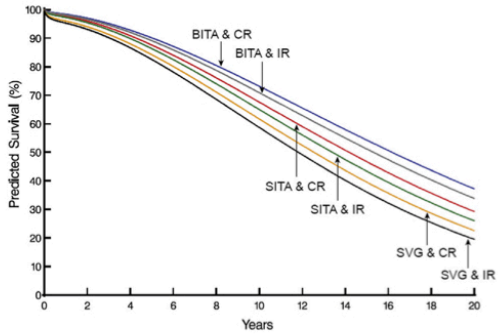


FIGURE 4. Risk-adjusted effect of bilateral (*BITA*) versus single (*SITA*) internal thoracic artery grafting and incomplete (*IR*) versus complete (*CR*) revascularization on predicted survival after coronary artery bypass grafting (*CABG*) in diabetic patients. Simulations were based on the multivariable model (Table 2), with the following variables held constant: 62-year-old non–insulin-treated diabetic man, New York Heart Association functional class II, preoperative cholesterol 200 mg/dL, bilirubin 0.6 mg/dL, creatinine 0.8 mg/dL, no carotid disease, heart failure, previous myocardial infarction, peripheral arterial disease, previous stroke, and on-pump coronary artery bypass grafting. *SVG*, Saphenous vein grafting.

However, because of its rare occurrence, it had little effect on overall survival (Figure E2, *B*).

Patients benefiting most from best versus worst combination of surgical techniques. We identified BITA plus complete revascularization plus off-pump CABG as the strategy with the best predicted survival, and no ITA grafts plus incomplete revascularization plus on-pump CABG with the worst (Figure E3, *A*). The survival benefit associated with the best combination of surgical techniques was driven by BITA grafting (Figure E3, *B*), with little increment of benefit from either complete revascularization (Figure E3, *C*) or off-pump CABG (Figure E3, *D*). We found that patients deriving the greatest survival benefit (greater than a 23% 10-year survival difference) from the best surgical combination were actually the sickest of all (Table 3, Figure E4)—older women undergoing emergency surgery, with higher bilirubin, previous stroke, peripheral arterial disease, and insulin-treated diabetes.

DISCUSSION

Principal Findings

Our study has shown that for patients with diabetes undergoing CABG, BITA grafting with complete revascularization results in the best long-term survival, whereas off-pump versus on-pump surgery resulted in similar long-term survival. Although BITA grafting was associated with a higher risk of DSWI than SITA grafting or SVG, the considerable mortality from DSWI minimally affected overall survival because of its rare occurrence. We also found

TABLE 2. Incremental risk factors for death after coronary artery bypass grafting

Risk factor	Coefficient ± SE	*P* value	Reliability (%)*
Early hazard phase			
Demographic data			
Female sex	0.38 ± 0.10	.0002	99
Older age†	0.49 ± 0.074	<.0001	100
Acuity			
NYHA functional class			93
II	−0.44 ± 0.15	.003	
III-IV	−0.10 ± 0.14	.5	
Emergency surgery	1.39 ± 0.15	<.0001	100
Noncardiac comorbidity			
Diabetes			74
Treated	0.29 ± 0.18	.10	
Insulin treated	0.20 ± 0.12	.08	
PAD	0.50 ± 0.11	<.0001	84
Previous stroke	0.58 ± 0.13	<.0001	87
Lower cholesterol‡	0.10 ± 0.022	<.0001	59
Higher bilirubin	0.16 ± 0.051	.002	74
Procedure			
ITA graft			99
Single	−0.69 ± 0.11	<.0001	
Bilateral	−1.13 ± 0.35	.001	
Incomplete revascularization	0.19 ± 0.12	.11	10§
Off-pump surgery	−0.03 ± 0.11	.8	<1§
More recent date of operation‖	0.00094 ± 0.0039	.8	24§
Late hazard phase			
Demographic data			
Female sex	0.085 ± 0.032	.010	75
Older age¶	1.02 ± 0.064	<.0001	100
Cardiac comorbidity			
Heart failure	0.48 ± 0.040	<.0001	100
Noncardiac comorbidity			
Diabetes			100
Treated	0.43 ± 0.044	<.0001	
Insulin treated	0.052 ± 0.039	.18	
PAD	0.42 ± 0.033	<.0001	100
Previous MI	0.12 ± 0.026	<.0001	99
Previous stroke	0.27 ± 0.049	<.0001	100
Carotid disease	0.13 ± 0.039	.0006	90
Higher creatinine#	0.14 ± 0.099	.2	100
Procedure			
ITA graft			100
Single	−0.18 ± 0.031	<.0001	
Bilateral	−0.40 ± 0.067	<.0001	
Incomplete revascularization	0.091 ± 0.032	.004	36§
Off-pump surgery	−0.096 ± 0.081	.2	<1§

SE, Standard error; *NYHA*, New York Heart Association; *PAD*, peripheral arterial disease; *ITA*, internal thoracic artery; *MI*, myocardial infarction. *Percentage of times the factor appeared in 500 bootstrap models. †Exp(age/50), exponential transformation. ‡(1/Cholesterol)^2, inverse squared transformation. §Variables were forced into the model, even though the reliability was low. ‖Date of operation (years since January 1, 1972). ¶(50/Age)^2, inverse squared transformation. #Log(creatinine), logarithmic transformation.

TABLE 3. Risk factors associated with maximum survival benefit from optimal combination of surgical techniques (BITA + complete revascularization + off-pump)

Factor	Estimate ± SE	OR (68% CL)	*P* value
Demographic data			
Female sex	1.86 ± 0.097	6.4 (5.8-7.1)	<.0001
Older age*	2.6 ± 0.086†	—	<.0001
Acuity			
NYHA functional class			<.0001
II	−2.1 ± 0.13	0.12 (0.11-0.14)	
III-IV	−0.43 ± 0.11	0.65 (0.58-0.73)	
Emergency surgery	6.0 ± 0.23	410 (330-520)	<.0001
Cardiac comorbidity			
Heart failure	−1.68 ± 0.13	0.19 (0.16-0.21)	<.0001
Noncardiac comorbidity			
Diabetes			<.0001
Pharmacologically treated	1.30 ± 0.20	3.7 (3.0-4.5)	
Insulin treated	0.90 ± 0.095	2.5 (2.2-2.7)	
PAD	2.5 ± 0.10	11.8 (10.7-13.1)	<.0001
Previous stroke	2.4 ± 0.12	10.8 (9.6-12.2)	<.0001
Lower cholesterol‡	1.19 ± 0.15†	—	<.0001
Higher bilirubin	0.58 ± 0.11†	—	<.0001

Reliability, defined as the number of times the factor appeared in 500 bootstrap models, was 100% for all factors; C-statistic = 0.96. *SE*, Standard error; *OR*, odds ratio; *CL*, confidence limits; *NYHA*, New York Heart Association; *PAD*, peripheral arterial disease. *Exp(age/50), exponential transformation. †See Figure E4. ‡(1/Preoperative cholesterol), inverse transformation.

that obese diabetic women with diffuse atherosclerotic burden were at the greatest risk of developing DSWIs.

BITA Versus SITA Grafting

BITA grafting has been found to be associated with better long-term survival than SITA grafting in both diabetic and nondiabetic patients undergoing CABG.[8-14] Nevertheless, BITA grafting was performed in only 4.4% of CABG cases in the STS national database in 2011.[15,16] This might have been due to the fear of an increased risk of DWSI,[16] a tradeoff with the long-term survival benefit. This increased risk is of particular concern for those with diabetes, because they are already at a greater risk than those without diabetes of developing surgical site infections. Our data show that BITA grafting is associated with a higher occurrence of DSWI than SITA grafting. However, although we found that DSWI after BITA or SITA grafting was associated with a high risk of death within the first year, it minimally affected overall survival because of its rare occurrence. We identified female sex, higher BMI, previous myocardial infarction, peripheral arterial disease, and medically treated versus diet-controlled diabetes as risk factors associated with the greatest risk of developing DSWI. In addition, we found that some of the factors associated with the greatest risk of developing DSWI after BITA grafting were also associated with deriving the greatest survival benefit from it. A recent study has also shown that obese diabetic women are at high risk of developing DSWI with BITA grafting.[17] Moreover, we recommend using a skeletonized approach instead of a pedicled approach for harvesting ITAs because the former has been shown to be associated with a lower risk of DSWI in patients with diabetes.[18] At our center, ITA harvesting is done using the skeletonized approach.

Complete Versus Incomplete Revascularization

Early studies of CABG highlighted the survival advantage of complete over incomplete revascularization.[19-21] Since then, a number of studies have evaluated this effect; however, the literature specifically focusing on patients with diabetes is sparse. Also, the definitions of complete and incomplete revascularization have remained controversial, with different studies reporting different definitions.[22] We found that incomplete revascularization was associated with a higher risk of late death, highlighting the importance of the completeness of revascularization for long-term survival benefit. A post hoc analysis from the BARI 2D (Bypass Angioplasty Revascularization Investigation) trial also showed that less complete revascularization was associated with a higher risk of long-term cardiovascular events in those with diabetes.[23]

Off-Pump Versus On-Pump CABG

Although a number of studies have compared the outcomes of off-pump versus on-pump CABG,[24-31] few have done so for diabetic populations.[32-35] The available studies have shown that in diabetic patients, off-pump CABG results in lower in-hospital morbidity and mortality and higher 1-year survival.[32-34] However, our study shows that the hospital outcomes and long-term survival of patients undergoing off-pump or on-pump surgery are similar. Therefore, both strategies represent skill sets that surgeons can use selectively. This is particularly relevant for patients with a greater risk of developing complications from cardiopulmonary bypass or aortic manipulation, because they will benefit the most from off-pump surgery.

Study Limitations

This was a nonrandomized, observational, comparative effectiveness study; thus, patient characteristics might have influenced our findings. To account for this, we performed multivariable adjustment. However, any patient factors importantly affecting outcomes that were not included in the analyses could have biased our findings. Because 4 decades of data from diabetic patients undergoing CABG were used for the analyses, the applicability of our results to contemporary patients could be questionable. To account for this, we adjusted for the date of surgery in each outcome model. BITA grafting, incomplete revascularization, and off-pump CABG all

represent small subsets of our study, which might have limited our ability to identify small incremental benefits within the 12 combinations of surgical strategies analyzed.

CONCLUSIONS

BITA grafting with complete revascularization maximizes long-term survival in patients with diabetes undergoing surgical revascularization. Therefore, BITA grafting should be used for all diabetic patients for whom the risk of DSWI is low. It might be best to avoid BITA grafting in obese diabetic women with diffuse atherosclerotic burden—patients at the greatest risk of developing these infections. Off-pump or on-pump surgery can be used with equal effectiveness, and every effort should be made to completely revascularize the patient.

ACD

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Discussion

Dr John G. Byrne *(Boston, Mass)*. No disclosures. This report adds to the considerable work our colleagues at Cleveland Clinic have contributed to the idea that bilateral internal mammary arteries (BIMAs) are preferable in most CABG patients, even in those with diabetes, and that although the use of BIMAs in patients

with diabetes comes at the expense of increased DSWI, it is worth it in terms of survival. I have 4 questions.

Although you found that factors such as female sex, large BMI, peripheral vascular disease, and so forth contributed to DSWI, you also state that it is in these very patients for whom BIMA is most preferable. So does that mean now that at the Cleveland Clinic your practice has changed? Do you recommend BIMAs for every single patient, even those who are massively obese, who perhaps have undergone radiotherapy, or have chronic obstructive pulmonary disease, emergencies, and so forth?

Dr Raza. Thank you, Dr Byrne, for the question. We believe that the therapy should be patient oriented and individualized. If a patient has a higher risk of developing DSWI, such as a massively obese woman, it is very unlikely that she would undergo bilateral ITA grafting electively at Cleveland Clinic. Thus, we recommend the use of bilateral ITA grafts for those patients for whom the risk of developing DSWI is low.

Dr Byrne. What I am wondering about is some sort of scoring system. Perhaps the next report at next year's The American Association for Thoracic Surgery might have a scoring system that could indicate, for instance, if this patient's score is low enough, that patient should undergo BIMA.

Dr Raza. That is an interesting idea.

Dr Byrne. Second question. You must have a glucose control protocol, such as a Portland type protocol.

Dr Raza. That is a great point. We do have a strict glucose monitoring protocol by which every patient's glucose is monitored closely in the perioperative period, and every effort is made to keep the glucose <160 mg/dL. Also, if a patient has uncontrolled diabetes and blood glucose levels are high, if time allows, we suggest achieving control of those levels before surgery is performed. That is perhaps one of the reasons that when we studied the effect of the HbA1c levels on the risk of developing DSWI, our data did not show any significant association.

Dr Byrne. What was the distribution of your BIMA grafts, to the left side, to the right side? Do you have any data to share with us on that? What is the Cleveland Clinic's preference and what is your practice?

Dr Raza. Of the right ITA?

Dr Byrne. Do you put it to the right side, the left side?

Dr Raza. Most right ITA grafts went to left-sided lesions, and nearly one quarter in our data set went to right-sided lesions. We believe that the right ITA should go to the second most important coronary artery, which is usually the circumflex. If we use a right ITA graft to the right coronary artery, we would see whether it is totally occluded or critically stenosed, say, >90%.

Dr Byrne. Thank you. Finally, you recommend in your report that you should skeletonize the left internal mammary artery to both mammary arteries and that this is mandatory for this notion, this concept, this practice pattern. Most of us, of course, use pedicle grafts. What happens when you use a pedicle graft? Also, what happens if the right internal mammary artery does not reach the target? Do you use it as a free graft, a T graft and so forth?

Dr Raza. That is a great point. If the target is distal, usually the right ITA is used as a free graft off the left ITA. That allows us to graft more vessels, and that is the usual practice at Cleveland Clinic and our preference.

Could you please repeat the second question?

Dr Byrne. The skeletonization.

Dr Raza. Sternal wound infection is the Achilles heel of bilateral ITA grafting, and the skeletonized approach has been shown to be associated with a decreased risk of sternal wound infections. Thus, we recommend and use a skeletonized approach for ITA harvest.

Dr Harold L. Lazar *(Boston, Mass).* I have no conflicts to report. I have 1 question about your long-term outcomes. Many patients who do receive a single internal mammary usually have a higher risk profile. Thus, can you tell us as far as the long-term deaths, what percentage were cardiac related versus noncardiac related and did they differ between the groups of bilateral and single mammary disease?

Dr Raza. Regarding the risk profile, the patients who were good candidates for bilateral ITA grafting were those with a lower BMI and good control of their blood glucose levels. We were aware that the patient characteristics might have influenced our findings, and, therefore, we adjusted for them. Our adjusted results showed that bilateral ITA grafting was associated with a 21% decrease in late mortality. So, we did adjust for the effects of all available patient characteristics.

Dr Lazar. But do you know, were the deaths cardiac related or noncardiac related in the long term?

Dr Raza. Sorry, the long-term survival?

Dr Lazar. The incidence of deaths for long-term survival, was there a difference between cardiac-related deaths versus noncardiac?

Dr Raza. We used the Social Security Death Master File for long-term follow-up. It takes into account all-cause mortality, but does not distinguish between cardiac-related and noncardiac-related death. Thus, the long-term survival in our study was just based on all-cause mortality.

Dr Antonio Laudito *(Duluth, Minn).* I thank you for continuing with your group to show the data, the reality. I am a little bit surprised when you look at the STS database that the use of the bilateral mammary artery, instead of increasing is decreasing. I was wondering if you have any idea of the reason? Of course, it is an ironical question. But it is interesting to see what happens always with your data in the past when you show the difference clearly between vein, a single mammary. The curve did not diverge when you showed, in a very excellent way, the difference. The curve diverged when the left internal mammary artery received a diagnosis-related group number.

Dr Raza. That is a great point. As you mentioned, we have shown that bilateral ITA grafting is associated with improved long-term survival compared with single ITA grafting. However, the reason it has not been widely adopted is, as I mentioned, that sternal wound infection is its Achilles heel. In recent years at our center, the risk of sternal wound infection has decreased because of several approaches we have adopted, including the use of perioperative prophylactic antibiotics and achieving control of the blood glucose levels before going to surgery, if time allows. The skeletonized approach for ITA harvest is another method that we use to decrease the risk of sternal wound infections. If these approaches are used, the risk of sternal wound infections can be lowered, making bilateral ITA grafting more likely to be adopted.

Dr Laudito. We have also to stop to be politically correct saying that a BIMA operation is not the usual coronary operation, occurred more times, more clinical experience, more surgical experience. It is not the usual CABG. So we need to have the appreciation and the time for that.

Thank you.

Dr Raza. Thank you for your comments.

Dr Saswata Deb *(Toronto, Ontario, Canada).* A very nice talk. High-grade target vessel stenosis is an important issue for radials. Did you consider that for mammary arteries, especially the right?

Dr Raza. Nearly 1200 patients in our data set underwent radial artery grafting. However, it was not within the scope of this project to specifically consider the outcomes of patients undergoing radial artery grafting or the issue of high-grade target vessel stenosis. Our usual practice is to use radial artery grafts to fill in the left-sided gaps. A radial graft can go to the right coronary artery, but only if it is totally occluded or the stenosis is >90%.

Dr Deb. My question was more for the right ITA. High-grade stenosis, was that factor considered for where the right ITA was going to be placed?

Dr Raza. Regarding right ITA grafting, we believe that it should go to the second most important coronary artery, which is usually the circumflex. Competitive flow, which you are getting at, becomes more of an issue when we graft the vessel to the right coronary artery. Thus, if we use the right ITA to graft the right coronary artery, we would first have determined whether it is totally occluded or critically stenosed, that is, >90%.

ACD

EDITORIAL COMMENTARY

Two internal thoracic arteries really are better

Andrea J. Carpenter, MD, PhD

The research reported by Raza and colleagues presents compelling evidence that best outcomes of surgical revascularization in persons with diabetes are achieved with the use of bilateral internal thoracic artery grafts and complete revascularization with only modest increase in deep sternal wound infection. It is time for greater adoption of bilateral internal thoracic artery grafting across coronary surgery centers.

Raza and colleagues[1] are to be congratulated on an elegant review of operative strategies that may improve or hinder outcomes of coronary revascularization in patients with diabetes. Mining the extensive outcomes database maintained at the Cleveland Clinic, they identified the optimal strategy for long-term survival among patients with diabetes to include use of bilateral internal thoracic arteries (BITAs) and achievement of complete revascularization. In their cohort with diabetes only 2 complications occurred more frequently with the use of BITA: reoperation for bleeding and deep sternal wound infection (DSWI).

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Almost all practicing cardiac surgeons believe that completeness of revascularization is important to good outcomes. However, the adoption of BITA use has been extremely slow, with surgeons avoiding BITA in the presence of diabetes, obesity, and chronic obstructive pulmonary disease because of concern regarding DSWI. This opinion persists in our culture despite a wealth of literature supporting the benefit of BITA on survival, symptom relief, and diminished repeat revascularization.

Although Dr Sabik has long been a proponent of BITA for coronary grafting, there were only 938 cases (8%) using BITA in this cohort of 11,922 patients with diabetes.[1] The rate of DSWI was statistically elevated compared with patients receiving a single internal thoracic artery graft, but the influence of DSWI on survival was small. Evaluating patient factors associated with DSWI revealed that women with body mass index > 30, peripheral artery disease, prior myocardial infarction, and pharmacologic therapy for diabetes were at highest risk. Men, nonobese women, and all patients with diet-controlled diabetes had very modest increased risk.

Acknowledging that the report by Raza and colleagues is a retrospective review and that the total number of patients having BITA was only 8% of the cohort,[1] these data still provide compelling evidence that the risk of excess DSWI with BITA grafting is small. Although the adverse effects of DSWI can be severe, the overall long-term survival is still better with BITA.

APPENDIX E1. VARIABLES CONSIDERED IN MULTIVARIABLE ANALYSES

Demographic Data

Age (y), sex, race, weight (kg), height (cm), weight/height ratio, body surface area (m^2), body mass index (kg/m^2).

Acuity

New York Heart Association functional class (I-IV), emergency surgery.

Cardiac Comorbidity

Previous myocardial infarction, atrial fibrillation/flutter, complete heart block or pacer, heart failure.

Noncardiac Comorbidity

Treated diabetes, insulin-treated diabetes (from 1990), non–insulin-treated diabetes (from 1990), diet-controlled diabetes, peripheral arterial disease, carotid disease, hypertension, history of smoking, previous stroke, bilirubin (mg/dL), cholesterol (mg/dL), triglycerides (mg/dL), creatinine (mg/dL).

Coronary Anatomy

Number of systems diseased (≥50% stenosis), left main disease (0%, ≥70%, and ≥50% stenosis), left anterior descending system disease (0%, ≥70%, and ≥50% stenosis), left circumflex system disease (0%, ≥70%, and ≥50% stenosis), right coronary artery system disease (0%, ≥70%, and ≥50% stenosis).

Procedure

Insertion of assist device, surgeon.

Procedure: Coronary Artery Bypass Grafting Detail

Number of internal thoracic artery (ITA) grafts used (none, 1, 2), complete revascularization, conduit (arterial grafts, only arterial grafts, gastroepiploic or inferior epigastric artery, ITA, free ITA, in situ ITA, left ITA, right ITA, other, radial artery, saphenous vein graft), graft location (left anterior descending, left anterior descending diagonals, left circumflex territory, right coronary artery territory).

Support

Cardiopulmonary bypass (off-pump vs on-pump).

Experience

Date of operation (years since January 1, 1972).

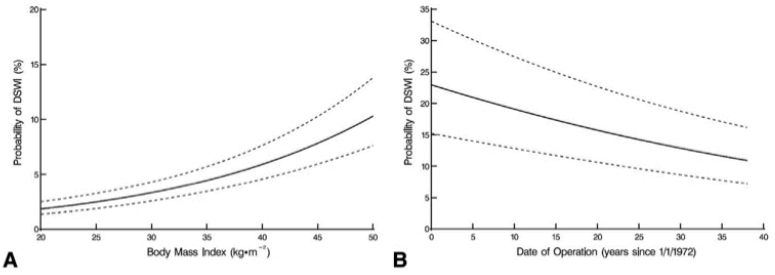


FIGURE E1. Probability of developing a deep sternal wound infection (*DSWI*). *Solid line* represents parametric estimate enclosed within a 68% confidence limit band. This graph represents a nomogram of the logistic regression equation for DSWI (Table 1). A, Effect of body mass index. Simulation was based on pharmacologically treated (non–insulin-treated) diabetic woman with no previous myocardial infarction or history of peripheral arterial disease undergoing coronary artery bypass grafting with cardiopulmonary bypass and bilateral internal thoracic artery grafts, receiving complete revascularization, and treated in 2007. B, Effect of date of operation. Simulation was based on pharmacologically treated (non–insulin-treated) diabetic woman with no previous myocardial infarction or history of peripheral arterial disease, body mass index of 29 kg/m^2, undergoing coronary artery bypass grafting with cardiopulmonary bypass, grafting with bilateral internal thoracic artery grafts, and complete revascularization.

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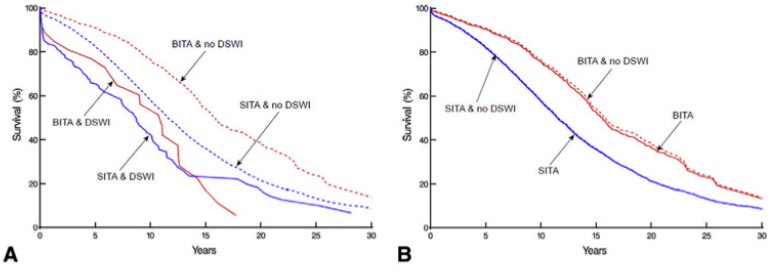
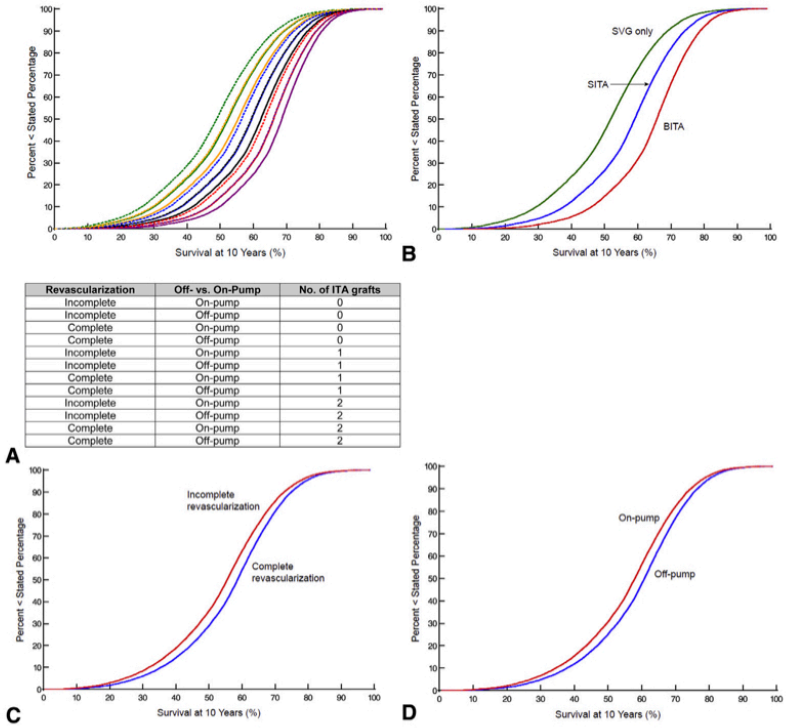


FIGURE E2. Survival of diabetic patients who underwent coronary artery bypass grafting estimated using the Kaplan-Meier method. A, Stratified by deep sternal wound infection (*DSWI*) and bilateral (*BITA*) and single (*SITA*) internal thoracic artery grafting. B, Stratified by BITA and SITA grafting and showing the effect of DSWI on survival.



Revascularization	Off- vs. On-Pump	No. of ITA grafts
Incomplete	On-pump	0
Incomplete	Off-pump	0
Complete	On-pump	0
Complete	Off-pump	0
Incomplete	On-pump	1
Incomplete	Off-pump	1
Complete	On-pump	1
Complete	Off-pump	1
Incomplete	On-pump	2
Incomplete	Off-pump	2
Complete	On-pump	2
Complete	Off-pump	2

FIGURE E3. Cumulative distribution of predicted 10-year survival. A, For a combination of surgical techniques. The increasing order of these cumulative distributions of 10-year survival from left to right is shown in the table underneath the graph. B, For the number of ITA grafts used. C, For complete versus incomplete revascularization. D, For off-pump versus on-pump coronary artery bypass grafting. *ITA*, Internal thoracic artery; *BITA*, bilateral ITA graft; *SITA*, single ITA graft; *SVG*, saphenous vein graft.

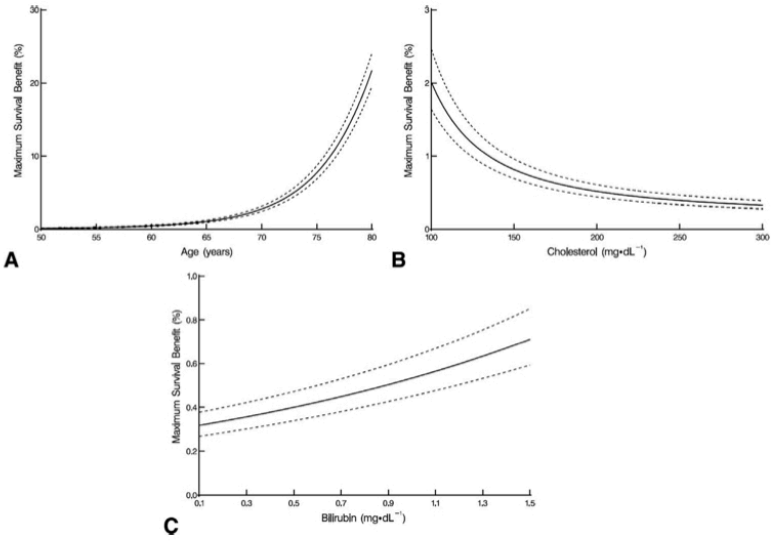


FIGURE E4. Patient factors associated with maximum survival benefit from best combination of surgical techniques (ie, bilateral internal thoracic artery grafting, complete revascularization, and off-pump surgery). *Solid line* represents parametric estimate enclosed within a 68% confidence limit band. This graph represents a nomogram of the logistic regression equation for maximum survival benefit (Table 3). A, Older age. Simulation is based on pharmacologically (non-insulin) treated diabetic woman presenting with mild symptoms of heart failure (New York Heart Association class II), cholesterol level 230 mg/dL, bilirubin 0.63 mg/dL, no history of heart failure or peripheral arterial disease, undergoing nonemergency surgery. B, Lower cholesterol. Simulation is based on a 60-year-old pharmacologically (non-insulin) treated diabetic woman presenting with mild symptoms of heart failure (New York Heart Association class II), bilirubin 0.63 mg/dL, no history of heart failure or peripheral arterial disease, undergoing nonemergency surgery. C, Lower bilirubin. Simulation is based on a 60-year-old pharmacologically (non-insulin) treated diabetic woman presenting with mild symptoms of heart failure (New York Heart Association class II), cholesterol level 230 mg/dL, no history of heart failure or peripheral arterial disease, undergoing nonemergency surgery.

TABLE E1. Patient characteristics and surgical details

Variable	n*	Mean ± SD or No. (%)
Demographic data		
Age (y)	11,922	62 ± 9.8
Female sex	11,922	3388 (28)
Race		
White	11,362	9789 (86)
Black	11,362	640 (5.6)
Other	11,362	933 (8.2)
Weight (kg)	9849	86 ± 18
Height (cm)	9847	170 ± 10
BMI (kg/m^2)	9838	30 ± 5.7
Acuity		
NYHA functional class	11,869	
I		2009 (17)
II		4584 (39)
III		1645 (14)
IV		3631 (31)
Emergency surgery	11,921	277 (2.3)
Cardiac comorbidity		
Previous MI	11,922	6736 (57)
Atrial fibrillation/flutter	10,231	180 (1.8)
Complete heart block or pacer	10,231	87 (0.85)
Ventricular arrhythmia	6533	415 (6.4)
Heart failure	11,922	1866 (16)
Coronary artery disease†		
Left main	10,695	2007 (19)
LAD system	11,370	10,733 (94)
LCx system	11,293	9124 (81)
RCA system	11,294	9805 (87)
No. of diseased systems	11,407	
0		81 (0.71)
1		762 (6.7)
2		2792 (24)
3		7772 (68)
Noncardiac comorbidity		
Diabetes		
Diet controlled		1687 (14)
Pharmacologically treated		10,234 (86)
Non-insulin treated		3766 (32)
Insulin treated		2743 (23)
Latest preoperative HbA1c	2541	7.8 ± 1.7
PAD	11,922	1995 (17)
Previous stroke	11,922	959 (8.1)
Carotid disease	11,922	2476 (21)
Hypertension	7337	5928 (81)
Renal dialysis	4495	108 (2.4)
Creatinine (mg/dL)	7142	1.3 ± 1.2
Creatinine clearance (Cockcroft-Gault)	6539	85 ± 41
Glomerular filtration rate‡	7172	72 ± 31
Blood urea nitrogen (mg/dL)	7139	22 ± 12
Cholesterol (mg/dL)		
Total	8591	210 ± 60
High-density lipoprotein	5871	39 ± 12
Low-density lipoprotein	4781	114 ± 46
Bilirubin (mg/dL)	6386	0.6 ± 0.5
Triglycerides (mg/dL)	7678	202 ± 172
Hematocrit (%)	6626	38 ± 5.5
Procedure		
No. of ITA grafts	11,922	
0§		2518 (21)
1		8466 (71)
2		938 (7.9)
Conduit: saphenous vein	11,922	11,110 (93)
SVG only	11,922	2491 (21)
Conduit: radial artery	11,922	1258 (11)
Incomplete revascularization†	11,922	2109 (18)

SD, Standard deviation; *BMI*, body mass index; *NYHA*, New York Heart Association; *MI*, myocardial infarction; *LAD*, left anterior descending coronary artery; *LCx*, left circumflex coronary artery; *RCA*, right coronary artery; *HbA1c*, hemoglobin A1c; *PAD*, peripheral arterial disease; *ITA*, internal thoracic artery; *SVG*, saphenous vein graft. *Patients with data available. †Stenosis ≥ 50%. ‡Modification of Diet in Renal Disease formula. §SVG only in 99%.

TABLE E2. Unadjusted in-hospital outcomes

Outcomes	BITA (n = 938)	SITA (n = 8466)	*P* value	Off-pump (n = 602)	On-pump (n = 11,320)	*P* value	Incomplete revascularization (n = 2109)	Complete revascularization (n = 9813)	*P* value
Mortality	7 (0.75)	105 (1.2)	.19	7 (1.2)	219 (1.9)	.18	47 (2.2)	179 (1.8)	.2
DSWI	32 (3.4)	181 (2.1)	.01	8 (1.3)	250 (2.2)	.15	42 (2.0)	216 (2.2)	.6
Stroke	9 (0.96)	148 (1.7)	.07	8 (1.3)	244 (2.2)	.17	52 (2.5)	200 (2.0)	.2
Renal failure	18 (1.9)	343 (4.1)	.001	46 (7.6)	400 (3.5)	<.0001	72 (3.4)	374 (3.8)	.4
Ventilation >24 h	9 (4.0)	228 (11)	.001	28 (11)	231 (11)	>.9	25 (13)	234 (11)	.5
Postoperative LOS >14 d	56 (6.0)	691 (8.2)	.02	49 (8.1)	1041 (9.2)	.4	193 (9.2)	897 (9.1)	>.9
Reoperation for bleeding	41 (4.4)	256 (3.0)	.03	16 (2.7)	385 (3.4)	.3	65 (3.1)	336 (3.4)	.4

Data presented as No. (%). *BITA*, Bilateral internal thoracic artery grafting; *SITA*, single internal thoracic artery grafting; *DWSI*, deep sternal wound infection; *LOS*, length of stay.

TABLE E3. Risk factors for in-hospital death

Factor	Estimate ± SE	*P* value	Reliability (%)*
Demographic data			
Female sex	0.61 ± 0.14	<.0001	95
Older age†	0.52 ± 0.11	<.0001	88
Acuity			
NYHA functional class			90
II	−0.77 ± 0.21	.0002	
III-IV	−0.38 ± 0.17	.02	
Emergency surgery	1.98 ± 0.20	<.0001	100
Cardiac comorbidity			
Previous MI	0.55 ± 0.15	.0003	80
Higher number of coronary systems diseased (≥50% stenosis)	0.31 ± 0.13	.01	50
Noncardiac comorbidity			
Diabetes			36‡
Pharmacologically treated	0.24 ± 0.24	.3	
Insulin treated	0.19 ± 0.18	.3	
PAD	0.56 ± 0.16	.0003	83
Procedure			
ITA graft			81
Single (vs SVG only)	−0.95 ± 0.17	<.0001	
Bilateral (vs SVG only)	−0.98 ± 0.42	.02	
Bilateral vs single§	−0.18 ± 0.43	.7	
Incomplete revascularization (vs complete)	−0.037 ± 0.18	.8	3.4‡
Off-pump surgery (vs on-pump)	−0.34 ± 0.41	.4	2.4‡
Earlier date of operation‖	−0.0085 ± 0.01	.4	79

C-statistic = 0.79. *SE*, Standard error; *NYHA*, New York Heart Association; *MI*, myocardial infarction; *PAD*, peripheral arterial disease; *ITA*, internal thoracic artery; *SVG*, saphenous vein graft. *Percentage of times the factor appeared in 500 bootstrap models. †Exp(age/50), exponential transformation. ‡Variables were forced into the model, even though the reliability was low. §Estimate derived by running the model with the same variables for patients with multivessel coronary artery disease. ‖Date of operation (years since January 1, 1972).

TABLE E4. Risk factors for stroke

Factor	Estimate ± SE	*P* value	Reliability (%)*
Demographic data			
Female sex	0.44 ± 0.14	.001	51
Older age†	0.55 ± 0.10	<.0001	100
Acuity			
NYHA functional class III-IV	0.29 ± 0.14	.03	62
Emergency surgery	1.2 ± 0.24	<.0001	99
Cardiac comorbidity			
LCx system disease‡	0.71 ± 0.29	.02	67
Noncardiac comorbidity			
Diabetes			64
Pharmacologically treated	0.51 ± 0.23	.03	
Insulin treated	−0.08 ± 0.18	.7	
Higher creatinine	0.11 ± 0.043	.01	67
Procedure			
ITA graft			23§
Single (vs SVG only)	−0.37 ± 0.16	.02	
Bilateral (vs SVG only)	−0.56 ± 0.37	.10	
Bilateral vs single‖	−0.15 ± 0.35	.7	
Incomplete revascularization (vs complete)	−0.01 ± 0.17	>.9	2.8§
Off-pump surgery (vs on-pump)	−0.33 ± 0.37	.4	16§
Earlier date of operation¶	−0.02 ± 0.0094	.07	69

C-statistic = 0.71. *SE*, Standard error; *NYHA*, New York Heart Association; *LCx*, left circumflex coronary artery; *ITA*, internal thoracic artery; *SVG*, saphenous vein graft. *Percentage of times the factor appeared in 500 bootstrap models. †Exp(age/50), exponential transformation. ‡Stenosis > 0%. §Variables were forced into the model, even though the reliability was low. ‖Estimate derived by running the model with the same variables for patients with multivessel coronary artery disease. ¶Date of operation (years since January 1, 1972).

TABLE E5. Risk factors for reoperation for bleeding

Factor	Estimate ± SE	*P* value	Reliability (%)*
Demographic data			
BMI†	1.19 ± 0.18	<.0001	89
Acuity			
Emergency surgery	0.64 ± 0.26	.01	100
Cardiac comorbidity			
2-System disease‡	−0.44 ± 0.14	.001	82
Noncardiac comorbidity			
Diabetes			30§
Pharmacologically treated	0.076 ± 0.15	.6	
Insulin treated	0.0049 ± 0.15	>.9	
History of smoking	−0.27 ± 0.11	.01	62
Procedure			
ITA graft			91
Single (vs SVG only)	0.081 ± 0.14	.6	
Bilateral (vs SVG only)	0.48 ± 0.20	.02	
Bilateral vs single‖	0.38 ± 0.18	.03	
Incomplete revascularization (vs complete)	−0.27 ± 0.14	.06	25§
Off-pump surgery (vs on-pump)	0.15 ± 0.27	.6	7.4§
Earlier date of operation¶	−0.3 ± 0.0068	<.0001	95

C-statistic = 0.66. *SE*, Standard error; *BMI*, body mass index; *ITA*, internal thoracic artery graft; *SVG*, saphenous vein graft. *Percentage of times the factor appeared in 500 bootstrap models. †$(25/\text{BMI})^2$, inverse squared transformation. ‡Stenosis ≥ 50%. §Variables were forced into the model, even though the reliability was low. ‖Estimate derived by running the model with the same variables for patients with multivessel coronary artery disease. ¶Date of operation (years since January 1, 1972).

TABLE E6. Risk factors for prolonged length of stay (>14 days)

Factor	Estimate ± SE	*P* value	Reliability (%)*
Demographic data			
Female sex	0.43 ± 0.073	<.0001	96
Older age†	0.38 ± 0.053	<.0001	100
BMI‡	0.12 ± 0.052	.02	67
Race: black or other (vs white)	0.21 ± 0.097	.03	58
Acuity			
NYHA functional class			89
II	−0.30 ± 0.098	.002	
III-IV	−0.0007 ± 0.091	>.9	
Emergency surgery	1.23 ± 0.15	<.0001	100
Cardiac comorbidity			
Complete heart block or pacer	0.61 ± 0.28	.03	54
Heart failure	0.46 ± 0.081	<.0001	99
Graft location (LCx territory)	0.34 ± 0.10	.0009	79
Noncardiac comorbidity			
Diabetes			96
Pharmacologically treated	0.31 ± 0.11	.005	
Insulin treated	0.041 ± 0.084	.6	
PAD	0.52 ± 0.077	<.0001	100
Previous stroke	0.58 ± 0.099	<.0001	99
Higher creatinine	0.34 ± 0.062	<.0001	99
Lower cholesterol§	−0.37 ± 0.14	.02	96
Procedure			
ITA graft			97
Single (vs SVG only)	−0.34 ± 0.087	<.0001	
Bilateral (vs SVG only)	−0.22 ± 0.17	.2	
Bilateral vs single‖	0.053 ± 0.16	.7	
Incomplete revascularization (vs complete)	0.0018 ± 0.093	>.9	12¶
Off-pump surgery (vs on-pump)	−0.27 ± 0.16	.10	35¶
Earlier date of operation#	−0.001 ± 0.006	.9	31¶

C-statistic = 0.70. *SE*, Standard error; *BMI*, body mass index; *NYHA*, New York Heart Association; *LCx*, left circumflex coronary artery; *PAD*, peripheral arterial disease; *ITA*, internal thoracic artery; *SVG*, saphenous vein graft. *Percentage of times the factor appeared in 500 bootstrap models. †Exp(age/50), exponential transformation. ‡$(\text{BMI}/25)^2$, squared transformation. §Log(preoperative cholesterol), logarithmic transformation. ‖Estimate derived by running the model with the same variables for patients with multivessel coronary artery disease. ¶Variables were forced into the model, even though the reliability was low. #Date of operation (years since January 1, 1972).

TABLE E7. Risk factors for renal failure (n = 11,814*)

Factor	Estimate ± SE	*P* value	Reliability (%)†
Demographic data			
Female sex	0.36 ± 0.11	.001	94
Race: black or other (vs white)	0.38 ± 0.13	.004	79
Acuity			
NYHA functional class III-IV	0.50 ± 0.11	<.0001	56
Emergency surgery	1.56 ± 0.21	<.0001	100
Cardiac comorbidity			
Heart failure	0.62 ± 0.11	<.0001	94
LCx system disease‡	0.47 ± 0.16	.003	65
Noncardiac comorbidity			
Diabetes			77
Pharmacologically treated	0.26 ± 0.18	.16	
Insulin treated	0.11 ± 0.11	.3	
PAD	0.42 ± 0.12	.0003	65
Carotid disease	0.39 ± 0.11	.0005	84
Higher creatinine§	1.24 ± 0.087	<.0001	100
Procedure			
ITA graft			62
Single (vs SVG only)	−0.034 ± 0.16	.8	
Bilateral (vs SVG only)	−0.39 ± 0.29	.18	
Bilateral vs single‖	−0.37 ± 0.25	.14	
Incomplete revascularization (vs complete)	−0.02 ± 0.14	.9	3.6¶
Off-pump surgery (vs on-pump)	0.19 ± 0.18	.3	11¶
More recent date of operation#	0.11 ± 0.008	<.0001	100

C-statistic = 0.76. *SE*, Standard error; *NYHA*, New York Heart Association; *LCx*, left circumflex coronary artery; *PAD*, peripheral arterial disease; *ITA*, internal thoracic artery; *SVG*, saphenous vein graft. *Patients with preoperative renal failure (n = 108) were removed from the denominator. †Percentage of times the factor appeared in 500 bootstrap models. ‡Stenosis ≥ 50%. §Log(preoperative creatinine), logarithmic transformation. ‖Estimate derived by running the model with the same variables for patients with multivessel coronary artery disease. ¶Variables were forced into the model, even though the reliability was low. #Date of operation (years since January 1, 1972).

TABLE E8. Risk factors for prolonged ventilation (>24 hours; n = 2272*)

Factor	Estimate ± SE	*P* value	Reliability (%)†
Demographic data			
BMI‡	0.28 ± 0.81	.0005	94
Acuity			
NYHA functional class III-IV	0.71 ± 0.15	<.0001	88
Emergency surgery	1.69 ± 0.41	<.0001	97
Cardiac comorbidity			
Previous MI	0.81 ± 0.16	<.0001	94
Left main disease§	0.61 ± 0.15	<.0001	98
Noncardiac comorbidity			
Diabetes			12‖
Pharmacologically treated	−0.075 ± 0.26	.8	
Insulin treated	−0.029 ± 0.15	.8	
Carotid disease	0.48 ± 0.16	.002	55
Higher creatinine¶	0.58 ± 0.12	<.0001	83
Lower cholesterol#	0.12 ± 0.05	.02	67
Procedure			
ITA graft			79
Single (vs SVG only)	−1.25 ± 0.31	<.0001	
Bilateral (vs SVG only)	−1.95 ± 0.46	<.0001	
Bilateral vs single**	−0.73 ± 0.36	.04	
Incomplete revascularization (vs complete)	−0.091 ± 0.25	.7	2.4‖
Off-pump surgery (vs on-pump)	−0.15 ± 0.23	.5	7.4‖
More recent date of operation††	0.10 ± 0.031	.002	67

C-statistic = 0.73. *SE*, Standard error; *BMI*, body mass index; *NYHA*, New York Heart Association; *MI*, myocardial infarction; *ITA*, internal thoracic artery; *SVG*, saphenous vein graft. *Prolonged ventilation data were available beginning January 2002. †Percentage of times the factor appeared in 500 bootstrap models. ‡$(BMI/25)^2$, squared transformation. §Stenosis ≥ 50%. ‖Variables were forced into the model, even though the reliability was low. ¶Log(preoperative creatinine), logarithmic transformation. #(230/Preoperative cholesterol), inverse squared transformation. **Estimate derived by running the model with the same variables for patients with multivessel coronary artery disease. ††Date of operation (years since January 1, 1972).

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TABLE E9. Effect of HbA1c on deep sternal wound infection (n = 2541*)

Factor	Estimate ± SE	*P* value	Reliability (%)†
Demographic data			
Shorter height‡	2.65 ± 0.79	.0007	71
Noncardiac comorbidity			
Diabetes			42§
Insulin treated	0.63 ± 0.30	.2	
Diet treated	−0.11 ± 0.63	.9	
HbA1c‖	0.62 ± 0.68	.4	22§
Procedure			
ITA graft			71
Single (vs SVG only)	0.31 ± 1.02	.8	
Bilateral (vs SVG only)	0.46 ± 1.14	.7	
Incomplete revascularization (vs complete)	−0.33 ± 0.53	.5	2.4§
Off-pump surgery (vs on-pump)	−0.53 ± 0.45	.2	28§
Earlier date of operation¶	−0.14 ± 0.047	.004	65

C-statistic = 0.70. *HbA1c*, Hemoglobin A1c; *SE*, standard error; *ITA*, internal thoracic artery; *SVG*, saphenous vein graft. *Number of patients with HbA1c values available for analysis. †Percentage of times the factor appeared in 500 bootstrap models. ‡$(180/\text{Height})^2$, inverse squared transformation. §Variables were forced into the model, even though the reliability was low. ‖Log(HbA1c), logarithmic transformation. ¶Date of operation (years since January 1, 1972).

TABLE E10. Incremental risk factors for death after CABG: multivessel disease

Risk factor	Coefficient ± SE	*P* value	Reliability (%)*
Early hazard phase			
Demographic data			
Female sex	0.42 ± 0.10	<.0001	99
Older age†	0.48 ± 0.079	<.0001	100
Acuity			
NYHA functional class			93
II	−0.067 ± 0.019	.0004	
III-IV	0.85 ± 0.22	<.0001	
Emergency surgery	1.43 ± 0.16	<.0001	100
Noncardiac comorbidity			
Diabetes			74
Treated	0.28 ± 0.18	.11	
Insulin-treated	0.20 ± 0.12	.10	
PAD	0.48 ± 0.11	<.0001	84
Previous stroke	0.54 ± 0.14	<.0001	87
Lower cholesterol‡	0.11 ± 0.023	<.0001	59
Higher bilirubin	0.15 ± 0.063	.02	74
Procedure			
Earlier date of operation§	−0.0086 ± 0.0072	.2	24‖
ITA graft			100
SVG (vs SITA)	0.72 ± 0.12	<.0001	
Bilateral (vs SITA)	−0.53 ± 0.36	.14	
Late hazard phase			
Demographic data			
Female sex	0.095 ± 0.033	.005	75
Older age¶	0.97 ± 0.071	<.0001	100
Cardiac comorbidity			
Heart failure	0.46 ± 0.041	<.0001	100
Noncardiac comorbidity			
Diabetes			100
Treated	0.44 ± 0.05	<.0001	
Insulin treated	0.04 ± 0.042	.4	
PAD	0.41 ± 0.034	<.0001	100
Previous MI	0.11 ± 0.028	.0001	99
Previous stroke	0.28 ± 0.05	<.0001	100
Carotid disease	0.11 ± 0.04	.005	90
Higher creatinine#	0.21 ± 0.10	.11	100
Procedure			
ITA graft			100
SVG (vs SITA)	0.20 ± 0.031	<.0001	
Bilateral (vs SITA)	−0.24 ± 0.063	.0001	

SE, Standard error; *NYHA*, New York Heart Association; *PAD*, peripheral arterial disease; *ITA*, internal thoracic artery; *SVG*, saphenous vein graft; *SITA*, single internal thoracic artery; *PAD*, peripheral arterial disease; *MI*, myocardial infarction. *Percentage of times the factor appeared in 500 bootstrap models. †Exp(age/50), exponential transformation. ‡$(1/\text{Cholesterol})^2$, inverse squared transformation. §Date of operation (years since January 1, 1972). ‖Variables were forced into the model, even though the reliability was low. ¶$(50/\text{Age})^2$, inverse squared transformation. #Log(creatinine), logarithmic transformation.

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Chapter 6

Research Question 5—Which Arterial Grafting Strategy Improves Outcomes of CABG in Diabetic Patients?

Based on Publication: Raza S, Blackstone EH, Houghtaling PL, Koprivanac M, Ravichandren K, Javadikasgari H, Bakaeen FG, Svensson LG, Sabik JF 3rd. **Similar Outcomes in Diabetic Patients After CABG With Single ITA Plus Radial Artery Grafting & Bilateral ITA Grafting.** Ann Thorac Surg. 2017;104(6):1923-1932.

6.1 Rationale

We showed in the previous study (chapter 5) that bilateral internal thoracic artery (BITA) grafting with complete revascularization maximizes long-term survival in diabetic patients undergoing CABG, and that off-pump or on-pump surgery can be used with equal effectiveness [1]. However, because BITA grafting, compared to single internal thoracic artery (SITA) grafting, was also associated with increased risk of deep sternal wound infections (DSWI), we recommended that it be used in diabetic patients whose risk of DSWI is low. The radial artery (RA) is another commonly used arterial graft conduit that has been shown to be associated with better clinical and angiographic outcomes than vein grafts [2,3]. Therefore, we sought to determine whether SITA+RA grafting yields outcomes similar to those of BITA grafting in diabetic patients. We hypothesized

that SITA+RA grafting would be associated with a lower occurrence of DSWI and similar long-term survival compared with BITA grafting in diabetic patients undergoing CABG.

6.2 Summary of Study Design & Methods

From January 1994 to January 2011, 1,325 diabetic patients with multisystem coronary artery disease (CAD) underwent primary isolated CABG with either (i) SITA plus RA with or without saphenous vein grafts (hereafter referred to as SITA+RA; n=965) or (ii) BITA with or without saphenous vein grafts (hereafter referred to as BITA; n=360). An internal thoracic artery was used in all patients to graft the left anterior descending coronary artery. The majority (88%) of coronary arteries with ≥50% stenosis that were grafted by either a radial artery or a second ITA were severely stenosed (≥70%); only 12% were moderately stenosed.

The endpoints were in-hospital outcomes and time-related mortality. The median follow-up was 7.4 years, with a total follow-up of 9,162 patient-years. Propensity-score matching was performed to identify 282 well-matched pairs for adjusted comparisons.

6.3 Summary of Results

The unadjusted in-hospital mortality was 0.52% for SITA+RA and 0.28% for BITA grafts, and the prevalence of DSWI was 3.2% and 1.7%, respectively. In

propensity-matched pairs, all hospital outcomes and lengths of stay were similar in the 2 groups.

The unadjusted survival at 1, 5, 10, and 14 years was 97%, 88%, 68% and 51% for the SITA+RA group and 97%, 95%, 80%, and 66% for the BITA group (see Figure 1A of manuscript). The instantaneous risk of death was substantially elevated early after surgery and then gradually decreased over the first 6 months for both groups. Thereafter, the risk of death gradually increased over time for both (see Figure 1B of manuscript).

In the propensity-matched patients, the survival was similar for the 2 groups: at 1, 5, 10, and 14 years, it was 97%, 90%, 70%, and 58% for the SITA+RA group and 97%, 93%, 79%, and 64% for the BITA group, respectively (early *P*=.8, late *P*=.2; see Figure 2A of manuscript). The instantaneous risk of death was substantially elevated early after surgery for both groups and gradually decreased during the first 6 months for SITA+RA patients and the first 12 months for BITA patients. Thereafter, the risk of death gradually increased over time, similarly for both groups (see Figure 2B of manuscript).

6.4 Findings Compared to Other Studies

A number of studies are available comparing the outcomes of SITA+RA vs. BITA grafting in patients undergoing CABG [4], but data regarding use of SITA+RA vs. BITA grafting specifically in diabetic patients are scarce [5,6]. Supporting our findings, a study by Hoffman et al [5] showed that among 202 matched pairs from each group, diabetic and non-diabetic patients, undergoing

CABG with left ITA (LITA) grafting of the LAD (LITA-LAD grafting), long-term survival was similar for those receiving either a right ITA (RITA) or RA graft to the circumflex system. However, RA grafting was associated with a lower prevalence of DSWI and respiratory complications. However, RA grafting was associated with lower prevalence of DSWI and respiratory complications. Contrary to our findings, a subgroup analysis in a study by Raja and colleagues [6] showed a trend toward increased risk for late mortality (hazard ratio [HR] 3.3; 95% confidence interval [CI] 1.1-9.7) and a need for repeat revascularization (HR 3.1; 95% CI 1.2-8.2) with RA (n=124) grafting vs. RITA (n=103) grafting in diabetic patients undergoing CABG with LITA-LAD.

Ten-year results of the Radial Artery Patency and Clinical Outcomes Trial (RAPCO) [7] showed that in younger patients (<70 years of age, or <60 if diabetic) undergoing CABG with a LITA-LAD graft, the use of the RA as a second conduit confers superior survival despite equivalent patency to the RITA. Contrary to this finding, a recent meta-analysis of 8 propensity score–matching studies [4] comparing long-term survival of patients (not specifically diabetic patients) receiving a RITA vs. RA as a second conduit for CABG showed that RITA use was associated with superior long-term survival and freedom from repeat revascularization, with similar operative mortality and prevalence of DSWI when the skeletonized harvesting technique was used. Why, then, is the long-term difference in survival among patients receiving RA or RITA grafts observed in clinical trials and meta-analyses but not in studies specifically involving diabetic patients? The answer likely lies in differences between the life

expectancies of diabetic and non-diabetic patients. Because diabetic patients have shorter life expectancies than non-diabetic patients, the long-term survival benefit of one type of second arterial graft over another may not be observed in diabetic patients. However, this hypothesis requires further testing.

6.5 Addition to Literature in Light of Systematic Review

A systematic literature search was done to identify studies that already existed on this topic at the time of paper preparation/publication, so the addition to the literature that the study made could be effectively evaluated in light of existing knowledge on the subject. Details of this systematic review are given in the Appendix (see section 10.5). Briefly, we searched the literature for studies reporting the clinical outcomes of SITA plus RA grafting vs. BITA grafting in diabetic vs. non-diabetic patients. Studies not reporting clinical outcomes were excluded. Only two studies were identified that met the specified criteria. These included the studies by Hoffman et al [5] and Raja et al [6] described in the previous sections. However, these studies showed conflicting results. The study by Hoffman et al supported our finding that both arterial grafting strategies yield similar long-term survival in diabetic patients, but the study by Raja et al, contrary to our findings, showed that BITA grafting was associated with better long-term survival in diabetic patients. The study by Hoffman et al was based on 908 diabetic patients, which yielded 202 match pairs for adjusted comparison, whereas the study by Raja et al was based on 227 diabetic patients. I believe that our study, by virtue of its larger sample size (1325 diabetic patients) and

robust propensity-matched analysis yielding 282 well-matched patient pairs, provides strong supporting evidence for our assertions and thus represents a valuable addition to the literature on this topic.

6.6 Critical Commentary

Help was taken from Critical Appraisal Skills Program (CASP) checklist for Cohort Studies for critical commentary on this manuscript. Available at: http://www.casp-uk.net/casp-tools-checklists.

6.6.1 Rationale

As mentioned in the introduction section of the manuscript, and in the background of the discussion section, this study addressed a clearly focused issue of identifying an arterial grafting strategy, SITA plus RA grafting or BITA grafting, that results in better short- and long-term outcomes in these patients. The introduction section of the manuscript, and the background of the discussion section of the paper, clearly explain the rationale and importance of the research question being addressed.

6.6.2 Study Design

This was a retrospective cohort study. An RCT comparing long-term outcomes of patients undergoing CABG with either BITA grafts or single ITA plus radial artery grafts would have been ideal. However, any meaningful trial comparing these strategies would have needed long-term follow-up (at least 10 years)

which is challenging and expensive. Therefore, studying this research question in a retrospective fashion was reasonable, and perhaps the only feasible way to study >10-year outcomes of CABG with BITA vs. single ITA plus radial artery grafting in diabetic patients.

6.6.3 Participant Selection

As for the other studies, Cleveland Clinic's Cardiovascular Registry (CVIR) was used to identify the desired study population. Pharmacologically treated and diet-controlled diabetic patients were included. Patients with unknown diabetic status were excluded. We were unable to discriminate between type I and type II diabetes. This maybe important because the long-term survival after CABG of type 1 diabetic patients is worse than the survival of type II diabetic patients [8]. However, this was not mentioned in the limitations section of the paper. Patients were reliably classified into groups, BITA and SITA+RA, as these details are clearly mentioned in operative reports.

It was not mentioned in the paper whether this study required any additional data-collection apart from the data retrieved from CVIR. No additional data was collected for this study. However, chart review was done for verification purposes of unusual combinations of grafts.

It was also not mentioned in the paper why the patients were included from 1994 onwards instead of 1972, like the previous studies. The reason was that CABG cases in which radial artery grafts were used in diabetic patients were only available from 1994 onwards. There were not many radial artery

cases before that year. Though CABG cases with BITA grafts used in diabetic patients were available for comparison from much earlier years, we didn't include them for fair comparison and only compared patients who underwent CABG with SITA+RA grafts from 1994 to 2011 with patients who underwent CABG with BITA grafts from 1994 to 2011. Furthermore, to adjust for medical and surgical advancements from 1994 to 2011, we adjusted for the date of surgery in the model to strengthen the results and conclusions that could be drawn from the analysis.

6.6.4 Sample Size

The unadjusted survival difference between the two study groups at 14 years was 15% (14-year survival after CABG: 51% for SITA+RA group and 66% for BITA group). To detect a difference of this magnitude, with a type I error rate (significance level) of 5%, and 360 patients in BITA group and 965 in SITA plus RA group, our unadjusted comparison was powered enough (>99% power). To detect the same 15% difference in survival, our propensity-matched comparison was powered enough (>90% power) with a type I error rate of 5%, and 268 patients in each group. However, to detect a difference in survival of 10%, our propensity-matched comparison was only 65% powered. Please note that some criticize the idea of retrospective power calculation. However, it was done only to provide an approximate idea regarding statistical power of the study.

6.6.5 End-points

The end-points of the study included hospital outcomes and long-term mortality. Please see 3.6.5 for a critical appraisal of our long-term mortality follow-up.

6.5.6 Data Analysis

As mentioned in the paper, the patient characteristics significantly differed between the two groups. To adjust for imbalances in measured characteristics and for fair comparison of outcomes, we performed matching based on propensity scores. A number of variables (detailed in the appendix of the paper) were considered in this analysis ranging from demographic variables, to cardiac and non-cardiac comorbidities, and date of operation. However, any patient factors not included in the propensity model that importantly affect outcomes may have biased our findings.

For the benefits of matching compared to other propensity score techniques please see "*Propensity Matching*" under 3.6.6.

Survival was assessed nonparametrically using the Kaplan-Meier method, and parametrically using a multiphase hazard model. Please see section 2.6.6 for details regarding this model and for explanation regarding use of 68% confidence interval.

6.4.7 Results & Discussion

The study showed that BITA versus SITA+RA grafting was associated with similar survival in diabetic patients undergoing CABG.

Survival was reported for up to 14 years after CABG. However, absolute risk reduction and hazard ratio were not reported in the manuscript. The results are believable because the study compared outcomes in a large number of diabetic and non-diabetic patients using data from a well-regarded registry and took appropriate measures to control for confounding.

The discussion clearly mentioned the principal findings of the study, and in the section of “findings in context”, we discussed the existing knowledge on the topic and compared our findings with the results of other studies. The limitations were also clearly mentioned.

The conclusions of the paper were supported by the data presented and mentioned the clinical implications of the study instead of just summarizing the results again.

6.7 References

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Similar Outcomes in Diabetes Patients After Coronary Artery Bypass Grafting With Single Internal Thoracic Artery Plus Radial Artery Grafting and Bilateral Internal Thoracic Artery Grafting

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Background. The purpose of this study was to determine in patients with diabetes mellitus whether single internal thoracic artery (SITA) plus radial artery (RA) grafting yields outcomes similar to those of bilateral internal thoracic artery (BITA) grafting.

Methods. From January 1994 to January 2011, 1,325 diabetic patients underwent primary isolated coronary artery bypass graft surgery with either (1) SITA plus RA with or without saphenous vein (SV) grafts (n = 965) or (2) BITA with or without SV grafts (n = 360); an internal thoracic artery was used in all patients to graft the left anterior descending coronary artery. Endpoints were in-hospital outcomes and time-related mortality. Median follow-up was 7.4 years, with a total follow-up of 9,162 patient-years. Propensity score matching was performed to identify 282 well-matched pairs for adjusted comparisons.

Results. Unadjusted in-hospital mortality was 0.52% for SITA plus RA with or without SV grafts and 0.28% for BITA with or without SV grafts, and prevalence of deep sternal wound infection was 3.2% and 1.7%, respectively. Unadjusted survival at 1, 5, 10, and 14 years was 97%, 88%, 68%, and 51% for SITA plus RA with or without SV grafts, and 97%, 95%, 80%, and 66% for BITA with or without SV grafts, respectively. Among propensity-matched patients, in-hospital mortality (0.35% versus 0.35%) and prevalence of deep sternal wound infection (1.4% versus 1.4%) were similar ($p > 0.9$) in the two groups, as was 1-, 5-, 10-, and 14-year survival: 97%, 90%, 70%, and 58% for SITA plus RA with or without SV grafting versus 97%, 93%, 79%, and 64% for BITA with or without SV grafting, respectively (early $p = 0.8$, late $p = 0.2$).

Conclusions. For diabetic patients, SITA plus RA with or without SV grafting and BITA with or without SV grafting yield similar in-hospital outcomes and long-term survival after coronary artery bypass graft surgery. Therefore, both SITA plus RA and BITA plus SV grafting should be considered for these patients.

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Forty percent of patients undergoing coronary artery bypass grafting (CABG) today have diabetes mellitus [1]. Use of arterial grafts, compared with venous grafts, is associated with better outcomes after CABG for diabetic patients [2]. However, it remains unclear which arterial grafting strategy—single internal thoracic artery (SITA) plus radial artery (RA) grafting or bilateral internal thoracic artery (BITA) grafting—results in better short- and long-term outcomes for these patients. Therefore, we sought to determine for diabetic patients whether SITA plus RA grafting yields in-hospital outcomes and long-term survival similar to those of BITA grafting.

Patients and Methods

From January 1994 to January 2011, 1,325 diabetic patients with multisystem coronary artery disease underwent

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Abbreviations and Acronyms

BITA = bilateral internal thoracic artery
CABG = coronary artery bypass grafting
DSWI = deep sternal wound infection
EF = ejection fraction
ITA = internal thoracic artery
LITA = left internal thoracic artery
RA = radial artery
RITA = right internal thoracic artery
SITA = single internal thoracic artery

primary isolated CABG with either (1) SITA plus RA with or without saphenous vein grafts (hereafter referred to as SITA plus RA; n = 965) or (2) BITA with or without saphenous vein grafts (hereafter referred to as BITA; n = 360). An internal thoracic artery (ITA) was used in all patients to graft the left anterior descending coronary artery (LAD). Mean age was 59 ± 8.8 years, and 83% were men (Table 1).

Patients were identified and preoperative, operative, and postoperative variables (Appendix E1) retrieved from the prospective Cleveland Clinic Cardiovascular Information Registry. This database is populated concurrently with patient care and has been approved for use in research by the Institutional Review Board, with patient consent waived.

Variables and Definitions

A coronary artery system was considered importantly stenotic if it contained 50% or greater diameter obstruction. The majority (88%) of coronary arteries with 50% or greater stenosis that were grafted by either a radial artery or a second ITA were severely stenosed (70% or more); only 12% were moderately stenosed. Incomplete revascularization was defined as failure to graft any coronary system containing 50% or more stenosis, or both LAD and circumflex coronary artery systems for 50% or greater left main trunk stenosis. Left ventricular function was echocardiographically graded as normal (ejection fraction [EF] 60% or more), mild (EF 40% to 59%), moderate (EF 25% to 39%), or severe (EF less than 25%).

Endpoints

Endpoints were (1) in-hospital adverse outcomes defined as for The Society of Thoracic Surgeons National database (http://www.ctsnet.org/file/rptdataspecifications252_1_forvendorspgs.pdf); and (2) time-related mortality. Vital status after hospital discharge was obtained by routine anniversary follow-up questionnaires supplemented with data from the Social Security Death Master File [3, 4], accessed on October 27, 2011, with a closing date of April 27, 2011. A total of 9,162 patient-years of follow-up data were available for analyses. Median follow-up was 7.4 years, with 10% of survivors followed for at least 13 years.

Statistical Analysis

All analyses were performed using SAS version 9.4 statistical software (SAS Institute, Cary, NC).

LONG-TERM SURVIVAL. Survival was assessed nonparametrically using the Kaplan-Meier method [5] and parametrically using a multiphase hazard model [6]. The latter involved resolving the number of hazard phases for instantaneous risk of death (hazard function) and estimating shaping parameters (for details, see: www.lerner.ccf.org/qhs/software/hazard).

PROPENSITY SCORE MATCHING. Because patient characteristics differed between the two groups (SITA plus RA and BITA; Table 1), in the spirit of a "natural experiment" we attempted to fairly compare outcomes using propensity score–based matching [7–9]. That was accomplished in two steps. First, a parsimonious multivariable logistic regression was used to identify differences in preoperative characteristics of patients in the SITA plus RA group and BITA group to obtain insight into these differences (see Appendix E1 for list of variables analyzed). Bootstrap bagging for variable selection, with automated analysis of 500 resampled data sets, was used to accomplish this, followed by tabulating the frequency of both single factors and closely related clusters of factors [10]. We retained factors that occurred in 50% or more of the bootstrap models (Supplemental Table E1). The C-statistic for this parsimonious model was 0.83. Second, the parsimonious model was augmented into a saturated propensity model by including patient characteristics that were not statistically significantly different between groups, but represented demographic, cardiac, and noncardiac comorbidities not represented (see Appendix E1). The C-statistic for this model was 0.84. A propensity score representing the probability of BITA group membership given the variables included in the propensity model, regardless of whether the patient received BITA grafts, was then calculated for each patient. A greedy matching strategy [11] based on propensity scores alone was used to match patients receiving SITA plus RA and BITA, yielding 282 well-matched pairs (78% of possible matches; Supplemental Fig E1). BITA cases with propensity scores deviating more than 0.10 from those of SITA plus RA cases were considered unmatched. Standardized differences demonstrated that covariable balance was achieved across nearly all variables (Supplemental Fig E2), and the two groups were balanced with respect to the target vessel for RA and second internal thoracic artery graft (Table 2).

MISSING VALUES. A number of variables examined in multivariable analyses had missing values (see "Patients with data available" in Table 1). Of the 35 variables used for the propensity score, 18 had no missing data, 8 had more than 0% but less than 2% missing data, 6 had between 10% and 15%, and 3 had greater than 20% missing data. The pattern of missing data appeared arbitrarily, so "missing at random" was assumed. We used fivefold multiple imputation [12] with a Markov chain Monte Carlo technique to impute missing values (SAS PROC MI; SAS Institute, Cary, NC). In multivariable

Table 1. Patient Characteristics Before and After Propensity Matching

	Before Matching					After Matching				
	SITA+RA (n = 965)		BITA (n = 360)			SITA+RA (n = 282)		BITA (n = 282)		
Characteristics	n[a]	No. (%) or Mean ± SD	n[a]	No. (%) or Mean ± SD	*p* Value	n[a]	No. (%) or Mean ± SD	n[a]	No. (%) or Mean ± SD	*p* Value
Demographics										
Age, years	965	60 ± 8.8	360	57 ± 8.7	<0.0001	282	58 ± 8.5	282	58 ± 8.6	0.6
Body mass index, kg/m^2	964	31 ± 6.0	360	29 ± 4.3	<0.0001	282	29 ± 5.1	282	29 ± 4.4	0.17
Female	965	193 (20)	360	37 (10)	<0.0001	282	36 (13)	282	31 (11)	0.5
Symptoms										
NYHA functional class	965		360		<0.0001	282		282		>0.9
I		122 (13)		80 (22)			54 (19)		57 (20)	
II		511 (53)		199 (55)			160 (57)		154 (55)	
III		155 (16)		37 (10)			30 (11)		31 (11)	
IV		177 (18)		44 (12)			38 (13)		40 (14)	
Prior myocardial infarction	965	590 (61)	360	184 (51)	0.001	282	149 (53)	282	145 (51)	0.7
Left ventricular dysfunction	797		323		0.005	237		259		0.16
None		438 (55)		199 (62)			153 (65)		161 (62)	
Mild		138 (17)		55 (17)			43 (18)		43 (17)	
Mild to moderate		36 (4.5)		14 (4.3)			11 (4.6)		14 (5.4)	
Moderate		80 (10)		34 (11)			14 (5.9)		26 (10)	
Moderate to severe		51 (6.4)		3 (0.93)			8 (3.4)		2 (0.77)	
Severe		54 (6.8)		18 (5.6)			8 (3.4)		13 (5.0)	
Noncardiac comorbidities										
COPD	965	99 (10)	360	21 (5.8)	0.01	282	14 (5.0)	282	17 (6.0)	0.6
Stroke	965	70 (7.3)	360	11 (3.1)	0.004	282	10 (3.5)	282	10 (3.5)	>0.9
Carotid disease	965	295 (31)	360	82 (23)	0.005	282	67 (24)	282	72 (26)	0.6
Cholesterol, mg/dL										
High-density lipoprotein	695	40 ± 10	281	40 ± 10	0.9	204	41 ± 11	222	40 ± 10	0.3
Low-density lipoprotein	688	110 ± 41	278	116 ± 50	0.17	202	112 ± 44	219	114 ± 48	0.8
Diabetes mellitus	965		360		0.01	282		282		0.7
Pharmacologically treated		849 (88)		298 (83)			227 (80)		231 (82)	
Diet controlled		116 (12)		62 (17)			55 (20)		51 (18)	
Bilirubin, mg/dL[b]	805	0.3/0.5/0.8	333	0.4/0.6/0.9	0.003	236	0.4/0.6/0.9	260	0.4/0.6/0.9	0.4
Creatinine, mg/dL	944	1.04 ± 0.57	356	1.08 ± 0.69	0.008	275	1.07 ± 0.78	278	1.07 ± 0.70	0.2
Triglycerides, mg/dL	693	91/159/293	282	78/140/286	0.004	202	84/149/237	223	82/145/290	0.5
Coronary anatomy										
No. systems diseased, ≥50% stenosis	965		360		0.7	282		282		0.8
0[c]		5 (0.51)	360	2 (0.56)			1 (0.35)		1 (0.35)	
1[d]		17 (1.8)		4 (1.1)			4 (1.4)		4 (1.4)	

(*Continued*)

ADULT CARDIAC

Table 1. Continued

Characteristics	Before Matching						After Matching					
	SITA+RA (n = 965)		BITA (n = 360)				SITA+RA (n = 282)		BITA (n = 282)			
	n[a]	No. (%) or Mean ± SD	n[a]	No. (%) or Mean ± SD	*p* Value		n[a]	No. (%) or Mean ± SD	n[a]	No. (%) or Mean ± SD	*p* Value	
2		236 (24)		97 (27)				81 (29)		76 (27)		
3		707 (73)		257 (71)				196 (70)		201 (71)		
Left main trunk disease	708	179 (25)	343	68 (20)	0.05		238	47 (20)	267	58 (22)	0.6	
LAD system disease	957	933 (97)	359	350 (97)	>0.9		280	275 (98)	281	273 (97)	0.4	
LCx system disease	929	811 (87)	359	309 (86)	0.6		274	235 (86)	281	240 (85)	0.9	
RCA system disease	940	866 (92)	356	310 (87)	0.005		275	244 (89)	279	246 (88)	0.8	
Procedural details												
Incomplete revascularization	965	90 (9.3)	360	34 (9.4)	>0.9		282	21 (7.4)	282	31 (11)	0.15	
On-pump CABG	965	858 (89)	360	334 (93)	0.04		282	260 (92)	282	259 (92)	0.9	
Jan 1, 1994, to index operation, years	965	6.5 ± 3.05	360	7.3 ± 5.2	0.4		282	7.1 ± 4.5	282	7.2 ± 4.5	0.9	

[a] Patients with data available. [b] Values are 15th/50th/85th percentiles. [c] Patients with left main trunk disease. [d] Patients with left main trunk disease plus one-system disease.

BITA = bilateral internal thoracic artery; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; No. = number; NYHA = New York Heart Association; RCA = right coronary artery; SITA+RA = single internal thoracic artery plus radial artery.

modeling, for each imputed complete data set, we estimated the regression coefficients and their variance–covariance matrix. Then, following Rubin [12], we combined estimates from the five models (SAS PROC MIANALYZE; SAS Institute) to yield final regression coefficient estimates, the variance–covariance matrix, and *p* values.

PRESENTATION. Continuous variables are summarized as mean ± SD, or 15th, 50th (median), and 85th percentiles when values were skewed; comparisons were made using Wilcoxon rank sum (nonparametric) tests. Categoric variables are summarized by frequencies and percentages; comparisons were made using the χ^2 test or Fisher's exact test when the frequency was less than 5. Transformation of scale of continuous variables was necessary to meet statistical model assumptions; therefore, results of logistic and multiphase hazard models are presented with their coefficients rather than odds or hazard ratios. Uncertainty is expressed by confidence limits equivalent to ±1 SE (68%).

Results

Patient Characteristics

Compared with patients receiving BITA grafts, patients receiving SITA plus RA grafts were older and more likely to be overweight and female (Table 1, Supplemental Table E1). In addition, they were more likely to have symptomatic heart failure, prior stroke, carotid disease, hypertension, and medically treated diabetes.

Hospital Outcomes

Unadjusted in-hospital mortality was 0.52% for SITA plus RA and 0.28% for BITA grafts, and prevalence of deep sternal wound infection (DSWI) was 3.2% and 1.7%, respectively (Table 3). In propensity-matched pairs, all hospital outcomes and lengths of stay were similar in the two groups (Table 3).

Long-Term Survival

Unadjusted survival at 1, 5, 10, and 14 years was 97%, 88%, 68%, and 51%, respectively, for the SITA plus RA group and 97%, 95%, 80%, and 66% for the BITA group (Fig 1A). Instantaneous risk of death was substantially elevated early after surgery and then gradually decreased over the first 6 months for both groups. Thereafter, risk of death gradually increased over time for both (Fig 1B).

In propensity-matched patients, survival was similar in the two groups: at 1, 5, 10, and 14 years, it was 97%, 90%, 70%, and 58% for the SITA plus RA group and 97%, 93%, 79%, and 64% for the BITA group, respectively (early $p = 0.8$, late $p = 0.2$; Fig 2A). Instantaneous risk of death was substantially elevated early after surgery for both groups and gradually decreased during the first 6 months for SITA plus RA patients and the first 12 months for BITA patients. Thereafter, risk of death gradually increased over time, similarly for both groups (Fig 2B).

Long-term survival for unmatched SITA plus RA patients was lower than for unmatched BITA patients (p [log rank] = 0.005; Supplemental Fig E3).

Table 2. Number of Bypasses by Conduit Type and Coronary Artery System

	Before Matching		After Matching	
	SITA+RA (n = 965)	BITA (n = 360)	SITA+RA (n = 282)	BITA (n = 282)
CABG Details	No. (%)	No. (%)	No. (%)	No. (%)
First ITA graft				
To LAD[a]	965 (100)	360 (100)	282 (100)	282 (100)
To LCx	3 (0.31)	3 (0.83)	1 (0.35)	2 (0.71)
To RCA	0 (0)	0 (0)	0 (0)	0 (0)
To diagonal	195 (20)	65 (18)	80 (28)	58 (21)
Radial artery graft				
To LAD	11 (1.1)	0 (0)	2 (0.71)	0 (0)
To LCx	753 (78)	0 (0)	230 (82)	0 (0)
To RCA	184 (19)	0 (0)	52 (18)	0 (0)
To diagonal	141 (15)	0 (0)	32 (11)	0 (0)
Second ITA graft				
To LAD	0 (0)	1 (0.28)	0 (0)	1 (0.35)
To LCx	0 (0)	270 (75)	0 (0)	207 (73)
To RCA	0 (0)	61 (17)	0 (0)	51 (18)
To diagonal	0 (0)	46 (13)	0 (0)	38 (13)

[a] Most internal thoracic artery (ITA) grafts to the left anterior descending coronary artery (LAD) were left rather than right: 959 (99%) in the single internal thoracic artery plus radial artery (SITA+RA) group and 260 (72%) in the bilateral internal thoracic artery (BITA) group. Among propensity-matched patients, 280 (99%) of the patients in the SITA+RA group and 214 (76%) in the BITA group had a left ITA to LAD graft.

CABG = coronary artery bypass grafting; LCx = left circumflex coronary artery; No. = number; RCA = right coronary artery.

Comment

Background

We have previously shown that BITA grafting with complete revascularization maximizes long-term survival of diabetic patients undergoing CABG and that off-pump or on-pump surgery can be used with equal effectiveness [2]. However, because BITA grafting was also associated with increased risk of DSWI, we recommended that it be used in diabetic patients whose risk of DSWI is low. The RA is another commonly used arterial graft conduit that has been shown to be associated with better clinical and

Table 3. In-Hospital Outcomes

	Before Matching		After Matching		
	SITA+RA (n = 965)	BITA (n = 360)	SITA+RA (n = 282)	BITA (n = 282)	
Outcome	No. (%) or Mean ± SD	No. (%) or Mean ± SD	No. (%) or Mean ± SD	No. (%) or Mean ± SD	*p* Value
Death	5 (0.52)	1 (0.28)	1 (0.35)	1 (0.35)	>0.9
Deep sternal wound infection	31 (3.2)	6 (1.7)	4 (1.4)	4 (1.4)	>0.9
Septicemia	21 (2.2)	2 (0.56)	5 (1.8)	2 (0.71)	0.2
Permanent stroke	11 (1.1)	3 (0.83)	3 (1.1)	3 (1.1)	>0.9
Perioperative myocardial infarction	3 (0.31)	2 (0.56)	1 (0.35)	1 (0.35)	>0.9
Reoperation for bleeding or tamponade	14 (1.5)	5 (1.4)	4 (1.4)	3 (1.1)	0.7
Atrial fibrillation	231 (24)	78 (22)	68 (24)	59 (21)	0.4
Renal failure	52 (5.4)	10 (2.8)	8 (2.8)	9 (3.2)	0.8
Renal failure requiring dialysis	5 (0.52)	0 (0)	2 (0.71)	0 (0)	0.16
Prolonged ventilation, >24 hours	16/228 (7.0)	8/169 (4.7)	7/94 (7.4)	6/132 (4.5)	0.4
Length of stay					
>14 days	51 (5.3)	15 (4.2)	11 (3.9)	11 (3.9)	>0.9
Hospital, days	9.8 ± 6.0	8.6 ± 5.7	9.0 ± 4.4	9.0 ± 6.0	0.3
Operative, days	7.4 ± 4.9	7.2 ± 5.1	7.0 ± 3.1	7.1 ± 5.3	0.9
Intensive care unit, hours[a]	24/24/72	24/24/72	24/24/72	24/24/70	0.4

[a] Values are 15th/50th/85th percentiles.

BITA = bilateral internal thoracic artery; No. = number; RA = radial artery; SITA = single internal thoracic artery.

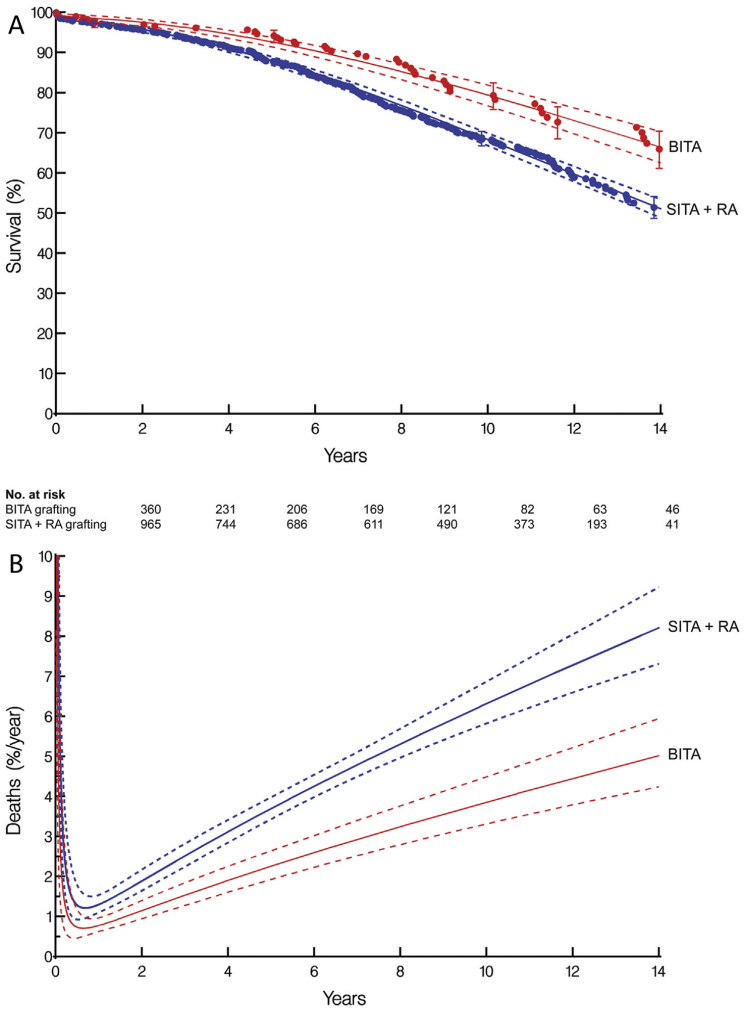


Fig 1. Unadjusted time-related death stratified by single internal thoracic artery plus radial artery (SITA + RA [blue]) and bilateral internal thoracic artery (BITA [red] grafting), n = 1,325. Solid lines are parametric estimates enclosed within dashed 68% confidence bands equivalent to ±1 SE. (A) Survival. Each symbol represents a death, and vertical bars are confidence limits equivalent to ±1 SE. (B) Instantaneous risk of death.

angiographic outcomes than vein grafts [13, 14]. Therefore, we sought to determine in diabetic patients whether SITA plus RA grafting yields outcomes similar to those of patients who undergo BITA grafting. We hypothesized that SITA plus RA grafting would be associated with lower occurrence of DSWI and similar long-term survival compared with BITA grafting in diabetic patients undergoing CABG.

Principal Findings

We found that SITA plus RA grafting is not associated with lower occurrence of DSWI compared with BITA grafting in diabetic patients undergoing CABG. Both surgical strategies carry similar surgical risk and yield similar long-term survival after CABG in diabetic patients.

Findings in Context

A number of studies are available comparing the outcomes of SITA plus RA versus BITA grafting in patients undergoing CABG [15], but data regarding use of SITA plus RA versus BITA grafting specifically in diabetic patients are scarce [16, 17]. Supporting our findings, Hoffman and colleagues [16] showed that among 202

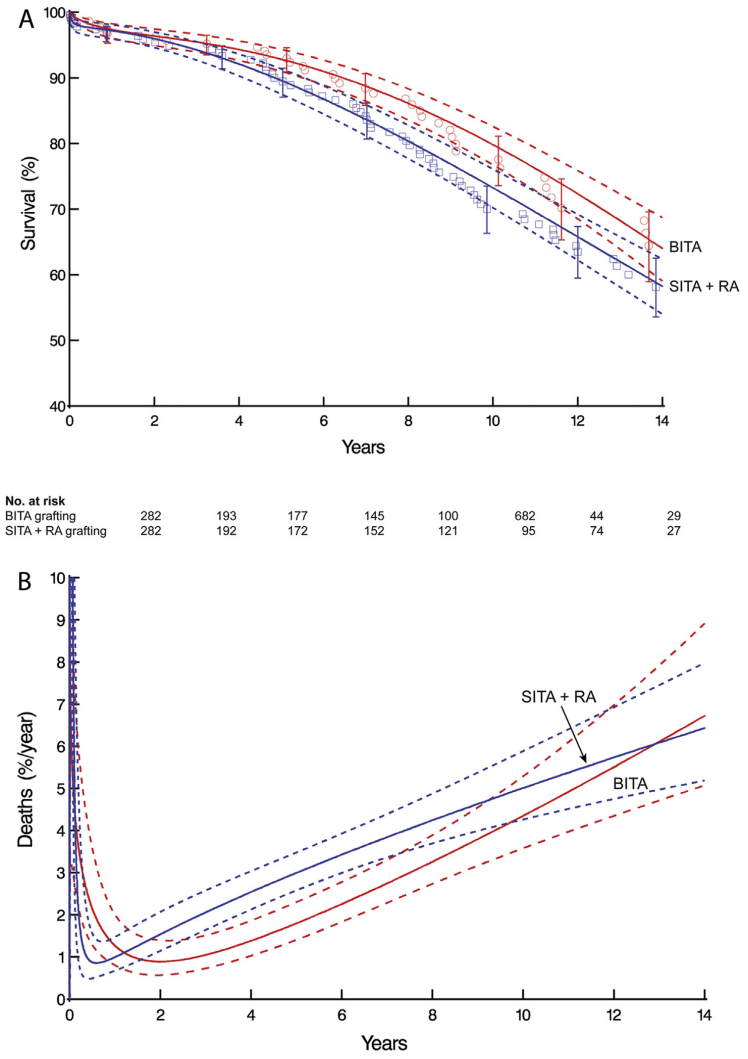


Fig 2. Adjusted (propensity-matched) time-related death stratified by single internal thoracic artery plus radial artery (SITA + RA [blue]) and bilateral internal thoracic artery (BITA [red] grafting), n = 564. Solid lines are parametric estimates enclosed within dashed 68% confidence bands equivalent to ±1 SE. (A) Survival. Each symbol represents a death, and vertical bars are confidence limits equivalent to ±1 SE. (B) Instantaneous risk of death.

well-matched diabetic patients undergoing CABG with left ITA (LITA) grafting of the LAD (LITA-LAD grafting), long-term survival was similar for those receiving either a right ITA (RITA) or RA graft to the circumflex system. However, RA grafting was associated with lower prevalence of DSWI and respiratory complications. Contrary to our findings, a subgroup analysis in a study by Raja and colleagues [17] showed a trend toward increased risk for late mortality (hazard ratio 3.3, 95% confidence interval 1.1 to 9.7) and need for repeat revascularization (hazard ratio 3.1, 95% confidence interval 1.2 to 8.2) with RA (n = 124) grafting versus RITA (n = 103) grafting in diabetic patients undergoing CABG with LITA-LAD. We believe that our study, by virtue of its larger sample size and robust propensity-matched analysis, more accurately reflects the truth.

Ten-year results of the Radial Artery Patency and Clinical Outcomes Trial (RAPCO) [18] showed that in

younger patients (less than 70 years of age, or less than 60 if diabetic) undergoing CABG with a LITA-LAD graft, use of the RA as a second conduit confers superior survival despite equivalent patency to the RITA. Contrary to this finding, a recent meta-analysis of eight propensity score matching studies [15] comparing long-term survival of patients (not specifically diabetic patients) receiving a RITA versus RA as a second conduit for CABG showed that RITA use was associated with superior long-term survival and freedom from repeat revascularization, with similar operative mortality and prevalence of sternal wound complications when the skeletonized harvesting technique was used. Why, then, is the long-term difference in survival among patients receiving RA or RITA grafts observed in clinical trials and meta-analyses but not in studies specifically involving diabetic patients? The answer likely lies in differences between the life expectancies of diabetic and nondiabetic patients. Because diabetic patients have shorter life expectancies than nondiabetic patients, the long-term survival benefit of one type of second arterial graft over another may not be observed in diabetic patients. However, this hypothesis requires further testing.

We believe that clinical decision making regarding the arterial grafting strategy in diabetic patients should focus on tailoring the operation to the individual patient. Therefore, although we recommend that BITA grafting be used in all diabetic patients whose risk of developing DSWI is low, in diabetic patients at high risk of DSWI, such as obese diabetic women with diffuse atherosclerotic burden, use of SITA plus RA grafting should be considered.

Study Limitations

This was a nonrandomized, observational, comparative effectiveness study, and therefore patient selection may play a role in our findings. To account for this, we used propensity score matching to identify similar groups of patients for fair comparison of outcomes. However, any patient factors not included in the propensity model that importantly affect outcomes might bias our findings. No angiographic patency and repeat coronary intervention data were included in the study. This was also a single-center study, and hence findings may not be generalizable.

Conclusion

For diabetic patients, SITA plus RA grafting and BITA grafting yield similar in-hospital outcomes and long-term survival after CABG. Therefore, both SITA plus RA grafting and BITA grafting should be considered in these patients.

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DISCUSSION

DR WALTER MERRILL (Nashville, TN): Dr Raza and his colleagues from the Cleveland Clinic are to be congratulated for bringing to our attention another contribution of the understanding of coronary artery disease and coronary artery bypass operations. We owe much of our understanding of this condition to the authors of this study and so many of their predecessors from Cleveland. They have tackled the problem of reporting the results of operations in more than 1,000 diabetic patients, and their study includes appropriate statistical manipulation of their patient population in order that we might get a better grasp on which operation—single internal thoracic artery (SITA) plus radial artery versus bilateral internal thoracic artery (BITA)—should be used in these patients. The findings from their study have demonstrated that it does not matter. The results, both short term and longer term, are similar. I have three questions for Dr Raza.

Firstly, in all cases, the left anterior descending artery (LAD) was grafted by an internal mammary artery. Does it matter if the graft is from the left side or right side?

Secondly, an artery was considered diseased if it had greater than a 50% diameter obstruction. This might be problematic, especially if a radial artery was used to graft this vessel. Was this done in some instances and what were the consequences?

And thirdly, we know that survival data from both groups were comparable, but do you know anything about patency or reinterventions that might have been carried out on these patients? Thank you.

DR RAZA: Thank you, Dr Merrill, for your encouraging comments. Regarding your first question about left versus a right ITA graft to the LAD, we did not specifically look into this, but we know from other studies that the patency of left and right ITAs is similar. However, in our study, most of the patients, 99% in the single ITA plus radial artery graft group and 72% in the BITA group, had a left ITA to the LAD.

Regarding your second question, we did consider 50% stenosis significant enough for grafting, but the majority, about 88% of the coronary arteries that were grafted by either a radial artery or second ITA, had severe ($\geq$ 70%) stenosis. Therefore, the majority of the coronary arteries that were grafted either by a radial artery or a second ITA were in the severe and not the moderate stenosis range.

Regarding your third question about whether we studied the angiographic outcomes or reinterventions on these patients, the answer is that we did not, but we are in the process of looking into the angiographic outcomes of radial artery grafts, particularly in diabetic patients, and of studying the risk factors for occlusion. One of the important questions that we will be studying regards the influence of preoperative stenosis, that is, competitive flow, on the long-term patency of a radial artery graft.

DR JOSEPH ARCIDI (Flint, MI): I am curious as to whether the implication from your study is that you have a threshold for using bilateral ITA grafting or whether you are changing and transitioning to single plus radial, and if there is a threshold, is it hemoglobin A1c levels? And a related question might be with this small incidence of deep sternal wound infection, how do you take the ITAs? Do you use adjunctive sternal closure methods and the like? Thank you very much. Another great Cleveland Clinic study.

DR RAZA: Thank you. That is a very important question. We published a study in *JTCVS* in 2014 in which we showed that bilateral ITA grafting is better than single ITA grafting for diabetic patients. However, there were certain patient populations in which the risk of deep sternal wound infection was simply too high, particularly in obese diabetic females who had diffuse atherosclerotic burden and were at the greatest risk of having these infections.

So the take-home message from the findings of this study is that single ITA plus radial artery grafting could be equally effective and should be considered, particularly in patient populations whose risk of sternal wound infection is high.

As far as techniques that we have adopted for reducing the risk of deep sternal wound infection at Cleveland Clinic are concerned, we use the skeletonized approach for ITA harvesting. That is one of the most important surgical techniques for reducing the risk of sternal wound infection. We use prophylactic antibiotics and clippers instead of razors. If time allows and the blood sugar level of the patient is high, we ask that they work to get it under control before surgery, if that is possible.

Those are some of the techniques that can reduce the risk of deep sternal wound infection, allowing more patients to benefit from bilateral ITA grafts. This study showed that single ITA plus radial grafting could be equally effective in diabetic patients. So patients who are not candidates for BITA grafting can benefit from single ITA plus radial use. We can tailor the procedure to individual patients based on their characteristics.

DR VINAY BADHWAR (Morgantown, WV): So just to follow up on your comments, a little cautionary note on absolute contraindication based on size and being female, because obviously, as you know well, there is some evidence in Europe that that is not really a factor. So just a clarifying question on that, because I missed it I think in your presentation and in your abstract. How did you account for body mass index and being female for that specific subset of these high-risk people? Were they covariates in your model?

DR RAZA: We performed propensity matching, including a variety of variables ranging from demographics to cardiac and noncardiac comorbidities. Body mass index, age, and other important factors that influence outcomes were included in the model that we used to calculate propensity scores. Thus, the propensity-matched patients were fairly well balanced in terms of their body mass index, sex, age, and so on.

DR FAISAL BAKAEEN (Cleveland, OH): So if I might build up on that, our preference at the Cleveland Clinic is to use a bilateral

mammary. Now, you could substitute a bilateral mammary in certain scenarios, certainly if you have a diabetic patient, certainly a fragile diabetic patient, because controlled diabetes in a nonobese patient, younger patient, will probably do better with skeletonized bilateral mammaries, but if you have an older patient with fragile diabetes, A1c greater than 9, that might be the kind of patient where you would substitute BITA with a radial graft.

As mentioned from the floor before this, there is absolutely no absolute indication for using bilateral mammary, and that would stay our baseline preference. Radial artery may be a substitute in select patients such as the ones that I mentioned.

DR BADWHAR: So to that point, did you have skeletonization versus pedicle as a variable in your propensity match?

DR RAZA: We do not have those data, but in the most recent era we have been using only a skeletonized approach, and our sternal wound infection number in 2015 was 0 for patients undergoing primary isolated CABG.

DR BADHWAR: It will be important I think in future work from your group to help define that, because you may find that as a new variable in The Society of Thoracic Surgeons database moving forward next year.

DR BAKAEEN: Yes, and I do not know if that is mentioned in the manuscript or not, but almost universally BITAs are skeletonized. So it is a practice mode.

DR TSUYOSHI KANEKO (Boston, MA): If there was bias toward doing a BITA on a diabetic patient, so, say, for instance, if the surgeon thought that the patient was too obese and if the patient was female and if you had done a BITA and if you do a propensity match to that population, you may not be looking at the really high risk population. Would that be a limitation in this study?

DR BAKAEEN: That is our current philosophy. Now, whether that was reflected over the years of the study, we do not know, but that is a retrospective study. We can never 100% eliminate biases such as that or confounders.

Supplemental (Online-Only) Material

APPENDIX: VARIABLES CONSIDERED IN ANALYSES

Demographics

Age (y),[a] sex,[a] race (white, black,[a] other[a]), weight (kg), height (cm), weight/height ratio, body surface area (m^2), body mass index ($kg \cdot m^{-2}$)[a]

Acuity

New York Heart Association functional class (I-IV),[a] emergency operation

Cardiac comorbidity

Prior myocardial infarction,[a] atrial fibrillation or flutter,[a] complete heart block or pacer,[a] heart failure,[a] ventricular arrhythmia, left ventricular dysfunction (none, mild, mild to moderate, moderate, moderate to severe, severe)[a]

Noncardiac comorbidity

Diabetes type (pharmacologically treated, insulin-dependent,[a] diet-controlled[a]), peripheral arterial disease,[a] carotid disease,[a] hypertension,[a] chronic obstructive pulmonary disease,[a] history of smoking,[a] prior stroke,[a] bilirubin ($mg \cdot dL^{-1}$),[a] creatinine ($mg \cdot dL^{-1}$),[a] blood urea nitrogen ($mg \cdot dL^{-1}$),[a] hematocrit (%),[a] cholesterol ($mg \cdot dL^{-1}$: total,[a] high-density lipoprotein,[a] low-density lipoprotein), triglycerides ($mg \cdot dL^{-1}$)[a]

Coronary anatomy

Number of systems diseased (≥50% stenosis),[a] left main trunk (LMT) disease, LMT disease (≥70% stenosis), LMT disease (≥50% stenosis),[a] left anterior descending (LAD) system disease,[a] LAD system disease (≥70% stenosis), LAD system disease (≥50% stenosis), left circumflex (LCx) system disease,[a] LCx system disease (≥70% stenosis), LCx system disease (≥50% stenosis),[a] right coronary artery (RCA) system disease,[a] RCA system disease (≥70% stenosis), RCA system disease (≥50% stenosis)[a]

Experience

Date of operation (years since 1/1/1994)[a]

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a. Variable used in saturated model to calculate propensity scores.

Table E1: Factors associated with BITA grafting (vs. SITA+RA grafting) among diabetic patients undergoing CABG (parsimonious model).

Factor	Estimate ± SE	*P*-value	Reliability (%)[a]
Demographics			
Younger age[b]	-0.30 ± 0.13	.02	73
Lower BMI[c]	-0.91 ± 0.15	<.0001	66
Symptoms			
NYHA functional class			
II	-0.42 ± 0.19	.03	65
III / IV	-0.82 ± 0.23	.0004	65
Noncardiac comorbidities			
Diet-controlled diabetes	0.68 ± 0.20	.0008	88
Higher hematocrit[d]	1.1 ± 0.33	.001	52
Experience			
More recent date of operation	0.82 ± 0.065	<.0001	91
Earlier date of operation[e]	5.0 ± 0.43	<.0001	91
Intercept	3.6 ± 0.74	<.0001	—

Note: C-statistic=.83

a. Percent of times factor appeared in 500 bootstrap models.

b. Exp(age/50), exponential transformation.

c. $(BMI/25)^2$, squared transformation.

d. $(Hematocrit/40)^2$, squared transformation.

e. Log(date of operation, years from 1/1/1974), logarithmic transformation.

BITA=bilateral internal thoracic artery; SITA=single internal thoracic artery; RA=radial artery; BMI=body mass index; NYHA=New York Heart Association; SE=standard error.

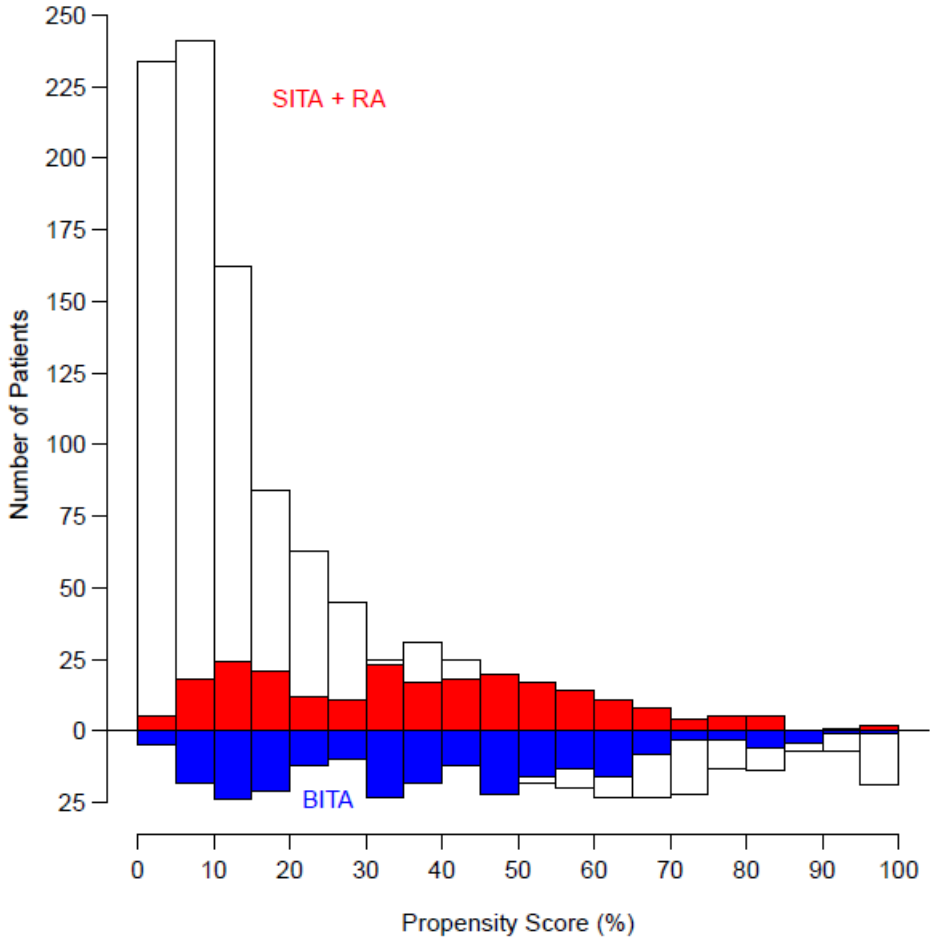


Figure E1. Mirrored histogram of distribution of propensity scores for SITA+RA vs. BITA (shaded area represents matched patient cohorts). Key: BITA=bilateral internal thoracic artery; SITA+RA=single internal thoracic artery plus radial artery.

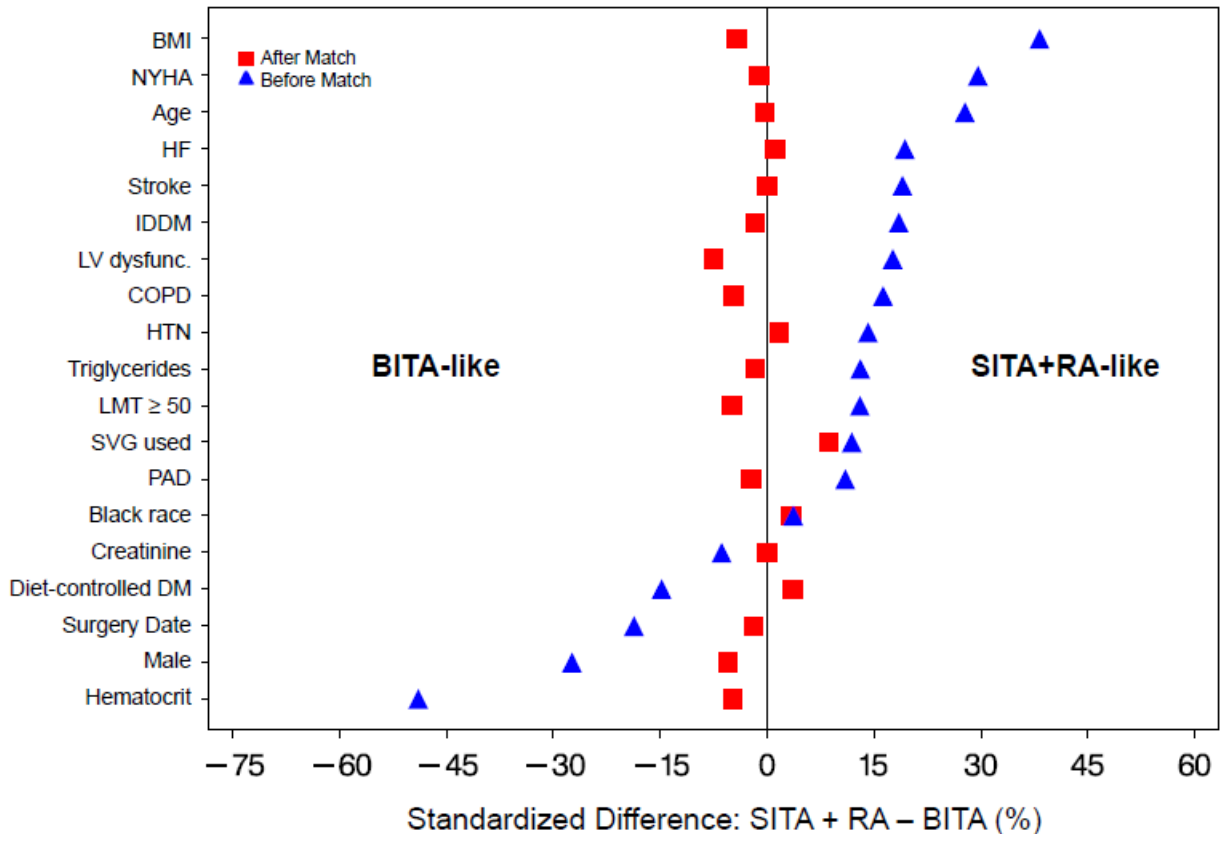
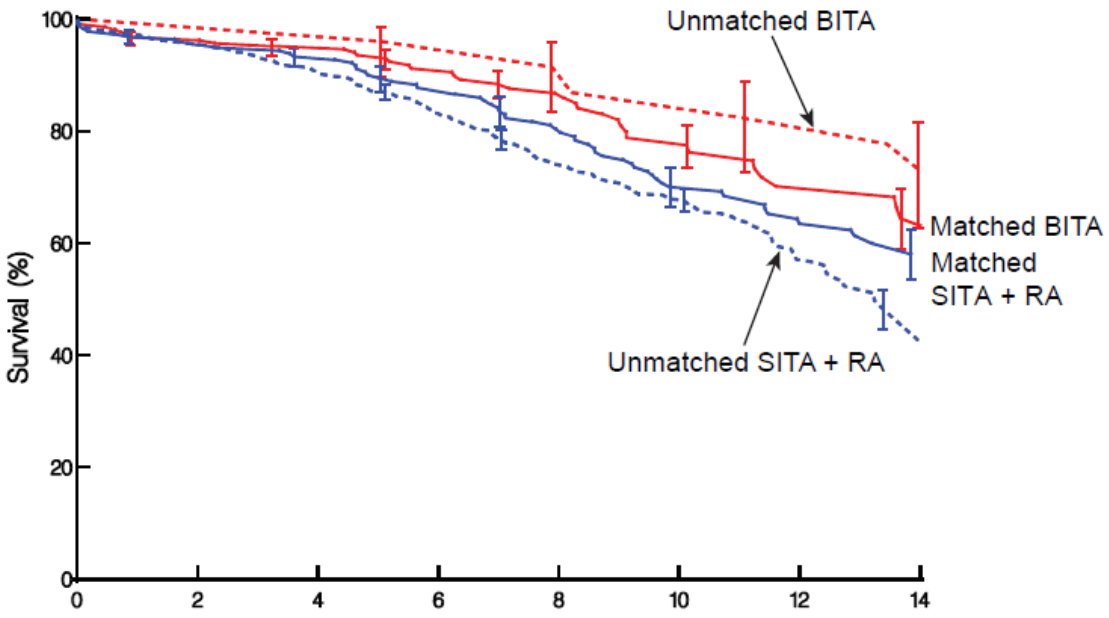


Figure E2. Covariate balance plot of standardized differences before and after the propensity score matching on selected covariables. Key: BITA=bilateral internal thoracic artery; BMI=body mass index; COPD=chronic obstructive pulmonary disease; DM=diabetes mellitus; HF=heart failure; HTN=hypertension; IDDM=insulin-dependent diabetes mellitus; LMT=left main trunk disease; LV dysfunc.=left ventricular dysfunction; NYHA=New York Heart Association; PAD=peripheral arterial disease; RA=radial artery; SITA=single internal thoracic artery; SVG=saphenous vein graft.



No. at risk								
BITA								
Unmatched	78	38	29	24	21	20	19	17
Matched	282	193	177	145	100	62	44	29
SITA+RA								
Matched	282	192	172	152	121	95	74	27
Unmatched	683	553	515	459	370	279	119	14

Figure E3. Time-related death stratified by SITA+RA vs. BITA matched (solid lines) and unmatched (dashed lines) groups. Curves are Kaplan-Meier estimates with associated 68% confidence limits (vertical bars). Key: BITA=bilateral internal thoracic artery; SITA+RA=single internal thoracic artery plus radial artery.

Chapter 7

Academic Importance of Papers

The study that forms the basis of chapter 2 (Research Question 1) got accepted for presentation at the Forty-ninth Annual Meeting of The Society of Thoracic Surgeons (STS), Los Angeles, CA, Jan 26–30, 2013, and I was selected as the STS poster crawl finalist for presenting this study. This study was published in Annals of Thoracic Surgery, which is one of the flagship cardiac surgery journals, and the official journal of the Society of Thoracic Surgeons and the Southern Thoracic Surgical Association. This paper was accompanied by an editorial written by Drs. Arie Pieter Kappetein and Ruben L.J. Osnabrugge from the department of thoracic surgery, Erasmus Medical Center, Netherlands [1]. A story describing this study was also featured in ‘Science Daily.

The study that forms the basis of chapter 3 (Research Question 2) was published in the Journal of Thoracic & Cardiovascular Surgery, which is one of the flagship cardiac surgery journals, and official journal of the American Association of Thoracic Surgery. Two editorials accompanied this study; one written by Drs. Mani Arsalan & Michael Mack from Baylor Research Institute, Baylor Scott & White Health, Dallas, TX [2], and the other by Dr. Paul Kurlansky from Columbia University NewYork, NY [3]. This study has been cited 24 times to date and has received coverage in Medscape Medical News, Clinical Endocrinology News, Hospitalist News, Cardiology News, ACS Surgery News and Thoracic Surgery News. The American Association of Thoracic Surgery

organized a press release accompanying this article's publication in Journal of Thoracic & Cardiovascular Surgery.

The study that forms the basis of Chapter 4 (Research Question 3) got accepted for oral presentation in the Scientific Sessions of the American College of Cardiology (ACC), held in April 2016 in Chicago, IL. It was published in Journal of American College of Cardiology in August 2017, which is the number one ranked cardiovascular journal in US with impact factor of 17.759 (2015). Drs. David P. Taggart and Umberto Benedetto from University of Oxford, UK and University of Bristol, UK, respectively, wrote an editorial on this study [4].

The study that is the basis of chapter 5 (Research Question 4) was accepted for presentation as the lead-off paper in the Plenary Session of the 94th Annual Meeting American Association of Thoracic Surgery (AATS), April 26 to 30, 2014, Toronto, Canada. The Plenary Session features presentations on some of the most cutting-edge research being performed in cardiothoracic surgery – all with the goal of improving outcomes and developing best practices. This study received front page coverage in Thoracic Surgery News and AATS Daily News. It was published in the Journal of Thoracic & Cardiovascular Surgery, which is one of the flagship cardiac surgery journals, and the official journal of the American Association of Thoracic Surgery and the Western Thoracic Surgical Association. Dr. Andrea Carpenter of the University of Texas Health Science Center, San Antonio, TX [5], wrote editorial commentary on this paper. Drs. Michael E. Halkos and Robert A. Guyton also commented on this study in their editorial [6]. This article has been cited 68 times to date and was

also cited in the 2014 European Society of Cardiology/European Association for Cardiothoracic Surgery Guidelines on myocardial revascularization.

The study that forms the basis of Chapter 6 (Research Question 5) was accepted for presentation at the Southern Thoracic Surgical Association Annual Meeting, held in Naples, Florida, from November 11 to 14, 2016, and was accepted for publication in Annals of Thoracic Surgery, which is one of the flagship cardiac surgery journals, and the official journal of the Society of Thoracic Surgeons and the Southern Thoracic Surgical Association.

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5) Carpenter AJ. Two internal thoracic arteries really are better. J Thorac Cardiovasc Surg. 2014;148(4):1266-1266.e9.
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Chapter 8

Lessons Learned

8.1 Importance of Multidisciplinary Research Team

The most important thing that I learned from my research work included in the thesis is the importance of a multidisciplinary research team in conducting high-quality streamlined research. As described in Chapter 6 of the book "Kirklin/Barratt-Boyes Cardiac Surgery", key players in such a team include a clinical-investigator, database manager, data gatherers, individuals assessing the quality of data, statistical programmers, expert statisticians and other professionals helping with different aspects of the research process. With the growing sophistication of data management and analytic tools, it becomes necessary to assemble a research group with varied roles and expertise, all focused on the goals of clinical investigation.

As described in the book mentioned above, the roles of key-personnel are as follows:

A clinical-investigator in collaboration with key individuals in data management, statistics, and study coordination, develop the clinical question, define the study group of interest, identify variables and end points of interest, review the literature, and develop all elements of a study protocol, adjudicate data quality, often gather values for variables in addition to the core data elements, help interpret the analyses performed, put them into clinical context, present the findings to colleagues, and write manuscripts.

The database manager is at the interface between data gathering and data analysis. The assembly of data for meaningful analysis is often complex, requiring information to be retrieved from a variety of electronic sources. Database managers help with this important task.

The statistical programmer converts data from database format into analysis data sets that make sense to the statistician.

Statisticians help the clinical investigator in choosing the most appropriate analytic methodology for a given study and perform the statistical analysis.

Other members of such research teams may include individuals who verify data, perform patient follow-up, do financial analysis, write grants, produce medical illustrations or computer graphics, and engage in many other support roles.

8.2 Development of Analysis Plan

In the department of Cardiac Surgery at the Cleveland Clinic, the inception of each study was followed by the process of writing the study proposal and submitting it to the research committee for approval. The committee used to review the proposal and either approve it with or without revisions, or disapprove it on the basis of feasibility and importance of research question. Every research proposal included a title, the names of investigators, the background of the project and key references, a clear research question, study group definition, end-points, required variables from databases, variables needing data-collection, proposed data-analysis methodology, and timeline and deliverables.

However, with time the need for a more comprehensive study roadmap was realized particularly for data analysis. Therefore, in an effort to improve and streamline the process of research, detailed analysis plans were developed for each study right after the proposal was approved. Statisticians in collaboration with the investigators developed these analysis plans. A typical analysis plan describes the different phases of a study, the work and analysis to be done during each phase, and the statistical methods to be used during each phase.

8.3 Best Data-collection Practices

Data Collection is an important part of any research study. Inaccurate data collection can lead to invalid results. The study that is the basis of Chapter 4 required extensive data-collection because from about 2000 to 2004, the diagnostic catheterization data was not routinely collected in existing registries. Therefore, I collected the missing diagnostic catheterization data. In the beginning, I was planning to collect this data in an excel sheet. However, I realized that collecting data in an excel sheet has its pitfalls as they are susceptible to trivial human errors. Instead, collecting data directly into the database, with preexisting variables' fields, was a better idea, as the registry data-collection interface was designed to minimize human errors in data-collection. Collecting data directly into the database was only possible because I was collecting missing data on variables already existing in the database.

In one of my other studies (not part of this thesis), I had to collect data on new variables, not existing in the database. For that project, it was not possible

to collect data directly in the database, as there was no field for those variables. For that study, I initially planned to use excel sheets for data-collection purposes. However, the research team introduced me to an online tool known as REDCap (Research Electronic Data Capture), which is a secure web application for building and managing online databases. While REDCap can be used to collect virtually any type of data, it is specifically geared to support online or offline data capture for research studies and operations. For my future studies, instead of collecting data in an excel sheet, I would prefer using REDCAP or a pre-existing database application.

8.4 Critical Role of Data Integration & Cleaning

I also learned from my projects that extracting data from different registries for the same patients, and then programming these data into analyzable format are daunting tasks that require expert and experienced statistical programmers. Data cleaning for analysis purposes can take much longer than anticipated but is critical for accurate analysis, particularly if the data is being combined after extraction from multiple data sources. Several issues can arise during this process, which have to be resolved appropriately before processing. Once data integration is complete, it might be beneficial to manually check data on some patients for verification, as this would ensure that the data merging from different sources was done accurately.

8.5 Importance of Exploratory Data Analysis

While working on the project, which is basis of Chapter 6, I made a fundamental mistake of not carefully reviewing the results of the initial exploratory data analysis. The statistician went on to do the analyses and when I received the analysis report I found some odd combinations of grafting strategies, which I could have identified in the initial descriptive analysis results. For example, I found that for some patients, multiple bypass grafts were going to the same coronary artery or one graft was going to multiple coronary arteries in a fashion that was not surgically possible. I reviewed the charts of patients with odd combinations of grafts and found some errors in the way these grafts were coded. I corrected this error, but the whole analysis had to be done again which led to wastage of precious time and resources. This experience emphasizes the critical role of exploratory data analysis and review of the descriptive statistics before performing in-depth sophisticated analyses.

8.6 Applicability of Past Data to Contemporary Patients

I learned from the peer-review process of my manuscripts that the value of observations obtained over a long period is often questioned because patient risk factors change with time and advances occur in surgical and medical therapy. Therefore, to account for patient factors, operative techniques, and medical therapies that may have changed over time and affected survival, but could not be included in the analysis, date of operation should be used as a surrogate.

8.7 Accounting for Selection Bias in Observational Studies

One of the limitations of using observational data to compare the outcomes of any two treatments or interventions (like patients receiving CABG vs. PCI, or patients receiving single vs. bilateral ITA grafts) is the difference in the baseline characteristics of the groups. These differences result from non-random assignment of patients into the comparison groups leading to selection bias. If these differences are not accounted for, they can significantly confound, or render such comparisons invalid. Therefore, it is important to adjust for these differences in order to make valid comparisons. Several statistical techniques exist that can be utilized in an attempt to balance these baseline characteristics in the nonrandomized subjects. These include a multivariable adjustment and the use of propensity scores. It is important to note that the effectiveness of these techniques in reducing bias depends on the comprehensiveness of the risk factors available for analysis. This is particularly true for studies using administrative data, as these databases are not clinically enriched. The Cardiovascular Information Registry (CVIR) of the Cleveland Clinic is a clinical registry designed for research purposes and therefore has much greater clinical granularity. All studies included in this thesis are based on data from CVIR and therefore a wide variety of demographic, cardiac comorbidities, non-cardiac comorbidities and other patient characteristics were available to make the statistical risk adjustment process thoroughly rigorous. Therefore, these studies present high quality observational evidence for clinical decision-making. The academic success of these studies, mentioned in Chapter 7, further highlights

the importance given to them by peers and relevant clinical societies. It is important to note, however, that these studies nonetheless continue to be limited by a reliance on measured variables. The unmeasured clinical conditions represent a source of residual confounding for any observational study. Only randomized comparisons can be balanced in terms of both measured and unmeasured confounders. However, it is also important to note that randomized controlled trials are not always feasible for studying the comparative effectiveness of surgical therapies because of a lack of equipoise. Moreover, for studying long-term outcomes (15-20) years in case of most studies presented in the thesis) of different surgeries or surgical techniques, long-term follow-up data is needed which is not always possible to obtain due to lack of resources and loss-to-follow-up given the long time period.

In support of using observational data for clinical research, I would also like to mention here an excerpt from a paper by Donald B Rubin, who was the John L. Loeb Professor of Statistics at Harvard University, where he had been professor since 1983, and Department Chair for 13 of those years. He has published widely regarding causal inference in experiments and observational studies. In a paper he published in the Journal *Statistics in Medicine* in 2007 [1] he wrote “For estimating causal effects of treatments, randomized experiments are generally considered the gold standard. Nevertheless, they are often infeasible to conduct for a variety of reasons, such as ethical concerns, excessive expense, or timeliness. Consequently, much of our knowledge of causal effects must come from non-randomized observational studies”. In this

article, he advocates the position that observational studies can and should be designed to approximate randomized experiments as closely as possible. In his other widely cited papers he describes the role of propensity scores in observational studies for causal effects and in reducing bias in observational studies [2,3].

8.8 References:

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Chapter 9

Concluding Remarks

This thesis provides further knowledge about how to improve the outcomes of coronary revascularization. The findings of the research work included in this thesis have major implications for clinical practice and can help healthcare providers in improving the outcomes of their diabetic patients undergoing CABG. They strongly suggest maximizing the use of internal thoracic artery grafts in diabetic patients due to their superior patency and association with better long-term survival. They suggest using radial artery grafts in diabetic patients in whom risk of deep sternal wound infections is high. Given that 50% of all patients undergoing CABG today are diabetics and this proportion is increasing, the findings of these studies have great relevance for this important and growing patient population. In addition to answering some very important questions, this work raises some more questions. These include:

1) We found that the proportion of patients presenting for CABG who have diabetes increased each year over the last 4 decades, as did the proportion with cardiovascular risk factors. Thus, compared with diabetics undergoing operation in the 1970s, 1980s, and 1990s, those operated on more recently were more likely to be obese and present with more comorbidities and advanced coronary artery disease. Does the nationwide data also show similar trends?

2) We found that diabetes does not influence long-term patency of internal thoracic artery and saphenous vein grafts. Is this the case with other arterial grafts too, such as radial artery grafts and gastroepiploic artery grafts?
3) We found that bilateral ITA grafting with complete revascularization is associated with better long-term survival and off-pump CABG or on-pump CABG yield similar results in diabetic patients undergoing CABG. Does a similar scenario exist in non-diabetic patients?
4) We found that SITA plus RA grafting vs. BITA grafting is associated with similar long-term survival in diabetic patients undergoing CABG. Is this also the case in non-diabetic patients? Also, what is the incremental benefit of third arterial graft in diabetic and non-diabetic patients undergoing CABG?

The research work presented in the thesis has led me to become a better researcher. It has equipped me with the tools to work as an independent researcher who can design and execute studies to answer important questions through the use of real-world data. It also provides valuable guidance regarding the way in which real-world data can be used to provide insights into appropriate strategies for improving the outcomes of different healthcare services and procedures.

Appendix

10.1 Systematic Review for Research Question 1 Presented in Chapter 2

Purpose

The purpose of this systematic literature search was to identify prediction models that predict long-term survival after CABG vs. PCI to compare the strength and limitation of our risk model against those.

Methods

Types of Studies Included

We sought to include randomized controlled trials and observational studies in this systematic review.

Inclusion Criteria: Models predicting long-term mortality/survival (at least 5 years) after CABG vs. PCI.

Exclusion Criteria: Models predicting only hospital mortality or early to midterm mortality (<5 years) were excluded.

Review of Studies

This was done by a single individual rather than two independent individuals which is the norm for systematic reviews because it was undertaken as part of a doctoral dissertation.

Searches

Sources:

Electronic databases like Ovid Medline, PubMed, and Embase, and the websites of highly relevant journals like Annals of Thoracic Surgery and Journal of Thoracic & Cardiovascular Surgery were searched for studies. Reference lists of relevant articles were also screened.

Search Strategy:

The search strategy included both free text and controlled vocabulary for the concept of models predicting long-term survival after CABG vs. PCI.

Search Limitations:

-The search was performed in September 2017 and was restricted to January 2013. This was done because the idea of the systematic search was to identify studies that already existed on this topic at the time of paper preparation/publication so that the addition to the literature that the study made could be effectively evaluated in the light of existing knowledge on the subject.

-Studies were excluded if not in English language.

Quality Assessment

A careful and detailed assessment of study methodology documenting methodological strengths and weaknesses was performed using PROBCAST checklist.

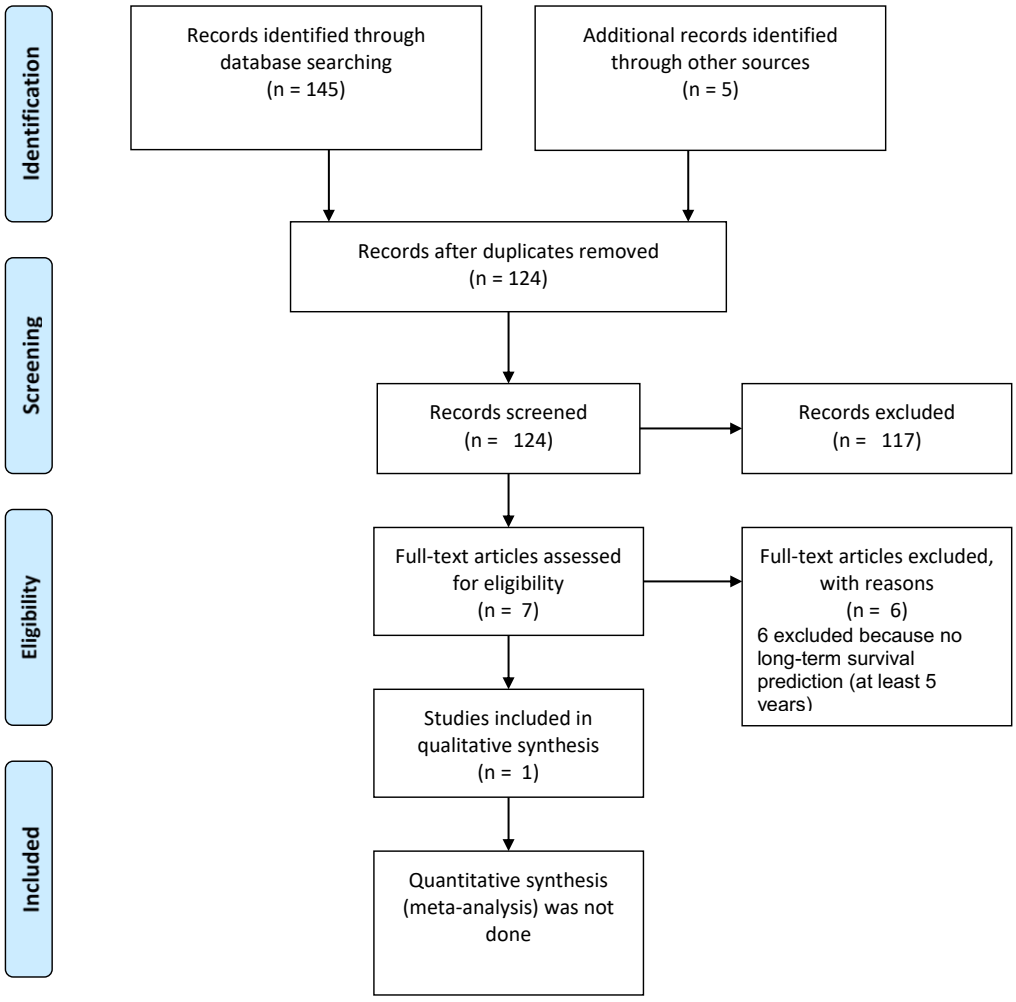
Data extraction and Analysis

Data was extracted based on a pre-specified list of elements including the number of patients in each comparison group. Quantitative analysis was not performed.

Results

From the initial literature search, 124 articles were identified after removing the duplicates. Of these, 117 were excluded after title and abstract review. Of the 7 studies [See references 1-7 below] selected for full-text review, 6 were excluded because they only predicted short term or mid-term survival (less than 5 years). Finally, only one study was identified that met the specified inclusion criteria (see PRISMA diagram and quality assessment below).

PRISMA 2009 Flow Diagram



Study Assessment Using PROBAST Checklist

Participant Selection

1. Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?
Yes, registry data was used.

2.Were all inclusions and exclusions of participants appropriate?
Yes. However, it was not clear whether the model is only for patients undergoing first time revascularization or repeat revascularization.

3.Were participants enrolled at a similar state of health, or were predictors considered to account for differences?
Predictors were considered to account for differences.

Predictors

1.Were predictors defined and assessed in a similar way for all participants in the study?
Yes

2.Were predictor assessments made without knowledge of outcome data?
Yes

3.Are all predictors available at the time the model is intended to be used?
Yes

4.Were all relevant predictors analyzed?
Yes

Outcome

1.Was a pre-specified outcome definition used?
Yes

2.Were predictors excluded from the outcome definition?
Yes

3.Was the outcome defined and determined in a similar way for all participants?
Yes

4.Was the outcome determined without knowledge of predictor information?
Yes

Sample Size and Participant Flow

1.Were there a reasonable number of outcome events?
Yes

2.Was the time interval between predictor assessment and outcome determination appropriate?
Yes

3.Were all enrolled participants included in the analysis?
Yes

4.Were participants with missing data handled appropriately?
Yes

Analysis

1.Were non-binary predictors handled appropriately?
Yes

2.Was selection of predictors based on univariable analysis avoided?
No mention that selection of predictors was based on univariate analysis.

3.Was model overfitting (optimism in model performance) accounted for, e.g. using bootstrapping or shrinkage techniques?
The C statistic was estimated with bootstrapping

4.Were any complexities in the data (e.g. competing risks, multiple events per individual) accounted for appropriately?
The end-point studied was death and not any longitudinal outcome so there were no multiple events per individual.

5.Do predictors and their assigned weights in the final model correspond to the results from multivariable analysis?
Yes

6.For the model or any simplified score, were relevant performance measures evaluated, e.g. calibration, discrimination, (re)classification and net benefit?
Yes

7.Was the model recalibrated or was it likely (based on the evidence presented, e.g. calibration plot) that recalibration was not needed?
No

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10.2 Systematic Review for Research Question 2 Presented in Chapter 3

Purpose

The purpose of this systematic literature search was to identify studies reporting the cost of CABG in diabetic vs. non-diabetic patients.

Methods

Types of Studies to be Included

We sought to include randomized controlled trials and observational studies in this systematic review.

Inclusion Criteria: Studies reporting the cost of CABG in diabetic vs. non-diabetic patients.

Exclusion Criteria: Studies only reporting cost of CABG in either diabetic or non-diabetic patients, and not both.

Review of Studies

This was done by a single individual rather than two independent individuals which is the norm for systematic reviews because it was undertaken as part of a doctoral dissertation.

Searches

Sources:

Electronic databases like Ovid Medline, PubMed, and Embase, and the websites of highly relevant journals like Annals of Thoracic Surgery and Journal

of Thoracic & Cardiovascular Surgery were searched for studies. Reference lists of relevant articles were also screened.

Search Strategy:

The search strategy included both free text and controlled vocabulary for the concepts of cost of CABG in diabetic vs. non-diabetic patients.

Search Limitations:

-The search was performed in September 2017 and was restricted to November 2014. This was done because the idea of the systematic search was to identify studies that already existed on this topic at the time of paper preparation/publication so that the study's addition to the literature could be effectively evaluated in the light of existing knowledge on the subject.

-Studies were excluded if not in the English language.

Quality Assessment

A careful and detailed assessment of study methodology documenting methodological strengths and weaknesses was performed using Newcastle Ottawa scale.

Data Extraction and Analysis

Data was extracted based on a pre-specified list of elements including number of patients in each comparison group. Quantitative analysis was not performed.

Results

From the initial literature search, 30 articles were identified after removing the duplicates. Of these, 26 were excluded after title and abstract review, and 1

study was excluded because we were unable to make from the abstract whether the study met the inclusion criteria or not and the full-text was not retrievable for further review. Three studies [See references 1-3 below] were selected for full-text review and all three were finally included as they met the inclusion criteria (see PRISMA diagram below). Table 1 provides the characteristics of the included studies. Quality assessment based on the Newcastle-Ottawa scale for included studies retained for qualitative synthesis is provided in Table 2.

PRISMA 2009 Flow Diagram

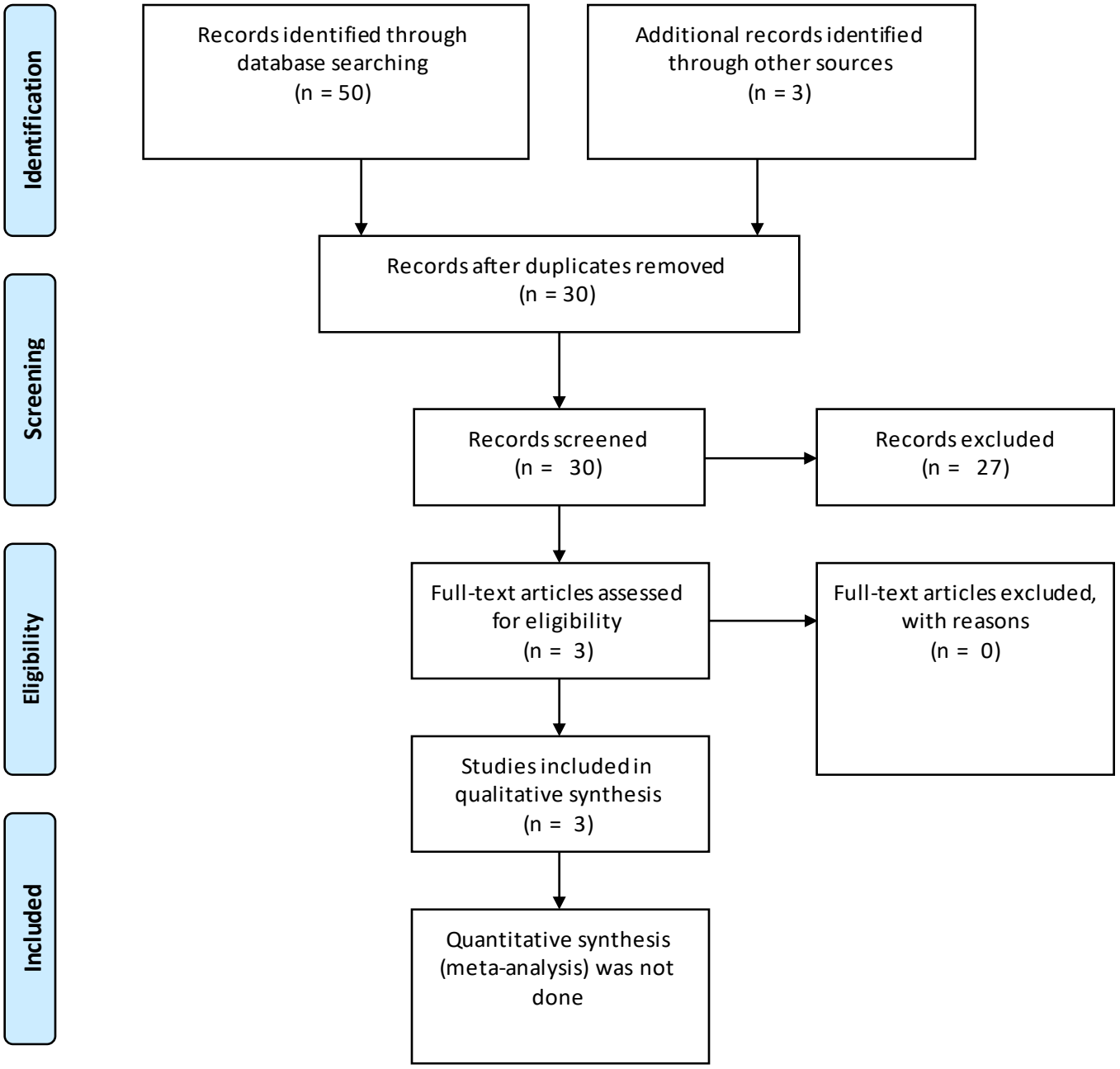


Table 1 Study Characteristics

Study	**Year**	**No. of Diabetic Patients**	**No. of Non-diabetic patients**	**Cost Outcome**
Stewart et al	1998	114	198	Hospital cost
Abizaid et al	2001	96	509	1-year cost
Zhang et al	2014	2682	6558	Hospital and 2-year cost

Table 2 Quality Assessment based on Newcastle-Ottawa scale

Study	Design	Selection				Comparability	Outcomes			Total
		Representativeness	Selection of Non-exposed cohort	Ascertainment	End-point not present at start	Confounding	Assessment of Outcome	Follow-up Duration	Adequacy of Follow-up	
Stewart et al	Cohort Study	*	*	*	*	**	*	*	*	9
Abizaid et al	Cohort Study	*	*	*	*	*	*	*	*	8
Zhang et al	Cohort Study	*	*	*	*	*	*	*	*	8

References

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10.3 Systematic Review for Research Question 3 Presented in Chapter 4

Purpose

The purpose of this systematic literature search was to identify studies reporting the influence of diabetes on long-term coronary artery bypass graft patency.

Methods

Types of studies to be included

We sought to include randomized controlled trials and observational studies in this systematic review.

Inclusion Criteria: Studies reporting mid to long-term (at least 5 years) angiographic outcomes of ITA and SV grafts in diabetic vs. non-diabetic patients were included.

Exclusion Criteria: Studies reporting only short-term patency (<5 years), or studies reporting the influence of diabetes on the overall patency of bypass grafts and not individually for ITA and SV grafts were excluded.

Review of Studies

This was done by a single individual rather than two independent individuals which is the norm for systematic reviews because it was undertaken as part of a doctoral dissertation.

Searches

Sources:

Electronic databases like Ovid Medline, PubMed, and Embase, and the websites of highly relevant journals like Annals of Thoracic Surgery and Journal of Thoracic & Cardiovascular Surgery were searched for studies. Reference lists of relevant articles were also screened.

Search Strategy:

The search strategy included both free text and controlled vocabulary for the concepts of internal thoracic artery and saphenous vein graft patency in diabetic vs. non-diabetic patients.

Search Limitations:

-The search was performed in September 2017 and was restricted to May 2016. This was done because the idea of the systematic search was to identify studies that already existed on this topic at the time of paper preparation/publication so that the study's addition to the literature could be effectively evaluated in the light of existing knowledge on the subject.

-Studies were excluded if not in English language.

Quality Assessment

A careful and detailed assessment of study methodology documenting methodological strengths and weaknesses was performed using the Newcastle Ottawa scale.

Data Extraction and Analysis

Data was extracted based on a pre-specified list of elements including the number of patients in each comparison group. Quantitative analysis was not performed.

Results

From the initial literature search, 77 articles were identified after removing the duplicates. Of these, 68 were excluded after title and abstract review. Of the 9 studies [See references 1-9 below] selected for full-text review, 2 were excluded because only early patency was reported for bypass grafts, 1 was excluded because the influence of diabetes on patency was not reported individually for ITA and SV grafts, 1 was excluded because I was unable to delineate whether the effect of diabetes was reported separately for ITA and SV grafts or just the combined effect was provided, and 1 was excluded because of non-availability of full-text (see PRISMA diagram below). Table 1 provides the characteristics of the 3 included studies. Quality assessment based on the Newcastle-Ottawa scale for included studies retained for qualitative synthesis is provided in Table 2.

PRISMA 2009 Flow Diagram

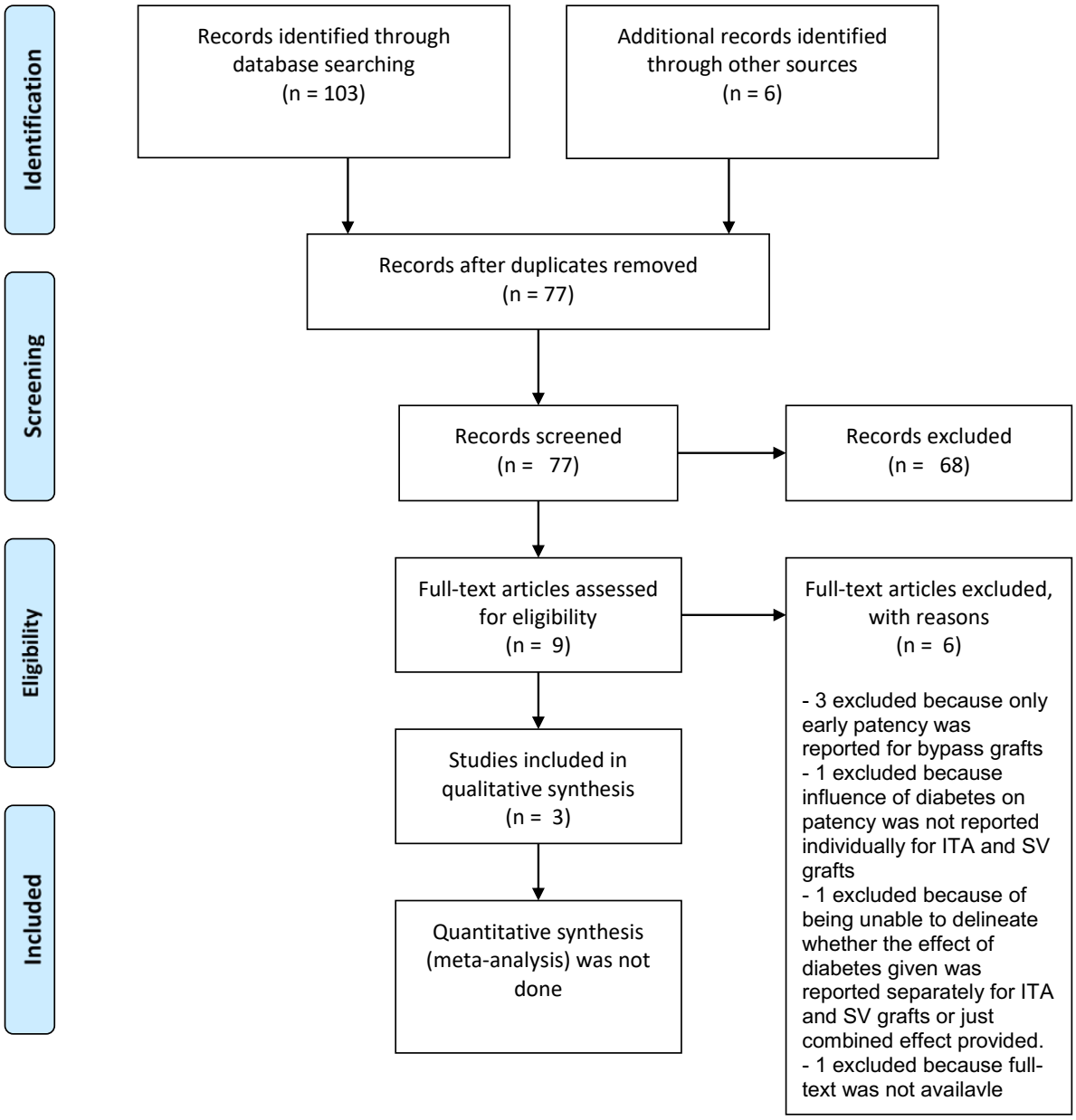


Table 1 Study Characteristics

Study	**Year**	**No. of Grafts in Diabetic Patients**	**No. of Grafts in Non-diabetic patients**	**Mean Follow-up**
Schwartz et al	2002	ITA=97 SV=200	ITA=454 SV=893	3.9 years
Hwang et al	2010	ITA=332	ITA=554	81 months
Deb et al	2014	SV grafts in 61 diabetic patients	SV grafts in 253 non-diabetic patients	≤ 5 years

Table 2 Quality Assessment based on Newcastle-Ottawa scale

Study	Design	Selection				Comparability	Outcomes			Total
		Representativeness	Selection of Non-exposed cohort	Ascertainment	End-point not present at start	Confounding	Assessment of Outcome	Follow-up Duration	Adequacy of Follow-up	
Schwartz et al	Cohort Study	*	*	*	*	**	*	*	*	9
Hwang et al	Cohort Study	*	*	*	*	**	*	*	*	9
Deb et al	Cohort Study	*	*	*	*	**	*	*	*	9

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10.4 Systematic Review for Research Question 4 Presented in Chapter 5

Purpose

To identify studies reporting the comparative effectiveness of (1) single internal thoracic artery (SITA) versus bilateral internal thoracic artery (BITA) grafting, (2) complete versus incomplete revascularization, and (3) off-pump versus on-pump CABG in terms of long-term survival in diabetic patients undergoing CABG.

Methods

Types of Studies to be Included

We sought to include randomized controlled trials or observational studies in this systematic review.

Inclusion Criteria

Studies reporting the long-term survival (at least 10 years) with or without early outcomes of studied surgical techniques specifically in diabetic patients were included.

Exclusion Criteria

Studies reporting less than 10-year long-term survival were excluded.

Review of Studies

This was done by a single individual rather than two independent individuals which is the norm for systematic reviews because it was undertaken as part of a doctoral dissertation.

Searches

Sources:

Electronic databases like Ovid Medline, PubMed, and Embase, and the websites of highly relevant journals like Annals of Thoracic Surgery and Journal of Thoracic & Cardiovascular Surgery were searched for studies. Reference lists of relevant articles were also screened.

Search Strategy:

The search strategy included both free text and controlled vocabulary for the concepts of surgical techniques compared in this study. These included: (1) SITA versus BITA grafting, (2) complete versus incomplete revascularization, and (3) off-pump versus on-pump CABG. Separate searches were conducted for each of these three comparative surgical strategies.

Search Limitations:

The search was performed in September 2017 and was restricted to April 2014. This was done because the idea of the systematic search was to identify studies that already existed on this topic at the time of paper preparation/publication so that the study's addition to the literature could be effectively evaluated in the light of existing knowledge on the subject.

-Studies were excluded if not in the English language.

Quality Assessment

A careful and detailed assessment of study methodology was done using the Newcastle-Ottawa scale.

Data Extraction and Analysis

Data was extracted based on a pre-specified list of elements including number of patients in each comparison group. Quantitative analysis was not performed.

Results

From the initial literature search for BITA vs. SITA grafting, 80 articles were identified after removing the duplicates. Of these, 67 were excluded after title and abstract review. Of the 13 studies [See references 1-13 below] selected for full-text review, 8 were excluded because long-term survival was not reported and 1 study was excluded because the results were not risk-adjusted (Figure 1). Table 1 provides the characteristics of the 4 included studies. Quality assessment based on the Newcastle-Ottawa scale for included studies retained for qualitative synthesis is provided in Table 2.

From the initial literature search for off-pump vs. on-pump CABG, 152 articles were identified after removing the duplicates. Of these, 150 were excluded after title and abstract review. Of the 2 studies [See references 14 & 15 below] selected for full-text review, 1 was excluded because long-term survival was not reported (Figure 2). Study characteristics and quality assessment based on the Newcastle-Ottawa scale for the included study are given in Tables 3 and 4, respectively.

From the initial literature search for complete vs. incomplete revascularization, 30 articles were identified after removing the duplicates. Of these, 29 were excluded after title and abstract review. One study [See

reference 16 below] was selected for full-text review but it was also excluded because long-term survival (at least 10 years) was not reported (Figure 3).

Table 1 Study Characteristics for BITA vs. SITA comparison

Study	**Year**	**Patients in SITA group**	**Patients in BTA group**	**Long-term survival reported**
Lytle et al	1999	601	211	12 years
Endo et al	2003	277	190	14 years
Steven et al	2004	419	214	16 years
Dorman et al	2012	646	461	20 years

Table 2 Quality Assessment based on Newcastle-Ottawa scale for studies in BITA vs. SITA comparison

Study	Design	Selection				Comparability	Outcomes			Total
		Representativeness	Selection of Non-exposed cohort	Ascertainment	End-point not present at start	Confounding	Assessment of Outcome	Follow-up Duration	Adequacy of Follow-up	
Lytle et al	Cohort Study	*	*	*	*	**	*	*	*	9
Endo et al	Cohort Study	*	*	*	*	**	*	*	*	9
Steven et al	Cohort Study	*	*	*	*	**	*	*	*	9
Dorman et al	Cohort Study	*	*	*	*	**	*	*	*	9

Table 3 Study Characteristics for Off-pump vs. On-pump comparison

Study	Year	Patients in Off-pump group	Patients in On-pump group	Long-term survival reported
Hemo et al	2013	232	567	13 years

Table 4 Quality Assessment based on Newcastle-Ottawa scale for studies in Off-pump vs. On-pump comparison

Study	Design	Selection				Comparability	Outcomes			Total
		Representativeness	Selection of Non-exposed cohort	Ascertainment	End-point not present at start	Confounding	Assessment of Outcome	Follow-up Duration	Adequacy of Follow-up	
Hemo et al	Cohort Study	*	*	*	*	**	*	*	*	9

Figure 1 Prisma Diagram for BITA vs. SITA Comparison

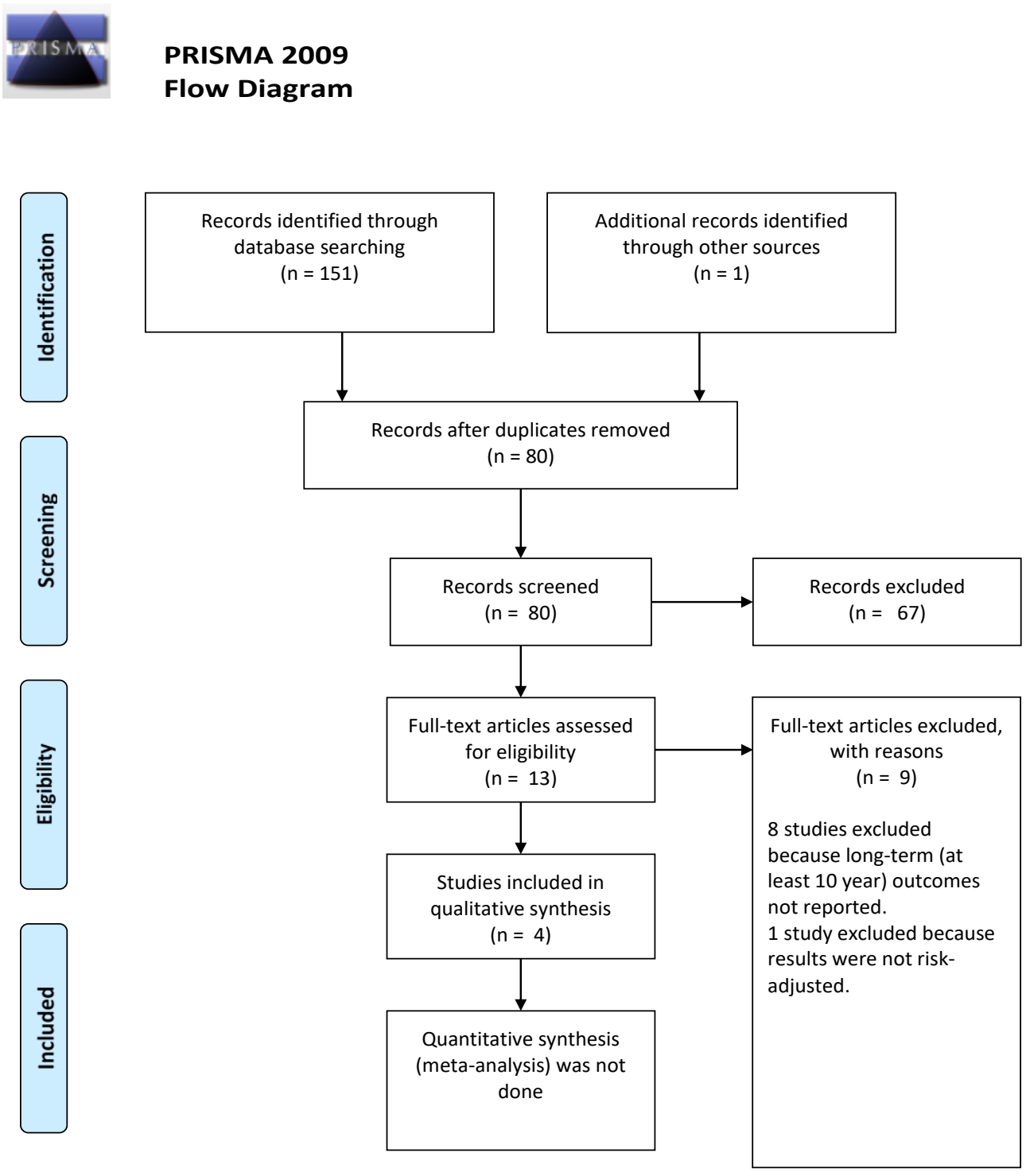


Figure 2 Prisma Diagram for Off-pump vs. On-pump Comparison

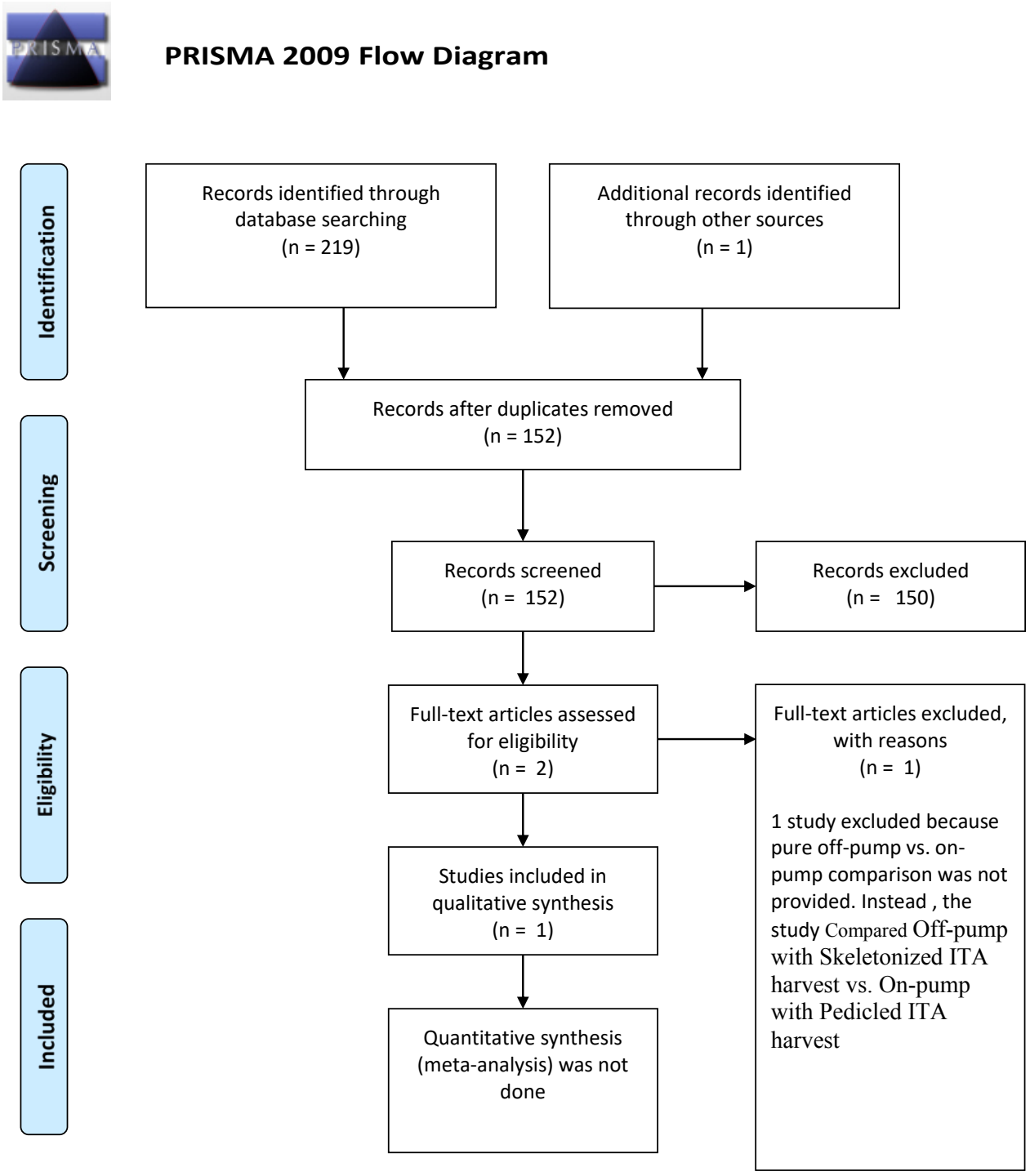
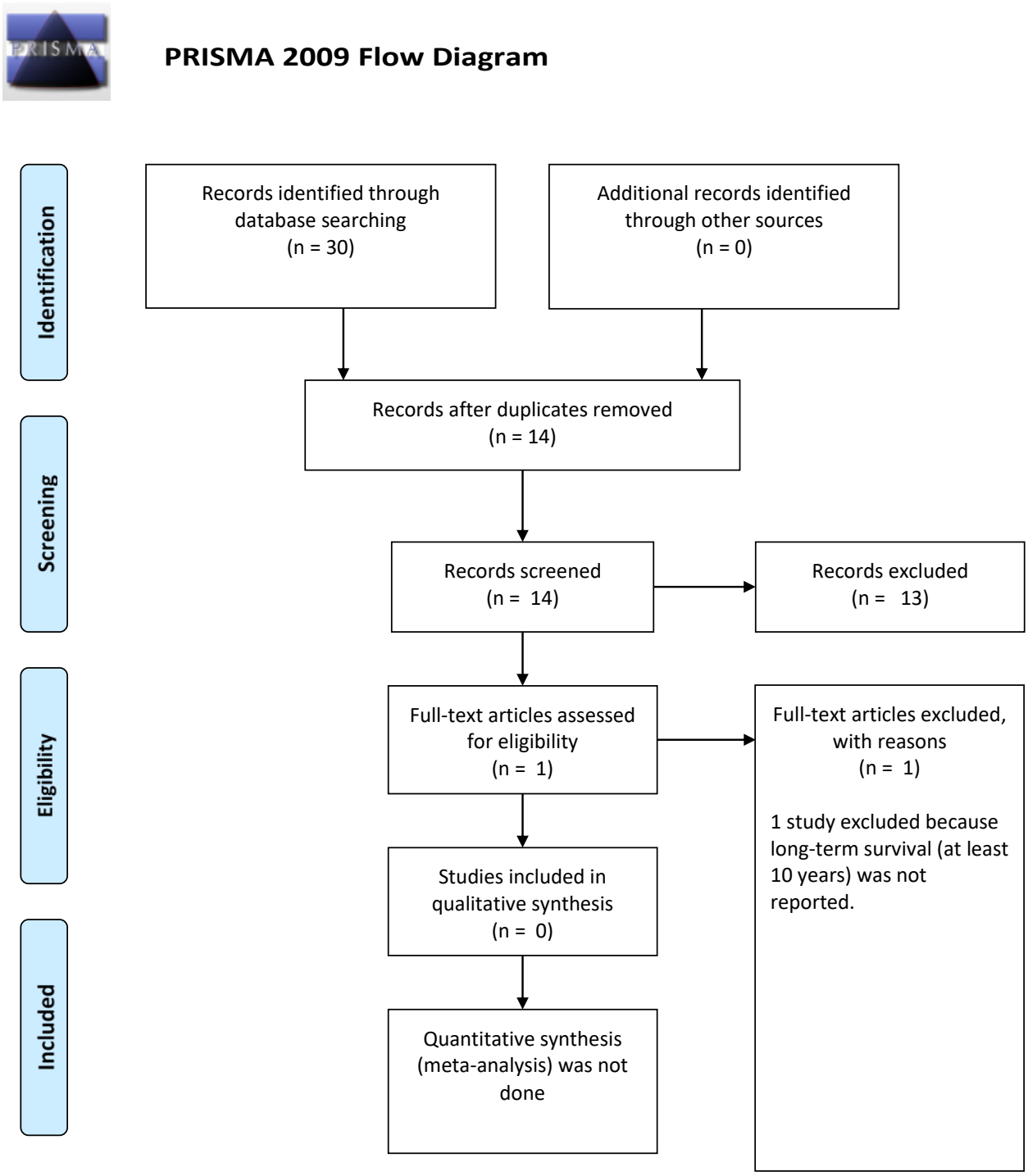


Figure 3 Prisma Diagram for Complete vs. Incomplete Revascularization comparison



Chapter 5

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long-term survival of diabetic patients? Ann Thorac Surg. 2006;81 (2): 599-606; discussion 606-7

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10.5 Systematic Review for Research Question 5 Presented in Chapter 6

Purpose

The purpose of this systematic literature search was to identify studies reporting the clinical outcomes of two arterial grafting strategies, SITA plus RA grafting and BITA grafting, in diabetic patients.

Methods

Types of Studies to be Included

We sought to include randomized controlled trials or observational studies (preferentially propensity-matched) in this systematic review.

Inclusion Criteria: Studies reporting clinical outcomes like post-operative mortality and morbidity and/or long-term outcomes of arterial grafting strategy specifically in diabetic patients were included.

Exclusion Criteria: Studies not reporting clinical outcomes were excluded.

Review of Studies

This was done by a single individual rather than two independent individuals which is the norm for systematic reviews because it was undertaken as part of a doctoral dissertation.

Searches

Sources:

Electronic databases like Ovid Medline, PubMed, and Embase, and the websites of highly relevant journals like Annals of Thoracic Surgery and Journal

of Thoracic & Cardiovascular Surgery were searched for studies. Reference lists of relevant articles were also screened.

Search Strategy:

The search strategy included both free text and controlled vocabulary for the concepts of radial artery grafts in diabetic patients undergoing coronary artery bypass grafting.

Search Limitations:

-The search was performed in September 2017, and unlike the systematic searches done for chapters 2 through 5, no date limits were applied as this paper was published in December, 2017, around the time this search was conducted.

-Studies were excluded if not in English language.

Quality Assessment

A careful and detailed assessment of study methodology was done using the Newcastle-Ottawa scale.

Data Extraction and Analysis

Data was extracted based on a pre-specified list of elements including number of patients in each comparison group. Quantitative analysis was not performed.

Results

From the initial literature search, 179 articles were identified after removing the duplicates. Of these, 171 were excluded after title and abstract review. Of the 8 studies [See references 1-8 below] selected for full-text review, 4 were excluded

because they did not provide results for diabetic patients, 1 was excluded because of poor study design, 1 was excluded because it was based on complete arterial revascularization rather than comparing different arterial grafting strategies in diabetic patients (see PRISMA diagram below). Table 1 provides the characteristics of the two included studies by Hoffman et al and Raja et al. Quality assessment based on the Newcastle-Ottawa scale for the included studies retained for qualitative synthesis is provided in Table 2.

PRISMA 2009 Flow Diagram

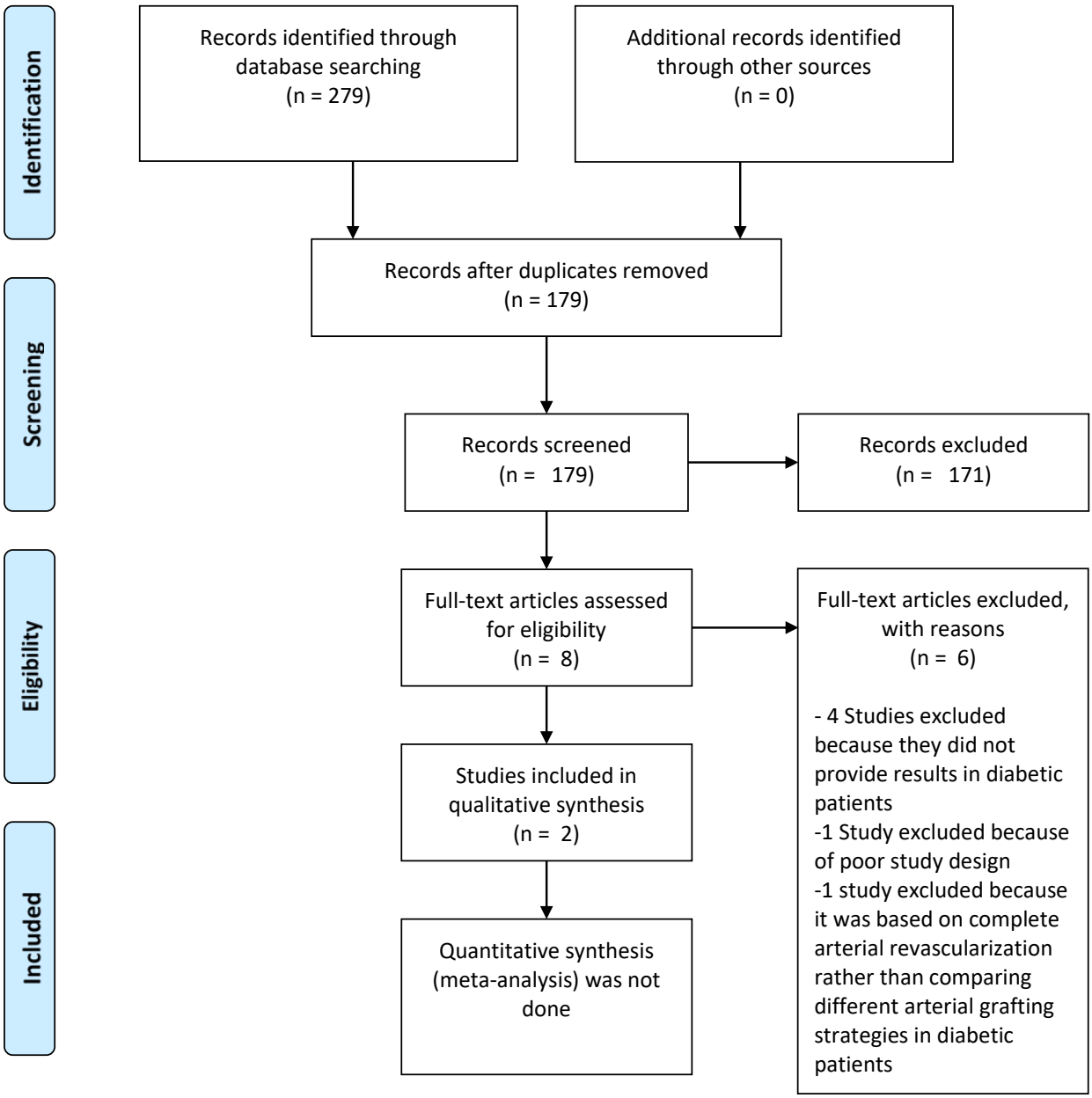


Table 1 Study Characteristics

Study	Year	Patients in SITA+RA group	Patients in BITA group	Mean Follow-up
Raja et al	2014	124	103	8 years
Hoffman et al	2014	659	502	SITA=10.57±4.43 BITA=9.87±4.34

Table 2 Quality Assessment based on Newcastle-Ottawa scale

Study	Design	Selection				Comparability	Outcomes			Total
		Representativeness	Selection of Non-exposed cohort	Ascertainment	End-point not present at start	Confounding	Assessment of Outcome	Follow-up Duration	Adequacy of Follow-up	
Raja et al	Cohort Study	*	*	*	*	**	*	*	*	9
Hoffman et al	Cohort Study	*	*	*	*	**	*	*	*	9

References

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2) Hoffman DM, Dimitrova KR, Lucido DJ, et al. Optimal conduit for diabetic patients: propensity analysis of radial and right internal thoracic arteries. Ann Thorac Surg. 2014;98 (1): 30-6; discussion 36-7
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