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Clinically-driven angiography after coronary artery bypass surgery

Results from the SWEDEHEART registry

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Abstract

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The success of coronary artery bypass grafting (CABG) arguably depends on the patency rate of the conduits. The saphenous vein grafts (SVGs) most often used are subject to graft disease and their reduced long-term patency compared to left internal mammary artery (IMA) grafts is well established. Postoperative coronary artery disease (CAD) symptoms, such as angina or myocardial infarction can undoubtedly be linked to graft failure or progression of atherosclerosis in the native coronary vessels, but the contribution from each of these processes is not completely understood.

The aim of this thesis was to use clinically-driven angiography as the main outcome measure in studying different bypass conduits and surgical techniques. This endpoint has a very low risk of misclassification, and is likely to have a high association with recurrence of CAD symptoms. The SWEDEHEART registry provides extensive data on all patients undergoing cardiac surgery in Sweden as well as records of angiographies and coronary interventions.

We studied the incidence of postoperative angiography in 46 663 CABG patients operated with IMA and SVGs. Young age, female sex, presence of diabetes, normal left ventricle function, previous PCI, prior MI, emergency surgery and one or two distal anastomoses were associated with a higher risk. We also studied 6 977 CABG operated individuals with three or more grafted vessels that experienced a postoperative angiography and had available records on individual graft patency. Almost one third of catheterized individuals with CAD symptoms did not demonstrate any failed grafts and in 18% of early and 10% of late angiographies the IMA-graft had failed.

We compared 862 patients operated with bilateral IMA grafts and 1036 cases of IMA and radial artery grafts with 46 343 cases of IMA and SVGs. When adjusted for risk factors no improvement in outcome could be seen for patients operated with multiple arterial grafts. We also compared 1371 patients operated with “no-touch” SVGs with a propensity-matched cohort of patients with conventional SVGs. An improvement in the risk for angiography could be seen for the “no-touch” group but not for the need of repeat intervention or survival.

Postoperative angiography is a useful endpoint in studying long-term outcome after CABG surgery. It is less sensitive than mortality to variations in the baseline covariates and thereby possibly less susceptible to confounding by indication. The causation behind the return of CAD symptoms after CABG surgery and the relative importance of the individual contributions from vein graft failures, failure of the IMA graft, as well as from progression of atherosclerotic plaques in both grafted and non-grafted coronary arteries, remains to be determined.

Keywords: CABG, Coronary artery bypass surgery, angiography, graft failure

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"One of the most important features of the later stages of capitalist civilization is the vigorous expansion of the education apparatus and particularly the facilities for high education." - Joseph Schumpeter

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Janiec, M., Nazari Shafti, T. Z., Dimberg, A., Lagerqvist, B., Lindblom, R. P. F. (2018**) Graft failure and recurrence of symptoms after coronary artery bypass grafting.** *Scandinavian Cardiovascular Journal*, 52(3):170

II Janiec, M., Dimberg, A., Nazari Shafti, T. Z., Lagerqvist, B., Lindblom, R. P. F. (2017) **No improvements in long-term outcome after coronary artery bypass grafting with arterial grafts as a second conduit: a Swedish nationwide registry study.** *European Journal of Cardiothoracic Surgery*, 53(2):448–454

III Janiec M., Friberg Ö., Thelin S. (2018), **Long-term clinical outcomes after coronary artery bypass grafting with pedicled saphenous vein grafts.** *Journal of Cardiothoracic Surgery*, 13(1):122

IV Janiec M., Ragnarsson S., Nozohoor S., (2019) **Long-term outcome after coronary endarterectomy adjunct to coronary artery bypass grafting.** *Interact Cardiovasc Thorac Surg. 2019 Jan 28.*

V Janiec M., Lindblom, R. P. F. **Discovery of failed grafts after coronary artery bypass grafting during clinically-driven angiography.** *(Manuscript)*

Contents

Abbreviations

BIMA	bilateral internal mammary artery
BMI	body mass index
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CE	coronary endarterectomy
COPD	chronic obstructive pulmonary disease
CX	left circumflex coronary artery
IMA	internal mammary artery
LAD	left anterior descending coronary artery
MACCE	major adverse cardiac and cerebrovascular event
MI	myocardial infarction
NT	“no-touch”
PCI	percutaneous coronary intervention
RCA	right coronary artery
RA	radial artery
SVG	saphenous vein graft
SD	standard deviation
SWEDEHEART	Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies

Background

Coronary artery bypass grafting

Coronary artery bypass grafting (CABG) was introduced during the second half of the 1960's as a method of bypassing stenotic lesions in the coronary arteries, thereby increasing blood flow to the myocardium [1, 2]. Early in the history of the procedure it was shown to improve survival compared to medical treatment [3, 4]. Even after the advent and widespread use of percutaneous coronary intervention (PCI) [5], CABG is still the recommended treatment for complex coronary artery disease (CAD) involving multiple vessels or the left main stem, with a survival benefit compared to PCI [6-9]. Worldwide it is the most common open-heart surgical procedure and about 2500 CABG operations are yearly performed in Sweden [10].

Limitations of the procedure

Saphenous vein grafts (SVGs) have been used from the early days of the CABG procedure [11] and have remained the most commonly used conduit, used in 90% of all CABG operations [12]. The saphenous vein is conveniently harvested, technically easy to use because of its relatively large diameter and wall characteristics, and is plentiful and can therefore be used to perform multiple grafts and can reach any coronary artery [13]. Its durability and longevity are, however, not ideal and 10 years after surgery about half of saphenous vein grafts are patent, and of those, only half are free of angiographic arteriosclerosis [14, 15]. Failure of SVGs during the first year of surgery is due to technical errors, thrombosis, and intimal hyperplasia [16]. Intimal injury during harvesting or exposure to arterial pressure may lead to platelet adherence resulting in graft thrombosis or could be the initial event in the development of intimal hyperplasia [17]. After adhering to the intima, platelets stimulate smooth muscle cell migration, resulting in intimal proliferation and hyperplasia [18-21]. Mural thrombi and intimal hyperplasia are also believed to be responsible for the later development of arteriosclerosis and further vein graft failure [16, 22]. Lipid becomes incorporated, resulting in arteriosclerotic plaque, and eventual graft stenosis or occlusion [16, 23]. Atherosclerosis in vein grafts is more diffuse but less calcified [24] and often complicated by aneurysmal dilatation [25]. The long-term success of the surgery will arguably to some degree depend on the patency of the grafts and graft failure has been linked to return of CAD symptoms and increased mortality [26].

Arterial grafting

One of the most important improvements of the CABG procedure was the widespread introduction of the use of the internal mammary artery (IMA) as graft. The improved long-term patency and outcome as compared to SVGs when used to bypass the left anterior descending coronary artery (LAD) is well established [27, 28]. Consequently, the left IMA (LIMA) is anastomosed to LAD in a large majority of all CABG operations. Fitzgibbon et al [26] demonstrated more than 20 years ago that overall survival after CABG closely follows the expected survival in a matched cohort in the general population. Despite these excellent results extensive attempts have been made to further improve outcome. There is an ongoing discussion regarding the possible benefits of multiple arterial grafting and a general interest in using more arterial grafts. Arterial grafts are believed to be more resilient toward graft disease affecting SVGs [24] and have demonstrated better patency [29, 30]. There are consequently expectations that the use of multiple arterial grafts should confer improved long-term outcome compared to a single IMA and SVGs. Data from non-randomized studies have indicated that the use of bilateral IMA (BIMA), i.e. the additional use of the right internal mammary artery (RIMA), is associated with improved long-term survival, as well as fewer non-fatal events such as myocardial infarction and need for reoperation [31]. One randomized trial has demonstrated improved clinical outcome after BIMA grafting [32], although this could not be confirmed during the first 10 years after surgery in a large randomized study [33, 34]. Similar promising improvements in long-term results have been seen in observational studies of radial artery (RA) grafting [35] as well as in randomised trials [32]. Current guidelines recommend that the use of arterial grafts in addition to the LIMA should be considered [36]. The vast majority of operations are, however, still performed using SVGs [12, 37], which may be due to a lack of conclusive evidence of a superior overall outcome and the increased risk of sternal wound complications after BIMA harvesting [38].

"No-touch" pedicled saphenous vein grafts

Attempts have been made to identify factors that could prevent the development of vein graft disease, thereby improving durability. Distention and damage to graft vessels during preparation promotes platelet and leukocyte adhesion and reduces short-term patency [39, 40]. Different perioperative storage solutions also seem to influence long-term vein graft function [41]. More than

20 years ago Souza et al. initiated studies of vein grafts harvested with a pedicle of surrounding tissue and without distending the grafts [42, 43]. This "no-touch" (NT) technique is believed to preserve the vasa vasora of the vein [44] and the grafts exhibit a slower progression of intimal hyperplasia [45] and atherosclerosis [46]. A single-centre randomized clinical trial with angiographic follow-up of these grafts has demonstrated better patency for NT harvested veins compared with both veins harvested with the conventional technique [47] as well as with radial artery grafts [48]. The patency of NT grafts was comparable to that of the IMA as long as 16 years after surgery [49]. Guidelines therefore recommend that NT vein harvesting should be considered [36], although the influence on clinical outcome that the presumably improved patency of grafts harvested with the NT technique could entail, has not been studied.

Sequential grafts

Since the beginning of the 1970s sequential bypass grafts have been used for coronary artery revascularization [50]. This technique primarily saves bypass material and the need of multiple proximal anastomoses. Furthermore early studies also suggested that this technique offers a hemodynamic advantage [51], potentially preventing neointimal proliferation and subsequent failure associated with a reduced flow [52]. In studies of early clinical series, the sequential vein bypass grafts seemed to retain their patency longer than single vein grafts with a higher patency rates in the proximal anastomoses than in the distal anastomoses [53, 54]. A more recent study has, however, shown inferior results for sequential grafts in patency rates as well as in clinical outcome [55], although this difference has not been consistently observed [56].

Pharmacological prevention of graft failure

Statins have both cholesterol lowering and anti-inflammatory properties reducing vascular oxidative stress and vascular thrombosis [57]. Low serum lipid levels are seemingly slowing disease progression [15] and aggressive cholesterol lowering treatment reduces neointimal hyperplasia [58], considerably improves SVG patency and reduces adverse cardiovascular events as well as the need for repeat revascularization [59, 60].

Although very early studies assessing the use of acetylsalicylic acid were not encouraging, later studies have shown an improvement in both short [22, 61] and long-term graft patency [16]. In addition it has also been shown to reduce in-hospital mortality without an associated increase in hemorrhage-related risks [62-64]. The benefit of double antiplatelet therapy in acute coronary syndrome is well established [65, 66], but the promising results of improved graft patency and clinical results after CABG reported in some studies [67, 68] have, however, failed to be repeated in others [69-72]. Limited data suggest that higher intensity (prasugrel or ticagrelor) but not lower intensity (clopidogrel) double antiplatelet therapy may be associated with a lower mortality [73].

Coronary endarterectomy

Coronary endarterectomy (CE) in CABG is occasionally required in order to achieve revascularization in diffusely diseased vessels with either continuous calcified, soft, or hard fibrous plaques. However, CE is reported as a challenging and time-consuming procedure, and its beneficial effect has been questioned due to an increased risk of perioperative mortality and morbidity [74]. An intact coronary endothelium can produce vasoactive factors counteracting leukocyte adhesion and platelet aggregation, whereas the damage caused by CE may lead to endothelium dysfunction potentiating the risk for inflammation and thrombosis [75]. Due to advances in percutaneous coronary interventions over the recent years, patients referred for CABG demonstrate an increasing complexity of coronary disease in addition to multiple comorbidities. Therefore, CE has to occasionally be reconsidered as a treatment strategy in selected cases although there is continued uncertainty regarding its influence on outcome [76-78]. The European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization have no reference to the clinical recommendation of CE due to the absence of randomized controlled trials [36]. Thus, the role of CE has generated keen interests, controversy and widespread discussion. There are two meta-analyses currently comparing the advantages and disadvantages of CABG with CE and isolated CABG [79, 80]. In both studies, the authors reported that adjunctive CE was associated with an increasing 30-day mortality and peri- and postoperative myocardial infarction when compared with isolated CABG although long-term survival was comparable for both groups [80]. However, only limited data on long-term complications, such as MI, angina, heart failure, and cardiovascular mortality, exists for patients undergoing CABG with CE [81].

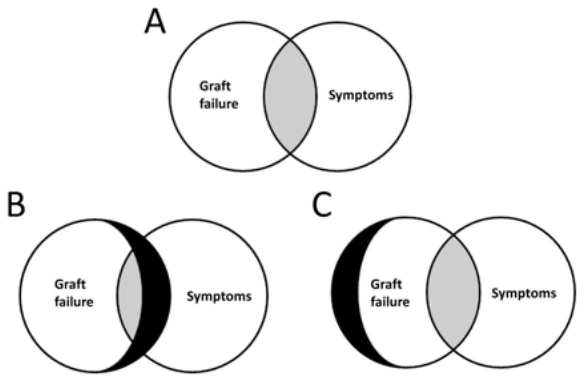

Figure 1. Illustration of the relationship between graft failure and the presentation of symptoms of coronary artery disease. Graft failure often occurs without symptoms and is only sometimes symptomatic. The grey area represents symptomatic graft failure (A). Depending on what type of graft failures are prevented (represented by black area) this may have a substantial (B) or negligible (C) effect on the risk of developing CAD symptoms.

Graft failure and symptoms of coronary artery disease

The presentation of postoperative CAD symptoms such as angina or myocardial infarction will undoubtedly be linked to either graft failure or the progression of atherosclerosis in the native coronary vessels; however, the contribution from each of these processes is not completely understood. The failure rate of IMA grafts to the LAD in early protocol angiography has been reported to be only 5–8% [27, 82, 83], although the rate seems to be higher in clinically-driven catheterizations [84]. The contribution to the recurrence of symptoms from these grafts could therefore be underestimated. Most SVG failures occur without symptoms and do not seem to influence mortality and cardiovascular events after CABG surgery [85, 86]. During protocol angiography early after CABG the reported failure rates have ranged between 13% and 43% [82, 83, 85, 87, 88]. From 1 to 5 years a further 5% to 10% of SVGs will close, and from years 6 to 10 an additional 20–25% will fail [14]. The main determinants of SVG failure during the first postoperative year appears to be a small target vessel diameter, reduced wall motion of the vessel-dependent myocardial region, and the right coronary as target vessel [86, 87], in particular when the vessel has a chronic total occlusion [88]. This indicates that grafts that fail early often are supplying less important myocardial regions or regions with well-developed collateral vessels and perhaps also why they generally do so without any symptoms or prognostic consequences. The prevention of a large part of the failures could therefore result in only a negligible reduction of clinical events (Figure 1). Asymptomatic graft failures will be discovered in conjunction with a later angiography regardless of indication and even though later failures more often may be symptomatic it is often not possible do determine what, if any, impact a specific failed graft has on the current symptoms and the significance of SVG failures could be exaggerated. The disease progression in the native coronary vessels may be a likely cause of a substantial part of clinical events after CABG and this could explain why the superior patency of arterial grafts, that presumably resulted in the improved outcome for IMA to LAD grafting, has not resulted in further clinical improvements for patients receiving multiple arterial grafts [33]. Suboptimal medical treatment is common after CABG and has been demonstrated to have a bigger impact on outcome than the choice of revascularization method [89]. Improved medical treatment to counter further disease development could therefore be more important than alternative grafts in improving long-term results after CABG surgery.

Long-term survival

The choice of relevant clinical endpoints to assess the outcome after CABG is not obvious. Mortality probably yields limited information as the long-term survival seems to approach the general population [26, 90] and a majority of deaths occurring during the first 10 years after surgery are not cardiac-related [91]. Short-term as well as long-term mortality is highly influenced by comorbidity at baseline [92, 93] and most probably only to a lesser degree influenced by the possible effects of SVG failure [86]. It is therefore quite remarkable that a large number of observational studies have reported an association between an increased number of arterial grafts and survival [94-96] as it may be unrealistic to expect that any substantial improvement can be achieved through the utilisation of superior grafts.

Postoperative angiography

Hospital readmission and composite endpoints combining death, myocardial infarction (MI) or recurrent ischemia, and stroke (MACCE) have been progressively introduced over the past decades as a more sensitive outcome measure to assess the risk-benefit ratio of various cardiovascular treatment options [6, 8]. More recently, death has been combined with recurrent ischemia, congestive heart failure or shock in primary endpoints. In a registry-based follow-up of patients e.g. by using data available in National Patient Registry, containing diagnoses at discharge for all hospital stays, the interpretation of the results may be difficult as previous diagnosis often are reiterated regardless of the current symptoms and the diagnostic accuracy as well as the adherence to strict definitions may be questionable. The misinterpretation of hospital readmissions for unrelated reasons may therefore lead to an overestimation of the recurrence of CAD symptoms.

We use incidence of clinically-driven angiography as the main endpoint for the evaluation of long-term results after CABG. This outcome is clinically relevant, easily defined, and has a very low risk of misclassification. It is likely to have a high association with recurrence of typical CAD symptoms resulting from both symptomatic graft failure and progression of atherosclerosis and related events. As an invasive diagnostic procedure, it is rarely performed without indication. The threshold is, however, believed to be low for patients previously operated with CABG when the treating physician has reason to suspect the return of CAD symptoms, or in the case of an absence of improvement in symptoms early after surgery. Despite the aforementioned beneficial properties there has been no previous registry-based studies using clinically-driven angiography as the main endpoint to evaluate results after CABG surgery. The Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry [97] provides data on all patients undergoing cardiac surgery in Sweden as well as records of angiographies and coronary interventions. The personal identity number facilitates the follow-up of registered patients and thereby enabling the study of long-term outcomes.

Aims

The aims of his thesis were to study the influence of different grafting and revascularisation techniques on the long-term outcome following CABG surgery by using data from the Swedish coronary angiography registry.

More specifically the aims were:

I. Establish postoperative clinically-driven angiography as an endpoint in studying outcome after CABG surgery and identify baseline prognostic factors for the long-term risk.

II Study the possible effects on the long-term risk of angiography for different methods of revascularisation:

- a) Investigate possible benefits of multiple arterial grafts, i.e. bilateral IMA or radial artery.
- b) Examine the impact of "no-touch" pedicled saphenous vein grafts.
- c) Study the results after coronary endarterectomy adjunct to coronary artery bypass grafting.

III Determine the distribution of the target coronary arteries of failed grafts found during clinically-driven angiography

Methods

Ethics

All studies were approved by the regional Human Research Ethics Committee in Uppsala, Sweden, and comply with the Declaration of Helsinki.

The SWEDEHEART registry

The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) includes patients admitted to hospital with symptoms suggestive of an acute coronary syndrome and patients undergoing coronary angiography or heart surgery for any indication. It provides detailed information on patient demographics, admission logistics, risk factors, past medical history, medical treatment in hospital data, and perioperative data on patients undergoing cardiac surgery as well as records of angiographies and coronary interventions. In addition to the indication for the angiography the patency of individual grafts is also registered. The registry was created in 2009 by the merger of the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS–HIA), the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), the Swedish Heart Surgery Registry and the National Registry of Secondary Prevention (SEPHIA) [97]. The Swedish Heart Surgery Registry was formed in 1992 and a national angioplasty and a coronary angiography registry, SCAAR, was formed in 1998. The registry captures 100% of the patients undergoing angiography or heart surgery. When compared with the National Patient Registry, 60% of patients with acute MI are captured by the SWEDEHEART registry with a large variation between hospitals [97]. To ensure a high validity of the data entered, a monitor visits randomly selected hospitals each year and compares hospital records with data entered into SWEDEHEART. In the 2007 revision of RIKS–HIA there was 96% agreement [97]. A recent revision of the Heart Surgery Registry also demonstrated an excellent reliability [98].

Study population

All papers were retrospective observational cohort studies. Individuals with no congenital cardiac malformations and with a permanent residence in Sweden, that underwent isolated CABG in Sweden 1995–2015, were identified within the SWEDEHEART registry. We obtained pre- and perioperative baseline data on all patients as well as records of angiographies and coronary interventions. We excluded individuals previously having undergone cardiac surgery, where no IMA was used or the types of grafts were unknown.

Paper I
Patients operated with multiple arterial grafts or with coronary endarterectomy were excluded and the remaining patients in the study cohort were divided into three groups according to the number of distal SVG anastomoses (0, 1 or multiple), i.e. IMA, 1 SVG, or 2+ SVG.

Paper II
Patients operated with arterial grafts other than IMA and RA or with coronary endarterectomy were excluded. The remaining study cohort was divided into three groups according to the graft material used; single IMA and SVGs (IMA + SVG), IMA and RA with possible additional SVGs (IMA + RA), and BIMA with possible additional grafts (BIMA)

Paper III
Patients operated with multiple arterial grafts or with coronary endarterectomy were excluded. Patients operated in Örebro that had received "no touch" saphenous vein grafts were identified in a local registry. The study cohort was composed of a group with "no touch" patients (NTT), and a control group (CT) of patients operated in other centres.

Paper IV
Patients operated with multiple arterial grafts were excluded. The remaining study cohort was divided into a group of patients where CE was performed (CE), and a control group (No CE).

Paper V
Patients operated with multiple arterial grafts or coronary endarterectomy and patients where only one or two vessels were grafted, were excluded.

Outcomes

Date of death was obtained from the national population registry. The dates for all operations and postoperative angiographies were available in SWEDEHEART. For each angiography the indication for the procedure, the presence of significantly stenosed or occluded grafts and the subsequent therapeutic decision, including recommendations for revascularization, is registered by the angiographer. For a subgroup of angiographies individual graft level patency data was also available. The elapsed time from the operation to death, first clinically-driven angiography and first need for reintervention was used as endpoints. The only patients that are believed to have been lost to follow-up are those having gone through angiography or reintervention outside of Sweden.

Statistics

Data management and statistical analyses were performed with the use of R version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Patient characteristics were described by using frequencies and percentages for categorical variables, and means and standard deviations for continuous variables. The outcome measures were evaluated in the population as the time from operation to death from any cause, to first angiography after surgery and to the first need for reintervention after surgery. The Kaplan-Meier method was used to illustrate outcome and the competing risk of death was not accounted for in the incidence calculations. Patients were followed from the date of surgery until the date of death from any cause or the end of follow-up (May 05, 2016). The indication for angiography and the occurrence of graft failure was also registered. P-values of <0.05 and confidence intervals (CIs) of 95% were used to establish a statistically significant difference.

Paper I

Missing base-line covariate data were assumed to be missing at random and were imputed by multiple imputation by chained equations. Multivariable Cox regression was used to estimate the associations of the number distal anastomosis and other of base-line prognostic factors with all-cause mortality, incidence of first angiography and need for repeat coronary intervention. The hazard ratios and 95% CIs calculated unadjusted and adjusted for available prognostic factors to reduce effects of confounding.

Paper II

Missing base-line covariate data were assumed to be missing at random and were imputed by multiple imputation by chained equations. Multivariable Cox regression was used to estimate the associations of the type of grafts used with all-cause mortality, incidence of first angiography and need for repeat coronary intervention. The hazard ratios and 95% CIs were calculated unadjusted and adjusted for available prognostic factors to reduce effects of confounding.

Paper III

Propensity score matching was used to reduce the effect of treatment-selection bias using a binary dependent variable representing the vein harvesting technique. Patients with missing data were assumed to be missing at random and excluded from the matching. The matching procedure was performed using "nearest neighbour matching" and the propensity score logit as distance measure to select the best control matches from patients operated with a conventional vein harvesting technique for each individual in the Örebro "no-touch" group. Cox regression was used to estimate the effect of the technique for vein harvesting on all-cause mortality, incidence of first angiography and need for repeat coronary intervention.

Paper IV

Propensity score matching was used to reduce the effect of treatment-selection bias using a binary dependent variable representing the presence of concomitant CE. Patients with missing data were assumed to be missing at random and were excluded or treated as a separate category and included in the matching. The matching procedure was performed using "nearest neighbour matching" and the propensity score logit as distance measure to select the best control matches from patients operated without concomitant CE for each individual in the CE group. The log-rank test was used to establish a difference in outcome between the groups.

Paper V

The hazard function for postoperative angiography both unadjusted and adjusted for mortality was calculated. In the subgroup of patients with a postoperative angiography and patency data on individual grafts the distribution of the target vessels of failed grafts was calculated. The patients were stratified by the indication for the procedure (i.e. CAD symptoms or other such as arrhythmia and valvular disease) and the time after surgery (≤1 or >1 year).

Results

Prognostic factors for postoperative angiography and need for reintervention (Paper I)

We compared patients operated with single IMA and no additional SVG (IMA), one additional SVG (1 SVG), and multiple additional SVGs (2+ SVG) with regard to mortality, clinically-driven angiography and reintervention.

Survival (95% CI) at 10 years was 77.2% (73.6–78.7), 76.4% (75.2–77.5), and 73.0% (72.5–73.6), respectively, for the three groups. The cumulative incidence (95% CI) at 10 years for the first clinically-driven postoperative angiography was 30.3% (27.6–32.2), 25.8% (24.6–27.0), and 21.2% (20.7–21.7), respectively, for the three groups. The cumulative incidence (95% CI) at 10 years for the first need for reintervention was 16.8% (14.6–19.4), 14.8% (13.9–15.9), and 11.0% (10.6–11.4), respectively, for the three groups (Figure 2).

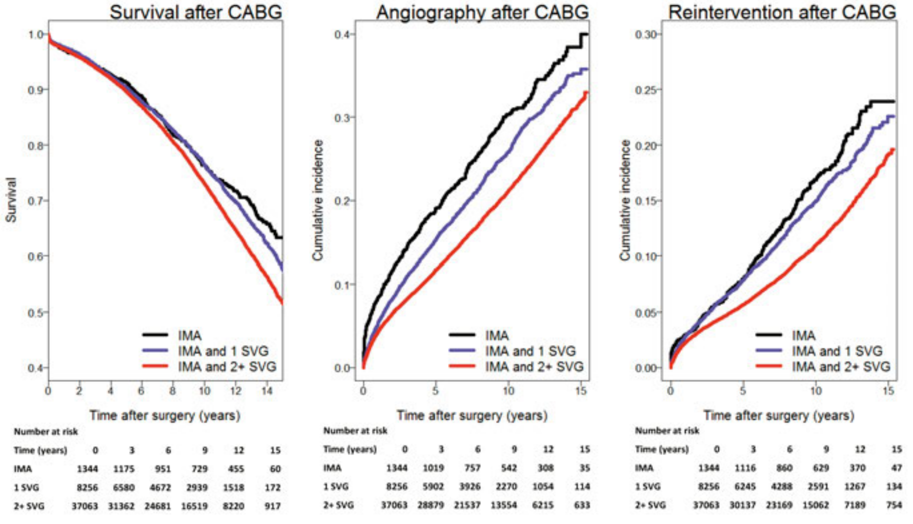

Figure 2. Overall survival, incidence of first clinically-driven angiography, and need for reintervention in individuals who underwent isolated CABG with single IMA and SVG in Sweden 2001–2015. Results for the three groups with a single IMA anastomosis, a single IMA and one SVG anastomosis, and a single IMA and two or more SVG anastomoses.

Among the most important known risk factors for early and long-term mortality in the base-line covariates [92, 99] we also identified prognostic factors for postoperative angiography and need for reintervention. Young age, female sex, presence of diabetes, normal left ventricle function, previous PCI, prior MI, emergency surgery were associated with a higher risk (Figure 3). Although the number of grafted vessels did not influence mortality, the incidence of angiography and the need for reintervention was higher in the patients operated with only a single or no SVG when compared to those with multiple additional SVGs. Most comorbidity covariates seem, however, to have a lesser degree of influence on the angiography related outcomes compared with mortality.

Variable	Death Hazard ratio [95%CI]	First angiography Hazard ratio [95%CI]	First reintervention Hazard ratio [95%CI]
Age group			
40-50 (ref.)	1	1	1
50-60	1.34 [1.15-1.57]	0.79 [0.73-0.87]	0.80 [0.72-0.90]
60-70	2.31 [1.99-2.68]	0.61 [0.56-0.67]	0.58 [0.52-0.65]
70-80	4.54 [3.91-5.27]	0.45 [0.41-0.50]	0.39 [0.34-0.44]
Female sex	0.85 [0.81-0.89]	1.14 [1.08-1.21]	1.13 [1.05-1.22]
BMI			
<25 (ref.)	1	1	1
25-30	0.99 [0.95-1.04]	1.04 [0.98-1.10]	1.06 [0.98-1.15]
>30	1.26 [1.19-1.33]	1.09 [1.02-1.16]	1.10 [1.01-1.21]
Diabetes	1.63 [1.57-1.70]	1.25 [1.19-1.32]	1.25 [1.17-1.34]
Renal impairment (CC)			
Normal (>85) (ref.)	1	1	1
Moderate (50-85)	1.19 [1.13-1.26]	1.01 [0.96-1.07]	1.01 [0.94-1.08]
Severe (<50)	1.92 [1.78-2.06]	0.98 [0.88-1.10]	1.00 [0.85-1.16]
On dialysis	3.87 [3.24-4.62]	1.49 [1.16-1.90]	1.42 [0.99-2.03]
Left ventricular ejection fraction			
Normal (ref.)	1	1	1
Moderate (30-50%)	1.34 [1.28-1.40]	0.95 [0.90-1.01]	0.87 [0.80-0.95]
Severe (<30%)	2.00 [1.84-2.18]	1.03 [0.92-1.17]	0.75 [0.62-0.91]
Peripheral vascular disease	1.38 [1.30-1.47]	1.15 [1.06-1.25]	1.19 [1.06-1.35]
COPD	1.35 [1.26-1.45]	1.11 [1.01-1.22]	1.03 [0.90-1.19]
Neurologic disability	1.32 [1.15-1.51]	1.06 [0.89-1.26]	1.09 [0.86-1.38]
Prior myocardial infarction	1.09 [1.04-1.13]	0.96 [0.91-1.01]	0.96 [0.90-1.03]
Previous PCI	0.98 [0.92-1.05]	1.24 [1.17-1.32]	1.24 [1.14-1.34]
Operation without CPB	1.12 [1.01-1.23]	1.11 [1.00-1.24]	1.10 [0.95-1.27]
Emergency surgery	1.17 [1.06-1.28]	1.26 [1.13-1.41]	1.17 [1.00-1.36]
Number of anastomoses			
3+ (ref.)	1	1	1
2	0.96 [0.91-1.01]	1.20 [1.13-1.26]	1.26 [1.17-1.36]
1	0.94 [0.83-1.08]	1.23 [1.09-1.39]	1.19 [1.01-1.41]

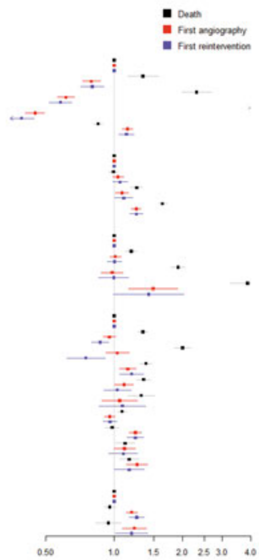

Figure 3. Multivariable Cox regression model. Adjusted hazard ratios and 95% CIs for death, first angiography, first need for reintervention in patients who underwent primary isolated CABG with IMA and SVG in Sweden between 2001 and 2015.

Angiography and occurrence of graft failure (Paper I)

Failed grafts were found in 21.4% of the angiographies following CAD symptoms in patients in the IMA group and 61.1% in the 2+ SVG group (Table 1). There were no failed grafts found in the IMA group and 32.5% of patients had failed grafts in the 2+ SVG group when the indication for the angiography was other than symptoms of CAD (arrhythmia, heart failure, valvular disease, research).

Table 1. *The reported occurrence of failed grafts with different indications for the postoperative angiography. Results are shown for single IMA with no, one or multiple SVG anastomoses.*

	IMA	**1 SVG**	**2+ SVG**
Total number	370	1649	6621
CAD symptoms			
Failed grafts	21.4%	41.6%	61.1%
No data	8.6%	6.3%	4.8%
Other indications			
Failed grafts	0.0%	18.8%	32.5%
No data	41.9%	12.1%	9.7%

Effects of multiple arterial grafting on long-term outcome (Paper II)

After exclusion, the study population comprised 46 343 cases of IMA + SVG, 1036 cases of IMA + RA and 862 cases of BIMA. The mean follow-up time (SD) was 9.3 (4.2) years for IMA + SVG, 10.7 (4.1) years for IMA + RA grafts and 5.5 (5.0) years for BIMA grafts (Figure 4).

Unadjusted survival (95% CI) at 10 years was 73.4% (73.0–73.9), 77.1% (74.1–79.8), and 77.0% (71.9–81.3), respectively, for the three groups. The cumulative incidence (95% CI) at 10 years for the first clinically-driven post-operative angiography was 21.9% (21.4–22.4), 22.4% (19.7–25.5), and 26.1% (21.5–31.3), respectively, for the three groups. The cumulative incidence (95% CI) at 10 years for the need for reintervention was 11.6% (11.2–12.0), 11.9% (9.8–14.6), and 15.5% (12.0–19.9), respectively for the three groups.

After adjustment for risk factors the outcome was similar for the IMA + SVG and IMA + RA but it seemed to be a trend towards a higher incidence of angiography and a higher incidence of reintervention in the BIMA group (Table 2).

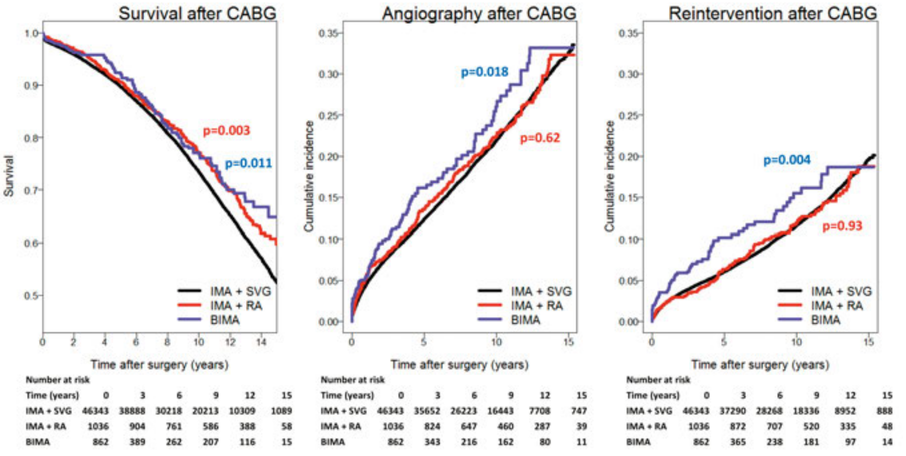

Figure 4. Survival, cumulative incidence of angiography and need for reintervention after CABG for the IMA + SVG, IMA + RA and BIMA group. Tables of number of patients at risk are also shown. The pairwise log-rank test was used to establish a difference between the IMA + SVG and the other groups and the resulting p-values are displayed in the graphs.

Table 2. *Cox regression for risk of death, first clinically-driven angiography and first reintervention for the IMA + SVG, IMA + RA and BIMA group. Hazard ratios (HR) were adjusted for age (40–50, 50–60, 60–70 or 70–80 years), sex, number of distal anastomoses (2, 3, 4 or 5+) , BMI (<25, 25-30 or >30), diabetes status, kidney function (creatinine clearance >85, 50-85, <50 or dialysis), COPD, neurologic disability, left ventricle ejection fraction (normal, 30-50%, <30%), MI prior to operation, previous PCI, urgency of operation (before first working day) and use of cardiopulmonary bypass.*

	IMA + SVG	IMA + RA	BIMA
Death			
HR unadjusted (CI 95%)	1 (ref.)	0.84 (0.74–0.94)	0.78 (0.64–0.95)
HR adjusted (CI 95%)	1 (ref.)	1.01 (0.89–1.14)	0.87 (0.72–1.06)
Angiography			
HR unadjusted (CI 95%)	1 (ref.)	1.03 (0.91–1.18)	1.24 (1.04–1.47)
HR adjusted (CI 95%)	1 (ref.)	0.96 (0.84–1.10)	1.13 (0.95–1.35)
Reintervention			
HR unadjusted (CI 95%)	1 (ref.)	0.99 (0.83–1.19)	1.39 (1.11–1.75)
HR adjusted (CI 95%)	1 (ref.)	0.91 (0.75–1.09)	1.26 (1.00–1.58)

Long-term outcome after grafting with “no-touch” saphenous vein grafts (Paper III)

We compared 1371 patients operated with “no-touch” saphenous vein grafts (NTT) with a propensity-matched cohort of patients with conventional vein grafts (CT) with regard to mortality, clinically-driven angiography and reintervention. The mean (SD) follow-up was 6.8 (3.3) years in the NTT group and 6.6 (3.2) years in the CT group (Figure 5).

Mortality occurred in 14.5% (196/1349) of NTT patients and 14.5% (195/1349) of CT patients during follow-up. Post-operative clinically-driven angiography occurred in 14.0% (189/1349) of NTT patients and 16.7% (225/1349) of CT patients and reintervention in 8.9% (120/1349) of NTT patients and 8.3% (122/1349) of CT patients during follow-up. Before as well as after adjustment for risk factors there was a higher risk of angiography in the CT group (Table 3).

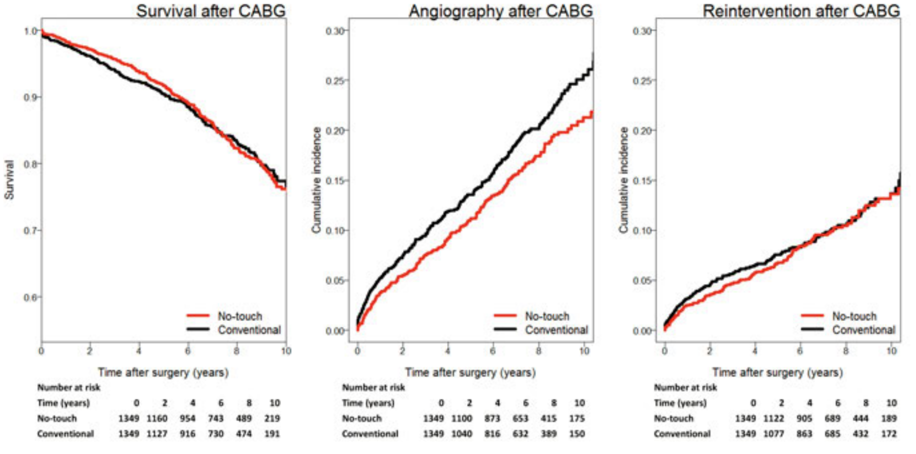

Figure 5*.* Survival, cumulative incidence of first angiography and first reintervention after CABG for the NTT and CT group. Tables of number of patients at risk are also shown.

Table 3. *Cox regression for risk of death, first clinically-driven angiography and first reintervention for the "no-touch" group as compared to the control group. Hazard ratios (HR) were adjusted for age (40–50, 50–60, 60–70 or 70–80 years), sex, number of distal anastomoses (2, 3, 4 or 5+) , BMI (<25, 25–30 or >30), diabetes status, kidney function (creatinine clearance >85, 50–85, <50 or dialysis), COPD, neurologic disability, left ventricle ejection fraction (normal, 30-50%, <30%), MI prior to operation, previous PCI, urgency of operation (before first working day) and use of cardiopulmonary bypass.*

	Conventional	No-touch	p-value
Death			
HR unadjusted (CI 95%)	1 (ref.)	1.03 (0.79–1.18)	0.76
HR adjusted (CI 95%)	1 (ref.)	0.97 (0.80–1.19)	0.80
Angiography			
HR unadjusted (CI 95%)	1 (ref.)	0.80 (0.66–0.97)	0.022
HR adjusted (CI 95%)	1 (ref.)	0.76 (0.63–0.93)	0.007
Reintervention			
HR unadjusted (CI 95%)	1 (ref.)	0.95 (0.74–1.22)	0.69
HR adjusted (CI 95%)	1 (ref.)	0.91 (0.71–1.17)	0.47

Outcomes after coronary endarterectomy (Paper IV)

We compared 537 patients operated with concomitant CE (CE) with a propensity-matched cohort of patients without CE (No CE) with regard to mortality, clinically-driven angiography and reintervention. The mean (SD) follow-up was 9.9 (4.6) years in the CE group and 10.0 (4.6) years in the No CE group (Figure 6).

Survival (95% CI) at 10 years was 65.8% (60.8–70.3) and 70.7% (65.9–74.9), respectively, for the two groups. The cumulative incidence (95% CI) at 10 years for the first clinically driven postoperative angiography was 28.2% (23.8–34.3) and 21.7% (17.8–26.3), respectively, for the two groups. The cumulative incidence (95% CI) at 10 years for the need for re-intervention was 11.6% (8.7–15.3) and 12.7% (9.7–16.6), respectively, for the two groups. The observed difference in incidence of postoperative clinically-driven angiography was statistically significant.

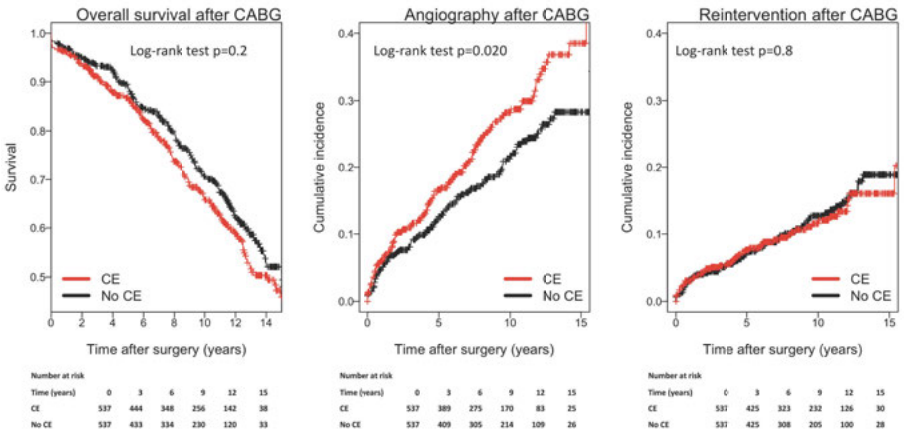

Figure 6. Survival, cumulative incidence of first angiography and first reintervention after CABG for the CE and No CE group. Tables of number of patients at risk are also shown.

Target coronary arteries of failed grafts (Paper V)

The study population was composed of 67 987 individuals, and of these, 6 977 had a postoperative angiography with patency data on individual grafts. Survival free from angiography at 10 and 20 years was (95% CI) 57.2% (56.8–57.6) and 16.8% (16.3–17.3), respectively. The proportion of the operated population that had been catheterized postoperatively at 10 and 20 years after surgery was (95% CI) 16.9% (16.6–17.2) and 27.9% (27.4–28.3), respectively. The hazard of experiencing a first postoperative angiography as well as the temporal distribution of all first angiographies (adjusted hazard) is presented in Figure 7.

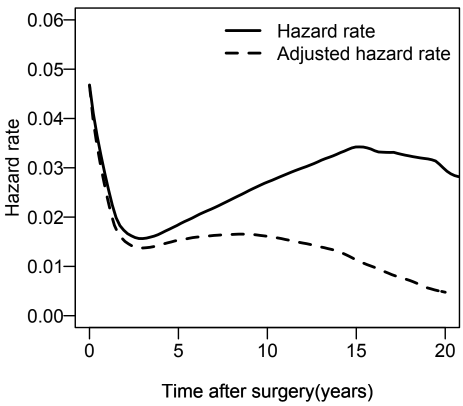

***Figure** 7.* Hazard rate and hazard rate adjusted for mortality for first angiography.

No failed grafts were found in 32.7% of individuals with symptoms suggestive of CAD ≤1 year after surgery, and in 33.7% >1 year after surgery (Table 4). In cardiac catheterizations ≤1 year after surgery a failed IMA graft to the left anterior descending coronary artery (LAD) was found in 18.4% of individuals with symptoms suggestive of CAD and 10.8% of individuals with other indications. A failed graft to a circumflex artery (CX) branch was found in 15.8% of individuals with symptoms suggestive of CAD and 4.3% of individuals with other indications, and multiple failed grafts to CX or right coronary artery (RCA) branches was found in 14.2% of individuals with symptoms suggestive of CAD and 6.5% of individuals with other indications. (Table 4) In cardiac catheterizations >1 year after surgery a failed IMA graft to the LAD was found in 10.2% of individuals with symptoms suggestive of CAD and 7.2% of individuals with other indications. A failed graft to a CX branch was found in 15.9% of individuals with symptoms suggestive of CAD and 9.6% of individuals with other indications, and multiple failed grafts to CX or RCA branches was found in 18.4% of individuals with symptoms suggestive of CAD and 8.8% of individuals with other indications (Table 4).

Table 4. *Target vessel(s) of individuals with failed graft(s). Data is presented for catheterizations performed ≤ or > 1 year after surgery and if the indication for the procedure was symptoms suggestive of coronary artery disease (CAD) or other indications (arrhythmia, valvular disease, heart failure). Failed grafts to the diagonal branch of LAD (Diagonal) are only registered if it is the only graft that has failed. LAD: Left anterior descending coronary artery, CX: Left circumflex coronary artery, RCA: Right coronary artery.*

	≤1year		**>1year**	
	CAD	**Other**	**CAD**	**Other**
Number of angiographies	660	46	5603	668
No failures	216 (32.7%)	30 (65.2%)	1889 (33.7%)	366 (54.8%)
LAD	46 (7.0%)	2 (4.3%)	301 (5.4%)	28 (4.2%)
LAD + CX or RCA	75 (11.4%)	3 (6.5%)	267 (4.8%)	20 (3.0%)
CX	104 (15.8%)	2 (4.3%)	893 (15.9%)	64 (9.6%)
Multiple CX or RCA	94 (14.2%)	3 (6.5%)	1031 (18.4%)	59 (8.8%)
RCA	87 (13.2%)	5 (10.9%)	936 (16.7%)	106 (15.9%)
Diagonal	38 (5.8%)	1 (2.2%)	286 (5.1%)	25 (3.7%)

Discussion

Postoperative angiography and reintervention as endpoints in studying outcome after CABG surgery

Base-line prognostic factors for angiography and need for reintervention

Most comorbidity covariates seem to have a lesser degree of influence on the risk of angiography and reintervention compared with mortality. Even though patients receiving multiple grafts presumably have more advanced coronary atherosclerosis and in addition carry the risk from potential graft failures, the incidence of repeated angiography and reintervention was lower than for the IMA group. This relation holds true after adjustment for other factors where notably young age and female sex seem to contribute to an increasing risk. Patients receiving few grafts could have done so as part of a planned hybrid procedure or as a consequence of an inability to find target vessels, but although an increased difference in the incidence of angiography is seen directly after surgery, the large majority of the procedures occur later. One interpretation of these results is that vessels grafted with vein grafts have a lower risk of failure compared to symptomatic disease progression in the native coronary arteries.

Angiography and occurrence of graft failure

Both symptomatic and asymptomatic graft failures will be discovered in conjunction with an angiography regardless of indication. In our study of clinically-driven angiographies we found failed grafts in 33% of angiographies with indications other than suspected symptomatic CAD in patients having received multiple SVGs. Assuming that effects of failed grafts did not influence the indication for angiography this also could reflect the graft status for other asymptomatic individuals. On the contrary, none of the patients with IMA graft only who performed an angiography for other reasons than CAD had a failed graft, suggesting that a failure of the IMA more rarely occurs without symptoms.

With symptoms of CAD as indication for the catheterization it was more common to find concurrent graft failure but although failed grafts were often found in multi-vessel grafted patients, 39% had no graft failures and substantial proportion of the failed grafts could be asymptomatic failures with no or only indirect relation to the presentation of symptoms. In more than 20% of angiographies following CAD symptoms in the IMA group, the graft had failed, implying that failure of the IMA graft possibly could be causing a substantial proportion of symptoms leading to the catheterizations where failed grafts were found, also in the 1 SVG and 2+ SVG groups.

Patients in the IMA and the 1 SVG groups had a higher risk of being submitted to angiography, but for the large majority no failed grafts were found in conjunction with the angiography. Graft failure does thereby not seem to be the main deciding factor for the long-term results in this group of patients. Again, this illustrates that the significance of disease progression in the native coronary vessels may be underestimated and likely to also be the cause of a substantial part of catheterizations and reinterventions after CABG with multiple grafts.

Effects of multiple arterial grafting on long-term outcome

An improved long-term survival in the Swedish CABG population receiving an arterial graft as a second conduit is to be expected, as these patients were overall younger and healthier than those receiving vein grafts. When adjusted for risk factors the observed improved survival in the IMA + RA and BIMA group disappears. The incidence of first clinically-driven angiography and need for repeat intervention was similar for the IMA + SVG and IMA + RA, but there seems to be a trend towards a higher incidence of angiography and a higher incidence of reintervention in the BIMA group. It appears as if this difference in incidence is established during the first years after surgery and later remains stable. An explanation for this finding could be that BIMA grafting is technically more challenging especially in combination with a setting when it is rarely performed. This in turn could contribute to a higher degree of technical failures during BIMA grafting, resulting in presentation of symptoms early after surgery and a subsequent reintervention. Even if some of these early failures could be avoided, do the overall results not support the view that any beneficial effects of multiple arterial grafting will become apparent during the first 10-15 years after surgery [34].

Long-term outcome after grafting with “no-touch” saphenous vein grafts

An improvement in the risk for new angiography could be seen for the “no-touch” group but not for the need of repeat intervention or survival. In the first randomised angiographic study of the NT vein, the patency in the group with conventional harvesting technique was high and the difference in patency between groups was initially small. This difference later increased gradually but was not significant and clinically relevant until the 8.5 and 16 years follow-up [49]. The mean follow-up in the current study could therefore be too short to be able to detect differences in clinical events.

There are large regional variations in Sweden how many CABG procedures are performed per number of inhabitants. Although partly explained by demographics and differences in incidence of CAD in the population, a substantial part of the variation is the result of a difference in the indications and threshold for referral for surgery versus PCI. According to the 2015 report from the SWEDEHEART registry the number of patients referred for CABG surgery in Örebro ranged between 25.4 and 28.2 per 100 000 inhabitants, which is close to the national average of 26.3 [100]. The medical therapy given to patients after surgery could also be subjected to regional differences. There is thus a possibility for regional variability during follow-up that could introduce confounding. The vast majority of patients in Örebro were operated with the NT technique making the patients receiving conventional vein grafts in this institution a highly selected population also depending on several factors not included in the baseline data. Conventional vein harvesting is more often preferred in the fragile patients where straight-forward surgery is the priority, especially in women in whom the harvesting of NT veins might be technically more demanding. NT is favoured in patients with expected long survival, but also in patients with coronary vessels of poor quality. In order to avoid confounding, patients with conventional vein grafts operated in Örebro were therefore not included in the analysis.

Outcome after adjunct coronary endarterectomy

In the current era, patients referred for CABG have more comorbidity and the considerable variations of baseline demographics in patients performing CE with CABG and isolated CABG cannot be neglected. Livesay et al. [101] reported that analysis of preoperative variables revealed a high proportion of male sex, diabetes mellitus, low ejection fraction and multiple vessel disease in patients requiring coronary endarterectomy. In the meta-analysis by Wang et al [80], it was shown that in high-risk patients, the incidence of perioperative MI after CE and CABG was markedly higher than that after isolated CABG. Furthermore, patients undergoing CE carry a higher degree of diffuse coronary artery disease.

We could demonstrate poorer short- and long-term outcome in patients undergoing isolated CABG with concomitant CE compared to those with isolated CABG. The incidence of postoperative clinically-driven angiography was higher in patients having CE although the endarterectomy cohort did not show higher rates of coronary re-intervention. CE still seems to be an acceptable treatment alternative with acceptable long-term results, for patients who have diffuse coronary artery disease which cannot be treated effectively by CABG alone.

There are potential biased effects of confounding factors on study endpoints, such as the supposedly more diffuse nature of the atherosclerosis in the CE patients. A second intervention is generally offered for a newly developed discrete lesion or graft failure in otherwise a good-quality target coronary artery. When an endarterectomised vessel is found occluded or thrombosed, it is often not considered amenable for reintervention, be it interventional or surgical. In addition, the supposedly more diffuse nature of atherosclerosis in the coronary endarterectomy patients will also be somewhat discouraging for a reintervention. Patients previously undergoing endarterectomy are therefore less than ideal candidates for a second revascularization procedure, possibly explaining why coronary re-intervention rate was less than expected in the coronary endarterectomy group, even though postoperative angiography was more frequent.

Target vessels of failed grafts

We present data in a large cohort of individuals operated with single IMA and SVGs with at least 3 distal anastomoses and study the distribution of target vessels of failed grafts found during clinically-driven angiography following symptoms suggestive of CAD or for other indications. As the other indications e.g., valvular disease or arrhythmia often are unrelated with ischemic heart disease these investigations resemble protocol angiography and most graft failures found during these catheterizations are presumably asymptomatic.

Postoperative angiography is not uncommon after CABG and 20 years after surgery 28% of the initially operated patients have experienced an angiography, most commonly due to the return of CAD symptoms. In our study almost one third of catheterized individuals with CAD symptoms did not demonstrate any failed grafts and of the remaining patients with failed grafts a significant proportion is expected to have asymptomatic failures. In 18.4% and 10.2% of early and late angiographies respectively, the IMA-graft had failed. It is therefore not unreasonable to believe that the symptoms are unrelated to SVG failure for a significant proportion of events leading to the early catheterizations.

The risk of re-angiography seems to be high the first year after surgery after which it sharply decreases and then again increases with time (Figure 7). Early graft failures are probably the result of technical failures or thrombosis [24] and the development of hemodynamically important atherosclerotic graft stenosis, both symptomatic and asymptomatic, rarely occur within the first 3 years after surgery [102]. The risk of presenting with CAD symptoms will be composed of the combined risks of early and late IMA and SVG failures as well as the risk of progression of atherosclerotic lesions in the coronary arteries (Figure 8). Assuming that the risk of clinically important coronary events in the native coronary arteries does not decrease with time, this baseline hazard can be estimated to be close to the total hazard at 3 years (Figure 7). The hazard consisting of both of coronary and graft events only seems to approach the double of this level after 15 years. Due to the high mortality in the operated population, only a minority of first postoperative angiographies will occur later than 10 years after surgery (Figure 7). Of these, as demonstrated in Figure 8, only a fraction will directly be caused by failing SVG grafts. This implies that it may be difficult to detect an improvement in long-term clinical outcomes in patients operated with any type of superior graft and may also explain the lack of improvement in mid-term results after grafting with multiple arterial conduits [34].

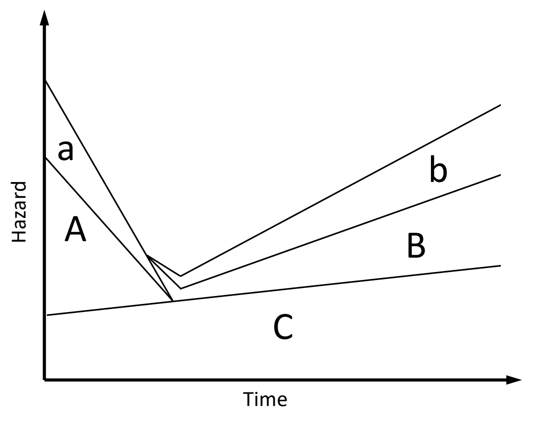

Figure 8. The hazard of the return of CAD related symptoms after CABG surgery can be described as the sum the hazard of early symptomatic vein graft failures (A) and IMA graft failure (a), late symptomatic failures due to vein graft disease (B) and atherosclerotic lesions in IMA (b) and symptomatic progression of atherosclerotic lesions in the coronary arteries (C). Only the hazard represented with area B will be affected by the use of alternatives to SVGs that are resilient to vein graft disease.

Limitations

The interpretation of the results in all of the studies is limited by the registry-based design and the possibility of residual confounding. Data was not available on all relevant prognostic factors and comorbidities and some of the co-variates have a large proportion of missing values. Methods for revascularisation are influenced by local surgical tradition, the surgeon's preference, undetermined patient-related factors and patients are not evenly distributed over all centres in Sweden. The incidence of angiography may reflect the return of CAD symptoms but is influenced by factors such as rates of surveillance with functional studies and physician threshold for repeat angiography versus optimisation of medical therapy. There could be different thresholds for different institutions and groups of patients and these could be changing over time. Neither the exact configuration of the grafts (e.g. sequential- or y-grafts) nor the targeted vessels can be identified in the registry and the degree of obstruction of the target vessels is also unknown. There was no formal definition of an occluded or significantly stenosed graft and it was completely operator-dependent. It is impossible to establish when a graft failed, what type it was or if the presence of the failed graft in any way was a contributing cause of the symptoms preceding the angiography. It is also not possible to determine to what extent the patients were completely revascularized at time of surgery. The smoking status and post-operative antithrombotic, antihypertensive or lipid lowering treatment was not known.

Conclusions

Postoperative angiography seems to be a useful endpoint in studying long-term outcome after CABG surgery. It is less sensitive than mortality to variations in the baseline covariates and thereby possibly less susceptible to confounding by indication. Data on catheterizations are probably more reliable than data on readmissions for CAD related events and more relevant than mortality in measuring improvements in outcome after surgery. Almost every possible aspect of CABG surgery has been intensely studied, but the process of graft failure has, despite having been much in focus, not yet been understood. Most graft failures occur early and are highly dependent on the properties of the target vessel or may be related to technical problems with the anastomosis. They are, furthermore, often asymptomatic and do not seem have any prognostic consequences. Failures related to the progressive atherosclerotic graft disease have been much less often studied and it is very difficult to assess how the outcome would be affected if this process could be slowed or avoided. The causation behind the return of CAD symptoms after CABG surgery and the relative importance of the individual contributions from early vein graft failures, vein graft disease, failure of the IMA graft, as well as from progression of atherosclerotic plaques in both grafted and non-grafted coronary arteries, remains to be determined.

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Sammanfattning på svenska

Bypasskirurgi har under lång tid varit världens vanligaste hjärtoperation och en hörnpelare i behandlingen av kranskärlssjukdom. Bara i Sverige genomförs årligen cirka 2500 operationer. De postoperativa resultaten efter ingreppet hör till de mer undersökta. Flertalet kliniska studier har visat att även de kärl som används till att leda blodet förbi förträngningar i kranskärlen löper en hög risk för att utveckla åderförkalkning och uttalade förträngningar vilket i sin tur kan leda till återkomst av kärlkramp eller hjärtinfarkter. Det har därför gjorts försök att förändra operationstekniken med målet att förbättra hållbarheten på de nya kärlen.

Genom att använda ett nationellt kvalitetsregister för hjärtkirurgi och kranskärlsröntgen har vi studerat långtidseffekterna av olika operationstekniker vid kranskärlskirurgi i Sverige. Som utfallsmått har vi primärt valt att använda förnyad kranskärlsröntgen då detta utfall vid sidan av överlevnad bedöms som ett av de mest relevanta för att utvärdera det kliniska långtidsresultatet efter kranskärlskirurgi. Det har dock inte använts tidigare använts in någon större omfattning i registerstudier.

Kranskärlsröntgen framstår i våra studier som ett mycket användbart utfallsmått då det förutom att vara en klinisk betydelsefull händelse också är relativt okänsligt för andra patientrelaterade faktorer såsom exempelvis samsjuklighet. Vi har vidare bland annat använt metoden till att studera långtidsresultaten efter bypassoperationer där artärer använts i större utsträckning än vener som bypasskärl och efter ingrepp där venerna som använts skördats med en mer skonsam teknik tillsammans med omgivande lager av bindväv. Trots att dessa typer av kärl i tidigare studier har visat sig ha en bättre hållbarhet kunde man inte se någon övertygande effekt på kliniska utfallsmått. Återkomst av kranskärlsrelaterade symptom efter bypasskirurgi beror på både utveckling av åderförkalkning i bypasskärlen och progress av sjukdom i hjärtats kranskärl där betydelsen av var och en av dessa processer ej är klarlagd. Hos en stor del av de bypasskärl som utvecklar förträngningar leder inte detta dessutom till några symptom och det är oklart hur mycket resultaten kan förbättras genom att bättre kärlmaterial används.

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