

Review

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# Choice of conduit for coronary artery bypass grafting: technical, anatomic, and pharmacologic considerations

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## Abstract

The choice of graft used to bypass stenoses in the coronary circulation is crucial to coronary artery bypass grafting (CABG) surgery and its success. Herein is a review of the existing literature on CABG grafts, including the discussion of utilization of different CABG grafts, patency of different grafts, and technical and other considerations pertinent to the use of each graft. Lastly, we present special considerations for graft selection in women.

**Keywords:** Coronary artery bypass grafting, graft selection, conduit selection

## INTRODUCTION

Coronary artery bypass grafting (CABG) provides blood flow distal to flow-limiting and non-flow-limiting coronary artery stenoses for the treatment of coronary artery disease (CAD). The choice of graft to bypass these stenoses is therefore of utmost importance to maximize the efficacy and biological benefits of CABG. Herein, we review the current literature on CABG grafts, their utilization in current clinical practice, and the most recent evidence on graft patency. We also review technical and anatomic considerations specific to the use of each graft, including harvesting technique, grafting strategy, and target vessel, among others. Lastly, given that women comprise roughly one-third of the CABG population yet have well-described



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poorer outcomes than men, we present special considerations for graft selection in women, as graft type and grafting strategy may contribute to this sex disparity.

## CABG GRAFTS

Grafts used for CABG can be grouped into two categories: arterial or venous. Arterial grafts include the left internal thoracic and right internal thoracic arteries (LITA and RITA, respectively), which are harvested from the chest wall, and the radial artery (RA), harvested from the upper extremities. The right gastroepiploic artery (RGEA), which is harvested from the abdomen, and the inferior epigastric artery, which is harvested from the abdominal wall, are rarely used in clinical practice<sup>[1,2]</sup>. Venous grafts include the greater and lesser saphenous veins (SVGs), harvested from the lower extremities, and the cephalic vein, which can be harvested from the upper arm.

## USE OF DIFFERENT CABG GRAFTS

The use of the LITA to bypass the left anterior descending artery (LAD) is widely accepted as the gold standard of CABG practice. A preponderance of observational data has demonstrated that the LITA has superior patency and outcomes compared with other grafts, venous or arterial, and accordingly, international professional guidelines give a Class 1 recommendation to use the LITA to bypass the LAD (American College of Cardiology [ACC]/American Heart Association [AHA]/Society for Cardiovascular Angiography and Interventions [SCAI] Class 1, Level of Evidence B-NR; European Society of Cardiology [ESC]/European Association for Cardio-Thoracic Surgery [EACTS]: Class 1, Level of Evidence B)<sup>[3,4]</sup>.

The RA is recommended by international professional guidelines as the second arterial graft (after the LITA to bypass the LAD) to bypass the second most important coronary target (ACC/AHA/SCAI Class 1, Level of Evidence B; ESC/EACTS: Class 1, Level of Evidence B-R)<sup>[3,4]</sup>. As interest in multiple arterial grafting (MAG), as opposed to single arterial grafting (SAG), has increased in the last two decades, the use rate of the RA has correspondingly increased. It has reported excellent patency rates but has more musculature than other arterial conduits, and therefore, vasospasm is a potential risk. In a recent analysis of the United Kingdom national cardiac surgery database including over 330,000 primary elective CABG patients from 1996-2018<sup>[5]</sup>, 84.4% of patients received SAG and 15.5% received MAG. Of those receiving MAG, the use rate of the RA ranged from 20% at the start of the study period to 60% at the endpoint of the study, with a peak of nearly 80% in 2001. The use rate of the RITA in MAG patients was at its peak of 80% at the start of the study period and fell to 40% at the endpoint of the study, with a nadir of 20% in 2001<sup>[5]</sup>. An analysis of the Society of Thoracic Surgeons (STS) database<sup>[6]</sup> from 2004 to 2015 of over 1.3 million CABG patients found that 10.6% of patients underwent MAG, with 61.4% of MAG patients receiving the RA and 46.0% of the MAG patients receiving the RITA (11,718 patients received both RITA and RA). Current ACC/AHA/SCAI guidelines give a weaker recommendation for the use of the RITA than for the RA, stating that it should be performed only in appropriately selected patients and only by surgeons with adequate experience (Class 2a, Level of Evidence B-NR)<sup>[3]</sup>, which is consistent with existing ESC/EACTS recommendations for bilateral ITA grafting<sup>[4]</sup>. This caution regarding the use of the RITA for MAG may be partly due to the reported increased risk of sternal wound infection seen when bilateral ITA grafting is used<sup>[7,8]</sup>, and should be considered during preoperative planning, particularly in high-risk patients<sup>[3]</sup>.

Despite professional guideline recommendations for the use of other grafts, SVGs remain the most commonly used CABG graft<sup>[6]</sup>, with a global use rate of nearly 90%<sup>[6,9]</sup>. Its high use rate despite its described poorer patency is likely due to the relative ease of harvesting the SVG, as well as surgeon familiarity, along with possible physician concerns such as spasm or sternal wound infection regarding the use of arterial grafts such as the RA and RITA, respectively<sup>[10]</sup>.

## CABG GRAFT FAILURE

While the majority of the data on graft failure, or graft occlusion that prevents blood flow to the myocardial territory targeted for revascularization, has been from older observational studies that are subject to confounders and biases<sup>[1,2]</sup>, there is recently available evidence from contemporary CABG trials. In an analysis of the Radial Artery Database International Alliance (RADIAL) database pooling patient data from six randomized CABG trials (1,091 pooled patients and 2,281 grafts) with mean angiographic follow-up of  $5.4 \pm 2.4$  years<sup>[11]</sup>, the SVG had a 17.5% occlusion rate. In comparison, the occlusion rate was 2.3% for the LITA<sup>[11]</sup>; all studied LITAs were grafted to the LAD. The occlusion rate of the RA was 9.4%<sup>[11]</sup>, including only RAs that were grafted to the non-LAD distribution. The occlusion rate of the RITA was 13.5%<sup>[11]</sup>, again, including only RITAs that were grafted to the non-LAD distribution.

A network meta-analysis of 18 randomized clinical trials (RCTs) including 6,543 patients and 8,272 grafts with 3.5-year mean angiographic follow-up, the conventionally harvested SVG had a pooled patency rate of 86.3% (95% confidence interval [CI] 81.2-90.2), the no-touch SVG had a pooled patency rate of 91.4% (95%CI: 87.3-94.3), the RA had a pooled patency rate of 94.1% (95%CI: 90.0-97.6), the RITA had a pooled patency rate of 89.2% (95%CI: 71.2-96.5), and the RGEA had a pooled patency rate of 61.2% (95%CI: 52.2-69.4)<sup>[12]</sup>.

The Radial Artery Patency and Clinical Outcomes (RAPCO) study compared RA outcomes and patency at 10-year follow-up in two trials: one comparing the RA and RITA and one comparing the RA and SVG. The 10-year analysis found that RA patency was 89% and RITA patency was 80% in the RA *vs.* RITA comparison (graft failure hazard ratio [HR] 0.45, 95%CI: 0.23-0.88), and RA patency was 85% and SVG patency was 71% for the RA *vs.* SVG comparison (graft failure HR 0.40, 95%CI: 0.15-1.00)<sup>[13]</sup>.

### Relationship between clinical outcomes and graft patency

Graft patency has historically been considered an important factor influencing graft choice, largely due to the accepted link between graft patency and clinical outcomes. Most published studies have demonstrated an association between graft failure and non-fatal clinical events, yet this association was derived from older observational studies that did not have protocolized, systematic graft imaging and that are also subject to selection and attrition biases<sup>[1,2,14]</sup>. A recent individual patient data meta-analysis by Gaudino *et al.* including seven CABG trials with per-protocol imaging, 4,413 patients, and 13,163 grafts (8,740 SVGs and 4,423 arterial grafts), examined the relationship of graft failure and clinical outcomes and found that graft failure was associated with an increased risk of the composite of myocardial infarction or repeat revascularization, both up until first imaging assessment at a median timepoint of 1.02 years (adjusted odds ratio [OR] 3.98, 95%CI: 3.54-4.47;  $P < 0.001$ ) and beyond (adjusted OR 2.59, 95%CI: 1.86-3.62;  $P < 0.001$ )<sup>[15]</sup>. Graft failure was also associated with all-cause death after the first imaging assessment (adjusted OR 2.79, 95%CI: 2.01-3.89;  $P < 0.001$ ). This analysis confirmed that in current practice, there is a strong association between graft failure and adverse cardiac events [Table 1]. In addition, Gaudino *et al.* found that both arterial (adjusted OR 2.09, 95%CI: 1.33-3.28;  $P = 0.001$ ) and vein (adjusted OR 1.97, 95%CI: 1.33-2.91,  $P = 0.001$ ) graft failure were associated with an increased risk of the composite of myocardial infarction or repeat revascularization before first imaging assessment<sup>[15]</sup>. However, some contemporary studies, including The Impact of Preoperative FFR on Arterial Bypass Graft Function (IMPAG) trial<sup>[16]</sup>, have suggested that lower degrees of preoperative native coronary artery stenosis may lead to chronic native competitive flow and thus asymptomatic arterial graft failure<sup>[16,17]</sup>. At angiographic six-month follow-up in the 64 IMPAG patients receiving arterial grafts, there was an association between preoperative fractional flow reserve (FFR) of  $\geq 0.78$  and better graft functionality<sup>[16]</sup>.

**Table 1. The relationship between graft failure and clinical events. A recent individual patient data meta-analysis by Gaudino et al. included seven CABG trials with per-protocol imaging and assessed the relationship between graft failure and clinical outcomes up until first imaging assessment (median timepoint of 1.02 years) and at all later timepoints<sup>[15]</sup>**

Timepoint	All grafts (n = 4,413), %	Graft failure (n = 1,487), %	No graft failure (n = 2,926), %	Adjusted odds ratio (95%CI)	I <sup>2</sup>
Before imaging					0%
MI or repeat revascularization	167 (3.8)	118 (8.0)	49 (1.7)	3.98 (3.54-4.47)	0%
MI	58 (1.3)	35 (2.3)	23 (0.8)	3.54 (1.78-7.01)	0%
Repeat revascularization	138 (3.1)	105 (7.1)	33 (1.1)	5.02 (3.23-7.82)	
After imaging					
MI or repeat revascularization	244 (5.5)	170 (11.4)	74 (2.5)	3.46 (1.44-8.34)	43%
MI	28 (0.6)	16 (1.1)	12 (0.4)	1.45 (0.67-3.14)	0%
Repeat revascularization	234 (5.3)	164 (11.0)	70 (2.4)	3.80 (1.24-10.83)	51%
Anytime					
MI or repeat revascularization	411 (9.3)	288 (19.4)	123 (4.2)	3.47 (2.43-4.95)	15%
MI	86 (1.9)	51 (3.4)	35 (1.2)	2.57 (1.56-4.25)	0%
Repeat revascularization	372 (8.4)	269 (18.1)	103 (3.5)	4.25 (2.31-7.80)	35%
All-cause mortality	223 (5.1)	163 (11.0)	60 (2.1)	2.79 (2.01-3.89)	0%

CI: Confidence interval; MI: myocardial infarction. Adapted from Gaudino et al.<sup>[15]</sup>.

## CLINICAL OUTCOMES WITH DIFFERENT CABG GRAFTS

Contemporary RCTs and meta-analyses have also compared the clinical outcomes of CABG by the type of graft used. Utilization of the RA has been associated with excellent clinical outcomes. Results were recently reported from 15-year follow-up of RAPCO, which reported the incidence of the primary outcome of the composite of mortality, myocardial infarction, and repeat revascularization was lower for the RA compared to RITA (39.4% vs. 48.5%, HR 0.74, 95%CI: 0.55-0.97;  $P = 0.04$ ) and for the RA compared to SVG (69.2% vs. 73.2%, HR 0.71, 95%CI: 0.52-0.98;  $P = 0.04$ )<sup>[18]</sup>. An individual patient data meta-analysis from the RADIAL database including five CABG RCTs and 1,036 patients<sup>[19]</sup> found that when compared with the use of the SVG, at 10 years, there was an association between the use of the RA and significantly lower incidence of both the composite of death, MI, or repeat revascularization (HR 0.73, 95%CI: 0.61-0.88;  $P < 0.001$ ) and with a lower incidence of the composite of death or myocardial infarction (HR 0.77, 95%CI: 0.63-0.94;  $P = 0.01$ ).

The Arterial Revascularization Trial (ART) was a large, multicenter RCT investigating the outcomes of 3,102 CABG in patients randomized to either single ITA or bilateral ITA grafting. At 10-year follow-up, there was no difference in mortality between patients receiving bilateral ITA grafting (20.3%) and single ITA grafting (21.2%, HR 0.96, 95%CI: 0.82-1.12;  $P = 0.62$ ). There was also no difference between groups in the composite outcome of mortality, myocardial infarction, or stroke (24.9% vs. 27.3%, HR 0.90, 95%CI: 0.79-1.03)<sup>[20]</sup>. This study had notable limitations, including a 13.9% crossover from bilateral ITA grafting to single ITA grafting, as well as a lack of pre-defined study criteria for the use of the second arterial conduit, such that 21.8% of the patients in the single ITA group receiving RA grafting. More data on clinical outcomes of CABG with MAG, with the RA and RITA as second arterial grafts, will be provided by the randomized comparison of the clinical outcome of single vs. multiple arterial grafts (ROMA) trial (NCT 03217006).

## CONSIDERATIONS FOR USE OF THE SVG

### Harvesting technique

Early graft failure secondary to acute thrombosis is predominantly observed in vein grafts rather than

arterial grafts<sup>[21]</sup>, and injury to the vein graft intima, often incurred intraoperatively during harvesting, is a risk factor for graft failure. The conventional open approach for SVG harvesting removes the perivascular tissue with subsequent manual distension of the graft with heparinized saline up to pressures of 600 mmHg<sup>[22]</sup>. The no-touch approach for SVG harvesting<sup>[23]</sup> preserves the perivascular tissue with the aim of minimizing damage to the graft, reducing intimal injury, and thus reducing vein graft occlusion, and has previously been described<sup>[23]</sup>. Small, single-center RCTs<sup>[24-26]</sup> have demonstrated lower rates of graft occlusion with no-touch SVG harvesting. One large trial, the Graft Patency Between no-touch Vein Harvesting Technique and Conventional Approach in Coronary Artery Bypass Graft Surgery (PATENCY) trial<sup>[27]</sup> randomized 2,655 CABG patients to either conventional or no-touch harvesting, and found that at 1-year postoperative follow-up, the risk of SVG occlusion was decreased in the no-touch compared with the conventional harvesting group (3.7% vs. 6.5%, OR 0.56, 95%CI: 0.41-0.77;  $P < 0.001$ ); however, the incidence of major adverse cardiac and cerebrovascular events was not different between groups (3.8% vs. 4.3%, OR 0.89, 95%CI: 0.61-1.29;  $P = 0.53$ ). The no-touch group had a higher incidence of local harvest site issues including exudation (4.3% vs. 1.9%;  $P < 0.01$ ), numbness (23.2% vs. 17.8%;  $P < 0.01$ ), and edema before discharge (19.0% vs. 12.9%;  $P < 0.01$ ); however, there was no difference in the need for re-intervention on the wound prior to hospital discharge (0.9% vs. 0.4%;  $P = 0.09$ ). The need for re-intervention or pain at the harvest site at one year was similar between groups. The ongoing SWEDEGRAFT trial (NCT 03501303) will provide additional information on this important topic<sup>[28]</sup>.

Endoscopic vein harvesting (EVH) was first introduced with the aim of decreasing the incidence of local harvest site complications and postoperative pain (the technique has been previously described<sup>[29]</sup>), but may risk endothelial injury secondary to greater intraoperative manipulation, as discussed above. A meta-analysis of 22 studies (five RCTs) and 27,911 patients with at least one-year follow-up found that local harvest site complications occurred less frequently with EVH than with open vein harvesting (OVH) (0.75% vs. 2.92%, OR 0.19, 95%CI: 0.12-0.30;  $P < 0.001$ )<sup>[30]</sup>, and with no difference in all-cause mortality (incidence rate ratio [IRR] 0.98, 95%CI: 0.48-1.99;  $P = 0.95$ ) and major adverse cardiac events (IRR 1.01, 95%CI: 0.12-0.31;  $P < 0.001$ ) between EVH and OVH. However, at one to five years, EVH was associated with lower SVG patency than OVH (73.7% vs. 77.81%, OR 0.80, 95%CI: 0.70-0.91;  $P < 0.001$ ). Similarly, another meta-analysis<sup>[31]</sup> of five studies and 6,504 grafts with angiographic follow-up found that EVH was associated with a higher risk of graft failure (OR 1.38, 95%CI: 1.01-1.88;  $P < 0.0001$ ), and a similar meta-analysis of 11 studies reported lower SVG failure with open vein harvesting at a mean 2.6-year follow-up (17.7% vs. 24.9%; OR: 0.61; 95%CI: 0.43-0.87;  $P = 0.01$ )<sup>[32]</sup>. An additional consideration for SVG harvesting is the type of intraoperative storage solution used, as this may also affect vein graft integrity and, therefore, risk of failure<sup>[33]</sup>. Current debate centers on commonly used storage solutions such as saline, pH-buffered saline solutions, as normal saline solution may be detrimental to the endothelial integrity of the vein graft, or blood solutions. Evidence from *ex-vivo* studies and animal studies on the relationship between vein graft solution and vein graft failure, and on the optimal storage solution, has remained inconclusive. There has not been a randomized, blinded trial comparing graft patency by vein graft storage solution, and consequently, variations in clinical practice persist.

### External stenting

Late vein graft failure, or that occurring at the first postoperative year or later, is characterized by intimal hyperplasia and atherosclerosis, processes to which vein grafts are particularly susceptible<sup>[9,21,34,35]</sup>. External, cobalt-chromium mesh stenting devices have been introduced to prevent this process<sup>[36-38]</sup>, and a series of RCTs, the Venous External Support Trials (VEST), were conducted to test these devices. VEST I enrolled 30 patients randomized to receive a single stented SVG to either the right or the circumflex coronary territories (30 grafts), while one or more SVGs were not stented (39 grafts). Intravascular ultrasound assessment found that the area of intimal hyperplasia was smaller in the stented group (mean 4.37 mm<sup>2</sup>) than in the non-

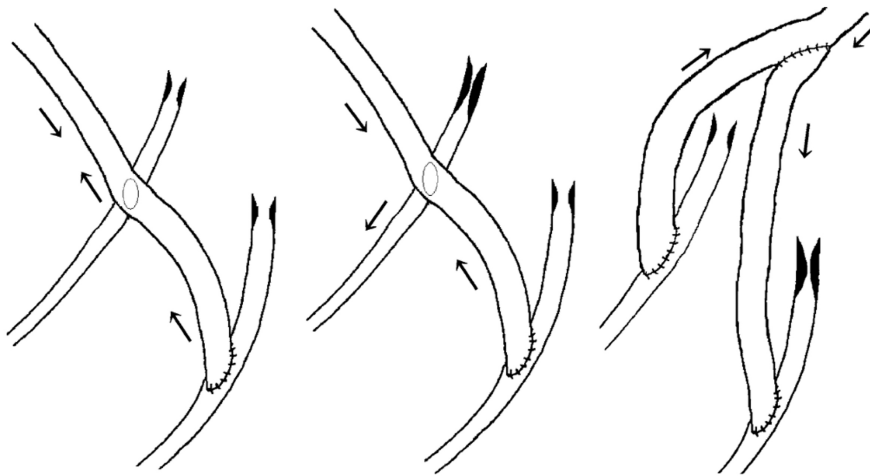
stented group (5.12 mm<sup>2</sup>;  $P = 0.04$ ); however, at angiographic follow-up at one year, there was no difference between groups in SVG failure (30.0% vs. 28.2%,  $P = 0.55$ )<sup>[39]</sup>. VEST IV, which reported a 4.5-year follow-up, similarly found no difference in SVG failure rate between stented grafts and those not stented (30.0% vs. 23.0%;  $P = 0.42$ )<sup>[40]</sup>. VEST II studied stented SVGs grafted to the right coronary territory and found that at a three-to-six-month follow-up, there was no difference in SVG patency between stented grafts and those not stented (86.2% vs. 88.8%)<sup>[41]</sup>. VEST III included 184 patients randomized to receive one stented SVG and found no difference in graft patency between stented grafts and those not stented at two-year follow-up (78.3% vs. 88.8%;  $P = 0.43$ )<sup>[42]</sup>.

### Anastomotic technique

There is limited and conflicting data on the relationship between the anastomotic technique of SVG grafting and angiographic and clinical outcomes. Both individual anastomosis and sequential anastomosis [Figure 1], which allows for a greater degree of myocardial revascularization by a single graft, may be used to graft the SVG<sup>[10]</sup>. An observational study of 901 propensity-matched pairs of CABG patients (891 matched pairs of grafts) with median 7.3-year follow-up found a lower risk of graft failure in the sequentially anastomosed SVG group than in the individually anastomosed SVG group (HR 0.69, 95%CI: 0.50-0.95;  $P < 0.02$ )<sup>[43]</sup>, yet there was no difference in the risk of the composite of death, non-fatal myocardial infarction, and repeat revascularization between the sequentially grafted and individually grafted SVG groups (36.8% vs. 41.4%, HR 0.91, 95%CI: 0.75-1.09;  $P = 0.30$ ). However, a sub-analysis of the Project of *ex-vivo* vein graft engineering via transfection (PREVENT-IV) trial of 3,014 CABG patients and 1,045 patients with sequentially grafted SVGs found that the sequentially grafted SVG group had a higher incidence of graft occlusion (30.5% vs. 24.1%, adjusted OR 1.24, 95%CI: 1.03-1.48;  $P = 0.025$ ) at one year, and at five years, the incidence of the adjusted composite of death, myocardial infarction, and repeat revascularization was significantly higher in patients with sequentially grafted SVGs (35.2% vs. 31.1%, adjusted HR 1.15, 95%CI: 1.00-1.31;  $P = 0.045$ )<sup>[44]</sup>.

### Pharmacotherapy

The mechanism of early SVG failure is acute graft thrombosis, and preventing it is the target of currently recommended antithrombotics after CABG<sup>[9,34,45]</sup>. Both American and European professional guidelines recommend the use of aspirin for antithrombosis after CABG, but with slight differences in timing and dosing: The ACC/AHA/SCAI recommendation for pharmacotherapy after CABG and is 100-325 mg of aspirin daily within 6 h of CABG, continued indefinitely, to reduce the risk of SVG closure and adverse cardiac events (Class of Recommendation 1, Level of Evidence A)<sup>[3]</sup>, and the ESC/EACTS recommendation is for 75-100 mg of aspirin within 24 h of CABG or once there are no bleeding concerns (Class of Recommendation 1, Level of Evidence C). However, both recommendations are based on decades-old RCTs<sup>[34,46,47]</sup>. Recent studies have investigated using an oral P2Y<sub>12</sub> inhibitor (ticagrelor) for the prevention of SVG failure, but a study comparing ticagrelor alone with aspirin alone did not reduce the risk of SVG failure at one- and two-year follow-up<sup>[48,49]</sup>. The addition of ticagrelor to aspirin as a dual antiplatelet regimen after CABG has also been investigated in recent RCTs<sup>[50,51]</sup>. An individual patient data meta-analysis<sup>[50]</sup> including four RCTs, 1,316 CABG patients, and 1,668 SVGs compared a ticagrelor and aspirin dual antiplatelet regimen with aspirin monotherapy and found that a ticagrelor-based dual antiplatelet regimen was associated with a lower risk of SVG failure (11.2% vs. 20%, OR 0.51, 95%CI: 0.35-0.71;  $P < 0.001$ ). However, ticagrelor-based dual antiplatelet therapy was also associated with an increased risk of clinically important bleeding events (22.1% vs. 8.7%, OR 2.98, 95%CI: 0.35-0.74;  $P < 0.001$ )<sup>[50]</sup>. Since the risk of acute graft thrombosis after CABG is the highest within one month of surgery<sup>[45]</sup>, short-term dual antiplatelet therapy (followed by continued aspirin therapy) may help prevent SVG failure in the first month, but with an attenuated risk of bleeding events compared with long-term dual antiplatelet therapy. The forthcoming ODIN trial (NCT 05997693) will provide important answers on this novel antithrombotic approach.



**Figure 1.** Diagram of sequential grafting. Adapted from Nakajima et al.<sup>[74]</sup>.

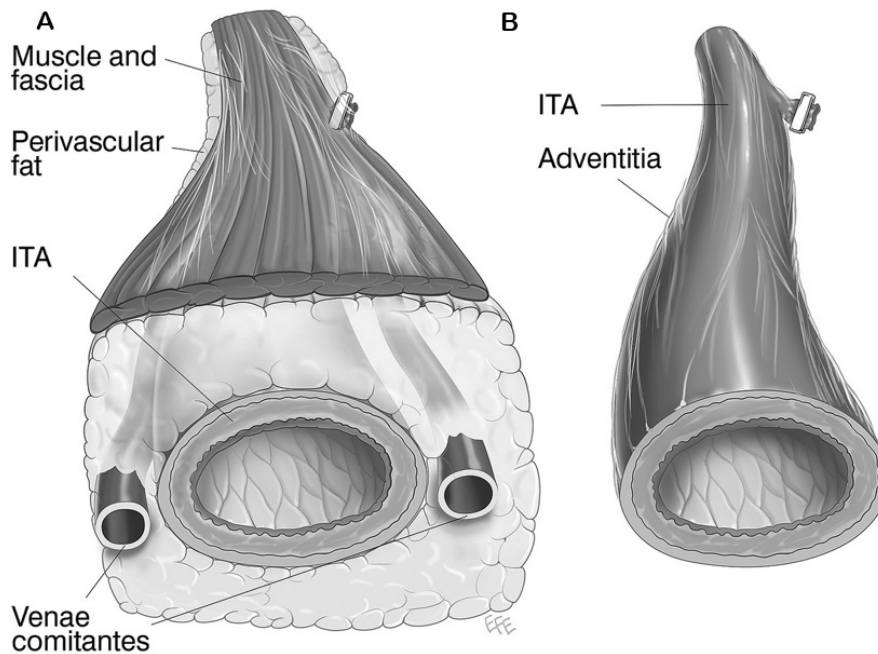
## CONSIDERATIONS FOR USE OF THE LITA

### Harvesting technique

Skeletonized ITA harvesting [Figure 2] has been accepted as the standard ITA harvesting technique compared with pedicled ITA harvesting<sup>[1,10]</sup>. Skeletonization of the ITA may help preserve sternal perfusion<sup>[1]</sup> and, in observational studies, has been associated with a lower risk of deep sternal wound infection, especially in CABG patients receiving bilateral ITA grafts<sup>[1]</sup>. Yet recent data suggest that skeletonization may result in lower patency rates and poorer clinical outcomes compared with pedicled harvesting, possibly due to greater intraoperative graft trauma incurred by manipulation during skeletonization<sup>[52,53]</sup>. A post-hoc analysis of the Cardiovascular Outcomes for People using Anticoagulation Strategies (COMPASS) trial<sup>[52]</sup> including 282 skeletonized ITA grafts (out of 1,002 CABG patients with ITA grafts) at mean 1.9-year follow-up reported a higher incidence of occlusion of skeletonized ITAs than of pedicled ITAs (9.6% vs. 3.9%, OR 2.41, 95%CI: 1.39-4.0). ITA skeletonization was also associated with higher rates of major adverse cardiac events (cardiovascular mortality, myocardial infarction, stroke, or revascularization) compared with pedicled ITA harvesting: 7.1% vs. 2.1%; adjusted HR 3.19, 95%CI: 1.53-6.67;  $P = 0.002$ , which was driven by repeat revascularization (5.0% vs. 1.4%; adjusted HR 2.75, 95%CI: 1.10-6.88;  $P = 0.03$ )<sup>[52]</sup>. A post-hoc 10-year analysis of ART including 995 patients with skeletonized ITAs (out of 2,161 CABG patients) found that ITA skeletonization was associated with a higher risk of major adverse cardiac events (all-cause mortality, myocardial infarction, and repeat revascularization) than pedicled ITA harvesting (34.2% vs. 28.6%, HR 1.25, 95%CI: 1.06-1.47), which was again attributed mainly to repeat revascularization (13.5% vs. 9.9%;  $P = 0.01$ ). Unfortunately, this study did not report angiographic data<sup>[53]</sup>.

### Anastomotic technique

Individual or sequential anastomosis may be used to graft the LITA<sup>[10]</sup>. Observational data has shown that there is no difference in patency between the individually anastomosed LITA and the sequentially anastomosed LITA<sup>[10,54-57]</sup>. A propensity-score matched study of 120 CABG patients reported no difference in LITA patency between patients receiving sequential LITA grafting to the diagonal artery and then the LAD and those receiving individual LITA grafting to the LAD (anastomotic patency: 99% for the diagonal site, 98% for the LAD site, and 98% for the individual LAD site;  $P > 0.05$ ). At 2.25-year follow-up, there was no difference between groups in the incidence of all-cause death (OR 0.79, 95%CI: 0.22-27,  $P = 0.72$ ) and repeat revascularization (OR 0.66, 95%CI: 0.13-4.12)<sup>[57]</sup>.



**Figure 2.** (A) Pedicled and (B) Skeletonized ITA Harvesting techniques. ITA: Internal Thoracic Artery. Reproduced from Markman et al.<sup>[105]</sup>.

Both the configuration of the anastomosis, either in a diamond with the graft at a right angle to the coronary target, or with the graft parallel to the coronary target, and target coronary artery stenosis may influence sequential LITA patency. A retrospective study of 452 CABG patients that compared individual and sequential LITA grafting found higher patency of the distal segment of the sequential graft with the diamond configuration compared with the parallel configuration (98.4% vs. 90.7%;  $P = 0.09$ )<sup>[56]</sup>. However, the diamond configuration is more technically challenging, and improper configuration can compromise the graft<sup>[10]</sup>. In addition, lower degrees of target coronary artery stenosis have been associated with greater competitive flow and sequential arterial graft failure. A post-hoc analysis of the IMPAG trial by graft configuration and location<sup>[58]</sup> found that FFR values  $< 0.80$  for the first anastomosis and  $< 0.77$  for the second anastomosis of sequential grafts to the anterior coronary circulation were associated with poorer graft functionality, compared with FFR values  $< 0.74$  for individual grafts. FFR values  $< 0.81$  for the first anastomosis and  $< 0.78$  for the second anastomosis of sequential grafts to the posterolateral coronary circulation were associated with poorer graft functionality, compared with FFR values  $< 0.79$  for individual grafts. The degree of target coronary artery stenosis should be taken into consideration prior to making the decision to proceed with sequential arterial grafting.

## CONSIDERATIONS FOR USE OF THE RA

### Harvest technique

RA harvesting can be performed using either open RA harvesting (ORAH) or endoscopic RA harvesting (ERAH) techniques. ORAH requires a 15-18 cm surgical incision, while ERAH requires two 2-3 cm incisions (the technique has been described in detail previously)<sup>[59]</sup>. ERAH has been found to reduce local harvest site complications. An analysis of 10 studies (four RCTs, six observational) and 1,368 patients found a lower risk of wound infection with ERAH compared with ORAH (OR 0.28, 95%CI: 0.13-0.63;  $P = 0.002$ )<sup>[60]</sup>, while an analysis pooling five observational studies and 779 CABG patients found a significantly lower risk of arm hematoma in ERAH patients compared with ORAH patients (OR 0.18, 95%CI: 0.05-0.67)<sup>[60]</sup>. In an RCT of 119 patients comparing ERAH (60 patients) with ORAH, ERAH was



associated with significantly lower early postoperative arm pain (mean visual analog scale [VAS] score 0.35 vs. 2.64;  $P < 0.001$ ) and an overall increase in patient satisfaction (mean VAS score 9.83 vs. 5.2,  $P < 0.001$ )<sup>[61]</sup>. However, ERAH may be associated with poorer graft patency and cardiac outcomes compared to ORAH, a safety concern based on studies that report lower patency rates of the endoscopically harvested SVG<sup>[31,32]</sup>. Older *in vitro* studies found no difference in endothelial function between ORAH and ERAH<sup>[62,63]</sup>, but a more recent organ bath study found ORAH to be associated with better preservation of endothelial function than ERAH<sup>[64]</sup>. The data on cardiac outcomes after ERAH are limited. A meta-analysis of four small RCTs and two propensity-matched observational studies and 743 patients (324 ERAH) comparing ERAH and ORAH found no difference in 30-day mortality (OR 0.78, 95%CI: 0.10-6.11;  $P = 0.81$ ), five-year mortality (OR 0.67, 95%CI: 0.11-4.17;  $P = 0.66$ ), or graft patency (OR 1.32, 95%CI 0.76-2.27;  $P = 0.32$ )<sup>[65]</sup>; another meta-analysis of 24 studies, including 15 observational studies (12 unadjusted studies) found a similar association between ERAH and ORAH and 30-day mortality, survival, and graft patency<sup>[66]</sup>. To date, there has been no adequately powered RCT comparing cardiac outcomes of ERAH and ORAH, and the topic requires further study.

### Graft configuration

The RA may be anastomosed directly to the aorta, or as a composite with other grafts<sup>[10]</sup>, typically the ITA as a Y-graft<sup>[67]</sup>. While the majority of available evidence about the RA is derived from RA-aortic anastomoses<sup>[67]</sup>, little evidence to date suggesting that RA graft configuration influences patency. In a retrospective study of 228 CABG patients receiving the RA (131 grafted directly to the aorta), there was no difference between the patency of the RA grafted directly to the proximal aorta (92.0%) and the RA grafted to the ITA (86.3%;  $P = 0.81$ ) at mean 6.5-year follow-up<sup>[68]</sup>.

### Target vessels

The RA is at higher risk of vasospasm and competitive flow than other conduits if grafted to coronary target vessels with only mild or moderate degrees of stenosis<sup>[69-71]</sup>. A retrospective study of 123 CABG patients (382 distal anastomoses) found an overall RA patency of 92% at a mean angiographic follow-up of 2.7 years; however, RA patency was lower when grafted to the right coronary circulation than to the left (79.4% vs. 94.4%;  $P < 0.05$ ) and was also lower when grafted to targets with 50%-90% stenosis than with  $> 90\%$  stenosis (83.3% vs. 98.0%;  $P < 0.05$ )<sup>[70]</sup>.

### Sequential grafting

Evidence on the effect of individual vs. sequential grafting on RA patency is limited. A recent study of 208 CABG patients (125 with individual grafting) and 293 anastomoses reported no difference in individually grafted or sequentially grafted RA patency at 10-year follow-up (88.7% vs. 87.4%;  $P = 0.88$ )<sup>[72]</sup>. However, another retrospective observational study of 410 CABG patients receiving the RA with five-year mean angiographic follow-up found that sequential RA grafting was associated with better patency compared with individual grafting (HR 2.53, 95%CI: 1.29-5.28;  $P = 0.006$ )<sup>[73]</sup>. The degree of target vessel stenosis may mediate the patency of the sequentially grafted RA. A recent study of 432 patients (1,221 distal RA sequential anastomoses) found that patency was higher for the sequentially grafted RA when grafted to coronary arteries with  $> 76\%$  stenosis than coronary arteries with 51%-75% stenosis (88.6% vs. 59.1%;  $P < 0.001$ )<sup>[74]</sup>.

### Pharmacotherapy

The RA is a highly muscular conduit with a potential risk of vasospasm, demonstrated in both pharmacologic studies and reporting from RA access during coronary angiography and stenting<sup>[66,75]</sup>, and its prevention is the target of antispasm medical treatment with calcium channel blockers (CCBs). However, the available data on the effect of CCB on the RA are mixed. Two small RCTs, one examining the effect of

discontinuing CCBs after the first postoperative year<sup>[76]</sup> and one examining the effect of no CCB in the early postoperative period<sup>[77]</sup>, found no difference in angiographic or clinical outcomes at one-year and five-year follow-up, respectively. A post-hoc analysis including 440 CABG patients receiving the RA from the Radial Artery Patency Study (RAPS) found that compliance with postoperative CCB regimen did not affect the incidence of the highest degree of RA graft spasm, demonstrated by string sign<sup>[78]</sup>. However, in a post-hoc analysis of 732 patients from the RADIAL database, CCB therapy was associated with a significantly lower risk of major adverse cardiac events (HR: 0.52, 95%CI: 0.31-0.89,  $P = 0.02$ ) and RA graft occlusion (HR: 0.20, 95%CI: 0.08-0.49,  $P < 0.001$ )<sup>[79]</sup>. In addition, if antispasm therapy is used, the choice of the best CCB is unclear. The aforementioned RADIAL analysis reported that compared with no CCB, amlodipine (HR: 0.30; 95%CI: 0.12-0.74,  $P = 0.009$ ) and diltiazem (HR: 0.20; 95%CI: 0.07-0.51,  $P < 0.001$ ) were associated with a similar protective effect on the risk of RA graft occlusion<sup>[79]</sup>. The use of antispasm therapy after CABG with RA grafting therefore requires further investigation.

## CONSIDERATIONS FOR USE OF THE RITA

### Graft configuration

The RITA can be used as a free graft from the aorta or as an *in-situ* graft. A longitudinal single-center study of over 1,331 CABG patients found that the patency of the *in-situ* RITA was 91% and the patency of the free RITA from the aorta was also 91% at 15-year follow-up<sup>[80]</sup>. In an RCT of 304 CABG patients receiving BITA grafting (147 *in-situ*, 152 Y-graft), there was no difference in RITA anastomotic patency by configuration at six-month follow-up (97.0% vs. 96.0%,  $P = 0.69$ )<sup>[81]</sup>, and no difference between groups in major adverse cerebral and cardiovascular events, defined as mortality, need for reoperation, ICU length of stay, and all cardiovascular morbidity ( $P > 0.05$  for all). At the mean 3.5-year angiographic follow-up, there was no difference between the *in-situ* RITA (93%) and Y-graft (96.5%;  $P = 0.10$ ) patency. However, at a mean seven-year follow-up, the *in-situ* RITA had a higher incidence of major adverse cerebral and cardiovascular events (34% vs. 25%)<sup>[82]</sup>. An additional consideration for the use of the *in-situ* RITA is the manner in which it is directed to the target vessels: if it crosses the midline anteriorly, there is an increased risk of injury during sternal reentry at reoperation. Directing the RITA via the transverse sinus may limit the target vessels of the RITA (i.e., it may only reach and revascularize the left circumflex branches).

### Target vessels

While the RITA has well-documented poorer patency than the LITA, the target coronary vessel may influence RITA patency. The aforementioned longitudinal single-center study of 1,331 patients with bilateral ITA grafting and 15-year imaging follow-up found that there was no difference between patency of the RITA and the LITA in instances when the RITA was grafted to the LAD (94.4% vs. 95.4%;  $P = 0.50$ ); however, the patency of the RITA was significantly lower when grafted to non-LAD coronary targets ( $P < 0.001$ )<sup>[80]</sup>. This study also found that RITA grafts anastomosed to target coronary arteries with  $< 60\%$  stenosis had lower patency rates, while those anastomosed to target coronary arteries with  $> 80\%$  stenosis had higher patency rates, showing again that the degree of target vessel stenosis affects arterial graft patency.

## ON-AND OFF-PUMP CABG AND GRAFT PATENCY

While the majority of CABG surgeries in the United States and Europe are performed with the use of cardiopulmonary bypass, off-pump CABG is an alternative approach that may avoid the negative effects of cardiopulmonary bypass on the patient<sup>[83]</sup>. The results of randomized trials of on- vs. off-pump CABG with angiographic follow-up have been mixed<sup>[84-87]</sup>. The Randomized On/Off Bypass (ROOBY) trial included 2,203 patients randomized to on- or off-pump CABG and at one-year follow-up found a higher patency rate in arterial (91.4% vs. 85.8%;  $P = 0.003$ ) and vein (80.4% vs. 72.7%;  $P < 0.001$ ) grafts<sup>[86]</sup>. However, the CABG Off or On Pump Revascularization Study (CORONARY) included 4,752 patients randomized to on- or off-

pump CABG (157 of whom had imaging at one-year follow-up) and found the proportion of non-occluded grafts was similar between groups (on-pump 95%, off-pump 89%;  $P = 0.09$ )<sup>[87]</sup>. A recent study-level meta-analysis of 16 RCTs, 6,227 patients, and 11,641 grafts<sup>[88]</sup> found that off-pump CABG was associated with a higher risk of graft failure (relative risk 1.31, 95%CI: 1.17-1.46;  $P < 0.001$ ); this increased risk was pronounced at follow-up one year after surgery and dissipated and longer follow-up. In addition, several of the included studies had high (> 10%) crossover rate, possibly skewing results and suggesting a question of physician expertise with off-pump CABG.

## MEDICAL THERAPY, CLINICAL OUTCOMES, AND GRAFT PATENCY

The role of medical therapy for CABG to maximize the benefits of revascularization cannot be overstated, irrespective of the choice of conduit. Antithrombotic regimens after CABG, as discussed in greater detail earlier in the text, play a crucial role in maintaining graft patency. The use of postoperative statins and antihypertensive therapy has been associated with improved clinical outcomes after CABG in numerous large-scale, retrospective studies<sup>[89-91]</sup>. Statin use has also been associated with a lower incidence of vein graft occlusion in CABG patients<sup>[91,92]</sup>, although the optimal dosing is not yet fully elucidated. The Aggressive Cholesterol Therapy to Inhibit Vein Graft Events (ACTIVE) trial<sup>[93]</sup> found that there was no difference in the incidence of vein graft occlusion at one-year follow-up between patients randomized to high-dose (80 mg, 11.4%) or low-dose (10 mg, 12.9%;  $P = 0.85$ ) statin.

## CONDUIT SELECTION IN WOMEN

Women have well-reported worse outcomes than men after CABG, including higher mortality and higher rates of postoperative major adverse events<sup>[94,95]</sup>. While the etiology of the sex disparity in outcomes is likely multifactorial, graft selection and strategies have been shown to differ between women and men, and may play a role in this outcomes disparity<sup>[96]</sup>. A retrospective study of 57,943 CABG patients (19% women)<sup>[96]</sup> found that incomplete revascularization, which was associated with lower survival in both sexes, was more common in women (26% vs. 22%;  $P < 0.001$ ). Women received fewer arterial grafts, were less likely to receive total arterial revascularization, and more frequently received SVG-only revascularization in lieu of any arterial grafting. A large retrospective study including more than one million CABG patients found that women were less likely to receive LITA grafting to the LAD (adjusted OR 0.79, 95%CI: 0.75-0.83;  $P < 0.001$ ), the gold standard of CABG, than men<sup>[97]</sup>. In addition, women were found to be less likely to receive MAG than men (adjusted OR 0.78, 95%CI: 0.75-0.81;  $P < 0.001$ ).

It is also unclear if women gain the same benefits from MAG as do men. In a retrospective cohort study of the Ontario database including 9,135 women undergoing CABG<sup>[98]</sup>, MAG was associated with a heightened risk of 30-day mortality (HR 1.48, 95%CI: 1.23-1.79); however, there was improved survival at nine years in women who received MAG (4.0% incremental improvement in survival over SAG). In a propensity-matched study from the New York State Cardiac Surgery Reporting System from 2005-2014, Gaudino *et al.* found that men who received MAG had a mortality benefit compared to men who received SAG (adjusted HR 0.80, 95%CI: 0.73-0.87;  $P < 0.001$ ), a similar benefit was not seen among women who received MAG (adjusted HR 0.99, 95%CI: 0.84-1.15;  $P = 0.85$ )<sup>[99]</sup>. Low-risk patients of both sexes who received MAG had a lower risk of mortality and morbidity than those receiving SAG (men: adjusted HR 0.80, 95%CI: 0.73-0.89;  $P < 0.001$  and women: adjusted HR 0.80, 95%CI: 0.65-0.97;  $P = 0.02$ ), but the high-risk patients of both sexes did not (men: adjusted HR 0.95, 95%CI: 0.82-1.10;  $P = 0.47$  and women: adjusted HR 1.14, 95%CI: 0.91-1.42;  $P = 0.26$ ). It is possible that the lack of any observed benefit with MAG in the overall cohort of women was due to the relatively greater proportion of women who fell into the 'high-risk' category compared with men. The ongoing ROMA:Women trial (NCT04124120), the first cardiac surgery trial in women, tests the MAG hypothesis in women and will provide more data on the benefits of MAG in women<sup>[100,101]</sup>.

The decision of which arterial graft should be used in women is also distinct from the decision-making process in men. Bilateral ITA grafting in women has been associated with sternal wound infection<sup>[96,102]</sup>; a retrospective study of 2,979 CABG patients (10% women) found that women who received BITA had a higher incidence of postoperative mediastinal infection compared with men who received BITA (3.3% vs. 1.5%;  $P = 0.02$ ). In addition, the same study found that the benefit of using the RA as the second arterial graft was heightened in women (HR 0.51, 95%CI: 0.36-0.72) compared with men (HR 0.84, 95%CI: 0.61-1.05)<sup>[19]</sup>.

Lastly, women remain underrepresented in CABG trials<sup>[103]</sup>, calling into question the applicability of the vast majority of cardiovascular and cardiac surgery evidence. In a recent study-level meta-analysis<sup>[104]</sup> of sex differences in SVG patency, no difference between the sexes was found (incidence rate ratio 0.96, 95%CI: 0.90-1.03;  $P = 0.24$ ), but more importantly, out of the 234 studies assessed in the final stage of screening, 100 were excluded as they did not report outcomes by sex, while an additional 44 studies had enrolled less than 10 women. Clearly, higher quality and more robust data are needed to guide graft selection in women.

## CONCLUSIONS

The choice of the graft to use in CABG can influence the efficacy of the surgery and the clinical benefits that the patient derives from CABG. There are many considerations for the choice of CABG graft: patency of the graft, its associated clinical outcomes, the amount of native coronary artery stenosis, the planned target vessel, and technical considerations such as harvesting and anastomotic techniques. In addition, the baseline characteristics and risk profile of the individual patient in which the graft is used should be accounted for in order to provide the best patient-centered care.

## DECLARATIONS

### Authors' contributions

Conceptualization, writing, research, revision: Harik L

Writing, revision, conceptualization: An KR

Research, revision, writing: Dimagli A, Dell'Aquila M

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### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

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