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Selecting conduits for coronary artery bypass grafting: caution regarding the right internal mammary artery

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Abstract

This narrative review summarizes the angiographic and clinical outcome results of the most common coronary artery bypass grafting (CABG) conduits. The left internal mammary artery is the preferred first conduit to bypass the left anterior descending artery due to superior long-term survival and graft patency. Recent studies suggest the radial artery may be the preferred second conduit for the circumflex or right coronary artery territories, challenging the belief that the right internal mammary artery is the best choice. Despite their historical high failure rates, saphenous vein grafts continue to be widely used as secondary conduits. Several recent studies report suboptimal rates of right internal mammary artery graft failure, with clinical outcomes comparable to or worse than saphenous veins. The suboptimal rates of RIMA graft failure may be attributed to several factors such as improvements in vein graft failure rates, the use of *in situ* and non-left anterior descending artery grafting configurations, and skeletonized harvesting techniques. While observational studies favor multiple over single arterial grafting, randomized studies are needed for confirmation. The ongoing Randomized comparison of the clinical Outcome of single *vs.* Multiple Arterial grafts (ROMA) trial aims to determine if multiple arterial grafting reduces major adverse cardiovascular events and mortality and how secondary conduit selection influences these outcomes. Greater adoption of arterial grafting strategies is likely to come from high-quality evidence of benefit and safety from ongoing and future large pragmatic trials.

Keywords: Coronary artery bypass grafting, left internal mammary artery, right internal mammary artery, radial artery, saphenous vein graft, multiple arterial grafting

INTRODUCTION

Coronary artery bypass grafting (CABG) surgery is one of the most common cardiac surgical procedures that improves clinical outcomes for patients with coronary artery disease[1]. The left internal mammary artery (LIMA) is often the conduit of choice in CABG surgery, specifically when grafted to the left anterior descending artery due to superior long-term patency rates[2,3]. While the use of saphenous veins remains common for supplementary grafts, surgeons often consider using supplementary arterial grafts instead, primarily the right internal mammary artery (RIMA) or the radial artery. This choice is primarily based on the arterial grafting hypothesis, which posits that arterial conduits should yield better patient outcomes than venous conduits. Recent meta-analyses of trials with angiographic data suggest that the radial artery might be the optimal conduit to the left circumflex or right coronary artery territories. This contradicts the widespread belief that RIMA, due to its biological equivalence to the LIMA, would be the logical choice[4,5]. However, recent reports of suboptimal rates of angiographic RIMA failure[6,7], and adverse clinical outcomes related to skeletonized RIMA harvesting are worrisome[8,9]. The latest surgical guidelines have given a Class 1 (Level of evidence B-R) recommendation to the use of the radial artery over the saphenous vein[10,11]. However, determining the best conduits for the left circumflex or right coronary territories remains challenging due to varying surgical characteristics such as conduit availability and quality, grafting configurations, and severity of coronary artery disease[12]. In this narrative review, we aim to provide a comprehensive summary of the angiographic and clinical outcomes of the most used conduits for coronary artery bypass grafting.

RELATIVE EFFICACY OF CABG CONDUITS

Individual patient meta-analyses

A recent individual patient meta-analysis (Gaudino *et al.*[13]) of seven randomized trials (ACTIVE[14], CASCADE[15], COMPASS CABG[6], DACAB[16], POPular CABG[17], PREVENT IV[18], TARGET[19]) that included 4,413 patients and 13,163 grafts, revealed that graft failure remains common 1 year after CABG surgery (33.7% of patients had at least 1 failed graft and 16.6% of all grafts had failed). Graft failure rates by conduit were 9.7% (387/4,006) for LIMA, 13.8% (21/152) for radial artery, 19.7% (172/8,740) for saphenous vein, and 23.0% (61/265) for RIMA [Table 1]. Unexpectedly, the RIMA had the highest failure rate of the conduits. With regard to target vessel location, RIMA graft failure rates were 17.6% (10/56) when grafted to the left anterior descending artery, 24.1% (39/162) to the left circumflex artery, and 25.5% to the right coronary artery. Graft failure was strongly associated with myocardial infarction, repeat revascularization, and an increased risk of mortality, indicating graft status may be a useful surrogate for these clinical outcomes.

A previous individual patient data meta-analysis (Gaudino *et al.*) of six other randomized trials (RAPCO[20], RAPS[21], RSVP[22], Petrovic[23], Stand-in-Y[24], Song[25]) from the Radial Artery Database International Alliance (RADIAL) database compared long-term rates of graft failure in 1,091 patients and 2,281 grafts[4]. After a lengthy angiographic follow-up of 5.4 years, graft failure rates were 2.3% (21/921) for LIMA, 9.4% (67/710) for radial artery, 13.5% (10/74) for RIMA, and 17.5% (101/576) for saphenous vein grafts[4]. When grafted specifically to the left circumflex artery, failure rates were 8.7% (38/439) for radial artery, 14.5% (8/55) for RIMA, and 16.4% (49/315) for saphenous veins. The combined rank order from both meta-analyses was LIMA (1st) > radial artery (2nd) > saphenous vein and RIMA (3rd or 4th), suggesting overall relative rates of RIMA graft failure are generally suboptimal (i.e., comparable to vein grafts).

It is worth noting that the rates of graft failure are much higher for all conduits in the more recent Gaudino 2023 meta-analysis compared with the earlier Gaudino 2020 meta-analysis despite a shorter follow-up [Table 1]. A key difference between these meta-analyses is that 5 of the 6 trials included in the 2020 analysis

Table 1. Graft failure rates from pooled and post hoc analyses of LIMA, radial artery, saphenous vein and RIMA grafts

Study	Included trials	Graft failure - *n/N* (%)					Time of imaging (years)
				Saphenous vein			
		LIMA	Radial artery	No-touch	Conventional	RIMA	
Individual patient meta-analyses							
Gaudino *et al.*, 2023[13]	7	387/4,006 (9.7)	21/152 (13.8)	172/8,740 (19.7)		61/265 (23.0)	1.02 (1.00, 1.03)*
Gaudino *et al.*, 2020[4]	6	21/921 (2.3)	67/710 (9.4)	101/576 (17.5)		10/74 (13.5)	5.4 ± 2.4†
Network meta-analyses							
Deng *et al.*, 2022[27]	18	-	5.9% (2.4-10.0)	8.6% (5.7-12.7)	13.7% (9.8-18.8)	10.8% (3.5-28.8)	3.5 (1.5-5.4)‡
Post hoc analysis							
Alboom *et al.*, 2022[7]	1	68/1,068 (6.4)	9/91 (9.9)	232/2239 (10.4)		22/82 (26.8)	1.13 ± 0.30

*Refers to median (IQR); †refers to mean ± SD; ‡refers to weighted mean (95%CI). CI: Confidence interval; LIMA: left internal mammary artery; RIMA: right internal mammary artery.

were early single-center trials (i.e., few surgeons from high-volume centers), whereas all 7 trials included in the 2023 analysis were multi-center trials (i.e., many surgeons from lower-volume centers). A volume-outcome relationship has been reported for BIMA grafting using meta-regression, with centers performing higher proportions of BIMA grafting associated with reduced long-term mortality[26]. Therefore, the discrepancy in rates of graft failure lends some support to the idea that a larger gradient in center or surgeon experience exists in multi-center CABG trials, where results of surgeons pooled from around the world (although more generalizable) are likely to be worse than results of surgeons from high-volume single-centers often pioneering arterial grafting.

Network meta-analyses

An update was recently reported for a network meta-analysis (Deng *et al.*) of 18 randomized trials that included 6,543 patients and 8,272 grafts with the aim of determining the second best conduit in CABG surgery based on rates of graft failure[5,27]. After a mean angiographic follow-up of 3.5 years, rates of graft failure were % (95%CI): 5.9% (2.4-10.0) for radial artery, 8.6% (5.7-12.7) for no-touch saphenous vein, 10.8% (3.5-28.8) for RIMA, and 13.7% (9.8-18.8) for conventionally harvested saphenous veins. Compared with conventionally harvested veins, rates of graft failure were lower using radial artery (incidence rate ratio, 0.56; 95%CI: 0.43-0.74) and no-touch saphenous veins (incidence rate ratio, 0.56; 95%CI: 0.44-0.70) but not RIMA (incidence rate ratio, 1.06; 95%CI: 0.72-1.54). Similar results were reported in another network meta-analysis (Yokoyama *et al.*) of 13 RCTs (3,728 patients and 2,773 grafts) indicating lower rates of graft failure with radial artery and no-touch saphenous veins compared with conventionally harvested veins at maximum angiographic follow-up and in sensitivity analyses restricted to trials with ≥ 3 and ≥ 5 years of follow-up[28]. These results suggest that the radial artery and no-touch saphenous veins may both be considered the best second conduit for minimizing graft failure over the medium to long term.

Post hoc analysis

We recently completed a post hoc analysis (Alboom *et al.*) of the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) CABG[6] study[7]. The analysis included 1,068 patients (3,480 grafts) who underwent CABG surgery and had complete angiographic follow-up at 1 year. The COMPASS CABG study was one of few that directly compared angiographic results of all the common CABG conduits (LIMA, RIMA, radial artery, and saphenous vein) within a single study using systematic angiography. The primary outcome was graft failure at 1 year diagnosed by computed tomography angiography. Our findings, which were collected from 83 centers across 22 countries, revealed graft failure rates of 6.4% (68/1,068) for LIMA, 9.9% (9/91) for radial artery, 10.4% (232/2,239) for the saphenous vein, and a notably high 26.8% (22/82) for RIMA grafts. The rate of RIMA graft failure was higher than both the radial artery (odds ratio: 2.69; 95%CI: 1.30-5.57) and saphenous veins (odds ratio: 2.07; 95%CI: 1.33-3.21). Particularly concerning were the extremely high failure rates of RIMA grafted to the left circumflex territory (42% [14/33]), which were more than double those to the left anterior descending territory (19% [6/32]) and right coronary artery territory (11.8% [2/17]). High rates of RIMA failure compared to other conduits are concerning and underscore the need for a comprehensive evaluation of angiographic and clinical outcomes of RIMA use in CABG surgery.

Clinical outcomes

Two main goals of CABG surgery are to prevent major non-fatal events such as myocardial infarction or stroke and to improve long-term survival. Thus, evaluation of the CABG conduits with regard to clinical outcomes is essential and complementary to direct visualization of the conduits using imaging. A recent individual patient meta-analysis (Gaudino *et al.*[29]) pooled data from four of the largest CABG trials (ART[30], CORONARY[31], PREVENT IV[18], RAPCO[32]) and included 10,256 patients, of whom 1,510 received RIMA, 1,385 received radial artery, and 7,361 received saphenous veins to supplement LIMA-to-LAD grafting [Table 2]. After nearly 8 years of follow-up, patients who received secondary radial arteries compared with saphenous veins had a reduced risk of all-cause mortality (hazard ratio, 0.62; 95%CI: 0.51-0.76) and the composite of all-cause mortality, any myocardial infarction, or any stroke (hazard ratio, 0.78; 95%CI: 0.67-0.90) after propensity score matching. Use of secondary radial artery compared with RIMA also reduced the risk of all-cause mortality (hazard ratio, 0.59; 95%CI: 0.48-0.71) and the composite of all-cause mortality, myocardial infarction, or stroke (hazard ratio, 0.75; 95%CI: 0.65-0.86). Results using RIMA and saphenous veins were comparable in terms of mortality and composite outcome.

A previous individual patient meta-analysis (Gaudino *et al.*) of 6 randomized trials (RAPCO[20], RAPS[21], RSVP[22], Petrovic[23], Stand-in-Y[24], Song[25]) from the RADIAL database compared long-term clinical outcomes in 1,036 CABG patients[33]. Use of radial arteries rather than saphenous veins resulted in a reduced risk of the composite of all-cause mortality, myocardial infarction, or repeat revascularization (12.5% [67/534] *vs.* 18.7% [94/502]; hazard ratio, 0.67; 95%CI: 0.49-0.90) and a lower rate of graft failure (8.1% [28/345] *vs.* 19.9% [61/307]) after 5 years of follow-up. The main drivers of the composite outcome were a reduced risk of myocardial infarction and repeat revascularization with radial artery use.

In a network meta-analysis (Gaudino *et al.*) of 4 randomized and 31 observational studies that included 149,902 CABG patients who received a secondary conduit (16,201 radial artery; 112,018 saphenous vein; 21,683 RIMA), the use of saphenous veins was associated with higher long-term mortality compared with the radial artery (incidence rate ratio, 1.23; 95%CI: 1.12-1.34) and RIMA (incidence rate ratio, 1.26; 95%CI: 1.17-1.35)[34]. However, the use of RIMA compared with radial artery resulted in similar rates of short-term and long-term mortality as well as perioperative myocardial infarction, stroke, and deep sternal wound infections (i.e., the arterial conduits were equivalent with respect to clinical outcomes).

In summary, the latest evidence suggests that the radial artery may be the best conduit to supplement LIMA-to-LAD grafting to reduce the rate of graft failure and risk of major adverse cardiovascular events compared with the other conduits. Given the biological equivalence of the RIMA and LIMA, higher failure rates in RIMA compared with saphenous veins in the most recent individual patient meta-analysis with clinical outcomes comparable to saphenous veins are concerning. Target vessel location, particularly to

Table 2. Comparison of clinical outcomes by CABG conduits used to supplement LIMA-LAD grafting

Outcome	RA *vs.* Vein HR (95%CI)	*P* value	Vein *vs.* RIMA HR (95%CI)	*P* value	RA *vs.* RIMA HR (95%CI)	*P* value
Gaudino *et al.*, 2022[29] (*n* = 10,256 patients)						
All-cause mortality, MI, or stroke	0.78 (0.67-0.90)	0.04	0.96 (0.84-1.10)	0.66	0.75 (0.65-0.86)	0.02
All-cause mortality	0.62 (0.51-0.76)	0.003	0.94 (0.79-1.12)	0.59	0.59 (0.48-0.71)	0.001
Gaudino *et al.*, 2018[33] (*n* = 1,036 patients)						
All-cause mortality, MI, or repeat revascularization	0.67 (0.49-0.90)	0.01				
All-cause mortality	0.90 (0.59-1.41)	0.68				
MI	0.72 (0.53-0.99)	0.04				
Repeat revascularization	0.50 (0.40-0.63)	< 0.001				

HR: Hazard ratio; LIMA-to-LAD: left internal mammary artery to left anterior descending artery; MI: myocardial infarction; RA: radial artery; RIMA: right internal mammary artery.

non-LAD targets, may be an important confounding factor to consider and therefore comparisons of the CABG conduits within the same target vessel region may be preferable. We note that modern angiography and clinical outcomes data reflect the expanded use of the radial artery and RIMA by an increasing number of surgeons to more distal (non-LAD) target vessels of varying size and degree of stenosis. In this context, the relatively high rates of RIMA failure, particularly to non-LAD targets, are concerning. Future randomized controlled trials should assess the efficacy and safety of RIMA use using both graft imaging and clinical outcome measures.

SUBOPTIMAL RATES OF CONTEMPORARY RIMA GRAFT FAILURE: POSSIBLE EXPLANATIONS

The potential of the RIMA in facilitating multiple arterial grafting, and consequently improving patient outcomes in CABG surgery, is widely recognized. However, the relative rate of RIMA graft failure has recently come under scrutiny. Several contemporary studies published after 2018 (e.g., Gaudino *et al.*, Yokoyama *et al.*, Lamy *et al.*, Alboom *et al.*) have reported failure rates that are often comparable to, or worse than, those of saphenous veins[4,6,7,13,28]. Despite this, the optimal failure rates of the LIMA-to-LAD graft and the biological equivalence of the RIMA and LIMA provide *a priori* evidence that the suboptimal RIMA graft failure is likely not due to the inherent biology of the graft, but rather the specific circumstances surrounding its use. Several factors may contribute to the overall suboptimal rates of RIMA graft failure compared with the other conduits. Firstly, recent trials have shown selective improvements in vein graft failure, which may diminish the true superiority of RIMA over saphenous veins. Secondly, RIMA is often grafted to the left circumflex artery, where higher failure rates are expected due to less severe stenosis of target vessels. Thirdly, skeletonized harvesting of RIMA conduits may result in higher failure rates compared with the traditional pedicled harvesting technique[8,9,35]. Fourthly, *in situ* RIMA grafts may have higher failure rates than free or composite proximal graft configurations[7,36]. Lastly, varying surgeon experience may contribute to suboptimal RIMA failure rates as RIMA use adds technical complexity to CABG surgery. These hypotheses will be explored in greater detail in the sections that follow.

Optimal rates of contemporary vein graft failure

Despite their historical suboptimal failure rate, saphenous vein grafts continue to be the most widely used conduit for CABG surgery worldwide. Historically, failure rates were 20%-25% at 12-18 months in the large PREVENT IV[18] (2003) and ROOBY[37] (2008) trials. However, a recent meta-analysis of individual patient data that included 48 studies and 41,530 vein grafts has shown a downward trend in early vein graft failure rates over time. In contemporary studies, which included patients enrolled after 2010, the estimated incidence of graft failure was only 7%[38]. This trend is also seen in our summary of trials with imaging follow-up evaluating the common CABG conduits [Table 3]. The mean vein graft failure rate in trials published before 2018 was 22.0% (1,996/9,077), compared with 8.6% (832/9,729) in trials published in 2018 or later. Notably, the overall 1-year rates of saphenous vein graft failure in our COMPASS CABG[6] study were 9.6% (221/2,292), and in the POPular CABG[17] trial, they were 9.9% (94/954). These rates are approximately half of those observed in the historic PREVENT IV or ROOBY trials, despite similar baseline patient characteristics. A recent large trial of vein harvesting techniques reported even lower failure rates, at 5.1% (214/4,224)[39]. It is important to note that this trend toward reduced rates of graft failure is specific to saphenous veins and not arterial grafts. Falling rates of vein graft failure in contemporary trials may contribute to the lack of superiority of RIMA compared with saphenous veins regarding both angiographic and clinical outcomes.

Recent progress in cholesterol-lowering and antithrombotic therapies following CABG surgery may be an important factor contributing to the downward trend in contemporary saphenous vein graft failure rates. In a large randomized controlled trial, aggressive cholesterol lowering was found to reduce rates of saphenous vein graft failure compared with moderate cholesterol lowering using lovastatin (6% [78/1,295] *vs.* 11% [136/1,238]; $P < 0.001$)[40]. Currently, lovastatin is commonly substituted with more potent medications such as atorvastatin or rosuvastatin.

Regarding antithrombotic treatments, a recent individual patient meta-analysis of 4 RCTs (TAP-CABG[41], DACAB[16], TARGET[19], POPular CABG[17]) that included 1,316 patients and 1,668 saphenous vein grafts, reported that dual antiplatelet therapy (DAPT) with ticagrelor compared with aspirin monotherapy was associated with a lower rate of saphenous vein graft failure at 1 year after CABG surgery (11.2% [54/481] *vs.* 20.0% [99/494]; odds ratio: 0.51; 95%CI: 0.35-0.74)[42]. Similarly, a recent network meta-analysis of 20 trials and 4,803 patients undergoing CABG surgery reported that dual antiplatelet therapy, either combining aspirin with ticagrelor (odds ratio: 0.50; 95%CI: 0.31-0.79) or aspirin with clopidogrel (odds ratio: 0.60; 95%CI: 0.42-0.86), proved to be more effective than aspirin alone in preventing saphenous vein graft failure[43]. Based on these studies, current North American guidelines recommend DAPT with aspirin and ticagrelor or clopidogrel for 1 year to improve vein graft patency compared with aspirin alone in selected CABG patients (Class 2b, level of evidence B-R)[10].

Skeletonized harvesting of IMA

The left and/or right internal mammary arteries (IMAs) are traditionally harvested as a pedicle, measuring 1 to 2 cm wide, which includes the artery, veins, fascia, and nerve [Figure 1]. Alternatively, the IMA may be harvested using a more challenging technique known as skeletonization, which involves direct dissection (i.e., removal of associated veins, fascia, and nerve). Skeletonized harvesting offers several advantages: it results in a longer conduit (+3.7 cm)[44], enabling it to reach more distant targets and facilitating bilateral IMA grafting. It also results in higher blood flow[44,45] and potentially fewer sternal infections[46,47] during CABG surgery. However, the close dissection and ligation of branches directly on the IMA during skeletonized harvesting may be associated with trauma to the IMA, thereby increasing the risk of thrombus formation, laceration, and lumen narrowing that may lead to premature graft failure.

Although many surgeons routinely use the skeletonization technique for IMA grafts, the long-term effects of skeletonized IMA on graft failure or clinical outcomes remain largely unknown. Few studies[45,48-52] have compared pedicled and skeletonized harvesting techniques following cardiac surgery [Table 4]. Aside from a small trial involving 200 patients, all other studies were non-randomized and conducted at centers that favored skeletonized over pedicled harvesting in their practice (i.e., approximately two-thirds of patients

Table 3. Summary of trials published before and after 2018 that evaluated patency of saphenous vein, radial artery and RIMA grafts

Study	Year	Conduit - n/N (%)			Patency definition	Design	Time of imaging (years)	CABG surgery type
		Saphenous vein	Radial artery	RIMA				
Gaudino et al.[73] (AVGSRS)	2005	-	1/40 (2.5)	2/40 (5.0)	occlusion	SC	4.3	On-pump
Alexander et al.[18] (PREVENT IV)	2005	1,198/4,537 (26.4)	-	-	occlusion	MC	1	On/off-pump
Collins et al.[22] (RSVP)	2008	6/44 (13.6)	1/59 (1.7)	-	occlusion	SC	5	On-pump
Kulik et al.[15] (CASCADE)	2010	6/90 (6.7)	-	-	occlusion	MC	1	On/off-pump
Hayward et al.[32] (RAPCO)	2010	7/112 (6.3)	8/311 (2.6)	10/196 (5.1)	occlusion	SC	5.5	On/off-pump
Goldman et al.[74] (VACSP)	2011	30/269 (11.2)	28/266 (10.5)	-	occlusion	MC	1	On/off-pump
Glineur et al.[75]	2011	5/81 (6.2)	-	8/37 (21.6)	occlusion	SC	3	On/off-pump
Mannacio et al.[76] (CRYSSA)	2012	35/267 (13.1)	1/52 (1.9)	1/63 (1.6)	occlusion	SC	1	On/off-pump
Deb et al.[21] (RAPS)	2012	50/269 (18.6)	24/269 (8.9)	-	occlusion	MC	7.7	On/off-pump
Song et al.[25]	2012	4/59 (6.8)	2/71 (2.8)	-	occlusion	SC	1	Off-pump
Hattler et al.[77] (ROOBY)	2012	513/2,603 (19.7)*	-	-	occlusion	MC	1	On/off-pump
Dreifaldt et al.[78]	2013	2/52 (3.8)	8/58 (13.8)	-	occlusion	SC	3	On-pump
Houlind et al.[79] (DOORS)	2014	140/694 (20.2)	44/176 (25.0)	9/36 (25.0)	> 50% or occlusion	MC	0.5	On/off-pump
Subtotal:		1,996/9,077 (22.0)	117/1,302 (9.0)	30/372 (8.1)				
Zhao et al.[16] (DACAB)	2018	211/1,460 (14.5)*	-	-	occlusion	MC	1	On/off-pump
Kim et al.[80] (SAVE RITA)	2018	10/214 (4.7)	-	4/173 (2.3)	occlusion	SC	5	Off-pump
Kulik et al.[14] (ACTIVE)	2019	30/247 (12.1)	-	-	occlusion	MC	1	On/off-pump
Lamy et al.[6] (COMPASS CABG)	2019	221/2,292 (9.6)	8/93 (8.6)	18/84 (21.4)	occlusion	MC	1	On/off-pump
Willemsen et al.[17] (POPular CABG)	2020	94/954 (9.9)	-	-	occlusion	MC	1	On/off-pump
Tian et al.[39]	2021	214/4,224 (5.1)*	-	-	occlusion	MC	1	On/off-pump
Kulik et al.[19] (TARGET)	2021	52/338 (15.4)	-	-	occlusion	MC	1	On/off-pump
Subtotal:		832/9,729 (8.6	8/93 (8.6)	22/257 (8.6)				
Overall: 95%CI:		2,822/18,716 (15.1)	>125/1,395 (9.0)	52/629 (8.3)				
		14.6-15.6	7.6-10.6	6.4-10.7				

*Rates of graft occlusion were significantly different among treatment groups (overall occlusion rate reported). CI: Confidence interval; LIMA: left internal mammary artery; MC: multi-centre; RIMA: right internal mammary artery; SC: single-centre.

received skeletonized rather than pedicled IMA). A meta-analysis of 5 studies, which included 1,988 patients and 1,764 grafts, found that the odds of failure was numerically higher in skeletonized compared with pedicled grafts, but this difference was not significant (odds ratio 1.35; 95%CI: 0.41-4.47)[35].

Table 4. Summary of studies examining rates of IMA graft occlusion by harvesting technique*

Study	Patients - *n/N* (%)		Grafts - *n/N* (%)		Conduit	Study design	Time of postoperative angiography	CABG surgery type
	SKT	PED	SKT	PED				
Calafiore *et al.*, 1999[49]	4/133 (3.0)	1/71 (1.4)	4/281 (1.4)	1/149 (0.7)	BIMA	P, SC	≤ 30 days or later (SKT 14.3 mo, PED 7.6 mo)	On/off-pump
Amano *et al.*, 2002[48]	1/96 (1.0)	0/76 (0.0)	1/159 (0.6)	0/106 (0.0)	IMA	P, MC	< 3 months	On/off-pump
Hirose *et al.*, 2003[50]	0/87 (0.0)	0/36 (0.0)	0/195 (0.0)	0/77 (0.0)	IMA	P, MC	In-hospital	On/off-pump
Kai *et al.*, 2007[51]	4/137 (2.9)	0/23 (0.0)	4/274 (1.5)	0/46 (0.0)	BIMA	RE, SC, SS	< 30 days	On-pump PED or off-pump SKT
Mannacio *et al.*, 2011[45]	0/100† (0.0)	0/100† (0.0)	0/100† (0.0)	0/100† (0.0)	LIMA	P, R, SC	2 years	Off-pump
Sun *et al.*, 2015[44]	9/778 (1.2)	12/795 (1.5)	9/778 (1.2)	12/795 (1.5)	LIMA	P, SC	1 year	Off-pump
Lamy *et al.*, 2021[9]	28/282 (9.9)	29/720 (4.0)	33/344 (9.6)	30/764 (3.9)	IMA	P, MC	1 year	On/off-pump
Dreifaldt *et al.*, 2021[54]	5/52 (9.6)	2/48 (4.2)	5/52 (9.6)	2/48 (4.2)	LIMA	P, R, SC	3 years	On-pump
Total:	51/1665 (3.1)	44/1869 (2.4)	56/2183 (2.6)	45/2085 (2.2)				
95%CI:	2.3-4.0	1.7-3.2	1.9-3.3	1.6-2.9				

*Graft occlusion is defined as 100% stenosis. Grafts with "string signs" were not included. Only patients with angiographic results were included. †5 patients were excluded after undergoing angiography but from which group was not reported. BIMA: Bilateral internal mammary artery grafting; LIMA: left internal mammary artery; PED: pedicled; P: prospective; RA: radial artery; R: randomized; RE: retrospective; SC: single-centre; SKT: skeletonized; SS: single surgeon; MC: multi-centre; NR: not reported.

Subsequently, a large single-center observational study[44] reported comparable rates of graft failure in both skeletonized (1.2% [9/778]) and pedicled (1.5% [12/795]) groups among patients who underwent off-pump CABG and completed the 1-year follow-up angiography. However, the angiographic follow-up period was notably shorter for the skeletonized LIMA group, averaging 19.4 months compared with 40.0 months for the pedicled group ($P < 0.001$), limiting the internal validity of the results.

We recently conducted a post hoc analysis of the COMPASS trial dataset to evaluate the impact of skeletonized or pedicled IMA harvesting on graft patency and clinical outcomes. The primary outcome was graft occlusion, determined by computed tomography angiography[9]. The occlusion rate was higher in skeletonized IMA compared with pedicled IMA (9.6% [33/344] *vs.* 3.9% [30/764]; odds ratio: 2.41; 95%CI: 1.39-4.20) 1 year after CABG surgery. This included the left internal mammary artery to the left anterior descending artery (7.3% [21/289] *vs.* 3.4% [25/725]; odds ratio: 2.10; 95%CI: 1.14-3.88). The results were consistent in both LIMA (adjusted odds ratio: 2.13; 95%CI: 1.16-3.91) and RIMA (adjusted odds ratio: 2.88; 95%CI: 0.62-13.49), although relatively few RIMA grafts were evaluated. Regarding clinical events, we observed that skeletonized harvesting was associated with a higher rate of major adverse cardiovascular events (hazard ratio, 3.19; 95%CI: 1.53-6.67), mainly driven by an increased risk of repeated revascularization (hazard ratio, 2.75; 95%CI: 1.10-6.88) after a mean follow-up of 23 months. We did not observe any mortality benefit from skeletonization (0.4% *vs.* 0%). Overall, our study suggested that the use of skeletonized IMA harvesting was associated with a higher rate of graft occlusion and complications compared with the traditional pedicled technique.

Subsequently, a similar post hoc analysis of the Arterial Revascularization Trial (ART) dataset was undertaken to assess the impact of skeletonized *vs.* pedicled IMA on long-term (10 year) clinical outcomes[8]. The risk of the composite of all-cause mortality, myocardial infarction, or repeat

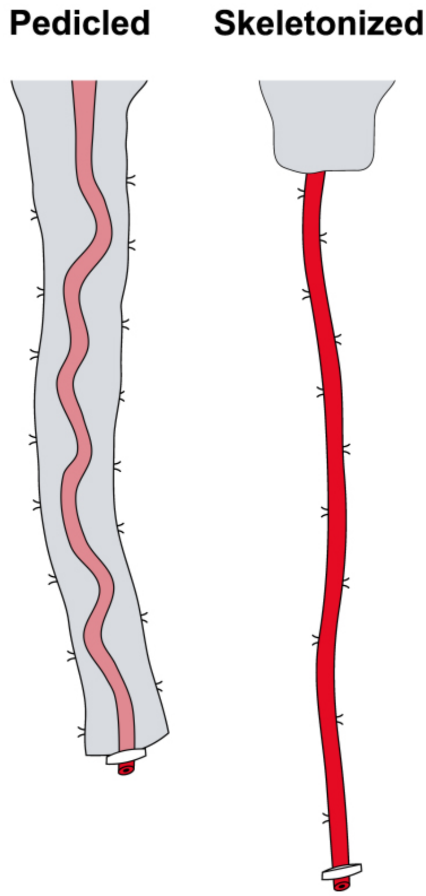

Figure 1. Illustration of pedicled and skeletonized internal mammary artery during coronary artery bypass grafting surgery. Adapted from Gurevitch *et al*.[72].

revascularization was higher in skeletonized compared with pedicled IMA harvesting (hazard ratio, 1.25; 95%CI: 1.06-1.47), mainly driven by an increased risk of repeat revascularization (hazard ratio, 1.42; 95%CI: 1.11-1.82). No mortality benefit of skeletonization was observed (hazard ratio, 1.12; 95%CI: 0.92-1.36). In a subgroup analysis, the authors noted that the difference in major adverse cardiovascular events was larger for patients operated on by surgeons who enrolled 50 patients or less in the trial, suggesting surgeon experience may be an important confounder. Likewise, authors of a recent narrative review of the subject pointed out that early divergence of Kaplan-Meier curves with regard to major adverse cardiovascular events in the COMPASS CABG study is consistent with a hypothesis that early technical issues relating to surgery rather than progression of the underlying atherosclerotic disease likely contributed to the poorer performance of the skeletonized IMA[53].

In a recent trial that randomly assigned 109 patients to receive a single skeletonized or pedicled LIMA graft to the left anterior descending artery, rates of graft failure were similar with either technique at 3 years (skeletonized 9.6% [5/52] *vs.* pedicled 4.2% [2/48]; absolute difference 5.4%; 95%CI: -4.2-14.5) and 8 years after surgery[54]. Subgroup analyses suggested that graft failure rates were higher when anastomosed to target arteries with less severe disease (stenosis < 70% *vs.* ≥ 70%).

At present, conflicting evidence from mostly single-center observational studies suggests similar overall rates of graft failure after skeletonized and pedicled IMA harvesting. However, recent reports of higher rates of graft failure and increased risks of major adverse cardiovascular events associated with the use of skeletonized IMA, warrant a more thorough evaluation in randomized trials.

Proximal RIMA graft configuration (*in situ*, free, or composite)

In situ vs. free

The RIMA is commonly used without removal from their proximal origin as an "*in situ*" graft (no proximal anastomosis) or removed from their origin and grafted proximally to the aorta as a "free" graft or to another graft, often as a Y-shaped "composite" graft (e.g., onto LIMA, radial artery, or saphenous vein grafts) [Figure 2]. In a single-center retrospective observational study of 7,092 patients undergoing bilateral internal mammary artery (BIMA) grafting with enrollment from 1972 to 2016, patient-level RIMA failure rates after 15 years were: 9% *in situ*, 9% free from aorta, 11% composite from LIMA, and 23% composite from saphenous vein grafts. The most important risk factor for graft failure was target vessel location (i.e., RIMA-to-LAD had lower rates of failure than RIMA to diagonal, left circumflex, or right coronary arteries). After adjusting for target vessel location, the risks of graft failure with *in situ vs.* free RIMA were similar regardless of the type of non-*in situ* configuration (i.e., free graft from aorta or composite graft from LIMA or vein), leading the authors to conclude that long-term rates of RIMA graft failure were independent of proximal configuration.

In our analysis of the COMPASS CABG dataset, we found that *in situ* RIMA failed more than twice as frequently as RIMA from the aortic or composite configuration when grafted to the left circumflex artery, although the difference was not significant (63% [10/16] *vs.* 24% [4/17]; odds ratio: 0.20; 95%CI: 0.03-1.03; $P = 0.054$)[7].

In a single-center retrospective observational study of BIMA grafting in 5,766 patients (enrollment 1986-2008), 10-year rates of graft failure were similar with *in situ* RIMA compared with free RIMA (11% [50/450] *vs.* 9% [49/541])[55]. When RIMA was grafted specifically to the left circumflex artery, 13% (10/76) failed using *in situ* compared with 6% (17/276) using a free RIMA graft. When grafted to the right coronary artery, failure rates were higher with *in situ* compared with free RIMA grafting (26% [37/141] *vs.* 7% [4/58]; $P = 0.02$). We speculate that the high failure rate observed with *in situ* RIMA may be attributed to challenges with reaching distant target vessels (e.g., inappropriate tension, mismatch in size between graft and the target vessel, potential kinking along lengthy grafts, *etc.*).

Similar results were observed in a more recent single-center retrospective observational study of 282 patients who underwent CABG with BIMA grafting (enrollment 2000-2012), where 69 patients received an *in situ* RIMA and 213 patients received a free RIMA grafted to the left circumflex territory to supplement LIMA-LAD grafting[36]. 5-year rates of patient-level graft failure, estimated from Kaplan-Meier curves, were higher with *in situ* RIMA compared with free RIMA (19.7% *vs.* 3%, respectively; $P = 0.01$). Current observational evidence suggests that a free proximal grafting configuration may be preferable to the *in-situ* configuration for RIMA grafting to non-LAD target vessels. However, we note that the confidence in this assertion should reflect the poor quality of the evidence.

In situ vs. composite

The use of the RIMA as a Y-composite, rather than *in situ* graft, facilitates sequential grafting (i.e., multiple distal anastomoses) of the RIMA. As a result, complete coronary revascularization can more often be achieved using BIMA without the need for additional conduits. In a single-center randomized controlled

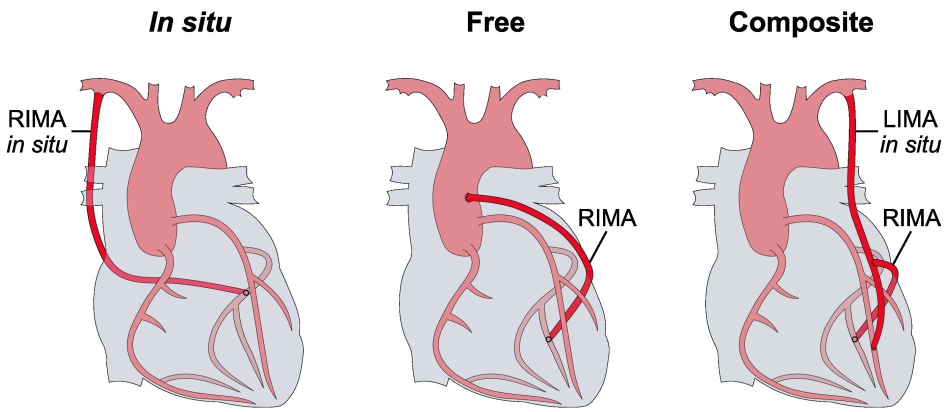

Figure 2. Illustration of *in situ*, free, and composite grafting of the right internal mammary artery to the left circumflex artery during coronary artery bypass grafting surgery. Adapted from Alboom *et al.*[7]. LIMA: Left internal mammary artery; RIMA, right internal thoracic artery.

trial of 304 isolated CABG patients assigned to receive *in situ* RIMA or Y-composite RIMA to supplement LIMA-LAD grafting, rates of RIMA graft failure were similar with either configuration at 6 months (4.0% [5/126] *vs.* 2.6% [7/267])[56] and 3 years (7% *vs.* 5.5%)[57]. However, the risk of major adverse cardiovascular and cerebrovascular events (i.e., a composite of all-cause mortality, myocardial infarction, stroke, or repeat revascularization) at 7 years was lower with Y-composite compared with *in situ* RIMA grafting (25% [38/152]) *vs.* 34% [51/152]). The main driver of the composite was a reduced risk of repeat revascularization with Y-composite RIMA (7% [10/152] *vs.* 13% [20/152]). Similar risks of all-cause mortality, myocardial infarction, and stroke were reported for both grafting configurations. The mean number of anastomoses with *in situ* RIMA was 1.8 compared with 1.0 in the Y-composite RIMA group, consistent with the need for an additional supplementary graft in the *in-situ* RIMA group.

Similar results were reported in a single-center retrospective observational study of 1,818 patients who underwent BIMA grafting and received either *in situ* RIMA or Y-composite RIMA[58]. Survival at 8 years was similar in both groups (95.8% *vs.* 94.8%) and angiograms obtained in 88 (5%) patients at a mean follow-up of 1.5 years revealed similar rates of graft failure in both *in situ* and Y-composite groups (0% [0/25] *vs.* 0.8% [2/63]). However, the very low participation in angiographic follow-up indicates the failure rates should be interpreted with caution (i.e., they are likely underestimates due to attrition bias).

Observation evidence suggests that free RIMA may be preferable to *in situ* RIMA, with comparable results between *in situ* and composite proximal RIMA grafting approaches. Failure rates are largely influenced by distal target vessel location, where free or composite RIMA grafting may be preferred to reach more distant target vessels in the left circumflex and right coronary artery territories. However, it is important to note that these results should be considered hypothesis-generating due to the methodological limitations of the studies. Most studies were retrospective or post hoc in nature, except for a single randomized controlled trial. Additionally, there was high variability in the proportion of patients completing angiographic follow-up (i.e., potential attrition bias) and timing of angiography, and potential selection bias may have been introduced by symptom-driven rather than systematic postoperative angiography. Randomized controlled trials are needed to determine the optimal proximal grafting configuration for RIMA grafting in CABG surgery.

MULTIPLE ARTERIAL GRAFTING

Single, multiple, or total arterial grafting

For decades, many surgeons have assumed that using arterial rather than venous conduits would improve outcomes for patients (i.e., the arterial grafting hypothesis). However, this remains to be proven in randomized studies. Currently, saphenous veins are most often used as secondary conduits as part of a single arterial grafting (SAG) strategy. Nevertheless, there is growing interest in using secondary RIMA (i.e., bilateral IMA grafting) or radial artery conduits to achieve multiple arterial grafting (MAG) and three or more arterial conduits with no vein grafts to achieve total arterial grafting (TAG). The proposed advantages of MAG or TAG over SAG include reductions in the incidence of mortality and major adverse cardiovascular events over the long term.

Observational studies have generally supported the arterial grafting hypothesis by associating MAG using secondary RIMA (i.e., bilateral IMA [BIMA]) with improved clinical outcomes compared with secondary veins (i.e., SAG)[34,59-62]. In a recent analysis of MAG *vs.* SAG in over one million patients included in the Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS-ACSD) (2008-2019), MAG was associated with improved 10-year survival (hazard ratio, 0.86; 95%CI: 0.85-0.88)[62]. Similarly, MAG was associated with a lower risk of all-cause mortality in a recent post hoc analysis of 1,466 patients from the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery Extended Survival (SYNTAXES) study after a lengthy follow-up of 12.6 years[63]. However, support for the hypothesis has not been demonstrated in a large randomized trial. In the Arterial Revascularization Trial (ART), which aimed to establish that BIMA was superior to SAG, there were no significant differences in the incidence of all-cause mortality and the composite of all-cause mortality, myocardial infarction, or stroke in 1,554 patients who received BIMA or SAG after 5 and 10 years of follow-up[30,64]. One reason for the lack of benefit of BIMA using RIMA provided by the authors was confounding by radial artery use (radial artery use improved outcomes for patients preferentially in the SAG group). Given the reports of suboptimal rates of RIMA graft failure, often comparable to or worse than saphenous veins (e.g. Gaudino *et al.*, Yokoyama *et al.*, COMPASS CABG[6,7]), an alternative hypothesis has emerged - benefits of BIMA were lost due to poor RIMA results[4,13,28]. Suboptimal outcomes with RIMA highlight an important limitation of the common MAG *vs.* SAG comparison, as it fails to account for the type of secondary arterial conduit used. Consequently, important heterogeneity (e.g., potential harm) within the MAG group can easily be missed. However, it is important to note that infrequent use of RIMA often limits separate reporting of RIMA results (i.e., low statistical power), particularly in randomized surgical studies that are typically much smaller than administrative database studies. Given the extensive sample size of the STS-ACSD, additional analyses separately reporting on the use of the RIMA and radial artery for MAG would be a welcomed contribution to the field.

Underutilization of MAG

Current guidelines recommend (Class 2a, level of evidence B-NR) that BIMA grafting be performed by experienced operators in appropriate patients to improve long-term cardiac outcomes[10]. However, the use of MAG (including BIMA grafting) remains infrequent. For instance, a recent registry study reported that most centers in the USA utilize MAG at an annualized rate of less than 5%[62]. Limited adoption is possibly due to challenges associated with multiple arterial grafting, such as a steep learning curve for surgeons, lengthier harvesting times, perceived higher risk of sternal wound complications, inconsistent experience and training in MAG techniques, and conflicting evidence between observational and randomized studies (e.g., the neutral results of the ART trial). Moreover, in retrospective observational studies, the lack of sufficient institutional experience in MAG using RIMA is associated with increased operative risk[60,65]; thus, likely contributing to hesitancy among institutions and surgeons that infrequently use MAG. The additional surgical expertise needed in MAG, particularly with RIMA, may also explain reports of suboptimal clinical results. However, we caution the use of institutional case volumes as a surrogate for individual surgeon experience.

In addition, we speculate that the observed suboptimal rates of RIMA graft failure could be due to the study settings. Single-center studies, which often report positive RIMA results, may be biased toward positive outcomes as they reflect the performance of a small, identifiable group of experienced surgeons. On the other hand, multi-center trials, which frequently report neutral or negative RIMA results, may present more balanced outcomes as they involve numerous surgeons of unknown experience across various institutions.

In order to improve the utilization of MAG, many surgeons have advocated for increased exposure to MAG techniques during cardiothoracic surgery training[66]. Single-center observational evidence suggests that adequately supervised trainees can perform MAG without compromising patient safety and long-term survival[67,68]. Since surgical training policies are often guided by high-quality clinical evidence, the pursuit of robust evidence of benefit and safety, from ongoing and future large pragmatic trials with long-term angiography and clinical follow-up, could not only foster wider acceptance but also address educational barriers impeding greater utilization of MAG.

Total arterial grafting and sex-based differences in MAG

The proposed benefits of MAG or TAG over SAG for improving patient outcomes are based on observational studies and have yet to be clearly established. Compared with SAG, MAG was associated with a numerically lower risk of 10-year all-cause mortality (hazard ratio, 0.84; 95%CI: 0.69-1.03) and TAG was associated with an even lower risk (hazard ratio, 0.68; 95%CI: 0.48-0.96), suggestive of an incremental benefit of arterial grafting in a recent post hoc analysis of 1,084 patients from of the ART trial[69]. Overall, both MAG and TAG were associated with a lower risk of the composite of all-cause mortality, myocardial infarction, stroke, or revascularization (MAG *vs.* SAG; hazard ratio, 0.82; 95%CI: 0.69-0.96 and TAG *vs.* SAG; hazard ratio, 0.71; 95%CI: 0.53-0.94).

Interestingly, in a retrospective analysis of New York's Cardiac Surgery Reporting System database that included 63,402 patients undergoing CABG surgery from 2005 to 2014, all-cause mortality was lower in men who underwent MAG compared with SAG (hazard ratio, 0.80; 95%CI: 0.73-0.87), but not women (hazard ratio, 0.99; 95%CI: 0.84-1.15), suggesting sex-based differences in outcomes after MAG that warrant further investigation[70].

The ROMA trial

The Randomized comparison of the clinical Outcome of single versus Multiple Arterial grafts (ROMA) trial is currently evaluating MAG *vs.* SAG for reducing major adverse cardiovascular or cerebrovascular events (MACCEs) in 4,300 patients undergoing isolated CABG surgery (ClinicalTrial.gov number, NCT03217006)[71]. Eligible patients are randomly assigned to receive SAG (one IMA-to-LAD graft with all additional grafts using saphenous veins) or MAG (one IMA-to-LAD graft and either a second IMA or RA grafted to the main target vessel of the lateral wall with additional grafts using saphenous vein or arterial conduits) [Figure 3]. The primary outcome is a composite of all-cause mortality, stroke, post-discharge myocardial infarction, or repeat revascularization reported as survival curves after the accrual of 845 events. The secondary outcome is all-cause mortality after 631 events.

In the ROMA trial, half of the MAG patients are expected to receive a secondary RIMA grafted to the lateral wall. In the context of the poor RIMA results summarized in this review, it is possible that poor RIMA performance may potentially mask a true benefit of MAG over SAG, resulting in an overall neutral trial (i.e.,

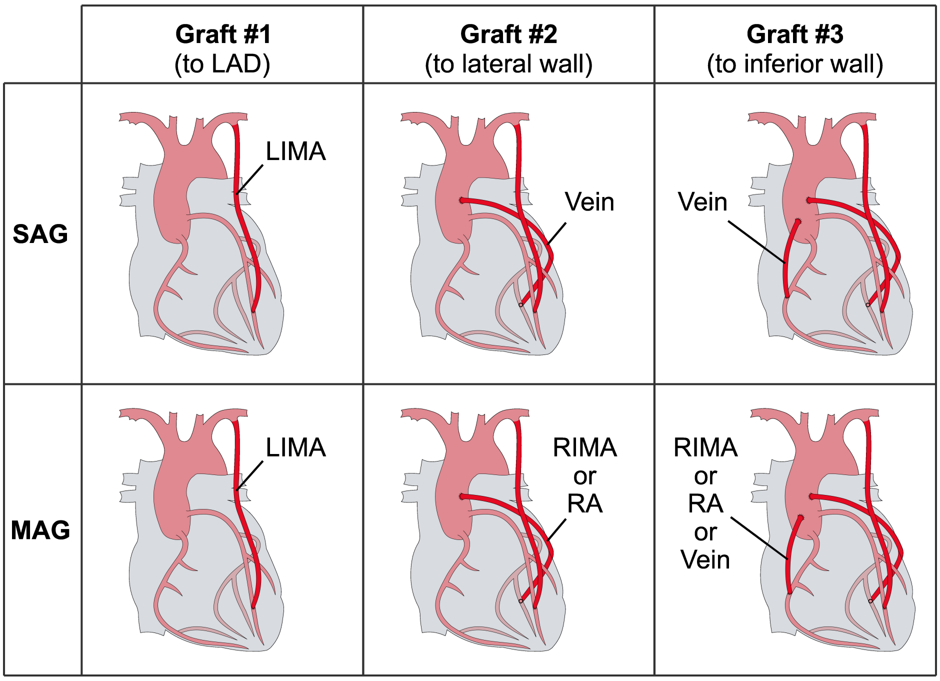

Figure 3. Illustration of single arterial grafting (SAG) and multiple arterial grafting (MAG) strategies for surgical revascularization during CABG surgery. Participants of the ROMA trial are randomized to SAG or MAG groups (1:1 ratio). For simplicity, only one grafting configuration is shown for each graft. LIMA: Left internal mammary artery; RA: radial artery; RIMA: right internal thoracic artery; Vein: saphenous vein.

as speculated for the preceding ART trial). Additionally, there is no postoperative angiography planned to directly evaluate the performance of the bypass grafts, which would complement the clinical outcomes and result in a more robust evaluation of these arterial grafting strategies. We eagerly await the results of the ROMA trial to clarify whether MAG reduces MACCEs and mortality and, importantly, whether secondary conduit selection (radial artery, RIMA, or veins) influences these relationships.

CONCLUSION

Many surgeons have advocated for greater adoption of a second arterial graft to minimize long-term graft failure rates and improve outcomes for CABG patients. At the moment, from both angiographic and clinical outcomes perspectives, the radial artery is the preferable second conduit for patients with a reasonable life expectancy undergoing isolated CABG surgery performed by experienced operators. Several observational studies have recently reported suboptimal rates of RIMA graft failure with clinical outcomes often comparable to or worse than saphenous veins. These results are concerning and reinforce the need to replace assumptions of equivalence to LIMA with evidence from multi-center randomized trials to evaluate the relative efficacy and safety of secondary RIMA use in CABG surgery. Greater adoption of arterial grafting strategies is likely to come from high-quality evidence of benefit and safety from ongoing and future large pragmatic trials with long-term angiography and clinical follow-up.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the review, as well as critical revision of the article and final approval of the article: Browne A, Lamy A

Performed literature search, wrote the article, as well as providing administrative, technical, and material support: Browne A

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Conflicts of interest
Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
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