Expert systematic review on the choice of conduits for coronary artery bypass grafting: endorsed by the European Association for Cardio-Thoracic Surgery (EACTS) and The Society of Thoracic Surgeons (STS)

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INTRODUCTION

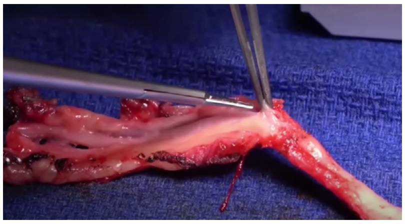
Coronary artery bypass grafting surgery (CABG) is the most common cardiac surgery operation in the USA and worldwide.[1] The first choice of conduit and standard of care is use of the left internal thoracic artery (LITA) to the left anterior descending (LAD) artery. While the saphenous vein graft (SVG) remains the most commonly used conduit for multivessel CABG, there is a variety of arterial conduits and technical variations of the SVG that may also be used for the operation. Individualization of the grafting strategy to the anatomic and clinical characteristics of each patient, as well as to the operating surgeon's experience and comfort with the different conduits, is key to the success of the operation. This document reviews and analyzes the existing evidence for the use of conduits for CABG.

METHODOLOGY

The leadership of the Society of Thoracic Surgeons (STS), American Association for Thoracic Surgery (AATS) and European Association for Cardio-Thoracic Surgery (EACTS) nominated a group of experts to systematically review the data on use of conduits in CABG as a comprehensive, international document. This paper reflects the opinion of the nominated authors as to how to approach and perform conduits selection in CABG.

Each of the members of the writing committee submitted conflict of interest disclosure forms, which were then reviewed by the co-Chairs of this document, the STS Joint Guideline Steering Committee and STS staff before confirmation for potential conflicts from relevant relationships with industry.

The writing committee then developed 5 questions for systematic review in the Population, Intervention, Comparator and Outcomes (PICO) format primarily related to comparisons of different grafts to the conventionally harvested SVG and to the use of endoscopic vein harvesting



Radial artery.

CENTRAL MESSAGE

Coronary artery bypass surgery is the most common operation in cardiac surgery. The conduit selection needs to be individualized according to the anatomic and clinical characteristics of each patient.

PERSPECTIVE

Individualization of the grafting strategy to the anatomic and clinical characteristics of each patient, as well as to the operating surgeon's experience and comfort with the different conduits, is key to the success of the operation.

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Abbreviations and Acronyms

ART	= arterial revascularization trial
BITA	= bilateral internal thoracic artery
CABG	= coronary artery bypass grafting
CCB	= calcium channel blockers
CON SVG	= conventional saphenous vein graft
DSWI	= deep sternal wound infection
EVH	= endovascular vein harvesting
GEA	= gastroepiploic artery
HR	= hazard ratio
IRR	= incidence relative risk
ITA	= internal thoracic artery
LITA	= left internal thoracic artery
LAD	= left anterior descending
MACE	= major adverse cardiovascular events
MI	= myocardial infarction
MLD	= minimal lumen diameter
NMA	= network meta-analysis
NT SVG	= no touch saphenous vein graft
OR	= odds ratio
OVH	= open vein graft harvesting
PICO	= population, intervention, comparator, outcomes
RA	= radial artery
RAO	= radial artery occlusion
RAPCO	= radial artery patency and clinical outcomes
RCA	= right coronary artery
RCT	= randomized control trial
RITA	= right internal thoracic artery
RGEA	= right gastroepiploic artery
SV	= saphenous vein
SVG	= saphenous vein graft
TRC	= transradial catheterization

(EVH). The PICO questions were sent to a research librarian in January 2021 to develop a strategy to identify relevant articles published in English with no time restrictions. Reference lists were manually scanned for additional relevant results. After duplicates were removed, this strategy resulted in 1009 potentially relevant abstracts, which were screened by 2 authors (S.F. and K.K.). A total of 166 articles met the inclusion criteria.

The primary reasons for exclusion were invalid patient populations (eg, those receiving percutaneous coronary intervention), a focus on non-clinical outcomes and inadequate study design (eg, lack of a comparison group or expert review). Two authors (S.F. and K.K.) developed an evidence table of the relevant papers and rated the studies for risk of bias. The Newcastle–Ottawa scale was used for observational studies, and a custom-made checklist was used for randomized control trials (RCTs) and meta-analyses.

Ethics Statement

Ethics approval was not requested as no individual patient data were included.

Left Internal Thoracic Artery to Left Anterior Descending

The LITA-LAD anastomosis represents the universally accepted gold standard for CABG. In the USA, it is the only recognized CABG quality metric related to the technique of the procedure. The evidence in support of the use of the LITA to graft the LAD is based on observational studies from the '80s and '90s showing better patency rate and clinical outcomes compared to the SVG, as well as on the unique morphologic and biological properties of the LITA.[2-4] While no appropriately powered RCT has formally tested the LITA-LAD hypothesis, there is no professional nor individual equipoise in the surgical community for such a study.

RADIAL ARTERY

Patency

Multiple RCTs and meta-analyses of RCTs have reported an improved patency rate for the radial artery (RA) compared to the saphenous vein (SV) at mid- and long-term follow-up.[5,6]

An individual participant data meta-analysis of 6 RCTs found that the use of the RA rather than the SV was associated with a statistically significant reduction in graft occlusion (hazard ratio [HR] 0.44, 95% confidence interval [CI] 0.28-0.70; $P < .001$) at a mean follow-up of 4.2 years.[7] It is important to note that the RAs were used to bypass mainly circumflex arteries with severe stenotic lesions with very few patients receiving radial grafting to the right coronary system. While these RCTs include a relatively limited number of patients for a procedure as common as CABG, the reported benefit is consistent starting in as few as 4 years.[8]

Long-Term Clinical Outcomes

Several observational series have found improved short- and long-term outcomes in patients who received the

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RA rather than the SV as the second conduit. In a meta-analysis of 14 adjusted observational studies (20,931 patients), the use of the RA was associated with a 26% relative risk reduction in mortality at 6.6-year follow-up.[9]

The aforementioned analysis of 6 RCTs also reported superiority for the RA in the composite outcome of death, myocardial infarction (MI) and repeat revascularization at 5 years follow-up (HR 0.67, 95% CI 0.49-0.90).[7] When the follow-up of the same database was extended to 10 years, use of the RA was associated with a statistically significant reduction in the incidence of the composite of death, MI or repeat revascularization (HR 0.73, 95% CI 0.61-0.88) and of the composite of death or MI (HR 0.77, 95% CI 0.63-0.94); a post hoc survival benefit for patients receiving the RA was also found, although the absolute benefit was small (HR 0.73, 95% CI 0.57-0.93).[10]

A Veteran Administration trial of 757 patients found no difference in patency rate at 1 year between the RA and the SV [odds ratio (OR) 0.99, 95% CI 0.56-1.74] and no difference in survival at 14.6 years of follow-up (HR 1.12, 95% CI 0.91-1.38.[11,12] No data on cardiac events were available. The Radial Artery Patency and Clinical Outcomes (RAPCO) trial found better patency rate at 10 years for the RA compared to the free right internal thoracic artery (RITA) (HR 0.45, 95% CI 0.23-0.88) and the SV (HR 0.40, 95% CI 0.15-1.00[13]: at 15 years of follow-up, the rate of the composite of death/MI and repeat revascularization were significantly lower in the RA arm (HR 0.74, 95% CI 0.55-0.97 vs the RITA and HR 0.71, 95% CI 0.52-0.98 vs the SV).

Hand Function

It is generally accepted that assessing the adequacy of ulnar collateral circulation should always be performed before RA harvesting—assessing RA morphology by ultrasound allows also detection of potential calcification and measurement of the RA diameter. Comparative studies on different methods of evaluation are lacking, but the clinical Allen test is highly operator dependent and is best complemented by an objective assessment.[14] The site of harvesting should be the one with better ulnar compensation and artery quality—there is no evidence to support the concept that the artery should be harvested from the nondominant arm although this has been the logical default approach. Harvesting of the RA is generally well tolerated; while arm paresthesia and pain have been reported, symptoms are generally transient and self-limited,[15] although long-term complications in some studies have been as high as 9%.[16] Ischemic hand complications, or changes in arm grip strength or dexterity are extremely rare, although there may be a publication bias.

Vascular diseases of the upper extremities are generally considered a contraindication to RA harvesting. Previous forearm trauma is a relative contraindication, especially if operative repair was needed, as well as previous surgery on the forearm or the wrist.

In patients with chronic renal failure the potential benefits of using the RA for CABG must be weighed against the possible need for an upper arm arteriovenous fistula for dialysis, but evidence is lacking.

Proximal Anastomosis

The RA can be anastomosed directly onto the aorta or to another conduit, typically the internal thoracic artery (ITA) as a Y or T graft—other configurations have been described but are seldom used.[17-19] Most of the available evidence on the RA is based on aorta-anastomosed grafts, while some studies have indicated higher radial graft patency with the aortic anastomosis approach,[20,21] other data did not reveal a difference.[22-25] The aortic anastomosed configuration is probably less at risk of failure due to competitive flow.[26]

From a technical point of view, concerns relating to high wall tension resulting from anastomosis of the RA directly onto the aorta have led some surgeons to craft a short interposition segment of SV, to which the RA is connected in end-to-end fashion. Whether this configuration negates some of the benefits of using the RA is not known.

Overall, data are currently insufficient to provide meaningful guidance on a preferred anastomotic technique.

Target Vessel Selection

Three factors are commonly considered: the degree of proximal coronary artery stenosis, the myocardial territory to be grafted and the size of the target vessel. There is ongoing controversy as to whether the RA should be used to graft target arteries with $\geq$90% proximal stenosis or $\geq$70% stenosis. In the RAPCO trial, grafted arteries required at least 70% proximal stenosis and a minimum diameter of 1.5 mm.[13] Similar inclusion criteria were used in the Radial Artery Patency Study (RAPS).[27] Only 21 late radial graft failures occurred in RAPCO, therefore limiting correlational analyses. Observational series, often long-term, have showed that $\geq$90% proximal target stenosis correlates with better graft patency than $\geq$70%, and a right coronary territory target with lower patency, a finding observed with most arterial grafts.[23,28-31] Limited information exists on ideal target vessel size, as trial patients were often selected to meet a minimum size. It is possible but unproven that the RA in comparison with a SVG, may be particularly suitable on small coronary targets—especially those with a high degree of proximal stenosis—due to the RA's more favorable match.

The Impact of Preoperative Fractional Flow Reserve on Arterial Bypass Graft Function (IMPAG) trial provided information on composite radial grafts, whereas a fractional flow reserve cut-off of 0.78 was predictive of anastomotic functionality at 6 months; however, most of the grafts used in IMPAG were ITA, not RA, grafts.[17] Available data remain susceptible to expertise, selection, recall, and publication biases.

Harvesting Method

The RA can be harvested in open fashion or endoscopically, the latter typically performed through small incisions at the distal and proximal ends of the in situ conduit. While open harvest is not usually associated with major pain locally, its incision is long and can be unsightly. Endoscopic harvesting involves a learning curve and may be associated with harvest-related spasm, less thorough clipping of branches and endothelial dysfunction.[32] Patient satisfaction, however, appears enhanced by endoscopic harvesting.[33] Both techniques have been shown to be safe in expert hands.[31,34,35]

Randomized data are sparse, involve small series and reveal short-term outcomes only. Most of the published RA trials employed open harvesting which, consequently, should be considered the standard. Available evidence with endoscopic radial harvest may be fraught with major expertise, selection, recall, and publication biases and no clear conclusion on RA patency and outcomes using the endoscopic technique can be drawn.

Transradial Catheterization

Previous catheterization of the RA is a contraindication to RA use for CABG, as there is evidence that the patency rate of RA grafts used for transradial procedures is significantly reduced compared to noncatheterized grafts[36] and it is known that transradial catheterization (TRC) produces significant endothelial damage.[37]

After TRC complete radial artery occlusion (RAO) may occur in up to 38%.[38] Measures to reduce RAO include, smaller hydrophilic sheaths, nitroglycerine solution flushes, and larger doses of heparin. Nevertheless, most current RAO rates are between 3% and 10%.[39,40] Recanalization occurs but it may take months, or the RAO may remain permanent.[38-40]

5F and 6F sheaths used for TRC are 7 to 10 cm long and the guidewires and catheters progressively traumatize the RA endothelium. Ultrasound, intravascular ultrasound[41] and optical coherence tomography studies[42,43] have documented intimal tears in 37% to 80%, media dissection in 10% to 37% and an increase in intima and media thickening, a marker of RA endothelial and vascular wall trauma, and a precursor to atherosclerosis.[41-43]

Histological and immunohistochemical examination of TRC-RA distal segments showed endothelial damage in all samples, with changes most pronounced if the instrumented RA was used within 24 h, still persisting though less prominent after several months.[36,37,44,45]

Excessive intimal hyperplasia in 68% to 73%, periarterial inflammation in 33%, fat and tissue necrosis in 26% were additional sequalae, most prominent in the 3 cm immediately upstream from the RA puncture, becoming less severe and less frequent proximally. These changes were not present in the noninstrumented RA.[44,45]

The diameter of the TRC-RA suffers a 10% reduction, most apparent in the distal 3 cm, which persists beyond 6 months.[36,37,46] As most RA punctures for TRC are 3 to 5 cm above the wrist,[38] and the vascular trauma affecting the most distal 3 cm adjacent to the puncture, 6 to 8 cm of a 20 cm length RA may be "unavailable" for use as a conduit—confining any potential instrumented RA use to a proximal coronary or as a Y graft. However, endothelial damage and dysfunction may not be confined to the distal portion of the artery, and the effect on graft patency is unknown.

Flow mediated dilatation assessed by ultrasound using the other RA as a control shows a significant 10% reduction compared to preinstrumentation and to the control, lasting up to 1 year after TRC[36,37,39,47]; longer follow-up have not been investigated and there is no evidence that endothelial function ever return to normal.

Nitrate-mediated vasodilatation is also impaired—maximally impaired early after TRC. The impairment gradually lessens over the next 9 to 26 weeks.[37,46-51] Endothelium dependent vasodilation is also impaired for up to a year.[37]

Instrumented RAs used in CABG have reduced patency in the only 2 published studies: 70% patency for TRC–RA versus 98% in pristine RAs 1 month postoperatively ($P = .017$),[36] and a markedly reduced patency for TRC-RAs (59% vs 78%) at 18 months.[52]

Calcium Channel Blockers

Prevention of perioperative RA spasm is key for successful RA grafting. Perioperative regimens, though varied, are well established and include topical and intraluminal RA papaverine, nitroglycerine, nitroprusside, diltiazem, verapamil, milrinone, and phenoxybenzamine.[53,54]

Some surgeons also use intravenous nitroglycerine or intravenous calcium channel blockers (CCBs) during surgery and for the first 12 to 24 h.[53,54] The optimum CCBs may be nifedipine and amlodipine. Both are up to 30 times more efficacious than diltiazem[55,56] whereas verapamil depresses myocardial function and conduction. There is less agreement regarding potential benefits of longer-term use of nitrates and CCBs.

There is no study evaluating the subacute or chronic use of oral or topical nitrates with respect to graft patency (including RA) and survival post CABG. Early small observational and randomized trials of postop CCBs (up to 12 months) reported inconsistent outcomes. However, most were underpowered, and used various CCBs.

In postoperative RA angiograms, areas of localized RA stenosis that dilated instantly with intragraft nitroglycerine were occasionally noted.[57] The meta-analysis of RCTs of RA versus SVG as a second graft by Gaudino and colleagues[58] showed significantly improved outcomes for death, MI, revascularization, and patency in those patients taking CCBs for at least 12 months postoperatively, although a treatment allocation bias may be present.

CCBs reduce preload, afterload and blood pressure. These actions may also contribute to better long-term outcomes. Drawbacks of CCBs, especially amlodipine are potential for headache, and mild peripheral edema (up to 20%).[54,57] The use of CCB may also prevent the use of other important secondary prevention therapies (beta-blockers, angiotensin-converting enzyme-inhibitors).

Bilateral Radial Artery Use

Few reports exist regarding the use of bilateral radial arteries (BRAs), mostly in cases of redo CABG, and conduit shortage.[32,33] Due to the increasing use of TRC and its potential clinical benefits, the use of bilateral radial artery should be balanced with the potential need for percutaneous coronary imaging or interventions.[59]

Key messages

- Randomized data support better patency rate and a reduction in adverse cardiac events for the RA compared to SVG.
- RA harvesting is generally well tolerated; there is limited evidence in support of the endoscopic harvesting method.
- The RA should be used to graft target vessel with low competitive coronary flow and should not be used after TRC.
- Observational evidence supports the use of vasodilators for the first year in patients with RA grafts.

RIGHT INTERNAL THORACIC ARTERY

Patency

Benedetto and colleagues[8] in a network meta-analysis (NMA) of 9 RCTs comparing angiographic outcomes of second conduits in CABG showed that when the analysis was restricted to 6 RCTs with ≥4 years of angiographic follow-up, the SVG (n = 377) was significantly associated with a 4-fold increased risk (OR 0.25, 95% CI 0.05-0.78) of functional graft occlusion when compared with the RITA (n = 145). In a rank probability analysis that also included the RA and the gastro-epiploic artery (GEA), the RITA achieved the highest probability (74%) to be the best conduit. More recently, however, Gaudino and colleagues[6] conducted an updated NMA of 14 RCTs that included 3396 patients and 3651 grafts from 5 additional studies comparing the angiographic patency of the RITA, RA, GEA, conventional SVG (CON-SVG) as well as the no-touch SVG (NT-SVG). The patency rates of the CON-SVG (n = 1362) and RITA (n = 399) after a mean angiographic follow-up of 5.1 years were 81.8% (95% CI 74.8-87.3) and 90.9% (95% CI 72.1-97.5), respectively. The RITA was not associated with a significantly lower rate of graft occlusion compared with the CON-SVG (incidence relative risk [IRR] 1.02, 95% CI 0.39-0.78).

Long-Term Clinical Outcomes

In the Arterial Revascularization Trial (ART), no difference was found in 10-year survival and event free survival among patients randomized to single versus bilateral ITA to the 2 most important left-sided targets.[60] There was a relatively high crossover rate from bilateral to single ITA and the RA was used in ~20% of the patients, potentially diluting the treatment effect. In an observational comparison, patients who received multiple arterial grafting (including the RA) had better survival and event free survival compared to patients who received a single ITA.

In an observational analysis of 7223 patients comparing long-term (>15 years) survival in 490 2:1 propensity-matched pairs of RITA-right coronary artery (RCA) versus SVG-RCA, time-segmented cox regression showed that during the first 9 years of follow-up the 2 strategies were associated with a similar risk of death (HR 1.13, 95% CI 0.67-1.90; P = .65).[61] However, beyond 9 years, RITA-RCA was associated with a significantly lower risk of death (HR 0.43, 95% CI 0.22-0.84; P = .01). A NMA of 31 adjusted observational studies and 4 RCTs including 1,49,902 patients (SVG 112 018; RITA 21 683) found that use of the RITA was associated with lower long-term mortality (IRR 0.80, 95% CI 0.73-0.86) at 8.5 years of follow-up when directly compared with the SVG.[62] This was confirmed in the NMA, showing that use of the SVG was associated with higher late mortality (IRR 1.26, 95% CI 1.17-1.35), operative mortality (OR 1.45, 95% CI 1.14-1.84), and perioperative MI (OR 1.30, 95% CI 1.06-1.61) compared with the RITA.[62] There was no difference in the risk of perioperative stroke (OR 1.24, 95% CI 0.93-1.64), while the risk of deep sternal wound infection (DSWI) (OR 0.71, 95% CI 0.55-0.91) was lower with SVG compared with the RITA. However, when limiting the analysis to studies in which the skeletonized harvesting technique for the ITA was used, no difference in DSWI between RITA and SVG was found in pairwise comparison.[62]

In summary, although long-term data do not currently show a consistent difference in terms of graft patency, adjusted observational data suggest superior long-term survival with use of the RITA compared with the SVG, and support use of the RITA over the SVG, particularly in patients with long life-expectancy. A volume to outcome effect for the use of bilateral internal thoracic artery (BITA) has been suggested in observational studies.[63]

Patient Selection

Selective use of BITA grafting is essential for safe and effective application. Because BITA harvesting is associated with increased sternal wound complications, alternative conduit options to BITA are recommended in patients at increased risk for such complications. In addition, patients with a limited life expectancy or those with severe comorbidities may not benefit from longevity associated with multiarterial grafting.[64,65] Three common patient groups where a thoughtful application of BITA grafting is particularly pertinent are discussed below:

Patients with diabetes. A 2013 meta-analysis of 1 RCT and 10 observational studies of patients with diabetes found that DSWI occurred in 3.1% and 1.6% for the BITA and single internal thoracic artery cohorts, respectively (relative risk 1.71, 95% CI 1.37-2.14).[66] Likewise, Dai and colleagues[67] reported higher DSWI in diabetic patients in another meta-analysis (relative risk 0.65, 95% CI 0.52-0.81). A third meta-analysis found a higher rate of DSWI regardless of how the ITAs were harvested.[68]

Recent retrospective data have not always supported these findings, failing to demonstrate a higher incidence of DSWI even in diabetic patients.[69-72] While the preponderance of evidence suggests higher DSWI risk in patients with diabetes, BITA has been used successfully in diabetic patients with equivalent safety results by centers experienced with the technique.[66,67]

Low ejection fraction. Low ejection fraction is strongly associated with increased perioperative mortality.[73] The priority in patients with ischemic cardiomyopathy is to mitigate the upfront risk of surgery.[74] Immediate flow in an arterial graft may not be as high as that in a vein graft with the potential for clinically significant early coronary hypoperfusion.[75,76] In addition, multiple arterial grafting usually adds to the complexity and duration of the operation which may not be well tolerated in patients with severe ventricular dysfunction.

Retrospective analyses suggest that the operative safety of using BITA is equivalent to single internal thoracic artery, although whether BITA improves long-term survival in this patient population is not clear with mixed results derived from observational studies.[77-80]

Although BITA grafting is not routinely recommended for patients with severe ventricular dysfunction, its use may be considered in select scenarios guided by the patient's anticipated survival and surgeon experience and judgement.[74]

Advanced age. An age-dependent benefit of BITA grafting was seen in a post hoc analysis of the ART, with a cut-off at 65 years.[81]

A meta-analysis of retrospective studies by Deo and colleagues[82] reported significantly higher DSWI in elderly patients associated with use of BITA (OR 1.86, 95% CI 1.3-2.5; $P < .01$) with no heterogeneity. Safety outcomes were equivalent, although long-term survival was not quantitatively analyzed and reported as mixed. Pevni and colleagues[83] reported similar safety and survival outcomes for BITA in octogenarians.

There is insufficient data on a specific age cut-off for use of BITA; however, observational studies including 2 large state registries suggest that the survival benefit associated with multiarterial grafting may be lost in patients over the age of 70 years.[64]

Target Vessel Selection

In addition to demographic factors, morphology and extent of cardiac disease may influence the outcome for BITA use. Bypassing with BITA multiple non-LAD target vessels that perfuse a large myocardial mass has been associated with improve long-term survival.[84] Additionally, a recent study suggests larger target vessels may be better suited for BITA use with a reduced rate of graft occlusion (OR 0.18, 95% CI 0.05-0.62; $P = .007$) and a cut-off of 1.93 mm.[85] Target vessel size, however, was not a factor in a previous analysis.[86]

Whether to use BITA in target vessels with moderate stenosis has long been an issue of debate. The impact of moderate proximal stenosis varies, with some studies suggesting a mild effect[87,88] to some suggesting significantly reduced patency. Composite grafts may fare particularly poorly compared to free grafts in bypassing these targets.[89] A prospective RCT associated an fractional flow reserve of $\leq$0.78 with improved RITA patency.[17]

The decision to use an in situ RITA or a free RITA depends on a number of factors, including coronary anatomy, a diseased ascending aorta, or high-risk for a redo sternotomy.[90] In limited data thus far, long-term RITA patency appears independent of its inflow configuration.[86,90] Clinical results have mostly been comparable between the in situ and composite configurations, although composite grafts tend to offer more complete revascularization at the potential risk of imbalanced flow.[91]

RITA Versus LITA to the LAD

The paper by Loop and colleagues[2] that established the use of the ITA to the LAD as the gold-standard did not differentiate between LITA and RITA, however both were used in an in situ configuration. One small RCT[92] and a few retrospective analyses, mostly from single centers, have compared BITA configurations where an in situ RITA is anastomosed to the LAD versus the standard in situ LITA to LAD. The evidence suggests that RITA to LAD is similar in terms of graft patency,[92-95] perioperative, operative,[92,93,95-97] or longer-term clinical outcomes.[96-99]

Patency. A randomized study by Deininger with 100 patients reported 100% patency after 6 months for both RITA-LAD and LITA-LAD.[92] Ji and colleagues[94] found no significant difference in rate of graft failure at mean follow-up of 36.6 $\pm$ 12.1 months.

A recent study by Ogawa and colleagues[95] reported that using the RITA for a vessel other than the LAD led to worse patency (HR 2.05, 95% CI 1.08-3.88; $P = .029$). Tatoulis and colleagues[93] reported similar overall patency in the

RITA and LITA with a mean of 100 months of follow-up in over 2000 grafts (RITA 94.6% vs 96.9%; P = .74), although this still represented a small portion of the total population. These findings were confirmed in a study by Bakaeen and colleagues[90] demonstrating that RITAs grafted to the LAD had patency similar to LITA to LAD.

The patency data are at higher risk of bias and generally come from clinically driven angiograms and many of the studies were not principally designed to test the patency of LITA versus RITA to the LAD. Another caveat is that use of pedicled ITAs was not well-represented in this data, and that many of the patients were operated on off-pump. Thus, the patency data should be interpreted with caution.

Long-term clinical outcomes. Deininger and colleagues[92] reported no adverse operative outcomes in either for both RITA-LAD and LITA-LAD groups, although it was clearly underpowered to find any differences for these rarer endpoints. Observational data, both matched and unmatched, have yet to find a significant difference in either operative or longer-term major adverse cardiovascular events (MACE) outcomes, individually or as a composite endpoint.[92] Raja and colleagues[98] reported a significant increase in perioperative mortality for LITA to LAD patients, but this unusual finding has not been reproduced in subsequent larger studies.

Ogawa and colleagues[95] reported a significant benefit to using the RITA for the LAD during their 6 years of follow-up in the composite outcome of death, MI, and revascularization (27.8% vs 41.5%; P = .029). Raja and colleagues[98] combined death and revascularization and found no significant difference between the groups (HR 0.81, 95% CI 0.64-1.14). Jabagi and colleagues[96] found no difference in 10-year reintervention rates.

The matched study by Ji and colleagues[94] combined mortality, MI, and stroke and found no significant difference between groups with a mean follow-up of over 3 years.

The matched cohort studies by Ogawa and colleagues[95] and Raja and colleagues[98] both explored mortality with at least 5 years of follow-up in nearly 1500 patients and found no significant difference in late death with up to 15 years after surgery. The multivariable analyses by Ben-Gal et al in 1990 patients and Mohammadi and colleagues in 1977 patients, as well as the entropy-balanced analysis by Jabagi and colleagues of 2050 patients likewise found no significant difference in long-term mortality between graft configurations.[96,97,99]

Technical considerations: RITA to LAD as part of a BITA revascularization strategy. The strategy and use of the in situ RITA to revascularize the LAD territory (and the LITA to bypass the circumflex territory) requires several important technical and clinical considerations:

Limited length. The RITA needs to be harvested for its maximal length especially proximally to reach coronary targets without tension. The very distal part of the ITA however has a small caliber, is very muscular and prone to spasm, and may be associated with inferior patency when used for grafting.

This limitation could potentially be mitigated by the use of the RITA as a Y or T graft to the lateral wall with a proximal anastomosis of the RITA to an in situ LITA to the LAD.

Potential injury at time of redo sternotomy. An in situ RITA crossing the midline either anteriorly or when the RITA is tunneled through the transverse sinus posteriorly is more prone to injury at the time of redo sternotomy.[100,101] Such injury could have potential devastating consequences. Specific location and proximity of crossing grafts to the sternum or cross-clamp must be carefully defined by preoperative gated computed tomography angiography and or angiography. Even with such careful and detailed preoperative assessments, because of the variable and unpredictable presence of adhesions, aortopathy, and significant residual native coronary artery disease, such injuries could have potentially very significant adverse consequences.[100]

Skeletonized ITA Harvesting

Evidence on skeletonized ITA harvesting has been mixed and generally highly dependent on retrospective and anecdotal experience. Randomized control data has documented that carefully harvested skeletonized ITA grafts can maintain structural integrity,[102,103] physiological response to vasoactive stimulation,[104,105] and acute graft flow that is at least comparable if not greater than that achieved with a pedicled approach.[106-108] Postanastomotic flow appears to be comparable or possibly increased.[109,110] Moreover, even though acute sternal microcirculation is clearly impaired with either approach,[111,112] sternal perfusion has been demonstrated to be better preserved over time with skeletonization.[113-115] Although this provides a rational substrate for fewer sternal wound complications, the data regarding reduced sternal wound infection, although abundant, is generally based on retrospective data without uniform definition of sternal infection, with or without controls and with minimal if any statistical adjustment.[116-119] Of note, post hoc analysis of the ITA harvesting technique from the ART revealed that pedicled BITA but not skeletonized single internal thoracic artery or BITA was associated with a significantly increased risk of any sternal wound complication.[120] Careful analysis of the STS Adult Cardiac Surgery Database, which reflects over 95% of cardiac operations performed in the USA,[121] revealed that skeletonized ITA harvesting, although less common than the pedicled approach, was associated with a significantly lower risk of DSWI (adjusted OR 0.66, 95% CI 0.44-1.00; P = .05) and an equivalent risk of operative mortality.[122] However, recent meta-analysis showed that the skeletonized approach did not eliminate the elevated risk of sternal infection in bilateral internal mammary artery grafting.[123]

Graft patency studies are generally retrospective, based on clinical indication and vary greatly in the length of follow-up, but have historically demonstrated comparable graft patency between the 2 approaches.[124,125] Some studies of late mortality favored the skeletonized approach.[126] However, 2 recent post hoc analyses of clinical trial data raise considerable concern regarding graft patency and clinical outcome in the contemporary practice of skeletonized ITA grafting. Data from the COMPASS trial which assessed the role of rivaroxaban plus/minus aspirin in patients with cardiovascular disease was able to study the 1-year graft patency (by computed tomography angiography) of 1002/1448 patients in the CABG arm and found graft occlusion in 33/344 (9.6%) of ITA grafts in the skeletonized group compared with 30/764 (3.9%) in the pedicled group (adjusted OR 2.41, 95% CI 1.39-4.20; $P = .002$). Perhaps of greater concern, at the end of the 2.5-year trial, the skeletonized graft patients had a higher risk of MACE including cardiovascular death, MI, stroke, or revascularization (adjusted HR 3.19, 95% CI 1.53-6.67; $P = .002$), driven by revascularization and stroke.[127] Patients were not randomized by surgical technique and the skeletonized group had a higher incidence of hypertension, elevated cholesterol, and medication profile. Overall, RITA occlusion was 18/84 (21.4%), reflecting potential variability in surgical technique. Post hoc analysis of the ART trial patients revealed similar mortality but higher MACE in the skeletonized versus the pedicled ITA patients at 10 years of follow-up (HR 1.25, 95% CI 1.06-1.47; $P = .01$) driven by a higher need for repeat revascularization (HR 1.42, 95% CI 1.11-1.82; $P = .01$). Interestingly, when limiting analysis to surgeons enrolling 51 patients or more, the difference disappeared.[128]

As with any surgical procedure, ITA skeletonization is subject to tremendous variability in surgical technique and experience: use of unipolar versus bipolar cautery versus harmonic scalpel, mobilization of the isolated artery versus use of surrounding tissue, clips versus cautery for branches, speed and experience of harvest, use of sequential and Y-grafts, in situ versus free-graft, off-pump versus on-pump application, may all play a role in surgical results. To date, RCTs have been small and limited to assessment of graft flow and histology and not powered for clinical outcomes. Discrepancy in clinical results may reflect the fact that earlier studies arose from centers specializing in the technique which may not be uniformly translatable to a more recent broadly applied experience. It appears as it is generally utilized, the skeletonized approach to ITA harvesting may be associated with a decreased risk of DSWI, comparable graft flow, but variable clinical results that are largely operator dependent. Therefore, use is best reserved for patients with increased risk of DSWI, such as diabetics or those undergoing BITA grafting, and for surgeons who have considerable experience with atraumatic harvest and good clinical outcomes.

Key messages

- Patency data are mixed, and there is no clear evidence of better patency for the RITA compared to SVG.
- Observational evidence shows that patients who received RITA rather than SVG for CABG have longer survival and better outcomes after surgery, but the only RCT was neutral.
- BITA harvesting may be associated with higher risk of DSWI and should be avoided in high-risk patients.
- The RITA should be used to graft target vessels with good run-off that perfuse a large myocardial mass.
- The evidence on skeletonization of the ITA is limited and suggests a decrease in sternal complications, but no clear conclusions can be drawn on the impact of skeletonization on graft patency and cardiovascular outcomes.

ENDOSCOPIC VEIN HARVESTING

A systematic review of studies comparing open vein graft harvesting (OVH) and EVH yielded 5 relevant meta-analyses and 1 RCT not included in any of the meta-analyses.[129-134]

The 2016 International Society for Minimally Invasive Cardiothoracic Surgery Systematic Review and Consensus Conference Statement[131] specifically examining patient-centered outcomes and resource utilization found that the risk of wound-related complications (ie, abscess, necrosis, dehiscence, drainage, seromas, lymphocele, edema, and hematoma) was significantly reduced with EVH (OR 0.29, 95% CI 0.22-0.37, 29 studies, 11,919 patients, $P < .00001$), as was pain during the postoperative period (OR 0.19, 95% CI 0.11-0.34, 7 studies, 834 patients, $P < .00001$). In addition, EVH was associated with a reduction in total hospital length of stay (mean difference = −0.73 days, 95% CI −1.18 to −0.28, 18 studies, 14,983 patients, $P < .00001$), and a reduced need for outpatient wound management resources.

The Randomized Endovein Graft Prospective (REGROUP) trial[134] did not find a significant difference between OVH and EVH in the risk of the primary outcome of a composite of MACE including death from any cause, nonfatal MI, and repeat revascularization (OVH 15.5% vs EVH 13.9%, HR 1.12, 95% CI 0.83-1.51; $P = .47$) over a median follow-up of 2.8 years that was confirmed over an extended median follow-up of 4.7 years (OVH 23.5% vs EVH 21.9%, HR 0.92, 95% CI 0.72-1.18; $P = .52$).[135] However, the trial did not include angiographic follow-up, and mandated minimum harvester experience for both techniques which has been shown to affect quality of the conduit, particularly for EVH.[136]

A meta-analysis by Sastry and colleagues[129] that included 4 studies (2 randomized, 2 nonrandomized) evaluating graft patency in 4700 patients with up to 18 months of angiographic follow-up found a higher rate of vein graft failure with EVH (OR 1.39, 95% CI 1.11-1.75; $P = .004$). When only the 2 RCTs[137,138] with angiographic follow-up of 3 and 6 months, respectively, were included in the analysis this finding no longer reached statistical significance (OR 1.21, 95% CI 0.76-1.90; $P = .42$). The meta-analysis by Deppe and colleagues[130] of 5 studies with angiographic follow-up of 6504 grafts reported a significantly higher risk of graft failure with EVH (OR 1.38, 95% CI, 1.01-1.88; $P < .0001$). Similarly, Kodia and colleagues[132] reported superior SVG patency with OVH at a mean follow-up of 2.6 years (OVH 82.3% vs EVH 75.1%; OR 0.61, 95% CI 0.43-0.87; $P = .01$). Both meta-analyses were driven by the nonrandomized post hoc analyses of the Project of Ex vivo Vein Graft Engineering via Transfection (PREVENT-IV)[139] and the Randomized On/Off Bypass (ROOBY)[140] trials. The latter study also reported a higher 30-day mortality rate (OVH 3.4% vs EVH 2.1%, OR 0.59, 95% CI 0.37-0.94; $P = .03$). Li and colleagues[133] also reported lower patency with EVH at 1 to 5 years (OR 0.80, 95% CI 0.70-0.91, 5 studies, 5235 patients; $P = .0005$).

Thus, the current evidence for SVG patency beyond 1-year of follow-up, which is mostly observational, suggests that EVH is associated with reduced patency in the longer term. An adequately powered RCT of EVH versus OVH with angiographic follow-up may address this gap in the evidence. Randomized data pointing to equipoise for EVH and OVH in terms of MACE underscores the highly complex and variable association of graft patency with clinical outcomes, particularly for SVG typically grafted to non-LAD territories.

Key messages

- EVH reduces the risk of leg wound complications.
- Patency data suggest that EVH is associated with reduced patency in the long term, but a large RCT found no difference between EVH and OVH in terms of MACE.
- More evidence on this important topic is needed.

NO TOUCH SAPHENOUS VEIN GRAFT

Given that the most commonly used graft continues to be the SVG and that there exist patient specific factors affecting graft patency and wound complications with the use of additional arterial grafts, there is a compelling rationale for improving outcomes using SVGs.

The no touch saphenous vein graft (NT SVG) is a Class IIA, LOE B recommendation in the 2018 European Revascularization Guidelines[141] based on 2 small graft patency RCTs.[142,143] The NT SVG harvesting method was designed to reduce vessel injury during surgical preparation. The key features are atraumatic harvesting with inclusion of a pedicle of adjacent fatty tissue to minimize graft spasm and avoid high-pressure dilation during vein preparation. A longitudinal single-center angiographic RCT of 104 patients by de Souza and colleagues comparing NT and conventional saphenous vein grafts (CON SVGs) revealed significantly better patency of the NT veins at 8.5 years (91% vs 77%; $P = .01$) which was maintained at 16 years (83% vs 64%; $P = .03$).[142] In an intravascular ultrasound substudy of the same patient population, there were significant differences which favored the NT SVGs according to multiple graft imaging endpoints 8.5 years postoperatively.[144] Two additional RCTs using angiographic patency have been completed—one multicenter trial of 250 patients[145] and one single-center trial of 60 patients.[146] Aggregated results from the 3 RCTs (525 SVGs) revealed a significant reduction of graft stenosis or occlusion at 1 year in the NT SVGs (OR 0.47, 95% CI 0.26-0.84; $P = .01$) and a trend for complete occlusion (OR 0.57, 95% CI 0.30-1.06; $P = .07$) with no evidence of heterogeneity between the studies.[145] De Sousa also compared the NT SVG with a RA in an angiographic trial using a within patient randomization in 108 patients. At 8.5 years, patency was similar between the 2 conduits (NT SVG 86%; RA 79%, $P = .22$) but NT was superior when analyzed per distal anastomosis (NT SVG 91%; RA 81%, $P < .05$).[143] A comprehensive NMA of 14 angiographic RCTs involving 3651 grafts at a mean follow-up of 5.1 years, confirmed that graft occlusion was reduced in NT compared to CON SVGs (IRR 0.55, 95% CI 0.39-0.78); the RA and NT SVG ranked as the best conduits (rank scores 0.87 and 0.85 respectively).[6] An additional NMA of 11 studies by Yokoyama and colleagues[147] was consistent with this result, reporting an IRR of 0.32 (95% CI 0.17-0.60) with at least 3 years of follow-up in favor of NT SVGs over CON SVGs. Kim and colleagues[148] reported better 1 year graft SVG patency of LITA-SVG composite grafts with NT SVGs compared to SVGs without a pedicle (97.3% vs 92.6%; $P = .05$) in a propensity score–matched study of 196 patients.

In a 2655-patient RCT from China graft failure was substantially reduced for the NT grafts compared with CON SVG, both at 3 months (OR, 0.57, 95% CI 0.41-0.80; $P < .001$) and 12 months (OR 0.56, 95% CI 0.41-0.76; $P < .001$).[149]

SWEDEGRAFT is an ongoing 900-patient registry-based RCT comparing NT and CON SVGs; the primary endpoint is the proportion of patients with SVG graft failure according to study CT angiography, SVG graft failure according to clinically driven angiography, or death over 2 years of follow-up.[150]

At this point, there is no convincing data that clinical outcomes are favorably affected using NT SVGs. The previously mentioned multicenter RCT by Deb and associates reported that major cardiac and cerebrovascular events were not statistically different at 1 year (HR 1.19, 95% CI 0.64-2.19).[145] A propensity-matched study of 2698 patients using the SWEDEHEART registry reported on mortality and repeat intervention at a mean of 6.6 years follow-up.[151] There was no difference in mortality (HR 0.97, 95% CI 0.80-1.19) or repeat revascularization (HR 0.91, 95% CI 0.71-1.17) although repeat angiography was reduced in the NT patients (HR 0.76, 95% CI 0.63-0.93).[151]

Two studies have reported on leg wound healing using standardized questionnaires serially postoperatively. The PATENT SVG study (n = 17) used a within patient randomization.[152] Leg assessment scores were worse in the NT legs at 3 months (P < 001) but similar and with minimal impairment at 1 year.[153] In the trial by Deb and colleagues,[145] the cumulative incidence of leg wound infection over 1 year was greater with NT SVG harvesting (25.4% vs 11.8%; P <.01), primarily because of differences at 1 and 3 months. Adverse leg outcomes using the standardized questionnaire were worse following NT SVG harvesting at 1 and 3 months but similar and with minimal impairment at 1 year. In the original trial by de Souza, leg wound complications were 11.1% with NT harvesting versus 4.3% in the controls.[153] EVH compared to OVH is associated improved wound healing.[129] Given the increased incidence of adverse harvest site outcomes using NT SVGs, endoscopic approaches have been considered. There are reports of small case series of minimally invasive NT SVG harvesting combining both techniques.[135]

Key messages

- Randomized data show that the patency rate of NT SVG is significantly better than that of the traditionally harvested SVG.
- There is no clear evidence of better clinical outcomes using the NT SVG compared to the CON SVG.
- The use of the NT SVG is associated with a significantly higher risk of harvesting site complications.

GASTROEPIPLOIC ARTERY

The right gastroepiploic artery (RGEA) conduit has most commonly been used as an in situ arterial bypass graft; however, it can also be used as a composite graft based on the ITA, or alternately as a free graft if a preoperative abdominal aortogram or computed tomography shows significant narrowing of the coeliac axis or if the RGEA had low free flow.[154,155]

Long-Term Patency

Available data on early and long-term outcomes are mostly from reports of in situ RGEA grafts anastomosed to the RCA.[156-162] The reported early postoperative angiographic patency rate ranges as high as 97.1% to 99.6%.[157-159,162] However, patency rate varies between 81.4% to 98.7% at 1 year,[156-159,162] 91.1% to 96% at 3 years,[156,159,161] 83.4% to 94.7% at 5 years,[156,157,159,161,162] and 66.5 to 90.2%[157,159-162] at 8 to 10 years. This is likely because the patency of RGEA graft is influenced by target vessel stenosis and graft harvesting technique.

Long-Term Clinical Outcomes

Few studies have directly compared use of in situ RGEA versus SVG, and the data that exists generally tests its use as the third conduit to supplement BITA.

A meta-analysis by Di Mauro and colleagues[163] compared 2548 patients from 6 studies receiving either in situ RGEA (n = 1023) or SVG (n = 1525) to supplement BITA. Overall, long-term survival was not different between the 2 conduits, albeit with a high degree of heterogeneity. When only propensity-matched studies were included, in situ GEA had a long-term survival advantage over SVG (HR 0.47, 95% CI 0.31-0.71, n = 1051; P < .001) and the heterogeneity was reduced.

One propensity-matched study compared long-term clinical outcomes of RGEA composite grafts with those of RITA composite grafts and found no statistically significant survival difference at 15 years (52.9% vs 49.4%; P = .470).[162]

Suzuki and colleagues[164] reported better freedom from MACE at 7 years for in situ RGEA over SVG, although this has not been replicated by other matched cohort studies whether an in situ or composite graft is used.[160,162]

Skeletonized/Pedicle Harvesting

Although RGEA is contractile and prone to vasospasm, skeletonization using the harmonic scalpel can reduce spasm by removing the periarterial nerve plexus, as well as extend the graft length and enable anastomosis with a larger diameter vessel.[165,166] Suzuki and colleagues[159] reported 8 years patency of 90.2% and Akita and colleagues[161] reported 10 years patency of 89.8%, when in situ RGEA was harvested in skeletonized or semi-skeletonized fashion and used as in situ graft, anastomosed to distal RCA with more than 90% stenosis or minimal lumen diameter (MLD) of <1 mm. These results were better than previously reported patency of in situ pedicled GEA, although direct comparisons are lacking.[157]

Patient and Target Vessel Selection

Contraindications for in situ GEA conduits include obese or very elderly patients, and those in whom future abdominal surgery may be needed. Although rerouting of the patent GEA graft using SVG in case of abdominal surgery is possible, it requires meticulous surgical management.[167]

In situ RGEA flow can be compromised by native flow competition when anastomosed to target coronary artery with moderate stenosis.[160,168] MLD of native RCA seems

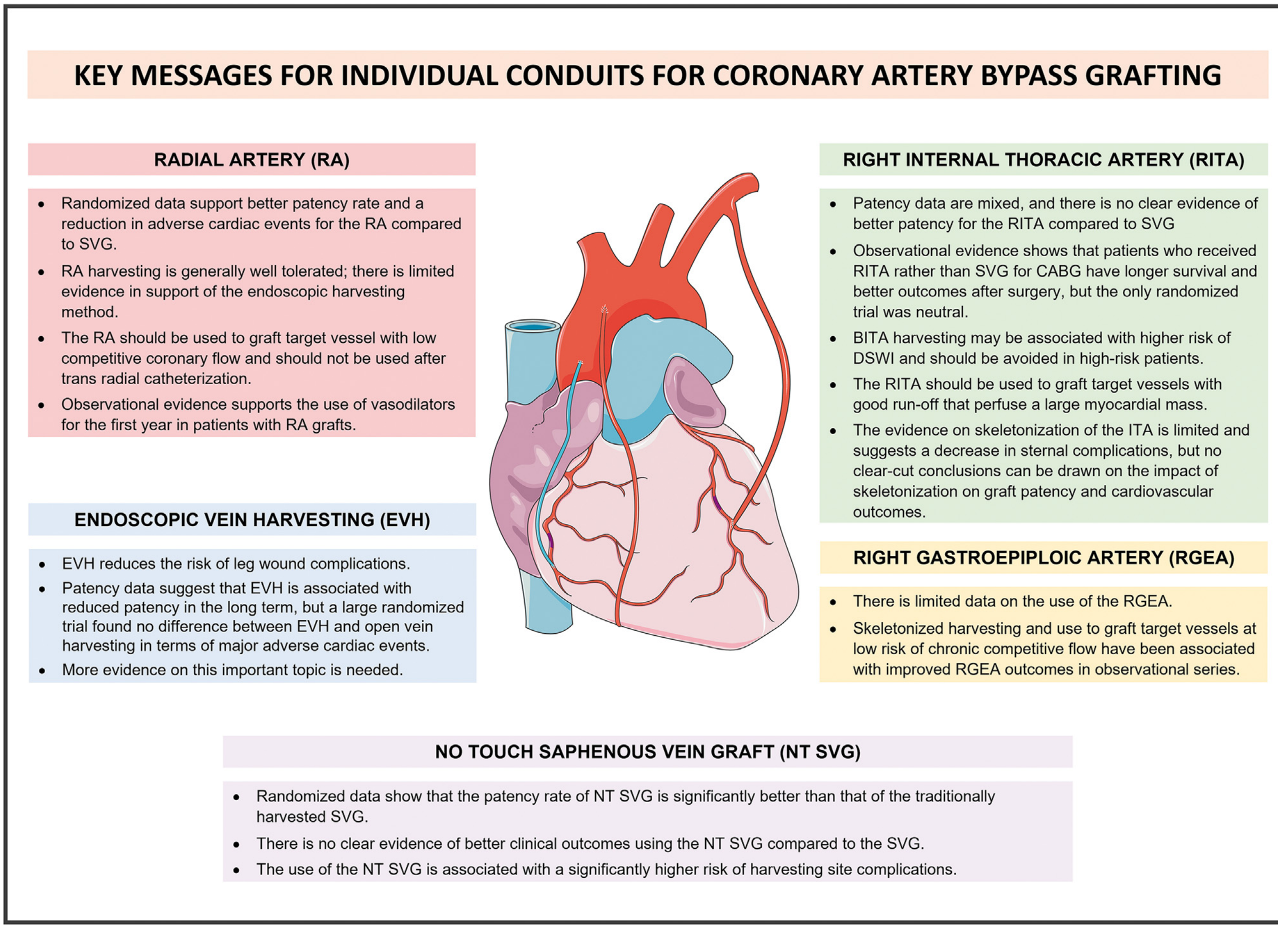

FIGURE 1. Visual summary of key messages. Parts of the figure were drawn by using pictures from Servier Medical Art (smart.servier.com). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

a more reliable indicator rather than angiographic stenosis, especially for the RCA. On the basis of systematic 3-year angiographic data, Glineur and colleagues[169] recommend that in situ RGEA should be used preferentially to graft the RCA system only when the MLD of target RCA is below 1.1 mm. Akita and colleagues[161] reported a 10-year patency rate of only 39.3% for in situ RGEA when it was anastomosed to RCA with MLD >1 mm, but a satisfactory patency of 89.8% when MLD was <1 mm. A visual summary of all the key messages is displayed in Figure 1.

Key messages

- There is limited data on the use of the RGEA.
- Skeletonized harvesting and use to graft target vessels at low risk of chronic competitive flow have been associated with improved RGEA outcomes in observational series.

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Data Availability

All relevant data are within the manuscript and its supporting information files.

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