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IN DEPTH

Arterial Grafts for Coronary Bypass

A Critical Review After the Publication of ART and RADIAL

ABSTRACT: Observational and randomized evidence shows that arterial grafts have better patency rates than saphenous vein grafts (SVGs) in coronary artery bypass grafting. Observational studies suggest that the use of multiple arterial grafts is associated with longer postoperative survival, but this must be interpreted in the context of treatment allocation bias and hidden confounders intrinsic to the study designs. Recently, a pooled analysis of 6 randomized trials comparing the radial artery with the SVG as the second conduit and the largest randomized trial comparing the use of single and bilateral internal thoracic arteries have provided apparently divergent results about a clinical benefit with the use of >1 arterial conduit. However, both analyses have methodological limitations that may have influenced their results. At present, it is unclear whether the well-documented increased patency rate of arterial grafts translates into clinical benefits in the majority of patients undergoing coronary artery bypass grafting. A large randomized trial testing the arterial grafts hypothesis (ROMA [Randomized Comparison of the Clinical Outcome of Single Versus Multiple Arterial Grafts]) is underway and will report the results in a few years.

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For >20 years, it has generally been accepted that patients who receive multiple arterial grafts at the time of coronary artery bypass surgery (CABG) have better long-term survival compared with those who receive only 1 arterial graft.[1–3] Accordingly, current US and European guidelines encourage the use of multiple arterial grafts in patients with a long life expectancy[4,5]; a position paper from the Society of Thoracic Surgeons strongly recommended wider use of arterial grafts.[6]

The evidence on the survival benefits of arterial grafts may appear compelling, but it is based almost exclusively on observational series.

ART (Arterial Revascularization Trial), the largest randomized, controlled trial (RCT) comparing the clinical outcomes of patients with CABG receiving 1 versus 2 internal thoracic arteries (ITAs), reported its 10-year results in early 2019.[7] In the intention-to-treat analysis, no difference was found in survival and event-free survival between patients randomized to receive 1 ITA and those randomized to receive 2 ITAs. A few months before, in the RADIAL (Radial Artery Database International Alliance) study, a patient-level pooled analysis of the RCTs comparing the radial artery (RA) and the SVG as the second conduit for CABG, a significant reduction in adverse cardiac events with the RA was reported at 5 years.[8]

Key Words: arteries ■ coronary artery bypass ■ myocardial revascularization

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We herein critically review the current evidence on the use of arterial grafts for CABG and further explore the implications of these findings for routine clinical practice.

METHODS

The ATLANTIC (Arterial Grafting International Consortium) Alliance is a voluntary international group of investigators dedicated to CABG with a particular focus on the use of multiple arterial grafts. The consortium was established in 2017 with the purpose of providing updated and comprehensive reviews on the topic; for projects requiring expertise in fields not covered by the members of the writing groups, external contribution was sought. The full list of the ATLANTIC members and of the published review papers is provided in the online-only Data Supplement.

Search Strategy

A search to identify relevant studies for the present narrative review was last updated on March 18, 2019, in the following databases: Ovid MEDLINE (all; 1946–present); Ovid EMBASE (1974–present); and the Cochrane Library (Wiley). The search strategy included all appropriate controlled vocabulary and key words for the interventions: radial artery, gastroepiploic artery, internal thoracic artery, and internal mammary artery coupled with coronary surgery, myocardial revascularization, coronary artery bypass, CABG, and patency. The full search strategy for Ovid MEDLINE is available in Table I in the online-only Data Supplement.

Study Selection

Searches across the chosen databases retrieved 53415 results. After duplicated results were removed, 2 independent reviewers (M.G. and A.D.F.) screened a total of 4535 citations. Discrepancies were resolved by consensus. Relevant abstracts were reviewed, and the related articles function was used for all included articles. References from selected studies were cross-checked. After collegial discussion, the most relevant articles according to the authors' opinion were selected and form the basis of the present critical review. Animal studies, case reports, conference presentations, editorials, expert opinions, and studies on pediatric populations were excluded (characteristics of the included papers are summarized in Table II in the online-only Data Supplement).

The full Preferred Reporting Items for Systematic Reviews and Meta-Analyses[9] flow diagram outlining the study selection process is available in Figure I in the online-only Data Supplement.

REVIEW

Angiographic Outcome of Arterial and Venous Grafts

Evidence From Observational Data

In observational series, the patency rate of arterial grafts has been shown to be excellent and generally superior to that of SVGs. Tatoulis and associates[10] reported 15-year left (LITA) and right ITA (RITA) patency rates of >95% and >90%, respectively. The RA shows patency rates of >90% at 10 years[11] and >85% at 20 years when anastomosed to a target vessel with ≥90% stenosis.[12]

In comparison, the patency of SVGs is considerably lower. SVG patency at 5 and 10 years ranges between 75% and 86% and 55% and 60%, respectively,[11,13,14] with an attrition rate of 1%/y to 2%/y between 1 and 6 years and of 4%/y between 6 and 10 years.[15]

Possible biases in terms of target vessel and patient selection and surgeon expertise must be taken into account in the evaluation of these observational series.

Evidence From RCTs

The randomized PREVENT IV (Project of Ex Vivo Vein Graft Engineering via Transfection IV; including 1828 patients undergoing protocol-mandated follow-up angiography 12–18 months after CABG or earlier clinically driven angiography) reported an SVG patency of only 75%.[16]

The RCT-based evidence of better patency rate for arterial conduits compared with SVG is based on 8 RCTs[11,17–23] (2166 patients) for the RA and on 2 RCTs[21,24] (304 patients) for the RITA.

Although no difference was reported in 1-year patency, in all the studies comparing the patency rates of the RA and the SVG that extended the follow-up beyond 1 year, better patency rates for the RA were demonstrated when the artery was used to bypass severe stenosis following guidelines and recommendations from societies (Figure 1).[11,17–23] In fact, the only study that reported lower patency rate for the RA was the one in which severity of the stenosis was not considered when the use of the RA was planned.[25]

Similarly, when RITA patency rate at 1 year was compared with that of SVG, no statically significant differences were shown (97.9% in the SVG group versus 96.9% in the RITA group; P=0.36),[24] whereas superior results were demonstrated for the artery at longer (4-year) follow-up (95% versus 90% patency rate for RITA versus SVG respectively, P=0.001).[21]

Benedetto and colleagues[26] summarized the randomized evidence in a network meta-analysis of 9 angiographic RCTs and showed a significantly increased risk of late (>4 years) SVG graft occlusion compared with the RITA (odds ratio [OR], 4.07 [95% CI, 1.28–20.88]) and RA (OR, 2.94 [95% CI, 1.36–9.00]).

In conclusion, evidence from not only observational data but also RCTs suggests that the use of arterial grafts results in improved late graft patency. The difference between the results at 1 year and at later follow-up is likely the result of the described progressive increase of the attrition rate of SVG grafts in the years after surgery.[27]

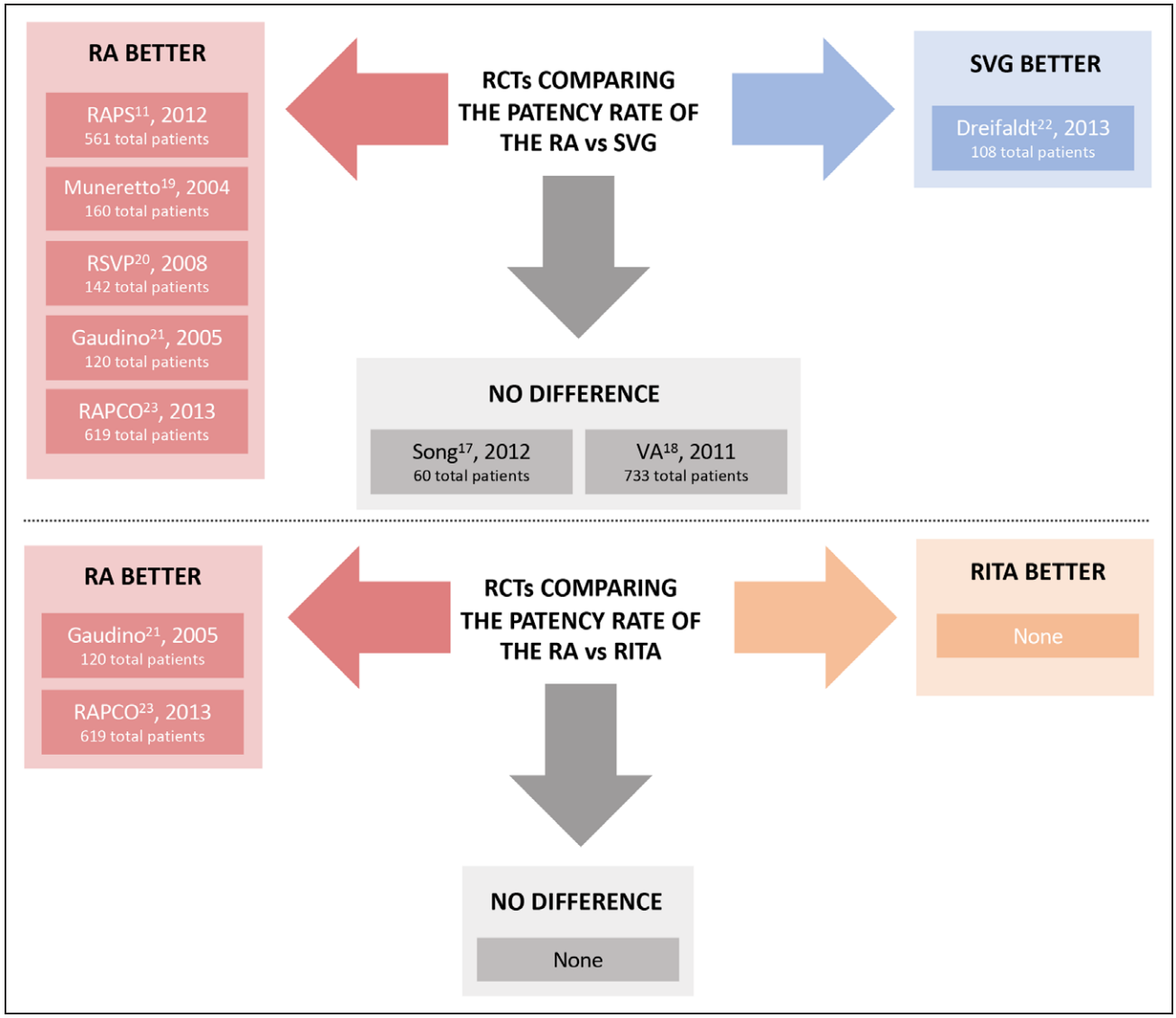

Figure 1. Results of randomized trials comparing the patency rate of the radial artery (RA) with other conduits.
In the study by Dreifaldt et al,[22] antispasm therapy was not systematically administered in patients with RA grafts, and no stenosis cutoff was used for RA grafting (RA anastomosed to target with stenosis <70% in 31% of the cases and <90% in 69% of the cases). RAPCO indicates Radial Artery Patency and Clinical Outcomes; RAPS, Radial Artery Patency Study; RCT, randomized, controlled trial; RITA, right internal thoracic artery; RSVP, Radial Artery Versus Saphenous Vein Patency; SVG, saphenous vein graft; and VA, Veterans Affairs.

Clinical Outcomes of Arterial and Venous Grafts

Two Arterial Grafts: Bilateral ITAs

Evidence From Observational Data

Since 2001, 5 systematic reviews and 1 meta-analysis have compared the clinical outcome of patients with CABG receiving single LITA and those receiving bilateral ITAs (BITA).[2,3,28–31] All of them reported a statistically significant survival advantage associated with the use of BITA.

In the most recent systematic review by Buttar and coauthors,[28] 29 observational studies (89 399 patients) were analyzed. Patients in whom BITAs were used had significantly improved long-term survival (hazard ratio [HR], 0.78; *P*<0.00001) and reduced hospital mortality (1.2% versus 2.1%; *P*=0.04), cerebrovascular accidents (1.3% versus 2.9%; *P*=0.0003), and need for revascularization (4.8% versus 10%; *P*=0.005) rates compared with those receiving only a single ITA graft, although the incidence of deep sternal wound infection was increased (1.8% versus 1.4%; *P*=0.0008). The lower risk of stroke could be related either to less aortic manipulation or to confounding related to lower-risk patients who received BITA.

Despite the potential benefit of BITA, the application of this technique in patients with diabetes mellitus has been controversial, mainly because of the potential for increased risk of deep sternal wound infections in this population.[32] However, 3 meta-analyses reported

that the risk of deep sternal wound infections in patients with diabetes mellitus is similar to that of LITA when skeletonized BITA harvesting is performed.[33–35] In the most recent analysis, Zhou and colleagues[35] pooled data from 129 871 patients with diabetes mellitus (124 233 LITA, 5638 BITA) and found that, although the overall incidence of deep sternal wound infection with BITA was significantly higher than with LITA (3.26% for BITA versus 1.70% for LITA; $P<0.001$), there was no significant difference between the 2 groups when skeletonized harvesting technique was adopted (2.46% for LITA versus 2.48% for BITA; $P=0.84$). Skeletonized harvesting better preserves sternal perfusion and has been shown to significantly reduce the risk of sternal wound complications.[36,37]

Evidence From RCTs

In contrast to the large observational evidence before ART, only 2 RCTs have compared the outcomes of patients receiving LITA and BITA. One of them was a feasibility analysis that clearly was underpowered to detect even large clinical differences between groups (162 patients, 81 per group).[38]

In the Stand-in-Y trial (which was also underpowered to detect any survival difference), 850 patients were randomized to LITA or 3 different strategies of multiple arterial grafting, including BITA. At the 2-year follow-up, the use of BITA was associated with significantly better event-free survival ($P<0.001$) but similar overall survival ($P=0.59$).[39]

The ART trial is the largest RCT designed to compare BITA and LITA, with a sample size of 3102 patients (enrollment phase, June 2004–December 2007).[7] The trial included 28 centers from 7 countries and was powered to detect a 20% relative difference and a 5% absolute difference in all-cause mortality at 10 years (primary outcome).

At 10 years, the intention-to-treat analysis showed no difference in survival and event-free survival between BITA and LITA (Figure 2).

Notably, as a result of a higher-than-anticipated rate of crossover from BITA to single ITA (14%) and the frequent use of the RA in both groups (≈20%), only 1330 of the 1554 patients with LITA actually received a single arterial graft. In an as-treated observational analysis comparing patients who received multiple arterial grafts (either LITA-RA or BITA) with those who received a single arterial graft, the risks of 10-year mortality and major adverse events were significantly lower in the multiple arterial grafting group (adjusted HR, 0.81 [95% CI, 0.68–0.95] and adjusted HR, 0.80 [95% CI, 0.69–0.93] for mortality and major adverse events, respectively; Figure 3). Although the baseline characteristics of the patients with single and multiple arterial grafts were very similar and risk adjustment is probably more solid in the context of an RCT, this analysis still shares the limitations of observational studies.

There are several possible explanations for the discrepancy between the results from ART and previous observational evidence. Comparative observational studies suffer from an intrinsic selection bias and from hidden potential confounders that even advanced statistical methods may not entirely eliminate.[40]

In addition, alternative explanations need to be considered. The sample size of ART was calculated on the basis of a meta-analysis published in 2001 that included studies from the 1970s, 1980s, and 1990s.[2] The progress in secondary prevention over the last 20 years has improved the postoperative survival of patients with CABG, and in fact, in the final analysis, the control event rate in ART was 20% lower than expected and identical to the hypothesized rate in the treatment arm. Patients in ART had high compliance with guideline-

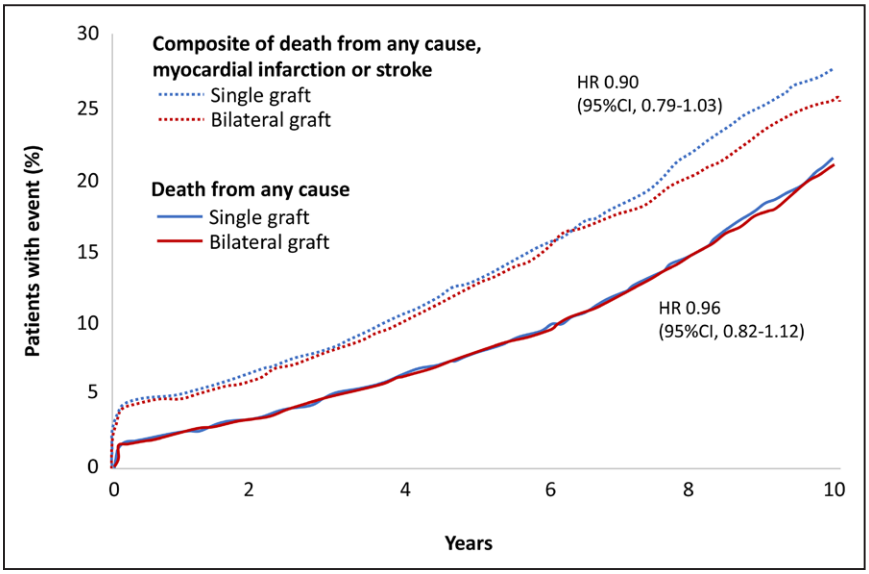

Figure 2. Intention-to-treat analysis for the primary outcome of death resulting from any cause and the composite outcome of death resulting from any cause, myocardial infarction, or stroke at 10 years in ART (Arterial Revascularization Trial).[7]
HR indicates hazard ratio.

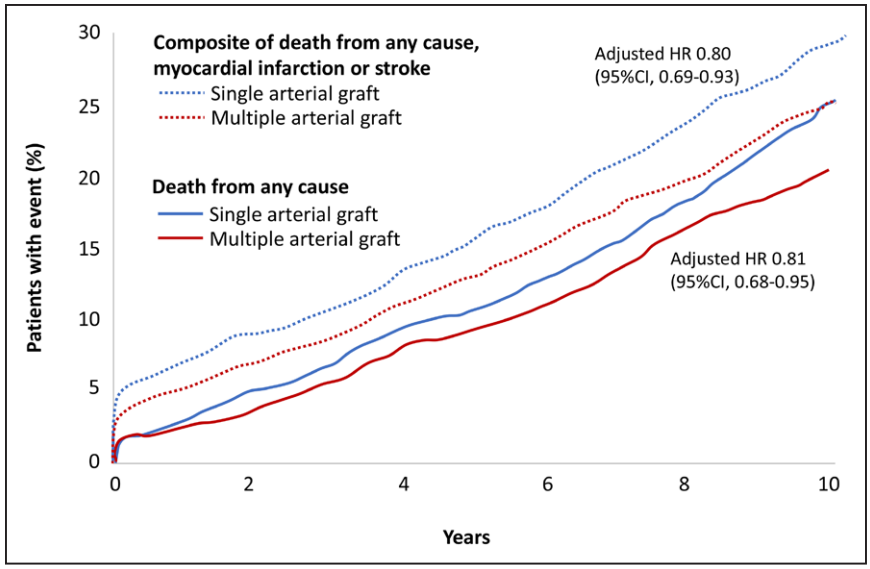

Figure 3. As-treated analysis of multiple (≥2) arterial grafts vs single arterial graft for death resulting from any cause and the composite outcome of death resulting from any cause, myocardial infarction, or stroke at 10 years in ART (Arterial Revascularization Trial).[7]
HR indicates hazard ratio.

directed medical therapy (81% of patients on aspirin, 74% on β-blockers, and 90% on statins at 10 years).

In addition, the sizeable proportion of patients in the LITA group who received an RA graft (23%) is a potentially important confounder, given the better patency rates and clinical outcomes of RA grafts compared with SVGs,[11,23,26] and may have further narrowed any potential differences in clinical outcome between the LITA and BITA groups. The ART investigators have published a post hoc analysis reporting that at 5 years the use of an RA graft was associated with significantly lower incidence of major adverse events in both groups, although selection bias could contribute to this finding.[41]

Finally, the high rate of crossover is of concern. Crossover was 4-fold higher in the BITA arm (16.4% versus 3.9% in the LITA group), and the crossover rate from BITA to single ITA varied from 0% to 100% among the 131 ART surgeons.[42] In the protocol, the ART investigators do not quantify the expected crossover rate but clearly state that they expected an high compliance with the protocol ("As the intervention is the operation, compliance is likely to be 100% except in the unusual situation where the planned operation is not possible for technical reasons"). The high crossover rate observed in ART not only dilutes the potential treatment effect but may indicate lack of confidence with the systematic use of BITA of some of the ART surgeons. As specified in the ART protocol, in experienced hands, conversion from BITA to single ITA is unlikely to occur. This is important because it has been shown that the results of BITA grafting are significantly associated with surgeon experience and that patients operated on by low-volume BITA surgeons have worse short- and long-term outcome than patients operated on by high-volume BITA surgeons.[43,44] Notably, even in the context of ART, for surgeons who enrolled >50 cases in the trial, the use of BITA was associated with better outcomes, including survival.[7]

Two Arterial Grafts: ITA and RA

Evidence From Observational Data

In a large propensity score–matched series including 9005 patients with CABG, survival was 83.2% versus 79.4% at 10 years for patients receiving RA versus SVG, respectively; RA use was associated with a lower risk for late death (HR, 0.75 [95% CI, 0.57–0.98]; *P*=0.03). Of note, the survival advantage associated with RA was maximum in patients ≤60 years of age (upper limit of 95% CI, <1) and gradually declined with increasing age.[45]

Tranbaugh and colleagues[46] compared 14-year outcomes in propensity-matched patients undergoing isolated, primary CABG with the use of the RA versus SVG. Although no differences between the groups were found in terms of hospital mortality (0.1% for the RA versus 0.2% for the SVG), RA use was associated with significantly improved long-term survival (Kaplan-Meier survival at 1, 5, and 10 years: 98.3%, 93.9%, and 83.1% for the RA group versus 97.2%, 88.7%, and 74.3% for the SVG; log rank *P*=0.001).

A recent meta-analysis of observational studies comparing the RA with the SVG as the second conduit in CABG (20931 patients; mean follow-up, 6.6 years) found similar risk for operative mortality (1.25% versus 1.33%; OR, 0.93 [95% CI, 0.68–1.28]), perioperative myocardial infarction (OR, 0.96 [95% CI, 0.59–1.56]), and stroke (OR, 0.70 [95% CI, 0.43–1.13]) but lower long-term mortality in the RA group (24.5% in RA versus 34.2% in SVG group; incidence rate ratio, 0.74 [95% CI, 0.63–0.87]; *P*<0.001).[47]

Evidence From RCTs

To date, 8 RCTs have compared the patency of the RA and SVG. All studies had primary angiographic out-

comes but were individually underpowered to detect moderate differences in mortality. Despite this, the 2 RCTs with the longest follow-up, RAPS (Radial Artery Patency Study; 7.7 years) and RAPCO (Radial Artery Patency and Clinical Outcomes; 10 years), reported a tendency toward better clinical outcomes for the RA.[11,23] An aggregate meta-analysis including 6 of the above-mentioned RCTs and a total of 1860 patients showed a trend to reduced cardiac death and myocardial infarction and significantly reduced repeat coronary procedures for the RA (OR, 0.72 [95% CI, 0.30–1.73]; OR, 0.68 [95% CI, 0.33–1.38]; and OR, 0.27 [95% CI, 0.13–0.56], respectively).[48]

Recently, RADIAL,[8] a pooled individual-patient analysis of 6 RCTs comparing the RA with the SVG as the second conduit for CABG with a follow-up of >2 years, showed that at midterm follow-up (5 years), the use of the RA led to a significant reduction of the composite of death, myocardial infarction, and repeat revascularization compared with the use of the SVG (HR, 0.67 [95% CI, 0.49–0.90]; Figure 4). Significant differences were also reported for the individual outcomes of myocardial infarction and repeat revascularization (HR, 0.72 [95% CI, 0.53–0.99] and HR, 0.50 [95% CI, 0.40–0.63], respectively) but not for mortality (HR, 0.90 [95% CI, 0.59–1.41]). The patency rate of the RA was significantly higher than that of the SVG (HR, 0.44; [95% CI, 0.28–0.70]), providing a biological explanation for the observed clinical differences. It is notable that in the RADIAL analysis the crossover rate ranged from 2.6% to 4.2%.

It must be noted, however, that the primary composite outcome was driven mainly by the rate of repeat revascularization, an outcome that may be inflated in angiographic trials. In addition, despite the use of a pooled analysis, the sample size of RADIAL was relatively small (1036 patients in the primary analysis), and confirmation of the results of RADIAL in other trials is mandatory.

In the most recent myocardial revascularization guidelines, the use of the RA to graft a target with severe stenosis is a Class I, Level of Evidence B indication (whereas the use of BITA is a Class IIa, Level of Evidence B recommendation).[5]

Three Arterial Grafts: BITAs and RA

Evidence From Observational Data

To date, there has been conflicting evidence for the potential benefit of a third arterial graft.[49–56] In the only meta-analysis of propensity-matched series (8 studies; 10 287 matched patients; 5346 two-artery grafts; 4941 three-artery grafts; mean follow-up time, 37.2–196.8 months), survival was significantly longer among patients receiving 3 versus 2 arterial grafts (HR, 0.8 [95% CI 0.75–0.87]).[57] In another meta-analysis including mostly unadjusted studies (130 305 patients; mean fol-

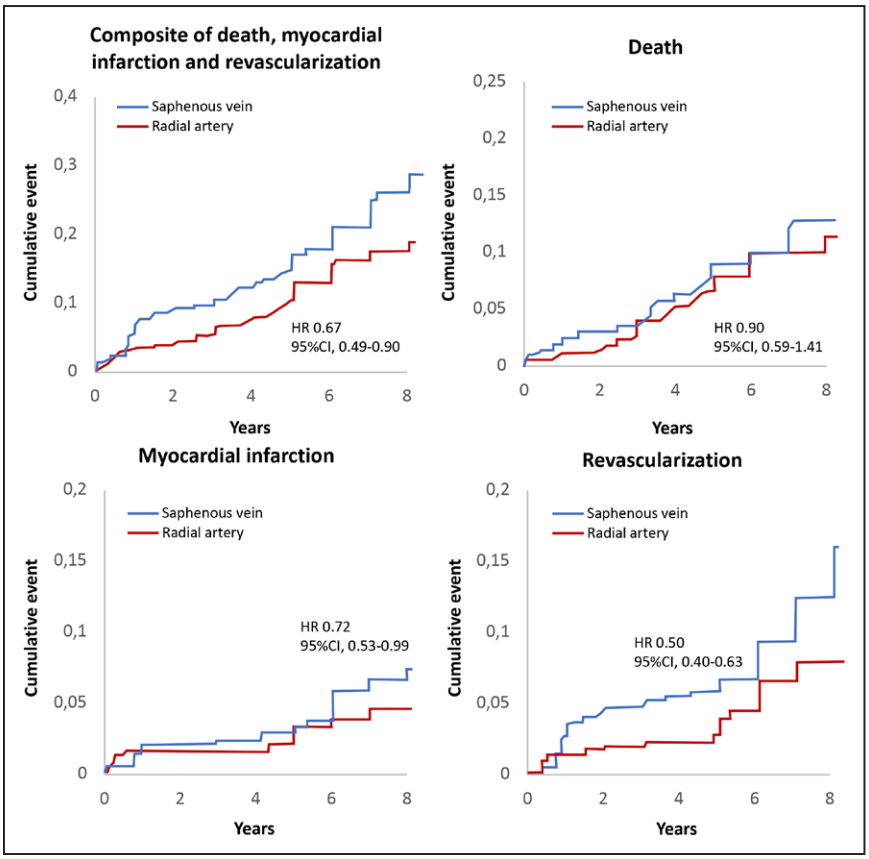

Figure 4. Cumulative incidence of the primary composite outcome and its individual components of death, myocardial infarction, and repeat revascularization in the RADIAL study (Radial Artery Database International Alliance).[8]
HR indicates hazard ratio.

low-up range, 1–15 years), Yanagawa and associates[58] showed that patients receiving total arterial revascularization had significantly longer survival compared with those who received single or double arterial grafts (incident rate ratio, 0.85 [95% CI, 0.73–0.99]; *P*=0.04).

A study of >50 000 patients based on the Australian and New Zealand Society of Cardiothoracic Surgeons database found that the use of any SVG was independently associated with reduced survival up to 12.5 years after surgery (HR, 1.24 [95% CI, 1.18–1.30]).[59] On the other hand, a propensity-matched analysis of the Ontario state registry found no difference in major adverse cardiac and cerebrovascular events, death, myocardial infarction, stroke, or repeat revascularization at a mean follow-up of 4.2 years for patients receiving 2 versus 3 arterial grafts (HR, 1.08 [95% CI, 0.94–1.25]).[60]

Evidence From RCTs

Limited evidence from RCTs on the effects of using 3 arterial grafts is available.

Muneretto et al[61] randomized 200 elderly patients (>70 years of age) to receive total arterial revascularization or conventional revascularization with LITA+SVG. At a mean follow-up of 15 months, mortality was similar in the 2 groups, but a significantly lower incidence of graft occlusion (*P*=0.009), angina recurrence (*P*<0.001), new myocardial infarction (*P*=0.026), or new percutaneous revascularization (*P*=0.012) was found in the total arterial revascularization group. In multivariable analysis, use of an SVG was found to be an independent predictor of graft occlusion and angina recurrence.

Le and colleagues[62] published a pilot RCT of 58 patients comparing total arterial grafting and conventional CABG. The trial was aimed at proving feasibility, but the authors found no differences in terms of main in-hospital outcomes (mortality, stroke, deep sternal wound infections) between the 2 groups. At the 6-month follow-up, no differences in terms graft patency were evident when arterial grafts were compared with SVGs (*P*= 0.99).

RITA Versus RA as the Second Arterial Conduit

Evidence From Observational Data

In terms of clinical outcomes, in a meta-analysis of 8 propensity score–matched studies including 15 374 patients, BITA compared with LITA/RA grafting was associated with a reduction in late death (HR, 0.75 [95% CI, 0.58–0.97]) and repeat revascularization (HR, 0.37 [95% CI, 0.16–0.85]), although treatment allocation bias and outlier effect could have been responsible for this difference.[63,64]

The accepted downside of BITA use is an increased risk of sternal complications. A meta-analysis of observational studies including 173 000 patients reported a 38% relative increase in deep sternal wound infection when a second ITA was used (1.6% LITA versus 2.05% BITA; relative risk, 1.38 [95% CI, 1.29–1.45]).[65] The risk increases in patients with diabetes mellitus, chronic pulmonary disease, and morbid obesity; of note, these subjects might benefit from RA grafting. The use of the skeletonization technique for harvesting significantly reduces the risk of sternal complications associated with the use of BITA.[37,42]

In a recent review of the Society of Thoracic Surgeons database including data from 1 493 470 patients, Schwann and associates[66] found that, compared with the standard operation with LITA+SVG, the use of BITA, but not of LITA+RA, was associated with a marginally increased risk of operative mortality (risk-adjusted OR, 1.14 [95% CI, 1.00–1.30; *P*=0.05] versus 1.01 [95% CI, 0.89–1.15; *P*=0.85] for BITA and LITA+RA, respectively) and a significant increase of the risk of sternal complications (risk-adjusted OR, 2.09 [95% CI, 1.80–2.43; *P*<0.001] versus 0.97 [95% CI, 0.83–1.13; *P*=0.70] for BITA and LITA+RA, respectively). The authors described a U-shaped volume-outcome relation, more evident for the BITA than for the LITA+RA procedure. A significant relationship between operator volume and short- and long-term outcomes for BITA has also been confirmed in a recent meta-analysis (34 studies included, 27 894 patients with BITA), showing that percentage use of BITA was significantly and inversely associated with long-term mortality (β=–0.02, *P*=0.02 and β=–0.03, *P*=0.04, univariable and multivariable meta-regression, respectively) and the rate of deep sternal wound infections (β=–0.001, *P*=0.006 and β=–0.02, *P*<0.001, univariable and multivariable meta-regression, respectively).[43]

Finally, a report based on 2006 to 2011 data from a large state registry including 126 centers in California found that, compared with RA grafts, BITA grafts were associated with similar survival (mortality rates at 7 years, 10.3% versus 10.7% for BITA and RA, respectively; HR, 1.10 [95% CI, 0.89–1.37]) but increased risk of sternal wound infection (2.29% versus 1.22% for BITA and RA, respectively; risk difference, 1.07% [95% CI, 0.15–2.07]).[67]

Evidence From RCTs

Presented results of the 10-year outcomes from the RAPCO trial (American Association for Thoracic Surgery 96th Annual Meeting; May 2016; Baltimore, MD; still unpublished) showed similar occlusion rates (8.0% for RA, 11.2% for RITA; *P*=0.19) but better overall survival when using the RA compared with the RITA (90.4% for RA versus 82.9% for RITA; *P*=0.03).

In the aforementioned angiographic network meta-analysis and in a smaller RCT, RITA patency and RA patency were statistically similar and superior to that of SVG.[21,26]

Graft Type and Effect on Disease Progression in the Native Coronary Circulation

Evidence From Observational Data

Initial evidence supports the concept that the type of conduit used at the time of CABG has the potential to influence the native circulation after surgery.

Indirect evidence suggests that grafting with SVGs may accelerate the progression of the native coronary stenosis to total occlusion, whereas grafting with an arterial graft is associated with a reduced incidence of progression. In a post hoc observational analysis of angiographic follow-up of 911 patients with CABG, the new occlusion rate of vessels with SVG grafts was the highest, followed by vessels with arterial grafts and vessels without bypass grafts, regardless of baseline stenosis (intermediate stenosis, 11.1% versus 5.2% versus 1.7%, $P<0.001$; severe stenosis, 23.7% versus 15.9% versus 9.9%, $P<0.001$).[68]

Dimitrova and associates[69] found that the use of arterial grafts (the RA in particular) was associated with a 75% decrease in disease progression in all coronary territories compared with SVGs in an observational series. Zhang and associates[70] compared the 5-year progression rate of distal disease in the left anterior descending coronary artery in patients who received percutaneous coronary intervention (PCI) with bare metal stents or drug-eluting stents (DES) versus CABG using ITA. Patients treated with ITA had a significantly lower incidence of downstream disease progression (12.4% for ITA, 85.9% for bare metal stents, 24.1% for DES; HR, 0.34 [95% CI, 0.20–0.59] and 0.39 [95% CI, 0.20–0.79], respectively).

Evidence From RCTs

In CASS (Coronary Artery Surgery Study), a significant increase in the left anterior descending coronary artery territory disease progression was observed in patients who received an SVG instead of an LITA graft.[71] In the RAPCO trial, the use of arterial grafts instead of an SVG was an independent predictor of disease regression in the native vessel at the 6-year follow-up.[72]

The mechanisms of this protective effect of arterial grafts are speculative, but it is likely that the same anti-inflammatory and antithrombotic mediators that protect arterial grafts from atherosclerosis might explain their protective action on the native downstream coronary bed after CABG. However, the great majority of the evidence on this subject is observational, and target vessel selection bias and hidden confounders may, at least in part, explain this finding.

CABG With Arterial Grafts Versus PCI

Evidence From Observational Data

Few propensity score–matched studies have compared CABG using >1 arterial grafts with PCI.

Herz and colleagues[73] analyzed 768 patients undergoing multivessel myocardial revascularization: 138 by PCI with DES and 630 by BITA. Assignment to the DES group was the only predictor of angina recurrence (OR, 2.78 [95% CI, 1.46–2.56]). One-year reintervention-free survival was 96% for BITA and 86.6% for DES ($P=0.005$). Moshkovitz et al[74] compared the outcomes in 226 patients with diabetes mellitus with BITA and 271 patients with diabetes mellitus with DES. The 5-year reintervention-free survival and major adverse cardiovascular events–free survival were significantly better in the BITA group (86% versus 65% and 81% versus 54%, respectively). The PCI group had decreased adjusted survival (HR, 3.01 [95% CI, 1.59–5.73]) and increased risk of reinterventions (HR, 7.00 [95% CI, 3.1–15.7]).

Raja et al[75] compared 4652 patients with CABG and 1474 with PCI. More than 1 arterial graft was used in 1372 patients with CABG (29.5%) and DES in 1222 patients with PCI (82.9%). Risk of late death at 4.9 years was comparable after DES-PCI and conventional CABG (HR, 1.11 [95% CI, 0.9–1.33]). However, DES-PCI was associated with an increased risk of late death compared with CABG with >1 arterial graft (HR, 1.53 [95% CI, 1.08–2.91]). DES-PCI was associated with a 3.5-fold increased risk for repeat revascularization over multiple arterial grafts CABG (95% CI, 2.60–4.75) and 2.66-fold increased risk of repeat revascularization over conventional CABG (95% CI, 2.11–3.36). Habib and colleagues[76] compared 2381 patients with DES with 2289 patients with LITA and 1525 patients with LITA-RA. Those with DES had survival similar to those with LITA (HR, 1.06). Compared with patients with LITA-RA, those with DES-PCI exhibited worse survival at 5 (86.3% versus 95.6%) and 9 (82.8% versus 89.8%) years (HR, 1.55; $P<0.001$). Reintervention was worse with PCI for all comparisons ($P<0.001$). Benedetto and coauthors[77] compared 3787 patients with multivessel disease treated by PCI with everolimus-eluting stents (696) and those with CABG with>1 arterial graft (3091). After a mean follow-up of 3.1-years, PCI with everolimus eluting stents was associated with a higher risk of late death (HR, 2.2 [95% CI, 1.18–4.16]).

A recently published network meta-analysis evaluating the relative benefits of CABG using single and multiple arterial grafting and DES in multivessel coronary disease (53 239 patients; mean follow-up, 5.42 years) showed that CABG was associated with reduced 5-year mortality (incident rate ratio, 0.77 [95% CI, 0.66–0.90]) and need for repeat revascularization (incident rate ratio, 0.37 [95% CI, 0.27–0.5]) compared with DES, with multiple arterial grafting ranking as the best treatment for the primary (long-term mortality) and all secondary (operative mortality, perioperative stroke, and follow-up repeat revascularization) outcomes.[78]

Of note, given the influence of patient and coronary morphology factors in driving grafting decisions in clinical practice, observational studies are prone to biases and hidden confounders and should be regarded only as hypothesis generating.

Evidence From RCTs

Many trials comparing CABG with PCI used a single arterial graft in the surgical arm. As an example, the SYNTAX trial (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) used a second arterial graft in 35.3% of patients.[79]

A prematurely terminated RCT[80] (BEST [Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease]) compared everolimus-eluting stents with CABG with a high number of arterial grafts (mean number of arterial grafts per patient, 2.1±1.1). At the long-term follow-up, the primary end point of death, myocardial infarct, or target vessel revascularization occurred in 15.3% patients with PCI and 10.6% patients with CABG (HR, 1.47 [95% CI, 1.01–2.13]).

BARRIERS AND CHALLENGES IN THE DIFFUSION OF THE USE OF MULTIPLE OF ARTERIAL GRAFTS

The idea of using multiple arterial grafts for CABG is certainly not new. The first studies suggesting a possible clinical benefit associated with the use of arterial grafts date back to the 70s.[81] However, the surgical community, particularly in the United States, has been clearly reluctant to embrace the multiartery grafting strategy.

A recent analysis of the Society of Thoracic Surgeons database by Schwann and colleagues[66] reported that between 2004 and 2015 a second arterial conduit was used in 170 677 of 1 334 511 patients (11.4%; 97 623 RAs and 73 054 BITAs; 6.5% and 4.9%, respectively).

Data from a state-maintained clinical registry including all 126 nonfederal hospitals in California showed that of a total of 59 432 primary, isolated, multivessel CABGs performed between 2006 and 2011, a second arterial conduit (RITA or RA) was used in 5866 cases (9.9%). Of note, second arterial conduit use decreased from 10.7% in 2006 to 9.1% in 2011 ($P<0.0001$).[67]

In a retrospective cohort analysis of 50 230 patients undergoing primary isolated CABG in Ontario, Canada, from October 2008 to March 2016, only 3044 (6.1%) and 8253 (16.4%) patients received 3 and 2 arterial grafts, respectively.[60]

Rates are moderately higher in Europe, where ≈20% to 30% of patients with CABG receive >1 arterial grafts,[82] and in Japan (95.4% of patients with CABG receiving at least 1 arterial graft, and 22.7% receiving all arterial graft CABGs).[83]

The explanation for this reluctance of the surgical community to systematically use >1 arterial graft is probably multifactorial. In a relatively old survey of UK consultants, the most quoted reasons to avoid the use of multiple arterial grafts were the increased technical difficulty and operating time and the perceived increased risk of postoperative complications.[84] A less common reason was the lack of solid evidence of benefit for the patients.

After >15 years, the reasons highlighted in the UK survey are probably still valid. The adoption of multiple arterial grafts adds some time to the procedure, is usually not taught during training, requires a learning curve, and if inappropriately applied, may potentially increase the risk of complications.

Surgeons seem to focus mainly on early quality metrics and on the avoidance of complications, and this is probably even more evident in the United States as a result of the increased employment of physicians by hospitals and the policy of many payers not to reimburse for postoperative events such as sternal wound problems that may be related to the use of arterial grafts.

As discussed, the lack of solid evidence of the clinical superiority of multiple arterial grafting is probably still an important barrier to their widespread adoption.

CONCLUSIONS

Observational and randomized evidence suggests that arterial grafts (particularly the RA) have better patency rate than SVGs at long-term follow-up. Arterial grafts may also potentially exert a protective effect on the native coronary circulation. Whether increased patency rates and potential reduction in the progression of native coronary atherosclerosis translate into clinical benefits in the majority of patients submitted to CABG remains to be proven.

Although evidence from large observational studies suggests better survival for patients receiving multiple arterial grafts, these results must be interpreted in the context of potential allocation bias and hidden confounders. A pooled analysis of 6 RCTs found better 5-year cardiac event–free survival for patients who received an RA compared with an SVG as the second CABG conduit.

On the other hand, the largest RCT comparing the use of single and multiple arterial grafts showed no survival and event-free survival benefit for BITA grafting in an intention-to-treat analysis but was confounded by the fact that 40% of patients actually received a different treatment from that initially proposed. In the as-treated analysis of those who actually received multiple

arterial grafts, there was a survival benefit in the multiple arterial graft group.

The ROMA trial (Randomized Comparison of the Clinical Outcome of Single Versus Multiple Arterial Grafts), designed to compare the use of single and multiple arterial grafts with a sample size 1.5 times larger than ART, started in January 2018 and is currently enrolling patients. Primary results will likely be available in 2025.

For the moment and on the basis of the current evidence, arterial grafts, in particular the RA, should be used to supplement the LITA in patients with reasonable life expectancy as long as the operating surgeon has adequate experience and no significant operative risk is added. Operator and center experience and individualization of the type of arterial graft used are key to achieving this goal.

ARTICLE INFORMATION

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Disclosures

None.

APPENDIX

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A list of the reviews published by the ATLANTIC Alliance (up to March 2019) is provided in References 1 to 5 in the online-only Data Supplement.

REFERENCES

1. Lytle BW, Blackstone EH, Loop FD, Houghtaling PL, Arnold JH, Akhrass R, McCarthy PM, Cosgrove DM. Two internal thoracic artery grafts are better than one. *J Thorac Cardiovasc Surg.* 1999;117:855–872. doi: 10.1016/S0022-5223(99)70365-X
2. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. *Lancet.* 2001;358:870–875. doi: 10.1016/S0140-6736(01)06069-X
3. Yi G, Shine B, Rehman SM, Altman DG, Taggart DP. Effect of bilateral internal mammary artery grafts on long-term survival: a meta-analysis approach. *Circulation.* 2014;130:539–545. doi: 10.1161/CIRCULATIONAHA.113.004255
4. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, Cigarroa JE, Disesa VJ, Hiratzka LF, Hutter AM Jr, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2011;124:e652–e735. doi: 10.1161/CIR.0b013e31823c074e
5. Sousa-Uva M, Neumann FJ, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, et al; ESC Scientific Document Group. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur J Cardiothorac Surg.* 2019;55:4–90. doi: 10.1093/ejcts/ezy289
6. Aldea GS, Bakaeen FG, Pal J, Fremes S, Head SJ, Sabik J, Rosengart T, Kappetein AP, Thourani VH, Firestone S, et al; Society of Thoracic Surgeons. The Society of Thoracic Surgeons clinical practice guidelines on arterial conduits for coronary artery bypass grafting. *Ann Thorac Surg.* 2016;101:801–809. doi: 10.1016/j.athoracsur.2015.09.100
7. Taggart DP, Benedetto U, Gerry S, Altman DG, Gray AM, Lees B, Gaudino M, Zamvar V, Bochenek A, Buxton B, et al; Arterial Revascularization Trial Investigators. Bilateral versus single internal-thoracic-artery grafts at 10 years. *N Engl J Med.* 2019;380:437–446. doi: 10.1056/NEJMoa1808783
8. Gaudino M, Benedetto U, Fremes S, Biondi-Zoccai G, Sedrakyan A, Puskas JD, Angelini GD, Buxton B, Frati G, Hare DL, et al; RADIAL Investigators. Radial-artery or saphenous-vein grafts in coronary-artery bypass surgery. *N Engl J Med.* 2018;378:2069–2077. doi: 10.1056/NEJMoa1716026
9. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* 2009;339:b2700. doi: 10.1136/bmj.b2700
10. Tatoulis J, Buxton BF, Fuller JA. The right internal thoracic artery: is it underutilized? *Curr Opin Cardiol.* 2011;26:528–535. doi: 10.1097/HCO.0b013e32834b9f87
11. Deb S, Cohen EA, Singh SK, Une D, Laupacis A, Fremes SE; RAPS Investigators. Radial artery and saphenous vein patency more than 5 years after coronary artery bypass surgery: results from RAPS (Radial Artery Patency Study). *J Am Coll Cardiol.* 2012;60:28–35. doi: 10.1016/j.jacc.2012.03.037
12. Gaudino M, Tondi P, Benedetto U, Milazzo V, Flore R, Glieca F, Ponziani FR, Luciani N, Girardi LN, Crea F, et al. Radial artery as a coronary artery bypass conduit: 20-year results. *J Am Coll Cardiol.* 2016;68:603–610. doi: 10.1016/j.jacc.2016.05.062
13. Fitzgibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. *J Am Coll Cardiol.* 1996;28:616–626. doi: 10.1016/0735-1097(96)00206-9
14. Goldman S, Zadina K, Moritz T, Ovitt T, Sethi G, Copeland JG, Thottapurathu L, Krasnicka B, Ellis N, Anderson RJ, et al; VA Cooperative Study Group #207/297/364. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study. *J Am Coll Cardiol.* 2004;44:2149–2156. doi: 10.1016/j.jacc.2004.08.064
15. Motwani JG, Topol EJ. Aortocoronary saphenous vein graft disease: pathogenesis, predisposition, and prevention. *Circulation.* 1998;97:916–931. doi: 10.1161/01.cir.97.9.916
16. Hess CN, Lopes RD, Gibson CM, Hager R, Wojdyla DM, Englum BR, Mack MJ, Califf RM, Kouchoukos NT, Peterson ED, et al. Saphenous vein graft failure after coronary artery bypass surgery: insights from PREVENT IV. *Circulation.* 2014;130:1445–1451.
17. Song SW, Sul SY, Lee HJ, Yoo KJ. Comparison of the radial artery and saphenous vein as composite grafts in off-pump coronary artery bypass grafting in elderly patients: a randomized controlled trial. *Korean Circ J.* 2012;42:107–112. doi: 10.4070/kcj.2012.42.2.107

18. Goldman S, Sethi GK, Holman W, Thai H, McFalls E, Ward HB, Kelly RF, Rhenman B, Tobler GH, Bakaeen FG, et al. Radial artery grafts vs saphenous vein grafts in coronary artery bypass surgery: a randomized trial. *JAMA*. 2011;305:167–174. doi: 10.1001/jama.2010.1976
19. Muneretto C, Bisleri G, Negri A, Manfredi J, Carone E, Morgan JA, Metra M, Dei Cas L. Left internal thoracic artery-radial artery composite grafts as the technique of choice for myocardial revascularization in elderly patients: a prospective randomized evaluation. *J Thorac Cardiovasc Surg.* 2004;127:179–184. doi: 10.1016/j.jtcvs.2003.08.004
20. Collins P, Webb CM, Chong CF, Moat NE; Radial Artery Versus Saphenous Vein Patency (RSVP) Trial Investigators. Radial artery versus saphenous vein patency randomized trial: five-year angiographic follow-up. *Circulation.* 2008;117:2859–2864. doi: 10.1161/CIRCULATIONAHA.107.736215
21. Gaudino M, Cellini C, Pragliola C, Trani C, Burzotta F, Schiavoni G, Nasso G, Possati G. Arterial versus venous bypass grafts in patients with in-stent restenosis. *Circulation.* 2005;112(suppl):I265–I269. doi: 10.1161/CIRCULATIONAHA.104.512905
22. Dreifaldt M, Mannion JD, Bodin L, Olsson H, Zagozdzon L, Souza D. The no-touch saphenous vein as the preferred second conduit for coronary artery bypass grafting. *Ann Thorac Surg.* 2013;96:105–111. doi: 10.1016/j.athoracsur.2013.01.102
23. Hayward PA, Buxton BF. Mid-term results of the Radial Artery Patency and Clinical Outcomes randomized trial. *Ann Cardiothorac Surg.* 2013;2:458–466. doi: 10.3978/j.issn.2225-319X.2013.07.18
24. Kim KB, Hwang HY, Hahn S, Kim JS, Oh SJ. A randomized comparison of the Saphenous Vein Versus Right Internal Thoracic Artery as a Y-Composite Graft (SAVE RITA) trial: one-year angiographic results and mid-term clinical outcomes. *J Thorac Cardiovasc Surg.* 2014;148:901–907. doi: 10.1016/j.jtcvs.2014.03.057
25. Wingo M, Gaudino MFL. RADIAL meta-analysis: following the rules usually pays off. *J Thorac Dis.* 2018;10:E785–E786. doi: 10.21037/jtd.2018.10.75
26. Benedetto U, Raja SG, Albanese A, Amrani M, Biondi-Zoccai G, Frati G. Searching for the second best graft for coronary artery bypass surgery: a network meta-analysis of randomized controlled trials. *Eur J Cardiothorac Surg.* 2015;47:59–65. doi: 10.1093/ejcts/ezu111
27. Gaudino M, Antoniades C, Benedetto U, Deb S, Di Franco A, Di Giammarco G, Fremes S, Glineur D, Grau J, He GW, et al; ATLANTIC (Arterial Grafting International Consortium) Alliance. Mechanisms, consequences, and prevention of coronary graft failure. *Circulation.* 2017;136:1749–1764. doi: 10.1161/CIRCULATIONAHA.117.027597
28. Buttar SN, Yan TD, Taggart DP, Tian DH. Long-term and short-term outcomes of using bilateral internal mammary artery grafting versus left internal mammary artery grafting: a meta-analysis. *Heart.* 2017;103:1419–1426. doi: 10.1136/heartjnl-2016-310864
29. Rizzoli G, Schiavon L, Bellini P. Does the use of bilateral internal mammary artery (IMA) grafts provide incremental benefit relative to the use of a single IMA graft? A meta-analysis approach. *Eur J Cardiothorac Surg.* 2002;22:781–786. doi: 10.1016/s1010-7940(02)00470-0
30. Weiss AJ, Zhao S, Tian DH, Taggart DP, Yan TD. A meta-analysis comparing bilateral internal mammary artery with left internal mammary artery for coronary artery bypass grafting. *Ann Cardiothorac Surg.* 2013;2:390–400. doi: 10.3978/j.issn.2225-319X.2013.07.16
31. Takagi H, Goto SN, Watanabe T, Mizuno Y, Kawai N, Umemoto T. A meta-analysis of adjusted hazard ratios from 20 observational studies of bilateral versus single internal thoracic artery coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 2014;148:1282–1290. doi: 10.1016/j.jtcvs.2014.01.010
32. Mastrobuoni S, Gawad N, Price J, Chan V, Ruel M, Mesana TG, Rubens FD. Use of bilateral internal thoracic artery during coronary artery bypass graft surgery in Canada: the Bilateral Internal Thoracic Artery Survey. *J Thorac Cardiovasc Surg.* 2012;144:874–879. doi: 10.1016/j.jtcvs.2012.01.022
33. Kajimoto K, Yamamoto T, Amano A. Coronary artery bypass revascularization using bilateral internal thoracic arteries in diabetic patients: a systematic review and meta-analysis. *Ann Thorac Surg.* 2015;99:1097–1104. doi: 10.1016/j.athoracsur.2014.09.045
34. Deo SV, Shah IK, Dunlay SM, Erwin PJ, Locker C, Altarabsheh SE, Boilson BA, Park SJ, Joyce LD. Bilateral internal thoracic artery harvest and deep sternal wound infection in diabetic patients. *Ann Thorac Surg.* 2013;95:862–869. doi: 10.1016/j.athoracsur.2012.11.068
35. Zhou P, Zhu P, Nie Z, Zheng S. Is the era of bilateral internal thoracic artery grafting coming for diabetic patients? An updated meta-analysis [published online February 23, 2019]. *J Thorac Cardiovasc Surg*. doi: 10.1016/j.jtcvs.2019.01.129. https://linkinghub.elsevier.com/retrieve/pii/S0022-5223(19)30452-0.
36. Boodhwani M, Lam BK, Nathan HJ, Mesana TG, Ruel M, Zeng W, Sellke FW, Rubens FD. Skeletonized internal thoracic artery harvest reduces pain and dysesthesia and improves sternal perfusion after coronary artery bypass surgery: a randomized, double-blind, within-patient comparison. *Circulation.* 2006;114:766–773. doi: 10.1161/CIRCULATIONAHA.106.615427
37. Benedetto U, Altman DG, Gerry S, Gray A, Lees B, Pawlaczyk R, Flather M, Taggart DP; Arterial Revascularization Trial Investigators. Pedicled and skeletonized single and bilateral internal thoracic artery grafts and the incidence of sternal wound complications: insights from the Arterial Revascularization Trial. *J Thorac Cardiovasc Surg.* 2016;152:270–276. doi: 10.1016/j.jtcvs.2016.03.056
38. Myers WO, Berg R, Ray JF, Douglas-Jones JW, Maki HS, Ulmer RH, Chaitman BR, Reinhart RA. All-artery multigraft coronary artery bypass grafting with only internal thoracic arteries possible and safe: a randomized trial. *Surgery.* 2000;128:650–659. doi: 10.1067/msy.2000.108113
39. Nasso G, Coppola R, Bonifazi R, Piancone F, Bozzetti G, Speziale G. Arterial revascularization in primary coronary artery bypass grafting: direct comparison of 4 strategies: results of the Stand-in-Y Mammary Study. *J Thorac Cardiovasc Surg.* 2009;137:1093–1100. doi: 10.1016/j.jtcvs.2008.10.029
40. Gaudino M, Di Franco A, Rahouma M, Tam DY, Iannaccone M, Deb S, D'Ascenzo F, Abouarab AA, Girardi LN, Taggart DP, et al. Unmeasured confounders in observational studies comparing bilateral versus single internal thoracic artery for coronary artery bypass grafting: a meta-analysis. *J Am Heart Assoc*. 2018;7:e008010. doi: 10.1161/JAHA.117.008010.
41. Taggart DP, Altman DG, Flather M, Gerry S, Gray A, Lees B, Benedetto U; ART (Arterial Revascularization Trial) Investigators. Associations between adding a radial artery graft to single and bilateral internal thoracic artery grafts and outcomes: insights from the Arterial Revascularization Trial. *Circulation.* 2017;136:454–463. doi: 10.1161/CIRCULATIONAHA.117.027659
42. Benedetto U, Altman DG, Flather M, Gerry S, Gray A, Lees B, Taggart DP; Arterial Revascularization Trial Investigators. Incidence and clinical implications of intraoperative bilateral internal thoracic artery graft conversion: insights from the Arterial Revascularization Trial. *J Thorac Cardiovasc Surg.* 2018;155:2346–2355.e6. doi: 10.1016/j.jtcvs.2018.02.012
43. Gaudino M, Bakaeen F, Benedetto U, Rahouma M, Di Franco A, Tam D, Iannaccone M, Schwann T, Habib R, Ruel M, et al. Use rate and outcome in bilateral internal thoracic artery grafting: insights from a systematic review and meta-analysis. *J Am Heart Assoc*. 2018;7:e009361.
44. Schwann TA, Habib RH, Wallace A, Shahian D, Gaudino M, Kurlansky P, Engoren MC, Tranbaugh RF, Schwann AN, Jacobs JP. Bilateral internal thoracic artery versus radial artery multi-arterial bypass grafting: a report from the STS database [published online April 1, 2019]. *Eur J Cardio-Thorac Surg*. doi: 10.1093/ejcts/ezz106. https://academic.oup.com/ejcts/advance-article-abstract/doi/10.1093/ejcts/ezz106/5425281?redirectedFrom=fulltext.
45. Benedetto U, Codispoti M. Age cutoff for the loss of survival benefit from use of radial artery in coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 2013;146:1078–1084. doi: 10.1016/j.jtcvs.2013.07.025
46. Tranbaugh RF, Dimitrova KR, Friedmann P, Geller CM, Harris LJ, Stelzer P, Cohen B, Hoffman DM. Radial artery conduits improve long-term survival after coronary artery bypass grafting. *Ann Thorac Surg.* 2010;90:1165–1172. doi: 10.1016/j.athoracsur.2010.05.038
47. Gaudino M, Rahouma M, Abouarab A, Leonard J, Kamel M, Di Franco A, Demetres M, Tam DY, Tranbaugh R, Girardi LN, et al. Radial artery versus saphenous vein as the second conduit for coronary artery bypass surgery: a meta-analysis. *J Thorac Cardiovasc Surg*. 2019;157:1819–1825. doi: 10.1016/j.jtcvs.2018.08.123.
48. Zhang H, Wang ZW, Wu HB, Hu XP, Zhou Z, Xu P. Radial artery graft vs. saphenous vein graft for coronary artery bypass surgery: which conduit offers better efficacy? *Herz.* 2014;39:458–465. doi: 10.1007/s00059-013-3848-5
49. Benedetto U, Caputo M, Zakkar M, Bryan A, Angelini GD. Are three arteries better than two? Impact of using the radial artery in addition to bilateral internal thoracic artery grafting on long-term survival. *J Thorac Cardiovasc Surg*. 2016;152:862–869.e2.
50. Di Mauro M, Contini M, Iacò AL, Bivona A, Gagliardi M, Varone E, Bosco P, Calafiore AM. Bilateral internal thoracic artery on the left side: a propensity score-matched study of impact of the third conduit on the right side. *J Thorac Cardiovasc Surg.* 2009;137:869–874. doi: 10.1016/j.jtcvs.2008.09.014
51. Glineur D. Importance of the third arterial graft in multiple arterial grafting strategies. *Ann Cardiothorac Surg.* 2013;2:475–480. doi: 10.3978/j.issn.2225-319X.2013.07.01

52. Grau JB, Kuschner CE, Johnson CK, Ferrari G, Zapolanski A, Brizzio ME, Shaw RE. The effects of using a radial artery in patients already receiving bilateral internal mammary arteries during coronary bypass grafting: 30-day outcomes and 14-year survival in a propensity-matched cohort. *Eur J Cardiothorac Surg.* 2016;49:203–210. doi: 10.1093/ejcts/ezv176
53. Locker C, Schaff HV, Dearani JA, Joyce LD, Park SJ, Burkhart HM, Suri RM, Greason KL, Stulak JM, Li Z, et al. Multiple arterial grafts improve late survival of patients undergoing coronary artery bypass graft surgery: analysis of 8622 patients with multivessel disease. *Circulation.* 2012;126:1023–1030. doi: 10.1161/CIRCULATIONAHA.111.084624
54. Mohammadi S, Dagenais F, Voisine P, Dumont E, Charbonneau E, Marzouk M, Paramythiotis A, Kalavrouziotis D. Impact of the radial artery as an additional arterial conduit during in-situ bilateral internal mammary artery grafting: a propensity score-matched study. *Ann Thorac Surg.* 2016;101:913–918. doi: 10.1016/j.athoracsur.2015.08.054
55. Nasso G, Popoff G, Lamarra M, Romano V, Coppola R, Bartolomucci F, Giglio MD, Romeo F, Tavazzi L, Speziale G. Impact of arterial revascularization in patients undergoing coronary bypass. *J Card Surg.* 2012;27:427–433. doi: 10.1111/j.1540-8191.2012.01481.x
56. Shi WY, Tatoulis J, Newcomb AE, Rosalion A, Fuller JA, Buxton BF. Is a third arterial conduit necessary? Comparison of the radial artery and saphenous vein in patients receiving bilateral internal thoracic arteries for triple vessel coronary disease. *Eur J Cardiothorac Surg.* 2016;50:53–60. doi: 10.1093/ejcts/ezv467
57. Gaudino M, Puskas JD, Di Franco A, Ohmes LB, Iannaccone M, Barbero U, Glineur D, Grau JB, Benedetto U, D'Ascenzo F, et al. Three arterial grafts improve late survival: a meta-analysis of propensity-matched studies. *Circulation.* 2017;135:1036–1044. doi: 10.1161/CIRCULATIONAHA.116.025453
58. Yanagawa B, Verma S, Mazine A, Tam DY, Jüni P, Puskas JD, Murugavel S, Friedrich JO. Impact of total arterial revascularization on long term survival: a systematic review and meta-analysis of 130,305 patients. *Int J Cardiol.* 2017;233:29–36. doi: 10.1016/j.ijcard.2017.02.010
59. Royse A, Pawanis Z, Canty D, Ou-Young J, Eccleston D, Ajani A, Reid CM, Bellomo R, Royse C. The effect on survival from the use of a saphenous vein graft during coronary bypass surgery: a large cohort study. *Eur J Cardiothorac Surg.* 2018;54:1093–1100. doi: 10.1093/ejcts/ezy213
60. Rocha RV, Tam DY, Karkhanis R, Nedadur R, Fang J, Tu JV, Gaudino M, Royse A, Fremes SE. Multiple arterial grafting is associated with better outcomes for coronary artery bypass grafting patients. *Circulation.* 2018;138:2081–2090. doi: 10.1161/CIRCULATIONAHA.118.034464
61. Muneretto C, Bisleri G, Negri A, Manfredi J, Metra M, Nodari S, Culot L, Dei Cas L. Total arterial myocardial revascularization with composite grafts improves results of coronary surgery in elderly: a prospective randomized comparison with conventional coronary artery bypass surgery. *Circulation.* 2003;108(suppl 1):II29–II33.
62. Le J, Baskett RJ, Buth KJ, Hirsch GM, Brydie A, Gayner R, Legare JF. A pilot randomized controlled trial comparing CABG surgery performed with total arterial grafts or without. *J Cardiothorac Surg.* 2015;10:1. doi: 10.1186/s13019-014-0203-8
63. Benedetto U, Gaudino M, Caputo M, Tranbaugh RF, Lau C, Di Franco A, Ng C, Girardi LN, Angelini GD. Right internal thoracic artery versus radial artery as the second best arterial conduit: insights from a meta-analysis of propensity-matched data on long-term survival. *J Thorac Cardiovasc Surg.* 2016;152:1083–1091.e15.
64. Gaudino M, Lorusso R, Rahouma M, Abouarab A, Tam DY, Spadaccio C, Saint-Hilary G, Leonard J, Iannaccone M, D'Ascenzo F, et al. Radial artery versus right internal thoracic artery versus saphenous vein as the second conduit for coronary artery bypass surgery: a network meta-analysis of clinical outcomes. *J Am Heart Assoc.* 2019;8:e010839. doi: 10.1161/JAHA.118.010839
65. Dai C, Lu Z, Zhu H, Xue S, Lian F. Bilateral internal mammary artery grafting and risk of sternal wound infection: evidence from observational studies. *Ann Thorac Surg.* 2013;95:1938–1945. doi: 10.1016/j.athoracsur.2012.12.038
66. Schwann TA, Habib RH, Wallace A, Shahian DM, O'Brien S, Jacobs JP, Puskas JD, Kurlansky PA, Engoren MC, Tranbaugh RF, et al. Operative outcomes of multiple-arterial versus single-arterial coronary bypass grafting. *Ann Thorac Surg.* 2018;105:1109–1119. doi: 10.1016/j.athoracsur.2017.10.058
67. Goldstone AB, Chiu P, Baiocchi M, Wang H, Lingala B, Boyd JH, Woo YJ. Second arterial versus venous conduits for multivessel coronary artery bypass surgery in California. *Circulation.* 2018;137:1698–1707. doi: 10.1161/CIRCULATIONAHA.117.030959
68. Yoon SH, Kim YH, Yang DH, Roh JH, Lee EY, Lee PH, Sugiyama D, Chang M, Ahn JM, Choi WJ, et al. Risk of new native-vessel occlusion after coronary artery bypass grafting. *Am J Cardiol.* 2017;119:7–13. doi: 10.1016/j.amjcard.2016.09.011
69. Dimitrova KR, Hoffman DM, Geller CM, Dincheva G, Ko W, Tranbaugh RF. Arterial grafts protect the native coronary vessels from atherosclerotic disease progression. *Ann Thorac Surg.* 2012;94:475–481. doi: 10.1016/j.athoracsur.2012.04.035
70. Zhang M, Guddeti RR, Matsuzawa Y, Sara JDS, Kwon T-G, Liu Z, Sun T, Lee S-J, Lennon RJ, Bell MR, et al. Left internal mammary artery versus coronary stents: impact on downstream coronary stenoses and conduit patency. *J Am Heart Assoc.* 2016;5:e003568. doi: 10.1161/JAHA.116.003568.
71. Alderman EL, Corley SD, Fisher LD, Chaitman BR, Faxon DP, Foster ED, Killip T, Sosa JA, Bourassa MG. Five-year angiographic follow-up of factors associated with progression of coronary artery disease in the Coronary Artery Surgery Study (CASS): CASS Participating Investigators and Staff. *J Am Coll Cardiol.* 1993;22:1141–1154.
72. Zhu YY, Nguyen TT, Buxton BF, Hare DL, Hayward PA. Regression of coronary disease after bypass surgery: urban myth or common finding? *J Thorac Cardiovasc Surg.* 2014;148:53–59. doi: 10.1016/j.jtcvs.2013.07.029
73. Herz I, Moshkovitz Y, Loberman D, Uretzky G, Braunstein R, Hendler A, Zivi E, Ben-Gal Y, Mohr R. Drug-eluting stents versus bilateral internal thoracic grafting for multivessel coronary disease. *Ann Thorac Surg.* 2005;80:2086–2090. doi: 10.1016/j.athoracsur.2005.05.053
74. Moshkovitz Y, Mohr R, Medalion B, Hyam E, Herz I, Deitch I, Uretzky G, Pevni D. Drug-eluting stents compared with bilateral internal thoracic artery grafts for diabetic patients. *Ann Thorac Surg.* 2012;94:1455–1462. doi: 10.1016/j.athoracsur.2012.05.026
75. Raja SG, Benedetto U, Ilsley CD, Amrani M; Harefield Cardiac Outcomes Research Group. Multiple arterial grafting confers survival advantage compared to percutaneous intervention with drug-eluting stents in multivessel coronary artery disease: a propensity score adjusted analysis. *Int J Cardiol.* 2015;189:153–158. doi: 10.1016/j.ijcard.2015.04.059
76. Habib RH, Dimitrova KR, Badour SA, Yammine MB, El-Hage-Sleiman AK, Hoffman DM, Geller CM, Schwann TA, Tranbaugh RF. CABG versus PCI: greater benefit in long-term outcomes with multiple arterial bypass grafting. *J Am Coll Cardiol.* 2015;66:1417–1427. doi: 10.1016/j.jacc.2015.07.060
77. Benedetto U, Caputo M, Vohra H, Bryan A, Angelini GD. State of the art in coronary revascularization: everolimus eluting stents versus multiple arterial grafting. *Int J Cardiol.* 2016;219:345–349. doi: 10.1016/j.ijcard.2016.06.059
78. Gaudino M, Rahouma M, Abouarab A, Tam DY, Di Franco A, Leonard J, Benedetto U, Iannaccone M, D'Ascenzo F, Biondi-Zoccai G, et al. Meta-analysis comparing outcomes of drug eluting stents versus single and multiarterial coronary artery bypass grafting. *Am J Cardiol.* 2018;122:2018–2025. doi: 10.1016/j.amjcard.2018.09.005
79. Mohr FW, Rastan AJ, Serruys PW, Kappetein AP, Holmes DR, Pomar JL, Westaby S, Leadley K, Dawkins KD, Mack MJ. Complex coronary anatomy in coronary artery bypass graft surgery: impact of complex coronary anatomy in modern bypass surgery? Lessons learned from the SYNTAX trial after two years. *J Thorac Cardiovasc Surg.* 2011;141:130–140. doi: 10.1016/j.jtcvs.2010.07.094
80. Park SJ, Ahn JM, Kim YH, Park DW, Yun SC, Lee JY, Kang SJ, Lee SW, Lee CW, Park SW, et al; BEST Trial Investigators. Trial of everolimus-eluting stents or bypass surgery for coronary disease. *N Engl J Med.* 2015;372:1204–1212. doi: 10.1056/NEJMoa1415447
81. Barner HB. Double internal mammary-coronary artery bypass. *Arch Surg.* 1974;109:627–630. doi: 10.1001/archsurg.1974.01360050025007
82. Head SJ, Parasca CA, Mack MJ, Mohr FW, Morice MC, Holmes DR Jr, Feldman TE, Dawkins KD, Colombo A, Serruys PW, et al; SYNTAX Investigators. Differences in baseline characteristics, practice patterns and clinical outcomes in contemporary coronary artery bypass grafting in the United States and Europe: insights from the SYNTAX randomized trial and registry. *Eur J Cardiothorac Surg.* 2015;47:685–695. doi: 10.1093/ejcts/ezu197
83. Committee for Scientific Affairs, the Japanese Association for Thoracic Surgery, Shimizu H, Endo S, Natsugoe S, Doki Y, Hirata Y, Kobayashi J, Motomura N, Nakano K, Nishida H, Okada M, et al. Thoracic and cardiovascular surgery in Japan in 2016 : annual report by the Japanese Association for Thoracic Surgery. *Gen Thorac Cardiovasc Surg.* 2019;67:377–411.
84. Catarino PA, Black E, Taggart DP. Why do UK cardiac surgeons not perform their first choice operation for coronary artery bypass graft? *Heart.* 2002;88:643–644. doi: 10.1136/heart.88.6.643