Review

Radial Artery Versus Saphenous Vein as Third Conduit in Coronary Artery Bypass Graft Surgery for Multivessel Coronary Artery Disease: a Ten-Year Literature Review

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Abstract. Coronary artery bypass grafting is the gold standard strategy for obtaining complete coronary revascularization in patients with multivessel coronary artery disease. The recent AHA and EACTS guidelines on myocardial revascularization recommend total arterial revascularization, especially in younger patients, whenever possible. However, the use of saphenous vein grafts in association with single or bilateral internal thoracic artery (SITA, BITA) instead of arterial grafts (radial arteries, right gastroepiploic artery and inferior epigastric artery) is widespread. We analyzed literature from the last ten years (January 2010 to December 2020) looking for evidence in favour of the use of a radial artery compared to a saphenous vein in association with BITA. We identified nine studies (4 Systematic Reviews and Meta-analyses and 6 large cohort observational studies with propensity score-matching) that compared arterial with saphenous grafts as third conduit. The main finding of the review is the higher rate of freedom from any cardiac adverse event in the population which reached Total Arterial myocardial Revascularization (TAR). A probable reason for the limited application of TAR as a strategy is the shortage of Randomized Controlled Trials (RCTs). (www.actabiomedica.it)

Key words: Coronary artery bypass grafting, bilateral internal mammary artery, bilateral internal thoracic artery, third arterial conduit CABG, third arterial graft CABG, total arterial revascularization CABG, saphenous venous graft

Introduction

According to the latest ESC/EACTS Guidelines on myocardial revascularization, Bilateral Internal Thoracic Artery (BITA) or radial artery for non-LAD targets show a better patency rates than Saphenous Vein Graft (SVG), especially for the left coronary artery system (1). TAR gives patients undergoing CABG a long-term benefit with the same low risk of morbidity and mortality as conventional CABG. Indeed, Left Internal Thoracic Artery (LITA) and SVG remain the standard operation procedure. However, at 10 years SVGs have an occlusion rate of 40-50%, which increases to 75% at 15 years. It is known that this is because endothelial and media hyperplasia cause atherothrombosis with the reduction of patency of the vein grafts.

The conduits usable in TAR are the left and the right ITA, the left and the right radial artery, the right gastroepiploic artery and inferior epigastric artery. There are specific concerns on the use of this types of arterial conduits and coronary artery-targets. For example, since the publication by Loop *et* Al. in 1986 it has been accepted worldwide that LITA is the best coronary graft, and LITA to LAD is an unavoidable anastomosis of any coronary revascularization (2). It is well known that, in three-vessel disease, BITA is not suitable for obtaining TAR, so that the use of Radial Artery (RA) or right Gastroepiploic Artery (rGEA) is required. The RA-graft and rGEA-graft demonstrate a better long-term patency where the percentage of stenosis of the coronary target is higher than 70%, and even better if it is higher than 90% (1, 2). Proximal anastomosis of RA can be constructed on the ascending aorta or on *in situ* LITA or RITA with "Y" or "T" graft. The rGEA is employed *in situ* and on the right coronary system, and its features of equal size, free-flow, length, low susceptibility to atherosclerosis and comparable pharmacological responses mean that it can be an alternative to RA for reaching TAR. In two retrospective studies by Formica *et* Al., the usage of rGEA is suggested in selected and younger patients together with pedicle BITA for TAR, because it provides an excellent survival at 9 years, and reduces the incidence of angina pectoris and any cardiac event (3, 4). In the second study, the survival rates after CABG only for cardiac related death at 1-, 3-, 5-, 7-, and 10-years were 97.4%, 97%, 96.6%, 96.6%, and 86.9%, respectively. Indeed, the rGEA can be considered as a valid arterial conduit, safe to use with a low perioperative risk, relatively easy to harvest, and offering good mid- and long-term performance and freedom from angina pectoris and cardiac-related mortality and morbidity.

Despite this, the use of rGEA instead of saphenous vein grafts (SVG) is not widespread, and TAR is more frequently achieved with RA. This is probably because RA is easier to harvest, shows low infection rates of forearm wounds because they heal well, and because patients can be mobilized more rapidly compared to those suffering from leg wounds after SV and rGEA harvesting.

Anatomical and technical issues in using RAs in CABG surgery:

RA is up to 20-22 cm long and its distal internal diameter is usually 2.5 mm, which ensures an appropriate size match for coronaries for both RAs. In 5-10% of the population, harvesting is prevented by calcification, prior trauma, collagen disease and RA dominance, presence of arterio-venous fistula for hemodialysis access, native RA disorders (i.e. vasculitis) and/or previous RA catheterization. But thanks to its length, RA can reach distally to any coronary vessel; and its toughness and size allow sequential grafting. Eco-Color-Doppler scanning can confirm the patency and the quality of the RA, and Allen's test modified by the use of oximetric plethysmography can estimate the patency of collateral circulation through the ulnar artery. The RA can be harvested using an open or endoscopic approach with ultrasonic scalpel with a skeletonizied or "no-touch" technique. It can be anastomosed proximally either on the ascending thoracic aorta or by "Y-" or "T-graft" on *in situ* ITAs. This technique is more frequently utilized in off-pump CABG (OPCAB). An important aspect is the pharmacological prevention of spasm to limit intraluminal narrowing after setting up CABG. The intraluminal instillation of papaverine solution, when the distal end of the RA is disconnected, the addition of intravenous nitroglycerine for the next 24 hours, and amlodipine 5 mg daily for 6 months, can prevent vasospasm (2).

In order to obtain TAR in three coronary vessel disease, ITAs and RAs can be used in different ways. These include, for example, LITA-LAD / free RITA-Cx/RA-PDA (posterior descending artery), ITA-RITA Y or T graft, and LITA-RA Y or T graft.

Another important aspect to be taken into consideration for a better of the long-term patency of the RA conduit is the degree of stenosis of a native coronary artery that may influence and establish a competitive flow inside the graft. All arterial grafts can be affected, but the risk of a competitive flow for RAs grafts is lower when the native coronary artery stenosis is higher than 80%, preferably higher than or equal to 90% (5, 6, 7,).

In this review, we investigate current evidence on Total Arterial Revascularization (TAR) by examining the recent literature. The aim is to identify best practice for performing myocardial revascularization in three-vessel coronary artery disease.

Methods

We examined all available articles published on PubMed from January 2010 to December 2020.

Articles published before January 2010 and after 31st December 2020 were excluded. The studies examined met the following inclusion criteria: (I) Patients had isolated CABG surgery, (II) Follow-up survival was ≥ 1 years and (III) They included a comparison in long-term survival between patients receiving, as a third conduit, GSV and patients receiving RAs, independently of the revascularization of the coronary system. We excluded case reports, editorials and non-systematic reviews, and all articles written in languages other than English. The keywords used for the research were: "bilateral internal mammary artery", "bilateral internal thoracic artery", "third arterial conduit CABG", "third arterial graft CABG", "Coronary artery bypass grafting", "Saphenous venous graft" and "total arterial revascularization CABG". We identified 4 Meta-analyses, including randomized controlled trials (one) and cohort studies using propensity score-matching (three), and 6 large cohort observational studies with propensity score-matching.

Discussion of the results

A recent Meta-Analysis was performed by Gaudino et al. who analyzed 8 propensity score-matched observational studies, comparing the long-term outcomes of coronary artery bypass grafting with the use of 2-arterial versus 3-arterial grafts (8). The primary end point was long-term mortality in the propensity score-matched populations, and the secondary end points were in-hospital mortality/30-day mortality for the propensity score matched populations, and long-term mortality for the unmatched populations. The mean follow-up time ranged from 37.2-196.8 months. The matched population analyzed includes 10,287 patients. The main conclusion was that the use of a third arterial graft is not associated with an increase in the operative risk, but rather with a 24% survival benefit at a mean follow-up of 77.9 months, regardless of the patient's sex and diabetic mellitus status. According to the findings of this study, the complete revascularization and the extensive use of arterial grafts should be the cornerstone of up-to-date coronary artery surgery. There were however some limitations in the Meta-Analysis (Gaudino et al.). Firstly, any matching system can only adjust for measurable and included variables. Secondly, generalizability may be sacrificed in order to increase internal validity in propensity matching studies. Finally, the population of patients included in most of studies examined is younger, and in general healthier, than those seen by most cardiac surgery centers in their everyday clinical practice.

Urso S. et al. produce a Meta-Analysis of propensity score-matched observational studies comparing TAR versus non-TAR strategy in terms of long term survival (primary end-point) and TAR with BIMA versus TAR without BIMA (secondary end-point). In this study, the TAR strategy shows a long-term survival benefit over non-TAR. In relation to the secondary end-point, patients receiving BIMA had a higher survival benefit in terms of patency of the arterial grafts, despite an increased risk of sternal and soft-tissue wound infections compared to the TAR group without BIMA (9).

Another Meta-Analysis comparing TAR versus non-TAR strategy in a population of 130,305 patients was performed by Yanagawa B. et al. (10). This study includes 4 smaller shorter follow-up randomized controlled trials (RCTs), plus 15 matched/adjusted and 6 unmatched/unadjusted larger follow-up observational studies. The most important findings were that there were no differences in perioperative stroke, myocardial infarction or mortality in the two groups and that TAR was associated with lower long-term all-causes mortality in observational studies matched/adjusted for confounders and unmatched/unadjusted for TAR. The mean or median follow-up range was 1-14 years. In conclusion, there was a statistically significant reduction in mortality for total arterial revascularization compared to non-TAR revascularization. Post-hoc analysis suggests that mortality decrease may become larger with longer follow-up. The authors also discern a suggestion of greater sternal complication with TAR compared to the BITA-group.

Gaudino M et al. performed a patient-level combined analysis of randomized controlled trials to compare RA grafts and SV graft for CABG to investigate whether there were better postoperative outcomes in patients receiving RAs than in those receiving SVs (11). The mean follow-up time was 60 ± 30 months, and during this interval the incidence of adverse cardiac events was significantly lower in the RA graft group than in the SV graft group (HR 0.67; 95% CI, 0.49 to 0.90; *P*=0.01). The authors found that at a mean follow-up time of 50 ± 30, the use of RA grafts was also associated with a significantly lower risk of angiography occlusion (HR, 0.44; 95% CI, 0.28 to 0.70; *P*<0.001), lower incidence of myocardial infarction (HR, 0.72; 95% CI, 0.53 to 0.99; *P*=0.04), and lower incidence of repeat revascularization (HR 0.50; 95% CI, 0.40 to 0.63; *P*<0.0001). The main conclusion of the study was that the use of radial-artery grafts for CABG resulted in a lower rate of adverse cardiac events and a higher rate of angiographic patency at 5 years follow-up. Subgroup analyses found that the age of the patient at the time of the operation (CABG) was an independent predictor of radial-artery-graft occlusion but not saphenous saphenous-vein-graft occlusion, and 75 years was identified as the cutoff age for the loss of benefit of using RA graft.

TAR (BITA + RAs) should be encouraged in patients with a reasonable life expectancy. This conclusion is also reached by the study by Buxton BF et al., in which they analyzed a cohort 3774 patients affected by triple-vessel coronary artery disease who underwent isolated coronary artery bypass grafting from 1995 to 2010 (2988 patients, 79%, underwent TAR, 786 patients, 21%, receiving only a SV to supplement a SITA) (12). The unadjusted 30-day mortality was lower in the TAR group (1.3% vs. 3.2%) in the context of a prevalence in the SITA + SV group of older age, diabetes mellitus, cerebrovascular disease and severe left ventricular dysfunction. The survival data were available with a mean of 10.0±4.8 years. Kaplan-Meier survival analysis showed that the TAR group had a higher unadjusted 15-year survival rate than the SITA+SV group (62% ± 1.1% vs. 35% ± 1.9%, *P* > 0.0001). In order to reduce the differences between the two groups in terms of cohort size and preoperative variables, propensity scores were matched, and 384 pairs of matched patients obtained. There were no statistically significant differences in intraoperative and early postoperative outcomes between the matched samples, but TAR patients showed an improved survival (54% ± 3.3% vs. 41% ± 3.0%, *P*=0.0003).

The importance of large cohort studies to better analyze the impact in long-term survival of the use RAs as a third conduit in conjunction to BIMA is demonstrated indirectly by Grau JB et al. in a retrospective propensity-score matched study (13). The two propensity-matched cohorts consist of 183 pairs of patients. The main findings of this study were that at 30-day follow up the BIMA + RA ± SVG group had more postoperative atrial fibrillation (24.65 vs. 12.05; *P*=0.001) and a longer median post-operative length of stay (6 vs. 5 days) than BIMA + SVG, and no statistically significant differences in long-term survival over a 14-year period. In fact, before Year 10, the BIMA + SVG group showed a trend towards higher survival, but the BIMA + RA ± SVG group, on further Cox regression analysis using a time-dependent covariate, had a statistically significant improvement in survival of between 10 and 14 years (adjusted HR 0.254, 95% CI, 0.062 to 0.977; *P*=0.048). (Table 1).

Table 1. Resume of principal findings of the four Meta-Analysis and Systematic Reviews analyzed in the Review. PSMs: Propensity Score-Matched Studies. Pts: Patients. HR: Hazard Ratio. CI: Confidence Interval. TAR: Total Arterial Revascularization. RCTs: Randomized Controlled Trials. RAs: Radial Arteries. GSVs: Great Saphenous Veins.

Study	Year	n studies included	Type of studies included	Mean follow-up time	n of patients	Main Results
Gaudino M. et al.	2017	8	PSMs	37.2 to 196.8 months	102867 pts (2-arterial graft: 5346; 3-arterial graft: 4941)	Reduction of late death in 3-arterial compared to 2-arterial: HR 08; 95% CI, 0.75-0.87; *P*<0.001
Urso S. et al.	2019	18	PSMs	3 to 14 years	25576 pts (12874 pts with TAR; 12702 pts with non-TAR)	Long-term survival benefit in TAR-group compared to non-TAR: HR 0.73; 95% CI: 0.68-0.78; *P*<0.001; I^2: 0%

Study	Year	n studies included	Type of studies included	Mean follow-up time	n of patients	Main Results
Yanagawa B. et al.	2017	25	RCTs (n 4) - PSMs (n 15) – Observational non-matched (n 6)	1 to 15 years	130305 pts	Reduction of all-cause mortality in matched studies (0.80, 95% CI:0.62-1.05,*P*=0.11)
						Reduction of all-cause mortality in unmatched studies (0.62,95% CI:0.42-0.93,*P*=0.02)
Gaudino M. et al.	2018	6	RCTs	60 ± 30 months	1036 pts (534 pts with RAs grafts; 502 with GSVs grafts)	Lower incidence of cardiac events in RAs group (HR 0.67;95% CI,0.49 to 0.90; *P*=0.01)
						Lower risk of graft' s occlusion in RAs group at FU angiography (HR 0.44; 95% CI, 0.28 to 0.70; *P*<0.001)
						Lower incidence of repeat revascularization in RAs-group (HR 0.50; 95% CI, 0.40 to 0.63; *P*<0.001)
						No lower incidence of death from any cause in RAs-group (HR 0.90, 95% CI, 0.59 to 1.41; *P*=0.68)

Formica F. et al. analyzed long-term survival benefits of full arterial revascularization with the use of RA in addition to BITA vs. SVGs in addition to BITA with a propensity score analysis (14). In this retrospective study, they analyze 660 3-vessel coronary artery disease subjects who received BIMA in addition to grafting with either RA (206 subjects) or SV (454 subjects) between June 1999 and November 2017. Propensity score matching yielded 190 matched pairs. In the matched groups, the median follow-up time was 9.2 years and survival at 5, 10 and 15 years was respectively 94.8 ± 1.7%, 83.7 ± 3.1% and 78.6 ± 3.9% in the BIMA + RA group and 96.2 ± 1.4%, 85.1 ± 2.9% and 80.4 ± 3.6% in the BIMA + SV group. These results demonstrated that in a small population of three-vessel coronary artery disease patients, the use of RA combined with BIMA as a third conduit did not confer a long-term survival benefit. The 15-year unadjusted and adjusted Hazard Ratio (HR) showed that the use of RA did not affect late mortality (HR, 1.07; 95% CI, 0.63-1.82; *P*= 0.78; HR, 1.05; 95% CI, 0.62-1.79; *P*= 0.83 respectively).

Mohammadi S et al. in a propensity score-matched study (249 pairs of patients divided into two groups: BIMA-RA and BIMA-SVG) sought to evaluate the early results and long-term mortality in two groups of patients (255 pairs of matched patients) undergoing CABG with the use of BIMA associated with RA grafts in the first group, and with SV grafts in the second group (15). There were no differences between the two cohorts in terms of hospital-mortality (0.8% in BIMA-RA group vs. 0.4% in BIMA-SVG, *P*=0.6), or in early outcomes or long-term survival (5-year, 10-year and 15-year survival rates were 98.3%, 92.0% and 92 %, in matched group BIMA-RA and 96.5%, 93.0% and 87.0% in the matched group BIMA-SVG with a log rank *P*=0.44). Neither were there any differences between two groups stratified according to the stenosis severity of the coronary artery grafted (log rank *P*=0.12).

The propensity score-matched study by Benedetto U *et* Al. yielded a similar conclusion. Their study compared 275 matched pairs with surgical low-risk subjected to myocardial revascularization with the use of BITA+RA and BITA+SV (16). The survival rates after a mean follow-up of 10.6 ± 4.8 years in matched group BITA+RA were 97.4% ± 0.9%, 90.3% ± 2.0% and 81.7 ± 3.2% at 5, 10 and 15 years; versus 97.0% ± 1.0%, 94.1% ± 1.5% and 82.1% ± 3.4% in matched group BITA-SV (log rank *P*=0.54; hazard ratio, 1.16; 95% confidence interval, 0.71-1.9). Indeed in selected low-risk patients undergoing BITA grafting there was no increase in long-time survival in the group where RA was used as a third conduit.

Yoshida et al. performed a study to demonstrate the superiority of RA respect SVG used for revascularization of the right coronary artery system (RCA) in multivessel coronary artery disease when BITA were grafted to the left coronary artery system (LCA) (17). The Authors analyze retrospectively 785 consecutive patients underwent isolated coronary artery artery bypass grafting surgery from January 1997 to December 2007. Among the 785 patients, 494 underwent grafting to the RCA. A propensity score-matched analysis was performed by identify 91 pairs of patients. Although the unadjusted survival curve at 5- and 10- years was significantly better in the RA group than the SVG group (respectively 91.0 and 79.6% in the RA group and 83.7 and 65.0% in the SVG group, *P*= 0.041); after the propensity score-matched analysis there was no difference in long-term mortality between the two groups (RA group: 5 years, 90.3%; 10 years 77.9%; SVG group: 5 years, 96.1%; 10 years, 86.3%; *P*=0.744). Throughout multivariable Cox proportional hazard regression analysis the Author identified two different independent preoperative predictors of graft occlusions between the two groups; which were, in the RA group mild stenosis of the native RAC (HR 0.958; 95% CI 0.924-0.993; *P*=0.018) and low indexing GFR for BSA (Body Surface Area) (HR 0.958, 95% CI 0.912-0.991; *P*=0.018) and in the SVG group were off-pump CABG (HR 5.488; 95% CI 2.122-14.191; *P*<0.000) and female gender (HR 2.533; 95% CI 1.101-5.829; *P*=0.029). In conclusion, this study, after propensity score-matched analysis, demonstrated that the use of RA as the third conduit grafted to the RCA in association with BITA grafted on LCA system, did not improve long-term survival, graft patency rates or cardiac prognosis. (Table 2).

Table 2. Resume of principal findings of the 5 observational Propensity Score-Matched Studies included in the review. PSMs: Propensity Score-Matched Study. Pts: Patients. BITA: Bilateral Internal Thoracic Arteries. RA: Radial Artery. SV: Saphenous Vein. HR: Hazard Ratio. CI: Confidence Interval. RCA: Right Coronary Artery. TAR: Total Arterial Revascularization.

Study	Year	Type of Study	Mean Follow-up time	n of Patients	Study Period	Main Results
Formica F. et al.	2019	Observational PSMs	9.2 years (interquartile range, 5.6-13 years)	660 pts (206 received BITA+RA; 454 received BITA+SV). 190 pairs of matched pts.	Between June 1999 and November 2017	Use of BITA+RA did not affect the late mortality (HR 1.05; 95% CI, 0.62-1.79; *P*=0.83)
Grau J. B. et al.	2015	Observational PSMs	_	751 pts (568 received BITA+SV; 183 received BITA+RA±SV. 183 pairs of matched pts.	From the beginning of 2000 to the of 2013	No statistical increase in survival in BITA+RA±SV during first 10 years (HR 1.056, 95% CI 0.507-2.201; *P*=0.496)
						Statistical increase in survival in BITA+RA±SV after first 10 years (HR 0.254, 95% CI 0.062-0.977; *P*=0.047)

Study	Year	Type of Study	Mean Follow-up time	n of Patients	Study Period	Main Results
Buxton B. F. et al.	2014	Observational PSMs	10.0 ± 4.8 years (range, 0 - 18.3 years)	3774 pts (2988 pts received BITA-RA, 786 received SITA+SVs). 384 pairs of matched pts.	From January 1995 to December 2010	No statistical differnces in intaoperative and early postoperative outcomes in matched populations
						Improved survival in matched population for TAR-group at 15 years (54% ± 3.3% vs. 41% ± 3.0%, *P*=0.0003)
Mohammadi S. et al.	2016	Observational PSMs	8 years	1750 pts (255 pts received BITA+RA, 1495 pts received BITA+SV. 249 pairs of matched pts.	From April 1991 to November 2013	The use of BITA + RA was not associated with an improved long-term survival (HR 0.9, 95% CI 0.4 to 2.0; *P*=0.7)
Benedetto U. et al.	2016	Observational PSMs	10.6 ± 4.8 years	764 pts (275 pts received BITA + RA, 489 pts received BITA + SV). 275 pairs of matched pts.	From the beginning of 1996 to April 2015	The early mortality between the matched groups was not statistically significant (HR 0.29, 95% CI 0.03-2.72; *P*=0.28)
						The late mortality between the matched groups was not statistically significant (HR 1.27, 95% CI 0.79-2.04; *P*=0.32)
Yoshida S. et al.	2016	Observational PSMs	7.5 ± 4.4 years	374 pts (110 pts received RA-graft for RCA revascularization, 264 pts received SV-graft for RCA revascularization). 91 pairs of matched pts.	From January 1997 to December 2007	No differences in long-term mortality.
						No difference in the rate of freedom from cardiac events.
						No difference in the long-term patency rate.

Conclusion

The conflicting findings noted above could explain why the RA is still not widely accepted as the third conduit in CABG, although both EACTS and AATS, in their latest guidelines on myocardial revascularization, suggest obtaining TAR in three-vessel coronary disease. Another important issue is the lack of randomized clinical trial (RCTs) on the use of RA grafts as third conduit. Most studies on this issue are in fact propensity score-matched studies with small populations.

However, the use of TAR as a surgical strategy, especially in younger patients, yields better long-term survival without increasing peri-operative or in-hospital mortality and morbidity. Saphenous vein grafting in association with ITA remains an acceptable alternative for reaching a complete revascularization in multivessel coronary artery disease in high-risk patients, such as those who are older, obese, diabetic, or affected by severe obstructive chronic broncopneumopathy.

In conclusion, two important variables to consider in selecting the best type of myocardial revascularization for a three-vessel coronary artery disease are the patient' s age and life expectancy at the time of surgery. In patients 60 years old or younger, or with a life expectancy of at least 15 to 20 years, total arterial myocardial revascularization is the best target, mainly because of the better long-term patency of arterial conduits compared to SVGs. Numerous studies confirm this conclusion.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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