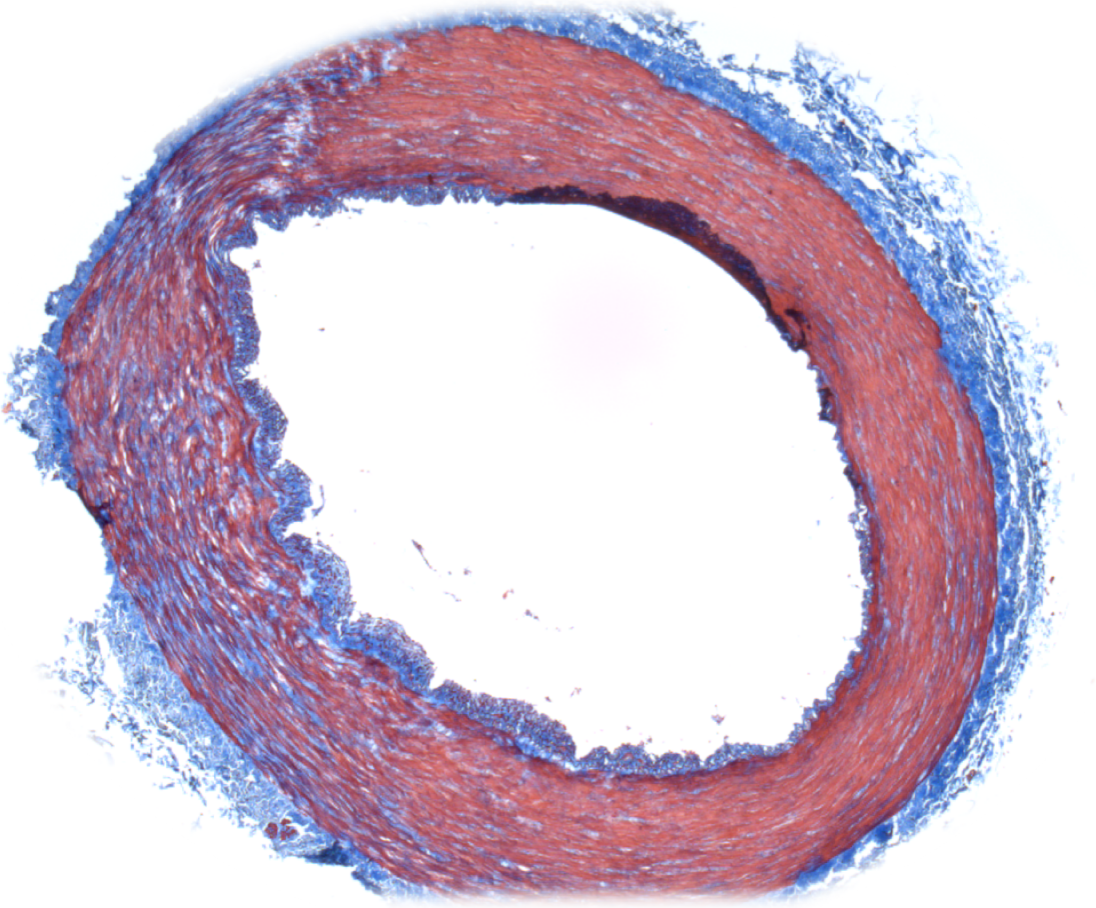
The radial artery for coronary artery bypass grafting

The Radial Artery for Coronary Artery Bypass Grafting



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Printing: ProefschriftMaken | www.proefschriftmaken.nl

Layout: Mario F. L. Gaudino

ISBN: 978-94-6423-050-5

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DISSERTATION

To obtain the degree of Doctor at Maastricht University,
on the authority of the Rector Magnificus, Prof. Dr. Rianne M. Letschert
in accordance with the decision of the Board of Deans,
to be defended in public
on Tuesday 1 December 2020 at 13.00 hrs

by

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This thesis was supported by:

Health Foundation Limburg
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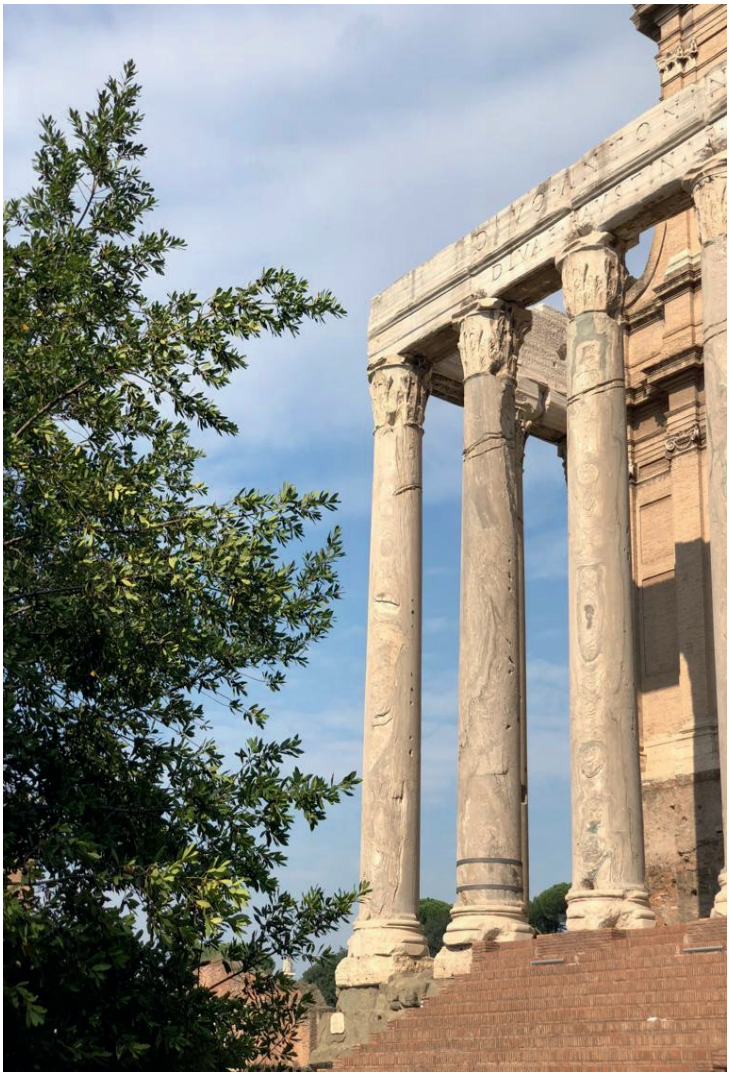

CHAPTER 1

GENERAL INTRODUCTION

General introduction to the radial artery for coronary artery bypass grafting

Introduced and then abandoned by Carpentier (1) and revived by Acar (2), the radial artery is a versatile, long, robust, facile coronary bypass graft with excellent long-term patency, provided spasm and competitive flow are avoided. Although, intuitively, the right internal thoracic artery (RITA) is the natural second arterial graft during coronary artery bypass grafting (CABG), it may not reach the desired target unless used as a free or composite graft. Concerns over sternal infection, adequacy of single inflow in T grafts, and unfamiliarity with bilateral internal thoracic artery (BITA) results in 95% of all CABG operations using only the left internal thoracic artery (LITA).

The majority of conduits are saphenous vein grafts (SVG) which develop atheroma and occlude in the long term with resulting recurrent symptoms, re-interventions, and poorer prognosis. Arterial grafts always have higher patencies than SVG. (3). Radial artery patency rates of 90% at 10 years and > 80% at 20 years are reported. (4, 5) Hence the radial artery can be used as the second graft of choice after the LITA and/or RITA. (6, 7) Of note, the radial artery carries a Class IB indication in the 2018 European Guidelines for myocardial revascularization (8). Radial arteries are especially useful in reoperations (prior SVG), in patients with severe pulmonary disease, in obese, and insulin dependent diabetics where BITA grafting has relative contraindications. (4)

Histologically, the radial artery has a thin intima, a fenestrated internal elastic lamina, a thick muscular media and an adventitia rich in vasa vasorum. The radial artery wall is up to 450 µm thick (2.5 times the internal thoracic artery [ITA]), and composed predominantly of the muscular media. It has more intimal thickening, lipid deposits and calcification, particularly

distally, and is slightly larger than the ITA. In organ bath models, vasoconstriction can be intense, prolonged, and twice that for the ITA due to the substantive muscular media. Spasm prophylaxis is then considered essential – by atraumatic harvest and smooth muscle relaxants, including topical or intraluminal papavarine, nitroglycerin, nitroprusside, diltiazem, milrinone or phenoxybenzamine.

The radial artery is an auto-regulatory "living graft ". In competitive flow situations vasoconstriction and a "string sign" may occur (4, 5). Conversely in high flow scenarios it can dilate to diameters of 5 – 8mm. The radial artery functions optimally when used to bypass tightly stenosed or occluded coronaries.

Although the evidence is anecdotal, radial artery graft spasm has been reported days or weeks post-operatively. Oral calcium channel antagonists are often given empirically for 6 months. However, after implantation in the coronary circulation, the radial artery undergoes a morpho-functional remodeling characterized by a progressive thinning of the muscular component of the media and switches from a muscular to an elastomuscular wall architecture (9). This change in histology is accompanied by a marked reduction of the initial hyper-reactive tendency. This adaptive phenomenon is probably the pathophysiologic background to the lack of clear benefits of chronic therapy with calcium channel blockers. (10).

When harvesting the radial artery, adequacy of the hand circulation must be assessed by the Allen's test and index finger wave plethysmography (reperfusion within 10 seconds). Pulse oximetry changes with radial artery occlusion can also be helpful. Ultrasound can assess radial artery size, flow and calcification.

Open and endoscopic techniques are used with excellent outcomes. The open technique allows securing of branches by diathermy, harmonic scalpel or small vascular clips. Endoscopic harvesting can be performed with various technologies through a 2-3cm longitudinal incision at the wrist and, occasionally, an additional incision at the elbow to secure the radial artery proximally. It appears that both endoscopic and open harvestings result in equivalent quality radial artery conduits with no differences in patency or survival. (11) Both techniques have very low rates (less than 1%) of infection and neurological complications. A small longitudinal drain and a firm dressing and bandage are used routinely for the endoscopic technique. The radial artery is stored in arterial blood at 37°C, with the preferred vasodilator. Some surgeons skeletonize the radial artery by removing the venae commitantes to maximize vasodilatation and length.

Contraindications to radial artery use include prior major forearm trauma, severe calcification, collagen vascular diseases and Raynaud's syndrome. In addition, patients with renal failure or end stage renal disease who may require vascular access for dialysis should not have routine radial artery grafting unless there are exceptional circumstances (e.g. no other suitable conduits). Traditionally, the radial artery has been harvested from the non-dominant arm, but harvesting of the arm with the best ulnar compensation, independently from dominance is performed by many groups. Previously cannulated radial arteries often have intimal damage and the distal portions are best avoided. Low patency rates have been reported for radial artery grafts from arteries previously used for transradial procedures. (12)

If used with the LITA, the radial artery should be used to bypass the next most important, tightly stenosed coronary artery. Alternatively, the radial artery can be deployed to a posterior

descending coronary artery with a thight stenosis in the context of BITAs, as they are usually deployed to the left side. The radial artery is best used as an aortocoronary graft and is suited to sequential grafting if required. A RITA- radial artery composite graft can also be used to bypass the posterior descending artery. The "Melbourne baby-Y graft" popularized by James Tatoulis is an excellent alternative to sequentials when grafting of more than one target is required, with the advantage of allowing more freedom in terms of location of the anastomosis. (13)

The patency of the radial artery has been described by different angiographic series. In protocol-driven series, the radial artery patency rate has ranged from 89% at 1 year in the Veterans Affairs (VA) trial, to 88% at 7.7 years in the Radial Artery Patency Study (RAPS) trial, and to 84.8% at 19 years in our series. (5) Results of the symptoms-driven angiographic studies are much more discordant. However, a major selection bias is obviously present in all symptoms-driven studies.

The location of the target vessel does not affect radial artery angiographic outcome, whereas the severity of the target vessel stenosis is a key determinant of patency. Target vessel stenosis > 70% in the left circulation and > 90% in the right circulation lead to the best patency rates. The long-term risk of occlusion of the radial artery compared to LITA has not been described (5).

There is some evidence that radial artery grafting results in improved long-term survival in patients undergoing CABG using the radial artery rather than the saphenous vein to bypass non-LAD targets. (25) Goldman et al (14) found no difference in survival at 1 year in the VA study while the RAPS trial (16) found a tendency to lower incidence of adverse follow-up events in the radial artery group. Propensity matched observational studies consistently found better survival in radial

artery patients. A recent meta-analysis of 14 studies and 20,931 patients reported that the use of the radial artery to graft the second target vessel was associated with a 26% relative risk reduction in mortality at 6.6-year follow-up compared to the use of the saphenous vein. (26) Despite guideline recommendations and studies showing benefit of radial artery grafting, there has been resistance to the use of multiple arterial grafts. This can be explained, at least in part, by the fact that the clinical benefit of additional arterial grafts reported in observational studies has not been confirmed in randomized clinical trials. While several trials have demonstrated superior angiographic patency rates with radial-artery grafts over saphenous-vein grafts, these studies were individually underpowered to detect differences in clinical events.

The most scientifically robust analysis to date, a patient-level meta-analysis of six randomized trials of radial artery vs SVG showed that the radial artery was associated with a significant reduction of the composite of death, myocardial infarction and repeat revascularization and better patency rate at 5 years follow-up (27) There is also evidence showing that higher risk subgroups of patients —the elderly, diabetics and women—benefit from radial artery grafting. (12)

A recent meta-analysis (28) of eight propensity matched studies concluded that the use of the RITA compared to the radial artery was associated with better long-term survival and freedom from repeat revascularization. However, there was significant heterogeneity in this meta-analysis indicating a great deal of variability among the 8 studies. Thus, on one hand, Tranbaugh et al (7) showed that the radial artery had a trend towards better survival (p=0.06) and similar patency to the RITA while older and chronic obstructive pulmonary disease patients had better survival with

radial artery grafting. Conversely, Ruttmann and colleagues (29) reported 2.6 times the in-hospital mortality and 10 times the number of strokes and myocardial infarctions in the radial artery group with no mortality in the RITA group to 8 years. Thus, their reported long-term mortality benefit (hazard ratio 0.23) of RITA grafting need further confirmation.

The 10-year results of the RAPCO trial were presented at the American Association for Thoracic Surgery 2016 Annual Meeting. (30) This well designed randomized controlled trial evaluated outcomes of 394 patients less than 70 years of age randomized to receive either a radial artery or free RITA to the second most important coronary target after the LAD. Most grafts went to the circumflex system. Survival was significantly better in the radial artery compared to the RITA arm (p=0.032) and event free survival was higher in the radial artery group, but the difference did not reach statistical significance (p=0.085). Patency was statistically similar although numerically better for radial artery (91.8%) versus RITA (88.5%, p=0.057).

Aim and outline of the thesis

The purpose of this thesis in to analyze the clinical outcomes of the radial artery as a coronary artery bypass conduit, compare it to other conduits, and describe the factors associated with graft patency. This was achieved through original research and several individual patient-data and aggregate meta-analyses.

The effects of different radial artery harvesting techniques (open versus endoscopic) on the structural integrity and functions of the endothelium of radial artery are first analyzed by evaluating endothelial-dependent vasorelaxation to acetylcholine as well as quantitative

structural analysis of the endothelial integrity. This is followed by presentation of the 20-year long-term results of patients receiving radial artery graft for myocardial revascularization. A patient-level meta-analysis of randomized trials comparing radial-artery grafts vs SVG for CABG to describe the clinical outcomes of radial artery grafting is described. The role of calcium-channel blockers after radial artery CABG and their effect on the midterm clinical and angiographic outcomes are also analyzed in an individual patient data meta-analysis by pooling data from multiple randomized controlled trials.

Finally, the radial artery is compared to other CABG conduits through a large patient-level dataset including six angiographic randomized controlled trials of CABG conduits to explore the incidence and determinants of coronary graft failure for the LITA, RITA, radial artery and saphenous vein. The differences in late survival and other clinical outcomes according to the type of second graft used (radial artery versus RITA versus SVG) for CABG are also compared in a network meta-analysis.

References

1. Carpentier A, Guermonprez JL, Deloche A, Frechette C, DuBost C. The aorta-to-coronary radial artery bypass graft. A technique avoiding pathological changes in grafts. Ann Thorac Surg 1973;16:111–21.
2. Acar C, Jebara VA, Portoghese M, Beyssen B, Pagny JY, Grare P, Chachques JC, Fabiani JN, Deloche A, Guermonprez JL. Revival of the radial artery for coronary artery bypass grafting. Ann Thorac Surg 1992;54:652–60.
3. Buxton BF, Shi WY, Tatoulis J, Fuller JA, Rosalion A, Hayward PA. Total arterial revascularization with internal thoracic and radial artery grafts in triple vessel coronary artery disease is associated with improved survival. J Thorac Cardiovasc Surg 2014;148:1238-44.
4. Tatoulis J, Buxton BF, Fuller JA, Meswani M, Theodore S, Powar N, Wynne R. Long-term patency of 1108 radial artery – coronary angiograms over 10 Years. Ann Thorac Surg 2009;88:23-30.
5. Gaudino M, Tondi P, Benedetto U, Milazzo V, Flore R, Glieca F, Ponziani FR, Luciani N, Girardi LN, Crea F, Massetti M. Radial artery as a coronary artery bypass conduit. 20 year results. J Am Coll Cardiol 2016;68:603-10.
6. 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 Cardio Thorac Surg 2016;50:53-60.
7. Tranbaugh RF, Dimitrova KR, Lucido DJ, Hoffman DM, Dincheva GR, Geller CM, Balaram SK, Ko W, Swistel DG. The second best arterial graft: A propensity analysis of the radial artery versus

the free right internal thoracic artery to bypass the circumflex coronary artery. J Thorac Cardiovasc Surg 2014;147:133-42.

8. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2018;00:1-96.
9. Gaudino M, Prati F, Caradonna E, Trani C, Burzotta F, Schiavoni G, Glieca F, Possati G. Implantation in coronary circulation induces morphofunctional transformation of radial grafts from muscular to elastomuscular. Circulation 2005;112(9 Suppl):I208-11.
10. Gaudino M, Glieca F, Luciani N, Alessandrini F, Possati G. Clinical and angiographic effects of chronic calcium channel blocker therapy continued beyond first postoperative year in patients with radial artery grafts: results of a prospective randomized investigation. Circulation. 2001;104(12 Suppl1):I64-7.
11. Dimitrova KR, Hoffman DM, Geller CM, DeCastro H, Dienstag B, Tranbaugh RF. Endoscopic radial artery harvest produces equivalent and excellent midterm patency compared to open harvest. Innovations 2010;5:265-269.
12. Aldea GS, Bakaeen FG, Pal J, Fremes S, Head SJ, Sabik J, Rosengart T, Kappetein AP, Thourani VH, Firestone S, Mitchell JD. The Society of Thoracic Surgeons clinical practice guidelines on arterial conduits for coronary artery bypass grafting. Ann Thorac Surg 2016;101:801-9.
13. Gaudino M, Fremes S, Schwann TA, Tatoulis J, Wingo M, Tranbaugh RF. Technical Aspects of the Use of the Radial Artery in Coronary Artery Bypass Surgery. Ann Thorac Surg 2018;pii:S0003-4975(18)31785-5.

14. Goldman S, Sethi GK, Holman W, Thai H, McFalls E, Ward HB, Kelly RF, Rhenman B, Tobler GH, Bakaeen FG, Huh J, Soltero E, Moursi M, Haime M, Crittenden M, Kasirajan V, Ratliff M, Pett S, Irimpen A, Gunnar W, Thomas D, Fremes S, Moritz T, Reda D, Harrison L, Wagner TH, Wang Y, Planting L, Miller M, Rodriguez Y, Juneman E, Morrison D, Pierce MK, Kreamer S, Shih MC, Lee K. Radial artery grafts vs saphenous vein grafts in coronary artery bypass surgery: a randomized trial. JAMA 2011;305(2):167-74.
15. Hayward PA, Buxton BF. Mid-term results of the Radial Artery Patency and Clinical Outcomes randomized trial. Ann Cardiothorac Surg 2013;2:458–66.
16. 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(1):28-35.
17. 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(22):2859-64.
18. Achouh P, Isselmou KO, Boutekadjirt R, D'Alessandro C, Pagny JY, Fouquet R, Fabiani JN, Acar C. Reappraisal of a 20-year experience with the radial artery as a conduit for coronary bypass grafting. Eur J Cardiothorac Surg 2012;41(1):87-92.
19. Possati G, Gaudino M, Prati F, Alessandrini F, Trani C, Glieca F, Mazzari MA, Luciani N, Schiavoni G. Long-term results of the radial artery used for myocardial revascularization. Circulation 2003;108(11):1350-4.

20. Maniar HS, Sundt TM, Barner HB, Prasad SM, Peterson L, Absi T, Moustakidis P. Effect of target stenosis and location on radial artery graft patency. J Thorac Cardiovasc Surg 2002;123(1):45-52.
21. Shah PJ, Bui K, Blackmore S, Gordon I, Hare DL, Fuller J, Seevanayagam S, Buxton BF. Has the in situ right internal thoracic artery been overlooked? An angiographic study of the radial artery, internal thoracic arteries and saphenous vein graft patencies in symptomatic patients. Eur J Cardiothorac Surg 2005;27:870-5.
22. Khot UN, Friedman DT, Pettersson G, Smedira NG, Li J, Ellis SG. Radial artery bypass grafts have an increased occurrence of angiographically severe stenosis and occlusion compared with left internal mammary arteries and saphenous vein grafts. Circulation 2004;109:2086-91.
23. Amano A, Hirose H, Takahashi A, Nagano N. Coronary artery bypass grafting using the radial artery: midterm results in a Japanese institute. Ann Thorac Surg 2001;72(1):120-5.
24. Dimitrova KR, Dincheva GR, Hoffman DM, DeCastro H, Geller CM, Tranbaugh RF. Results of endoscopic radial artery harvesting in 1577 patients. Innovations (Phila) 2013;8(6):398-402.
25. Tranbaugh RF, Lucido DJ, Dimitrova KR, Hoffman DM, Geller CM, Dincheva GR, Puskas JD. Multiple arterial bypass grafting should be routine. J Thorac Cardiovasc Surg 2015;150:1537-45.
26. Gaudino M, Rahouma M, Abouarab A, Leonard J, Kamel M, Di Franco A, Demetres M, Tam DY, Tranbaugh R, Girardi LN, Fremes SE. Radial artery versus saphenous vein as the second conduit for coronary artery bypass surgery: A meta-analysis. J Thorac Cardiovasc Surg 2018;pii:S0022-5223(18)32924-6.

27. Gaudino M, Benedetto U, Fremes S, Biondi-Zoccai G, Sedrakyan A, Puskas JD, Angelini GD, Buxton B, Frati G, Hare DL, Hayward P, Nasso G, Moat N, Peric M, Yoo KJ, Speziale G, Girardi LN, Taggart DP. Radial-Artery or Saphenous-Vein Grafts in Coronary-Artery Bypass Surgery. N Engl J Med 2018;378(22):2069-2077.
28. 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;152:1083-91.
29. Ruttmann E, Fischler N, Sakic A, Chevtchik O, Alber H, Schistek R, Ulmer H, Grimm M. Second internal thoracic artery versus radial artery in coronary artery bypass grafting: a long-term, propensity score-matched follow up study. Circulation. 2011;124:1321-29.
30. Deb S, Fremes SE. The 3 *R*'s: The radial artery, the right internal thoracic artery, and the race for the second best. J Thorac Cardiovasc Surg 2016;152:1092-4.

CHAPTER 2

Open radial artery harvesting better preserves endothelial function compared to the endoscopic approach

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Interact Cardiovasc Thorac Surg. 2019 Oct 1;29(4):561-567.

ABSTRACT

Objective: Both the open and the endovascular techniques are commonly used for harvesting the radial artery (ORAH and ERAH respectively). Yet, very little is known on the effects of these two techniques on endothelial integrity and function of the radial artery (RA). This study was designed to assess the preservation of endothelial integrity and function of RA harvested using the two approaches.

Methods: Two independent surgical teams working in the same institution routinely use the RA for coronary artery bypass grafting using exclusively either ORAH or ERAH. Thirty-nine consecutive patients were enrolled in this comparative study. Endothelial function of ORAH and ERAH was assessed by using the wire myograph system. The integrity of the RA endothelium was evaluated by immuno-histochemical staining for erythroblast transformation specific-related gene (ERG).

Results: The vasodilation in response to acetylcholine was significantly higher in RA harvested with ORAH ($p \leq 0.001$ vs. ERAH). Endothelial integrity was not different between the two groups.

Conclusions: ORAH is associated with a significantly higher endothelium-dependent vasodilation. Further investigation on the potential implications of these findings in terms of graft spasm and patency as well as clinical outcomes are needed.

Key question

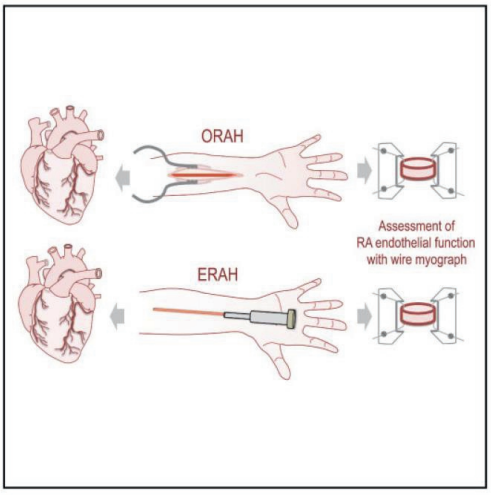
Does open and endoscopic radial artery (RA) harvesting impact endothelial integrity and function?

Key finding(s)

Open RA harvesting better preserves endothelial function than endoscopic RA harvesting. No histological differences observed between the groups.

Take-home message

Open RA harvesting better preserves endothelial function than endoscopic RA harvesting. There are potential clinical implications.



INTRODUCTION

Coronary artery bypass grafting (CABG) is the gold standard approach in the treatment of multi-vessel coronary artery diseases. Traditionally, the internal mammary artery and saphenous veins have been used for CABG (3). In the 1970s, the radial artery (RA) was introduced and soon abandoned due to the high failure rate, likely due to a traumatic harvesting technique (4). In the early 1990s, the RA was reconsidered after Acar and colleagues introduced a more refined method of harvesting, which was associated with improved RA patency rate (5). Currently, the RA is often used as complementary arterial conduit for CABG. Data from the Society of Thoracic Surgery Adult Cardiac Surgery Database indicate that the RA is preferred to the right internal thoracic artery as the second arterial graft in the United States (6). Recently, we published the first randomized-based study demonstrating the clinical benefits of the use of the RA versus the saphenous vein in CABG(7). In light of these findings, it seems likely that the interest toward this conduit will increase in the near future.

Traditionally, the RA has been harvested using the open technique (ORAH) (8). In the early 2000s, the endoscopic technique (ERAH), less invasive and cosmetically more acceptable, was developed (9). However, the endoscopic dissection of the RA occurs in a narrow space, raising concerns regarding potential mechanical injuries to the conduit, particularly on the endothelium. Preservation of the functional integrity of the endothelium is of critical importance for maintaining the endothelial cell functions, including vascular tone regulation, anti-inflammatory and anti-thrombotic functions and inhibition of smooth muscle cell proliferation and migration (10). Endothelium-derived vasoactive substances, including nitric oxide (NO), prostaglandin I_2 and the

endothelium-derived hyperpolarizing factor, control RA vasoactive tone and flow. Hence, even skilled surgical maneuvers during ERAH could potentially impact the 'health' of the endothelium and lead to graft spasm and thrombosis, ultimately compromising the clinical outcomes.

Initial clinical studies assessing the short-term patency of RAs harvested using the two techniques reported similar outcomes (11, 12). However, due to the rarity of clinical events after CABG with the RA, it is likely that all the published series and meta-analyses are underpowered to detect even moderate differences.

Our current understanding of the impact of ERAH versus ORAH on the integrity of the endothelial structure and function is based on older series with negative results (1, 2). The intrinsic limitations of the methods used in those series, and the difficulties to assess the vasoreactivity of RA due to the peculiar intense vasomotions prompted us to further investigate the effects of the ORAH versus ERAH on the structural integrity and functions of the endothelium of RA. In this study, endothelial-dependent vasorelaxation to acetylcholine as well as quantitative structural analysis of the endothelial integrity were performed in open and endoscopic harvested RAs using a more contemporary approach.

METHODS

Study design

Two independent and experienced teams working in the same institution routinely use the RA for CABG, with each individual team performing either ORAH or ERAH exclusively. From January to October 2017 all consecutive patients undergoing primary CABG with the RA were screened and included if the laboratory personnel was available for the evaluation. The study was approved by the institutional review board and patient consent was obtained prior to enrollment.

Radial Artery Harvesting

In the endoscopic group the RA was harvested according to a method described by Connolly and colleagues (13). Briefly, a small 2-3 cm incision was made on the distal volar aspect of the forearm just proximal to the radial styoid prominence. A 30-degree 5mm endoscope aided by subcutaneous retractors and harmonic shears were used to harvest the RA with its surrounding pedicle. A 2-3 cm counter incision was made at the proximal end of the dissection to aid in vessel transection and ligation.

In the open group the RA was harvested according to the method described by Gaudino and Lau (14). Briefly, a linear incision was made from the lateral edge of the biceps tendon and carried distally following the round curvature of the brachio-radialis muscle and terminated just proximal to the radial styoid prominence. Dissection was aided with the use of a harmonic ultrasonic device and the RA was harvested as a pedicle according to the “no touch” technique (15).

All harvestings were performed by highly experienced operators who routinely perform their respective techniques (namely, ERAH and ORAH); none of the RAs included in our study was harvested by trainees or rotating residents. Before harvesting, no patient received vasodilators. No tourniquet was employed irrespective of the harvesting technique. Heparin was administered in both groups.

After dissection, a 1 cm segment was cut from the proximal end of the RA and immediately placed in cold (4°C) Krebs buffered solution and transferred to the lab for functional studies. Prior to placing in Krebs solution, a RA ring of approximately 2 mm in length was cut from the RA and placed in 4% formalin for histological analysis.

Assessment of RA vascular reactivity in organ bath

Following the harvesting by open or endoscopic approach, the RA specimens were placed in a cold (4°C) Krebs solution at pH 7.2±0.2 comprised of (mmol/L) NaCl 118, KCl 4.7, $MgCl_2$ 1.2, KH_2PO_4 1.2, $CaCl_2 \bullet H_2O$ 2.5, $NaHCO_3$ 25, and glucose 11, and carbooxygenated with a gas mixture of 95% O_2 and 5% CO_2. By using a dissecting scope (Zeiss Discovery.V8 Stereo) at low magnification, the RA was carefully dissected and cleaned of all surrounding fat and loose connective tissue and then cut into approximately 2 mm rings. From each patient, one to four RA rings (about 2 mm length) were mounted in the wire myograph system (Danish MyoTechnology, Denmark). Each chamber was filled with 5 ml of Krebs solution maintained at 37°C and continuously carboxygenated. Ring length (L) was measured before each experiment in order to aid in pressure calculations. The rings were then allowed to equilibrate upstretched for about 60 minutes before passive tension was increased stepwise until they reached a transmural pressure of 60 mmHg,

calculated as previously reported for large vessels (16). A known intrinsic characteristic of the RA is the vasospasm. In *in vitro* experiments, when the RA were stretched beyond 60 mmHg, the vasomotions overpowered the contraction and relaxation effects in response to pharmacological agents (both, vasoconstrictors and vasodilators), creating a confounding factor of the interpretation of the data. Thus, to overcome this confounding factor in the assessment of vascular reactivity, we assessed lower transmural pressures within physiological range (90, 80, 70 and 60 mmHg), until frequency and magnitude of the vasomotions did not interfere with the pharmacological studies. Thus, we found that the optimal transmural pressure to avoid the interference of vasomotion was 60 mmHg.

Vessel Stabilization and Force Calculations

After equilibration, the brackets were slowly moved apart and the rings were then sequentially stretched to apply a tension equivalent to 60 mmHg. The internal diameter, the length of the RA ring and the passive tension were used to calculate the pressure applied as previously reported (17).

The vasoreactivity to the pharmacological agents was assessed once the tension of RA rings was stable (the tension equivalent to the one the ring was exposed at 60 mmHg). RA rings were constricted with phenylephrine (PE, $1x10^{-6}$ mol/L) until the tension evoked was consistent between two consecutive PE stimulations. Next, the RA rings were pre-constricted with PE ($1x10^{-6}$ mol/L) followed by a cumulative concentration-response curve of acetylcholine (Ach $1x10^{-9}$ – $3x10^{-5}$ mol/L) to evaluate the integrity and the function on the RA endothelium. Of note, Ach

induces an endothelium-dependent vasorelaxation. Vessels were washed between experiments and allowed to re-stabilize, before repeating the concentration-response curve of Ach.

Histological Analysis

Following harvesting, RA specimens were immediately fixed in a 10% formalin solution and embedded in paraffin. Immunohistochemistry was performed on 4 µm-thick sections. The unstained slides were deparaffinized and rinsed in deionized (DI) water, followed by antigen retrieval, by using the sodium citrate buffer (pH = 6). The endothelial cells were detected by performing immunohistochemical staining for erythroblast transformation specific-related gene (18) (ERG, Abcam, Cambridge, MA. Cat. N. ab92513). Sections were incubated with anti-ERG antibody (1:100 dilution) for 25 min at room temperature. ERG was detected using an HRP conjugated compact polymer system and DAB as the chromogen. Each section was counterstained with hematoxylin and mounted with Leica Micromount.

Images of stained RA were acquired by using 20x objective of Aperio AT2 whole slide scanner (Leica Biosystems, San Diego, CA, USA). The scanned images were evaluated for quality and loaded onto the HALO™ Digital Image Analysis (DIA) platform (Indica Labs, Corrales, New Mexico, USA) for the quantification of the endothelial cell ERG-positive and the circumference of the RA, as previously described (19). The endothelial integrity of each RA specimen was expressed as the number of cells per unit circumference (mm). To increase the robustness of the analysis, the same RA specimens were quantified manually and blindly for the number of endothelial cells per length of circumference of RA. The outcome was consistent between the two methods of

quantification. The data represented in **Fig. 2** are the quantification performed with the manual approach.

Statistical analysis.

Data are expressed as mean ± SEM in Fig. 1A, and as mean± SD in Fig. 1B and 2B. Two-way ANOVA was employed for statistical analyses in Fig. 1A. Two-tailed unpaired Student's t test was used for statistical analysis in **Fig. 1B** and **Fig. 2B**. Differences were considered statistically significant at $P< 0.05$. All tests were 2-sided. GraphPad Prism software (version 8.0, GraphPad Software) was used for all statistical analyses.

Based on preliminary data from 7 patients we estimated that the mean of endothelial cells/micron in the open group was 0.03 with a standard deviation of 0.01. In order to detect a 33% difference (from 0.03 to 0.02) with a power of 0.80 at alpha of 0.05, 32 patients (16 from each group) were required. The same simple size give >80% power to detect a difference ≥ 10% in the mean of the maximal relaxation response to Ach.

RESULTS

Patient population

Table 1: Baseline patients profile

	ORAH ($n=23$)	ERAH ($n=16$)	*P*-value
Age (years), mean ± SD	61.35 ± 9.72	59.19 ± 9.88	0.50
Male gender, *n* (%)	20 (87)	13 (81)	0.67
Height (m), mean ± SD	1.71 ± 0.10	1.7 ± 0.07	0.73
Weight (kg), mean ± SD	86.78 ± 14.27	84.88 ± 29.45	0.79
BMI (kg/m^2), mean ± SD	29.74 ± 4.27	29.87 ± 8.89	0.95
Hypertension, *n* (%)	18 (78)	16 (100)	0.06
Hyperlipidaemia, *n* (%)	17 (74)	14 (87)	0.43
Congestive heart failure, *n* (%)	5 (22)	0 (0)	0.06
Obesity, *n* (%)	8 (34)	9 (56)	0.32
Smoking history, *n* (%)	13 (56)	8 (50)	0.94
Diabetes, *n* (%)	9 (39)	10 (62)	0.27

Hypertension was defined as either a systolic blood pressure >140/90 mmHg. Obesity was defined as a body mass index ≥30 kg/m^2. Congestive heart failure was defined by laboratory findings of elevated natriuretic peptides in patients with concomitant signs and symptoms consistent with this syndrome. Dyslipidaemia was defined as LDL-cholesterol above recommended levels as a function of patients total cardiovascular risk. Diabetes was defined as fasting plasma glucose ≥7.0 mmol/l (126 mg/dl) or 2 h plasma glucose ≥11.1 mmol/l (200 mg/dl).
BMI: body mass index; ERAH: endoscopic radial artery harvesting; LDL: low density lipoprotein ORAH: open radial artery harvesting; SD: standard deviation.

From a total of 138 screened patients, 39 were enrolled in the study (23 in the ORAH group and 16 in the ERAH). The baseline patient profile was similar between the two groups (see **Table 1**).

Endothelial-dependent vasodilation was preserved by ORAH approach

As shown in **Fig. 1A**, Ach-induced vasodilation was significantly reduced (P<0.001) in the ERAH rings compared to ORAH suggesting that the endothelium was better preserved in conduits harvested with the open compared to the endoscopic approach (**Fig.1A**). Maximal relaxation response was significantly higher in the ORAH vs. ERAH group (98.2±0.7% and 89.8±3.7%, respectively, with P=0.03). The EC50 values for Ach were not statistically different between the two groups (P=0.51). The tension induced by PE was comparable between both groups (**Fig. 1B**, P=0.25), suggesting that different pre-contractions by PE were not accountable for the greater Ach-induced endothelial-dependent vasodilation in the ORAH group.

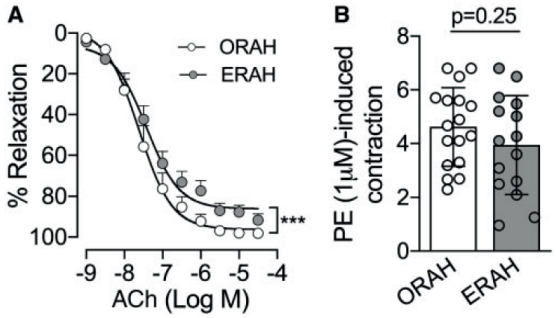


Figure 1: Ach-mediated vasodilation was preserved in the radial artery (RA) harvested via open technique. Two to three RA rings from each patient were mounted in the wire myograph system (620M, DMT). (**A**) After stabilization, RA rings were assessed for vasodilation in response to increasing concentrations of ACh (1×10^{-9}–3×10^{-6} M) as indicated. Two-way analysis of variance was used for the statistical analysis. ***$P < 0.001$ for the group effect, specifically ORAH compared to ERAH. ORAH = 23 patients; ERAH = 16 patients. (**B**) Vasoconstriction in response to PE (1×10^{-6} M) was also assessed in both groups, ORAH ($n = 8$) and ERAH ($n = 9$). Data are presented in (**A**) as mean with standard error of the mean and (**B**) as mean with standard deviation. ACh: acetylcholine; ERAH: endoscopic radial artery harvesting; ORAH: open radial artery harvesting; PE: phenylephrine.

Endothelial integrity of RA assessed by immunohistochemistry

The number of endothelial cells per section were quantified and expressed as ratio to the length of the internal circumference. The endothelial cells/internal circumference ratio was not statistically different between ERAH and ORAH groups (**Fig. 2**).

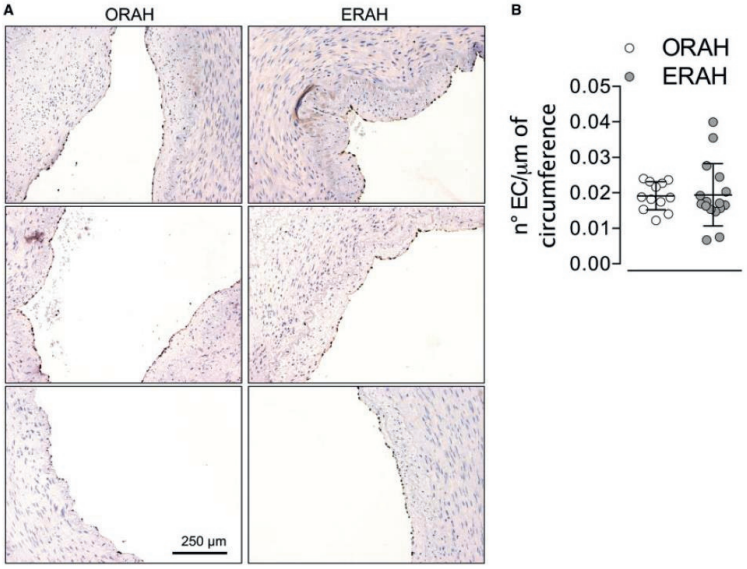


Figure 2: Histological analysis did not evidence endothelial disruption in ERAH versus ORAH. (**A**) Immunohistochemistry for erythroblast transformation specific-related gene, transcriptional factor expressed in the endothelial cells, was performed in 16 ERAH and 12 ORAH formalin-fixed specimens. Representative images erythroblast transformation specific-related gene-staining of the endothelium in both groups. (**B**) Quantitative analysis of the number of the endothelial cells lining the circumference of the radial artery. The data were expressed as ratio of the number of the endothelial cells and the circumference (μm). Data are presented as mean with standard deviation. ERAH: endoscopic radial artery harvesting; ORAH: open radial artery harvesting.

DISCUSSION

This study shows, for the first time that ORAH harvesting is associated with better preservation of the endothelial function compared to the endoscopic harvesting.

Notably, the proximal RA segments were investigated in light of the demonstrated higher vasospastic tendency, greater incidence of string sign, and lower midterm perfect patency rate of the distal RA segments; for these characteristics the proximal RA is indeed considered the segment of choice when performing CABG(20).

In the past, several studies have compared the clinical, angiographic or biologic results of the open and endoscopic techniques for RA harvesting. In a small-randomized trial, Burns et al. reported similar mid-term patency rate for RA grafts harvested using the open and endoscopic techniques (21). Bisleri and colleagues in a propensity score analysis including 470 patients found significantly lower incidence of wound infection, significantly lower pain and better wound healing with the endoscopic technique, in absence of any difference in cardiac-related mortality (22).

In a meta-analysis of 6 randomized controlled and propensity matched studies including 743 patients, Rahouma et al. found that the use of the endoscopic technique was associated with a significantly reduced incidence of wound complications (OR 0.33, 95 CI 0.14-0.77) in absence of significant differences in graft patency and 5-year clinical outcomes (12).

However due to a very low event rate in patients with RA grafts, all these studies, including the meta-analysis, are probably underpowered to detect even moderate differences in outcomes.

A number of studies have previously compared endoscopic versus open harvesting, mostly with regard to saphenous vein graft (23). A post-hoc analysis from the PREVENT IV trial showed higher risk of graft failure following endoscopic versus open harvesting of the saphenous vein (odds ratio, 1.41; 95% confidence interval, 1.16-1.71), although the trial itself was not adequately powered to detect significant differences between the two techniques (24). In the recently published REGROUP trial, 1150 patients were randomized to undergo open versus endoscopic saphenous vein harvesting. Over a median follow-up of 2.78 years, no differences were shown between the 2 groups in terms of the primary composite endpoint of major adverse cardiac events, including death from any cause, nonfatal myocardial infarction, and repeat revascularization (hazard ratio, 1.12; 95% confidence interval, 0.83 to 1.51; P=0.47) (23).

Different studies investigated the endothelial mechanical damage of the endoscopic versus open RA harvesting techniques, by using the histological analysis. In agreement with previous studies (2, 25), histological analysis showed no difference in the endothelial coverage of the RA between ORAH and ERAH. However, it needs to be considered that the histological analysis can only detect mechanical damage of significant degrees, such as the loss of the endothelial cells or disruption of the endothelial layer. The histological approach might not evidence "micro-mechanical damages" that may not physically break the endothelial layer of the RA, but compromise the endothelial function, as shown by the endothelial-dependent vasodilation (**Fig. 1A**). Our study has demonstrated for the first time not only that ORAH better preserves the functional integrity of the endothelium compared to ERAH, but also that assessing the endothelial-dependent vasodilation of RA should be the gold standard approach to evaluate the preservation of the RA endothelium between the two surgical approaches.

Shapira and colleagues, in a small randomized cohort, found no differences between open versus conventional harvesting of RA in the maximal relaxation in response to acetylcholine and nitroglycerin, in RA pre-contracted with U46619, a thromboxane A_2 mimetic (25). It is difficult to compare their findings with ours as the experimental conditions used were different. For instance, RA rings were stored in papaverine before pharmacological studies, which were conducted in presence of indomethacin, cyclooxygenase inhibitor. The resting tension applied was the one necessary to induce the maximal response to 80mmol/L KCL (25), and the RA rings were pre-contracted with U46619 whereas we used PE.

Shapira and colleagues also assessed the expression of adhesion molecules by immunohistochemistry between the two groups and found no differences. Adhesion molecules, such as intercellular adhesion molecule-1 (ICAM1), vascular cadherin adhesion molecule (VCAM) and P-selectin are considered a marker of endothelial activation following pro-inflammatory cytokine stimulation, such as tumor necrosis factor-α (TNF-α), or mechanical stimuli (disturbed shear stress, injury)(26). However, although no images of adhesion molecule staining were included in the manuscript, the expression of adhesion molecules as means to discriminate the mechanical damage or stress on the endothelium imposed by the open versus the endoscopic procedure, might not be a reliable method. Indeed, the narrow time frame between the harvesting and the fixation of the RA specimens, may not be sufficient to allow the expression of adhesion molecules. Most likely, what the authors reported reflected an underline vascular inflammatory condition of the patients undergoing CABG.

Nowicki and coauthors used immunohistochemistry specifically for CD31 and eNOS, to evaluate endothelial integrity of RA grafts after open and endoscopic harvesting. The authors reported significantly higher endothelium preservation using the endoscopic approach. This fairly unique finding is in sharp contrast with almost all the published literature on the comparison of endoscopic vs. open conduit harvesting (including the saphenous vein) and is mainly explained by the surprising 42% endothelial preservation in the open group (a finding that was never reproduced in the other published series) (27). One puzzling aspect of their data is the expression of CD31 and eNOS in all the cells of the intima, media and adventitia. This finding suggests a poor specificity of the immunohistochemical approach employed. It is also important to consider that RA are from patients affected by cardiovascular diseases who have risk factors and therefore there is a generalized disease level of the vasculature, including inflammation, neointima proliferation, and some lipid depositions. In our study, we stained the endothelium with ERG which is a transcriptional factor expressed in the endothelial cells in some pathological conditions and has been reported as a better marker than CD31(18). Indeed, the ERG staining is highly specific and restricted to the endothelium (**Fig. 2A**).

Finally, Medalion and colleagues used organ bath studies to evaluate the differences between the two harvesting techniques and found similar results between the two groups (2). Unfortunately, in this study the concentration-response to ACh was not performed but it was assessed only the vasodilation induced by $1x10^{-6}$ M of ACh, which limits the interpretation of these data. It is noteworthy to notice, that although not statistically significant, the vasodilation induced by ACh $1x10^{-6}$M had a tendency towards higher values in the open compared to the endoscopic RA, suggesting that the concentration-response curve of ACh could have evidenced differences

between the two groups while a single dose of Ach might have overlooked. In this study, hematoxylin and eosin, Masson Trichrome and von Gieson staining revealed that all three arterial layer were preserved, indicating that no major mechanical damages were imparted by the surgical procedure. However, there was no specific staining for the endothelial cells and quantification of the endothelial integrity was not performed, and the histology-based conclusions were rather qualitative.

Of note, it has been suggested that endoscopic saphenous vein graft harvesting is associated with lower patency rates (28), which closely correlates with higher endothelial damage during the endoscopic compared to open procedure. Considering that arteries have spastic characteristics compared to veins, and that RA tends to be more spastic than other arterial graft, it is intuitive that even a small endothelial damage may potentially have a greater impact on the patency of the RA compared to the saphenous vein.

The RA is the most used complementary arterial graft for CABG (1) , and it is a class IB recommendation in the 2018 ESC/EACTS Guidelines in the cases of target vessels with >90% stenosis (29). Due to its muscular wall, the RA is more prone to spasm than any other conduit used for CABG. For this reason, preservation of the functional integrity of the endothelium during harvesting is of paramount importance. It must be reminded that the suboptimal results reported in the initial experiences with RA grafts were mainly attributed to the traumatic preparation technique, and therefore to the high degree of vessel wall damage during the harvesting (30).

CONCLUSIONS

Our data show that the functional integrity of the endothelium of RA is better preserved with ORAH compared to ERAH. We cannot speculate on the effect of the observed differences in the endothelial layer on short and long-term clinical outcomes. It is possible that the compromised endothelial function imposed by the ERAH is a self-limiting effect without any detrimental consequence in terms of graft spasm or failure.

However, confirmation on our results in a larger cohort, including mid and long-term comparison of the patency rate and clinical outcomes of RA grafts obtained using the two harvesting technique, are needed to clarify this important questions.

REFERENCES

1. Shapira OM, Eskenazi BR, Hunter CT, Anter E, Bao Y, Murphy R, Lazar HL, Shemin RJ 2006 Endoscopic versus conventional radial artery harvest--is smaller better? J Card Surg 21:329-335.

2. Medalion B, Tobar A, Yosibash Z, Stamler A, Sharoni E, Snir E, Porat E, Hochhauser E 2008 Vasoreactivity and histology of the radial artery: comparison of open versus endoscopic approaches. Eur J Cardiothorac Surg 34:845-849.

3. Diodato M, Chedrawy EG 2014 Coronary artery bypass graft surgery: the past, present, and future of myocardial revascularisation. Surg Res Pract 2014:726158.

4. Curtis JJ, Stoney WS, Alford WC, Jr., Burrus GR, Thomas CS, Jr. 1975 Intimal hyperplasia. A cause of radial artery aortocoronary bypass graft failure. Ann Thorac Surg 20:628-635.

5. Acar C, Jebara VA, Portoghese M, Beyssen B, Pagny JY, Grare P, Chachques JC, Fabiani JN, Deloche A, Guermonprez JL 1992 Revival of the radial artery for coronary artery bypass grafting. Ann Thorac Surg 54:652-659; discussion 659-660.

6. Schwann TA, Ramia PS, Habib JR, Engoren MC, Bonnell MR, Habib RH 2018 Effectiveness of radial artery-based multiarterial coronary artery bypass grafting: Role of body habitus. J Thorac Cardiovasc Surg 156:43-51 e42.

7. Gaudino M, Benedetto U, Taggart DP 2018 Radial-Artery Grafts for Coronary-Artery Bypass Surgery. N Engl J Med 379:1967-1968.

8. Bisleri G, Giroletti L, Hrapkowicz T, Bertuletti M, Zembala M, Arieti M, Muneretto C 2016 Five-Year Clinical Outcome of Endoscopic Versus Open Radial Artery Harvesting: A Propensity Score Analysis. Ann Thorac Surg 102:1253-1259.

9. Genovesi MH, Torrillo L, Fonger J, Patel N, McCabe JC, Subramanian VA 2001 Endoscopic radial artery harvest: a new approach. Heart Surg Forum 4:223-224; discussion 224-225.

10. Kinlay S, Libby P, Ganz P 2001 Endothelial function and coronary artery disease. Curr Opin Lipidol 12:383-389.

11. Kim G, Jeong Y, Cho Y, Lee J, Cho J 2007 Endoscopic radial artery harvesting may be the procedure of choice for coronary artery bypass grafting. Circ J 71:1511-1515.

12. Rahouma M, Kamel M, Benedetto U, Ohmes LB, Di Franco A, Lau C, Girardi LN, Tranbaugh RF, Barili F, Gaudino M 2017 Endoscopic versus open radial artery harvesting: A meta-analysis of randomized controlled and propensity matched studies. J Card Surg 32:334-341.

13. Connolly MW, Torrillo LD, Stauder MJ, Patel NU, McCabe JC, Loulmet DF, Subramanian VA 2002 Endoscopic radial artery harvesting: results of first 300 patients. Ann Thorac Surg 74:502-505; discussion 506.

14. Lau C, Gaudino M 2018 Open radial artery harvesting. Multimed Man Cardiothorac Surg 2018.

15. Blitz A, Osterday RM, Brodman RF 2013 Harvesting the radial artery. Ann Cardiothorac Surg 2:533-542.

16. He GW, Yang CQ 1998 Characteristics of adrenoceptors in the human radial artery: clinical implications. J Thorac Cardiovasc Surg 115:1136-1141.

17. He GW, Angus JA, Rosenfeldt FL 1988 Reactivity of the canine isolated internal mammary artery, saphenous vein, and coronary artery to constrictor and dilator substances: relevance to coronary bypass graft surgery. J Cardiovasc Pharmacol 12:12-22.

18. Sullivan HC, Edgar MA, Cohen C, Kovach CK, HooKim K, Reid MD 2015 The utility of ERG, CD31 and CD34 in the cytological diagnosis of angiosarcoma: an analysis of 25 cases. J Clin Pathol 68:44-50.

19. McIntire PJ, Zhong E, Patel A, Khani F, D'Alfonso T, Chen Z, Shin SJ, Ginter PS 2018 Hotspot enumeration of CD8+ tumor infiltrating lymphocyte using digital image analysis in triple negative breast Cancer yields consistent results. Hum Pathol.

20. Gaudino M, Nasso G, Canosa C, Glieca F, Salica A, Alessandrini F, Possati G 2005 Midterm angiographic patency and vasoreactive profile of proximal versus distal radial artery grafts. Ann Thorac Surg 79:1987-1989.

21. Burns DJ, Swinamer SA, Fox SA, Romsa J, Vezina W, Akincioglu C, Warrington J, Guo LR, Chu MW, Quantz MA, Novick RJ, Kiaii B 2015 Long-term patency of endoscopically harvested radial arteries: from a randomized controlled trial. Innovations (Phila) 10:77-84.

22. Bisleri G, Muneretto C 2015 Endoscopic saphenous vein and radial harvest: state-of-the-art. Curr Opin Cardiol 30:624-628.

23. Zenati MA, Bhatt DL, Bakaeen FG, Stock EM, Biswas K, Gaziano JM, Kelly RF, Tseng EE, Bitondo J, Quin JA, Almassi GH, Haime M, Hattler B, DeMatt E, Scrymgeour A, Huang GD, Investigators RT 2019 Randomized Trial of Endoscopic or Open Vein-Graft Harvesting for Coronary-Artery Bypass. N Engl J Med 380:132-141.

24. Hess CN, Lopes RD, Gibson CM, Hager R, Wojdyla DM, Englum BR, Mack MJ, Califf RM, Kouchoukos NT, Peterson ED, Alexander JH 2014 Saphenous vein graft failure after coronary artery bypass surgery: insights from PREVENT IV. Circulation 130:1445-1451.

25. Shapira OM, Eskenazi BR, Anter E, Joseph L, Christensen TG, Hunter CT, Lazar HL, Vita JA, Shemin RJ, Keaney JF, Jr. 2006 Endoscopic versus conventional radial artery harvest for coronary artery bypass grafting: functional and histologic assessment of the conduit. J Thorac Cardiovasc Surg 131:388-394.

26. Galkina E, Ley K 2007 Vascular adhesion molecules in atherosclerosis. Arterioscler Thromb Vasc Biol 27:2292-2301.

27. Nowicki M, Misterski M, Malinska A, Perek B, Ostalska-Nowicka D, Jemielity M, Witkiewicz W, Zabel M 2011 Endothelial integrity of radial artery grafts harvested by minimally invasive surgery--immunohistochemical studies of CD31 and endothelial nitric oxide synthase expressions: a randomized controlled trial. Eur J Cardiothorac Surg 39:471-477.

28. Lopes RD, Hafley GE, Allen KB, Ferguson TB, Peterson ED, Harrington RA, Mehta RH, Gibson CM, Mack MJ, Kouchoukos NT, Califf RM, Alexander JH 2009 Endoscopic versus open vein-graft harvesting in coronary-artery bypass surgery. N Engl J Med 361:235-244.

29. Sousa-Uva M, Neumann FJ, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO, Group ESCSD 2018 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur J Cardiothorac Surg.

30. Gaudino M, Crea F, Cammertoni F, Massetti M 2015 The radial artery: a forgotten conduit. Ann Thorac Surg 99:1479-1485.

CHAPTER 3

Radial Artery as a Coronary Artery Bypass Conduit: 20-Year Results

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J Am Coll Cardiol. 2016;9;68(6):603-610.

ABSTRACT

Background: There is a lack of evidence for the choice of the second conduit in coronary surgery. The radial artery (RA) is a possible option, but few data on very long-term outcomes exist.

Objective: We describe 20-year results of RA grafts used for coronary artery bypass grafting and the effects of RA removal on forearm circulation.

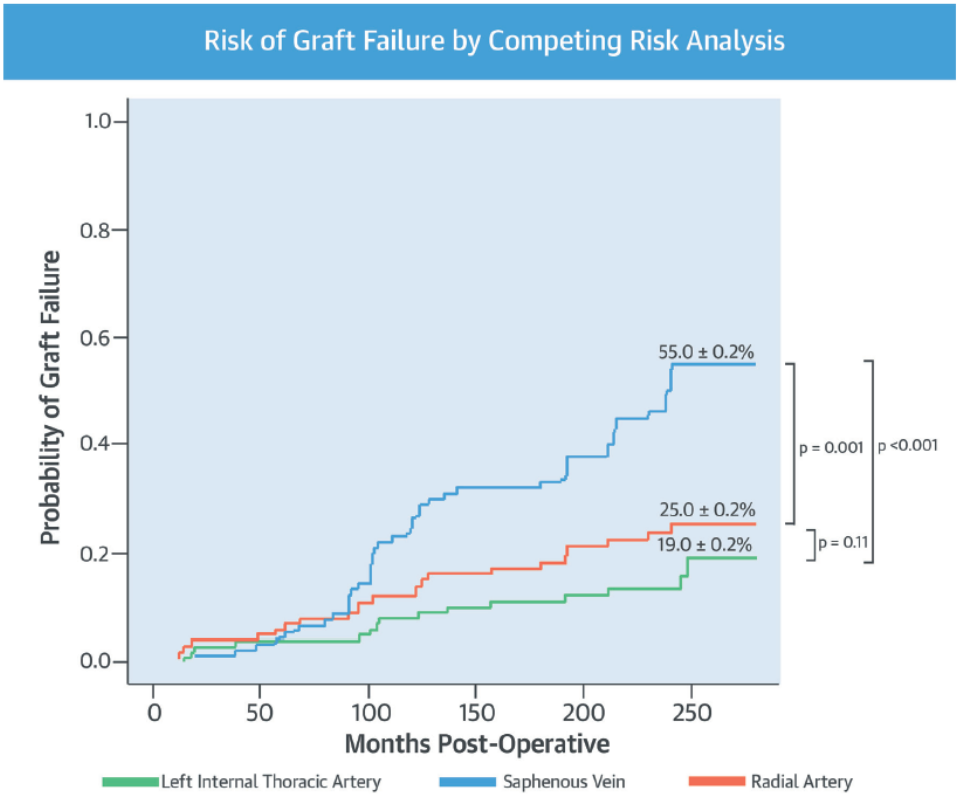
Methods: We report the results of the prospective 20-year follow-up of the first 100 consecutive patients who received the RA as a coronary bypass conduit at our institution.

Results: Follow-up was 100% complete. There were 64 deaths, 23 (35.9%) from cardiovascular causes. Kaplan-Meier 20-year survival was 31%. Thirty-three of 36 survivors (91.6%) underwent RA graft control at a mean of 19.0 ± 2.5 years after surgery. The RA was found to be patent in 24 cases (84.8% patency). In the overall population, probability of graft failure at 20 years was 19.0% ± 0.2% for the left internal thoracic artery (ITA), 25.0% ± 0.2% for the RA, and 55.0% ± 0.2% for the saphenous vein (SV) ($p = 0.002$ for RA vs. SV, 0.11 for RA vs. ITA, and <0.001 for ITA vs. SV). Target vessel stenosis >90%, but not location of distal anastomosis significantly influenced long-term RA graft patency. No patients reported hand or forearm symptoms. The ulnar artery diameter was increased in the operated arm (2.44 ± 0.43 mm vs. 2.01 mm ± 0.47 mm; $p < 0.05$) and correlated with the peak systolic velocity of the second palmar digital artery (Pearson's coefficient 0.621; $p < 0.05$).

Conclusion: The 20-year patency rate of RA grafts is good, and not inferior to the ITA, especially

when the conduit is used to graft a vessel with >90% stenosis. RA harvesting does not lead to hand or forearm symptoms, even at a very long-term follow-up.

CENTRAL ILLUSTRATION **Radial Artery as a Coronary Artery Bypass Conduit**



Gaudino, M. et al. J Am Coll Cardiol. 2016;68(6):603-10.

Risk of graft failure by competing risk analysis for the radial artery, the left internal thoracic artery, and the saphenous vein. In the very long term, the angiographic outcome of radial artery grafts is similar to that of internal thoracic artery grafts.

INTRODUCTION

The radial artery (RA) is the conduit most recently introduced in coronary artery bypass graft (CABG) surgery, after the great saphenous vein (SV) and the internal thoracic artery (ITA) (1). To date, there is evidence that the conduit has a postoperative patency rate higher than the SV and equivalent to the right ITA, and its use can lead to substantial clinical advantages in selected groups of patients (2). However, the RA is relatively underused. In a recent report from the Society of Thoracic Surgery Adult Cardiac Surgery Database, the RA was used in <6% of all primary isolated CABGs in the United States in the 2000 to 2009 period (3).

One of the reasons for its limited adoption is probably the fact that, up to now, only limited information exists on very long-term results of using the RA, with the great majority of the studies reporting a mean follow-up of <10 years. In addition, previous reports (including ours) have expressed concerns about possible harm to the forearm circulation after RA harvesting (4). This has possibly further limited adoption of this conduit by the surgical community.

In order to contribute to the diffusion of use of the RA as a coronary artery bypass conduit, we herein describe the results of the 20-year prospective follow-up of our initial cohort of 100 patients who received a RA graft for myocardial revascularization.

METHODS

The use of the RA as a coronary artery bypass conduit was started prospectively at the Catholic University of Rome in January 1993, upon approval by the local Ethics Committee (5). For the first 100 consecutive patients, we adopted a very strict follow-up protocol that included:

- Yearly clinical examination
- Yearly stress test or stress myocardial scintigraphy
- 1-, 5- and 10-year angiographic control studies
- 1-, 5- and 10-year echo Doppler evaluation of forearm circulation.

Results of the 1-5- and 10-year clinical and angiographic follow-ups, as well as detailed descriptions of the modifications of the forearm circulation after RA removal, and of the effects of the calcium-channel blocker therapy and morphofunctional remodeling of the artery after implantation in the coronary circulation were previously published (4-10). In this report, we describe the 20-year clinical, angiographic, and echo Doppler results for this cohort of patients. *Patient Population and Surgical Technique*

TABLE 1 Pre-Operative and Intraoperative Characteristics

Male/female ratio	72/28
Mean age, yrs	63.7 ± 6.6
Cardiovascular risk factors	
Diabetes	20
Smoking	56
Dyslipidemia	51
Hypertension	44
Previous myocardial infarction	60
Number of diseased vessels	2.8 ± 0.4
Mean ejection fraction	0.62 ± 0.15
Number of anastomoses per patient	2.9 ± 0.1

Values are n or mean ± SD.

Preoperative clinical details are summarized in **Table 1.**

Details of our surgical technique have been published (5). Briefly, the same surgical team performed all operations, using cardiopulmonary bypass and cardioplegic arrest. The left ITA was usually used to graft the left anterior descending artery (LAD), whereas the RA was grafted to the

second target vessel. The RA target vessel was a branch of the circumflex artery in 53 cases, a branch of the right coronary artery in 36, and a diagonal in 11. SV grafts usually completed the revascularization, whereas the right ITA and the gastroepiploic artery were used in a minority of cases. The RA was anastomosed to the ascending aorta in 85 patients, and to the left ITA in the remaining patients.

Since beginning our study, we adopted systematic Doppler or echo Doppler assessment of the adequacy of collateral ulnar circulation before RA removal, according to a published method (10). The RA was always harvested from the nondominant arm, and bilateral RA harvesting was never performed.

Long-term calcium-channel blocker therapy (diltiazem, 120 mg/day) was prescribed for all patients for the first postoperative year. After the results of 2 prospective randomized trials by our group (8,9), calcium-channel blocker therapy was abandoned, and is not currently part our routine.

Each patient was followed up regularly at our institution 6 months after surgery and every year thereafter. At each time interval, clinical examination and echo Doppler evaluation of the forearm were performed, and the results of surface electrocardiography, stress myocardial scintigraphy, 24-h Holter monitoring, and transthoracic echocardiography were reviewed. In the case of death during the follow-up period, all medical and autopsy reports were reviewed for attribution of the cause. For out-of-hospital fatalities, the death certificate was requested and reviewed. Death was considered cardiac in origin when it was preceded by evidence of myocardial ischemia, heart failure, or arrhythmia.

Angiographic control or (in recent years) computed tomography (CT)-angiographic

assessment was proposed to all patients at the early (1 year), midterm (5-year), long-term (10-year), and very long-term (20-year) follow-up visits, and at any time when there was instrumental evidence of inducible ischemia.

Two experienced observers independently graded angiographies using a previously described 4-grade angiographic scale (perfectly patent, patent with irregularities, stringed, occluded) (6).

Statistical Analysis

Data are expressed as mean ± standard deviation (SD). Statistical analysis was performed with an unpaired, 2-tailed Student *t* test for means or the chi-square test for categorical variables. Competing risks analysis was used to estimate the cumulative incidence function for late graft occlusion for the 3 different conduits (10). In this analysis, patients who died from causes that could possibly be related to acute graft occlusion (myocardial infarction, arrhythmias) without perimortem angiographic verification of graft patency were considered as having all grafts occluded. Subgroup analysis was conducted according to the RA target (circumflex or right coronary artery) and the RA target stenosis degree (≥90% vs. <90%).

Adjustment for baseline characteristics was not required, as each of the 3 conduits analyzed was used in all patients, except for 9 subjects who did not receive SV grafts. All analyses were conducted with R (11). Spearman's coefficient correlation was used to explore the association between morphological and hemodynamic measures at echo Doppler evaluation.

RESULTS

Clinical results

Follow-up was 100% complete, and the mean follow-up time was 20.8 ± 1.5 years.

During this period, 64 of 100 patients died (64%). The cause of death was noncardiac in 41 cases and cardiac in 23 (35.9%). The causes of cardiac and noncardiac death are summarized in **Table 2.** The Kaplan-Meier 20-year survival curve is shown in **Figure 1.** During the follow-up, clinical or instrumental evidence of myocardial ischemia occurred in 79 patients; thus, the 20-year ischemia-free survival was 21%.

TABLE 2 Causes of Follow-Up Deaths

	First Decade of Follow-Up	Second Decade of Follow-Up
Cardiac deaths	2	21
MI	1	5
CHF	1	11
Arrhythmia	0	4
Re-CABG	0	1
Noncardiac deaths	4	37
Cancer	4	11
Stroke	0	10
Accident	0	4
Suicide	0	1
Aortic aneurysm	0	5
Respiratory failure	0	4
Pulmonary embolism	0	2

Values are n.
CHF = congestive heart failure; MI = myocardial infarction; Re-CABG = reoperative coronary artery bypass grafting.

20-year results

Thirty-three of the 36 survivors (91.6%) underwent angiographic (30 patients) or angio- CT (3 cases) control studies at a mean of 19.0 ± 2.5 years after surgery. The main angiographic results are reported in **Table 3.**

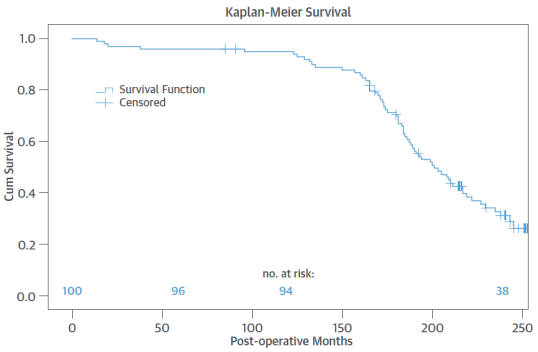
TABLE 3 20-Year Angiographic Results*

	LITA (n = 33)	RA (n = 33)	RITA (n = 4)	RGEA (n = 8)	GSV (n = 31)
Perfectly patent	31	24	3	5	8
Patent with irregularities	0	4	0	0	6
String	0	1	0	1	0
Occluded	2	4	1	2	17
Patency rate, %	93.9	84.8			45.1
Perfect patency rate, %	93.9	72.7			25.8

Values are n or %. *19.0 ± 2.5 years. p = 0.23 for comparison between RA and ITA, and p < 0.0001 for comparisons between ITA and GSV and between RA and GSV.
GSV = great saphenous vein; LITA = left internal thoracic artery; RA = radial artery; RGEA = right gastroepiploic artery; RITA = right internal thoracic artery.

In these 33 patients, the very long-term patency and perfect patency rates were, respectively, 93.9% and 93.9% for the left ITA, 84.8% and 72.7% for the RA, and 45.1% and 25.8% for the SV (p = 0.23 for the left ITA vs. RA comparison and

FIGURE 1 Clinical Follow-Up: Long-Term Survival Curve Using the Kaplan-Meier Method



	12 Months (95% CI)	60 Months (95% CI)	120 Months (95% CI)	240 Months (95% CI)
Survival	100%	96.0% (92.1-99.9%)	94.0% (89.3-98.7%)	43.8% (33.6-54.0%)

Follow-up was 100% complete, and the mean follow-up time was 20.8 ± 1.5 years. During follow-up, 64 patients died, mostly from noncardiac causes. Estimated 10- and 20-year survival were 94% and 43.8%, respectively. CI = confidence interval.

< 0.001 for both the ITA vs. SV and RA vs. SV comparisons).

The great majority (4 of 5 = 80%) of the cases of RA occlusion or string sign occurred in patients in whom the artery was anastomosed to coronary arteries with stenosis ≤90%. No correlation was found between the location of the distal anastomosis (circumflex or right coronary artery) and the very long-term angiographic status (**Table 4**).

TABLE 4 Long-Term Radial Artery Angiographic Results in Relation to the Location of Target Vessel

	Patent	Occluded
Left anterior descending	0	0
Diagonal	4	0
Circumflex	16 (84.2)	3
Right coronary artery	8 (80.0)	2

Values are n or n (%).

Table 5 compares the 10- and 20-year angiographic studies in the 30 patients who underwent both angiographies. Two RA grafts that were perfectly patent at 10 years were occluded at 20 years, and 2 others developed some irregularity between the 2 controls, leading to a drop in the patency and perfect patency rates, from 93.3% and 86.6% at 10 years to 86.6% and 76.6%, respectively, at 20 years.

TABLE 5 Comparison of Radial Artery Graft Status Between the 10- and 20-Year Angiographic Controls in the 30 Patients Who Underwent Both Studies

	10-Year Angiographic Control		20-Year Angiographic Control
Perfectly patent	26	2	22
Patent with irregularities	2	2	4
String	1		1
Occluded	1		3
Patency rate	93.3		86.6
Perfect patency rate	86.6		73.3

Values are n or %.

Overall experience

During the 20 years of follow-up, 98 of the 100 patients underwent at least 1 angiographic control study: 9 patients underwent 1, 49 underwent 2, and the remaining 40 underwent more than 2. The cumulative incidence of graft occlusion at 20 years was 19.0 ± 0.2% for the left ITA, 25.0 ± 0.2% for the RA and 55.0 ± 0.2% for the SV (p = 0.002 for RA vs. SV, 0.11 for RA vs. ITA and <0.001 for ITA vs. SV; **Central Illustration**).

As detailed in the Methods section, in this analysis, patients who died from causes that may have been related to acute graft occlusion were considered as having all grafts occluded even in the absence of perimortem angiography. Graft occlusion was verified angiographically in 18 patients, and inferred from the clinical course in 8 cases.

The severity of target vessel stenosis had a major influence on graft patency. When the target vessel stenosis was ≥90%, the patency of the RA was similar to that of the left ITA, 25.8% for the SV (p = 0.23 for the left ITA vs. RA comparison and < 0.001 for both the ITA vs. SV and RA vs. SV comparisons).

The great majority (4 of 5 = 80%) of the cases of RA occlusion or string sign occurred in patients in whom the artery was anastomosed to coronary arteries with stenosis ≤90%. No correlation was found between the location of the distal anastomosis (circumflex or right coronary artery) and the very long-term angiographic status (**Table 4**).

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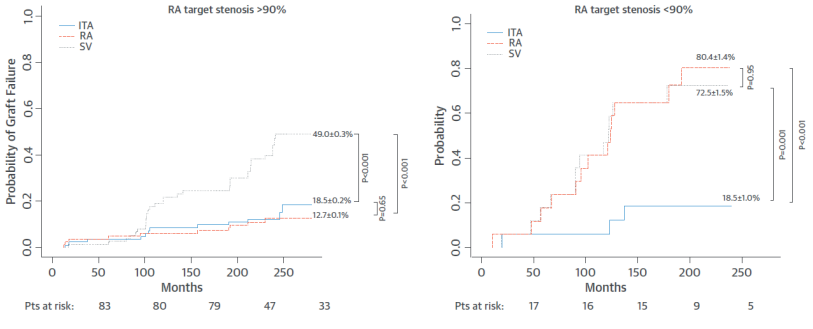
FIGURE 2 RA Status in Relation to Target Vessel Stenosis



Risk of graft failure by competing risk analysis for RA grafts anastomosed to target vessels with >90% and <90% stenosis. The severity of target vessel stenosis has a major impact on RA graft status. For target vessel stenosis >90%, the patency of the RA was similar to that of the ITA, whereas for <90% stenosis, the angiographic outcome was more similar to that of the SV (modified chi-square test). ITA = internal thoracic artery; RA = radial artery; SV = saphenous vein.

As detailed in the Methods section, in this analysis, patients who died from causes that may have been related to acute graft occlusion were considered as having all grafts occluded even in the absence of perimortem angiography. Graft occlusion was verified angiographically in 18 patients, and inferred from the clinical course in 8 cases.

The severity of target vessel stenosis had a major influence on graft patency. When the target vessel stenosis was ≥90%, the patency of the RA was similar to that of the left ITA, whereas for less severe stenosis, the angiographic outcome was more similar to that of the SV (**Figure 2**). The location of the distal anastomosis on the circumflex or right coronary system did not influence RA patency (**Figure 3**).

FIGURE 3 RA Patency Rate, According to Location of the Distal Anastomosis

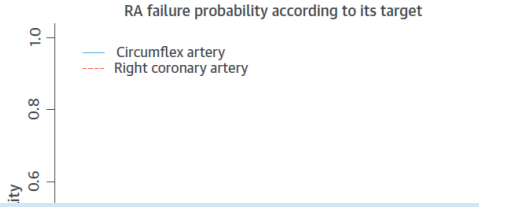


TABLE 6 Echo Doppler Comparison of the Operated and Control Arms

	Operated Arm	Control Arm	p Value
UA diameter, mm	2.44 ± 0.43	2.01 ± 0.47	<0.05
UA IMT, mm	0.47 ± 0.19	0.40 ± 0.16	0.42
UA PSV, cm/s	92.6 ± 27.9	86.0 ± 28.0	0.58
UA resistance index	0.87 ± 0.1	0.92 ± 0.08	0.19
UA pulsatility index	8.07 ± 10.11	6.31 ± 5.40	0.61
Second PPDA PSV, cm/s	38.56 ± 11.53	50.13 ± 18.79	0.09
Fourth PPDA PSV, cm/s	38.90 ± 18.09	36.82 ± 21.83	0.81
UA atherosclerosis	3	1	0.53

Values are mean ± SD or n.
IMT = intima-media thickness; PPDA = proper palmar digital arteries; PSV = peaks systolic velocity; UA = ulnar artery.

cumflex not in- s anas- tomosed to the circumflex or right coronary artery had similar patency rates. Abbreviation as in Figure 2.

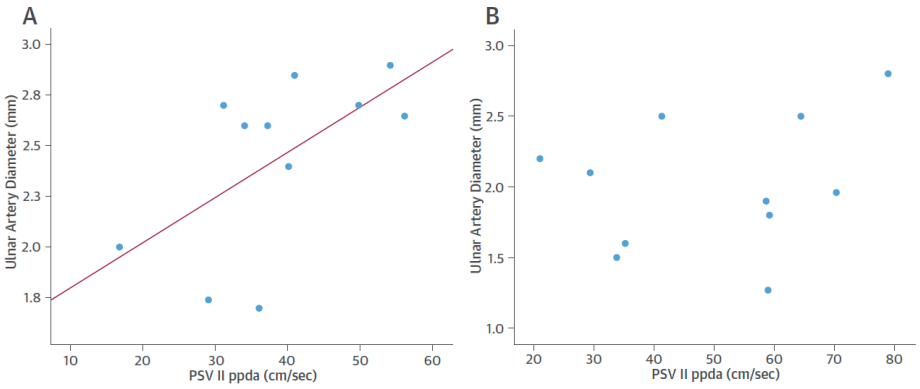
P=0.52

Evaluation of forearm circulation

None of the patients had signs of symptoms of hand ischemia during the postoperative follow-up. Twenty-five patients underwent echo Doppler evaluation of the forearm circulation at a mean interval of 17.6 ± 2.1 years from surgery. In the operated forearm, there was a significant increase in the diameter of the ulnar artery (2.44 ± 0.43 mm vs. 2.01 ± 0.47 mm; $p < 0.05$). All others flow parameters were similar between the operated and control arms (**Table 6**). In the operated arm, there was a significant correlation between the

diameter of the ulnar artery and the PSV of the second proper palmar digital artery (Spearman's coefficient 0.621; p = 0.41, **Figure 4A**). This correlation was absent in the control arm (**Figure 4B**).

FIGURE 4 Long-Term Effect of RA Removal on the Forearm Circulation



Correlation between ulnar artery diameter and PSV of the II PPDA in the operated **(A)** and control **(B)** forearms. In the long term, after harvesting of the RA, the ulnar collateral circulation provides collateral flow to the arm. In the operated arm (but not in the control arm), there is a significant correlation between the ulnar artery diameter and the PSV of the II PPDA (Spearman coefficient: 0.621; p = 0.41). II PPDA = second proper palmar digital artery; PSV = peak systolic velocity; other abbreviation as in Figure 2.

DISCUSSION

Since the reintroduction of the RA as a conduit in coronary surgery in the early 1990s (1), its morphofunctional features, biological properties, and vasoreactive profile of RA grafts have been mostly elucidated (11). The early and intermediate angiographic patency rates have been published (2), and the Radial Artery Patency and Clinical Outcome trial should be reporting its 10-year angiographic and clinical results this year. There is growing evidence that the patency rate of the RA is better than that of the SV (2). The RA contends with the right ITA for the role of the second artery for CABG, and is probably a better choice in patients at high risk of sternal complications (2,12).

Despite that, the RA is markedly underutilized. In a recent report from the Society of Thoracic Surgeons Adult Cardiac Surgery Database, this conduit was used in slightly more than 5% of all primary isolated CABG procedures performed in the United States from 2000 to 2009 (3). Possible reasons for this underuse are the lack of very long-term data and concerns of regarding accelerated atherosclerosis of the ulnar artery after RA removal (4).

To date, only 1 group has reported a RA follow-up of >10 years. Acar et al. (who rediscovered the RA in the 1990s) reported their 20-year experience in a cohort of 563 patients. At a 9.2-year mean follow-up, freedom from overall and cardiovascular death was 80.3% and 92.7%, respectively. Angiographic follow-up was obtained in 351 patients at a mean interval of 7.0 years from surgery, and the RA patency rate was 87.9%. In patients with the longest follow- up interval, the RA patency rate was 81.4% at 13.1 years (13).

In our series, the RA patency rate in the group of patients who reached the 20-year follow-up was 84.8%, with a perfect patency rate of 72.7%. The status of the graft remained substantially

stable in the very long term, with only 2 occlusions occurring between the 10- and the 20-year control studies in the group of patients who underwent both (**Table 5**). Overall, the long-term patency rate of the RA was not statistically different than that of the gold-standard ITA.

Confirming previous observations (14), we found a strong correlation between the severity of the target vessel stenosis and the RA patency. When the RA was used to revascularize target vessels with ≥90% stenosis, the patency rate of the conduit was similar to that of the left ITA, whereas for a lower degree of coronary stenosis, the angiographic outcome was more similar to that of the SV (**Figure 2**).

As in our previous reports (2,6), the location of the target vessel did not influence the graft outcome. In fact, the circumflex and right coronary artery distributions had similar RA graft patency rates (**Figure 3**).

The echo Doppler evaluation of the forearm circulation testified to the development of an adequate ulnar collateral circulation several years after surgery. The great majority of flow parameters were similar between the 2 forearms, and there was a clear correlation between the diameter of the ulnar artery and the PSV of the second proper palmar digital artery in the operated site. Most importantly, no patient had signs or symptoms of hand ischemia during the 20-year follow-up (and this is common to our overall experience in more than 1,600 RA cases). The small echo Doppler differences reported between the operated and control arms did not have a clinical correlate and, at this point of the follow-up, are unlikely to ever have any.

On this basis, previous concerns about possible accelerated atherosclerosis in the ulnar artery of the operated forearm (4) seem unsubstantiated. This is an observational prospective

study, and has obvious limitations related to the sample size and lack of a control group.

However, the main strength of this study is the 100% complete prospective 20-year clinical and serial angiographic follow-up.

In conclusion, the 20-year angiographic outcome of RA conduits used for CABG is not inferior to that of the gold standard left ITA. The status of the artery remains stable during the very long-term follow-up. The location of the target vessel does not influence graft status, whereas the severity of the coronary stenosis is a major determinant of patency. Finally, after harvesting of the RA, the ulnar collateral circulation provides sufficient flow to the arm and clinically evident forearm or hand ischemia never occurs, even at extended follow-up.

References

1. Acar C, Jebara VA, Portoghese M, et al. Revival of the radial artery for coronary artery bypass grafting. Ann Thorac Surg 1992;54:652-9; discussion 659-60.

2. Gaudino M, Crea F, Cammertoni F, et al. The radial artery: a forgotten conduit. Ann Thorac Surg 2015;99:1479-85.

3. ElBardissi AW, Aranki SF, Sheng S, et al. Trends in isolated coronary artery bypass grafting: an analysis of the Society of Thoracic Surgeons adult cardiac surgery database. J Thorac Cardiovasc Surg 2012;143:273-81.

4. Gaudino M, Serricchio M, Tondi P, et al. Chronic compensatory increase in ulnar flow and accelerated atherosclerosis after radial artery removal for coronary artery bypass. J Thorac Cardiovasc Surg 2005;130:9-12.

5. Manasse E, Sperti G, Suma H, et al. Use of the radial artery for myocardial revascularization. Ann Thorac Surg 1996;62:1076-82; discussion 1082-3.

6. Possati G, Gaudino M, Prati F, et al. Long-term results of the radial artery used for myocardial revascularization. Circulation 2003;108:1350-4.

7. Gaudino M, Prati F, Caradonna E, et al. Implantation in the coronary circulation induces morphofunctional transformation of radial artery grafts from muscular to elastomuscular. Circulation 2005;112:I208–11.

8. Gaudino M, Glieca F Luciani N, et al. Clinical and angiographic effects of chronic calcium

channel blocker therapy continued beyond first postoperative year in patients with radial artery grafts: results of a prospective randomized investigation. Circulation 2001;104:I64-7

9. Gaudino M, Luciani N, Nasso G, et al. Is postoperative calcium channel blocker therapy needed in patients with radial artery grafts? J Thorac Cardiovasc Surg 2005;129:532-5.

10. Gray B. cmprsk: Subdistribution Analysis of Competing Risks. R package version 2.2-7. 2014. Available at: https://cran.r-project.org/web/packages/cmprsk/index.html. Accessed May 27, 2016.

11. R Core Team. R: A language and environment for statistical computing. 2015. R Foundation for Statistical Computing, Vienna, Austria. Available at: https://www.R-project.org/. Accessed May 27, 2016.

12. Pola P, Serricchio M, Flore R, et al. Safe removal of the radial artery for myocardial revascularization: a Doppler study to prevent ischemic complications to the hand. J Thorac Cardiovasc Surg 1996;112:737-44.

13. Gaudino M, Crea F, Cammertoni F, et al. Morpho-functional features of the radial artery: implications for use as a coronary bypass conduit. Ann Thorac Surg 2014;98:1875-9.

14. Gaudino M, Taggart D, Suma H, et al. The choice of conduits in coronary artery bypass surgery. J Am Coll Cardiol 2015;66:1729-37.

15. Achouh P, Isselmou KO, Boutekadjirt R, et al. Reappraisal of a 20-year experience with the radial artery as a conduit for coronary bypass grafting. Eur J Cardiothorac Surg 2012;41:87- 92.

16. Tatoulis J, Buxton BF, Fuller JA, et al. Long-term patency of 1108 radial arterial-coronary angiograms over 10 years. Ann Thorac Surg 2009;88:23-9; discussion 29-30.

CHAPTER 4

Radial-artery or saphenous-vein grafts in coronary-artery bypass surgery

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N Engl J Med. 2018;31;378(22):2069-2077.

ABSTRACT

Background: Use of radial-artery grafts for coronary-artery bypass grafting (CABG) may improve postoperative outcomes as compared with use of saphenous-vein grafts. However, randomized controlled trials comparing radial-artery grafts and saphenous-vein grafts have been individually underpowered to detect differences in clinical outcome. We performed a patient-level meta-analysis of randomized controlled trials comparing radial-artery grafts and saphenous-vein grafts for CABG.

Methods: Six trials were identified. The primary outcome was a composite of death, myocardial infarction and repeat revascularization. The secondary outcome was graft patency at follow-up angiography. Mixed-effect Cox regression models were used to estimate the treatment effect on outcomes.

Results: A total of 1036 patients were included in the analysis (534 patients with radial-artery grafts and 502 patients with saphenous-vein grafts). After a mean follow-up time of 60±30 months, use of radial-artery grafts was associated with a significantly lower incidence of adverse cardiac events (HR 0.67; 95%CI 0.49-0.90; P=0.01). At follow-up angiography (mean follow-up 50±30 months), use of radial-artery grafts was associated with a significantly lower risk of occlusion (HR 0.44; 95%CI 0.28-0.70; P<0.001). Use of radial-artery grafts was associated with a nominally lower incidence of myocardial infarction (HR 0.72; 95%CI 0.53-0.99; P=0.04) and a lower incidence of repeat revascularization (HR 0.50; 95%CI 0.40-0.63; P<0.001) but not a lower incidence of all-cause death (HR 0.90; 95%CI 0.59-1.41; P=0.68).

Conclusions: In comparison to use of saphenous-vein grafts, use of radial-artery grafts for CABG resulted in a lower rate of adverse cardiac events and a higher patency rate at 5-year follow-up.

INTRODUCTION

Despite the recommendations of the current guidelines, the use of multiple arterial grafts for coronary-artery bypass grafting (CABG) has not been widely adopted by the surgical community, and the great majority of patients in North America and Europe currently receive saphenous-vein grafts in addition to an internal-thoracic-artery graft to the left anterior descending coronary artery.(1) Surgical resistance to the use of multiple arterial grafts can be explained, at least in part, by the fact that the clinical benefit of additional arterial grafts reported in observational studies has not been confirmed in randomized clinical trials.(2) While several trials have demonstrated superior angiographic patency rates with radial-artery grafts over saphenous-vein grafts,(2) these studies were individually underpowered to detect differences in clinical events. Therefore, whether use of radial-artery grafts can improve clinical outcomes remains unknown. To overcome the limitations of individual studies in detecting differences in clinical outcomes, a patient-level meta-analysis of randomized trials comparing radial-artery grafts vs saphenous-vein grafts for CABG was performed.

METHODS

The RADIAL (Radial Artery Database International Alliance) project was initiated in March 2015 by a group of clinical investigators conducting trials and research related to radial-artery grafting. One key aim of RADIAL was to combine individual patient-level data from individual trials comparing use of the radial artery and other conduits for CABG to provide the basis for meta-analytic studies. The full list of the RADIAL investigators and the list of the detailed individual contributions to this study can be found in the **Supplementary Appendix**. The project was funded by the Department of Cardiothoracic Surgery of Weill Cornell Medicine. The funder had no role in the design or conduct of the study; in the collection, analysis, or interpretation of the data; or in the writing of the manuscript or the decision to submit it for publication.

Search strategy and study selection

The present analysis includes only randomized trials comparing the long-term (≥2 years) outcomes for patients randomized to receive either radial-artery grafting or saphenous-vein grafting to supplement left internal-thoracic-artery grafting during isolated CABG surgery. The full search strategy is listed in the **Supplementary Appendix**.

After identification of trials for inclusion, the RADIAL investigators compared trial protocols and publications from each trial and then provided a detailed specification of core minimum data requirements to each trial team to prepare the data for pooling. After receipt, data were checked for missing values and for consistency. Data queries were resolved through direct consultation with each trial team before analysis. The most up-to-date follow-up information was also

requested from the trial investigators. Renal insufficiency was defined as preoperative serum creatinine >1.5 mg/dl.(3)

The design of this analysis was published a priori on the International Prospective Register of Systematic Reviews (CRD42017077562) and the present report was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.

Outcomes

The primary outcome was a composite of major adverse cardiac events during follow-up, including death, myocardial infarction or repeat revascularization. Each item of the composite outcome was also analyzed individually. Pre-specified subgroup analyses for the primary outcome were performed by age, gender, presence of diabetes, prior myocardial infarction, left ventricular ejection fraction <35%, preoperative renal insufficiency, and radial-artery graft target vessel. The secondary outcome was graft patency at protocol-defined follow-up angiography. Patency rate was graded according to the Fitzgibbon classification, (4) which grades graft patency as A (widely patent), B (flow limited), or O (occluded). For the purposes of our analysis, Grades A and B were considered patent and grade O occluded.

Statistical analysis

Baseline categorical variables were reported as counts and percentages and compared with a conditional regression analysis stratified by trial. Baseline continuous variables were reported as mean and standard deviation and compared with a 2-way analysis of variance

stratified by trial. Outcomes were reported as raw numbers and linearized event rates per 1,000 patient-years to account for different follow-up durations across trials. Cumulative incidences were determined and graphically presented.

The primary analysis for clinical and angiographic end points was performed based on the intention-to-treat principle using a 1-stage approach. Patient data were combined in a single dataset and fitted in a Cox regression model stratified by trial, using trial identifiers as random effects. A competing-risk framework was used to compute pseudo hazard ratios (HR) for myocardial infarction and repeat revascularization.(5) Treatment effect was presented as HR and 95% confidence interval (CI). The proportional-hazard assumptions were verified using Schoenfeld residuals. Multivariable Cox models were implemented to investigate independent risk factors for graft occlusion including baseline characteristics and the chronic use of agents to prevent arterial-graft spasm.

For the primary end point, subgroup and interaction term analyses were used to investigate the pre-specified possible effect modifiers. A non-linear relationship between age and treatment effect was investigated by comparing model fitting using age as a linear term vs. as a spline function with an increasing number of knots. A potential age cut-off for the loss of benefit with the radial artery was evaluated with nonparametric bootstrap pointwise confidence limits computation across a range of ages.

As a sensitivity analysis, the treatment effect for the primary end point was re-estimated using an as-treated analysis and a 2-step approach. The as-treated analysis was implemented using the conduit received as the treatment indicator, thus accounting for crossovers. For the 2-stage

approach, individual participant data were first analyzed in each separate study independently with Cox regression. This step produced aggregate data for each study with a mean treatment effect estimate and its standard error. Aggregate data were then synthesized in the second step using the generic inverse variance method and a fixed or random effects model in the case where I^2 was lower or higher than 50%, respectively. An influence analysis was used to assess the influence of individual studies on the final estimate. Publication bias was evaluated by means of funnel plot and linear regression test for asymmetry.

In a supplementary analysis, a generalized mixed-effect logistic regression using the original trials as a random effect was performed to assess the effect of conduit selection on the risk of perioperative stroke. A mixed-effect Cox regression was used to investigate potential risk factors for radial-artery graft occlusion and saphenous-vein graft occlusion (**Supplementary Appendix**). The saphenous-vein graft group was used as the reference in all analyses. All P values are two-sided. P values <0.05 were considered significant, without correction for multiple testing. Statistical analyses were performed using R 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study selection

From 612 titles, 38 pertinent studies were included for full-text review. After review, 32 studies were excluded because they did not meet the inclusion criteria. A total of six randomized trials were selected for the present analysis (6-11) including a total of 1305 patients with 5266 patient-years of follow-up. Further details and the PRISMA flowchart and checklist are shown in **Supplementary Appendix Figure S1** and **Table S1**. An overview of the included studies is reported in **Table 1**. The principal investigators of the six individual studies were contacted and all agreed to provide individual patient data. The principal investigators of the Stand-in-Y trial also provided updated follow-up data.

Table 1. Trials Included in the Combined Analysis.*

Trial	Years of Enrollment	Country or Countries	No. of Patients	Radial-Artery Group	Saphenous-Vein Group	Radial-Artery Grafts to CCA	Mean Age	Male Sex	Clinical Follow-up Duration	Crossover	Follow-up Angiography	Median Time to Angiography
				no. of patients		%	*yr*	%	*yr*	%	*no. of patients*	*yr*
Petrovic et al.[10]†	2001–2003	Serbia	200	100	100	83	56.4±6.1	72.5	8	0	47	6
RAPCO[9]	1997–2004	Australia	225	113	112	100	72.8±4.7	80.9	5	3.6	84	5
RAPS[11]‡	1996–2001	Canada, New Zealand	269	269	269	49.8	60.4±8.0	84.8	8.4	2.6	269	7.7±1.5
RSVP[6]	1998–2000	United Kingdom	142	82	60	100	58.5±6.7	96.5	5.5	0	122	5.5
Stand-in-Y[7]	2003–2006	Italy	409	204	205	47	70.3±7.7	57.0	3.3	4.2	405	3.5
Yoo and colleagues[8]	2008–2009	Korea	60	35	25	98	75.7±5.4	50.0	5.8	0	41	0.7

* Plus–minus values are means ±SD. CCA denotes circumflex coronary artery, RAPCO Radial Artery Patency and Clinical Outcomes, and RSVP Radial Artery versus Saphenous Vein Patency.
† The trial by Petrovic et al. is not included in the analyses of graft occlusion.
‡ The Radial Artery Patency Study (RAPS) was not included in the analysis of clinical outcomes or in the main analysis of graft occlusion. Each patient in the trial received both a radial-artery graft and a saphenous-vein graft, and randomization was performed for the target coronary territory. The subset of 269 patients in this trial who underwent late angiography were included in the sensitivity analysis of graft occlusion.

Some of the individual trials had important study design issues that were addressed before pooling the data. The Stand-in-Y trial compared saphenous-vein grafts with either radial-artery grafts or right internal-thoracic-artery grafts in different arms of the trial. (7) The Radial Artery Patency and Clinical Outcomes (RAPCO) trial consisted of two separate trials, one of radial-artery grafts versus right internal-thoracic-artery grafts and one of radial-artery grafts versus saphenous-

vein grafts. (9) For the present analysis, only patients included in the radial-artery graft vs. saphenous-vein graft comparison from Stand-in-Y and RAPCO were included. The trial of Petrovic et al. had no per-protocol angiography and patients underwent repeat angiography only for clinical indications.(10) The angiographic results of this trial were therefore not used for the analyses of graft occlusion. In the Radial Artery Patency Study (RAPS), each patient received both a radial-artery graft and a saphenous-vein graft, and randomization was performed for the target coronary territory (within-patient randomization).(11) Due to the difficulty of attributing clinical events to the radial-artery graft or the saphenous-vein graft for any given patient, this study was used only for the sensitivity analysis of graft occlusion (**Supplementary Appendix**).

Meta-analysis

Overall, 534 and 502 patients receiving radial-artery grafts and saphenous-vein grafts, respectively, were compared for clinical outcomes. Baseline characteristics for these patients are summarized in **Table 2**. Age, sex, diabetes prevalence, severe left ventricular dysfunction (left ventricular ejection fraction <35%) and renal insufficiency were comparable between the two groups. Endoscopic harvesting of either the saphenous vein or the radial artery was not used in any study. The total number of grafts performed was similar in the radial-artery graft and the saphenous-vein graft groups. The target vessel was the left circumflex coronary artery and the right coronary artery in about 75% and 25% of cases respectively.

The main study outcomes are reported in **Table 3**. The mean follow-up time was 60±30 months (median 60; 1st-3rd quartile 39-83; range 0-146). There was a significant reduction in the incidence of the composite primary end point of death, myocardial infarction or repeat revascularization in the radial-artery graft group compared with the saphenous-vein graft group (25 vs 39 events per 1000 patient-years; HR=0.67 [95% CI 0.49-0.90], P=0.01; **Figure 1 Panel A**). Radial-artery grafts were associated with a nominally lower incidence of myocardial infarction (6 vs 9 per 1000 patient-years; HR=0.72 [95% CI 0.53-0.99], P=0.04) and a lower incidence of repeat revascularization (9 vs 17 per 1000 patient-years; HR=0.50 [95% CI 0.40-0.63], P<0.001) but not of

Table 2. Characteristics of the Patients at Baseline.*

Characteristic	Radial-Artery Group (N=534)	Saphenous-Vein Group (N=502)	P Value
Age — yr	66.6±9.28	67.1±9.83	0.42
Female sex — no. (%)	158 (29.6)	151 (30.1)	0.92
Diabetes — no. (%)	181 (33.9)	177 (35.3)	0.69
Previous myocardial infarction — no. (%)	164 (30.7)	160 (31.9)	0.74
Elective admission — no. (%)	469 (87.8)	456 (90.8)	0.14
Renal insufficiency — no. (%)†	45 (8.4)	46 (9.2)	0.76
Left ventricular ejection fraction <35% — no. (%)	25 (4.7)	32 (6.4)	0.29
Target vessel — no. (%)			0.13
Left circumflex coronary artery	415 (77.7)	369 (73.5)	
Right coronary artery	119 (22.3)	133 (26.5)	
No. of grafts	3.1±0.65	3.1±0.55	0.53
Proximal anastomosis site — no. (%)			0.10
Ascending aorta	489 (91.6)	474 (94.4)	
Internal thoracic artery	45 (8.4)	28 (5.6)	

* Plus–minus values are means ±SD.
† Renal insufficiency was defined as a preoperative serum creatinine level of more than 1.5 mg per deciliter.[3]

Table 3. Main Outcomes.*

Outcome	Radial-Artery Group (N=534)		Saphenous-Vein Group (N=502)		Treatment Effect†	
	No. of Events (%)	Events per 1000 Patient-Yr‡	No. of Events (%)	Events per 1000 Patient-Yr‡	Hazard Ratio (95% CI)	P Value
Death, myocardial infarction, or repeat revascularization	67 (12.5)	25	94 (18.7)	39	0.67 (0.49–0.90)	0.01
Death	40 (7.5)	15	42 (8.4)	17	0.90 (0.59–1.41)	0.68
Myocardial infarction	16 (3.0)	6	21 (4.2)	9	0.72 (0.53–0.99)	0.04
Repeat revascularization	23 (4.3)	9	43 (8.6)	17	0.50 (0.40–0.63)	<0.001
Graft occlusion§	28/345 (8.1)	19	61/307 (19.9)	46	0.44 (0.28–0.70)	<0.001

* The analyses of clinical outcomes included all patients enrolled in the RAPCO, RSVP, Stand-in-Y, Yoo and colleagues, and Petrovic et al. trials.
† Results are from a mixed-effect Cox regression model with individual trials included as a random effect (saphenous-vein group is the reference group).
‡ The total numbers of patient-years were 2675 in the radial-artery group and 2510 in the saphenous-vein group.
§ The main analysis of graft occlusion included all the patients with follow-up angiography with data available from the RAPCO, RSVP, Stand-in-Y, and Yoo and colleagues trials. Data were available for 345 of 434 radial-artery grafts (1454 patient-years) and 307 of 402 saphenous-vein grafts (1311 patient-years).

all-cause death (15 vs 17 per 1000 patient-years; HR=0.90 [95% CI 0.59-1.41], P=0.68; **Supplementary Appendix Figure S2**).

Protocol-defined follow-up angiography was performed in 345 of 434 (79%) patients in the radial-artery graft group and in 307 of 402 (76%) patients in the saphenous-vein graft group. A comparison of baseline characteristics for patients with and without follow-up angiographic data is presented in **Supplementary Appendix Table S2**. The mean follow-up time to protocol angiography was 50±30 months (median 51; 1st-3rd quartile 29-68; range 1-143 months). The incidence rates for graft occlusion were 19 vs 46 events per 1000 patient-year in the radial-artery graft and the saphenous-vein graft groups, respectively; radial-artery grafts were associated with a significantly lower risk of occlusion (HR=0.44 [95% CI 0.28-0.70], P<0.001; **Figure 1 Panel B**).

The results of the sensitivity analyses were consistent with the main analysis (**Supplementary Appendix, Figures S3, S4 and S5,** and **Table S3**). A funnel plot of the included trials, shown in **Supplementary Appendix Figure S6**, did not suggest evidence of publication bias (P=0.32). No significant difference in perioperative stroke was found between the two groups (radial-artery grafts 0.7% vs saphenous-vein grafts 1.4%, odds ratio=0.71 [95% CI 0.23-2.11], P=0.53).

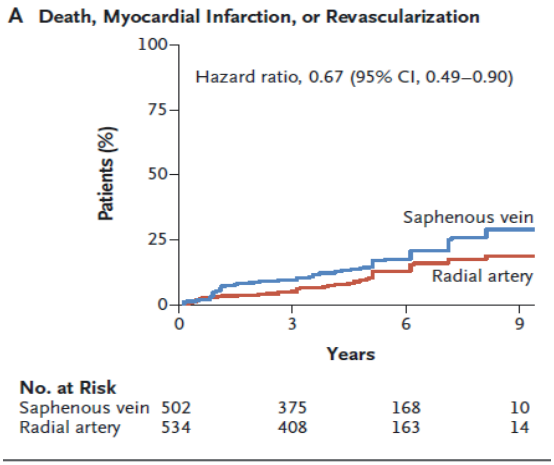


Figure 1. Cumulative Incidence of the Primary Composite Outcome of Death, Myocardial Infarction, or Repeat Revascularization and of Graft Failure in the Intention-to-Treat Analysis.

Subgroup analysis

A nominally significant interaction between age and treatment effect on major adverse cardiac events was found (P=0.04), and an age of 75 was identified as the cut-off for the loss of benefit from the radial artery. Interaction term analysis (**Figure 2**) showed a larger reduction in major adverse cardiac events with radial-artery grafts compared to saphenous-vein grafts in patients younger than 75 (P=0.008), in females (P=0.01) and, nominally, in those without renal insufficiency (P=0.02). Diabetes (P=0.35), left ventricular ejection fraction <35% (P=0.37) and prior

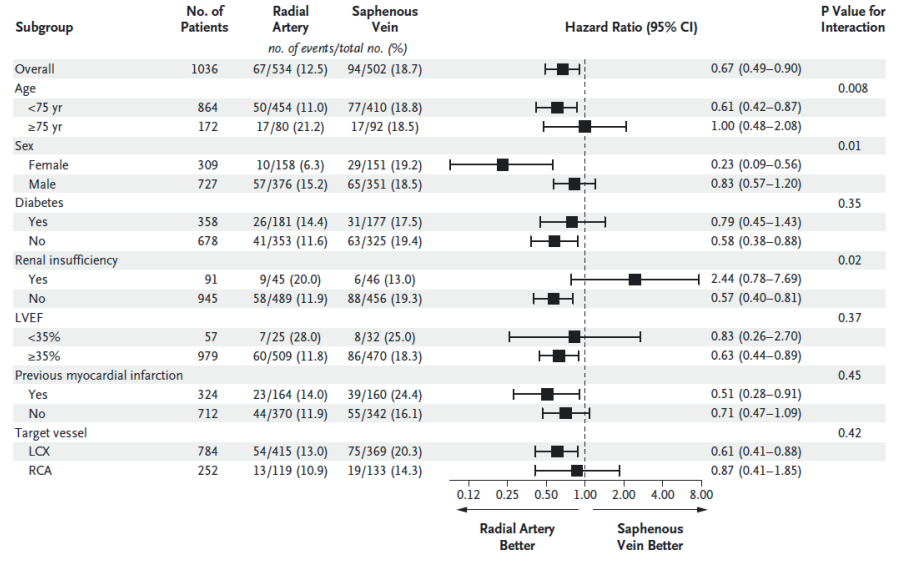


Figure 2. Subgroup Analyses and Interaction Terms for the Primary Composite Outcome of Death, Myocardial Infarction, or Repeat Revascularization.

The P values given are the P values for the interaction-term analyses. Renal insufficiency was defined as a preoperative serum creatinine level of more than 1.5 mg per deciliter.[3] LCX denotes left circumflex coronary artery, LVEF left ventricular ejection fraction, and RCA right coronary artery.

myocardial infarction (P=0.45) did not modify the treatment effect. The radial-artery graft target vessel did not significantly influence the treatment effect (P=0.42).

The risk factors for occlusion of radial-artery grafts and saphenous-vein grafts are reported in **Supplementary Appendix Table S4**. Age was found to be an independent predictor of radial-artery- but not saphenous-vein-graft occlusion. Female sex was found to be associated with a lower risk of radial-artery-graft occlusion and higher risk of saphenous-vein-graft occlusion. The use of chronic calcium channel antagonist therapy was found to be associated with a nominally significant lower risk of radial-artery-graft occlusion (details of the agents used to prevent arterial-graft spasm are given in **Supplementary Appendix Table S5**).

DISCUSSION

In this patient-level meta-analysis of randomized controlled trials comparing the radial artery and the saphenous vein as a second conduit for CABG, the use of radial-artery grafts was associated with a significantly lower risk of the composite of death, myocardial infarction or repeat revascularization and of the individual risk of myocardial infarction and repeat revascularization at a mean follow-up of 5 years. The use of radial-artery grafts was also associated with superior angiographic patency rates at protocol-defined angiography, which offers a biologically mechanistic explanation of the observed improvement in clinical outcomes.

The clinical benefit associated with the use of radial-artery grafts seemed more evident in patients younger than 75 years, in females and in those without renal insufficiency. The radial-artery graft target vessel was not found to be a significant effect modifier. As the attrition rate of saphenous-vein grafts but not of radial-artery grafts increases almost exponentially with time,(12) it is as yet unknown if the clinical difference in outcome apparent between the groups at 5 years could increase with a longer follow-up period.

The use of multiple arterial grafts is recommended by current guidelines and professional societies' position papers predominantly on the basis of large observational studies that have reported improved patient outcomes after CABG.(13-15) Despite these recommendations, arterial grafts have not been widely adopted; in the United States currently fewer than 10% of elective CABG patients receive more than one arterial graft and in less than 7% a radial-artery graft is used.(1) One of the reasons for their low use is that the superior clinical outcomes with multiple arterial grafts reported in registries have not been replicated in the randomized controlled trials.

Concerns exist that observational studies can be biased in favor of arterial conduits by unmatched confounders based on the unmeasurable (and unmatchable) judgment of the operating surgeons.[16] None of the randomized controlled trials which compared radial-artery grafts with saphenous-vein grafts have individually found a difference in clinical outcome.(6-11) The present patient-level meta-analysis aimed to overcome limitations from individual studies by pooling those trials.

Our analysis also revealed that superior patency of radial-artery grafts did not translate into a significant difference in survival at 5 years. The traditional concept of a direct relationship between coronary graft patency and survival is both intuitive and biologically plausible and is indirectly supported by studies demonstrating better survival for patients receiving a conduit with higher long-term patency when placed to the left anterior descending coronary artery.(17,18) However, while there is clear evidence that failure of grafts to the left anterior descending artery adversely affects survival, failure of grafts to other target vessels is more likely to result in non-fatal cardiac events.(19,20) The present analysis has several limitations. Even using a meta-analytic approach, the overall number of patients is relatively small for a procedure as common as CABG. Also, patients enrolled in the six trials were highly selected. These aspects clearly limit the external validity of our work. The different trials used various surgical techniques, harvesting protocols and postoperative secondary prevention regimens. Also, different trials used various methods to evaluate the morbidity related to radial-artery harvesting and a pooled analysis of data for this outcome was not possible. However, in all the individual studies radial-artery harvesting was associated with only minor clinical symptoms and no overt hand complications.

There are also several limitations of the patency analysis in our study. In the main analysis, protocol-directed angiography was performed in only about three-quarters of trial participants, and the patients with and without follow-up angiography differed in clinical characteristics and risk. Also, two trials accounted for more than two thirds of all the angiographic data. However, we found no heterogeneity across included trials. The use of protocol-directed angiography renders the estimation of graft occlusion according to clinically directed angiography difficult. Finally, the estimates of repeat revascularization rates in angiographic trials may be inflated compared to results in clinical outcome studies, as repeat revascularization may be driven based on the angiographic rather than clinical findings.

In summary, in a pooled analysis of randomized controlled trials comparing radial-artery grafts versus saphenous-vein grafts as second conduit for CABG, the use of radial-artery grafts resulted in a significantly lower rate of major adverse cardiac events and a better patency rate at a postoperative follow-up of 5 years.

REFERENCES

1. ElBardissi AW, Aranki SF, Sheng S, O'Brien SM, Greenberg CC, Gammie JS. Trends in isolated coronary artery bypass grafting: an analysis of the Society of Thoracic Surgeons adult cardiac surgery database. J Thorac Cardiovasc Surg 2012;143:273–81.

2. Gaudino M, Taggart D, Suma H, Puskas JD, Crea F, Massetti M. The Choice of Conduits in Coronary Artery Bypass Surgery. J Am Coll Cardiol 2015;66:1729–37.

3. Gowda S, Desai PB, Kulkarni SS, Hull VV, Math AAK, Vernekar SN. Markers of renal function tests. North Am J Med Sci 2010;2:170–3.

4. 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;28:616–26.

5. Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;496–509.

6. 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;117:2859–64.

7. 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;137:1093–100.

8. Song S-W, Sul S-Y, Lee H-J, Yoo K-J. 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;42:107–12.

9. Buxton BF, Raman JS, Ruengsakulrach P, et al. Radial artery patency and clinical outcomes: five-year interim results of a randomized trial. J Thorac Cardiovasc Surg 2003;125:1363–71.

10. Petrovic I, Nezic D, Peric M, et al. Radial artery vs saphenous vein graft used as the second conduit for surgical myocardial revascularization: long-term clinical follow-up. J Cardiothorac Surg 2015;10:127.

11. Deb S, Cohen EA, Singh SK, et al. 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.

12. Gaudino M, Tondi P, Benedetto U, et al. Radial Artery as a Coronary Artery Bypass Conduit: 20-Year Results. J Am Coll Cardiol 2016;68:603–10.

13. Hillis LD, Smith PK, Anderson JL, 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:e652–735.

14. Authors/Task Force members, Windecker S, Kolh P, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery

(EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541–619.

15. Aldea GS, Bakaeen FG, Pal J, et al. The Society of Thoracic Surgeons Clinical Practice Guidelines on Arterial Conduits for Coronary Artery Bypass Grafting. Ann Thorac Surg 2016;101:801–9.

16. Gaudino M, Di Franco A, Rahouma M, 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. doi: 10.1161/JAHA.117.008010.

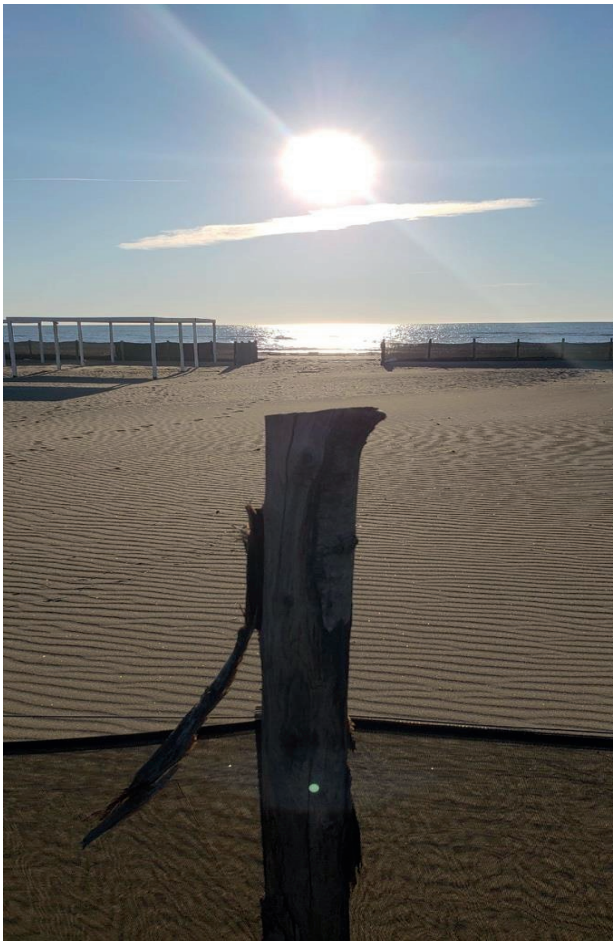
17. Loop FD, Lytle BW, Cosgrove DM, et al. Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. N Engl J Med 1986;314:1–6.

18. Garcia S, Sandoval Y, Roukoz H, et al. Outcomes after complete versus incomplete revascularization of patients with multivessel coronary artery disease: a meta-analysis of 89,883 patients enrolled in randomized clinical trials and observational studies. J Am Coll Cardiol 2013;62:1421–31.

19. Lopes RD, Mehta RH, Hafley GE, et al. Relationship between vein graft failure and subsequent clinical outcomes after coronary artery bypass surgery. Circulation 2012;125:749–56.

20. Shavadia J, Norris CM, Graham MM, Verma S, Ali I, Bainey KR. Symptomatic graft failure and impact on clinical outcome after coronary artery bypass grafting surgery: Results from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry. Am Heart

J 2015;169:833–40.



CHAPTER 5

Effect of Calcium-Channel Blocker Therapy on Radial Artery Grafts After Coronary Bypass Surgery

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J Am Coll Cardiol. 2019;14;73(18):2299-2306.

ABSTRACT

Background: Few studies have evaluated the effect of chronic calcium-channel blocker therapy (CCB) on the angiographic and clinical outcome of radial artery (RA) grafts used for coronary bypass surgery (CABG).

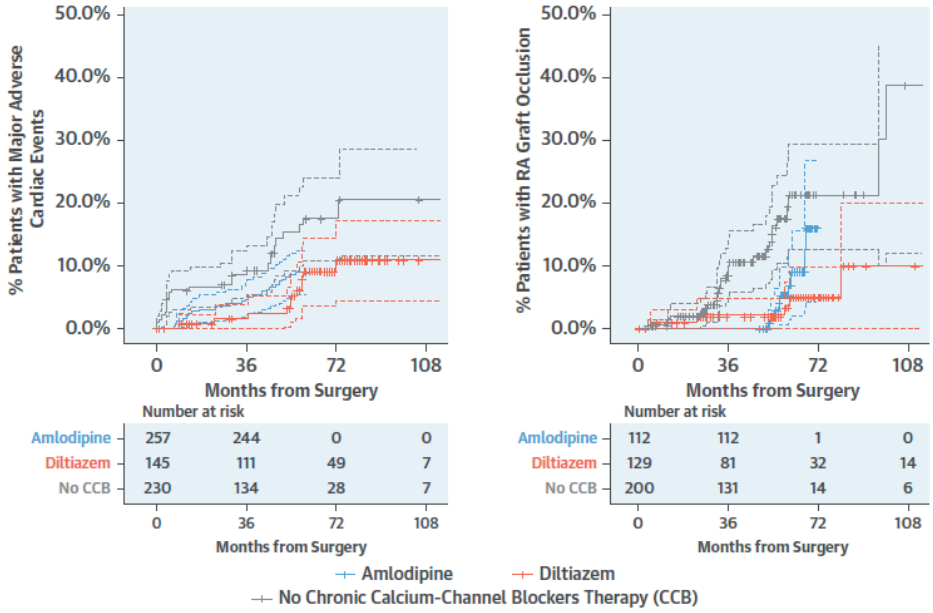
Objectives: To evaluate if CCB influences mid-term clinical and angiographic outcomes of RA grafts.

Methods: Patient-level data of six angiographic randomized trials evaluating RA graft status at mid-term follow-up were joined in this observational analysis. Cox regression and propensity score methods were used to evaluate the effect of CCB on the incidence of a composite of major adverse cardiac events (death, myocardial infarction and repeat revascularization-MACE) and graft occlusion.

Results: The study population included 732 patients (502 on CCB). The median clinical follow-up was 60 months. The cumulative incidence of MACE at 36, 72 and 108 months was 3.7% vs. 9.3%, 13.4% vs 17.6% and 16.8% vs 20.5% in the CCB and no CCB groups respectively (log-rank P=0.003). Protocol-driven angiographic follow-up was available in 243 patients in the CCB group and 200 in the no CCB. The median angiographic follow-up was 55 months. The cumulative incidence of RA occlusion at 36, 72 and 108 months was 0.9% vs. 8.6%, 9.6% vs 21.4% and 14.3% vs 38.9% in the CCB and no CCB group respectively (log-rank P<0.001). After controlling for known confounding, CCB therapy was found to be consistently associated with a significantly lower risk of MACE (multivariate Cox HR 0.52[95%CI .31-0.89]; P=0.02) and RA graft occlusion (multivariate Cox HR 0.20[95%CI 0.08-0.49]; P<0.001).

Conclusions: In patients with RA grafts CCB is associated with significantly better mid-term clinical and angiographic RA outcomes.

CENTRAL ILLUSTRATION Calcium-Channel Blockers for Radial Artery Grafts



Gaudino, M. et al. J Am Coll Cardiol. 2019;73(18):2299-306.

Cumulative incidence of major adverse cardiac events **(left)** and radial artery graft occlusion **(right)** according to calcium-channel blocker classes received. RA = radial artery.

INTRODUCTION

The RADIAL (Radial Artery Database International ALliance) project is a combined patient-level dataset including six randomized trials (RCTs) that have compared the radial artery (RA) with other conduits at mid-term follow-up. In a recent publication from the RADIAL database we have shown for the first time using randomized data that the use of the RA as the second conduit for coronary artery bypass (CABG) is associated with a significant reduction in the risk of mid-term cardiac events compared to the use of the saphenous vein (1).

Although in recent years the use of the RA has been very limited among the surgical community, the publication of the results of the primary analysis of RADIAL and the consequent Class I indication in the 2018 ESC/EACTS Guidelines,(2) are likely to elicit renewed interest for the artery and the issues related to its use for CABG. One of the most important unsolved questions is the role of chronic calcium-channel blocker therapy (CCB) for CABG patients who received one or more RA grafts.

In fact, due to the thick muscular wall of the RA and of the concerns of graft spasm, CCB is traditionally prescribed postoperatively for CABG RA patients (3). This practice, however, is weakly supported by the published literature.

Only few studies to date have evaluated the effect of CCB on the angiographic and clinical outcome of RA grafts and, in most cases, the results have been neutral.(4) One major problem is that, due to the high patency rate and excellent clinical outcome of the RA, a very large sample

size is required to detect even moderate differences in angiographic and clinical outcomes. All the published series were very likely largely underpowered for this purpose.

CCB is associated with non-negligible side-effects and costs.(5) Also, due to its hypotensive effect, the use of CCB may preclude the use of other evidence-based therapy such as beta blockers or angiotensin converting enzyme inhibitors. For these reasons the evaluation of CCB efficacy in patients with RA grafts is of major relevance for the patients and the cardiovascular community.

Our primary study objective was to assess whether CCB use after RA CABG affects the midterm clinical and angiographic outcomes and address the described power limitations by pooling individual patient data from multiple RCTs in this post-hoc analysis.

METHODS

Dataset

The RADIAL initiative was created in March 2015 with the aim to combine dataset from trials on the RA to facilitate meta-analytic studies. Details of the projects have previously been published (1). The list of the RADIAL investigators is enclosed in **Online Table 1**.

In the present study, we analyzed individual patient level data from all patients who received the RA in the published RCTs comparing the long-term (≥2 years) outcomes of the RA and other conduits. The 6 RCTs included are: the Radial Artery Patency and Clinical Outcomes (groups 1 and 2), the Radial Artery Patency Study (RAPS), Radial Artery Versus Saphenous Vein Patency Study, Petrovic, Stand-in-Y and Yoo trials.(6–11) Postoperative CCB was recommended per protocol in each of the individual trials, with differences in the type of drug used and the duration of the treatment (**Online Table 2**).

The RA was used on the second most important coronary target vessel in all trials except for RAPS. In RAPS, within-patient randomization was used and patients with three vessel disease were randomized to receive both a saphenous vein and a RA graft randomly allocated to the right or the circumflex coronary artery. For this reason, in RAPS the RA was used on either the second or third most important target coronary vessel. To minimize confounders, data from RAPS were not used for the main analysis but were included in a sensitivity analysis on RA graft occlusion.

Outcomes

The primary outcome was a composite of major adverse cardiac events (death, myocardial infarction and repeat revascularization - MACE) at maximum follow-up. The secondary outcome was RA graft occlusion at maximum follow-up. Patency rate was graded according to Fitzgibbon classification (12). Grade A and B were considered patent and grade O occluded. Individual components of the primary composite outcome were also analyzed individually.

Statistical analysis

Continuous variables were tested for normality and were reported as means and standard deviations or median and interquartile range (IQR) and the two groups (CCB and no CCB) were compared using with t-test or Wilcoxon–Mann–Whitney. Baseline categorical variables were reported as counts and percentages and compared with chi-squared test. Time-to-event outcomes were reported as a cumulative incidence using Kaplan Meier estimates and the two groups were compared using log-rank test. For the primary composite endpoint of death, myocardial infarction and repeat revascularization and for RA graft occlusion, cumulative incidences were graphically presented using Kaplan Meier estimates (survival and survminer R package). To account for differences in baseline characteristics between patients who received CCB and those who did not, several adjustment methods were used for the computation of treatment effect estimates on primary endpoints. Treatment effect was initially calculated using univariate and multivariable Cox models forcing all baseline characteristics with further stratification by individual trials. Covariates included in the Cox models were: CCB, age, gender, diabetes, previous myocardial infarction, surgical priority, renal insufficiency, target vessel, location of RA proximal anastomosis and off-pump surgery. Treatment effect was reported as

hazard ratios (HR) with 95% confidence intervals (CI). The proportional hazard assumptions were verified using the Schoenfeld residuals. Furthermore, propensity score methods including inverse propensity score weighting (IPSW) and propensity score stratification were used to adjust for confounding (details provided in the **Supplementary Material, Online Figures 1 and 2, and Online Tables 3-5**) (13). The effect of individual CCB classes (amlodipine and diltiazem) was also tested using univariate and multivariate Cox regression. Finally, we investigated whether CCB therapy duration influenced the incidence of primary outcomes (MACE and graft occlusion) by forcing CCB therapy duration (as linear or spline terms) in a Cox regression model (patients who did not receive CCB therapy included as CCB duration =0). Non-linearity between CCB therapy duration and incidence of endpoint of interest was tested by means of ANOVA test and the model with highest X^2 and lowest degree of freedom was selected (restricted cubic spline 2 knots). R version 3.1.2 (2014-10-31) was used for all statistical.

RESULTS

The study population included 732 patients (502 treated with CCB). Protocol-driven angiographic follow-up was available in 243 patients in the CCB group and 200 in the no CCB. Details of the baseline and intraoperative characteristics of patients of the two group are given in **Table 1**. Median clinical follow-up was 60[IQR 39-66] months and median angiographic follow-up was 55[IQR 31-65] months. The main clinical outcomes are summarized in **Table 2**. The cumulative incidence of MACE at 36, 72 and 108 months was 3.7% vs. 9.3%, 13.4% vs 17.6% and 16.8% vs 20.5% in the CCB and no CCB groups respectively (log-rank P=0.003; **Figure 1 left**). The cumulative incidence of RA occlusion at 36, 72 and 108 years was 0.9% vs. 8.6%, 9.6% vs 21.4% and 14.3% vs 38.9% in the CCB and no CCB group respectively (log-rank P<0.001; **Figure 1 right**). After controlling for confounding with several methods (**Table 3** and **Figure 2**), CCB therapy was found to be consistently associated with a

TABLE 1 Pre-Operative and Intraoperative Characteristics of the Patients

	CCB (n = 502)	No CCB (n = 230)	p Value
Age, yrs	62.28 ± 9.01	70.18 ± 8.44	<0.001
Female	96 (19.1)	84 (36.5)	<0.001
Diabetes	120 (23.9)	70 (30.4)	0.075
Prior MI	156 (31.1)	83 (36.1)	0.209
Elective admission	434 (86.5)	195 (84.8)	0.625
Renal insufficiency	30 (6.0)	21 (9.1)	0.162
LVEF <0.35	11 (2.2)	18 (7.8)	0.001
Target vessel RCA	386 (76.9)	128 (55.7)	<0.001
Number of grafts	3.20 ± 0.73	3.28 ± 1.48	0.288
OPCABG	38 (7.6)	0 (0.0)	<0.001
Proximal anastomosis on AA	461 (91.8)	221 (96.1)	0.050
First author/trial (ref. #)			
Petrovic et al. (9)	100 (19.9)	0 (0.0)	
RAPCO (6)	257 (51.2)	51 (22.2)	
RSVP (8)	82 (16.3)	0 (0.0)	
Stand-in-Y (10)	28 (5.6)	179 (77.8)	
Song et al. (11)	35 (7.0)	0 (0.0)	

Values are mean ± SD or n (%).

AA = ascending aorta; CCB = chronic calcium-channel blocker therapy; LVEF = left ventricular ejection fraction; MI = myocardial infarction; OPCABG = off pump coronary bypass; RAPCO = Radial Artery Patency and Clinical Outcomes trial; RCA = right coronary artery; RSVP = Radial Artery Versus Saphenous Vein Patency Study.

TABLE 2 Kaplan-Meier Estimates of the Primary and Secondary Outcomes*

Group	Months of Follow-Up	MACE	Graft Occlusion	Death	Myocardial Infarction	Repeat Revascularization
CCB (n = 502)						
	36	3.7 (2.0-5.4)	0.9 (0.0-2.2)	2.1 (0.8-3.4)	0.2 (0.0-0.6)	1.5 (0.4-2.5)
	72	13.4 (9.5-17.8)	9.6 (4.2-14.9)	7.5 (4.5-10.5)	2.0 (0.7-3.3)	4.8 (2.8-6.8)
	108	16.8 (11.8-21.7)	14.3 (4.0-24.7)	9.3 (5.5-13.1)	2.4 (0.9-3.8)	5.5 (3.3-7.7)
No CCB (n = 230)						
	36	9.3 (5.4-13.2)	8.6 (4.2-12.9)	5.3 (2.0-8.5)	3.1 (0.8-5.3)	3.1 (0.8-5.4)
	72	17.6 (11.0-24.1)	21.4 (13.0-29.8)	8.2 (3.7-12.8)	4.2 (1.1-7.2)	7.5 (2.8-12.2)
	108	20.5 (12-29)	38.9 (16.5-61.2)	11.5 (3.8-19.2)	4.2 (1.1-7.2)	7.5 (2.8-12.2)
Univariate Cox p value		0.003	<0.001	0.09	0.02	0.13

Values are Kaplan-Meier estimates (95% confidence interval) unless otherwise indicated. *Angiography available in 243 patients in the chronic calcium-channel blocker therapy group and in 200 patients in the no chronic calcium-channel blocker therapy group.

CCB = chronic calcium-channel blocker therapy; MACE = major adverse cardiac events.

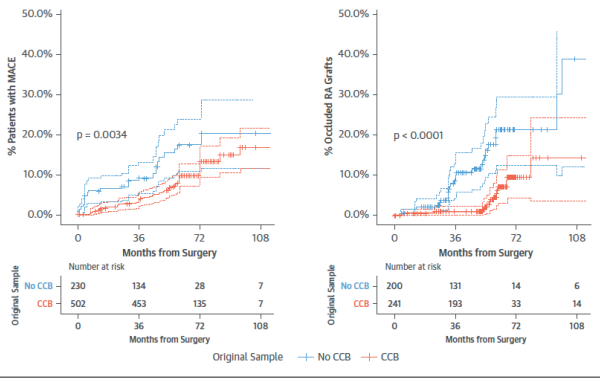
TABLE 3 Treatment Effect Estimations

Outcome	Model	HR (95%CI)	p Value
MACE			
	Unadjusted	0.52 (0.33-0.81)	0.004
	MV Cox	0.52 (0.31-0.89)	0.02
	MV Cox stratified by trial	0.33 (0.16-0.65)	0.002
	IPSW Cox	0.53 (0.30-0.95)	0.03
	Doubly robust	0.49 (0.26-0.92)	0.03
	Doubly robust stratified by trial	0.33 (0.16-0.66)	0.002
	PS stratification	0.51 (0.28-0.91)	0.02
RA graft occlusion			
	Unadjusted	0.28 (0.14-0.54)	<0.001
	MV Cox	0.20 (0.08-0.49)	<0.001
	MV Cox stratified by trial	0.18 (0.06-0.51)	0.001
	IPSW Cox	0.28 (0.13-0.60)	0.001
	Doubly robust	0.13 (0.05-0.36)	<0.001
	Doubly robust stratified by trial	0.11 (0.03-0.39)	<0.001
	PS stratification	0.21 (0.08-0.52)	<0.001

HR = hazard ratio; IPSW = inverse propensity score weighting; MACE = major adverse cardiac events; MV = multivariate; PS = propensity score; RA = radial artery.

significantly lower risk of MACE (multivariate Cox HR 0.52[95%CI .31-0.89]; P=0.02) and RA graft occlusion (multivariate Cox HR 0.20[95%CI 0.08-0.49]; P<0.001). When classes of CCB were analyzed separately, we found that both diltiazem (multivariate Cox HR 0.29[0.11-0.73]; P=0.008) and amlodipine (multivariate Cox HR 0.42[95%CI 0.23-0.76]; P=0.005) were associated with a lower risk of MACE when compared to no-CCB (**Central illustration**). Among patients undergoing angiographic follow-up, we found that both diltiazem (multivariate Cox HR 0.20[95%CI 0.07-0.51]; P<0.001) and amlodipine (multivariate Cox HR 30[95%CI 0.12-0.74]; P=0.009) were associated with a lower risk of RA graft occlusion when compared to no CCB (**Central Illustration**). Finally, we found that CCB therapy duration was associated with the risk of MACE (P<0.001, **Figure 3 left**) and graft failure (P= 0.03, **Figure 3right**). Specifically, we found that CCB therapy for 1 year was associated with a greater reduction in MACE than a shorter duration of CCB treatment (P<0.001).

FIGURE 1 Cumulative Incidence of MACE and RA Graft Occlusion in the 2 Groups



(Left) MACE; **(right)** RA graft occlusion. CCB = chronic calcium-channel blockers therapy; MACE = major adverse cardiac events; RA = radial artery.

A benefit of a longer duration of CCB therapy was not demonstrated (P=0.08), although the numbers of patients on prolonged CCB therapy was small. A similar relationship was found between CCB therapy duration and the risk of graft occlusion, with a significant reduction in graft occlusion for CCB therapy lasting 1 year compared to shorter period (P=0.006) but a further trend could not be demonstrated with longer treatment (P=1). The sensitivity angiographic analysis including RAPS confirmed the robustness of the primary analysis (**Online Tables 6-9**).

DISCUSSION

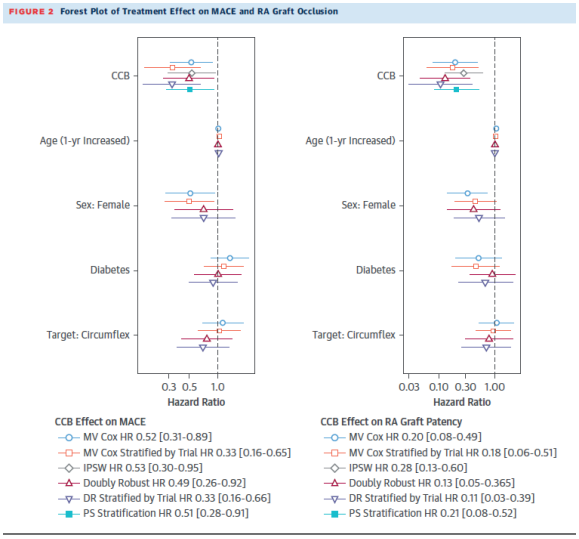


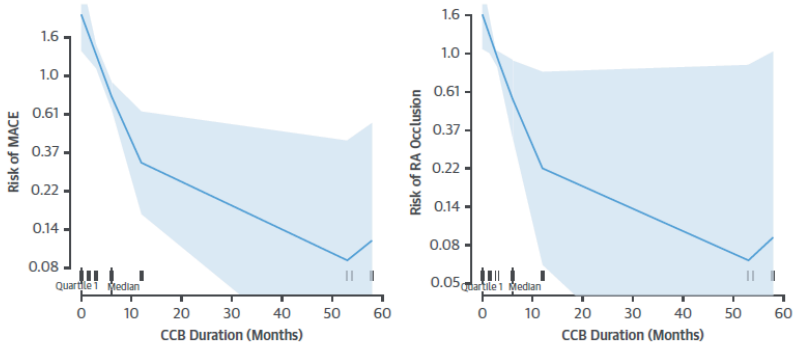
FIGURE 2 Forest Plot of Treatment Effect on MACE and RA Graft Occlusion

(Left) MACE; **(right)** RA graft occlusion. DR = doubly robust; HR = hazard ratio; IPSW = inverse propensity score weighting; MV = multivariate; PS = propensity score; other abbreviations as in Figure 1.

In this patient-level pooled analysis of six RCTs on the mid-term clinical and angiographic outcomes of RA graft we found that the use of CCB was associated with a significantly lower risk of MACE and higher RA patency rate. We also found that duration of CCB for at least one year was associated with a reduction of clinical events and graft occlusion compared to shorter treatment and that diltiazem and amlodipine were associated with a similar protective effect.

Among all the conduits used for CABG, the RA is the only muscular artery. Histologic studies have shown that the thickness of the muscular component of the RA is almost twice that of the internal thoracic artery.(14) This thick muscular media is the anatomic explanation of the well-known hyper-reactivity of RA rings reported in pharmacological studies. Chardigny and coauthors in a classic organ bath experiment have shown that the spastic response of the RA to norepinephrine, serotonin, and thromboxane A2 is significantly higher than that of any other conduit used for CABG (15).

FIGURE 3 Effect of the Duration of Chronic CCB on the Risk of MACE and RA Graft Occlusion



(Left) MACE; **(right)** RA graft occlusion. Reference point is 6-month duration, which corresponds to the median duration in the overall sample. CCB therapy duration <6 months was associated with increased risk of graft occlusion (hazard ratio, risk >1), whereas CCB therapy duration >6 months was associated with lower risk of graft occlusion (hazard ratio: risk <1). Abbreviations as in Figure 1.

Those peculiar morpho-functional features of the RA and the consequent concerns of postoperative RA spasm are the reasons behind the empiric use of CCB in patients with RA grafts.

It must be noted that in the years after implantation in the coronary circulation, RA grafts lose most of the muscular component of the media and of their spastic tendency, becoming very similar to internal thoracic artery grafts (16). On this basis, it is possible that the benefits of CCB are limited to the initial postoperative period.

The previous literature on the effect of CCB in patients with RA graft is controversial. In a small previous RCT Gaudino et al assigned 120 patients who received the RA for CABG to continue or suspend the CCB using Diltiazem after the first postoperative year and found no difference in graft patency, graft reactivity, scintigraphically-evident myocardial ischemia or clinical outcomes at 5-year follow-up. (17). Subsequently the same authors in another small trial randomized 100 patients to receive or not the same CCB regimen from the early postoperative period and reported again lack of differences in clinical, scintigraphic and angiographic outcomes (18). In a angiographic

series of 50 patients, Moran and colleagues found similar clinical outcomes and angiographic patency among RA patients who received CCB with Diltiazem or not.(19) Similarly, a post-hoc analysis of the Radial Artery Patency Study found that among 440 RA patients the incidence of string sign (the highest degree of RA graft spasm) was not affected by the compliance with the prescribed postoperative CCB, although compliance with CCB use was high (419/440).(20). Due to the very high patency rate and excellent clinical outcomes of RA grafts however it is very likely that all the individual published studies were largely underpowered to detect even moderate differences in outcome.

Despite this lack of solid evidence, CCB is routinely prescribed in most centers after RA grafting. A 2003 survey of all Canadian cardiac surgery centers reported that some form of anti-spastic therapy was adopted in almost all institutions (25/27) after RA grafting (3) and to our knowledge, similar postoperative protocols are used in other parts of the world.

The chronic use of calcium channel blockers or other anti-spastic agent is associated with non-negligible side-effects and considerable costs. In a large community-based study, Kloner and associates reported that edema occurred in 24% of the patients on chronic therapy with amlodipine, headache in 8.8% and fatigue and dizziness in more than 4%.(21) Also, the hypotensive effect of CCB may preclude the use of other preventive therapies such as beta blockers and angiotensin converting enzyme inhibitors. For these reasons, an objective evaluation of the effect of CCB in patients with RA grafts is of relevance for the patients and cardiovascular community.

Our data suggest that in patients with RA grafts, the use of CCB for at least the first 12 months is associated with better clinical and angiographic outcomes.

Some limitations of this analysis must be acknowledged. Most importantly, although the original studies were randomized and had similar inclusion criteria, this post-hoc analysis shares the limitations of observational studies especially in term of indication biases. Despite the extensive use of statistical adjustments, it is likely that hidden and unmeasured confounders and biases may persist. Matching and adjustment techniques can only adjust for measurable and measured variables while they are ineffective with regards to unknown or unmeasured confounders. Subtle but important differences in surgical expertise, pre- and postoperative care and complementary secondary prevention strategies may have influenced the observed results. Also, despite being the largest study on this topic published to date, the sample size of the analysis is limited and its estimates may be relatively imprecise. However, the reproducibility of the main finding in all the analyses using different statistical techniques is a strong argument in favor of the solidity of our main findings.

In conclusion, our results show that the use of CCB is associated with higher patency rate and better clinical outcomes at 5 years in patients with RA grafts. Those data support the routine use of CCB, at least for the first 12 months after CABG using the RA.

REFERENCES

1. Gaudino M, Benedetto U, Fremes S, et al. Radial-Artery or Saphenous-Vein Grafts in Coronary-Artery Bypass Surgery. N Engl J Med 2018;378:2069–77.

2. Sousa-Uva M, Neumann F-J, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur J Cardiothorac Surg 2018;doi: 10.1093/ejcts/ezy289.

3. Myers MG, Fremes SE. Prevention of radial artery graft spasm: a survey of Canadian surgical centres. Can J Cardiol 2003;19:677–81.

4. Patel A, Asopa S, Dunning J. Should patients receiving a radial artery conduit have post-operative calcium channel blockers? Interact Cardiovasc Thorac Surg 2006;5:251–7.

5. Park C, Wang G, Durthaler JM, Fang J. Cost-effectiveness Analyses of Antihypertensive Medicines: A Systematic Review. Am J Prev Med 2017;53:S131–42.

6. Buxton BF, Raman JS, Ruengsakulrach P, et al. Radial artery patency and clinical outcomes: five-year interim results of a randomized trial. J Thorac Cardiovasc Surg 2003;125:1363–71.

7. Deb S, Cohen EA, Singh SK, et al. 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.

8. 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;117:2859–64.

9. Petrovic I, Nezic D, Peric M, et al. Radial artery vs saphenous vein graft used as the second conduit for surgical myocardial revascularization: long-term clinical follow-up. J Cardiothorac Surg 2015;10:127.

10. 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;137:1093–100.

11. Song S-W, Sul S-Y, Lee H-J, Yoo K-J. 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;42:107–12.

12. 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;28:616–26.

13. Benedetto U, Head SJ, Angelini GD, Blackstone EH. Statistical primer: propensity score matching and its alternatives. Eur J Cardiothorac Surg 2018;53:1112–7.

14. van Son JA, Smedts F, Vincent JG, van Lier HJ, Kubat K. Comparative anatomic studies of various arterial conduits for myocardial revascularization. J Thorac Cardiovasc Surg 1990;99:703–7.

15. Chardigny C, Jebara VA, Acar C, et al. Vasoreactivity of the radial artery. Comparison with

the internal mammary and gastroepiploic arteries with implications for coronary artery surgery. Circulation 1993;88:II115-127.

16. Gaudino M, Prati F, Caradonna E, et al. Implantation in coronary circulation induces morphofunctional transformation of radial grafts from muscular to elastomuscular. Circulation 2005;112:I208-211.

17. Gaudino M, Glieca F, Luciani N, Alessandrini F, Possati G. Clinical and angiographic effects of chronic calcium channel blocker therapy continued beyond first postoperative year in patients with radial artery grafts: results of a prospective randomized investigation. Circulation 2001;104:I64-67.

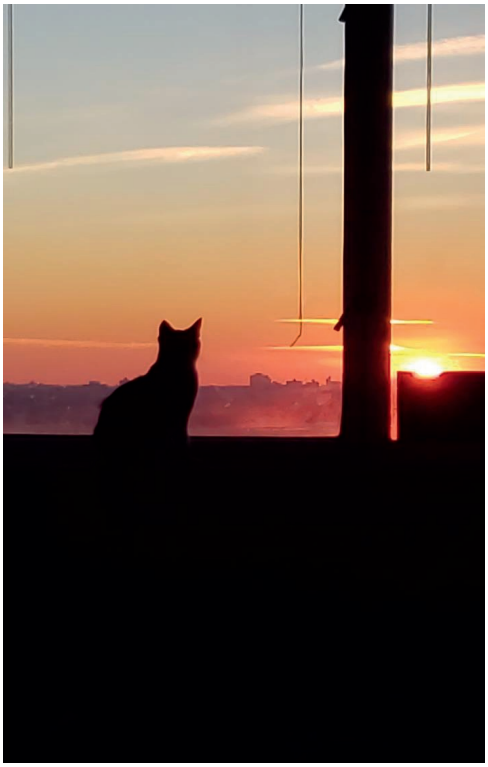
18. Gaudino M, Luciani N, Nasso G, Salica A, Canosa C, Possati G. Is postoperative calcium channel blocker therapy needed in patients with radial artery grafts? J Thorac Cardiovasc Surg 2005;129:532–5.

19. Moran SV, Baeza R, Guarda E, et al. Predictors of radial artery patency for coronary bypass operations. Ann Thorac Surg 2001;72:1552–6.

20. Miwa S, Desai N, Koyama T, et al. Radial artery angiographic string sign: clinical consequences and the role of pharmacologic therapy. Ann Thorac Surg 2006;81:112–8; discussion 119.

21. Kloner RA, Sowers JR, DiBona GF, Gaffney M, Wein M. Sex- and age-related antihypertensive effects of amlodipine. The Amlodipine Cardiovascular Community Trial Study

Group. Am J Cardiol 1996;77:713–22.



CHAPTER 6

Angiographic outcome of coronary artery bypass grafts: Radial Artery Database International Alliance

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Ann Thorac Surg. 2019;27. pii: S0003-4975(19)31226-3.

ABSTRACT

Background: We used a large patient-level dataset including six angiographic randomized trials (RCTs) on coronary artery bypass conduits to explore incidence and determinants of coronary graft failure.

Methods: Patient-level angiographic data of six RCTs comparing long-term outcomes of the radial artery and other conduits were joined. Primary outcome was graft occlusion at maximum follow-up. The analysis was divided as follows: 1) left anterior descending coronary (LAD) distribution, 2) non-LAD distribution (circumflex and right coronary artery). To identify predictors of graft occlusion, mixed model multivariable Cox regression including all baseline characteristics with stratification by individual trials was used.

Results: 1091 patients and 2281 grafts were included (921 left internal mammary arteries, 74 right internal mammary arteries, 710 radial artery and 576 saphenous veins; all left internal mammary arteries were used on the LAD, the other conduits were used on the non-LAD distribution; mean angiographic follow up: 65±29 months). Occlusion rate was 2.3%, 13.5%, 9.4%, 17.5% for the left internal mammary arteries, right internal mammary arteries, radial artery and saphenous veins, respectively. At multivariable analysis type of conduit used, age, female gender, left ventricular ejection fraction<50% and use of the Y graft were significantly associated with graft occlusion in the non-LAD distribution.

Conclusions: Our analyses showed that failure of the left internal mammary arteries to LAD bypass is a very uncommon event. For the non-LAD distribution, the non-use of radial artery, age, female

gender, left ventricular ejection fraction<50% and use of the Y graft configuration were significantly associated with mid-term graft failure.

INTRODUCTION

Although the relationship between graft status and clinical outcome is less clear than usually accepted,(1) it seems reasonable to say that the primary goal of coronary bypass grafting (CABG) operations is long-term patency of the bypass grafts.

Despite the five decades history of CABG surgery and the fact that it is the most common cardiac surgery procedure performed in adults, the current evidence on the frequency of and risk factors determining graft occlusion is surprisingly limited.

The great majority of observational series have major biases and limitations in particular with regards to the completeness of the angiographic follow-up. On the other hand angiographic randomized trials (RCTs) have minimal risk of bias and much higher completeness of follow-up, but taken individually have usually a sample size inadequate to allow a meaningful exploration of the determinants of graft patency.

In this manuscript we use a large patient-level dataset including six angiographic RCTs of CABG conduits to explore the incidence and determinants of coronary graft failure.

METHODS

Dataset

Details of the Radial Artery Database International Alliance (RADIAL) project have previously been published (2). The list of the RADIAL investigators is enclosed in **Supplementary Table 1**. Briefly, RADIAL is a patient-level database pooling six RCTs comparing the long-term outcomes of the radial artery (RAD) and other conduits at a mean follow-up ≥2 years. The 6 RCTs included are: the Radial Artery Patency and Clinical Outcomes (RAPCO, groups 1 and 2), the Radial Artery Patency Study (RAPS), the Radial Artery Versus Saphenous Vein Patency Study (RSVP), Petrovic, Stand-in-Y and Yoo trials.(3–8)

In the present analysis, we included all available individual angiographic patient level data from all the angiographic trials. As Petrovic's trial had no angiographic follow-up, it was excluded from the present analysis.

Outcomes

The primary outcome was graft occlusion at maximum follow-up. Graft angiographic status was graded according to the Fitzgibbon classification (9). Grade A and B were considered patent and grade O occluded.

Statistical analysis

Continuous variables were tested for normality and were reported as means and standard deviations or median and interquartile range (IQR). The t-test or Wilcoxon–Mann–Whitney test

were used to compare continuous variables. Categorical variables were reported as counts and percentages and compared with Chi-squared test. Time-to-event outcomes were reported as a cumulative incidence using Kaplan Meier estimates and curves were compared using log-rank test.

Due to the differences in target vessel characteristics and conduits used, the analysis for graft occlusion was divided as follows: 1) left anterior descending coronary (LAD) distribution, 2) non- LAD distribution (including the circumflex and the right coronary artery [LCX and RCA]).

To identify predictors of graft occlusion, mixed model multivariable Cox regression including all baseline characteristics with stratification by individual trials was used. Covariates included in the Cox models were: age, gender, diabetes, previous myocardial infarction (MI), surgical priority, renal insufficiency, left ventricular ejection fraction (LVEF), target vessel, location of proximal anastomosis, number of grafts per patient and off-pump surgery (OPCABG). Treatment effect was reported as hazard ratios (HR) with 95% confidence intervals (CI). The proportional hazard assumptions were verified using Schoenfeld residuals. R version 3.1.2 (2014-10-31) was used for all statistical analyses and p value significance was set at 0.05.

RESULTS

Overall, 1091 patients and 2281 grafts were included in the angiographic analysis, representing 71.8% of the total number of the patients enrolled in the five RCTs (1091/1519).

Table 1. Demographics of the Study Population

Variable	Patients n = 1091/1519 (71.8%)
Age, y	64.96 ± 9.48
Male	825 (75.6)
Diabetes	329 (30.2)
Previous MI	349 (32.0)
LVEF <0.50	170 (15.6)
Renal dysfunction[a]	64 (5.9)
Elective	874 (80.1)
OPCABG	43 (3.9)
Grafts, No.	3.4 ± 0.7
Grafts	2281
Radial artery	710
RIMA	74
Saphenous vein	576
LIMA	921

[a]Renal dysfunction was defined as preoperative serum creatinine >1.5 mg/dL.[2]

Data are presented as the mean ± SD or n (%).

LIMA, left internal mammary artery; OPCABG, off-pump coronary artery bypass grafting; RAD, radial artery; RIMA, right internal mammary artery.

The mean age was 64.9±9.5 years, there were 825 males (75.6%), 329 cases were diabetics (30.2%), 349 (32.0%) had previous MI, and 170 (15.6%) had LVEF <50%. The mean number of grafts per patient was 3.4±0.7. Demographics of the study population are reported in **Table 1**.

There were 921 left internal mammary arteries (LIMA), 74 right internal mammary arteries (RIMA), 710 RAD and 576 saphenous veins (SVG). All LIMA were used on the LAD, while the other conduits were used on the non-LAD distribution.

The mean angiographic follow up was 65±29 months, with small variations for the different conduits. The occlusion rate was 2.3% (21/921) for the LIMA, 13.5% (10/74) for the RIMA, 9.4% (67/710) for the RAD and 17.5% (101/576) for the SVG (see **Table 2**). Baseline features and

Table 2. Occlusion Rates

Variable	RAD (n = 710)	RIMA (n = 74)	SVG (n = 576)	LIMA (n = 921)
Angio follow-up duration, mo	67.2 ± 30.9	61.6 ± 6.16	70.8 ± 30.2	64.1 ± 28.7
Occluded graft	67 (9.4)	10 (13.5)	101 (17.5)	21 (2.3)

Data are presented as mean ± SD or n (%).

LIMA, left internal mammary artery; RAD, radial artery; RIMA, right internal mammary artery; SVG, saphenous vein graft.

angiographic follow-up data stratified for the second conduit received are provided in **Supplementary Table 2**; Occlusion rates stratified according to the type of second conduit and target vessel are shown in **Supplementary Table 3**.

LAD analysis

Age, previous MI, surgical priority and LVEF <50% were significantly different between patients with open and occluded graft (**Supplementary Table 4**). However, at multivariable regression none of these variables was significantly associated with graft occlusion (**Table 3**).

Table 3. Risk Factors for Left Internal Thoracic Artery-to-Left Anterior Descending Occlusion

	Hazard Ratio (95% Confidence Interval)			
Variable	Univariable	*P* Value	Multivariable	*P* Value
Age, y	1.00 (0.95-1.06)	.86	…	…
Sex				
Female	…	…	…	…
Male	1.08 (0.36-3.21)	.89	…	…
Diabetes				
No	…	…	…	…
Yes	1.29 (0.54-3.08)	.56	…	…
Prior MI				
No	…	…	…	…
Yes	2.57 (1.07-6.14)	**.03**	2.38 (0.99-5.68)	.053
Elective surgery				
No	…	…	…	…
Yes	0.50 (0.21-1.18)	.11	…	…
Renal insufficiency				
No	…	…	…	…
Yes	0.74 (0.10-5.64)	.77	…	…
LVEF <0.50				
No	…	…	…	…
Yes	1.40 (0.57-3.44)	.47	…	…
Number of grafts	1.66 (0.98-2.82)	.06	1.60 (0.92-2.77)	.10
OPCABG				
No	…	…	…	…
Yes	0.00 (0.00-Inf)	.99	…	…

Bold *P* values are statistically significant.

Inf, infinity; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OPCABG, off-pump coronary artery bypass grafting.

Non-LAD analysis

At multivariable analysis the type of conduit used, age ≥ 75 years, female gender, LVEF <50% and use of the Y graft technique were significantly associated with graft occlusion (**Table 4**).

The RAD has significantly better patency rate than all the other conduits (**Figure 1**). This was confirmed for both the LCX and RCA distribution (**Figure 2**).

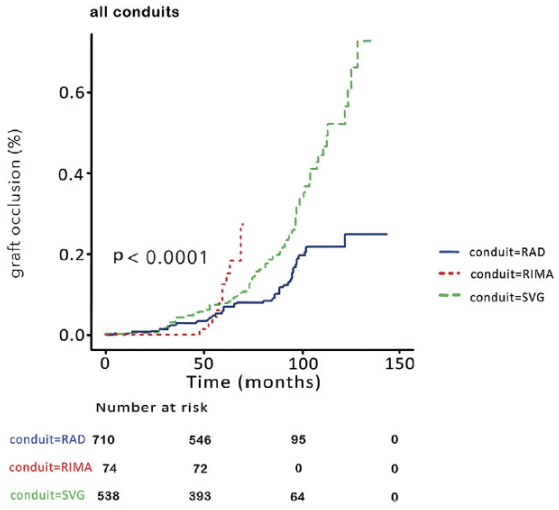


Figure 1. Occlusion rate by conduit. (RAD, radial artery; RIMA, right internal mammary artery; SVG, saphenous vein graft.)

The better patency rate of the RAD was confirmed for both genders, although for women the level of statistical significance was higher (**Figure 3**).

The use of the Y graft technique was associated with a significantly higher occlusion rate (**Figure 4**). This was mainly driven by the lower patency rate of RAD Y grafts; for the SVG the difference between aorta-anastomosed and Y grafts did not reach statistical significance (**Supplementary Figure 1**). Occlusion rates stratified for the type of proximal anastomosis are provided in **Supplementary Table 5**.

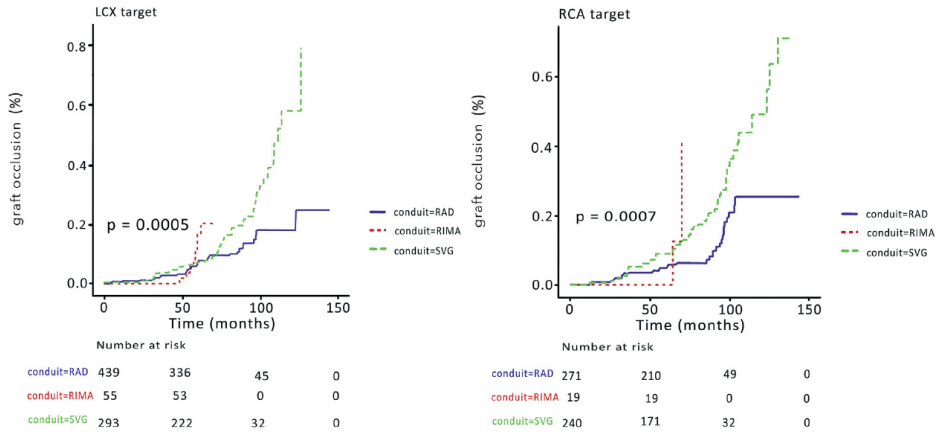


Figure 2. Occlusion rate by (Left) target vessel and (Right) conduit. (LCX, left circumflex coronary artery; RAD, radial artery; RCA, right coronary artery; RIMA, right internal mammary artery; SVG, saphenous vein graft.)

DISCUSSION

With 1091 patients and 2281 grafts at a mean follow-up of 65±29 months and a re-angiography rate of almost 72% RADIAL is one of the largest and the most complete coronary graft angiographic databases. The results of our analysis show that the failure of the LIMA to LAD bypass is a very uncommon event, so that even with a large patient sample, it was not possible to define independent risk factors for it.

For the non-LAD distribution, the non-use of the RAD, age ≥ 75 years, female gender, LVEF <50% and use of the Y graft configuration were significantly associated with mid-term graft failure.

Published observational angiographic databases on coronary graft failure are usually limited by the low rate of angiographic follow-up and the selection bias due to the fact that symptomatic patients are more likely to be submitted to re-angiography. Most of the available angiographic series on graft patency have a re-angiography rate between 20 and 40% (10,11) and are of often limited to cases of angina recurrence. The Project of Ex-vivo Vein Graft Engineering via Transfection (PREVENT) IV trial, the second largest prospective angiographic database after RADIAL, had an angiographic follow-up rate of 51%.(12) The low re-angiography rate and the fact that patients who missed follow up are likely to be different from patients who underwent re-angiography make extrapolation of the published results to the overall CABG population unreliable.

On the other hand, most of the included angiographic RCTs had a good re-angiography rate, and by pooling the five angiographic RCTs, this post-hoc analysis of RADIAL was aimed to overcome the power limitations of the individual studies.

The better patency rate of the RAD compared to the SVG has been firmly established.(2) We were able to confirm that the RAD outperforms the SVG for both the circumflex and right coronary distribution and in both genders (although the difference was larger in women). This is concordant with observational series with a high re-angiography rate.(13)

The RADIAL Database was not designed to compare the RIMA with any conduit. Although in this series the patency rate of the RITA is lower than reported, this analysis is clearly underpowered and should be viewed with skepticism.

Our finding of an increased failure rate for Y grafts is in contrast with those of other authors.(14) However, it is known that Y grafts (in particular using the RAD) are more sensitive to the detrimental effect of competitive flow (15) and this may be a potential mechanism behind their higher failure rate.

This study has important limitations. While the original studies were RCTs, this analysis shares the problems of observational series. Hidden and unmeasured confounders may persist despite statistical adjustment. Differences in surgical expertise, and follow-up angiographic protocols among trials may have influenced our findings.

Despite these limitations, RADIAL is one of the largest and most complete angiographic databases on CABG conduits. We confirm that failure of the LIMA to LAD bypass is a very

uncommon event. For the non-LAD distribution, the non-use of RAD, age ≥75 years, female gender, LVEF <50% and use of the Y graft configuration were significantly associated with mid-term graft failure. These patency data should inform future surgical planning and clinical decision making.

Table 4. Risk Factors for Graft Occlusion in the Non-Left Anterior Descending Distribution

	Hazard Ratio (95% Confidence Interval)			
Variable	Univariable	*P* Value	Multivariable	*P* Value
Conduit				
RAD	…	…	…	…
RIMA	2.83 (1.43-5.59)	.003	3.17 (1.57-6.38)	.001
SVG	2.02 (1.49-2.76)	<.001	2.08 (1.52-2.84)	<.001
Age				
<75 y	…	…	…	…
≥75 y	4.05 (2.57-6.40)	<.001	3.43 (2.08-5.64)	<.001
Sex				
Female	…	…	…	…
Male	0.56 (0.41-0.77)	<.001	0.59 (0.43-0.83)	.002
Diabetes				
No	…	…	…	…
Yes	1.21 (0.89-1.63)	.22	…	…
Prior MI				
No	…	…	…	…
Yes	1.07 (0.79-1.45)	.66	…	…
Elective surgery				
No	…	…	…	…
Yes	1.27 (0.89-1.81)	.19	…	…
Renal insufficiency				
No	…	…	…	…
Yes	1.27 (0.67-2.41)	.47	…	…
LVEF <0.50				
No	…	…	…	…
Yes	0.59 (0.41-0.84)	.003	0.68 (0.48-0.98)	.03
Target vessel				
LCX	…	…	…	…
RCA	1.03 (0.77-1.38)	.85	…	…
Proximal				
Aorta	…	…	…	…
Y graft	5.19 (2.62-10.30)	<.001	3.96 (1.43-10.97)	.008
Number of grafts	0.80 (0.64-0.99)	.04	…	…
OPCABG				
No	…	…	…	…
Yes	7.54 (3.05-18.62)	<.001	0.61 (0.15-2.44)	.48

Bold *P* values are statistically significant.

LCX, left circumflex coronary artery; LIMA, left internal mammary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OPCABG, off-pump coronary artery bypass grafting; RAD, radial artery; RCA, right coronary artery; RIMA, right internal mammary artery; SVG, saphenous vein graft.

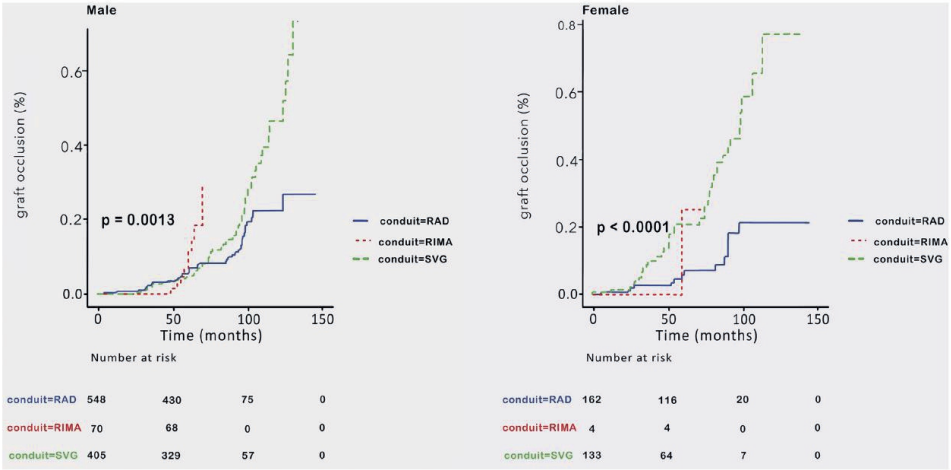


Figure 3. Occlusion rate by (Left) male and (Right) female sex and conduit. (RAD, radial artery; RIMA, right internal mammary artery; SVG, saphenous vein graft.)

REFERENCES

1. Halabi AR, Alexander JH, Shaw LK, et al. Relation of early saphenous vein graft failure to outcomes following coronary artery bypass surgery. Am J Cardiol 2005;96:1254–9.

2. Gaudino M, Benedetto U, Fremes S, et al. Radial-Artery or Saphenous-Vein Grafts in Coronary-Artery Bypass Surgery. N Engl J Med 2018;378:2069–77.

3. Buxton BF, Raman JS, Ruengsakulrach P, et al. Radial artery patency and clinical outcomes: five-year interim results of a randomized trial. J Thorac Cardiovasc Surg 2003;125:1363–71.

4. Deb S, Cohen EA, Singh SK, et al. 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.

5. 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;117:2859–64.

6. Petrovic I, Nezic D, Peric M, et al. Radial artery vs saphenous vein graft used as the second conduit for surgical myocardial revascularization: long-term clinical follow-up. J Cardiothorac Surg 2015;10:127.

7. 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;137:1093–100.

8. Song S-W, Sul S-Y, Lee H-J, Yoo K-J. 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;42:107–12.

9. 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;28:616–26.

10. Ruttmann E, Dietl M, Feuchtner GM, et al. Long-term clinical outcome and graft patency of radial artery and saphenous vein grafts in multiple arterial revascularization. J Thorac Cardiovasc Surg 2018; pii: S0022-5223(18)32929-5. doi: 10.1016/j.jtcvs.2018.10.135.

11. Tatoulis J, Buxton BF, Fuller JA. The right internal thoracic artery: the forgotten conduit--5,766 patients and 991 angiograms. Ann Thorac Surg 2011;92:9–15; discussion 15-17.

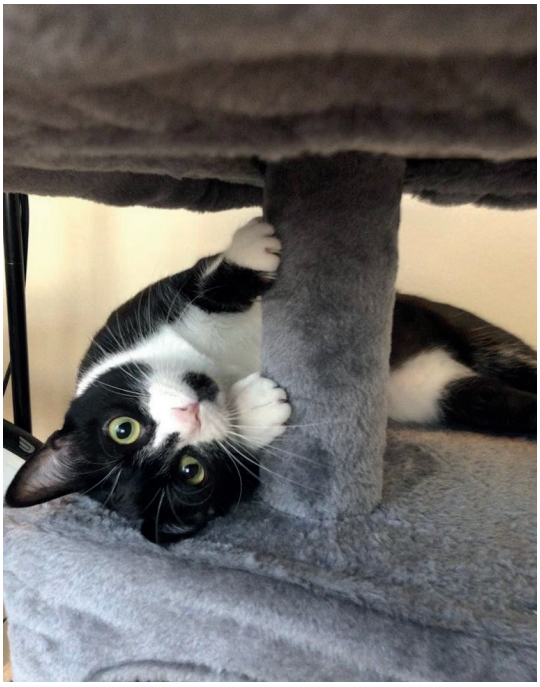
12. Harskamp RE, Alexander JH, Ferguson TB, et al. Frequency and Predictors of Internal Mammary Artery Graft Failure and Subsequent Clinical Outcomes: Insights From the Project of Ex-vivo Vein Graft Engineering via Transfection (PREVENT) IV Trial. Circulation 2016;133:131–8.

13. Gaudino M, Tondi P, Benedetto U, et al. Radial Artery as a Coronary Artery Bypass Conduit: 20-Year Results. J Am Coll Cardiol 2016;68:603–10.

14. Royse AG, Brennan AP, Ou-Young J, Pawanis Z, Canty DJ, Royse CF. 21-Year Survival of Left Internal Mammary Artery-Radial Artery-Y Graft. J Am Coll Cardiol 2018;72:1332–40.

15. Gaudino M, Alessandrini F, Pragliola C, et al. Effect of target artery location and severity of

stenosis on mid-term patency of aorta-anastomosed vs. internal thoracic artery-anastomosed radial artery grafts. Eur J Cardiothorac Surg 2004;25:424–8.



CHAPTER 7

Radial Artery vs Right Internal Thoracic Artery vs Saphenous Vein as the Second Conduit for Coronary Artery Bypass Surgery: a Network Meta-Analysis of Clinical Outcomes

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J Am Heart Assoc. 2019;22;8(2):e010839.

ABSTRACT

Background: There remains uncertainty regarding the second best conduit after the internal thoracic artery (ITA) in coronary artery bypass grafting (CABG). Few studies directly compared the clinical results of the radial artery (RA), right ITA (RITA) and saphenous vein (SV). No network meta-analysis (NMA) has compared these three strategies.

Methods and Results: MEDLINE and EMBASE were searched for adjusted observational studies and randomized controlled trials comparing the RA, SV and/or RITA as the second conduit for CABG. The primary endpoint was all-cause long-term mortality. Secondary endpoints were operative mortality, perioperative stroke, perioperative myocardial infarction (MI) and deep sternal wound infection (DSWI). Pairwise and NMAs were performed. 149,902 patients (4 randomized, 31 observational studies) were included (RA=16,201, SV=112,018, RITA=21,683). At NMA, the use of SV was associated with higher long-term mortality compared to the RA (incidence rate ratio (IRR)=1.23, 95%CI=1.12-1.34) and RITA (IRR=1.26, 95%CI=1.17-1.35). The risk of DSWI for SV was similar to RA but lower than RITA (OR=0.71, 95%CI=0.55-0.91). There were no differences for any outcome between RITA and RA, although DSWI trended higher with RITA (OR=1.39, 95%CI=0.92-2.1). The risk of DSWI in BITA studies was higher when the skeletonization technique was not used.

Conclusions: The use of the RA or the RITA is associated with a similar and statistically significant long-term clinical benefit compared to the SV. There are no differences in operative risk or complications between the two arterial conduits, but DSWI remains a concern with bilateral ITA when skeletonization is not used.

INTRODUCTION

One of the most important unresolved question in contemporary coronary artery bypass (CABG) surgery is the choice of the conduit to complement the internal thoracic to left anterior descending artery anastomosis.

The radial artery (RA), the right internal thoracic artery (RITA) and the saphenous vein (SV) are all being currently used routinely, although the majority of the surgeons favor the SV.

Abundant observational evidence suggests a survival benefit for the use of arterial grafts and the current guidelines encourage a wider use of the RA or the RITA especially in patients with long life expectancy.(1–4) However, the reported benefit of arterial grafts has not been confirmed in a large RCT and it has been hypothesized that the survival benefit seen in observational studies may be due to unmatched confounders and treatment allocation bias.(5,6) An important additional unresolved question is the relative role of the RITA and RA. Although the RITA is biologically identical to the left internal thoracic artery, data comparing the patency rate and clinical outcome of the two arterial grafts has been contradictory and inconclusive.(7,8)

Network meta-analysis (NMA) with adjusted indirect comparison among treatments is a useful technique to reduce potential for heterogeneity or allocation biases, in particular when analyzing both RCT and observational studies.(9)

To date, the only published NMA comparing the SV, RITA and RA as the second conduit in CABG focused only on angiographic patency and not on clinical outcomes.(10) Due to the well-known discrepancy between occlusion of grafts to non-left anterior descending arteries and

clinical outcomes,(11) a similar analysis focusing on clinical endpoints is of particular relevance to the surgical community.

Here, we performed a NMA with the aim to specifically investigate the differences in late survival (primary outcome) and other clinical outcomes according to the type of second graft used for CABG.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files. This systematic review and network meta-analysis, follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.(12)

Data sources and Systematic Literature Review

Ovid's version of MEDLINE and EMBASE were searched from add year here to February 2018 (full search strategy attached in **Supplementary Table 1**). Inclusion criteria were: English language publications, adjusted or matched observational studies or RCTs comparing RA and/or SV and/or RITA as the second conduit for CABG. In addition, we searched recent meta-analyses and reviews on this topic for potential additional studies. All citations were reviewed by three investigators independently (A.A., A.D.F. and M.R.) and any disagreements were resolved by consensus. In case of overlapping studies, the largest series were included.

Data extraction and quality assessment

Data extraction was performed independently by two investigators (A.A. and A.D.F.). The following variables were included: study demographics (sample size, number of centers, institutions involved, publication year, study period, design and country, length of follow-up), patient demographics (age, sex, diabetes and ejection fraction) and procedural (use of skeletonization) and postoperative data. The quality of the included studies was assessed by the Newcastle-Ottawa Scale (NOS - **Supplementary Table 2**).(13) Only RCTs and observational studies of high quality (NOS score >6) were included in the final analysis.

Outcomes

The primary outcome was all-cause long-term mortality. The secondary outcomes were operative mortality, perioperative stroke, perioperative myocardial infarction (MI), and deep sternal wound infection (DSWI), as defined in the original articles.

Two levels of analyses were conducted for all outcomes: A) Pairwise meta-analysis between arterial grafts (with either RITA or RA) and SV and between RITA and RA. B) Network meta-analyses between RITA, RA and SV.

Data synthesis and analysis

Pairwise Meta-analysis

Late outcomes were pooled as the natural logarithm of the incident rate ratio (IRR) to account for potentially different follow-up durations between the groups. We estimated the IRR through several means depending on the available study data. When hazard ratios (HRs) for matched (preferentially) /adjusted cohorts were provided, we took the natural logarithm of the HR; the standard error (SE) was derived from the 95% CI or log rank p-value.(14) When Kaplan Meier (K-M) curves were present, we estimated the event rates from the curves using GetData Graph Digitizer software 2.26 (http://getdata-graph-digitizer.com/). In case of missing K-M curves, we used the reported event rates in order to calculate the IRR, as previously described.(15,16) Short-term binary outcomes were pooled using log odds ratio (OR) with 95% confidence interval (95%CI) using the generic inverse variance method.[9] Random effect meta-analysis was performed using meta and metafor packages in R (version 3.3.3 R Project for Statistical Computing).(17,18)

Heterogeneity was reported as: low (I^2=0-25%), moderate (I2 =26-50%), high (I^2>50%).(19) In random-effects meta-analysis, the extent of variation among the effects observed in different studies (between-study variance) is referred to as Tau^2 (i.e. the variance of the true effect size parameters across the population of studies). Tau^2 reflects the amount of true variance (heterogeneity) while Tau is the estimated standard deviation of underlying true effects across studies and they are used to describe the distribution of true effects; if there is no variance between studies, Tau^2 is low (or zero).(20–22) We reported Tau^2 values throughout Tables and Figures, as appropriate.

Sensitivity analysis using leave-one-out analysis and publication bias assessment by funnel plot and Egger's test were conducted for the primary outcome. Subgroup analysis was used to compare the relative results of RITA and RA vs SV. Meta-regression was used to explore the effect of age, gender diabetes and preoperative ejection fraction on the IRR for the primary outcome.

Network meta-analysis

Network (Multiple-treatment) meta-analysis was conducted in R (version 3.3.3 R Project for Statistical Computing) using "netmeta" statistical package based on the method described by Rücker.(23–25) Inconsistency was evaluated with Cochran's Q.(26) Pooled log incidence rate ratios (IRR) with 95% confidence intervals (CIs) was used to determine the relative effect estimates of late outcomes. Odds ratios (ORs) with 95% CIs were used for the binary outcomes. A random effect model was preferentially used to improve the model fit but results using a fixed model were also reported.

Inconsistency in NMA was evaluated by conducting conventional pairwise meta-analyses and testing consistency by comparing the direct and indirect evidence. Consistency equation used was μBC = μAC - μAB where μAB is the treatment effect for treatment B compared to treatment A.(27,28) We used Cochran's Q statistic to assess inconsistency and presence of $P<0.05$ signifies inconsistency. Statistical significance (at the 5% level) was declared when 95% confidence interval did not cross the line of no effect. For the primary outcome, a Network Meta-Regression (NMR) was used to relate the size of treatment effect to potential effect modifiers (mean age, percentage of female, percentage of diabetics and mean preoperative ejection fraction). NMR was conducted using logit transformation method with random effect model with no priori. The logit transformation was used as suggested by other authors.(29,30)

RESULTS

Description of the included studies and of the population

A total of 2,455 studies were retrieved and 35 met inclusion criteria and were included in the final meta-analysis (**Supplementary Figure 1**). Seven studies were international and multicenter, eleven studies were from USA, four from Canada, three from each of Italy and United Kingdom, two from each of Japan and Australia and one from each of Austria, Serbia and Argentina (**Tables 1 and 2**).(31–65)

A total of 149,902 patients were included (RA =16,201, SV=112,018 and RITA=21,683) from 4 RCTs (n=1,932) and 31 observational studies (n=147,970). Demographics of the included studies are shown in **Tables 1 and 2**.

The number of patients in the individual studies ranged from 182 to 48,241 (91 to 4577 in the RA group, 91 to 46343 in the SV group and 118 to 2215 in the RITA group). The mean age ranged from 56.0 to 72.1 (56.3 to 72.1 years in the RA group, 57.1 to 70.6 years in the SV group and 56.2 to 69.2 in the RITA group). Female gender ranged from 1.1 to 43.8% (1.0 to 43.1% in the RA group, 1.1 to 41.6% in the SV group and 7.3 to 43.8% in the SV group). Most patients had a normal or low-normal EF (range 42-59.4%). The incidence of diabetes ranged from 5.1 to 53.2% (6.5 to 45.1% in the RA group, 12.0 to 43.8% in the SV group and 5.1 to 53.3% in the RITA group).

Pairwise Meta-analysis

The main results of the pairwise meta-analysis are summarized in **Table 3**.

At a mean follow-up of 6.9 years, the use of any arterial graft (RA or RITA) was associated with lower long-term mortality compared to the use of the SV (IRR 0.80, 95%CI= 0.75-0.85). There was a significantly higher risk of DSWI (OR 1.27, 95%CI=1.05-1.54) in the arterial graft group. Operative mortality (OR 0.68, 95%CI= 0.55-0.83), perioperative MI (OR 0.77, 95%CI= 0.64-0.92) and perioperative stroke (OR 0.80, 95%CI= 0.65-0.98) were lower in the arterial graft group.

The use of the RA was associated with lower long-term mortality (IRR=0.81, 95%CI=0.73-0.90) at a mean follow-up of 8.1 years compared to the SV. Operative mortality (OR 0.66, 95%CI= 0.46-0.95) and perioperative stroke (OR= 0.73, 95%CI=0.54-1.00) were lower in the RA group, while the risk of perioperative MI (OR= 0.67, 95%CI 0.42-1.07) and DSWI were similar (OR= 1.10, 95%CI= 0.80-1.51).

The use of the RITA was associated with lower long-term mortality (IRR=0.80, 95%CI= 0.73-0.86) at mean 8.5 years follow-up compared to SV. Perioperative MI (OR=0.79, 95%CI 0.65-0.96) and operative mortality (OR=0.68, 95%CI= 0.53-0.87) were lower in the RITA arm. There was no difference in perioperative stroke (OR=0.85, 95%CI= 0.62-1.16), while the risk of DSWI higher in the RITA group (OR=1.33, 95%CI= 1.04-1.69).

When directly comparing the two arterial grafts, the use of RITA was associated with similar long-term mortality (IRR=0.96, 95%CI=0.83-1.11) at 7.1 years mean follow-up compared to the RA. The risk of perioperative MI (OR=0.32, 95%CI 0.03-3.13) and perioperative stroke (OR= 0.87, 95%CI=0.45-1.68) were similar between the two arterial grafts. There was a significantly higher risk of DSWI (OR=2.22, 95%CI=1.09-4.54) and operative mortality (OR=1.76, 95%CI: 1.21-2.55) in the RITA group. When limiting the analysis to the studies where the skeletonization technique was

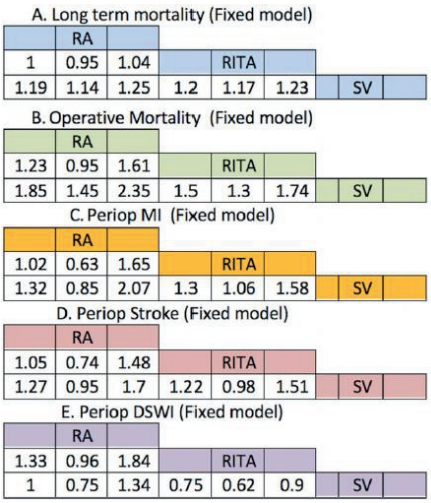
used for ITA harvesting, no difference in DSWI between the RA and RITA groups was found (**Supplementary Figure 2)**.

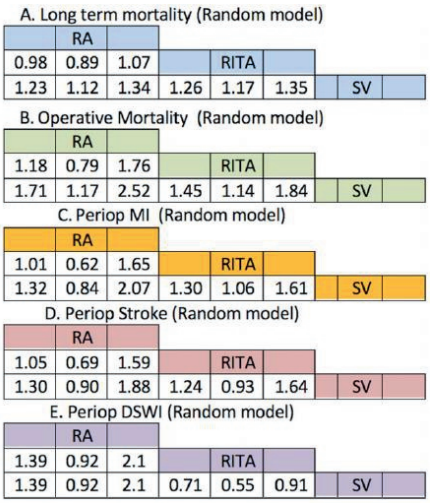
A subgroup analysis for the primary outcome comparing the results of RCTs vs non-RCTs studies is provided in the **Supplementary Material** (**Supplementary Figure 3**).

Leave one out analysis was robust for the primary outcome in the main analysis (arterial grafts vs SV. (**Supplementary Figure 4a**). Funnel plot Egger's test intercept for the primary outcome in arterial versus venous comparison was -0.64±0.46, P=0.17 (**Supplementary Figure 4b**).

Network Meta-analysis

The results of the network meta-analysis are summarized in **Figure 1, Supplementary Tables 3 and 4**.





The use of the SV was associated with higher late mortality (IRR=1.23, 95%CI=1.12-1.34) and operative mortality (OR=1.71, 95%CI=1.17-2.52) compared to the RA. The risk of perioperative MI (OR=1.32, 95%CI=0.84-2.07) perioperative stroke (OR=1.30, 95%CI=0.90-1.88) and DSWI (OR=0.98, 95%CI=0.67-1.46) was not statistically different was similar when compared to the RA.

The use of the SV 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 to the RITA. The risk of perioperative stroke (OR=1.24, 95%CI=0.93-1.64) was not

Table 3. Outcomes Summary of the Pairwise Meta-Analysis

Model	Studies*	Point Estimate†	95% CI	Overall Effect (Z-Value, *P* Value)	Heterogeneity (I^2, *P* Value)	Tau^2	Interpretation
Long term mortality							
RA/SV	11	0.81	0.73 to 0.90	···	47, 0.04	0.0110	Better in RA
RITA/SV	17	0.80	0.73 to 0.86	···	73, <0.01	0.0136	Better in RITA
RITA/RA	9	0.96	0.83 to 1.11	···	57, 0.02	0.0204	ND
ART/SV	28	0.80	0.75 to 0.85	−6.93, <0.0001	66, <0.01	0.0115	Better in ART
Perioperative DSWI							
RA/SV	8	1.10	0.80 to 1.51	···	0, 0.48	0	ND
RITA/SV	14	1.33	1.04 to 1.69	···	24, 0.20	0.0463	Higher in RITA
RITA/RA	6	2.22	1.09 to 4.54	···	40, 0.14	0.2795	Higher in RITA
ART/SV	21	1.27	1.05 to 1.54	2.41, 0.0159	14, 0.27	0.0264	Higher in ART
Perioperative mortality							
RA/SV	7	0.66	0.46 to 0.95	−2.27, 0.0234	29, 0.21	0.0599	Better in RA
RITA/SV	17	0.68	0.53 to 0.87	−3.11, 0.0019	56,	0.1327	Better in RITA
RITA/RA	7	1.76	1.21 to 2.55	2.98, 0.0029	11.7, 0.34	0.0310	Better in RA
ART/SV	24	0.68	0.55 to 0.83	−3.79, 0.0002	49.1, 0.004	0.1043	Better in ART
Perioperative stroke							
RA/SV	7	0.73	0.54 to 1.00	···	0, 0.72	0	Better in RA
RITA/SV	11	0.85	0.62 to 1.16	···	36, 0.11	0.0875	ND
RITA/RA	5	0.87	0.45 to 1.68	···	29, 0.23	0.1653	ND
ART/SV	18	0.80	0.65 to 0.98	−2.11, 0.0350	14, 0.29	0.0266	Better in arterial
Perioperative MI							
RA/SV	7	0.67	0.42 to 1.07	···	0, 0.56	0	ND
RITA/SV	8	0.79	0.65 to 0.96	···	0, 0.65	0	Better in RITA
RITA/RA	2	0.32	0.03 to 3.13	···	61.1, 0.11	1.67	ND
ART/SV	15	0.77	0.64 to 0.92	−2.82, 0.0048	0, 0.73	0	Better in ART

ART indicates all arterial grafts; DSWI, deep sternal wound infections; MI, myocardial infarction; ND, no difference; RA, radial artery; RITA, right internal thoracic artery; SV, saphenous vein.
*Articles reporting the outcomes in RA, RITA, and SV cohorts were included as 3 studies (RA/SV, RITA/SV, and RITA/RA).
†Incidence rate ratio was used for long-term mortality, while odds ratio was used for operative mortality and perioperative outcomes.

statistically different, and the risk of DSWI (OR=0.71, 95%CI=0.55-0.91) was lower with the SV compared to the RITA.

The use of RITA was associated with similar late mortality (IRR 0.98, 95%CI 0.89-1.07) and perioperative MI (OR 1.01, 95%CI 0.62-1.65) compared to the RA. There was a trend towards higher risk of DSWI in the RITA group (OR=1.39, 95%CI=0.92-2.1), while operative mortality and stroke were similar for the two arteries.

At NMR, mean age, percentage of female, percentage of diabetics and mean preoperative ejection fraction were not found to significantly modify the treatment effect (**Supplementary Figure 5**).

DISCUSSION

The balance between possible better long-term clinical and angiographic outcomes of arterial grafts and the potential risk of harvesting site complications and the increased technical complexity associated to their use, has been the center of a continuous debate over the last 25 years.(66) Also, the relative efficacy of the RITA and RA as the second arterial grafts remains controversial.(7)

Several pairwise meta-analysis on the topic have been previously published.(1,67,68) However pairwise meta-analyses have known limitations in terms of heterogeneity of the included studies and potential for treatment allocation bias. NMAs have been proposed to overcome the limitations of the pairwise comparison, especially when summarizing the evidence of RCT and observational studies.(9,69) It has been suggested that NMA can be superior to classical pairwise analyses especially in case of comparison of a new treatment to a standard one.(70)

This is the first NMA specifically addressing the differences in clinical outcomes according to the type of second graft used for CABG. The only published network meta-analysis on the subject focused only on the patency rates of conduits and did not include clinical outcomes.(10) Due to the demonstrated absence of a consistent correlation between angiographic failure and clinical events,(11) a deeper understanding of the clinical impact of the type of second conduit used for CABG seems of major relevance.

The results of our study support the superiority of the use of a second arterial over venous graft, and suggest the equivalence in long-term and perioperative outcomes among RITA and RA.

The superior mid-term patency rate of arterial grafts (especially the RA) has been convincingly demonstrated in RCTs and observational studies.(50,71–74) A large amount of observational evidence also suggest a clinical benefit in term of survival and event-free survival for the use of the RA or the RITA instead of the SV as the second graft.(1,7,75,76) However, we have recently shown how unmatched confounders are present even in the best comparative observational studies and suggested that a treatment allocation bias may be responsible for the better clinical outcome of patients receiving more than one arterial graft.(6)

This type of bias is potentially present even in the present meta-analysis, but the additional power and precision of NMA in defining relations and interactions between treatments from the aggregated estimates of all the available evidence should permit a more efficient comparison among different strategies.(9)

Our results are in line with those of a recent patient-level meta-analysis on the comparison between the RA and the SV.(76) However, at first sight, our results appear to contradict the overall neutral findings of the Arterial Revascularization Trial (ART) where, on the primary intention to treat analysis, there was no difference in survival between single and bilateral ITA grafts at 10 years (in press). However, 40% of patients in the ART trial received a different treatment from that initially proposed and an as treated analysis showed a significant survival benefit in patients receiving more than one arterial graft consistent with the results of the current study. Difference in sample size and length of follow-up and the fact that in observational studies the revascularization strategy is based on surgical judgement and not mandated by protocol are possible explanations for these apparent contradictions.

A key finding of this study is the demonstration of equivalence between the RITA and RA in respect to all the short and long-term clinical outcomes. Of note, in our analysis the relative survival benefit of the RITA and RA compared to the SV were identical (SV versus RITA and RA IRR=1.26, 95%CI=1.17-1.35). Although there was a trend towards higher risk of DSWI with RITA, this risk became non-significant in a subgroup analysis of studies where the skeletonization of ITA was employed. This finding is in accordance with what reported by previous meta-analyses(7) and by a post-hoc analysis of the ART trial.(77)

The literature on the comparison between RITA and RA is discordant. We previously published a pairwise meta-analysis of the propensity matched studies comparing the two arterial grafts and found that the use of RITA was associated with a 25% relative reduction in the risk of long-term mortality.(7) The reason underlying the discrepancy between our previous meta-analysis and the present findings is probably related to the different sample size (149,902 patients with 6.9 years of follow-up for the present analysis versus 15,374 patients and a range of 45 to 168 months follow-up for the previous pairwise comparison). Also, our previous analysis did not include two recent large studies comparing the two arterial grafts.(33,40) Finally, the use of NMA and direct/indirect comparisons allow for better precision around estimates compared to pairwise comparisons.

Of note, in a large study the Society of Thoracic Surgeons National Database of more than 1.4 million patients, Schwann et al. showed significantly higher perioperative mortality and risk of DSWI using the RITA, but not the RA, versus the SV as the second graft – findings that were also demonstrated in this present study.(8) The authors also described a significant volume to outcome

relation for the use of RITA, but not of the RA. Similarly, in a meta-analysis of 34 BITA series and 27,000 BITA patients, we recently identified a highly significant BITA use-to-outcome relationship for long-term survival and incidence of DSWI that was independent from the well-known CABG volume/outcome effect.(78) These findings suggest that BITA grafting may be more technically demanding than the use of the single ITA and that a volume/outcome relation can explain the marginally increased operative risk in the RITA arm.

A key point when using the RA for CABG is the degree of target vessel stenosis. It has been shown that the patency rate of RA grafts is strongly influenced by the degree of target coronary stenosis.(79–81) In fact, a target vessel stenosis >70% was a common criteria for using the RA in the studies included in this meta-analysis (**Table 2**).

This study shares the usual limitations of meta-analyses of observational studies.(82) Despite statistical adjustment and the use of NMA, between-studies heterogeneity remains a source of bias. Important details such as the etiology of follow-up of death, the protocols used to reduce the risk of DSWI (with the exception of skeletonization of the ITA) and the incidence of repeat revascularization were not systematically retrievable and could not be included in our analyses.

Additionally, we recognize that despite including only adjusted studies, the presence of unmeasured confounders and treatment allocation biases cannot be excluded.(6) However, the NMA approach utilized and the low-moderate grade heterogeneity found across the studies should have attenuated these biases.

In conclusion, in a NMA of adjusted observational and randomized studies comparing the RA, the RITA and the SV as the second conduit for CABG, we found that the use of the RITA or the RA was associated with a similar long term clinical benefit compared to the use of the SV. No differences in late and operative mortality, and postoperative complications was found between the two arterial conduits, although DSWI remains a concern after BITA grafting if skeletonization is not used.

REFERENCES

1. 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 Br Card Soc 2017;103:1419–26.

2. Authors/Task Force members, Windecker S, Kolh P, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541–619.

3. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. Circulation 2016;134:e123-155.

4. Aldea GS, Bakaeen FG, Pal J, et al. The Society of Thoracic Surgeons Clinical Practice Guidelines on Arterial Conduits for Coronary Artery Bypass Grafting. Ann Thorac Surg 2016;101:801–9.

5. Taggart DP, Altman DG, Gray AM, et al. Randomized Trial of Bilateral versus Single Internal-Thoracic-Artery Grafts. N Engl J Med 2016;375:2540–9.

6. Gaudino M, Di Franco A, Rahouma M, 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.

7. Benedetto U, Gaudino M, Caputo M, et al. 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.

8. Schwann TA, Habib RH, Wallace A, et al. Operative Outcomes of Multiple-Arterial Versus Single-Arterial Coronary Bypass Grafting. Ann Thorac Surg 2018;105:1109–19.

9. Song F, Harvey I, Lilford R. Adjusted indirect comparison may be less biased than direct comparison for evaluating new pharmaceutical interventions. J Clin Epidemiol 2008;61:455–63.

10. 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 Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg 2015;47:59–65; discussion 65.

11. Gaudino M, Antoniades C, Benedetto U, et al. Mechanisms, Consequences, and Prevention of Coronary Graft Failure. Circulation 2017;136:1749–64.

12. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;151:W65-94.

13. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M. Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in metaanalysis. 3rd Symp Syst Rev Basics Improv Qual Impact 2000;

14. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998;17:2815–34.

15. Yanagawa B, Verma S, Jüni P, et al. A systematic review and meta-analysis of in situ versus composite bilateral internal thoracic artery grafting. J Thorac Cardiovasc Surg 2017;153:1108-1116.e16.

16. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.

17. Schwarzer G. meta: An R package for meta-analysis. R News 2007;7:40–5.

18. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 36:1–48.

19. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

20. Deeks J, Higgins J, Altman DG. Analysing data and undertaking meta-analyses. In: Cochrane handbook for systematic reviews of interventions: Cochrane book series. 2008. p. 243–96.

21. Borenstein M, Hedges L, Higgins J, Rothstein H. Introduction to meta-analysis. West Sussex, England: John Wiley & Sons; 2009.

22. Borenstein M, Hedges L, Rothstein H. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010;1:97–111.

23. Rücker G, Schwarzer G, Krahn U, König J. netmeta:Network Meta-Analysis using Frequentist Methods. R package version 0.9-7. [Internet]. 2017;Available from: https://CRAN.R-project.org/package=netmeta

24. Rücker G, Schwarzer G, König J. Netmeta: Network meta-analysis with R. Version 0.6-0 2014. 12. 2014;

25. Rücker G. Network meta-analysis, electrical networks and graph theory. Res Synth Methods 2012;3:312–24.

26. Krahn U, Binder H, König J. A graphical tool for locating inconsistency in network meta-analyses. BMC Med Res Methodol 2013;13:35.

27. Higgins JP, Whitehead A. Borrowing strength from external trials in a meta-analysis. Stat Med 1996;15:2733–49.

28. Higgins JP. Identifying and addressing inconsistency in network meta-analysis. Cochrane comparing multiple interventions methods group Oxford training event. 2013;

29. Gengsheng Qin null, Hotilovac L. Comparison of non-parametric confidence intervals for the area under the ROC curve of a continuous-scale diagnostic test. Stat Methods Med Res 2008;17:207–21.

30. Snell KI, Ensor J, Debray TP, Moons KG, Riley RD. Meta-analysis of prediction model performance across multiple studies: Which scale helps ensure between-study normality for the C-statistic and calibration measures? Stat Methods Med Res 2018;27:3505–22.

31. 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;146:1078–84; discussion 1084-1085.

32. Benedetto U, Amrani M, Gaer J, et al. The influence of bilateral internal mammary arteries on short- and long-term outcomes: a propensity score matching in accordance with current recommendations. J Thorac Cardiovasc Surg 2014;148:2699–705.

33. Benedetto U, Caputo M, Gaudino M, et al. Right internal thoracic artery or radial artery? A propensity-matched comparison on the second-best arterial conduit. J Thorac Cardiovasc Surg 2017;153:79-88.e4.

34. Buxton BF, Komeda M, Fuller JA, Gordon I. Bilateral internal thoracic artery grafting may improve outcome of coronary artery surgery. Risk-adjusted survival. Circulation 1998;98:II1-6.

35. Calafiore AM, Di Giammarco G, Teodori G, et al. Late results of first myocardial revascularization in multiple vessel disease: single versus bilateral internal mammary artery with or without saphenous vein grafts. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg 2004;26:542–8.

36. Carrier M, Cossette M, Pellerin M, et al. Statin treatment equalizes long-term survival between patients with single and bilateral internal thoracic artery grafts. Ann Thorac Surg 2009;88:789–95; discussion 795.

37. Cohen G, Tamariz MG, Sever JY, et al. The radial artery versus the saphenous vein graft in contemporary CABG: a case-matched study. Ann Thorac Surg 2001;71:180–5; discussion 185-186.

38. Dewar LR, Jamieson WR, Janusz MT, et al. Unilateral versus bilateral internal mammary revascularization. Survival and event-free performance. Circulation 1995;92:II8-13.

39. Goldman S, Sethi GK, Holman W, et al. Radial artery grafts vs saphenous vein grafts in coronary artery bypass surgery: a randomized trial. JAMA 2011;305:167–74.

40. Goldstone AB, Chiu P, Baiocchi M, et al. Second Arterial Versus Venous Conduits for Multivessel Coronary Artery Bypass Surgery in California. Circulation 2018;137:1698–707.

41. Grau JB, Johnson CK, Kuschner CE, et al. Impact of pump status and conduit choice in coronary artery bypass: A 15-year follow-up study in 1412 propensity-matched patients. J Thorac Cardiovasc Surg 2015;149:1027-1033.e2.

42. Hayward PA, Buxton BF. Mid-term results of the Radial Artery Patency and Clinical Outcomes randomized trial. Ann Cardiothorac Surg 2013;2:458–66.

43. Ioannidis JP, Galanos O, Katritsis D, et al. Early mortality and morbidity of bilateral versus single internal thoracic artery revascularization: propensity and risk modeling. J Am Coll Cardiol 2001;37:521–8.

44. Janiec M, Dimberg A, Nazari Shafti TZ, Lagerqvist B, Lindblom RPF. No improvements in long-term outcome after coronary artery bypass grafting with arterial grafts as a second conduit: a Swedish nationwide registry study. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg 2017;

45. Kurlansky PA, Traad EA, Dorman MJ, Galbut DL, Zucker M, Ebra G. Thirty-year follow-up defines survival benefit for second internal mammary artery in propensity-matched groups. Ann Thorac Surg 2010;90:101–8.

46. LaPar DJ, Crosby IK, Rich JB, et al. Bilateral Internal Mammary Artery Use for Coronary Artery Bypass Grafting Remains Underutilized: A Propensity-Matched Multi-Institution Analysis. Ann Thorac Surg 2015;100:8–14; discussion 14-15.

47. Lin J, Cheng W, Czer LS, et al. Coronary artery bypass graft surgery using the radial artery as a secondary conduit improves patient survival. J Am Heart Assoc 2013;2:e000266.

48. Locker C, Schaff HV, Dearani JA, Daly RC. Improved late survival with arterial revascularization. Ann Cardiothorac Surg 2013;2:467–74.

49. Lytle BW, Blackstone EH, Sabik JF, Houghtaling P, Loop FD, Cosgrove DM. The effect of bilateral internal thoracic artery grafting on survival during 20 postoperative years. Ann Thorac Surg 2004;78:2005–12; discussion 2012-2014.

50. 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;137:1093–100.

51. Navia DO, Vrancic M, Piccinini F, et al. Myocardial Revascularization Exclusively With Bilateral Internal Thoracic Arteries in T-Graft Configuration: Effects on Late Survival. Ann Thorac Surg 2016;101:1775–81.

52. Parsa CJ, Shaw LK, Rankin JS, et al. Twenty-five-year outcomes after multiple internal thoracic artery bypass. J Thorac Cardiovasc Surg 2013;145:970–5.

53. Petrovic I, Nezic D, Peric M, et al. Radial artery vs saphenous vein graft used as the second conduit for surgical myocardial revascularization: long-term clinical follow-up. J Cardiothorac Surg 2015;10:127.

54. Pusca SV, Kilgo PD, Vega JD, et al. Propensity-score analysis of early outcomes after bilateral versus single internal thoracic artery grafting. Innov Phila Pa 2008;3:19–24.

55. Rosenblum JM, Harskamp RE, Hoedemaker N, et al. Hybrid coronary revascularization versus coronary artery bypass surgery with bilateral or single internal mammary artery grafts. J Thorac Cardiovasc Surg 2016;151:1081–9.

56. Ruttmann E, Fischler N, Sakic A, et al. Second internal thoracic artery versus radial artery in coronary artery bypass grafting: a long-term, propensity score-matched follow-up study. Circulation 2011;124:1321–9.

57. Santarpino G, Onorati F, Cristodoro L, Scalas C, Mastroroberto P, Renzulli A. Radial artery graft flowmetry is better than saphenous vein on postero-lateral wall. Int J Cardiol 2010;143:158–64.

58. Schwann TA, Hashim SW, Badour S, et al. Equipoise between radial artery and right internal thoracic artery as the second arterial conduit in left internal thoracic artery-based coronary artery bypass graft surgery: a multi-institutional study†. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg 2016;49:188–95.

59. Stevens LM, Carrier M, Perrault LP, et al. Single versus bilateral internal thoracic artery grafts with concomitant saphenous vein grafts for multivessel coronary artery bypass grafting: effects on mortality and event-free survival. J Thorac Cardiovasc Surg 2004;127:1408–15.

60. Tarelli G, Mantovani V, Maugeri R, et al. Comparison between single and double internal mammary artery grafts: results over ten years. Ital Heart J Off J Ital Fed Cardiol 2001;2:423–7.

61. Tranbaugh RF, Dimitrova KR, Friedmann P, et al. Radial artery conduits improve long-term survival after coronary artery bypass grafting. Ann Thorac Surg 2010;90:1165–72.

62. Tranbaugh RF, Schwann TA, Swistel DG, et al. Coronary Artery Bypass Graft Surgery Using the Radial Artery, Right Internal Thoracic Artery, or Saphenous Vein as the Second Conduit. Ann Thorac Surg 2017;104:553–9.

63. Tsuneyoshi H, Komiya T, Shimamoto T, et al. The second best arterial graft to the left coronary system in off-pump bypass surgery: a propensity analysis of the radial artery with a proximal anastomosis to the ascending aorta versus the right internal thoracic artery. Gen Thorac Cardiovasc Surg 2015;63:335–42.

64. Yoshida S, Numata S, Tsutsumi Y, et al. Short- and long-term results of radial artery and saphenous vein grafts in the right coronary system: a propensity-matched study. Surg Today 2017;47:335–43.

65. Zacharias A, Habib RH, Schwann TA, Riordan CJ, Durham SJ, Shah A. Improved survival with radial artery versus vein conduits in coronary bypass surgery with left internal thoracic artery to left anterior descending artery grafting. Circulation 2004;109:1489–96.

66. 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;95:1938–45.

67. 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;130:539–45.

68. Takagi H, Goto S, 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;148:1282–90.

69. Greco T, Landoni G, Biondi-Zoccai G, D'Ascenzo F, Zangrillo A. A Bayesian network meta-analysis for binary outcome: how to do it. Stat Methods Med Res 2016;25:1757–73.

70. Chalmers I, Matthews R. What are the implications of optimism bias in clinical research? Lancet Lond Engl 2006;367:449–50.

71. Gaudino M, Tondi P, Benedetto U, et al. Radial Artery as a Coronary Artery Bypass Conduit: 20-Year Results. J Am Coll Cardiol 2016;68:603–10.

72. Buxton BF, Raman JS, Ruengsakulrach P, et al. Radial artery patency and clinical outcomes: five-year interim results of a randomized trial. J Thorac Cardiovasc Surg 2003;125:1363–71.

73. Glineur D, D'hoore W, de Kerchove L, et al. Angiographic predictors of 3-year patency of bypass grafts implanted on the right coronary artery system: a prospective randomized comparison of gastroepiploic artery, saphenous vein, and right internal thoracic artery grafts. J Thorac Cardiovasc Surg 2011;142:980–8.

74. Deb S, Cohen EA, Singh SK, et al. 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.

75. Taggart DP, Altman DG, Flather M, et al. 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;136:454–63.

76. Gaudino M, Benedetto U, Fremes S, et al. Radial-Artery or Saphenous-Vein Grafts in Coronary-Artery Bypass Surgery. N Engl J Med 2018;

77. Benedetto U, Altman DG, Gerry S, et al. 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;152:270–6.

78. Gaudino M, Bakaeen F, Benedetto U, 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.

79. Maniar HS, Sundt TM, Barner HB, et al. Effect of target stenosis and location on radial artery graft patency. J Thorac Cardiovasc Surg 2002;123:45–52.

80. Hashimoto H, Isshiki T, Ikari Y, et al. Effects of competitive blood flow on arterial graft patency and diameter. Medium-term postoperative follow-up. J Thorac Cardiovasc Surg 1996;111:399–407.

81. Manninen HI, Jaakkola P, Suhonen M, Rehnberg S, Vuorenniemi R, Matsi PJ. Angiographic predictors of graft patency and disease progression after coronary artery bypass grafting with arterial and venous grafts. Ann Thorac Surg 1998;66:1289–94.

82. Song F, Xiong T, Parekh-Bhurke S, et al. Inconsistency between direct and indirect comparisons of competing interventions: meta-epidemiological study. BMJ 2011;343:d4909.

Table 1. Characteristics of the Included Studies

Author/Year	Study Period	Mean/Median SD Follow-Up (Years)	Hospitals/Centers	Type
Benedetto 2013[31]	1996–2012	6.4±3.6	Papworth Hospital, Cambridge, England	PSM
Benedetto 2014[32]	2001–2013	4.0±3.2	Harefield Hospital, London, United Kingdom	PSM
Benedetto 2017[33]	1996–2015	10.2±4.5	Bristol Heart Institute, United Kingdom	PSM
Buxton 1998[34]	1985–1995	4.3	Austin and Repatriation Medical Center, University of Melbourne, Victoria, Australia	Adjusted
Calafiore 2004[35]	1986–1999	Overall: 7.3±4.8 RITA: 7.1±5.0 SV: 7.5±4.7	University Hospital, Torino, Italy and "G D'Annunzio" University, Chieti, Italy	PSM
Carrier 2009[36]	1995–2007	10.0	Montreal Heart Institute, Montreal, Quebec, Canada	Adjusted
Cohen 2001[37]	1994–1999	Max 3.0	Sunnybrook and Women's College Health Sciences Centre, Toronto, Canada	PSM
Dewar 1995[38]	1984–1992	4.0	Vancouver Hospital and Health Sciences Centre, University of British Columbia, Vancouver, Canada	PSM
Goldman 2011[39]	2003–2009	Max 1.0	Multicenter	RCT
Goldstone 2018[40]	2006–2011	Median arterial: 5.3 (IQR: 3.8–6.7) Median venous: 5.2 (IQR: 3.7–6.6)	Multicenter	PSM
Grau 2015[41]	1994–2013	Overall: 10.5±5.0 RITA: 10.9±5.0 SV: 10.1±5.0	Columbia University College of Physicians and Surgeons, Ridgewood, NJ, United States	PSM
Hayward 2013 (RAPCO)[42]	1996–2004	6 (1.8–10.4)	University of Melbourne, Victoria, Australia	RCT
Ioannidis 2001[43]	1993–1996	NR	Multicenter	Adjusted
Janiec 2017[44]	2001–2015	SV: 9.3 (4.2) RA: 10.7 (4.1) RITA: 5.5 (5.0)	Multicenter	Adjusted
Kurlansky 2010[45]	1972–1994	Overall: 11.0±0.5 RITA: 12±.0.7.0 SV: 11.0±1.0	Florida Heart Research Institute, Miami, FL, United States	Adjusted
LaPar 2015[46]	2001–2013	30.0 days	VCSQI database, Virginia, United States	PSM
Lin 2013[47]	1997–2001	9.4 (5.7–11.9)	Cedars-Sinai Medical Center in Los Angeles, CA	PSM
Locker 2013[48]	1993–2009	7.6	Mayo Clinic, Rochester, MN, United States	Adjusted
Lytle 2004[49]	1971–1989	RITA: 16.2±2.4 SV: 16.3±2.5	The Cleveland Clinic Foundation, Cleveland, OH, United States	PSM
Nasso 2009[50]	2003–2006	24.1±9.8 months	Multicenter	RCT
Navia 2016[51]	1996–2014	Median: 5.5 (IQR: 2.6–8.8)	Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina	PSM
Parsa 2013[52]	1984–2009	NR	Duke University Medical Center, Durham, NC, United States	Adjusted
Petrovic 2015[53]	2001–2003	Max 8.0	Belgrade University School of Medicine, Belgrade, Serbia	RCT
Pusca 2008[54]	1997–2006	NR	Emory University School of Medicine, Atlanta GA, United States	Adjusted
Rosenblum 2016[55]	2003–2013	Median: 2.8 (1.1–4.9)	Emory University School of Medicine, Atlanta, GA, United States	PSM
Ruttman 2011[56]	2001–2010	Overall: 57.7 (3.0–112.0) months RITA: 32.7 (3–111.0) RA: 67.3 (3–112.0)	Innsbruck Medical University, Austria	PSM
Santarpino 2010[57]	2003–2007	3.17±0.07	Magna Graecia University of Catanzaro, Italy	Adjusted

Author/Year	Study Period	Mean/Median SD Follow-Up (Years)	Hospitals/Centers	Type
Schwann 2016[58]	1987–2011	4.7	Multicenter	PSM
Stevens 2004[59]	1985–1995	Overall: 11.0±3.0 RITA: 8.0±2.0 SV: 12.0±3.0	Montreal Heart Institute, Montreal, Quebec, Canada	Adjusted
Tarelli 2001[60]	1988–1990	Overall: 9.2 RITA: 9.2±2.8 SV: 9.1±2.5	Varese Hospital, Varese, Italy	PSM
Tranbaugh 2010[61]	1995–2009	7.7 (0.1–13.8)	Beth Israel Medical Center, New York, NY, United States	PSM
Tranbaugh 2017[62]	1995–2012	RA: 8.8±4.0 RITA: 8.9±4.9 SV: 9.1	Multicenter	Adjusted
Tsuneyoshi 2015[63]	2000–2013	6.1±7.8	"Kurashiki Central Hospital, Okayama, Japan"	PSM
Yoshida 2017[64]	1997–2007	7.5±4.4	Fukui Cardiovascular Center, Shinbo, Fukui, Japan	PSM
Zacharias 2004[65]	1996–2002	3.7±1.9	Mercy St Vincent Medical Center, Toledo, OH, United States	PSM

IQR indicates interquartile range; NR, not reported; PSM, propensity score matched; RA, radial artery; RAPCO, Radial Artery Patency and Clinical Outcomes randomized trial; RCT, randomized controlled trial; RITA, right internal thoracic artery; SV, saphenous vein; VCSQI, Virginia Cardiac Services Quality Initiative.

Table 2. Patient Demographics and Surgical Details

Author/ Year	Total Number			Age, y (Mean±SD)			Sex (Female) N (%)			Ejection Fraction (Mean±SD)			COPD N (%)			Diabetes Mellitus N (%)			RA Target Vessel Stenosis (%)	OPCAB/ ONCAB Details
	RA	SV	RITA	RA	SV	RITA	RA	SV	RITA	RA	SV	RITA	RA	SV	RITA	RA	SV	RITA		
RA vs SV studies																				
Benedetto 2013[31]	809	809	…	64±10	65±10	…	178 (22)	157 (19.4)	…	NR	NR	…	83 (10.3)	92 (11.4)	…	82 (10.1)	98 (12.1)	…	NR	OPCAB: RA, 27.8% SV, 25.5%
Cohen 2001[37]	478	956	…	60.7±8.8	61.2±8.7	…	76 (15.9)	152 (15.9)	…	NR	NR	…	40 (4.2)	23 (4.8)	…	160 (33.5)	238 (24.9)	…	NR	NR
Goldman 2011[39]	366	367	…	61±8	62±8	…	1 (1)	5 (1)	…	NR	NR	…	NR	NR	…	154 (42)	153 (42)	…	>70	OPCAB: RA, 11% SV, 13%
Lin 2013[47]	260	260	…	70.6±8.7	70.6±8.7	…	79 (30.4)	77 (29.4)	…	NR	NR	…	39 (15.0)	33 (12.7)	…	101 (38.8)	91 (33.5)	…	NR	OPCAB: RA, 16.5% SV, 18.1%
Petrovic 2015[53]	100	100	…	56.3±6.1	57.1±6.5	…	27 (27)	27 (27)	…	48.8±10.7	48.0±10.8	…	8 (8)	9 (9)	…	39 (39)	43 (43)	…	>80	NR
Santarpino 2010[57]	150	180	…	72.19±9.9	70.52±9.586	…	20 (11.1)	49 (27.2)	…	53.5±9.92	49.2±10.7	…	27 (18)	24 (13.3)	…	49 (27.2)	36 (24)	…	>80	OPCAB: RA, 28.9% SV, 24%
Tranbaugh 2010[61]	862	862	…	60.8±8.1	60.8±9.2	…	203 (23.5)	185 (22.5)	…	48.3±11.8	47.7±13.2	…	173 (20.1)	187 (21.7)	…	314 (36.4)	332 (38.3)	…	>70	OPCAB: SV, 4.1% RA, 1.3%
Yoshida 2017[64]	91	91	…	64±8.8	64.7±9.7	…	21 (23.1%)	22 (24.2%)	…	NR	NR	…	NR	NR	…	35 (38.5)	38 (41.8)	…	87.2± 13.2%	OPCAB: RA, 30.9% SV: 26.1%
Zacharias 2004[65]	925	925	…	63±10	63±10	…	268 (28.1)	271 (28.5)	…	49±10	49±10	…	174 (18.3)	177 (18.6)	…	326 (34.2)	327 (34.3)	…	From <70 to >90	NR
RITA vs SV studies																				
Benedetto 2014[32]	…	750	750	…	NR (Ranges)	NR (Ranges)	…	(21.2)	(10.8)	…	<50% in 22.1%	<50% in 13.2%	…	10.6	7.7	…	31.5	15.9	…	OPCAB: RITA, 71.7% SV, 72.5%
Buxton 1998[34]	…	1557	1269	…	64.9±9	58.6±9	…	(22)	(10.6)	…	<50% in 24.2%	<50% in 4.9%	…	NR	NR	…	19.9	6.8	…	NR
Calafiore 2004[35]	…	570	570	…	60.8±9.0	60.7±8.3	…	(17.5)	(19.3)	…	59.3±13.8	59.4±13.1	…	3	2.8	…	24.2	24.2	…	OPCAB: RITA, 32.5% SV, 24.2%
Canfer 2009[36]	…	5420	1235	…	68±8	61±9	…	29	16	…	NR	NR	…	NR	NR	…	31	21	…	NR
Dewar 1995[38]	…	765	377	…	NR	NR	…	16.6	15.4	…	NR	NR	…	NR	NR	…	19.3	17.7	…	NR
Grau 2015[41]	…	1006	1006	…	62±9	60±9	…	12.1	10.4	…	50±12	51±11	…	5.9	5.1	…	13.3	11	…	OPCAB: RITA, 49.2% SV 49.2%
Ioannidis 2001[43]	…	830	867	…	65.2 (9.8)	62.0±10.3	…	37.3	22.6	…	42.0 (13.1)	46.5±13.7	…	19.3	13	…	38.4	25.6	…	All ONCAB
Kurtansky 2010[45]	…	2369	2215	…	67.5±9.4	62.9±10.0	…	25.7	14.9	…	CAT	CAT	…	NR	NR	…	27.3	20.8	…	All ONCAB
LaPar 2015[46]	…	1333	1333	…	59±10	56±10	…	18.7	14.3	…	55 (50–60)	55 (50–60)	…	11.4	10.7	…	34.9	18.2	…	NR
Lytle 2004[49]	…	1152	1152	…	57.8±8.3	57.5±8.1	…	14	12	…	NR	NR	…	NR	NR	…	12	12	…	NR
Navia 2016[51]	…	485	485	…	NR	63.7±9.1	…	NR	9.8	…	NR	NR	…	NR	4.2	…	NR	25.9	…	ONCAB: RITA, 0.4% SV, 61%

Continued

Table 2. Continued

Author / Year	Total Number			Age, y (Mean±SD)			Sex (Female) N (%)			Ejection Fraction (Mean±SD)			COPD N (%)			Diabetes Mellitus N (%)			RA Target Vessel Stenosis (%)	OPCAB / ONCAB Details
	RA	SV	RITA	RA	SV	RITA	RA	SV	RITA	RA	SV	RITA	RA	SV	RITA	RA	SV	RITA		
Parsa 2013[52]	...	16 881	728	...	64 (median)	59 (median)	...	28.5	19.8	...	52% (median)	51% (median)	...	8.2	3.9	...	29.9	14.7	...	NR
Puca 2008[54]	...	10 212	599	...	62.9 (10.7)	58.0±0.34	...	2810 (27.5)	17.4	...	50.1 (12.7)	51.6±11.4	...	1564 (15.3) 7	12	...	3725 (36.5)	25.2	...	OPCAB: SV, 39% RITA, 90%
Rosenblum 2016[55]	...	306	306	...	63.8±10.6	59.0±10.1	...	28.7	15.5	...	51.7±12.4	52.2±11.0	...	6.3	1.8	...	43.8	27.6	...	ONCAB: SV, 33.7% RITA: 18.8%
Stevens 2004[59]	...	2547	1835	...	63±9	57±9	...	25	12	...	NR	NR	...	6	4	...	18	12	...	NR
Tarelli 2001[60]	...	150	150	...	59.3±8.3	56.5±8.2	...	17.3	7.3	...	54.5±13.5	57.2±13.6	...	NR	NR	...	24.7	11.3	...	NR (presumably all ONCAB)
RA vs RITA studies																				
Benedetto 2017[53]	764	...	764	58±8	...	57±9	53 (6.9)		54 (7.1)	CAT	...	CAT	36 4.7	...	38 5.0	49 (6.5)	...	39 (5.1)	>75	OPCAB: RA, 6.9% RITA, 44.9%
Hayward 2013 (RAPCI)[42]	198	...	196	59.2 (37.9–71.0)	...	59.5 (36.2–70.9)	23 (12)	...	18 (9)	NR	...	NR	NR	...	NR	22 (11%)	...	20 (10%)	>70	All ONCAB
Ruttman 2011[56]	277	...	277	57.8±9.0	...	56.6±9.6	28 (10.1)	...	28 (10.1)	52.9±12.1	...	54.9±10.8	92 (33.2)	...	92 (33.2)	62 (22.4)	...	59 (21.3)	NR	NR
Tsuneyoshi 2015[63]	118	...	118	67.9±10	...	68.3±8	30 (25)	...	22 (19)	CAT	...	CAT	2 (1.6)	...	2 (1.6)	53 (45)	...	63 (53)	"Severe"	All OPCAB
RA vs SV vs RITA studies																				
Goldstone 2018[40]	4268	5813	1574	62.1±10.5	62.5±10.4	61.7±10.3	614 (14.5)	916 (15.8)	229 (14.3)	55.5±12.0	55.6±12.0	56.1±12.0	629 (14.8)	856 (14.7)	250 (15.6)	1525 (35.7)	2066 (35.5)	528 (33.7)	NR	NR
Janiec 2017[44]	1036	46 343	862	64.5 (9.7)	66.4 (8.4)	63.9 (9.0)	277 (26.7%)	8879 (19.2%)	146 (16.9%)	CAT	CAT	CAT	39 (5.7%)	2551 (6.9%)	59 (7.7%)	212 (20.7%)	11 077 (24.3%)	206 (24.0%)	NR	OPCAB: SV, 2.4% RA, 2.4% RITA 6.7%
Locker 2013[48]	169	1153 (Matched)	589	NR	59±10	NR	NR	187 (16.2)	NR	NR	58±13	NR	NR	86 (7.5)	NR	NR	221 (19.2)	NR	NR	OPCAB: SV, 4.4% MultiArt, 3.3%
Nasso 2009[50]	202	202	201	70.5±3.1	69.7±3.5	69.2±3.9	87 (43.1)	84 (41.6)	88 (43.8)	CAT		CAT	57 (28.2)	56 (27.7)	55 (27.4)	73 (36.1)	77 (38.1)	76 (37.8)	>70	All ONCAB
Schwann 2016[58]	551	551	551	58.4±10.2	60.6±10.3	59.5±9.7	72 (13)	97 (18)	77 (14)	52±10	54±10	53±11	46 (8.3)	39 (7.1)	41 (7.4)	100 (18)	94 (17)	93 (17)	>75	ONCAB: RITA, 98% RA, 96% SV, 95%
Tranbaugh 2010[61]	4577	7073	1674	60.3±9.7	67.4±9.9	64.9±10.3	1033 (22.6)	2448 (34.6)	460 (27.5)	49.1±10.9	47.2±12.9	46.4±14.3	781 (17.1)	1804 (25.5)	149 (8.9)	702 (37.2)	2704 (38.2)	597 (35.7)	LCX:>70 RCA>90	OPCAB: SV, 3.5% RA, 3.0% RITA, 1.4%

CAT indicates reported as categories; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EF, ejection fraction; LCX, left circumflex artery territory; MultiArt, multiple arterial grafting group; NR, not reported; ONCAB, on-pump coronary artery bypass; OPCAB, off-pump coronary artery bypass; RA, radial artery; RCA, right coronary artery territory; RITA, right internal thoracic artery; SV, saphenous vein.

CHAPTER 8

GENERAL DISCUSSION

Since the reintroduction of the radial artery as a conduit in coronary surgery in the early 1990s (1), its morphofunctional features, biological properties, and vasoreactive profile have been mostly elucidated (1). The early and intermediate angiographic patency rates have been published (2), and the Radial Artery Patency and Clinical Outcome trial should be reporting its 10-year angiographic and clinical results this year. There is clear evidence that the patency rate of the radial is better than that of the saphenous vein (2). The radial artery contends with the right internal thoracic artery for the role of the second artery for coronary artery bypass grafting (CABG), and is probably a better choice at least in patients at high risk of sternal complications. (2,3)

Among all the conduits used for CABG, the radial artery is the only muscular artery. Histologic studies have shown that the thickness of the muscular component of the radial artery is almost twice that of the internal thoracic artery.(4) This thick muscular media is the anatomic explanation of the well-known hyper-reactivity of radial artery rings reported in pharmacological studies. Chardigny and coauthors in a classic organ bath experiment have shown that the spastic response of the radial artery to norepinephrine, serotonin, and thromboxane A2 is significantly higher than that of any other conduit used for CABG.(5) Our study showed for the first time that open radial artery harvesting is associated with better preservation of the endothelial function compared to the endoscopic harvesting. We found vasodilation in response to acetylcholine to be significantly higher in radial artery harvested with open approach ($p \leq 0.001$ vs endoscopically). Endothelial integrity was not different between the two groups.

The use of multiple arterial grafts is recommended by current guidelines and professional societies' position papers predominantly on the basis of large observational studies that have reported improved patient outcomes after CABG.(6-8) Despite these recommendations, arterial grafts have not been widely adopted; in the United States currently fewer than 10% of elective CABG patients receive more than one arterial graft and in less than 7% a radial-artery graft is used.(9) One of the reasons for their low use is that the superior clinical outcomes with multiple arterial grafts reported in registries have not been replicated in the randomized controlled trials.

In our analysis of the 20-year outcomes of radial artery grafting, the radial artery patency rate in the group of patients who reached the 20-year follow-up was 84.8%, with a perfect patency rate of 72.7%. The status of the graft remained substantially stable in the very long term, with only 2 occlusions occurring between the 10- and the 20-year control studies in the group of patients who underwent both. We found that the long-term patency rate of the radial artery was not statistically different than that of the gold-standard internal thoracic artery. Confirming previous observations (10), we found a strong correlation between the severity of the target vessel stenosis and the radial artery patency. When the radial artery was used to revascularize target vessels with ≥90% stenosis, the patency rate of the conduit was similar to that of the left internal thoracic artery, whereas for a lower degree of coronary stenosis, the angiographic outcome was more similar to that of the saphenous vein.

In our patient-level meta-analysis of randomized controlled trials comparing the radial artery and the saphenous vein as a second conduit for CABG, the use of radial-artery grafts was associated with a significantly lower risk of the composite of death, myocardial infarction or repeat

revascularization and of the individual risk of myocardial infarction and repeat revascularization at a mean follow-up of 5 years. The use of radial-artery grafts was also associated with superior angiographic patency rates at protocol-defined angiography, which offers a biologically mechanistic explanation of the observed improvement in clinical outcomes. The clinical benefit associated with the use of radial-artery grafts seemed more evident in patients younger than 75 years, in females and in those without renal insufficiency. The radial-artery graft target vessel was not found to be a significant effect modifier. Our analysis also revealed that superior patency of radial-artery grafts did not translate into a significant difference in survival at 5 years.

The previous literature on the effect of calcium channel blockers (CCB) in patients with radial artery graft is controversial. In a small previous randomized controlled trial, we assigned 120 patients who received the radial artery for CABG to continue or suspend CCB therapy using Diltiazem after the first postoperative year and found no difference in graft patency, graft reactivity, scintigraphically-evident myocardial ischemia or clinical outcomes at 5-year follow-up. (11) Subsequently, in another small trial, we randomized 100 patients to receive or not the same CCB regimen from the early postoperative period and reported again lack of differences in clinical, scintigraphic and angiographic outcomes.(12) In a angiographic series of 50 patients, Moran and colleagues found similar clinical outcomes and angiographic patency among radial artery patients who received CCB with Diltiazem or not.(13) Similarly, a post-hoc analysis of the Radial Artery Patency Study found that among 440 radial artery patients, the incidence of string sign (the highest degree of radial artery graft spasm) was not affected by the compliance with the prescribed postoperative CCB, although compliance with CCB use was high (419/440).(14) Due to the very high patency rate and excellent clinical outcomes of radial artery grafts, however, it is very likely

that all the individual published studies were largely underpowered to detect even moderate differences in outcome. We overcame this limitation by pooling patient-level data of six angiographic randomized trials evaluating radial artery graft status at mid-term follow-up.

We found that the use of CCB was associated with a significantly lower risk of major adverse cardiac events and higher radial artery patency rate. We also found that duration of CCB for at least one year was associated with a reduction of clinical events and graft occlusion compared to shorter treatment and that diltiazem and amlodipine were associated with a similar protective effect.

In our analysis of angiographic outcome of coronary artery bypass grafts in 1091 patients and 2281 grafts at a mean follow-up of 65±29 months using the Radial Artery Database International ALliance (RADIAL) database, we found the failure of the left internal mammary artery to left anterior descending artery (LAD) bypass to be a very uncommon event, so that even with a large patient sample, it was not possible to define independent risk factors for it. For the non-LAD distribution, the non-use of the radial artery, age ≥ 75 years, female gender, left ventricular ejection fraction <50%, and use of the Y graft configuration were significantly associated with mid-term graft failure.

The balance between possible better long-term clinical and angiographic outcomes of arterial grafts and the potential risk of harvesting site complications and the increased technical complexity associated to their use, has been the center of a continuous debate over the last 25 years.(15) Also, the relative efficacy of the right internal thoracic artery and radial artery as the second arterial grafts remains controversial.(16) Several pairwise meta-analysis on the topic have

been previously published.(17–19) However pairwise meta-analyses have known limitations in terms of heterogeneity of the included studies and potential for treatment allocation bias. Network meta-analyses (NMA) have been proposed to overcome the limitations of the pairwise comparison, especially when summarizing the evidence of randomized controlled trials and observational studies.(20) It has been suggested that NMA can be superior to classical pairwise analyses especially in case of comparison of a new treatment to a standard one.(21)

We performed the first NMA specifically addressing the differences in clinical outcomes according to the type of second graft used for CABG. The only published NMA on the subject focused only on the patency rates of conduits and did not include clinical outcomes.(22) Due to the demonstrated absence of a consistent correlation between angiographic failure and clinical events,(23) a deeper understanding of the clinical impact of the type of second conduit used for CABG seemed of major relevance. The results of our study showed the superiority of the use of a second arterial over venous graft, and suggest the equivalence in long-term and perioperative outcomes among right internal thoracic artery and radial artery.

In conclusion, the radial artery is an easily harvested and versatile conduit with a growing body of literature supporting the safety and efficacy of radial artery grafting during CABG. Current Guidelines clearly support radial artery grafting use during CABG as an adjunct to a left internal thoracic artery to LAD. It increasingly appears that either the radial artery or right internal thoracic artery may be used as the preferred second arterial conduit supporting the left internal thoracic artery to LAD graft. Multiple arterial bypass grafting using the radial artery should be routine in

those patients with the appropriate coronary anatomy, life expectancy and no contraindications to radial artery use.

References

1. Acar C, Jebara VA, Portoghese M, et al. Revival of the radial artery for coronary artery bypass grafting. Ann Thorac Surg 1992;54:652–9; discussion 659-660.

2. Gaudino M, Crea F, Cammertoni F, Massetti M. The radial artery: a forgotten conduit. Ann Thorac Surg 2015;99:1479–85.

3. Pola P, Serricchio M, Flore R, Manasse E, Favuzzi A, Possati GF. Safe removal of the radial artery for myocardial revascularization: a Doppler study to prevent ischemic complications to the hand. J Thorac Cardiovasc Surg 1996;112:737–44.

4. van Son JA, Smedts F, Vincent JG, van Lier HJ, Kubat K. Comparative anatomic studies of various arterial conduits for myocardial revascularization. J Thorac Cardiovasc Surg 1990;99:703–7.

5. Chardigny C, Jebara VA, Acar C, et al. Vasoreactivity of the radial artery. Comparison with the internal mammary and gastroepiploic arteries with implications for coronary artery surgery. Circulation 1993;88:II115-127.

6. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg 2012;143:4–34.

7. Kolh P, Windecker S, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg 2014;46:517–92.

8. Aldea GS, Bakaeen FG, Pal J, et al. The Society of Thoracic Surgeons Clinical Practice Guidelines on Arterial Conduits for Coronary Artery Bypass Grafting. Ann Thorac Surg 2016;101:801–9.

9. ElBardissi AW, Aranki SF, Sheng S, O'Brien SM, Greenberg CC, Gammie JS. Trends in isolated coronary artery bypass grafting: an analysis of the Society of Thoracic Surgeons adult cardiac surgery database. J Thorac Cardiovasc Surg 2012;143:273–81.

10. Gaudino M, Taggart D, Suma H, Puskas JD, Crea F, Massetti M. The Choice of Conduits in Coronary Artery Bypass Surgery. J Am Coll Cardiol 2015;66:1729–37.

11. Gaudino M, Glieca F, Luciani N, Alessandrini F, Possati G. Clinical and angiographic effects of chronic calcium channel blocker therapy continued beyond first postoperative year in patients with radial artery grafts: results of a prospective randomized investigation. Circulation 2001;104:I64-67.

12. Gaudino M, Luciani N, Nasso G, Salica A, Canosa C, Possati G. Is postoperative calcium channel blocker therapy needed in patients with radial artery grafts? J Thorac Cardiovasc Surg 2005;129:532–5.

13. Moran SV, Baeza R, Guarda E, et al. Predictors of radial artery patency for coronary bypass operations. Ann Thorac Surg 2001;72:1552–6.

14. Miwa S, Desai N, Koyama T, et al. Radial artery angiographic string sign: clinical consequences and the role of pharmacologic therapy. Ann Thorac Surg 2006;81:112–8; discussion 119.

15. 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;95:1938–45.

16. Benedetto U, Gaudino M, Caputo M, et al. 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.

17. 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;130:539–45.

18. Takagi H, Mitta S, Ando T. A Contemporary Meta-Analysis of Antegrade versus Retrograde Cerebral Perfusion for Thoracic Aortic Surgery. Thorac Cardiovasc Surg 2018;

19. 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 Br Card Soc 2017;103:1419–26.

20. Song F, Harvey I, Lilford R. Adjusted indirect comparison may be less biased than direct comparison for evaluating new pharmaceutical interventions. J Clin Epidemiol 2008;61:455–63.

21. Chalmers I, Matthews R. What are the implications of optimism bias in clinical research? Lancet Lond Engl 2006;367:449–50.

22. 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.

23. Gaudino M, Antoniades C, Benedetto U, et al. Mechanisms, Consequences, and Prevention of Coronary Graft Failure. Circulation 2017;136:1749–64.

VALORIZATION

This thesis analyzes the clinical outcomes of the radial artery as a coronary artery bypass conduit, compares it to other conduits, and describes the factors associated with graft patency. This was achieved through original research and several individual patient-data and aggregate meta-analyses.

The first part of this thesis (Chapter2) describes the effects of different radial artery harvesting techniques (open versus endoscopic) on the structural integrity and functions of the endothelium of radial artery. The harvesting techniques were analyzed by evaluating endothelial-dependent vasorelaxation to acetylcholine as well as quantitative structural analysis of the endothelial integrity. Open radial artery harvesting was found to be associated with a significantly higher endothelium-dependent vasodilation. However, further investigation on the potential implications of these findings in terms of graft spasm and patency as well as clinical outcomes are needed.

This is followed by a presentation of the 20-year long-term results of the radial artery as a coronary artery bypass surgery (CABG) conduit in our institution in Chapter 3. The 20-year patency rate of radial artery grafts is good, and not inferior to the internal thoracic artery, especially when the conduit is used to graft a vessel with >90% stenosis. Radial artery harvesting does not lead to hand or forearm symptoms, even at a very long-term follow-up. To provide the most robust evidence to date on the use of the radial artery, Chapter 4 summarizes our patient-level meta-analysis of randomized trials comparing radial-artery grafts to saphenous-vein grafts for CABG to describe the clinical outcomes of radial artery grafting. The purpose of this was to pool data from all the randomized controlled trials comparing the radial artery to the saphenous vein that

individually were underpowered to detect clinical differences. In comparison to use of saphenous-vein grafts, use of radial-artery grafts for CABG resulted in a lower rate of adverse cardiac events and a higher patency rate at 5-year follow-up.

In Chapter 5, we study the role of calcium channel blockers on the midterm clinical and angiographic outcomes of the radial artery. In patients with radial artery grafts, calcium channel blocker use is found to be associated with significantly better mid-term clinical and angiographic radial artery outcomes. Chapters 6 and 7 compare the radial artery to other CABG conduits through large patient-level datasets including six angiographic randomized controlled trials of CABG conduits to explore the incidence and determinants of coronary graft failure for different conduits. Our analyses showed that failure of the left internal mammary arteries to left anterior descending artery (LAD) bypass is a very uncommon event. For the non-LAD distribution, the non-use of radial artery, age, female gender, left ventricular ejection fraction<50% and use of the Y graft configuration were significantly associated with mid-term graft failure.

The differences in late survival and other clinical outcomes according to the type of second graft used (radial artery versus right internal thoracic artery versus saphenous vein grafts) for CABG are also compared in a network meta-analysis. The use of the radial artery or the right internal thoracic artery is associated with a similar and statistically significant long-term clinical benefit compared to the saphenous vein. There are no differences in operative risk or complications between the two arterial conduits, but deep sternal wound infection remains a concern with bilateral internal thoracic artery when skeletonization is not used.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SUMMARY

Chapter 2. In this study, endothelial-dependent vasorelaxation to acetylcholine as well as quantitative structural analysis of the endothelial integrity were performed in open and endoscopic harvested radial arteries using a more contemporary approach. Our study showed for the first time that open radial artery harvesting is associated with better preservation of the endothelial function compared to the endoscopic harvesting.

Chapter 3. To contribute to the diffusion of use of the radial artery as a coronary artery bypass conduit, we described the results of the 20-year prospective follow-up of our initial cohort of 100 patients who received a radial artery graft for myocardial revascularization. In our series, the radial artery patency rate in the group of patients who reached the 20-year follow-up was 84.8%, with a perfect patency rate of 72.7%. The status of the graft remained substantially stable in the very long term, with only 2 occlusions occurring between the 10- and the 20-year control studies in the group of patients who underwent both. Overall, the long-term patency rate of the radial artery was not statistically different than that of the gold-standard internal thoracic artery.

Chapter 4. To overcome the limitations of individual studies in detecting differences in clinical outcomes, a patient-level meta-analysis of randomized trials comparing radial-artery grafts vs saphenous-vein grafts for coronary artery bypass grafting was performed. The use of radial-artery grafts was associated with a significantly lower risk of the composite of death, myocardial infarction or repeat revascularization and of the individual risk of myocardial infarction and repeat revascularization at a mean follow-up of 5 years. The use of radial-artery grafts was also associated with superior angiographic patency rates at protocol-defined angiography, which offers a biologically mechanistic explanation of the observed improvement in clinical outcomes.

Chapter 5. This study assesses whether calcium channel blocker use after radial artery coronary artery bypass grafting affects the midterm clinical and angiographic outcomes by pooling individual patient data from multiple randomized controlled trials. The use of calcium channel blocker was associated with a significantly lower risk of major adverse cardiac events and higher radial artery patency rate. We also found that duration of calcium channel blocker use for at least one year was associated with a reduction of clinical events and graft occlusion compared to shorter treatment and that diltiazem and amlodipine were associated with a similar protective effect.

Chapter 6. In this manuscript, we use a large patient-level dataset including six angiographic randomized controlled trials of coronary artery bypass grafting conduits to explore the incidence and determinants of coronary graft failure. With 1091 patients and 2281 grafts at a mean follow-up of 65±29 months and a re-angiography rate of almost 72%, our Radial Artery Database International ALliance (RADIAL) database is one of the largest and the most complete coronary graft angiographic databases. The results of our analysis show that the failure of the left internal mammary artery to left anterior descending bypass is a very uncommon event, so that even with a large patient sample, it was not possible to define independent risk factors for it.

Chapter 7. We performed a network meta-analysis with the aim to specifically investigate the differences in late survival (primary outcome) and other clinical outcomes according to the type of second graft used for coronary artery bypass grafting. The use of the radial artery or the right internal thoracic artery is associated with a similar and statistically significant long-term clinical benefit compared to the saphenous vein. There are no differences in operative risk or

complications between the two arterial conduits, but deep sternal wound infection remains a concern with bilateral internal thoracic artery when skeletonization is not used.

ACKNOWLEDGEMENTS

University of Maastricht Medical Center, leading institution in medicine, research and innovation.

Prof. Dr. R. Lorusso, promotor. Dear Professor Lorusso (Roberto), I'm extremely thankful for your support and advices. Your example and friendship have been key to achieving this PhD. Grazie!!

Prof. Dr. J.G. Maessen, co-promotor. Dear Professor Maessen, I'm deeply grateful for the time and attention that you have dedicated to this project.

This thesis is dedicated to my family and friends, and to my mentors:

Mamma e Papà, Stefania, Federico Possati, Antonio Maria Calafiore, Stephen Fremes, David Taggart, Leonard Girardi and Umberto Benedetto (in the order I met them)

They taught me everything I know and made me the man and the surgeon I am. They probably taught me much more, but I did not understand…

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coronary artery bypass surgery (the ROMA trial). He has given expert presentations at national and international meetings to share his exquisite knowledge of coronary artery bypass surgery and the use of multiple arterial grafts. He currently serves as the Chair of the Coronary Artery Surgery Task Force of the European Association for Cardio-thoracic Surgery.

Dr. Gaudino's interests include all aspects of adult cardiac surgery. Along with his expert training and knowledge in coronary artery bypass surgery, including the use of multiple arterial grafting.

Mario likes sports (running in particular) and books. He adores Roma (both the city and his cat).


SF

LIST OF PUBLICATIONS

1. Shunt atriale sinistro-destro dopo valvuloplastica mitralica percutanea. Alessandri N, Rondoni G, Franzin S, Martuscelli E, Mangeri E, Berni A, **Gaudino M**, Nigri A. *Cuore 1993;10:465-474.*
2. Procedure diagnostiche in pazienti con displasia aritmogena ventricolare destra. Alessandri N, Rondoni G, Franzin S, Martarelli L, Mosti G, **Gaudino M**, Conti G, Bufi M, Campa PP. *Acta Anaesthesiologica Italica 1993;44:365-374.*
3. Immunohistochemical evidence for sympathetic denervation and reinnervation after necrotic injury in rat myocardium. Nori SL, **Gaudino M**, Alessandrini F, Bronzetti E, Santarelli P. *Cellular and Molecular Biology 1995;41:799-807.*
4. Tecniche di analisi elettrofisiologica transesofagea nell'era dell'ablazione transcatetere a radiofrequenza. Rillo M, Pappone C, Taglieri A, Santangelo L, Corbo P, Raucci D, Nave C, **Gaudino M**, Lombardi S. *Cardiostimolazione 1995;13:15-22.*
5. Surgical treatment of massive pulmonary embolism - Il trattamento chirurgico dell'embolia polmonare massiva. Luciani N, **Gaudino M**, Possati F. *RAYS 1996;21:432-438.*
6. The use of pulmonary allografts for aortic valve replacement. Pragliola C, Pennestri' F, Manasse E, Marchetti C, **Gaudino M**, Possati F. *J Cardiovasc Surg 1996;37:603-607.*
7. La rivascolarizzazione miocardica con condotti arteriosi. Possati G, **Gaudino M**, Luciani N, Glieca F, Alessandrini F, Pragliola C, Canosa C, Morelli M. *Cardiologia 1996;41(Suppl 4):443-449.*
8. Il trapianto cardiaco. Linee guida per il donatore e il ricevente. Piancone FL, Bruno P, **Gaudino M**, Alessandrini F. *Annali di Medicina e Chirurgia 1996;11:45-49.*
9. The use of mechanical prostheses in native aortic valve endocarditis. **Gaudino M**, De Filippo C, Pennestri' F, Possati G. *J Heart Valve Disease 1997;6:79-83.*

10. Conventional left atrial vs superior septal approach for mitral valve replacement. **Gaudino M**, Alessandrini F, Glieca F, Martinelli L, Santarelli P, Bruno P, Possati G. *Ann Thorac Surg 1997;63:1123-1127.*

11. The internal mammary artery malperfusion syndrome: late angiographic verification. **Gaudino M**, Trani C, Luciani N, Alessandrini F, Possati G. *Ann Thorac Surg 1997;63:1257-1261.*

12. Are pulmonary homografts subjected to pulmonary hypertension more appropriate for aortic valve replacement than normal pulmonary homografts ? Results of echocardiography in a multicentric study. **Gaudino M**, Van Geldorp T, Daenen W, Kalmar P, Goffin Y. *Eur J Cardio-thorac Surg 1997;11:676-681.*

13. Early results of the minimally invasive thoracotomy for myocardial revascularization. Alessandrini F, Luciani N, Marchetti C, **Gaudino M**, Possati G. *Eur J Cardio-thorac Surg 1997;11:1081-1085.*

14. Transient neurological deficit immediately after central venous line removal: a poorly explained finding. **Gaudino M**, Glieca F, Bruno P, Possati G. *Eur J Cardio-thoracic Surgery 1997;11:1185.*

15. Surgical treatment of recurrence of an aneurysm of aberrant right subclavian artery. Luciani N, **Gaudino M**, Mattens M, De Geest R. *J Cardiac Surgery 1997;12:51-55.*

16. Basi elettrofisiologiche della conduzione intraventricolare aberrante durante fibrillazione atriale. Nave C, Nardi S, **Gaudino M**, Curcio N, Cirillo T, Iacono A. *Cardiologia 1996;41:1193-1198.*

17. Unusual right coronary artery anomaly with major implication during cardiac surgery procedures. **Gaudino M**, Glieca F, Bruno P, Piancone FL, Alessandrini F, Possati G. *Ann Thorac Surg 1997;64:838-839.*

18. Tepid systemic perfusion and intermittent isothermic blood cardioplegia in coronary surgery. Luciani N, Martinelli L, **Gaudino M**, Alessandrini F, Glieca F, Possati F. *J Cardiovasc Surg 1998;39:599-607.*

19. La rivascolarizzazione miocardica per via minitoracotomica: risultati del controllo angiografico precoce. Possati G, **Gaudino M**, Alessandrini F, Zimarino M, Glieca F, Bruno P. *Giorn Ital Cardiol 1997;27:749-757.*

20. Lesions of the target vessels during minimally invasive myocardial revascularization. Alessandrini F, **Gaudino M**, Glieca F, Luciani N, Piancone FL, Zimarino M, Possati G. *Ann Thorac Surg 1997;64:1349-1353.*

21. Central venous line and neurological deficit (Letter). **Gaudino M**, Glieca F, Bruno P, Piancone FL Possati G. *Lancet 1997;349:1699.*

22. Palliative coronary artery surgery in patients with severe non-cardiac diseases. **Gaudino M**, Santarelli P, Bruno P, Piancone FL, Possati G. *Am J Cardiol 1997;15:1351-1352.*

23. Perioperative management of a patient with Werlhof disease undergoing myocardial revascularization. **Gaudino M**, Luciani N, Piancone FL, Bruno P, Rossi M, Schiavello R, Possati G. *J Cardiovasc Surg 1999;40:227-278.*

24. Systematic clinical and angiographic follow-up of patients submitted to minimally invasive coronary artery bypass. Possati G, **Gaudino M**, Alessandrini F, Zimarino M, Glieca F, Luciani N. *J Thorac Cardiovasc Surg 1998;115:785-790.*

25. Non-invasive evaluation of mammary artery flow reserve and adequacy to increased myocardial oxygen demand. **Gaudino M**, Serricchio M, Tondi P, Glieca F, Giordano A, Trani C, Pola P, Possati G. *Eur J Cardio-thoracic Surg 1998;13:404-409.*

26. Integrated approach for revascularization in cases of multivessel disease and porcelain aorta. **Gaudino M**, Cellini C, Bruno P, Zimarino M, Possati G. *J Card Surg 1998;13:140-142.*

27. Steal phenomenon from mammary side-branches: when does it occur ? **Gaudino M**, Serricchio M, Glieca F, Bruno P, Tondi P, Giordano A, Trani C, Calcagni ML, Pola P, Possati G. *Ann Thorac Surg 1998;66:2056-2062.*

28. Mid term clinical and angiographic results of radial artery grafts used for myocardial revascularization. Possati G, **Gaudino M**, Alessandrini F, Luciani N, Glieca F, Trani C, Cellini C, Canosa C, Di Sciascio G. *J Thorac Cardiovasc Surg 1998;116:1015-1021.*

29. Individualised surgical strategy for the reduction of stoke risk in coronary artery bypass patients. **Gaudino M**, Glieca F, Alessandrini F, Cellini C, Luciani N, Pragliola C, Schiavello R, Possati G. *Ann Thorac Surg 1999;67:1246-1253.*

30. La chirurgia coronarica senza circolazione extracorporea. Possati G, **Gaudino M**, Alessandrini F, Pragliola C, Cellini C, Morelli M. *Cardiologia 1998;43 (Suppl 2):519-522.*

31. Repair of an ascending aorta pseudoaneurysm by way of superior ministernotomy. **Gaudino M**, Alessandrini F, Canosa C, Possati G. *Ann Thorac Surg 1999;67:1798-1800.*

32. L'arteria radiale in chirurgia coronarica: risultati clinici ed angiografici a medio termine e variazione della vasoreattivita' nel tempo. Possati G, **Gaudino M**, Santarelli F, Morelli M, Cellini C, Di Sciascio G, Trani C, Serricchio M, Tondi P. *Giorn Ital Cardiol 1999;29:135-142.*

33. Internal mammary artery grafts and competitive flow. Controversies persist. **Gaudino M**, Bruno P, Piancone FL, Pragliola C, Manzoli A, Possati G. *J Cardiovasc Surg 1999;40:553-554.*

34. Do internal mammary artery side-branches have the potential for hemodynamically significant flow steal ? **Gaudino M**, Serricchio M, Tondi P, Glieca F, Bruno P, Possati G, Pola P. *Eur J Cardio-thoracic Surgery 1999;15:251-254.*

35. Effect of skeletonization of the internal thoracic artery on vessel wall integrity. **Gaudino M**, Toesca A, Nori SL, Glieca F, Possati G. *Ann Thorac Surg 1999;68:1623-1627.*

36. Patent side branches do not affect coronary blood flow in internal thoracic artery-left anterior descending anastomosis: an experimental study. Pragliola C, **Gaudino M**, Bombardieri G, Barilaro C, Bruno P, Varano C, Santoro T, Possati G. *J Thorac Cardiovasc Surg 1999;118:66-70.*

37. Rimodellamento dei graft in arteria radiale a cinque anni dall'intervento di bypass aortocoronarico. Lupi A, Trani C, **Gaudino M**, Canosa C, Di Sciascio G, Ramazzotti V, Alessandrini F, Mazzari MA, Schiavoni G, Possati G. C*ardiologia 1999;44:381-384.*

38. Superior extension of intraoperative brain damage in case of normothermic systemic perfusion during coronary artery bypass operations. **Gaudino M**, Martinelli L, Di Lella G, Glieca F, Marano P, Schiavello R, Possati G. *J Thorac Cardiovasc Surg 1999;118:432-437.*

39. Hemodynamic and functional consequences of radial artery removal for coronary artery bypass grafting. Serricchio M, **Gaudino M**, Tondi P, Gasbarrini A, Gerardino L, Santoliquido A, Pola P, Possati G. *Am J Cardiol 1999;84:1353-1356.*

40. Mid-term endothelial function and remodeling of aorta-anastomosed radial artery grafts. **Gaudino M**, Glieca F, Trani C, Lupi A, Mazzari MA, Schiavoni G, Possati G. *J Thorac Cardiovasc Surg 2000;120:298-301.*

41. The unclampable ascending aorta in coronary artery bypass patients: a surgical challenge of increasing frequency. **Gaudino M**, Glieca F, Alessandrini F, Luciani N, Cellini C, Pragliola C, Possati G. *Circulation 2000;102:1497-1502.*

42. Are pulmonary homografts which were subjected to pulmonary hypertension more appropriate for aortic valve replacement than normal pulmonary homografts? A long-term multicentric echography study. Jashari R, Van Hoeck B, **Gaudino M**, Daenen W, Van Geldorp T, Kalmar P, Goffin Y. *Eur J Cardiothorac Surg 2000;17:140-145.*

43. Can a muscular artery be used as a coronary artery bypass conduit? Lessons learned from the mid-term control of radial artery grafts. (ed) Possati G, **Gaudino M**. *Ital Heart J 2000;1:581-584.*

44. An unusual source of massive intra-abdominal haemorrhage during cardiopulmonary bypass. Di Pietrantonio F, **Gaudino M,** Luciani N, Glieca F, Possati G. *J Cardiovasc Surg 2001;42:499-500.*

45. Should severe monolateral asymptomatic carotid artery stenosis be treated at the time of coronary bypass operation ? **Gaudino M,** Glieca F, Luciani N, Cellini C, Morelli M, Spatuzza P, Di Mauro M, Alessandrini F, Possati G. *Eur J Cardio-thorac Surg 2001;19:619-626.*

46. Clinical and angiographic effects of chronic calcium channel blocker therapy continued beyond the first postoperative year in patients with radial artery grafts. Results of a prospective randomized investigation. **Gaudino M**, Glieca F, Luciani N, Alessandrini F, Possati G. *Circulation 2001;104[Suppl I]:I-64-I-67.*

47. Normothermia does not improve postoperative haemostasis nor reduce inflammatory activation in primary isolated coronary artery bypass patients. **Gaudino M**, Zamparelli R,

Andreotti F, Burzotta F, Iacoviello F, Glieca F, Donati MB, Maseri A, Schiavello R, Possati G. *J Thorac Cardiovasc Surg 2002;123:1092-1100.*

48. Finding a compromise between the heart and the brain: strategies for neurologic risk reduction in coronary artery bypass surgery. (ed). **Gaudino M**, Possati G. *Ital Heart J 2002;3:146-50.*

49. Caratterizzazione dell'attivazione infiammatoria e fibrinolitica dopo intervento di by-pass aortocoronarico in circolazione extracorporea. **Gaudino M**, Nasso G, Zamparelli R, Andreotti F, Burzotta F, Iacoviello L, Santarelli F, Lapenna E, Bruno P, Di Pietrantonio F, Schiavello R, Maseri A, Possati G. *Ital Heart J Suppl 2002;3:646-651.*

50. Heart surgery interventions in chronic dialysis patients: short- and long-term results. Luciani N, Nasso G, D'Alessandro C, Testa F, Glieca F, **Gaudino M**, Possati G. *Ital Heart J Suppl 2002;3:746-52*.

51. Severity of coronary stenosis at preoperative angiography and midterm mammary graft status. **Gaudino M**, Alessandrini F, Nasso G, Bruno P, Manzoli A, Possati G. *Ann Thorac Surg 2002;74:119-121.*

52. Immunohistochemical scintigraphic correlation of sympathetic cardiac innervation in post-ischemic left ventricular aneurysms. **Gaudino M**, Giordano A, Santarelli P, Alessandrini F, Nori SL, Trani C, Gaudino S, Possati G. *J Nucl Cardiol 2002;9:601-7.*

53. Early vasoreactive profile of skeletonized versus pedicled internal thoracic artery grafts. **Gaudino M**, Trani C, Glieca F, Mazzari MA, Rigattieri S, Nasso G, Alessandrini F, Schiavoni G, Possati G. *J Thorac Cardiovasc Surg 2003;125:638-641.*

54. Surgical management of an uterine leiomyoma extending through the inferior vena cava to the right heart. **Gaudino M**, Spatuzza P, Snider F, Luciani N, Cina G, Possati G. *Heart and Vessels 2002;17:80-82.*

55. Preoperative C-reactive protein level and outcome following coronary surgery. **Gaudino M**, Nasso G, Andreotti F, Minniti G, Iacoviello L, Donati MB, Schiavello R, Possati G. *Eur J Cardio-thoracic Surgery 2002;22:521-526.*

56. Il by-pass aorto coronarico nei pazienti affetti da insufficienza renale in terapia dialitica: risultati immediati a follow up a lungo termine. Luciani N, Nasso G, Glieca F, **Gaudino M**, Minati A, De Rosis G, Maestri M, Pecoraro AM, Santarelli G, Possati G. *In By-Pass 2002;XV:1379-1384.*

57. Il by-pass aorto coronarico nei pazienti affetti da diabete mellito tipo II in trattamento insulinico. Luciani N, Nasso G, Alessandrini F, **Gaudino M**, Minati A, Girola F, De Rosis MG, Piscitelli MA, Spatuzza P, Pula R, Maestri M, Santarelli G, Formica ML. *In By-Pass 2002;XV:1501-1509*.

58. Localization of nitric oxide synthase type III in the internal thoracic and radial arteries and the great saphenous vein: a comparative immunohistochemical study. **Gaudino M**, Toesca A, Maggiano N, Pragliola C, Possati G. *J Thorac Cardiovasc Surg 2003;125:1510-1515.*

59. Early and late arrhythmias in patients in preoperative sinus rhythm submitted to mitral valve surgery via superior septal approach. **Gaudino M**, Nasso G, Minati A, Salica A, Luciani N, Morelli M, Possati G. *Ann Thorac Surg 2003;75:1181-1184.*

60. Quale rivascolarizzazione è preferibile nel diabetico. Alessandrini F, Nasso G, **Gaudino M**, Possati G. *Cardiologia per Immagini 2002, Dies Edizioni, Roma, pgg. 117-128.*

61. Genetic control of postoperative systemic inflammatory reaction and pulmonary and renal complications after coronary surgery. **Gaudino M**, Di Castelnuovo A, Zamparelli R, Andreotti F, Burzotta F, Iacoviello F, Glieca F, Alessandrini F, Nasso G, Donati MB, Maseri A, Schiavello R, Possati G. *J Thorac Cardiovasc Surg 2003;126:1107-1112.*

62. Immediate flow reserve of Y mammary grafts: an intraoperative flowmetric study. **Gaudino M**, Di Mauro M, Iacò AL, Canosa C, Vitolla G, Calafiore AM. *J Thorac Cardiovasc Surg 2003;126:1076-1079.*

63. Risks of using internal thoracic artery grafts in patients in chronic hemodialysis via upper extremity arteriovenous fistula. **Gaudino M**, Serricchio M, Luciani N, Giungi S, Salica A, Pola R, Pola P, Luciani G, Possati G. *Circulation 2003;107:2653-2655.*

64. Coronary artery bypass grafting in type II diabetic patients. A comparison between insulin dependent and non-insulin dependent patients at short and mid-term follow-up. Luciani N, Nasso G, **Gaudino M**, Abbate A, Glieca F, Alessandrini F, Girola F, Santarelli P, Possati G. *Ann Thorac Surg 2003;76:1149-54.*

65. Treatment of mediastinitis using an open irrigation and delayed sternal reconstruction with a pectoralis major muscle flap. Luciani N, Nasso G, **Gaudino M**, Glieca F, Alessandrini F, Abbate A, Biondi-Zoccai GG, Santarelli F, Dipietrantonio F, Salica A, Possati G. *Ital Heart J 2003;4:468-472.*

66. Composite Y internal thoracic artery saphenous vein grafts: early angiographic results and vasoreactive profile. **Gaudino M**, Alessandrini F, Pragliola C, Luciani N, Trani C, Burzotta F, Girola F, Guarini G, Nasso G, Possati G. *J Thorac Cardiovasc Surg 2004;127:1139-1144.*

67. Atherosclerotic involvement of the radial artery in patients with coronary artery disease and its relation with mid-term radial artery grafts patency and endothelial function. **Gaudino M**, Tondi P, Serricchio M, Spatuzza P, Santoliquido A, Flora R, Girola F, Nasso G, Pola P, Possati G. *J Thorac Cardiovasc Surg 2003;126:1968-1971.*

68. Long-term results of radial artery grafts used as coronary artery bypass conduit. Possati G, **Gaudino M**, Prati F, Alessandrini F, Trani C, Glieca F, Luciani N, Mazzari MA, Schiavoni G. *Circulation 2003;108:1350-1354.*

69. The 174 G/C Interleukin-6 promoter polymorphism influences Interleukin-6 levels and postoperative atrial fibrillation. Is atrial fibrillation an inflammatory complication? **Gaudino M**, Di Castelnuovo A, Zamparelli R, Andreotti F, Burzotta F, Iacoviello F, Glieca F, Alessandrini F, Nasso G, Donati MB, Maseri A, Schiavello R, Possati G. *Circulation* 2003;108 Suppl 1:II195-199.

70. Skeletonization does not influence internal thoracic artery innervation. **Gaudino M**, Toesca A, Glieca F, Girola F, Luciani N, Possati G. *Ann Thorac Surg 2004;77:1257-1261.*

71. Effect of target artery location and severity of stenosis on mid-term patency of aorta-anastomosed vs. internal thoracic artery-anastomosed radial artery grafts. **Gaudino M**, Alessandrini F, Pragliola C, Cellini C, Glieca F, Luciani N, Girola F, Possati G. *Eur J Cardiothorac Surg 2004;25:424-428.*

72. Myocardial ischemia, stunning, inflammation, and apoptosis during cardiac surgery: a review of evidence. Anselmi A, Abbate A, Girola F, Nasso G, Biondi-Zoccai GG, Possati G, **Gaudino M**. *Eur J Cardiothorac Surg 2004;25:304-311. Review.*

73. Effect of surgical revascularization of a right coronary artery tributary of an infarcted nonischemic territory on the outcome of patients with three-vessel disease: a prospective

randomized trial. **Gaudino M**, Alessandrini F, Glieca F, Luciani N, Cellini C, Pragliola C, Morelli M, Girola F, Possati G. *J Thorac Cardiovasc Surg 2004;127:435-439.*

74. High risk coronary artery bypass patient: incidence, surgical strategies, and results. **Gaudino M**, Glieca F, Alessandrini F, Nasso G, Pragliola C, Luciani N, Morelli M, Possati G. *Ann Thorac Surg 2004;77:574-579.*

75. Left ventricular mass regression after aortic valve replacement for aortic stenosis: time course and determinants. **Gaudino M**, Glieca F, Luciani N, Cellini C, Morelli M, Girola F, Guarini G, Possati G. *J Heart Valve Dis 2004;13 Suppl 1:S55-8.*

76. Survival after aortic valve replacement for aortic stenosis: does left ventricular mass regression have a clinical correlate? **Gaudino M**, Alessandrini F, Glieca F, Luciani N, Cellini C, Pragliola C, Morelli M, Canosa C, Nasso G, Possati G. *Eur Heart J 2005;26:51-57.*

77. Managing latex-free mitral valve replacement. Rossi M, De Paulis S, **Gaudino M**, Guarneri S, Martinelli L, Zamparelli R, Possati G, Schiavello R. *Ann Thorac Surg 2005;79:703-705.*

78. Is postoperative calcium channel blocker therapy needed in patients with radial artery grafts? **Gaudino M**, Luciani N, Nasso G, Salica A, Canosa C, Possati G. *J Thorac Cardiovasc Surg 2005;129:532-535.*

79. Different profiles of patients who require dialysis after cardiac surgery. **Gaudino M**, Luciani N, Giungi S, Caradonna E, Nasso G, Schiavello R, Luciani G, Possati G. *Ann Thorac Surg 2005;79:825-829.*

80. Midterm angiographic patency and vasoreactive profile of proximal versus distal radial artery grafts. **Gaudino M**, Nasso G, Canosa C, Glieca F, Salica A, Alessandrini F, Possati G. *Ann Thorac Surg 2005;79:1987-1990.*

81. Chronic compensatory increase in ulnar flow and accelerated atherosclerosis after radial artery removal for coronary artery bypass. **Gaudino M**, Serricchio M, Tondi P, Gerardino L, Giorgio AD, Pola P, Possati G. *J Thorac Cardiovasc Surg 2005;130:9-12*.

82. Harmonic scalpel reduces bleeding and postoperative complications in redo cardiac surgery. Luciani N, Anselmi A, **Gaudino M**, Nasso G, Glieca F, Martinelli L, Santarelli F, Perisano M, Possati G. *Ann Thorac Surg 2005;80:934-938.*

83. Thoracic radiation therapy and suitability of internal thoracic arteries for myocardial revascularization. Nasso G, Canosa C, De Filippo CM, Modugno P, Anselmi A, **Gaudino M**, Alessandrini F. *Chest 2005;128:1587-92.*

84. Arterial versus venous bypass grafts in patients with in-stent restenosis. **Gaudino M**, Cellini C, Pragliola C, Trani C, Burzotta F, Schiavoni G, Nasso G, Possati G. *Circulation 2005;112(9 Suppl):I265-9*

85. Implantation in coronary circulation induces morphofunctional transformation of radial grafts from muscular to elastomuscular. **Gaudino M,** Prati F, Caradonna E, Trani C, Burzotta F, Schiavoni G, Glieca F, Possati G. *Circulation 2005;112(9 Suppl):I208-11.*

86. Ten-year Echo-Doppler evaluation of forearm circulation following radial artery removal for coronary artery bypass grafting. **Gaudino M**, Glieca F, Luciani N, Lo Sasso G, Tondi P, Serricchio M, Pola P, Possati G. *Eur J Cardiothorac Surg 2006;29: 71-73.*

87. Impaired coronary and myocardial flow in severe aortic stenosis is associated with increased apoptosis: a transthoracic Doppler and myocardial contrast echocardiography study. Galiuto L, Lotrionte M, Crea F, Anselmi A, Biondi-Zoccai GGL, De Giorgio F, Baldi A, Baldi F, Possati G, **Gaudino M**, Vetrovec GW, Abbate A, *Heart 2006;92:208-212.*

88. Repeat valvular operations: bench optimization of conventional surgery. Luciani N, Nasso G,Anselmi A, Glieca F,**Gaudino M**, Girola F, Piscitelli M, Perisano M, Martinelli L, Possati G. *Ann Thorac Surg 2006;81:1279-1283.*

89. Patients with in-stent restenosis have an increased risk of mid-term venous graft failure. **Gaudino M**, Luciani N, Glieca F, Cellini C, Pragliola C, Trani C, Burzotta F, Schiavoni G, Anselmi A, Possati G. *Ann Thorac Surg 2006;82:802-4.*

90. Polydioxanone sternal sutures for prevention of sternal dehiscence. Luciani N, Anselmi A, Gandolfo F, **Gaudino M**, Nasso G, Piscitelli M, Possati G. *J Card Surg 2006;21:580-4.*

91. Long-term survival and quality of life of patients with prolonged postoperative intensive care unit stay: unmasking an apparent success. **Gaudino M**, Girola F, Piscitelli M, Martinelli L, Anselmi A, Della Vella C, Schiavello R, Possati G. *J Thorac Cardiovasc Surg 2007;134:465-9.*

92. Myocardial apoptosis predicts postoperative course after aortic valve replacement in patients with severe left ventricular hypertrophy. **Gaudino M**, Anselmi A, Abbate A, Galiuto L, Luciani N, Glieca F, Possati G. *J Heart Valve Dis 2007;16:344-8.*

93. Late haemodynamic and functional consequences of radial artery removal on the forearm circulation. **Gaudino M**, Anselmi A, Serricchio M, Flore R, Santoliquido A, Gerardino L, Pola R, Possati GF, Tondi P. *Int J Cardiol 2008;26;129:255-8.*

94. Role of apoptosis in pressure-overload cardiomyopathy.Anselmi A, **Gaudino M**, Baldi A, Vetrovec GW, Bussani R, Possati G, Abbate A. *J Cardiovasc Med (Hagerstown). 2008;9:227-32.*

95. Assessment of the position of retrograde cardioplegia catheter: comparison of hemodynamic versus manual evaluation in a prospective randomized trial.**Gaudino M**, Anselmi A, Glieca F, Luciani N, Perisano M, Piscitelli M, Possati G. *J Card Surg 2008;23:638-41.*

96. Is early tracheostomy a risk factor for mediastinitis after median sternotomy? **Gaudino M**, Losasso G, Anselmi A, Zamparelli R, Schiavello R, Possati G. *J Card Surg 2009;24:632-6.*

97. Postoperative inflammatory reaction and atrial fibrillation: simple correlation or causation? Anselmi A, Possati G, **Gaudino M**. *Ann Thorac Surg 2009;88:326-33.*

98. Aortic expansion rate in patients with dilated post-stenotic ascending aorta submitted only to aortic valve replacement long-term follow-up. **Gaudino M**, Anselmi A, Morelli M, Pragliola C, Tsiopoulos V, Glieca F, Possati G. *J Am Coll Cardiol 2011;58:581-4.*

99. Contemporary results for isolated aortic valve surgery. **Gaudino M**, Anselmi A, Glieca F, Tsiopoulos V, Pragliola C, Morelli M, Possati G. *Thorac Cardiovasc Surg 2011;59:229-32.*

100. Asymptomatic carotid artery disease in valvular heart surgery: impact of systematic screening on surgical strategy and neurological outcome. Anselmi A, **Gaudino M**, Risalvato N, Lauria G, Glieca F. *Angiology 2012;63:171-7.*

101. Giant coronary sinus aneurysm secondary to right coronary arteriovenous fistula leading to pseudo-mitral stenosis. **Gaudino M**, Anselmi A, Lombardo A, Marano R, Possati G. *Arch Med Sci 2011;7:533-5.*

102. Sirens versus facts: Mastering good old techniques in an era of innovation enthusiasm. **Gaudino M**. *Cardiology 2012;3:152.*

103. Increased plasma homocysteine predicts arrhythmia recurrence after minimally invasive epicardial ablation for nonvalvular atrial fibrillation. Nasso G, Bonifazi R, Romano V, Brigiani MS, Fiore F, Bartolomucci F, Lamarra M, Fattouch K, Rosano G, **Gaudino M**, Spirito R, Gaudio C, Speziale G. *J Thorac Cardiovasc Surg* 2013;146:848-53

104. Constrictive pericarditis following cardiac surgery. **Gaudino M**, Anselmi A, Pavone N, Massetti M. *Ann Thorac Surg 2013;95:731-6.*

105. From ECMO to VAD without sternotomy. Massetti M, **Gaudino M**, Saplacan V, Farina P. *J Heart Lung Transpl* 2013;32:138-9.

106. The use of internal thoracic artery grafts in patients with aortic coarctation. **Gaudino M,** Farina P, Toesca A, Bonalumi G, Tsiopoulos V, Bruno P, Massetti M. *Eur J Cardiothorac Surg. 2013 Feb 22***.** [Epub ahead of print] PMID:23435522.

107. How to transform peripheral extracorporeal membrane oxygenation in the simplest mid-term paracorporeal ventricular assist device. Massetti M, **Gaudino M**, Crea F. *Int J Cardiol. 2013 Jul 1;166(3):551-3. doi: 10.1016/j.ijcard.2013.01.271. Epub 2013 Feb 22. PMID:23462637*

108. Long-term morphofunctional remodeling of internal thoracic artery grafts: a frequency-domain optical coherence tomography study. Porto I, **Gaudino M**, De Maria GL, Di Vito L, Vergallo R, Bruno P, Bonalumi G, Prati F, Bolognese L, Crea F, Massetti M. *Circ Cardiovasc Interv 2013;6:269-76*.

109. Acute aortic pathology, Munchausen syndrome, and confirmation bias. **Gaudino M**, Nasso G, Romano V, Pragliola C, Di Cesare A, Speziale G, Massetti M. *J Emerg Med 2013;45:e183-6. doi: 10.1016/j.jemermed.2013.05.067*. Epub 2013 Sep 21.

110. Randomized trial of HTK versus warm blood cardioplegia for right ventricular protection in mitral surgery. **Gaudino M**, Pragliola C, Anselmi A, Pieroni M, De Paulis S, Leone A, De Caterina AR, Massetti M. *Scand Cardiovasc J 2013;47:359-67*.

111. Growth properties of cardiac stem cells are a novel biomarker of patients' outcome after coronary bypass surgery. D'Amario D, Leone AM, Iaconelli A, Luciani N, **Gaudino M**, Kannappan

R, Manchi M, Severino A, Shin SH, Graziani F, Biasillo G, Macchione A, Smaldone C, De Maria GL, Cellini C, Siracusano A, Ottaviani L, Massetti M, Goichberg P, Leri A, Anversa P, Crea F. *Circulation 2014 14;129:157-72.*

112. Staged transthoracic approach to persistent atrial fibrillation (TOP-AF): study protocol for a randomized trial. Pragliola C, Mastroroberto P, **Gaudino M**, Chello M, Covino E. *Trials 2014 26;15:190.*

113. Chronic competitive flow from a patent arterial or venous graft to the circumflex system does not impair the long-term patency of internal thoracic artery to left anterior descending grafts in patients with isolated predivisional left main disease: Long-term angiographic results of 2 different revascularization strategies. **Gaudino M**, Massetti M, Farina P, Hanet C, Etienne PY, Mazza A, Glineur D. *J Thorac Cardiovasc Surg 2014 Feb 10. pii: S0022-5223(14)00165-2.doi: 10.1016/j.jtcvs.2014.02.009. [Epub ahead of print]*

114. On pump evaluation of the anastomotic patency of in situ arterial grafts. Tsiopoulos V, Pragliola C, **Gaudino M**, Massetti M. *J Card Surg 2014;29:487-9.*

115. Long-term results of an open flexible prosthetic band for mitral insufficiency. Pragliola C, Chello M, **Gaudino M**, Mazza A, Cellini C, Spadaccio C, Covino E. *Asian Cardiovasc Thorac Ann 2014;22:811-5*.

116. Extracorporeal membrane oxygenation for resuscitation and cardiac arrest management. Massetti M, **Gaudino M**, De Paulis S, Scapigliati A, Cavaliere F. *Heart Fail Clin 2014;10(1 Suppl):S85-93*.

117. Ventricular assistance devices as bridge to transplantation. **Gaudino M**, Farina P, Bernazzali S, Bruno P, Colizzi C, Sani G, Massetti M. *Heart Fail Clin 2014;10(1 Suppl):S39-45.*

118. Morpho-functional features of the radial artery: implications for use as a coronary bypass conduit. **Gaudino M**, Crea F, Cammertoni F, Mazza A , Toesca A, Massetti M. *Ann Thorac Surg 2014;98:1875-9.*

119. Technical issues in the use of the radial artery as a coronary artery bypass conduit. **Gaudino M**, Crea F, Cammertoni F, Mazza A , Toesca A, Massetti M. *Ann Thorac Surg 2014;98:2247-54.*

120. Myocardial Revascularization with both internal thoracic arteries twenty-five years after delayed repair for aortic coarctation. **Gaudino M**, farina P, Cammertoni F, Massetti M. *Interact Cardiovasc Thorac Surg 2015;20:278-9.*

121. Morphological and functional consequences of transradial coronary angiography on the radial artery: implications for its use as a bypass conduit. **Gaudino M**, Leone A, Lupascu A, Toesca A, Mazza A, Ponziani FR, Flore R, Tondi P, Massetti M. *Eur J Cardiothorac Surg 2015;48:370-4.*

122. The radial artery: a forgotten conduit. **Gaudino M**, Crea F, Cammertoni F, Massetti M. *Ann Thorac Surg 2015;99:1479-85.*

123. Results of emergency postoperative re-angiography after cardiac surgery procedures. **Gaudino M**, Nesta M, Burzotta F, Trani C, Coluccia V, Crea F, Massetti M. *Ann Thorac Surg 2015;99:1576-82.*

124. Postoperative coronary artery spasm after mitral valve replacement. Pragliola C, **Gaudino M**, Farina P, Massetti M. *Int J Surg Case Rep 2015;8C:185-8.*

125. On diet, exercise ... and arterial grafting. (Ed) **Gaudino M.** *International Journal of Cardiology 2015;189:232–233.*

126. Nonischemic postoperative seizure does not increase mortality after cardiac surgery. Ivascu NS, **Gaudino M**, Lau C, Segal AZ, Debois WJ, Munjal M, Girardi LN. *Ann Thorac Surg 2015;100:101-6.*

127. Open repair of ruptured descending thoracic and thoracoabdominal aortic aneurysms. **Gaudino M**, Lau C, Munjal M, Girardi LN. *J Thorac Cardiovasc Surg 2015;150:814-23.*

128. Outcomes of open repair of mycotic descending thoracic and thoracoabdominal aortic aneurysms. Lau C, **Gaudino M**, de Biasi AR, Munjal M, Girardi LN. *Ann Thorac Surg 2015;100:1712-7.*

129. Contemporary outcomes of surgery for aortic root aneurysms: A propensity-matched comparison of valve-sparing and composite valve graft replacement. **Gaudino M**, Lau C, Munjal M, Avgerinos D, Girardi LN. *J Thorac Cardiovasc Surg 2015;150:1120-29.*

130. A Hypertensive Man With Repaired Type A Aortic Dissection Presents With Enlarging Thoracic Aorta. Lau C, **Gaudino M**, Girardi LN. *http://www.acc.org*. August 12, 2015. Accessed 8/25/2015.

131. The choice of conduits in coronary artery bypass surgery**. Gaudino M**, Taggart D, Suma H, Puskas JD, Crea F, Massetti M. *J Am Coll Cardiol 2015;66:1729-37.*

132. Long-Term survival and quality of life of patients undergoing emergency coronary artery bypass grafting for postinfarction cardiogenic shock. **Gaudino M**, Glineur D, Mazza A, Papadatos S, Farina P, Etienne PY, Fracassi F, Cammertoni F, Crea F, Massetti M. *Ann Thorac Surg 2015 Oct 28. pii: S0003-4975(15)01427-7. doi: 10.1016/j.athoracsur.2015.08.066. [Epub ahead of print].*

133. Don't be afraid of the skeleton: it is your patient's best friend! (Ed) **Gaudino M**, Girardi LN, Salemi A. *Cardiology. 2016;133:109-10.*

134. Surgical treatment of renal cell carcinoma with cavoatrial involvement: a systematic review of the literature. **Gaudino M**, Lau C, Cammertoni F, Vargiu V, Gambardella I, Massetti M, Girardi LN.*Ann Thorac Surg 2016 Jan 28. pii:S0003-4975(15)01663-X. doi: 10.1016/j.athoracsur.2015.10.003. [Epub ahead ofprint]*

135. The same angiographic factors predict venous and arterial graft patency: a retrospective study. **Gaudino M***, Niccoli G*, Roberto M, Cammertoni F, Cosentino N, Falcioni E, Panebianco M, D'Amario D, Crea F, Massetti M *Medicine (Baltimore) 2016 Jan;95(1):e2068. doi: 10.1097/MD.0000000000002068.*

136. Coronary surgery is superior to drug eluting stents in multivessel disease. Systematic review and meta-analysis of contemporary randomized controlled trials. Benedetto U*, **Gaudino M***, Ng C, Biondi-Zoccai G, D'Ascenzo F, Frati G, Girardi LN, Angelini GD, Taggart DP. *International Journal of Cardiology 2016 doi: S0167527316303205. [Epub ahead ofprint]*

137. Resection of intra-abdominal tumors with cavoatrial extension using deep hypothermic circulatory arrest. Lau C, O'Malley P, **Gaudino M**, Scherr DS, Girardi LN. *Ann Thorac Surg 2016 May 9. pii: S0003-4975(16)30100-X. doi:10.1016/j.athoracsur.2016.03.012. [Epub ahead of print]*

138. Secondary prevention for CABG patients: take two arterial grafts at the time of your coronary operation. (Ed) **Gaudino M**, Di Franco A, Crea F, Girardi LN. *J Thorac Dis 2016 Jun;8:1057-9.*

139. Reoperative aortic valve replacement in a previous biologic composite valve graft. Lau C, **Gaudino M**, Mazza A, Munjal M, Girardi LN *Ann Thorac Surg 2016 Nov;102(5):e477-e480. doi: 10.1016/j.athoracsur.2016.04.095.*

140. Academic productivity of US cardiothoracic surgical centers. Rosati CM, Vardas PN, **Gaudino M**, Tahboub MT, Blitzer D, Girardi LN, Turrentine MW, Brown JW, Koniaris LG. *J Card Surg 2016 Jun 8. doi: 10.1111/jocs.12773.*

141. Gender differences in in-hospital outcomes after coronary artery bypass grafting. Swaminathan RV, Feldman DN, Pashun RA, Patil RK, Shah T, Geleris JD, Wong SC, Girardi LN, **Gaudino M**, Minutello RM, Singh HS, Bergman G, Kim LK. *Am J Cardiol. 2016 May 14. pii: S0002-9149(16)30858-X. doi: 10.1016/j.amjcard.2016.05.004. [Epub ahead of print]*

142. Radial Artery as a Coronary Artery Bypass Conduit. 20-Year Results. **Gaudino M**, Tondi P, Benedetto U, Milazzo V, Flore R, Glieca F, Ponziani FR, Luciani N, Girardi LN, Massetti M. *J Am Coll Cardiol 2016;68:603–1.*

143. Congestive kidney failure in cardiac surgery: the relationship between central venous pressure and acute kidney injury. Gambardella I, **Gaudino M,** Ronco C, Lau C, Ivascu N, Girardi LN *Interact Cardiovasc Thorac Surg 2016 Jul 15. pii: ivw229.*

144. Training patterns and lifetime career achievements of US academic cardiothoracic surgeons. Rosati CM, Vardas PN, **Gaudino M**, Tahboub MT, Blitzer D, Girardi LN, Turrentine MW, Brown JW, Koniaris LG *Word J Surg 2016 Oct 12.PubMed PMID: 27734077.*

145. "Second" Primary Cardiac Sarcoma in a Patient With Ewing Sarcoma. Always Expect The Unexpected. Di Franco A, **Gaudino M**, Weinsaft JW, Pun SC, Narula N, Khan SA, Malik ZM,

Skubas NJ, Girardi LN. *Ann Thorac Surg. 2017 Feb;103(2):e131-e133. doi: 10.1016/j.athoracsur.2016.07.063*

146. Early and mid-term outcomes after aortic root replacement using a biologic composite valved graft with and without neo-sinuses. **Gaudino M**, Weltert L, Munjal M, Lau C, Elsayed M, Salica A, Gambardella I, Mills E, De Paulis R, Girardi LN. The Cornell International Consortium for Aortic Surgery (CICAS). *Eur J Cardio-thorac Surg 2017;51:316-321.*

147. 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. Benedetto U*, **Gaudino M***, Caputo M, Tranbaugh RF, Lau C, Di Franco A, Ng C, Girardi LN, Angelini GD. *J Thorac Cardiovasc Surg. 2016 Oct;152(4):1083-1091.e15. doi: 10.1016/j.jtcvs.2016.05.022.*

148. Considerations about the Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial. Di Franco A, **Gaudino M**, Girardi LN. *J Thorac Dis 2016;8:E599.*

149. International medical graduates among top US transplant surgeons. Rosati CM, Ekser B, Kaafarani HM, **Gaudino M**, Koniaris LG. *Int J Surg 2016 Sep 9. pii:S1743-9191(16)30853-6. doi: 10.1016/j.ijsu.2016.09.005.*

150. Right internal thoracic artery or radial artery: A propensity matched comparison on the second best arterial conduit. Benedetto U, Caputo M, **Gaudino M**, Marsico R, Rajakaruna C, Bryan A, Angelini GD. *J Thorac Cardiovasc Surg. 2016 Sep 12. pii: S0022-5223(16)31099-6. doi: 10.1016/j.jtcvs.2016.08.060.*

151. Surgical outcomes of chronic descending dissections: type I vs III DeBakey. Gambardella I, **Gaudino M**, Munjal M, Lau C, Girardi L. *Ann Thorac Surg 2017 Feb 9. pii: S0003-4975(16)31561-2. doi: 10.1016/j.athoracsur.2016.10.056.*

152. Acute respiratory distress syndrome after cardiac surgery. Rong LQ, Di Franco A, **Gaudino M**. *J Thorac Dis 2016;8(10):E1177-E1186.*

153. The evolution of coronary bypass surgery will determine its relevance as the standard of care for the treatment for multivessel coronary artery disease. Glineur D, **Gaudino M**, Grau J. *Circulation. 2016;134:1206-1208.*

154. Characteristics of cardiothoracic surgeons practicing at the top-ranked US institutions. Rosati CM, Koniaris LG, Molena D, Blitzer D, Su KW, Tahboub M, Vardas PN, Girardi LN, **Gaudino, M**. *J Thorac Dis 2016;8(11):3232-3244. doi: 10.21037/jtd.2016.11.72*

155. Impact of preoperative pulmonary function on outcomes after open repair of descending and thoracoabdominal aortic aneurysms. Girardi LN, Lau C, Munjal M, Elsayed M, Gambardella I, Ohmes L, **Gaudino M**. *J Thorac Cardiovasc Surg 2016 DOI: http://dx.doi.org/10.1016/j.jtcvs.2016.10.055.*

156. Academic vs. clinical productivity of cardiac surgeons in the state of New York: who publishes more and who operates more. Rosati CM, **Gaudino M**, Vardas PN, Weber DJ, Blitzer D, Hameedi F, Koniaris LG, Girardi LN. *The American Surgeon in press*

157. Impact of multiple arterial grafts in off-pump and on-pump coronary artery bypass surgery. Benedetto U, Caputo M, **Gaudino M**, Mariscalco G, Angelini GD. *J Thorac Cardiovasc Surg 2017;153:300-9*

158. Open repair of descending thoracic and thoracoabdominal aortic aneurysms in patients with preoperative renal failure. Girardi LN, Ohmes LB, Lau C, Di Franco A, Gambardella I, Elsayed M, Hameedi F, Munjal M, **Gaudino M**. *Eur J Cardiothorac Surg. 2017 May 1;51(5):971-977. doi: 10.1093/ejcts/ezx007.*

159. Biological solutions to aortic root replacement: valve-sparing versus bioprosthetic conduit. **Gaudino M**, Di Franco A, Ohmes LB, Weltert A, Lau C, Gambardella I, Salica A, Munjal M, Elsayed M, Girardi LN, De Paulis R. The Cornell International Consortium for Aortic Surgery (CICAS). *Interact Cardiovasc Thorac Surg. 2017;24:855-861.*

160. Contemporary results of hemi-arch replacement. Gambardella I*, **Gaudino M***, Lau C, Munjal M, Di Franco A, Ohmes L, Hameedi F, Girardi LN. *Eur J Cardiothorac Surg. 2017 Apr 6. doi: 10.1093/ejcts/ezx071. [Epub ahead of print]*

161. Three arterial grafts Improve late survival: a meta-analysis of propensity matched studies. **Gaudino M**, Puskas JP, Di Franco A, Ohmes L, Iannaccone M, Barbero U, Glineur D, Grau J, Benedetto U, D'Ascenzo F, Gaita F, Girardi LN, Taggart DP *Circulation. 2017 Mar 14;135(11):1036-1044. doi: 10.1161/CIRCULATIONAHA.116.025453*

162. Reoperative repair of descending thoracic and thoracoabdominal aneurysms. Lau C, **Gaudino M**, Gambardella I, Mills E, Munjal M, Elsayed M, Girardi LN. *Eur J Cardiothorac Surg. 2017 Apr 27. doi: 10.1093/ejcts/ezx072*

163. How safe is it to train residents to perform coronary surgery with multiple arterial grafting? Nineteen years of training at a single institution. Benedetto U, Caputo M, **Gaudino M**, Vohra H, Chivasso P, Bryan A, Angelini GD. *Semin Thorac Cardiovasc Surg. 2017;29:12-22.*

164. Composite bilateral internal thoracic artery grafts: Y not? Benedetto U, **Gaudino M**. *J Thorac Cardiovasc Surg. 2017 Feb 5. pii: S0022-5223(17)30158-7. doi: 10.1016/j.jtcvs.2017.01.033*

165. Techniques for intraoperative graft assessment in coronary artery bypass surgery. Ohmes LB, Di Franco A, Di Giammarco G, Rosati CM, Lau C, Girardi L, Massetti M, **Gaudino M**. *J Thorac Dis. 2017 Apr;9(Suppl 4):S327-S332. doi: 10.21037/jtd.2017.03.77.*

166. Bilateral versus sngle internal-thoracic-artery grafts. **Gaudino M**, Tranbaugh R, Fremes S. N Engl J Med. 2017 May 4;376(18):e37. doi: 10.1056/NEJMc1703358.

167. The role of neo-sinus reconstruction in aortic valve-sparing surgery. **Gaudino M**, Di Franco A, Weltert L, Benedetto U, Lau C, Gambardella I, De Paulis R, Girardi LN; Cornell International Consortium for Aortic Surgery (CICAS). J Card Surg. 2017 May 8. doi: 10.1111/jocs.13143.

168. Endoscopic versus open radial artery harvesting: A meta-analysis of randomized controlled and propensity matched studies. Rahouma M, Kamel M, Benedetto U, Ohmes LB, Di Franco A, Lau C, Girardi LN, Tranbaugh RF, Barili F, **Gaudino M**. J Card Surg. 2017 May 17. doi: 10.1111/jocs.13148. [Epub ahead of print]

169. Imagine all the people sharing all the world…. **Gaudino M**, Di Franco A, Rong LQ. J Thorac Dis. 2017 Apr;9(Suppl 4):S223-S224. doi: 10.21037/jtd.2017.04.15.

170. Serendipity and innovation: history and evolution of transthoracic echocardiography. Di Franco A, Ohmes LB, **Gaudino M**, Rong LQ, Girardi LN, Sarullo FM, Salerno Y, Sarullo S, Weinsaft JW, Kim J. J Thorac Dis. 2017 Apr;9(Suppl 4):S257-S263. doi: 10.21037/jtd.2017.03.90.

171. Left main coronary stenosis: surgery is still king. Ruel M, Kawajiri H, Glineur D, Grau J, **Gaudino M**, Vermac S. *Curr Opin Cardiol in press*

172. Valve-sparing root replacement: still so much to learn. Girardi LN, **Gaudino M**. *J Thorac Cardiovasc Surg in press*

173. Mechanisms, consequences, and prevention of coronary graft failure. **Gaudino M,** Antoniades C, Benedetto U, Deb S, Di Franco A, Di Giammarco G, Fremes S, Glineur D, Girardi LN, Grau J, He GW, Marinelli D, Ohmes L, Puskas J, Tranbaugh RT, Taggart D. The ATLANTIC (ArTeriaL grAftiNg inTernatIonal Consortium) Alliance. *Circulation Circulation 2017;136:1749-1764.*

174. Contemporary prevalence, in-hospital outcomes and prognostic determinants of triple valve surgery: National database review involving 5,234 patients. Ohmes L, Kim L, Feldman D, Lau C, Munjal M, Di Franco A, Gambardella I, Girardi LN, **Gaudino M**. *Int J Surg. 2017 Aug;44:132-138. doi: 10.1016/j.ijsu.2017.06.046.*

175. Does a balanced transfusion ratio of plasma to packed red blood cells improve outcomes in both trauma and surgical patients? A meta-analysis of randomized controlled trials and observational studies. Rahouma M, Kamel M, Benedetto U, Ohmes LB, Di Franco A, Lau C, Girardi LN, Guy TS **Gaudino M**. *The American Journal of Surgery in press*

176. What a great aortic surgeon would Messer Leonardo have been …. **Gaudino M**, Girardi LN. *J Thorac Cardiovasc Surg. 2017 Jun 21. pii: S0022-5223(17)31348-X. doi: 10.1016/j.jtcvs.2017.06.032 (Ed)*

177. Randomized comparison of the clinical outcome of single versus multiple arterial grafts: the ROMA trial-rationale and study protocol. **Gaudino M**, Alexander JH, Bakaeen FG, Ballman K, Barili F, Calafiore AM, Davierwala P, Goldman S, Kappetein P, Lorusso R, Mylotte D, Pagano D, Ruel M, Schwann T, Suma H, Taggart DP, Tranbaugh RF, Fremes S. *Eur J Cardiothorac Surg. 2017;52:1031-1040.*

178. Retrograde Cerebral Perfusion Is Effective for Prolonged Circulatory Arrest in Arch Aneurysm Repair. Lau C, **Gaudino M**, Mills Iannacone E, Gambardella I, Munjal M, Ohmes LB, Degner BC, Girardi LN. *Ann Thorac Surg. 2017 Nov 1. pii: S0003-4975(17)31043-3. doi: 10.1016/j.athoracsur.2017.07.018*

179. Left main coronary stenosis: surgery still reigns. Ruel M, Kawajiri H, Glineur D, Grau J, **Gaudino M**, Verma S. *Curr Opin Cardiol. 2017 Sep;32(5):590-593. doi: 10.1097/HCO.0000000000000434*

180. Valve-sparing root replacement: Still so much to learn. Girardi LN, **Gaudino M**. *J Thorac Cardiovasc Surg. 2017;154:798-799*. (Ed)

181. Secondary open aortic procedure following thoracic endovascular aortic repair: meta-analytic state of the art. Gambardella I, Antoniou GA, Torella F, Spadaccio C, Oo AY, **Gaudino M**, Nappi F, Shaw MA, Girardi LN. *J Am Heart Assoc. 2017 Sep 13;6(9). pii: e006618. doi: 10.1161/JAHA.117.006618.*

182. Hands off, the radial artery is mine! **Gaudino M**, Benedetto U. *J Thorac Cardiovasc Surg 2017;154:163-164.*

183. Fenestrated thoracic endovascular aortic repair for zone 2 lesions: Not just basic blocking and tackling. **Gaudino M**, Girardi LN. J Thorac Cardiovasc Surg. 2018 Feb;155(2):494-495. doi: 10.1016/j.jtcvs.2017.09.118. Epub 2017 Oct 7.

184. Heart Team 2.0: Keep your friends close…and your enemy closer! **Gaudino M**, Crea F, Massetti M, Girardi LN. J Thorac Cardiovasc Surg. 2018 Mar;155(3):874. doi: 10.1016/j.jtcvs.2017.10.050.

185. Accessory mitral valve mimicking aortic valve endocarditis as a cause of cerebrovascular accident. Degner BC, Gaudino M, Iannacone E, Lau C, Girardi LN. J Card Surg. 2017 Nov;32(11):691-693. doi: 10.1111/jocs.13237. Epub 2017 Nov 23.

186. Does a balanced transfusion ratio of plasma to packed red blood cells improve outcomes in both trauma and surgical patients? A meta-analysis of randomized controlled trials and observational studies. Rahouma M, Kamel M, Jodeh D, Kelley T, Ohmes LB, de Biasi AR, Abouarab AA, Benedetto U, Guy TS, Lau C, Lee PC, Girardi LN, **Gaudino M**. Am J Surg. 2017 Sep 23. pii: S0002-9610(17)31145-5. doi: 10.1016/j.amjsurg.2017.08.045

187. Off- vs. on-pump coronary artery bypass graft surgery on hospital outcomes in 134,117 octogenarians. Benedetto U, Angelini GD, Caputo M, Feldman DN, Kim LK, Lau C, Di Franco A, Girardi LN, **Gaudino M**. J Thorac Dis. 2017 Dec;9(12):5085-5092. doi: 10.21037/jtd.2017.11.10.

188. Incidence, risk factors, and prognostic impact of re-exploration for bleeding after cardiac surgery: A retrospective cohort study. Ohmes LB, Di Franco A, Guy TS, Lau C, Munjal M, Debois W, Li Z, Krieger KH, Schwann AN, Leonard JR, Girardi LN, **Gaudino M**. Int J Surg. 2017 Dec;48:166-173. doi: 10.1016/j.ijsu.2017.10.073.

189. Is the right internal thoracic artery superior to saphenous vein for grafting the right coronary artery? A propensity score-based analysis. Benedetto U, Caputo M, **Gaudino M**, Mariscalco G, Bryan A, Angelini GD. J Thorac Cardiovasc Surg. 2017 Oct;154(4):1269-1275.e5. doi: 10.1016/j.jtcvs.2017.04.070. Epub 2017 May 22.

190. Radial artery and right internal thoracic artery: jousting for the throne of coronary artery bypass grafting. Baudo M, **Gaudino M**. Ann Transl Med. 2017 Sep;5(17):354. doi: 10.21037/atm.2017.05.17.

191. Multiple arterial grafting and ostriches: let's all take heart! Di Franco A, Sarullo FM, **Gaudino M**. Oncotarget. 2017 Sep 30;8(49):84622-84623. doi: 10.18632/oncotarget.21392. eCollection 2017 Oct 17.

192. Blaise Pascal and the evidence on the use of multiple arterial grafts for coronary artery bypass surgery after the interim analysis of the Arterial Revascularization Trial. **Gaudino MFL**, Ruel M, Taggart DP; ATLANTIC (ArTeriaL grAftiNg inTernatIonal Consortium) Alliance. Curr Opin Cardiol. 2018 Mar;33(2):245-248. doi: 10.1097/HCO.0000000000000492.

193. Posterior Left pericardiotomy for the prevention of postoperative Atrial fibrillation after Cardiac Surgery (PALACS): study protocol for a randomized controlled trial. Abouarab AA, Leonard JR, Ohmes LB, Lau C, Rong LQ, Ivascu NS, Pryor KO, Munjal M, Crea F, Massetti M, Sanna T, Girardi LN, **Gaudino M**. Trials. 2017;18):593.

194. Comparison of Outcomes for Off-Pump Versus On-Pump Coronary Artery Bypass Grafting in Low-Volume and High-Volume Centers and by Low-Volume and High-Volume Surgeons. Benedetto U, Lau C, Caputo M, Kim L, Feldman DN, Ohmes LB, Di Franco A, Soletti G, Angelini GD, Girardi LN, **Gaudino M**. Am J Cardiol. 2018 Mar 1;121(5):552-557. doi: 10.1016/j.amjcard.2017.11.035.

195. Unmeasured Confounders in Observational Studies Comparing Bilateral Versus Single Internal Thoracic Artery for Coronary Artery Bypass Grafting: A Meta-Analysis. **Gaudino M**, Di Franco A, Rahouma M, Tam DY, Iannaccone M, Deb S, D'Ascenzo F, Abouarab AA, Girardi LN, Taggart DP, Fremes SE. J Am Heart Assoc. 2018 Jan 6;7(1). pii: e008010. doi: 10.1161/JAHA.117.008010.

196. Fixing nature's mistakes on the aortic valve: Will the normal form ensure normal function in the long term? **Gaudino M**, Lau C. J Thorac Cardiovasc Surg. 2018 Mar;155(3):942. doi: 10.1016/j.jtcvs.2017.12.037.

197. New-generation stents compared with coronary bypass surgery for unprotected left main disease: A word of caution. Benedetto U, Taggart DP, Sousa-Uva M, Biondi-Zoccai G, Di Franco A, Ohmes LB, Rahouma M, Kamel M, Caputo M, Girardi LN, Angelini GD, **Gaudino M**. J Thorac Cardiovasc Surg. 2018 May;155(5):2013-2019.e16. doi: 10.1016/j.jtcvs.2017.11.066.

198. Transcatheter aortic valve replacement, The Journal of Thoracic and Cardiovascular Surgery, and the evolution of clinical research in cardiothoracic surgery. **Gaudino M**. J Thorac Cardiovasc Surg. 2018 May;155(5):1977. doi: 10.1016/j.jtcvs.2017.12.021.

199. Optimal management of radial artery grafts in CABG: Patient and target vessel selection and anti-spasm therapy. Schwann TA, **Gaudino M**, Baldawi M, Tranbaugh R, Schwann AN, Habib RH. J Card Surg. 2018 May;33(5):205-212. doi: 10.1111/jocs.13517.

200. Novel insights by 4D Flow imaging on aortic flow physiology after valve-sparing root replacement with or without neosinuses. Galea N, Piatti F, Sturla F, Weinsaft JW, Lau C, Chirichilli I, Carbone I, Votta E, Catalano C, De Paulis R, Girardi LN, Redaelli A, **Gaudino M**; Cornell International Consortium for Aortic Surgery (CICAS). Interact Cardiovasc Thorac Surg. 2018;26:957-964

201. The radial artery: Results and technical considerations. Leonard JR, Abouarab AA, Tam DY, Girardi LN, **Gaudino MFL**, Fremes SE. J Card Surg. 2018 May;33(5):213-218. doi: 10.1111/jocs.13533. Epub 2018 Feb 5.

202. Incomplete revascularization and long-term survival after coronary artery bypass surgery. Benedetto U, **Gaudino M**, Di Franco A, Caputo M, Ohmes LB, Grau J, Glineur D, Girardi LN, Angelini GD. Int J Cardiol. 2018 Mar 1;254:59-63. doi: 10.1016/j.ijcard.2017.08.005.

203. Academic versus Clinical Productivity of (Elite) United States Transplant Surgeons: Who Publishes More and Who Operates More. Rosati CM, Koniaris LG, **Gaudino M**, Milgrom DP, Girardi LN, Ekser B. Am Surg. 2018 Jan 1;84(1):e36-38.

204. Academic versus Clinical Productivity of Cardiac Surgeons in the State of New York: Who Publishes More and Who Operates More. Rosati CM, **Gaudino M**, Vardas PN, Weber DJ, Blitzer D, Hameedi F, Koniaris LG, Girardi LN. Am Surg. 2018 Jan 1;84(1):71-79.

205. Nonbacterial Thrombotic Endocarditis Presenting with Leg Pain and a Left Atrial Mass Lesion. Abouarab AA, Elmously A, Leonard JR, Arisha MJ, **Gaudino M**, Narula N, Salemi A. Cardiology. 2018;139(4):208-211. doi: 10.1159/000486635. Epub 2018 Feb 15.

206. The Radial Artery for Percutaneous Coronary Procedures or Surgery? **Gaudino M**, Burzotta F, Bakaeen F, Bertrand O, Crea F, Di Franco A, Fremes S, Kiemeneij F, Louvard Y, Rao SV, Schwann TA, Tatoulis J, Tranbaugh RF, Trani C, Valgimigli M, Vranckx P, Taggart DP; Arterial Grafting International Consortium Alliance. J Am Coll Cardiol. 2018 Mar 13;71(10):1167-1175. doi: 10.1016/j.jacc.2018.01.013.

207. Open repair of descending and thoracoabdominal aortic aneurysms in octogenarians. Girardi LN, Lau C, Ohmes LB, Degner BC, Leonard JR, Abouarab A, Di Franco A, Iannacone EM, Munjal M, **Gaudino M**. J Vasc Surg. 2018 Mar 29. pii: S0741-5214(18)30296-9. doi: 10.1016/j.jvs.2017.12.083.

208. Open radial artery harvesting. Lau C, **Gaudino M**. Multimed Man Cardiothorac Surg. 2018 Mar 6;2018. doi: 10.1510/mmcts.2018.021.

209. Academic versus Clinical Productivity of (Elite) United States Transplant Surgeons: Who Publishes More and Who Operates More. Rosati CM, Koniaris LG, **Gaudino M**, Milgrom DP, Girardi LN, Ekser B. Am Surg. 2018 Jan 1;84(1):36-38.

210. Totally endoscopic coronary artery bypass surgery: A meta-analysis of the current evidence. Leonard JR, Rahouma M, Abouarab AA, Schwann AN, Scuderi G, Lau C, Guy TS, Demetres M, Puskas JD, Taggart DP, Girardi LN, **Gaudino M**. Int J Cardiol. 2018 Jun 15;261:42-46. doi: 10.1016/j.ijcard.2017.12.071.

211. Continuing Conundrum of Multiple Arterial Conduits for Coronary Artery Bypass Grafting. **Gaudino M**, Fremes SE, Taggart DP. Circulation. 2018 Apr 17;137(16):1658-1660. doi: 10.1161/CIRCULATIONAHA.117.031670.

212. On the pooling and subgrouping of data from percutaneous coronary intervention versus coronary artery bypass grafting trials: a call to circumspection. Freemantle N, Ruel M, **Gaudino MFL**, Pagano D. Eur J Cardiothorac Surg. 2018 May 1;53(5):915-918. doi: 10.1093/ejcts/ezy140.

213. Systematic bilateral internal mammary artery grafting: lessons learned from the CATHolic University EXtensive BIMA Grafting Study. **Gaudino M**, Glieca F, Luciani N, Pragliola C, Tsiopoulos V, Bruno P, Farina P, Bonalumi G, Pavone N, Nesta M, Cammertoni F, Munjal M, Di Franco A, Massetti M. Eur J Cardiothorac Surg. 2018 Apr 16. doi: 10.1093/ejcts/ezy148.

214. Implications of coronary artery bypass grafting and percutaneous coronary intervention on disease progression and the resulting changes to the physiology and pathology of the native

coronary arteries. Fortier JH, Ferrari G, Glineur D, **Gaudino M**, Shaw RE, Ruel M, Grau JB. Eur J Cardiothorac Surg. 2018 Apr 23. doi: 10.1093/ejcts/ezy171.

215. Retrograde perfusion through superior vena cava reaches the brain during circulatory arrest. **Gaudino M**, Ivascu N, Cushing M, Lau C, Gambardella I, Di Franco A, Ohmes LB, Munjal M, Girardi LN. J Thorac Dis. 2018 Mar;10(3):1563-1568. doi: 10.21037/jtd.2018.01.166.

216. Radial-Artery or Saphenous-Vein Grafts in Coronary-Artery Bypass Surgery. **Gaudino M**, Benedetto U, Fremes S, Biondi-Zoccai G, Sedrakyan A, Puskas JD, Angelini GD, Buxton B, Frati G, Hare DL, Hayward P, Nasso G, Moat N, Peric M, Yoo KJ, Speziale G, Girardi LN, Taggart DP; RADIAL Investigators. N Engl J Med. 2018 May 31;378(22):2069-2077. doi: 10.1056/NEJMoa1716026.

217. Use Rate and Outcome in Bilateral Internal Thoracic Artery Grafting: Insights From a Systematic Review and Meta-Analysis. **Gaudino M**, Bakaeen F, Benedetto U, Rahouma M, Di Franco A, Tam DY, Iannaccone M, Schwann TA, Habib R, Ruel M, Puskas JD, Sabik J, Girardi LN, Taggart DP, Fremes SE. J Am Heart Assoc. 2018 May 17;7(11). pii: e009361. doi: 10.1161/JAHA.118.009361.

218. The SAVE RITA trial at 5 years: More evidence is needed to transform a vein to an artery. **Gaudino M**, Fremes SE. J Thorac Cardiovasc Surg. 2018 May 3. pii: S0022-5223(18)31242-X. doi: 10.1016/j.jtcvs.2018.04.103.

219. Long-term clinical outcome and graft patency of radial artery and saphenous vein grafts in multiple arterial revascularization. Ruttmann E, Dietl M, Feuchtner GM, Metzler B, Bonaros N, Taggart DP, **Gaudino M**, Ulmer H; RADIAL Investigators. J Thorac Cardiovasc Surg. 2018 Nov 14. pii: S0022-5223(18)32929-5. doi: 10.1016/j.jtcvs.2018.10.135. [Epub ahead of print]

220. Myocardial Revascularization Trials. Ruel M, Falk V, Farkouh ME, Freemantle N, **Gaudino MF**, Glineur D, Cameron DE, Taggart DP. Circulation. 2018 Dec 18;138(25):2943-2951. doi: 10.1161/CIRCULATIONAHA.118.035970.

221. Radial artery as a conduit for coronary artery bypass grafting: a state-of-the-art primer. Sousa-Uva M, **Gaudino M,** Schwann T, Acar C, Benedeto U, Ruel M. Eur J Cardiothorac Surg. 2018 Dec 1;54(6):971-976. doi: 10.1093/ejcts/ezy335.

222. Meta-Analysis Comparing Outcomes of Drug Eluting Stents Versus Single and Multiarterial Coronary Artery Bypass Grafting. **Gaudino M**, Rahouma M, Abouarab A, Tam DY, Di Franco A, Leonard J, Benedetto U, Iannaccone M, D'Ascenzo F, Biondi-Zoccai G, Vallely M, Girardi LN, Fremes SE, Taggart DP. Am J Cardiol. 2018 Dec 15;122(12):2018-2025. doi: 10.1016/j.amjcard.2018.09.005. Epub 2018 Sep 13.

223. RADIAL meta-analysis: following the rules usually pays off. Wingo M, **Gaudino MFL.** J Thorac Dis. 2018 Nov;10(11):E785-E786. doi: 10.21037/jtd.2018.10.75.

224. Open repair of descending and thoracoabdominal aortic aneurysms in octogenarians. Girardi LN, Lau C, Ohmes LB, Degner BC, Leonard JR, Abouarab A, Di Franco A, Iannacone EM, Munjal M, **Gaudino M**. J Vasc Surg. 2018 Nov;68(5):1287-1296.e3. doi: 10.1016/j.jvs.2017.12.083. Epub 2018 Mar 30.

225. Off-pump coronary artery bypass surgery: The long and winding road. Farina P, **Gaudino M**, Angelini GD. Int J Cardiol. 2019 Mar 15;279:51-55. doi: 10.1016/j.ijcard.2018.09.101. Epub 2018 Sep 28. Review.

226. Multiple Arterial Grafting Is Associated With Better Outcomes for Coronary Artery Bypass Grafting Patients. Rocha RV, Tam DY, Karkhanis R, Nedadur R, Fang J, Tu JV, **Gaudino M,** Royse

A, Fremes SE. Circulation. 2018 Nov 6;138(19):2081-2090. doi: 10.1161/CIRCULATIONAHA.118.034464.

227. Is the non-use of a saphenous vein graft the true question in coronary surgery? **Gaudino M**, Fremes S, Kolh P. Eur J Cardiothorac Surg. 2018 Dec 1;54(6):1100-1101. doi: 10.1093/ejcts/ezy281.

228. Pooled meta-analysis on cerebrospinal-fluid-drain-related complications. Response to Br J Anaesth 2018; 121: 987. Rong LQ, **Gaudino M.** Br J Anaesth. 2018 Oct;121(4):987-988. doi: 10.1016/j.bja.2018.07.026. Epub 2018 Aug 24.

229. New Strategies for Surgical Myocardial Revascularization. **Gaudino M,** Bakaeen F, Davierwala P, Di Franco A, Fremes SE, Patel N, Puskas JD, Ruel M, Torregrossa G, Vallely M, Taggart DP. Circulation. 2018 Nov 6;138(19):2160-2168. doi: 10.1161/CIRCULATIONAHA.118.035956

230. Radial-Artery Grafts for Coronary-Artery Bypass Surgery. **Gaudino M**, Benedetto U, Taggart DP. N Engl J Med. 2018 Nov 15;379(20):1967-1968. doi: 10.1056/NEJMc1813097. No abstract available.

231. Systematic preoperative CT scan is associated with reduced risk of stroke in minimally invasive mitral valve surgery: A meta-analysis. Leonard JR, Henry M, Rahouma M, Khan FM, Wingo M, Hameed I, Di Franco A, Guy TS, Girardi LN, **Gaudino M**. Int J Cardiol. 2019 Mar 1;278:300-306. doi: 10.1016/j.ijcard.2018.12.025. Epub 2018 Dec 12.

232. Off-pump coronary artery bypass surgery: The long and winding road. Farina P, **Gaudino M**, Angelini GD. Int J Cardiol. 2019 Mar 15;279:51-55. doi: 10.1016/j.ijcard.2018.09.101. Epub 2018 Sep 28. Review.

233. Four-dimensional flow magnetic resonance imaging: Beyond beautiful pictures! Weinsaft JW, **Gaudino M**, Girardi LN. J Thorac Cardiovasc Surg. 2019 Feb;157(2):477-478. doi: 10.1016/j.jtcvs.2018.06.075. Epub 2018 Jul 20. No abstract available.

234. Off- Versus On-Pump Coronary Surgery and the Effect of Follow-Up Length and Surgeons' Experience: A Meta-Analysis. **Gaudino M**, Benedetto U, Bakaeen F, Rahouma M, Tam DY, Abouarab A, Di Franco A, Leonard J, Elmously A, Puskas JD, Angelini GD, Girardi LN, Fremes SE, Taggart DP. J Am Heart Assoc. 2018 Nov 6;7(21):e010034. doi: 10.1161/JAHA.118.010034

235. Fifty years after Favaloro, coronary artery bypass surgery is still an ART. **Gaudino M**, Taggart DP. Cardiovasc Res. 2018 Nov 1;114(13):e99-e101. doi: 10.1093/cvr/cvy236.

236. Not perfect, but….**Gaudino M**. J Thorac Cardiovasc Surg. 2018 Nov;156(5):1853. doi: 10.1016/j.jtcvs.2018.05.028

237. The ROMA trial: why it is needed. **Gaudino MFL**, Taggart DP, Fremes SE. Curr Opin Cardiol. 2018 Nov;33(6):622-626. doi: 10.1097/HCO.0000000000000565.

238. Implications of coronary artery bypass grafting and percutaneous coronary intervention on disease progression and the resulting changes to the physiology and pathology of the native coronary arteries. Fortier JH, Ferrari G, Glineur D, **Gaudino M,** Shaw RE, Ruel M, Grau JB. Eur J Cardiothorac Surg. 2018 Nov 1;54(5):809-816. doi: 10.1093/ejcts/ezy171.

239. Open repair of descending and thoracoabdominal aortic aneurysms in octogenarians. Girardi LN, Lau C, Ohmes LB, Degner BC, Leonard JR, Abouarab A, Di Franco A, Iannacone EM, Munjal M, **Gaudino M**. J Vasc Surg. 2018 Nov;68(5):1287-1296.e3. doi: 10.1016/j.jvs.2017.12.083. Epub 2018 Mar 30.

240. Absence of proof or proof of absence? The risk of underpowered studies in cardiovascular medicine. **Gaudino M**, Benedetto U, Taggart DP. EuroIntervention. 2018 Sep 20;14(7):727-728. doi: 10.4244/EIJV14I7A126.

241. Percutaneous coronary intervention or coronary artery bypass graft in left main coronary artery disease: a comprehensive meta-analysis of adjusted observational studies and randomized controlled trials. Bertaina M, De Filippo O, Iannaccone M, Colombo A, Stone G, Serruys P, Mancone M, Omedè P, Conrotto F, Pennone M, Kimura T, Kawamoto H, Zoccai GB, Sheiban I, Templin C, Benedetto U, Cavalcante R, D'Amico M, **Gaudino M**, Moretti C, Gaita F, D'Ascenzo F. J Cardiovasc Med (Hagerstown). 2018 Oct;19(10):554-563. doi: 10.2459/JCM.0000000000000703

242. Editor's Choice - Aortic Re-operation After Replacement of the Proximal Aorta: A Systematic Review and Meta-Analysis. **Gaudino M**, Girardi LN, Rahouma M, Leonard JR, Di Franco A, Lau C, Mehta N, Abouarab A, Schwann AN, Scuderi G, Demetres M, Devereux RB, Benedetto U, Weinsaft JW. Eur J Vasc Endovasc Surg. 2018 Oct;56(4):515-523. doi: 10.1016/j.ejvs.2018.06.038. Epub 2018 Jul 20. Review.

243. Aortic symmetry index: Initial validation of a novel preoperative predictor of recurrent aortic insufficiency after valve-sparing aortic root reconstruction. Di Franco A, Rong LQ, Munjal M, Weinsaft JW, Kim J, Sturla F, Girardi LN, **Gaudino M**. J Thorac Cardiovasc Surg. 2018 Oct;156(4):1393-1394. doi: 10.1016/j.jtcvs.2018.05.047. Epub 2018 Jun 2. No abstract available.

244. Radial arteries for coronary angiography and coronary artery bypass surgery: Are two arteries enough? An KR, Tam DY, **Gaudino MFL**, Fremes SE. J Thorac Cardiovasc Surg. 2019

Feb;157(2):573-575. doi: 10.1016/j.jtcvs.2018.06.006. Epub 2018 Jun 23. No abstract available.

245. Individual Operator Experience and Outcomes in Transcatheter Aortic Valve Replacement.Salemi A, Sedrakyan A, Mao J, Elmously A, Wijeysundera H, Tam DY, Di Franco A, Redwood S, Girardi LN, Fremes SE, **Gaudino M**. JACC Cardiovasc Interv. 2019 Jan 14;12(1):90-97. doi: 10.1016/j.jcin.2018.10.030. Epub 2018 Dec 12.

246. Aortic flow after valve sparing root replacement with or without neosinuses reconstruction. **Gaudino M**, Piatti F, Lau C, Sturla F, Weinsaft JW, Weltert L, Votta E, Galea N, Chirichilli I, Di Franco A, Francone M, Catalano C, Redaelli A, Girardi LN, De Paulis R.J Thorac Cardiovasc Surg. 2019 Feb;157(2):455-465. doi: 10.1016/j.jtcvs.2018.06.094. Epub 2018 Jul 27.

247. 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. **Gaudino M**, Lorusso R, Rahouma M, Abouarab A, Tam DY, Spadaccio C, Saint-Hilary G, Leonard J, Iannaccone M, D'Ascenzo F, Di Franco A, Soletti G, Kamel MK, Lau C, Girardi LN, Schwann TA, Benedetto U, Taggart DP, Fremes SE. J Am Heart Assoc. 2019 Jan 22;8(2):e010839. doi: 10.1161/JAHA.118.010839.

248. Are we doing a good job with coronary artery bypass grafting? Spadaccio C, **Gaudino MFL**. Eur J Cardiothorac Surg. 2019 Jan 10. doi: 10.1093/ejcts/ezy428. [Epub ahead of print] No abstract available.

249. The effect of surgical versus transcatheter aortic valve replacement on endothelial function. An observational study. Moscarelli M, Devito F, Fattouch K, Lancellotti P, Ciccone

MM, Rizzo P, **Gaudino M**, Marchese A, Angelini G, Speziale G. Int J Surg. 2019 Jan 28. pii: S1743-9191(19)30021-4. doi: 10.1016/j.ijsu.2019.01.014. [Epub ahead of print]

250. Reply to Sajja. **Gaudino M**. Eur J Cardiothorac Surg. 2019 Jan 14. doi: 10.1093/ejcts/ezy468. [Epub ahead of print]

251. What is the best graft to supplement the bilateral internal thoracic artery to the left coronary system? A meta-analysis. Di Mauro M, Lorusso R, Di Franco A, Foschi M, Rahouma M, Soletti G, Calafiore AM, **Gaudino M**. Eur J Cardiothorac Surg. 2019 Jan 12. doi: 10.1093/ejcts/ezy476. [Epub ahead of print]

252. Commentary: When the back of the envelope calculation just isn't good enough, use decision analysis modeling. Tam DY, **Gaudino M**. J Thorac Cardiovasc Surg. 2019 Jul 18. pii: S0022-5223(19)31415-1. doi: 10.1016/j.jtcvs.2019.06.094.

253. Preventing treatment failures in coronary artery disease: what can we learn from the biology of in-stent restenosis, vein graft failure and internal thoracic arteries. Spadaccio C, Antoniades C, Nenna A, Chung C, Will R, Chello M, **Gaudino M**FL. Cardiovasc Res. 2019 Aug 9. pii: cvz214. doi: 10.1093/cvr/cvz214.

254. Multiarterial coronary artery bypass grafting: is the radial artery fulfilling the unkept promise of the right internal thoracic artery? Affronti A, Ruel M, **Gaudino M**FL. Curr Opin Cardiol. 2019 Aug 5. doi: 10.1097/HCO.0000000000000670.

255. The Evidence on the Ten Most Common Surgical Interventions in the United States From 1970 to 2018. Henry M, Rong LQ, Wingo M, Rahouma M, Girardi LN, **Gaudino M**. Ann Surg. 2019 Aug;270(2):e16-e17. doi: 10.1097/SLA.0000000000003258.

256. Modality Selection for the Revascularization of Left Main Disease. Tam DY, Bakaeen F, Feldman DN, Kolh P, Lanza GA, Ruel M, Piccolo R, Fremes SE, **Gaudino M**. Can J Cardiol. 2019 Aug;35(8):983-992. doi: 10.1016/j.cjca.2018.12.017.

257. Stroke After Coronary Artery Bypass Grafting and Percutaneous Coronary Intervention: Incidence, Pathogenesis, and Outcomes. **Gaudino M**, Angiolillo DJ, Di Franco A, Capodanno D, Bakaeen F, Farkouh ME, Fremes SE, Holmes D, Girardi LN, Nakamura S, Head SJ, Park SJ, Mack M, Serruys PW, Ruel M, Stone GW, Tam DY, Vallely M, Taggart DP. J Am Heart Assoc. 2019 Jul 2;8(13):e013032. doi: 10.1161/JAHA.119.013032.

258. Perfusion: Is higher better? Hameed I, **Gaudino M**. J Thorac Cardiovasc Surg. 2019 Jun 21. pii: S0022-5223(19)31138-9. doi: 10.1016/j.jtcvs.2019.05.037. [Epub ahead of print] No abstract available.

259. Unbalanced mitral valve remodeling in ischemic mitral regurgitation: Implications for a durable repair. Calafiore AM, Totaro A, Sacra C, Foschi M, Tancredi F, Pelini P, **Gaudino M**, Di Mauro M. J Card Surg. 2019 Jun 24. doi: 10.1111/jocs.14119.

260. Commentary: Who needs evidence when patient preference is a Class I indication? **Gaudino M**, Chikwe J. J Thorac Cardiovasc Surg. 2019 May 30. pii: S0022-5223(19)31121-3. doi: 10.1016/j.jtcvs.2019.05.021.

261. Right internal thoracic or radial artery as the second arterial conduit for coronary artery bypass surgery. Spadaccio C, Fremes SE, **Gaudino M**FL. Curr Opin Cardiol. 2019 Sep;34(5):564-570. doi: 10.1097/HCO.0000000000000654.

262. Early Versus Delayed Stroke After Cardiac Surgery: A Systematic Review and Meta-Analysis. **Gaudino M**, Rahouma M, Di Mauro M, Yanagawa B, Abouarab A, Demetres M, Di Franco A,

Arisha MJ, Ibrahim DA, Baudo M, Girardi LN, Fremes S. J Am Heart Assoc. 2019 Jul 2;8(13):e012447. doi: 10.1161/JAHA.119.012447. Epub 2019 Jun 19.

263. Characteristics and anatomic distribution of early vs late stroke after cardiac surgery. Ivascu NS, Khan FM, Rahouma M, Hameed I, Abouarab A, Segal AZ, **Gaudino M**FL, Girardi LN. J Card Surg. 2019 Aug;34(8):684-689. doi: 10.1111/jocs.14121. Epub 2019 Jun 18.

264. The SYNTAX score according to diabetic status: What does it mean for the patient requiring myocardial revascularization? Ruel M, Sun LY, **Gaudino M**F. J Thorac Cardiovasc Surg. 2019 Jun 13. pii: S0022-5223(19)31025-6. doi: 10.1016/j.jtcvs.2019.04.088.

265. Management of Less-Than-Severe Aortic Stenosis During Coronary Bypass: A Systematic Review and Meta-Analysis. Yanagawa B, An KR, Ouzounian M, **Gaudino M**, Puskas JD, Asaoka N, Verma S, Friedrich JO. Innovations (Phila). 2019 Aug;14(4):291-298. doi: 10.1177/1556984519849639. Epub 2019 Jun 11.

266. Echocardiographic predictors of intraoperative right ventricular dysfunction: a 2D and speckle tracking echocardiography study. Rong LQ, Yum B, Abouzeid C, Palumbo MC, Brouwer LR, Devereux RB, Girardi LN, Weinsaft JW, **Gaudino M**, Kim J. Cardiovasc Ultrasound. 2019 Jun 7;17(1):11. doi: 10.1186/s12947-019-0161-3.

267. Open radial artery harvesting better preserves endothelial function compared to the endoscopic approach. **Gaudino M**F, Lorusso R, Ohmes LB, Narula N, McIntire P, Gargiulo A, Bucci MR, Leonard J, Rahouma M, Di Franco A, He GW, Girardi LN, Tranbaugh RF, Di Lorenzo A. Interact Cardiovasc Thorac Surg. 2019 Jun 3. pii: ivz129. doi: 10.1093/icvts/ivz129.

268. Impact of preoperative fractional flow reserve on arterial bypass graft anastomotic function: the IMPAG trial. Glineur D, Grau JB, Etienne PY, Benedetto U, Fortier JH, Papadatos

S, Laruelle C, Pieters D, El Khoury E, Blouard P, Timmermans P, Ruel M, Chong AY, So D, Chan V, Rubens F, **Gaudino M**F. Eur Heart J. 2019 Jun 1. pii: ehz329. doi: 10.1093/eurheartj/ehz329.

269. Commentary: Postoperative atrial fibrillation can last years? Oh snap! Yanagawa B, Ad N, **Gaudino M**F. J Thorac Cardiovasc Surg. 2019 Apr 24. pii: S0022-5223(19)30923-7. doi: 10.1016/j.jtcvs.2019.04.028. [Epub ahead of print] No abstract available.

270. State of the art and meta-analysis of secondary open aortic procedure after abdominal endovascular aortic repair. Gambardella I, Antoniou GA, **Gaudino M**, D'Ayala M, Girardi LN, Torella F. J Vasc Surg. 2019 May 27. pii: S0741-5214(19)30497-5. doi: 10.1016/j.jvs.2019.01.092.

271. Current Readings on Outcomes After Off-Pump Coronary Artery Bypass Grafting. Patel V, Unai S, **Gaudino M**, Bakaeen F. Semin Thorac Cardiovasc Surg. 2019 May 21. pii: S1043-0679(18)30412-X. doi: 10.1053/j.semtcvs.2019.05.012. [Epub ahead of print]

272. Commentary: We have mastered off-pump coronary artery bypass grafting technique, but not the indications for it. **Gaudino M**, Worku B. J Thorac Cardiovasc Surg. 2019 Apr 24. pii: S0022-5223(19)30922-5. doi: 10.1016/j.jtcvs.2019.04.027.

273. Pulmonary artery aneurysms: Preoperative, intraoperative, and postoperative findings. Worku BM, de Angelis P, Wingo ME, Leonard JR, Khan FM, Hameed I, Ruan Y, **Gaudino M**FL, Girardi LN. J Card Surg. 2019 Jul;34(7):570-576. doi: 10.1111/jocs.14070. Epub 2019 May 15.

274. Cardiotoxicity with immune system targeting drugs: a meta-analysis of anti-PD/PD-L1 immunotherapy randomized clinical trials. Rahouma M, Karim NA, Baudo M, Yahia M, Kamel M, Eldessouki I, Abouarab A, Saad I, Elmously A, Gray KD, Ghaly G, Gaber O, Kamal M, A Hassan

A, Rahouma M, D'Ascenzo F, Morris J, Mohamed A, Girardi L, **Gaudino M**. Immunotherapy. 2019 Jun;11(8):725-735. doi: 10.2217/imt-2018-0118.

275. Effect of Calcium-Channel Blocker Therapy on Radial Artery Grafts After Coronary Bypass Surgery. **Gaudino M**, Benedetto U, Fremes SE, Hare DL, Hayward P, Moat N, Moscarelli M, Di Franco A, Nasso G, Peric M, Petrovic I, Puskas JD, Speziale G, Yoo KJ, Girardi LN, Taggart DP; RADIAL Investigators. J Am Coll Cardiol. 2019 May 14;73(18):2299-2306. doi: 10.1016/j.jacc.2019.02.054.

276. Percutaneous Coronary Intervention vs Coronary Artery Bypass Grafting: A Surgical Perspective. **Gaudino M**, Taggart DP. JAMA Cardiol. 2019 Jun 1;4(6):505-506. doi: 10.1001/jamacardio.2019.1046.

277. Commentary: Coincidence or consequence, and the effect of sex on either. Worku B, **Gaudino M**. J Thorac Cardiovasc Surg. 2019 Apr 4. pii: S0022-5223(19)30750-0. doi: 10.1016/j.jtcvs.2019.03.072.

278. Experience Is Crucial in Off-Pump Coronary Artery Bypass Grafting. Puskas JD, **Gaudino M**, Taggart DP. Circulation. 2019 Apr 16;139(16):1872-1875. doi: 10.1161/CIRCULATIONAHA.119.039584.

279. Commentary: Knowledge is power. Sandner SE, **Gaudino M**. J Thorac Cardiovasc Surg. 2019 Feb 27. pii: S0022-5223(19)30507-0. doi: 10.1016/j.jtcvs.2019.02.062. [Epub ahead of print] No abstract available.

280. Pneumonitis as a complication of immune system targeting drugs?-a meta-analysis of anti-PD/PD-L1 immunotherapy randomized clinical trials. Rahouma M, Baudo M, Yahia M, Kamel

M, Gray KD, Elmously A, Ghaly G, Eldessouki I, Abouarab A, Cheriat AN, Karim NA, Mohamed A, Morris J, **Gaudino M**. J Thorac Dis. 2019 Feb;11(2):521-534. doi: 10.21037/jtd.2019.01.19.

281. Early failure of tricuspid annuloplasty. Should we repair the tricuspid valve at an earlier stage? The role of right ventricle and tricuspid apparatus. Calafiore AM, Foschi M, Kheirallah H, Alsaied MM, Alfonso JJ, Tancredi F, **Gaudino M**, Di Mauro M. J Card Surg. 2019 Jun;34(6):404-411. doi: 10.1111/jocs.14042. Epub 2019 Apr 8.

282. Sinus of Valsalva aneurysm repairs: Operative technique and lessons learned. Wingo M, de Angelis P, Worku BM, Leonard JR, Khan FM, Hameed I, Lau C, **Gaudino M**, Girardi LN. J Card Surg. 2019 Jun;34(6):400-403. doi: 10.1111/jocs.14041. Epub 2019 Apr 6.

283. Bilateral internal thoracic artery versus radial artery multi-arterial bypass grafting: a report from the STS database†. Schwann TA, Habib RH, Wallace A, Shahian D, **Gaudino M**, Kurlansky P, Engoren MC, Tranbaugh RF, Schwann AN, Jacobs JP. Eur J Cardiothorac Surg. 2019 Apr 1. pii: ezz106. doi: 10.1093/ejcts/ezz106.

284. Cerebral protection strategies in aortic arch surgery: A network meta-analysis. Hameed I, Rahouma M, Khan FM, Wingo M, Demetres M, Tam DY, Lau C, Iannacone EM, Di Franco A, Palaniappan A, Anderson H, Fremes SE, Girardi LN, **Gaudino M**. J Thorac Cardiovasc Surg. 2019 Feb 21. pii: S0022-5223(19)30483-0. doi: 10.1016/j.jtcvs.2019.02.045.

285. The search for the second best conduit: A 40-year-old debate. **Gaudino M**. J Thorac Cardiovasc Surg. 2019 Apr;157(4):e196. doi: 10.1016/j.jtcvs.2018.11.014.

286. Quality metrics in coronary artery bypass grafting. Khan FM, Hameed I, Milojevic M, Wingo M, Krieger K, Girardi LN, Prager RL, **Gaudino M**. Int J Surg. 2019 May;65:7-12. doi: 10.1016/j.ijsu.2019.03.007. Epub 2019 Mar 15

287. High-dose versus low-dose opioid anesthesia in adult cardiac surgery: A meta-analysis. Rong LQ, Kamel MK, Rahouma M, Naik A, Mehta K, Abouarab AA, Di Franco A, Demetres M, Mustapich TL, Fitzgerald MM, Pryor KO, **Gaudino M**. J Clin Anesth. 2019 Nov;57:57-62. doi: 10.1016/j.jclinane.2019.03.009.

288. Bilateral versus single internal thoracic artery for coronary artery bypass grafting with end-stage renal disease: A systematic review and meta-analysis. Tam DY, Rahouma M, An KR, **Gaudino M**FL, Karkhanis R, Fremes SE. J Card Surg. 2019 Apr;34(4):196-201. doi: 10.1111/jocs.14010. Epub 2019 Mar 9.

289. Tricuspid valve intervention at the time of mitral valve surgery: a meta-analysis. Tam DY, Tran A, Mazine A, Tang GHL, **Gaudino M**FL, Calafiore AM, Friedrich JO, Fremes SE. Interact Cardiovasc Thorac Surg. 2019 Mar 8. pii: ivz036. doi: 10.1093/icvts/ivz036.

290. Failure of annuloplasty alone to correct ischemic mitral regurgitation. What we learned from two randomized controlled trials. Calafiore AM, Totaro A, Sacra C, Foschi M, **Gaudino M**, Di Mauro M. J Card Surg. 2019 Apr;34(4):155-157. doi: 10.1111/jocs.14011. Epub 2019 Mar 8.

291. AngioVac for extraction of venous thromboses and endocardial vegetations: A meta-analysis. Hameed I, Lau C, Khan FM, Wingo M, Rahouma M, Leonard JR, Di Franco A, Worku BM, Salemi A, Girardi LN, **Gaudino M**. J Card Surg. 2019 Apr;34(4):170-180. doi: 10.1111/jocs.14009. Epub 2019 Mar 6.

292. State-of-the-Art Coronary Artery Bypass Grafting: Patient Selection, Graft Selection, and Optimizing Outcomes. **Gaudino M**FL, Spadaccio C, Taggart DP. Interv Cardiol Clin. 2019 Apr;8(2):173-198. doi: 10.1016/j.iccl.2018.11.007. Epub 2019 Jan 28.

293. A meta-analysis of the performance of small tissue versus mechanical aortic valve prostheses. Moscarelli M, Fattouch K, Speziale G, Nasso G, Santarpino G, **Gaudino M**, Athanasiou T. Eur J Cardiothorac Surg. 2019 Feb 27. pii: ezz056. doi: 10.1093/ejcts/ezz056.

294. Inflammation in coronary artery disease: Which biomarker and which treatment? **Gaudino M**, Crea F. Eur J Prev Cardiol. 2019 May;26(8):869-871. doi: 10.1177/2047487319829307. Epub 2019 Feb 27. No abstract available.

295. Authors' reply to Preoperative CT scan for Postoperative Stroke Prediction in Minimally Invasive Mitral Valve Surgery: Statistical Concern for Clinical Factors in Regression analyses. Leonard JR, Di Franco A, **Gaudino M**. Int J Cardiol. 2019 Apr 15;281:157. doi: 10.1016/j.ijcard.2019.01.086.

296. Preoperative atorvastatin reduces bleeding and blood transfusions in patients undergoing elective isolated aortic valve replacement. Nenna A, Spadaccio C, Lusini M, Nappi F, Mastroianni C, Giacinto O, Pugliese G, Casacalenda A, Barbato R, Barberi F, Greco SM, Satriano U, Forte F, Miano N, Colicchia C, Di Lorenzo D, **Gaudino M**, Chello M. Interact Cardiovasc Thorac Surg. 2019 Jul 1;29(1):51-58. doi: 10.1093/icvts/ivz012.

297. Fruit salad. **Gaudino M**. J Thorac Cardiovasc Surg. 2019 May;157(5):e254-e255. doi: 10.1016/j.jtcvs.2018.11.059. Epub 2019 Feb 6. No abstract available.

298. Are racial differences in hospital mortality after coronary artery bypass graft surgery real? A risk-adjusted meta-analysis. Benedetto U, Kamel MK, Khan FM, Angelini GD, Caputo M, Girardi LN, **Gaudino M**. J Thorac Cardiovasc Surg. 2019 Jun;157(6):2216-2225.e4. doi: 10.1016/j.jtcvs.2018.12.002. Epub 2018 Dec 1

299. The effect of surgical versus transcatheter aortic valve replacement on endothelial function. An observational study. Moscarelli M, Devito F, Fattouch K, Lancellotti P, Ciccone MM, Rizzo P, **Gaudino M**, Marchese A, Angelini G, Speziale G. Int J Surg. 2019 Mar;63:1-7. doi: 10.1016/j.ijsu.2019.01.014.

300. Bilateral versus Single Internal-Thoracic-Artery Grafts at 10 Years. Taggart DP, Benedetto U, Gerry S, Altman DG, Gray AM, Lees B, **Gaudino M**, Zamvar V, Bochenek A, Buxton B, Choong C, Clark S, Deja M, Desai J, Hasan R, Jasinski M, O'Keefe P, Moraes F, Pepper J, Seevanayagam S, Sudarshan C, Trivedi U, Wos S, Puskas J, Flather M; Arterial Revascularization Trial Investigators. N Engl J Med. 2019 Jan 31;380(5):437-446. doi: 10.1056/NEJMoa1808783.

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Books Chapters

1. Evoluzioni delle indicazioni a nuova rivascolarizzazione nel paziente gia' operato di by-pass aortocoronarico. Possati G, **Gaudino M**, Luciani N. In: *Cardiologia 1997, Scientific Press*
2. Cardiopatia ischemica. Possati G, **Gaudino M**, Alessandrini F. In: Santini M, Pede S, Cirrincione V, Mazzotta G, Merlini PA, Scherilli M, Tubaro M eds*, Trattato di cardiologia dell'ANMCO,* Excerpta Medica, San Donato Milanese, 2000 pgg. 3479-3512.
3. Revascularization of ischemic myocardium: Radial Artery Grafting. **Gaudino M**, Prati F, Possati G. *Multimedia Manual of CardioThoracic Surgery. 2006 Jan 1;2006(109):mmcts.2004.000752.doi:1510/mmcts.2004.000752.*
4. Mechanical support of the circulation. Saplacan V, **Gaudino M**, Massetti M. *Oxford Textbook of Cardiothoracic Anaesthesia, pp.139-148. DOI: 10.1093/med/9780199653478.003.0013*

5. Competitive blood flow and graft patency **Gaudino M**, Niccoli G, Scalone G, Mazza A, cammertoni F, Crea F, Massetti M. In: *Tintoiou IC. Coronary graft failure – state of the art.* Tintoiu, I.C., Underwood, M.J., Cook, S.P., Kitabata, H.,Abbas, A. (Eds) pgg. 277-284. Springer-Verlag London Ltd 2016 ISBN 978-3-319-26515-5.
6. Open repair of thoracic and thoracoabdominal aortic aneurysms. Lau C**, Gaudino M**, Girardi LN. In: *Tintoiou IC. New Approaches to the Aortic Disease from Valve to Abdominal Bifurcation. Elsevier 2017 in press.*
7. The radial artery. Tranbaugh R, **Gaudino M**, Buxton B,Tatoulis J. *In: Taggart D, Puskas J. Coronary Artery Bypass Grafting, Oxford University Press in press*
8. Quality Metrics in Coronary Artery Bypass Grafting. **Gaudino M**, Zamvar V, Prager RL. *In: Taggart D, Puskas J. Coronary Artery Bypass Grafting, Oxford University Press in press*
9. The history of the surgical treatment of coronary artery disaese. *Gaudino M, Head S, taggart D. In: Taggart D, Puskas J. Coronary Artery Bypass Grafting, Oxford University Press in press*
10. Conduits for Coronary Artery Bypass Surgery. Spadaccio C, **Gaudino M**. *In: Raja SG. Concise Cardiac Surgery Complete Guide, Springer International Publishing AG in press*