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CRITICAL APPRAISAL OF TRIALS

Second best conduit—is it the tag or patency that counts?

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Abstract
The Radial Artery Patency and Clinical Outcomes (RAPCO) trial compared radial artery (RA) with free right internal thoracic artery (RITA) and saphenous vein grafts (SVG). This was a prospective, randomized, single-center trial with two separate arms (RA-RITA and RA-SVG). The study showed that RA was superior to free RITA in terms of 10-year angiographic patency and provided a survival advantage as well. In contrast, RA-SVG comparison suggested a trend towards better outcomes with RA but no statistically significant difference in patency or survival. In this appraisal of the RAPCO trial, both the conduct and the findings have been critically evaluated. The concerns over using free RITA as aorto-coronary grafts as opposed to composite grafts and the insufficient sample size for the RA-SVG comparison have been highlighted. In the RAPCO trial that spanned almost quarter of a century, patency of all three conduits studied in the trial appears satisfactory.

Keywords RAPCO · Radial artery · Free RITA · Saphenous vein graft · Patency

Introduction

Left internal thoracic artery (LITA) grafting to left anterior descending (LAD) artery in coronary artery bypass grafting (CABG) is the established gold standard. However, controversy exists regarding the second best graft. The recently published long-term outcomes of the Radial Artery Patency and Clinical Outcomes (RAPCO) trial takes this discussion forward [1]. Considering that the Arterial Revascularisation Trial (ART) failed to demonstrate a clear superiority of bilateral internal thoracic artery, the findings of the RAPCO trial become even more pertinent and worth evaluating [2].

The RAPCO was a prospective, randomized, single-center trial that was designed to test if radial artery (RA) was superior to free right internal thoracic artery (RITA) or saphenous vein grafts (SVG). There were two separate randomization arms—RA-RITA and RA-SVG. Patients younger than 70 years of age and diabetics under 60 were randomized to either RA or free RITA. Patients ≥ 70 years or diabetics ≥ 60 years were randomized to either RA or SVG. The RA-RITA cohort was larger with 394 (RA—198, RITA—196) patients while the RA-SVG comparison included 225 patients (RA—113, RITA—112). Primary outcome was angiographic patency and all-cause mortality. Secondary outcome was major adverse cardiac events. Patency of conduits was assessed by conventional angiography. Ten percent of the patients had angiography at 1 year, 10% at 2 years, 20% at 5 years, 30% at 7.5 years, and 30% at 10 years.

Findings of the study

1. Patency: 10-year patency rate of the RA was significantly better than that of free RITA. Patency of RA was also better than that of SVG but not statistically significant.

RA-RITA—Protocol directed angiography was done in 317 of 394 patients (80.5%). Median angiographic follow-up was 7.1 years (5.0–9.4). Graft failure was seen in 15 (RA) and 27 (RITA) patients. Ten-year estimated patency was 89% (RA) and 80% (RITA) and the hazard ratio (HR) for graft failure was 0.45 (95% CI, 0.23–0.88; $p - 0.01$).

RA-SVG—Protocol directed angiography was done in 146 of 225 patients (64.9%). Median angiographic follow-up was 6.1 years (4.6–8.8). Graft failure was seen in 6 (RA) and 12 (SVG) patients. Ten-year estimated patency was 85% (RA) and 71% (SVG) and the HR for graft failure was 0.40 (95% CI, 0.15–1.00; $p - 0.05$).

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2. Survival—There was a survival benefit with RA in the RA-RITA arm but not in the RA-SVG arm. At 10 years, survival estimate was 90.9% (RA) and 83.7% (RITA) (p-0.03) in the RA-RITA arm and 72.6% (RA) versus 65.2% (SVG) (p − 0.18) in the RA-SVG group.
3. Secondary outcomes: Major adverse events (death, myocardial infarction, and re-intervention) were lower for RA in the RA-RITA group ($p = 0.03$). In the RA-SVG group, no difference was seen ($p = 0.19$).

Appraisal of the conduct of the trial

The recruitment rate of 33% (619/1882) is higher than most reported trials and suggests that the trial was representative of real-life practices. Timing of angiography was protocol driven and not directed by symptoms. In symptom-directed angiography graft failures are overestimated and in protocol-driven angiography as in the RAPCO trial the exact time at which the graft may have failed cannot be ascertained accurately.

With only 2 patients lost in the study, follow-up was excellent. Thirty-five (5.6%) patients did not get the assigned conduit (27 in RA-RITA and 8 in RA-SVG groups). The major limitation of the study was that only 80% of patients in RA-RITA and 65% in RA-SVG underwent angiography. Moreover, the study was a single-center study which was carried out at a center of excellence for arterial grafting and there may be concerns over the results not being reproducible.

Appraisal of the trial findings

While the early and mid-term results of the RAPCO trial did not show any difference between the conduits studied, the long-term results have shown that the RA is a superior conduit to the "free RITA" in terms of patency as well as survival [1–4]. With respect to the SVG, RA also had a higher though statistically non-significant patency than the SVG with no difference in survival. It is important to critically examine these conclusions drawn by the RAPCO trial.

RA-RITA

Firstly, it has to be stressed that RA was compared only to "free RITA" anastomosed directly to the aorta. The trial did not include either in situ RITA or a composite LITA-RITA grafting strategy. This is in contrast to the ART trial which used RITA predominantly as an "in situ" graft or a composite LITA-RITA graft. These contrasting strategies are a reflection of changing practices in arterial revascularisation. Despite some evidence of similar angiographic patency of "free" and "in situ RITA", it remains debateable if the superiority of RA over "free aorto-coronary RITA" can be extrapolated to the in situ and composite LITA-RITA grafts [5]. Another important observation is grafting RITA to the right coronary system. The ART trial did not allow an ITA to be grafted to the right coronary artery (RCA) due to concern over long-term patency [2]. The RAPCO trial made no such distinction and 26% of the RITA were grafted to the RCA. Finally, the RAPCO trial mandated a minimum native artery stenosis of 70%, irrespective of the coronary territory. However, current recommendations state that an arterial graft should not be used to bypass the RCA with stenosis < 90% [6].

This final point on native artery stenosis needs to be stressed further. Even though the minimum stenosis was set at 70%; earlier analysis of the RAPCO data showed significantly higher RA patency (93.3%) with native artery stenosis > 80% as opposed to only 64.7% when the stenosis was < 80% [7]. Another study reported 100% angiographic patency for RA at 3 years in presence of > 90% stenosis [8]. Thus, using the RA in territories with more severe stenosis can contribute towards further improvement of patency.

RA-SVG

The RA had a higher but non-significant patency compared to SVG and unlike the RA-RITA comparison showed no survival benefit over SVG. This superiority of RA over free RITA but statistical equivalence with the SVG appears a little odd.

The explanation for this oddity lies in the sample size which was calculated for patency but not for mortality. Besides, sample size for RA-SVG patency comparison was 211 but angiography was carried out in only 146 patients. Thus, the study was grossly underpowered to identify patency difference between RA-SVG. Despite this, there was a definite trend towards RA being superior to SVG in terms of patency ($p = 0.05$) and the lack of statistical difference is likely to be a type II error. The superiority of the RA over SVG has also been confirmed in a previous meta-analysis which reported significantly better patency rate and clinical outcomes for RA at 5 years [9].

In the multiple comparisons between different conduits, it is easy to forget data presented regarding the long-term patency of SVG. In the 146 patients who underwent angiography, only 12 venous grafts were found to have failed. The 10-year estimated angiographic patency of SVG has been reported as 71%. One has to also bear in mind that while randomization was only done for the second best target, majority of the third and fourth choice targets were grafted using SVG. It could be therefore argued that if just like the RA and the RITA, only SVGs used on second best targets were considered in the comparison this patency rate could be even higher. Moreover, the participants received low-dose aspirin (100 mg) as antiplatelet therapy. Use of higher dose aspirin or dual-antiplatelet therapy could have perhaps further improved the patency rates.

The most remarkable point about the RAPCO trial is that the first patient was recruited nearly quarter of a century ago.

However, the discussion remains relevant even today. With the ART and the ongoing Randomization of Single vs. Multiple Arterial Grafts (ROMA) trial setting the tone, the narrative in the current era in CABG seems to be about arterial grafting. And to that effect, the comparison between RA and SVG may appear to be reflection of an earlier era to some. However, it has to be borne in mind that with only 10% of patients receiving more than 1 arterial grafts, vein grafts are still the most commonly used conduit in CABG [10]. In this respect, the RAPCO trial has provided valuable, even reassuring, data on long-term patency of vein grafts With regard to the RA-RITA comparison, the argument that a different RITA configuration may have shown a different result is certainly valid but is largely academic. The real take-home message from the RAPCO trial should be the excellent long-term patency of the RA. We should perhaps just look at the RA patency in isolation and the fact that aorto-coronary RA grafting does not require special expertise and is associated with minimum morbidity. Thus, irrespective of whether the RA deserves the tag of the "second best" conduit or not, there appears absolutely no reason why the RA should not be used as a second arterial conduit wherever possible. Cardiac surgeons world over should congratulate the endeavors of Dr. Brian Buxton and his team for this insight that has taken 25 years of hard work.

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Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest.

Informed consent and ethical approval Not applicable as review article.

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