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One-year results of total arterial revascularization vs. conventional coronary surgery: CARRPO trial

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Aims To investigate clinical and angiographic outcomes after coronary surgery using total arterial revascularization (TAR).

Methods and results We randomized 331 patients with multivessel or isolated left main disease to TAR [internal thoracic (ITA) and radial arteries] vs. conventional revascularization (CR) using left ITA and vein grafts. The primary angiographic outcome was the patency index: number of patent grafts (<50% stenosed) divided by number of constructed grafts. One-year angiography was complete for 83% of patients. Mean patency index (±SD) was 87 ± 22% in the TAR group and 88 ± 18% in the conventional group ($P = 0.52$). In 72% of TAR patients and 67% of the conventional group, all grafts were patent ($P = 0.45$). Multiple imputation of missing angiographic data did not influence on results. Within 1 year, 37 (23%) TAR patients and 43 (25%) conventional group patients suffered cardiac events (HR 1.09, 95% CI 0.70–1.69, $P = 0.70$). One patient (0.6%) in the TAR group and two (1.2%) in the conventional group died ($P = 1.00$).

Conclusion Within 1 year post-operatively, TAR seems at least as safe and effective as CR. Prolonged follow-up will reveal whether this is sustained or superior results of TAR can justify a more general use.

Keywords Coronary surgery • Total arterial revascularization • Angiography • Clinical outcomes

Introduction

Coronary artery bypass grafting (CABG) has for more than 20 years been an evidence-based treatment for multivessel and left main (LM) coronary disease.[1] Patient outcome is closely related to bypass durability,[2] and it is evident that the internal thoracic artery (ITA) graft to the left anterior descending coronary artery has superior patency compared with the saphenous vein graft (SVG).[3] More importantly, it improves survival considerably for more than 10 years,[3] and bilateral ITA grafts appear to add further survival benefit.[4] However, the need for additional grafts and concern of sternal complications[5] have moved focus to the radial artery (RA).[6] In retrospective cohort studies, a combination of ITA and RA grafts for total arterial revascularization (TAR) improves survival and reduces cardiac events compared with conventional revascularization (CR) using left ITA (LITA) and SVGs.[7,8]

Despite the potential benefits of TAR, only 12% of patients in Europe and North America had arterial grafts only in the run-in phase of the SYNTAX study (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) (CABG vs. Taxus stents for three-vessel or LM disease).[9] When it comes to randomized data, there are not many trials to justify abandoning CR. Three centres have published conflicting results after TAR vs. CR regarding clinical outcome and graft patency.[10–15] We report 1-year results of the Copenhagen Arterial Revascularization Randomized Patency and Outcome (CARRPO) trial, which compares CABG with the use of TAR vs. CR in patients with multivessel or isolated LM coronary disease.

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Methods

Patient population and interventions

Patients with isolated LM or two- or three-vessel disease (≥50% stenosis) referred for elective or urgent CABG (more than one graft planned) were eligible provided they were <70 years of age with a left ventricular ejection fraction >35%. Patients should have a normal Allen's test on one of the hands and be able to give informed consent. In case of concurrent malignant disease with expected survival <5 years, unsuitable SVGs evaluated pre-operatively, emergency, redo, or other concomitant heart surgery, the patient was excluded. The trial complied with the Declaration of Helsinki and was approved by The Regional Research Ethics Committee for Copenhagen (01-137/01). Written informed consent was obtained from all patients.

Patients received a trial number and were randomly allocated to TAR (LITA, right ITA/RA, or both) vs. CR (LITA and SVGs) the day before surgery. Because randomization was stratified by sex and diabetes state (insulin-treated), there were four groups of opaque envelopes. These were coded with patient trial numbers and contained notes allocating the patient to TAR or CR. Randomization envelopes were kept in a locked room and administered by a nurse unrelated to the project. Post-operative medications for all patients in both groups were aspirin, a statin, and amlodipine for 3 months if tolerated.

Outcome measures and definitions

The primary outcome measures are distal anastomotic graft patency reported as mean patency index, and cardiac event-free survival, 1 and 5 years post-operatively. Secondary outcome measures are angina class and need for anti-anginal medication.

Patency was defined as angiographic filling of the graft and the target vessel without graft failure (any stenosis of ≥50%). Sequential grafts with two distal anastomoses were counted as two grafts. For sequential grafts with failure of the proximal attachment, all distal anastomoses were counted as graft failures. The patency index expressed as a percentage is defined as the number of patent grafts divided by the total number of grafts actually made in the patient.

Cardiac event-free survival was defined as survival without re-admission to hospital due to: myocardial infarction [MI, verified by electrocardiogram (ECG) and/or serum markers of myocardial necrosis], observation for suspected MI (hospitalized >6 h with repeated non-elevated markers), unstable angina (sustained chest pain, without marker release, causing changed anti-anginal medication or angiography), arrhythmias (symptomatic, ECG-verified, and requiring treatment), heart failure (dyspnoea leading to changed medication), need for coronary angiography, percutaneous coronary intervention, and redo CABG.

Operative procedures

Median sternotomy and normothermic extracorporeal circulation using cold blood cardioplegia were standard. The RA and SVGs were harvested by the open technique and stored in the same type of solution. The LITA or both ITAs were prepared as pedicles. Seven certified cardiac surgeons performed both types of revascularization at their discretion, including choice and configuration of grafts for TAR; they contributed equally to both groups. Details have been reported recently.[16] Infusion of nitroglycerin was started before releasing the aortic cross-clamp and continued to the next morning.

One-year follow-up and angiography

All patients were invited for follow-up approximately 1 year post-operatively. Those not showing up were contacted by telephone. All admissions were double-checked in the national Danish patient admission database (Green System, CSC Scandihealth, Aarhus, Denmark).

Angiography was carried out on an outpatient basis through the femoral artery. Grafts were examined in two orthogonal projections by an invasive cardiologist using intracardial injection of nitroglycerin and verapamil. Two experienced, blinded, and trial-independent cardiac surgeons visually interpreted the angiograms and graded all grafts as having no stenosis (<50%), between 50–90%, >90%, or being occluded. The conclusive interpretation of the angiograms was reached through consensus.

Statistical analysis

The sample size was calculated according to the primary outcome measure, 5-year graft patency. A 15% absolute improvement in overall patency (i.e. mean patency index) 5 years after TAR (85%) vs. CR (70%) was regarded as clinically relevant. Based on a 90% power and a 5% significance level, 330 patients were to be included. The statistician, blinded to the methods of intervention, analysed data by the intention to treat principle using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Normally distributed continuous data are presented as mean and standard deviation and analysed using unpaired *t*-test. Median and quartiles and the Mann–Whitney test are used for not normally distributed continuous data. The patency index was analysed with the Mann–Whitney test, but presented as mean and standard deviation. Categorical data are presented as number and percentages and analysed using χ^2 test or Fisher's exact test. All tests were two-tailed and $P < 0.05$ was considered significant. For missing angiographic data, we performed sensitivity analysis (best-case and worst-case scenarios with respect to TAR: missing angiograms in the TAR group recoded as all grafts patent and in the conventional group as all grafts failed and vice versa) and multiple imputation in the program NORM (Joe Schafer, Department of Statistics, Penn State University, USA). Multiple imputation was performed for the covariates: graft patency (0–49% stenosis) and total cholesterol level on a dataset comprising the following covariates: age, sex, type of revascularization, number of grafts, hypercholesterolaemia, total cholesterol level, cardiac event, insulin-treated diabetes, and number of patent grafts. On every of 10 datasets constructed by imputation, a Mann–Whitney test was performed for the median patency index. Also a Student's *t*-test for the mean patency index was performed (testing the difference between the two groups from zero) and the results were aggregated.[17–19] Time to first cardiac event, time to first graft failure, and possible predictors of graft failure were analysed using the Cox proportional hazards regression analysis, and results are presented as hazard ratios (HR) and 95% confidence intervals (CI). We performed univariate analysis in association with time to detecting at least one cardiac event and multivariable analysis by forcing the stratification variables such as sex, age, and insulin-treated diabetes and the design variable[20] such as total number of grafts into the model. The assumption of proportional hazards was checked plotting cumulative hazard functions for type of revascularization, males and females, and diabetes status. The cumulative hazard functions as well as the log minus log plots were very close to parallel and did not suggest violation of the assumption of proportional hazards.

Results

Patient population

Of 1969 primary isolated CABG procedures (21 February 2002–22 February 2005), 1136 patients were available for screening (*Figure 1*).

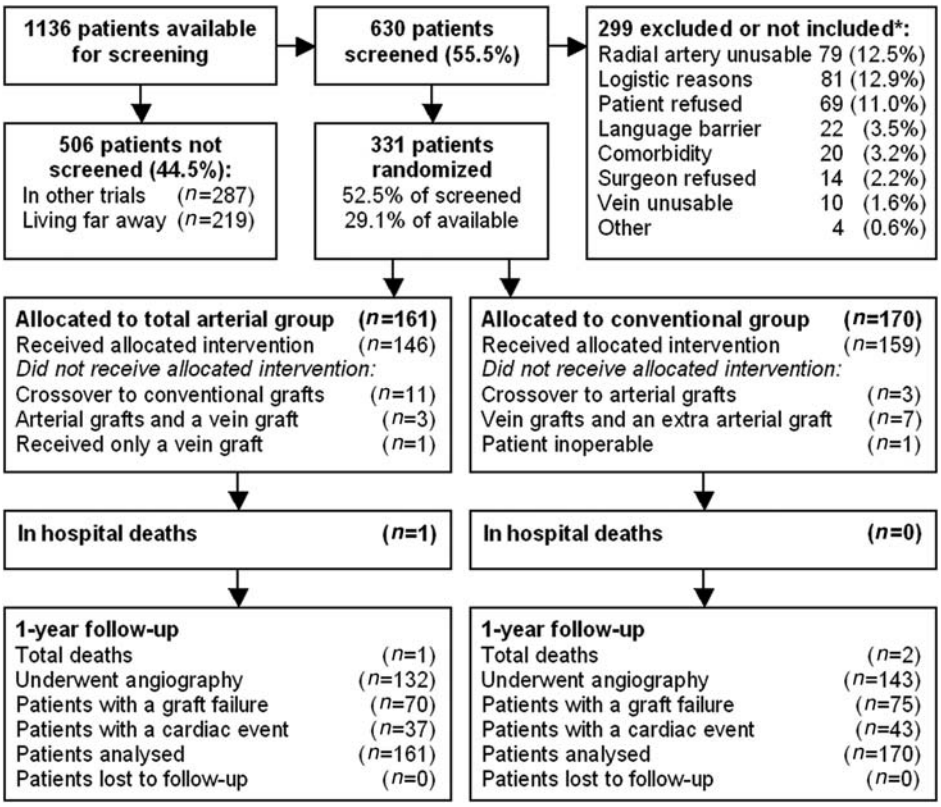

Figure 1 Flowchart. *Percentages of screened patients.

We randomly assigned 161 patients to TAR and 170 to CR. Baseline characteristics were comparably distributed between groups (*Table 1*). For details of grafts and distal anastomoses, see *Tables 2* and *3*. Overall, patients received a mean of three distal anastomoses; however, in the TAR group, the mean number was 2.9 ± 0.9 vs. 3.2 ± 0.9 in the CR group ($P = 0.004$). In the TAR group, 128 patients (79.5%) and in the CR group 141 patients (82.9%) were completely revascularized ($P = 0.509$). There were no differences in clinical outcome up to 3 months post-operatively.[16]

Graft patency

In the TAR group 82% of patients and in the CR group 84% of patients underwent angiography and were available for the analysis of the overall mean patency index. Of these, five TAR group patients and two CR group patients had one or more not definitive graft failures, as these were not visualized. Thirty patients refused angiography, 12 were not examined for logistic reasons, in 11 there was a medical contraindication, and 3 had died.

There was no statistically significant difference in the overall mean patency index between the two groups (*Table 4*). The average patient had a stenosis >50% in 12–13% of grafts 1 year post-operatively. RA grafts in the TAR group and SVGs in the CR group had comparable patency indices. Type of revascularization did not statistically significantly affect whether patients had graft failure in univariate (HR 0.99, 95% CI 0.65–1.52, $P = 0.97$) or multivariable analysis (HR 2.53, 95% CI 0.37–17.6, $P = 0.35$), but in both analyses, the number of grafts did seem to have an influence ($P = 0.003$), and in the multivariable analysis, this was the only covariate remaining (HR 1.41, 95% CI 1.12–1.77, $P = 0.003$). However, for the effect of type of revascularization adjusted for age, sex, insulin-treated diabetes, and total number of grafts, the HR for graft failure is 0.91 (95% CI 0.59–1.40, $P = 0.66$). When adjusted only for sex and insulin-treated diabetes, the HR for graft failure is 0.99 (95% CI 0.65–1.52, $P = 0.98$).

Analyses of missing angiographic data

The sensitivity analysis revealed a highly significant benefit on graft patency of TAR (best case) and of CR (worst case), i.e. the treatment effect seemed dependent on the distribution of missing data. However, after multiple imputation, all the Mann–Whitney tests for the median patency index were statistically insignificant ($P > 0.4$). The aggregated results of Student's *t*-tests also showed an insignificant effect of TAR vs. CR, with a difference in the mean patency index of −0.8% (95% CI −6.2 to 4.6, $P = 0.78$). The proportion of patients having all grafts patent was 66% in the TAR group vs. 63% in the CR group, with an aggregated intervention effect of 3% (95% CI −20 to 27, $P = 0.79$).

Cardiac event-free survival

There were no statistically significant differences in the occurrence of cardiac events in the two groups (*Table 5* and *Figure 2*). In the univariate analysis, type of revascularization was not statistically

Table 1 Pre-operative characteristics

	Type of revascularization		
	Total arterial ($n = 161$)	Conventional ($n = 170$)	*P*-value
Female sex	19 (11.8)	20 (11.8)	0.99
Age, years	59 ± 8	59 ± 8	0.96
Body mass index, kg/m^2	27 ± 4	28 ± 4	0.29
CCS class ≥3	51 (31.7)	43 (25.3)	0.20
NYHA class ≥3	35 (21.7)	27 (15.9)	0.17
EuroSCORE[a]	2 (1–3)	3 (1–4)	0.36
Diabetes—insulin	6 (3.7)	9 (5.3)	0.49
Diabetes—diet/tablets	33 (20.5)	34 (20.0)	0.91
Hypercholesterolaemia	140 (87.0)	147 (86.5)	0.90
Hypertension	82 (50.9)	81 (47.6)	0.55
Ejection fraction 35–49%	48 (29.8)	42 (24.7)	0.30
Ejection fraction ≥50%	113 (70.2)	128 (75.3)	—
LM stenosis only	13 (8.1)	14 (8.2)	0.20
One-vessel disease	4 (2.5)	0	—
Two-vessel disease	44 (27.3)	53 (31.2)	—
Three-vessel disease	100 (62.1)	103 (60.6)	—

Number (%), mean ± SD. CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LM, left main.
[a]Median and quartiles.

significant (HR 1.09, 95% CI 0.70–1.69) ($P = 0.70$), but in the multivariable analysis, it came close to statistical significance ($P = 0.14$). However, for the effect of type of revascularization adjusted for age, sex, insulin-treated diabetes, and total number of grafts, the HR for a cardiac event is 1.16 (95% CI 0.74–1.80, $P = 0.51$). When adjusted only for sex and insulin-treated diabetes, the HR for a cardiac event is 1.09 (95% CI 0.71–1.70, $P = 0.69$).

Secondary outcomes and adverse events

In the TAR group, 137 patients (85.1%) were in Canadian Cardiovascular Society (CCS) class 1, and 12 patients (7.5%) were in CCS class 2. In the CR group, 148 patients (87.1%) were in CCS class 1, 10 patients (5.9%) were in CCS class 2, and 1 was in class 3 (0.6%) ($P = 0.61$). The status was unknown for 12 (7.5%) and 11 patients (6.5%), respectively. The use of calcium channel blockers, beta-blockers, and nitrates was comparable between groups.

Within the 1-year follow-up period, stroke was verified in four patients (2.5%) in the TAR group and in three patients (1.8%) in the CR group ($P = 0.72$). In the TAR group, five patients (3.1%) needed sternal rewiring, whereas this was the case for two patients (1.2%) in the conventional group ($P = 0.27$). During control angiography, three patients in the CR group and one in the TAR group were direct-current cardioverted due to ventricular arrhythmia. In one patient in each group, transient cerebral ischaemia was suspected during catherization. All patients were discharged without sequels.

Per protocol analysis

Of TAR patients 9.3% and of CR patients 6.5% did not receive the intended intervention (*Figure 1*). Per protocol analysis did not have any noticeable influence on the results.

Table 2 Graft status

	Type of revascularization		
	Total arterial ($n = 161$)	Conventional ($n = 170$)	*P*-value
LITA (%)	156 (96.9)	166 (97.6)	0.75
Sequence	19 (11.8)	7 (4.1)	0.009
RITA	77 (47.8)	3 (1.8)	<0.0001
Free	12 (7.5)	0	<0.0001
Extended with RA	15 (9.3)	1 (0.6)	<0.0001
RA	128 (79.5)	2 (1.2)	<0.0001
Sequence	54 (33.5)	2 (1.2)	<0.0001
From aorta	96 (59.6)	1 (0.6)	<0.0001
From ITA	39 (24.2)	1 (0.6)	<0.0001
SVG	16 (9.9)	164 (96.5)	<0.0001
Sequence	6 (3.7)	86 (50.6)	<0.0001
Only BITA	15 (9.3)	2 (1.2)	0.001
BITA and RA	61 (37.9)	1 (0.6)	<0.0001
LITA and RA	63 (39.1)	1 (0.6)	<0.0001
LITA and SVGs	12 (7.5)	160 (94.1)	<0.0001
Only LITA	5 (3.1)	2 (1.2)	0.27
Only RA	3 (1.9)	0	0.11
Only SVGs	1 (0.6)	3 (1.8)	0.33
RITA and RA	1 (0.6)	0	0.49

Number of patients (%). LITA, RITA, and BITA, left, right, and bilateral internal thoracic artery; RA, radial artery; SVG, saphenous vein graft.

Table 3 Distal anastomoses

TV stenosis	Type of revascularization					
	Total arterial (n = 161)				Conventional (n = 170)	
	LITA	RITA	RA	SVG	LITA	SVG
LAD 50–90%	90 (51.4)	2 (3.2)	1 (0.5)		99 (57.2)	1 (0.3)
LAD 91–100%	49 (28.0)	3 (4.8)			58 (33.5)	
Diag. 50–90%	15 (8.6)	0	10 (5.0)		8 (4.6)	31 (8.5)
Diag. 91–100%	9 (5.1)	1 (1.6)	7 (3.5)	2 (7.4)	7 (4.0)	19 (5.2)
OM 50–90%	3 (1.7)	12 (19.0)	58 (28.9)	5 (18.5)	0	100 (27.5)
OM 91–100%	9 (5.1)	10 (15.9)	46 (22.9)	10 (37.0)	1 (0.6)	84 (23.1)
RCA 50–90%		9 (14.3)	8 (4.0)	1 (3.7)		9 (2.5)
RCA 91–100%		19 (30.2)	8 (4.0)	4 (14.8)		18 (5.0)
PDA 50–90%		3 (4.8)	20 (10.0)	2 (7.4)		32 (8.8)
PDA 91–100%		4 (6.3)	43 (21.4)	3 (11.1)		69 (19.0)

Number (%). TV, target vessel; LITA and RITA, left and right internal thoracic artery; RA, radial artery; SVG, saphenous vein graft; LAD, left anterior descending; Diag., diagonals; OM, obtuse marginals; RCA, right coronary artery; PDA, posterior descending artery.

Table 4 Angiography

	Type of revascularization		
	Total arterial (n = 132)	Conventional (n = 143)	P-value
Months to angiography	10.8 ± 2.1	11.1 ± 2.1	0.30
Grafts <50% stenosed			
Overall mean patency index (%)	87 ± 22	88 ± 18	0.52
Treatment difference (95% CI)	−0.9 (−5.8 to 3.9)		0.71
LITA mean PI (%)	94 ± 24	95 ± 22	0.73
RA vs. SVG mean PI (%)	85 ± 36	86 ± 35	0.83
RITA mean PI (%)	91 ± 29		
Patients with all grafts patent (%)	91 (71.7)	95 (67.4)	0.45
Grafts ≤90% stenosed			
Overall mean patency index (%)	90 ± 21	90 ± 17	0.52
Treatment difference (95% CI)	−0.1 (−4.6 to 4.4)		0.96
LITA mean PI (%)	96 ± 20	98 ± 14	0.35
RA vs. SVG mean PI (%)	89 ± 31	87 ± 34	0.63
RITA mean PI (%)	91 ± 29		
Patients with all grafts patent (%)	98 (77.2)	101 (71.6)	0.30

Mean ± SD, 95% confidence interval (CI). Patency index (PI), percentage of patent grafts of total number of grafts per patient; LITA and RITA, left and right internal thoracic artery; RA, radial artery; SVG, saphenous vein graft.

Discussion

Based on the angiographic and clinical primary outcome measures expressed as the mean patency index, the proportion of patients with all grafts patent, and a composite clinical outcome of cardiac events, we could not demonstrate a statistically significant difference in TAR vs. CR 1 year post-operatively in the CARRPO trial. The power analysis prior to initiation of the study thus enables us to exclude a 1-year difference in the patency index of ≥15%.

There was a comparable amount of completely revascularized patients in the two groups even though CR patients received slightly more grafts. Because no differences in clinical outcome or angina class were noted, more stenoses of minor importance seem to have become grafted in the CR group. We completely revascularized 81% of patients, which is comparable with a previous randomized trial in which grafting of target vessels <1.5 mm was not required.[21] The robust cardiac events were few: death, MI, and revascularization did not occur more often than in contemporary randomized trials.[21,22]

We have used the patency index as a measure of overall function of grafts in the individual patient, but it is readily comparable with the usual expression of graft patency: proportion of patent

Table 5 Clinical outcome

Type of revascularization	Total arterial (n = 161)	Conventional (n = 170)	P-value
Months to follow-up, mean ± SD	11.0 ± 2.0	11.2 ± 2.0	0.36
Patients with a cardiac event (%)	37 (23.0)	43 (25.0)	0.70
Cardiac events, admissions			
Observation for MI	16 (9.9)	20 (11.8)	0.59
Arrhythmia	10 (6.2)	12 (7.1)	0.76
Unstable angina	4 (2.5)	5 (2.9)	0.99
Verified non-fatal MI	2 (1.2)	4 (2.4)	0.69
Heart failure	2 (1.2)	4 (2.4)	0.69
Symptom-driven angiography	9 (5.6)	10 (5.9)	0.91
PCI	4 (2.5)	3 (1.8)	0.72
Cardiac death	1 (0.6)	0	0.49
Non-cardiac death	0	2 (1.2)	0.50

MI, myocardial infarction; PCI, percutaneous coronary intervention.

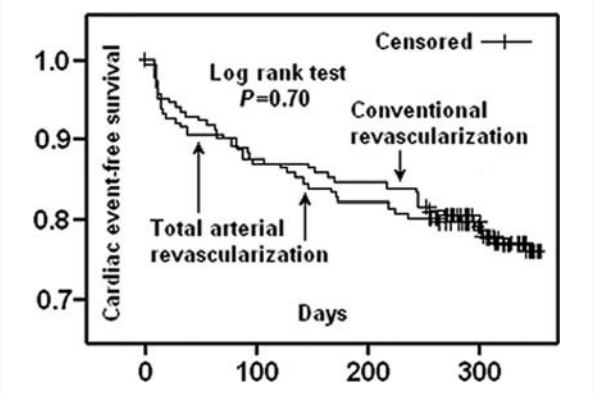

Figure 2 Kaplan–Meier plot showing cardiac event-free survival for patients randomized to total arterial vs. conventional revascularization.

grafts of the total number of constructed grafts in a population. In our trial, the 1-year mean patency index of the LITA is acceptable, whereas a lower right ITA patency index of 91% could be a consequence of the 12% of grafts anastomosed to moderately stenosed right coronary arteries.[23] The RA mean patency index in our study appears lower than that reported in a randomized multicentre RA patency study.[22] In that, 8.2% of RAs were occluded after 1 year, but additionally 7% showed diffuse narrowing <1 mm (string sign), which in our trial was regarded as a graft failure.

Our results are in contrast with randomized studies of Muneretto *et al.*[11–14] showing superiority of TAR; however, these patients were older, more diabetic, and had a higher operative risk. In a randomized trial with low-risk patients, Myers *et al.*[15] compared TAR (only ITAs) with CR and found no differences in survival or cardiac events 5 years post-operatively, but angiography was not performed. Buxton *et al.*[10] did a 5-year interim analysis of graft patency and clinical outcomes in their randomized study and found no significant differences. The RA was a primary focus, but nonetheless TAR was compared with CR; however, only around 30% of patients underwent angiography.

Our data represent a reliable baseline for future follow-up, but future analyses could preferably be adjusted for the number of constructed grafts. Also, an even higher frequency of missing angiographic data has to be expected in the future due to an ageing population with comorbidities. The influence on the presented results was limited, but multiple imputation of missing angiographic data seems to become mandatory in future analyses. However, new non-invasive examinations like computed tomography angiography may turn out to be equally or even more effective tools to monitor graft patency in the future.

Study limitations

It was a single centre trial, and the individual surgeon decided the choice and configuration of grafts. Our primary focus was TAR as a treatment modality, and this led to a heterogeneous population regarding the different graft types. It may be considered suboptimal TAR that only 47% of patients in the TAR group received bilateral ITAs, although there are no data available from randomized trials to show the superiority of bilateral ITAs vs. a single ITA. Additionally, the RA was placed as a graft also to coronary arteries with moderate degrees of stenoses. This use of arterial grafts may have given less favourable results in the TAR group and may explain the absence of benefit of TAR vs. CR.

The trial eligibility criteria were made to ensure that a majority of patients are alive for angiography 5 years post-operatively. However, this has also led to a relatively young and low-risk study population compared with the present CABG population.

Conclusion

One year after TAR vs. CR for multivessel and LM coronary disease, there were no statistically detectable differences in outcomes regarding graft patency and cardiac event-free survival. TAR seems at least as safe and effective as CR. Thus, patients without usable vein graft material are treated well with only arterial grafts. Prolonged follow-up will reveal whether our results are sustained or if TAR confers advantages that justify a more general use.

Acknowledgements

The CARRPO trial is registered with clinicaltrials.gov, number NCT00159991.

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