International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Impact of total arterial revascularization on long term survival: A systematic review and meta-analysis of 130,305 patients

Bobby Yanagawa [a,*], Subodh Verma [a], Amine Mazine [a], Derrick Y Tam [a], Peter Jüni [b], John D Puskas [c], Shamini Murugavel [a], Jan O Friedrich [d]

[a] Division of Cardiac Surgery, Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada
[b] Applied Health Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Toronto, ON, Canada
[c] Department of Cardiovascular Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[d] Critical Care and Medicine Departments, Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada

ARTICLE INFO

Article history:
Received 31 August 2016
Received in revised form 26 December 2016
Accepted 1 February 2017
Available online xxxx

Keywords:
Total arterial revascularization
Coronary artery bypass graft
Graft patency

ABSTRACT

Objectives: This meta-analysis compares total arterial revascularization (TAR) versus conventional coronary artery bypass and additionally to two arterial grafts.
Methods: We searched MEDLINE and EMBASE Databases from 1996-to-2016 for studies comparing TAR versus non-TAR for multi-vessel surgical revascularization. Data were extracted by 2 independent investigators. Meta-analysis used random effects, which incorporates heterogeneity.
Results: There were 4 smaller shorter follow-up randomized controlled trials (RCTs), plus 15 matched/adjusted and 6 unmatched/unadjusted larger longer follow-up observational studies that met inclusion criteria (N = 130.305 patients; mean follow-up range: 1–15 years). There were no differences in perioperative stroke, myocardial infarction or mortality. However, TAR was associated with lower long term all-cause mortality in observational studies matched/adjusted for confounders (incident rate ratio 0.85, 95% CI: 0.81–0.89, $p < 0.0001$; I^2 = 0%) and unmatched/unadjusted (incident rate ratio 0.67, 95% CI: 0.59–0.76, $p < 0.0001$; I^2 = 67%) for TAR. Decreases in major cardiovascular outcomes and revascularization did not achieve statistical significance. There were greater sternal complications with TAR in the matched/adjusted studies (pooled risk ratio 1.21, 95% CI: 1.03–1.42, $p = 0.02$; $I^2 = 0\%$). When compared to patients with two arterial grafts, TAR was still associated with reduced long-term all-cause mortality (incident rate ratio 0.85, 95% CI: 0.73–0.99, $p = 0.04$) with minimal heterogeneity ($I^2 = 5\%$).
Conclusions: Data from primarily observational studies suggest that TAR may improve long-term survival compared with conventional coronary bypass by 15–20% even when compared with two arterial grafts. Prospective randomized trials of TAR with long term follow-up are needed.

1. Introduction

Coronary artery bypass graft (CABG) is the revascularization strategy of choice, particularly for diabetics and those with complex coronary disease [1–3]. Maintenance of long term graft patency is critical as graft failure begets recurrent angina, need for repeat intervention and poor survival. Three recent meta-analyses have clearly demonstrated an incremental benefit of bilateral ITA (BITA) over single ITA (SITA) with regard to long term survival [4–6]. The Arterial Revascularization Trial (ART) demonstrated no difference in survival at 5 years but the primary 10-year primary endpoint data is pending [7]. Large randomized controlled trials and retrospective series have also demonstrated that the use of the radial artery (RA) to the second best target confers patency and outcome benefits [8,9]. On balance, there is strong support for multiple arterial grafting but it is only utilized in approximately 9% of surgical revascularization performed in North America [10].

On the basis of excellent graft patency and clinical outcomes with multiple arterial grafting, the use of total arterial revascularization (TAR) is supported by American (Class IIb) and European (Class IIa) guidelines for young patients with reasonable life expectancy [11,12]. However, whether there is incremental improvement in outcomes for TAR over a two-arterial revascularization approach is equivocal. This is an important question as all-arterial grafting is more technically demanding, often requiring the need for complex composite and sequential grafting. It is our belief that if complete and high-quality arterial

* Corresponding author at: Department of Surgery, University of Toronto, Division of Cardiac Surgery, St. Michael's Hospital, 30 Bond Street, 8th Floor, Bond Wing, Toronto, ON M5B 1W8, Canada.
E-mail address: yanagawab@smh.ca (B. Yanagawa).

http://dx.doi.org/10.1016/j.ijcard.2017.02.010
0167-5273/

revascularization can be performed, then the patient should benefit from greater long-term graft patency.

Consequently, we set out to conduct a meta-analysis to evaluate the outcomes of TAR versus conventional coronary bypass (non-TAR) in the current era. We further attempt to determine whether there is any incremental benefit of TAR compared with revascularization with two arterial grafts.

2. Methods

2.1. Data sources

We systematically searched OVID versions of MEDLINE and EMBASE Classic (1996-to-2016 Jan 31 [performed on Feb 9, 2016]) for relevant studies using "total (or "totally") arterial revascularization" search terms in duplicate (see Supplementary Fig. 1 for detailed search strategy). We also searched bibliographies of included studies and personal files.

2.2. Study selection

We included all studies comparing TAR vs non-TAR in patients undergoing CABG that reported any of the pre-specified peri-operative or long-term clinical (i.e. all-cause mortality, myocardial infarction [MI], stroke, repeat revascularization, recurrent angina) or angiographic outcomes (i.e. graft occlusion). For studies with multiple groups with varying use of arterial grafts, cohorts were combined, when possible, to compare TAR vs non-TAR. Any patient cohorts with all-vein graft CABG were excluded from analysis. Studies were excluded if no clinical outcomes were reported or data published only as an abstract. Citations were screened in duplicate and full text review, also in duplicate, was performed to determine eligibility when either screening reviewer felt that a citation potentially met inclusion criteria. Disagreements regarding inclusion were reconciled via consensus.

2.3. Data extraction and quality assessment

Two reviewers independently abstracted data including details of the publication (i.e. trial authors, enrolment period, year of publication), inclusion/exclusion criteria, demographics and cardiac risk factors of the enrolled patients, description of the interventions used, and outcome definitions and events. Risk of bias in RCTs (randomized controlled trials; including blinding of participants, method of sequence generation and allocation concealment, intention-to-treat analysis, early trial stoppage for efficacy before planned enrollment completion, and loss to follow-up) and cohort studies (including retrospective versus prospective data collection, concurrent versus historical controls, and comparable baseline characteristics of cases and controls) were assessed with disagreements resolved by consensus.

2.4. Data analysis

All analyses were performed using Review Manager (RevMan version 5.2; Cochrane Collaboration, Oxford, UK) and random effects models, which incorporate between-trial heterogeneity and give wider and more conservative confidence intervals (CI) when heterogeneity is present [13]. We assessed statistical heterogeneity among trials using I^2, defined as the percentage of total variability across studies attributable to heterogeneity rather than chance, and used published guidelines for low ($I^2 = 25\%$ to 49%), moderate ($I^2 = 50\%$ to 74%) and high ($I^2 \geq 75\%$) heterogeneity [14]. For peri-operative outcome with similar follow-up between groups, relative risks (RR) were used to pool binary outcomes and weighted mean differences (MD) to pool continuous data. For long-term outcomes with potentially different follow-up between groups, we pooled incidence rate ratios on the logarithmic scale using the generic inverse variance method. When hazard ratios (assumed to be equivalent to incidence rate ratios) were not provided, incidence rate ratios (IRRs) for each study were calculated in one of two ways: 1) using Kaplan-Meier survival curve estimates for each group, and the log-rank survival curve *p*-value to estimate the standard error of the logarithm-transformed incidence rate ratio, or 2) using absolute events divided by patient-years of follow-up when group specific mean follow-up durations were provided. Individual trial and pooled summary results are reported with 95% CIs.

Study results were sub-grouped by study type: RCT vs propensity-score matched or risk-adjusted observational data vs unmatched/unadjusted observational data. Observational studies that reported both matched or risk-adjusted, and unmatched/unadjusted data were included separately for subgroup comparisons. For one study that reported only adjusted odds ratios for 30-day mortality [15], we estimated proportions that gave near identical RR and 95% CI. Excluding this study did not significantly change any of the pooled results.

3. Results

3.1. Characteristics and quality of included studies

The initial search strategy yielded 631 citations from MEDLINE and EMBASE, of which 49 were retrieved for full text review. Four unique RCTs, 15 matched observational studies and 6 unmatched observational studies that met criteria were included ($N = 130.305$ patients; mean follow-up range: 1–15 years; Supplementary Table 1A). For one RCT [15], interim results based on their similarity appeared to have been published in two other publications [16,17], which were excluded. In addition, it was unclear whether this RCT [15] which enrolled patients >70 years old had partial overall with another RCT by the same research group with similar inclusion and exclusion criteria except that it enrolled patients ≥50 years old [18]. Author contact was unsuccessful. We retained both RCTs in the primary analysis. Sensitivity analysis by excluding the results of either study did not significantly change any of the pooled results. All RCTs were single center with up to 1-year follow-up. Outcome assessors were unblinded in all RCTs. Other quality measures were only reported in two of the four included RCTs but were high with adequate allocation concealment, intention-to-treat analysis, and minimal loss to follow-up.

We also identified 21 observational studies described in Supplementary Table 1B. For studies reporting on groups with varying use of multiple arterial grafts, we selectively compared only TAR vs non-TAR. In Medalion et al. [19] cohorts BITA and LITA + RA (TAR) were compared to cohort SITA + SVG (saphenous vein graft; non-TAR); in Korompai et al. [20] "all arterial" was compared to "2 or more arterial grafts + SV" and "SITA + SVG"; in Nasso et al. [21] Group C (total arterial) was compared to Groups A + B (one and two mammary grafts, respectively, plus SVG's); in Mohammadi et al. [22] BITA/RA was compared to BITA/SVG; in Attaran et al. [23] "total arterial" was compared to "LITA + SV" and the "total SV" cohort was excluded entirely; in Baskett et al. [24] "All Arterial" was compared to "A1V + A2V + A3V". All observational studies were retrospective and all but 5 were single center. All studies compared to concurrent controls though in most the proportion of TAR increased over time. In all studies choice of surgical procedure was at the surgeon's discretion and TAR patients were typically younger with fewer comorbidities though in many of the studies TAR patients had higher rates of previously failed PCI. In some studies, some differences remained even after matching or risk adjustment.

Supplementary Table 2 provides demographic information for the 4 RCTs [15,18,25,26], 15 matched [20–24,27–37] and 6 unmatched observational studies [19,38–42]. Two studies focused specifically on diabetics [29,34], four on elderly patients [16,17,19,31] and one on patients with ventricular dysfunction [23]. The mean age for all patients in all trials was 62.4 ± 0.6 years. Enrolled individuals were 19.6% female and 25.0% were diabetic.

Please cite this article as: B. Yanagawa, et al., Impact of total arterial revascularization on long term survival: A systematic review and meta-analysis of 130,305 patients, Int J Cardiol (2017), http://dx.doi.org/10.1016/j.ijcard.2017.02.010