JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 80, NO. 19, 2022

THE PRESENT AND FUTURE

JACC REVIEW TOPIC OF THE WEEK

Coronary Artery Bypass Surgery Without Saphenous Vein Grafting

JACC Review Topic of the Week

Alistair Royse, MBBS, MD,[a,b,*] Justin Ren, BMEDSc,[a,*] Colin Royse, MBBS, MD,[a,b,c] David H. Tian, MD, PhD,[d] Stephen Fremes, MD, MSc,[e] Mario Gaudino, MD, PhD,[f] Umberto Benedetto, MD, PhD,[g] Y. Joseph Woo, MD,[h] Andrew B. Goldstone, MD, PhD,[i] Piroze Davierwala, MBBS, PhD,[e,j] Michael Borger, MD, PhD,[j] Michael Vallely, MBBS, PhD,[k] Christopher M. Reid, MSc, BA, PhD,[l] Rodolfo Rocha, MD, PhD,[e] David Glineur, MD, PhD,[m,n] Juan Grau, MD, PhD,[m] Richard Shaw, MD,[o] Hugh Paterson, MBBS,[p] Doa El-Ansary, BAppSc (PhTy), PhD,[a,q] Stuart Boggett, BSci, MC-BMedSc,[a] Nilesh Srivastav, MBBS,[a] Zulfayandi Pawanis, MBBS, MBiomedSci,[r] David Canty, MBBS, PhD,[a] Rinaldo Bellomo, MD, PhD[s]

ABSTRACT

Approximately 95% of patients of any age undergoing contemporary, coronary bypass surgery will receive at least 1 saphenous vein graft (SVG). It is recognized that SVG will develop progressive and accelerated atherosclerosis, resulting in a stenosis, and in occlusion that occurs in 50% by 10 years postoperatively. For arterial conduits, there is little evidence of progressive failure as for SVG. Could avoidance of SVG (total arterial revascularization [TAR]) lead to a different late (>5 year) survival? A literature review of 23 studies (N = 100,314 matched patients) at a mean 8.8 years postoperative found reduced all-cause mortality for TAR (HR: 0.77; 95% CI: 0.71-0.84; $P < 0.001$). An expanded analysis with a new unpublished data set (N = 63,288 matched patients) was combined with the literature review (N = 127,565). It found reduced all-cause mortality for TAR (HR: 0.78; 95% CI: 0.72-0.85; $P < 0.001$). Additional Bayesian analysis found a very high probability of a TAR-associated reduction all-cause mortality. (J Am Coll Cardiol 2022;80:1833–1843) Crown Copyright © 2022 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Surgery, University of Melbourne, Melbourne, Victoria, Australia; [b]Royal Melbourne Hospital, Melbourne, Victoria, Australia; [c]Outcomes Research Consortium, Cleveland Clinic, Cleveland, Ohio, USA; [d]Department of Anesthesia, Westmead Hospital, Sydney, New South Wales, Australia; [e]Department of Surgery, University of Toronto, Toronto, Ontario, Canada; [f]Department of Surgery, Weill Cornell Medicine, New York, New York, USA; [g]Universita degli Studi G. d'Annunzio, Chieti-Pescara, Italy; [h]Surgery, Stanford University, San Francisco, California, USA; [i]Department of Surgery, New York Presbyterian Morgan Stanley Children's Hospital, New York, New York, USA; [j]Department of Surgery, University Clinic of Cardiac Surgery, Leipzig Heart Center, Leipzig, Germany; [k]Department of Surgery, Ohio State University, Columbus, Ohio, USA; [l]Department of Epidemiology, Curtin University, Perth, Western Australia, Australia; [m]Department of Surgery, Ottawa Heart Institute, Ottawa, Ontario, Canada; [n]Department of Surgery, Clinique St Luc Bouge, Bouge, Belgium; [o]Department of Surgery, Valley Health, Ridgewood, New Jersey, USA; [p]Department of Surgery, University of Sydney, Sydney, New South Wales, Australia; [q]Swinburn University, Melbourne, Victoria, Australia; [r]Department of Surgery, Universitas Airlangga, Surabaya, Indonesia; and the [s]Department of Critical Care, University of Melbourne, Melbourne, Victoria, Australia. *Prof A. Royse and Mr J. Ren are joint first authors.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received May 17, 2022; revised manuscript received July 27, 2022, accepted August 17, 2022.

Listen to this manuscript's audio summary by Editor-in-Chief Dr Valentin Fuster on www.jacc.org/journal/jacc.

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2022.08.795

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

IMA = internal mammary artery graft

MAG = multiple arterial grafting

RA = radial artery

RCT = randomized controlled trial

SVG = saphenous vein graft

TAR = total arterial revascularization

A patient referred today for coronary artery bypass grafting (CABG), almost without regard for age, sex, comorbidities, prospects for long-term survival, or geographical locality, would receive 1 or more arterial grafts and 1 or more saphenous vein grafts (SVG).[1-3]

There are 2 schools of thought governing this strategy: the conventional view is that if arteries are considered better than SVG, then more than 1 arterial conduit may lead to incremental benefit, and there is evidence to support this view.[4-10] The alternative and bespoke viewpoint is that SVG is considered to be the conduit that is known to progressively fail.[11,12] Therefore, it is the vein, rather than the artery, that may be more influential to the long-term fate of CABG by the mechanism of graft failure leading to ischemic sequelae; and there is a logical basis to this view. To date, there have been no large, prospective, randomized controlled trials (RCTs) for the use of total arterial revascularization (TAR) vs non-TAR.

The complicating factor in the consideration of multiple arterial grafting (MAG) relates to this group also receiving supplementary SVG. Specifically, in most series, use of SVG is present in the majority of MAG patients and nearly 100% in the single arterial grafting comparison arm, and this represents a confounding variable of considerable importance. For example, in the ART (Arterial Revascularisation Trial),[13] patients were randomized to single or double internal mammary artery grafts (IMA). The confounding variable was that SVG was used in both arms. Additionally, the radial artery (RA) was analyzed as for SVG (the trial considered only IMA for group allocation and not arterial conduits in general). We now know RA has better late patency than for SVG.[9] Thus, ART has been hailed by many as evidence of lack of late outcome benefit for 2 IMA over 1 IMA and has been subject to some criticism due to a high cross-over between groups. However, when the most important confounder, SVG, was separately considered in a post hoc analysis where SVG was excluded from 1 comparison arm, the finding was of improved survival for TAR ($P = 0.03$).[14]

In order to address these issues, we combined a meta-analysis of the existing literature with a new unpublished multicenter international collaborative registry analysis. We aimed to evaluate the long-term survival benefits of TAR over the use of SVG and test the hypothesis that TAR has better long-term survival than non-TAR.

HIGHLIGHTS

- Saphenous vein graft is the only conduit known to progressively fail.
- Avoidance of saphenous vein grafts may reduce late conduit failure.
- Survival is affected by conduit failure.
- Avoidance of saphenous vein grafts may improve survival.

METHODS

ANALYSIS STRATEGY AND ENDPOINT. This paper includes 3 analyses using conventional meta-analysis methods with: 1) a systematic literature review; 2) a new unpublished multicenter collaboration of separately analyzed registries; and 3) a combined analysis of both data sets for the single consideration of late all-cause mortality for the use or avoidance of SVG in primary, isolated CABG. Additionally, a Bayesian calculation was performed for these 3 analyses (**Central Illustration**).

Two comparison groups were considered, based on use of SVG, in adult, primary, isolated CABG comprising at least 2 grafts according to:

1. No SVG used—TAR; and
2. Use of at least 1 SVG—non-TAR.

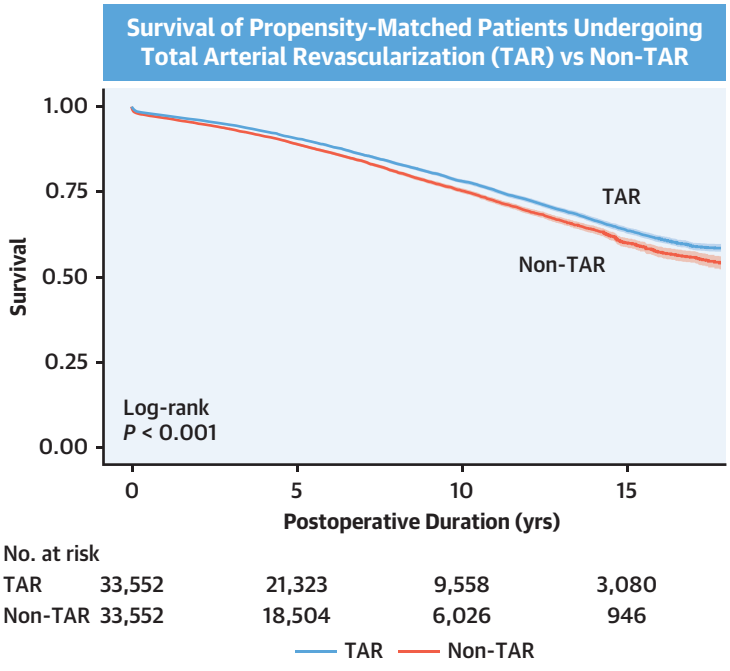
The endpoint was all-cause mortality at the longest available follow-up.

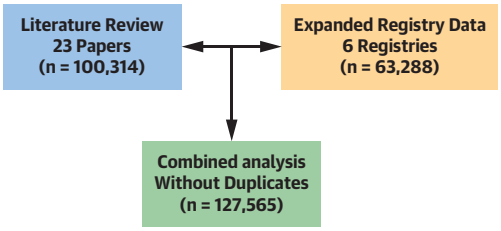
Full details of all methods can be found in the Supplemental Appendix.

LITERATURE REVIEW. This review was approved by the local institutional human ethics committee and PROSPERO registration (Long-Term Survival of Total Arterial Revascularisation in Coronary Bypass Patients: A Systematic Review and Meta-Analysis on Randomised Controlled Trials and Propensity-Score Studies; CRD42021273333). The study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[15] and Cochrane Collaboration guidelines.[16] The review checklist is reported in Supplemental Table 1. An Ovid-based literature search was performed through MEDLINE, Embase, and Cochrane Central Register of Controlled Trials from the dates of database inception to May 21, 2021.

EXPANDED ANALYSIS: NEW META-ANALYSIS OF UNPUBLISHED MULTICENTER REGISTRY DATA. A retrospective cohort registry study was established across multiple international jurisdictions according

CENTRAL ILLUSTRATION **Survival Advantage for Total Arterial Revascularization in Coronary Artery Bypass Grafting**





Literature Review	HR (95% CI)	Improved Survival
Random-effect	0.77 (0.71-0.84)	TAR
Bayesian-model	0.77 (0.70-0.84)	TAR
Expanded Registry		
Random-effect	0.83 (0.74-0.92)	TAR
Bayesian-model	0.82 (0.66-0.96)	TAR
Combined Analysis		
Random-effect	0.78 (0.72-0.85)	TAR
Bayesian-model	0.79 (0.71-0.87)	TAR

Royse A, et al. J Am Coll Cardiol. 2022;80(19):1833-1843.

From a combination of literature and expanded current international registry data, in matched patients, survival for those exclusively receiving arterial coronary grafts (TAR) was greater than those that received supplementary saphenous vein grafts (non-TAR).

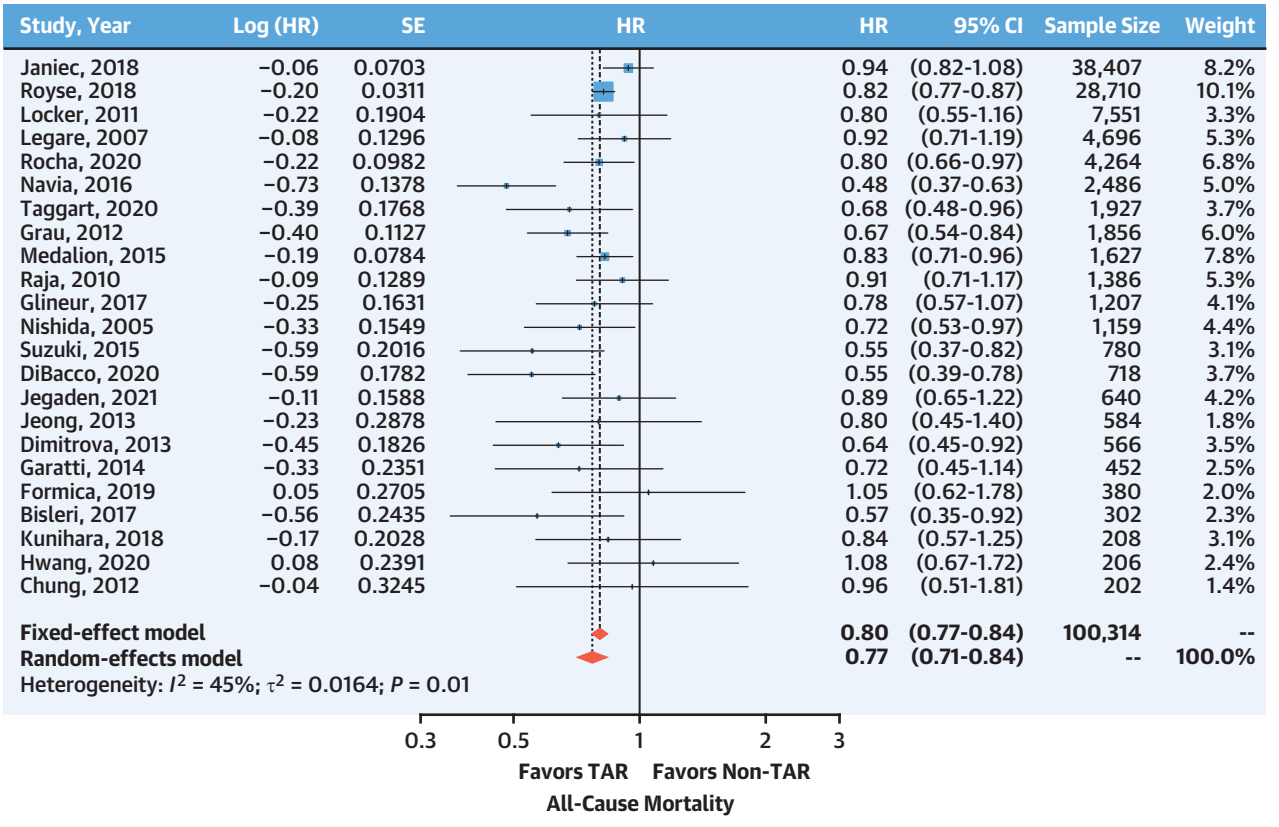
to an affiliated consortium of researchers. Each site was requested to analyze their individual data sets according to prespecified requirements, namely appropriate propensity matching of TAR and non-TAR patients within their jurisdiction (Supplemental Table 8). Each jurisdictional database was distinct and may have led to differences in coding, but for simple categorization of graft selection, it was considered that minimal bias was present. Overall distribution of preoperative variables was similar between groups (Supplemental Table 9). The frequency of TAR varied widely with each jurisdiction (Supplemental Table 8), and the distribution of double or triple vessel revascularization varied (Supplemental Table 10), which may have contributed to patient selection bias.

COMBINED LITERATURE REVIEW AND MULTICENTER COLLABORATION ANALYSES. Four published series[4,17-19] included in the literature review were excluded from the combined analysis if any data from these publications did, or could have, formed some of the data analyzed in the previously unpublished multicenter study. The impact of excluding each analysis on the overall literature review effect size was analyzed (Supplemental Figures 3 and 4).

STATISTICAL METHODS. Continuous variables are reported as mean ± SD or median (IQR) as appropriate. Categorical variables are reported as number (percentage). All adjusted or estimated HRs were pooled with random-effects and fixed-effect models using generic inverse variance weighting. Full details can be found in the Supplemental Appendix.

LITERATURE REVIEW. Baseline characteristics were pooled with random-effects meta-analysis of proportions or means. Where required, medians and IQR were converted to mean ± SD.[20] HRs and 95% CIs were extracted from individual studies where available. Leave-one-out analyses and Baujat plots were used to identify studies with disproportional impacts on overall heterogeneity (Supplemental

FIGURE 1 Literature Review Meta-Analysis



Data from individual publications were included if they compared total arterial revascularization (TAR) or any use of saphenous vein (non-TAR). Data were pooled using a meta-analysis methodology. A HR <1 indicates a survival benefit. This data set was larger than any previously reported, with 100,314 propensity score–matched or propensity score–adjusted patients. Most studies found a HR favoring TAR, with 11 reporting a statistically significant benefit for TAR. Meta-analysis found a significant survival advantage for TAR by both random effects and fixed effect models.

Figures 3 and 4). Publication bias was assessed visually with funnel plots[21] and quantitated with Egger's tests[22] (Supplemental Figures 5 and 6).

Expanded analysis. Propensity score matching was applied by each jurisdiction to reduce the effect of confounding by indication and produce comparable cohort baselines for comparison. Details of analyses for each site are listed in the Supplemental Appendix. Post-matching diagnostics were assessed with standardized mean differences. The overall HRs and standard errors were provided to the central analysis team, whereby they were pooled with results from the literature review to produce a combined treatment effect estimate.

BAYESIAN ANALYSIS. We also conducted a Bayesian[23-25] normal-normal hierarchal model meta-analysis to further explore the robustness of the results, as well as to calculate the probability of treatment effect lying on a particular range of values, such as HR <1.00. Results are presented using the median μ and credible intervals. The bayesmeta software package, version 2.7, was used for this analysis (R Foundation for Statistical Computing). All analyses were performed using R, version 4.0.5 (R Foundation for Statistical Computing).

RESULTS

LITERATURE REVIEW. After removing duplicates and merging search results, 1,478 records were identified (Supplemental Figure 1, **Figure 1, Table 1**). From abstracts and titles, 201 articles were selected to undergo full-text assessment. Three RCTs[26-28] with TAR were identified, but 2 trials[27,28] investigated different clinical endpoints, and the remaining trial[26] did not report adequate survival statistics for HR extraction, and all were excluded. Authors for the RCTs

TABLE 1 Literature Review: Details of Studies Included in the Meta-Analysis

First Author	Institution	Country	Patients		Study Period	Adjustment Methodology	Follow-Up, y[a]		Source of HR
			TAR	Non-TAR			TAR	Non-TAR	
Royse et al[4]	Multicenter	Australia	14,355	14,355	2001-2013	PS-matching	9.5 ± 4.2		From study
Janiec et al[30]	Multicenter	Sweden	1,344	37,063	2001-2015	Multivariable Cox regression	10.3 ± 4.1	9.4 ± 4.2	From study
Rocha et al[17]	Multicenter	Canada	2,132	2,132	2008-2017	PS-matching	4.6		From study
Taggart et al[14]	Multicenter	United Kingdom	843	1,084	2004-2007	PS-matching	5.2		From study
Raja et al[45]	Multicenter	United Kingdom	580	806	1998-2008	PS-adjustment	4.9 ± 2.0	5.1 ± 2.0	From study
Glineur et al[19]	Multicenter	Belgium	771	436	2000-2010	PS-matching	7.8		From study
Grau et al[18]	The Valley Heart and Vascular Institute	United States	928	928	1994-2010	PS-matching	9.0 ± 5.0		From study
Medalion et al[43]	Tel Aviv Medical Center	Israel	1,045	582	1996-2008	PS-adjustment	8.2 ± 4.5		From study
Locker et al[31]	Mayo Clinic	United States	270	7,281	1993-2009	Multivariable Cox regression	7.6 ± 4.6		From study
Navia et al[29]	Institute Cardiovascular of Buenos Aires	Argentina	2,098	388	1996-2014	Multivariable Cox regression	5.5[b]		From study
Legare et al[42]	Queen Elizabeth II Health Sciences Center	Canada	1,019	3,677	1995-2003	PS-adjustment	4.8 ± 2.0	6.1 ± 3.0	From study
Nishida et al[44]	The Heart Institute of Japan	Japan	532	627	1985-1999	PS-stratification	7.8	10.3	From study
Suzuki et al[46]	Shiga Medical University Hospital	Japan	520	260	2002-2013	PS-matching	4.6 ± 3.9		From KM
Di Bacco et al[34]	University of Brescia and Spedali Civili Hospital	Italy	359	359	2005-2015	PS-matching	8.8 ± 2.3[c]		From study
Jegaden et al[39]	Mediclinic Middle East Abu Dhabi	United Arab Emirates	320	320	1989-2014	PS-matching	13.6 ± 7.2		From study
Jeong et al[40]	Samsung Medical Centre	South Korea	292	292	2001-2010	PS-matching	4.4[b]		From KM
Dimitrova et al[35]	Beth Israel Medical Center	United States	283	283	1995-2010	PS-matching	13 ± 0.3		From study
Garatti et al[37]	IRCCS Istituto Policlinico San Donato	Italy	209	243	1994-1996	PS-matching	13.8 ± 3.6		From KM
Formica et al[36]	San Gerado Hospital	Italy	190	190	1999-2017	PS-matching	9.3 ± 5.5		From study
Bisleri et al[32]	University of Brescia and Spedali Civili Hospital	Italy	151	151	1999-2004	PS-matching	9.3[b]		From KM
Kunihara et al[41]	The Cardiovascular Institute Tokyo	Japan	104	104	1995-2001	PS-matching	11.2 ± 4.4		From study
Hwang et al[38]	Seoul National University Hospital	South Korea	103	103	2006-2008	PS-matching	10.3 ± 0.6[c]		From KM
Chung et al[33]	Asan Medical Center	South Korea	101	101	2003-2005	PS-matching	6.1 ± 0.9		From study

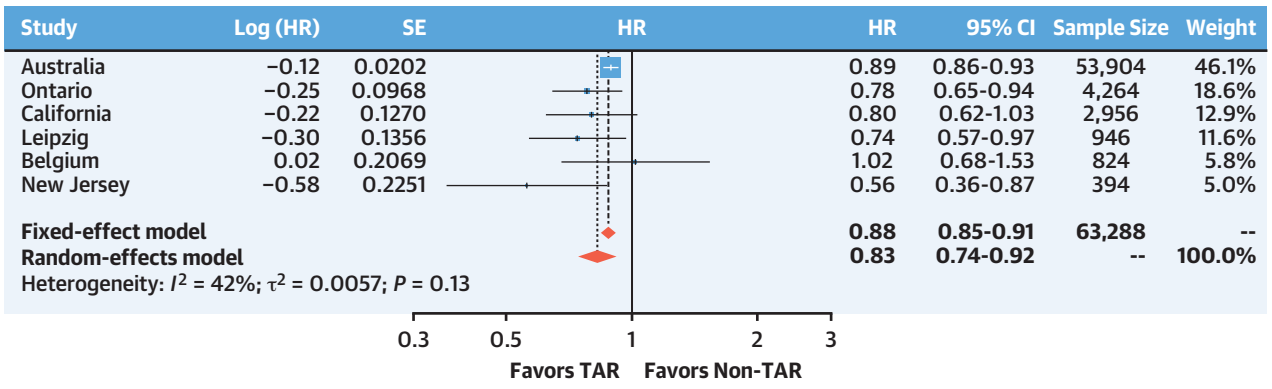
[a]Values are n or mean ± SD unless otherwise indicated. [b]Median. [c]Means and SD were estimated from median, ranges, or IQR using algorithms described in the Methods section.
KM = Kaplan-Meier survival curve; PS = propensity score; TAR = total arterial revascularization.

were contacted, but unsuccessfully. Consequently, 23 eligible studies[4,14,17-19,29-46] were deemed suitable for quantitative analysis, all retrospective in design, with a total of 100,314 matched or adjusted patients included (TAR n = 28,549; non-TAR n = 71,765). Five studies did not report HRs, requiring Kaplan-Meier digitization and recalculation to derive these figures.[32,37,38,40,46]

Details of studies. The study characteristics are listed in **Table 1** and Supplemental Tables 1 to 5. This review included 2 large national registries from Sweden with 38,407 patients[30] (37.9%) and Australia with 28,710 patients[4] (28.4%). Four studies [14,17,19,45] were regional databases, whereas the remaining were single institutional series. The weighted mean follow-up duration was 8.8 years (95% CI: 7.1-10.4 years). There were relatively similar characteristics between both cohorts (Supplemental Table 5). The overall mean age for individual reports was 63.6 years for TAR and 64.3 years for non-TAR. The prevalence of diabetes mellitus was 30.5% in the TAR cohort and 30.0% in the non-TAR cohort. The study grafting details were insufficiently precise to allow for the accurate calculation of the number of arterial grafts in the non-TAR arm. Detailed baseline demographics and perioperative profiles of patients are included in Supplemental Tables 3 to 5.

Survival. The use of TAR was associated with a significant relative reduction in all-cause mortality compared with non-TAR with the random-effect model (HR: 0.77; 95% CI: 0.71-0.84; $P < 0.001$) (**Figure 1**). There was evidence of low-to-moderate heterogeneity ($I^2 = 45\%$). Reconstructed individual patient data confirmed survival benefit for TAR

FIGURE 2 Expanded Multicenter Collaboration Meta-Analysis



Data from individual international registries, previously unpublished, were separately analyzed and pooled using a meta-analysis methodology. A cohort of 63,288 propensity score–matched patients allocated to total arterial revascularization (TAR) or non-TAR were compared for late all-cause mortality at 7.1 years (95% CI: 5.9-8.3 years). A HR <1 indicates a survival benefit. All but 1 study found a survival benefit favoring TAR. Meta-analysis found a significant survival advantage for TAR by both random effects and fixed effect models.

patients (log-rank $P < 0.001$) (Supplemental Figure 2). Prespecified meta-regression tests did not associate the use of on/off pump or the presence of multivessel disease on influencing heterogeneity. Leave-one-out analysis did not identify significant study outliers (Supplemental Figures 3 and 4).

Qualitative analysis and publication bias. The signaling domains showed no critical risk of bias. Only 5 studies[14,18,29,30,41] were categorized as a serious risk of bias, mainly due to improper control of preinterventional covariates (Supplemental Figure 5). The endpoint was classified as high-quality evidence by the GRADE guideline (Supplemental Table 5). Visual inspection of the funnel plot did not identify asymmetry (Supplemental Figure 6), which suggests an absence of publication bias, and was confirmed by Egger's test for asymmetry ($P = 0.178$).

EXPANDED MULTICENTER ANALYSIS. Participants. From 1994 to 2019, a total of 225,099 unmatched patients were identified before matching (Supplemental Tables 6 to 8). Total arterial revascularization varied across sites from 2.4% to 75.1%. In the largest data set (Australia), the TAR rate was 30.5%. Aggregated demographic characteristics are listed in Supplemental Table 9. Only matched patient analyses are presented. with a total of 63,288 patients with a weighted mean duration postoperatively of 7.1 years (95% CI: 5.9-8.3 years) in matched cohorts (**Figure 2**). Most patients received triple coronary territory revascularization (Supplemental Table 10). Results for each individual jurisdiction are included in the Supplemental Appendix. For the largest data set in Australia, MAG was used in 23.7% in the matched non-TAR (Supplemental Table 11). Surgical emergent/salvage cases represented a small proportion in California (1.8%) (Supplemental Table 16) and 2.8% in Australia (Supplemental Table 13).

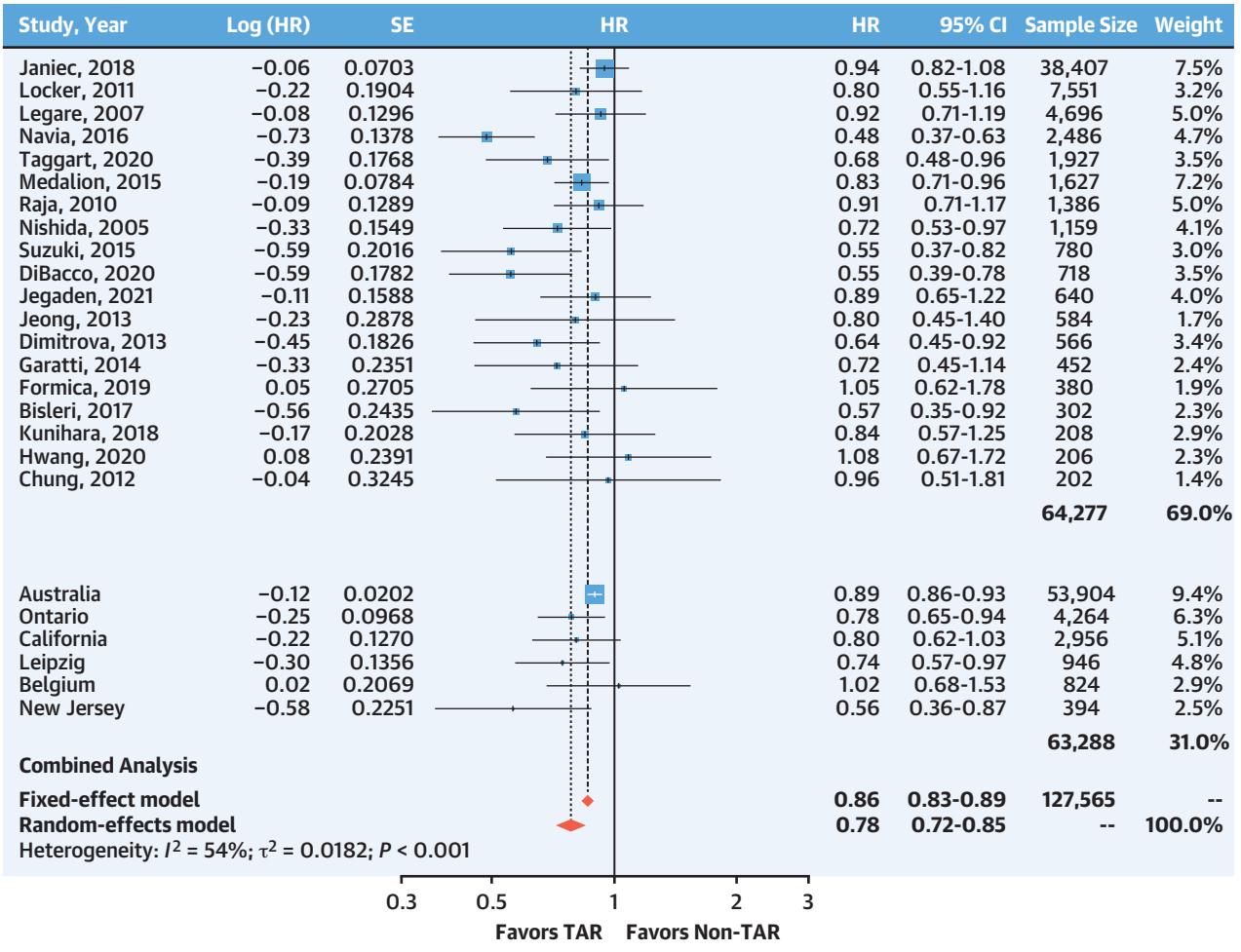
Survival. Individual results from all jurisdictions favored TAR, though the California and Belgium data sets did not reach statistical significance (**Figure 2**). The meta-analysis identified a significant decrease in mortality favoring TAR with a HR: 0.83 (95% CI: 0.74-0.92; $P < 0.001$). The heterogeneity was low to moderate ($I^2 = 33\%$). Additional sensitivity tests were conducted, which were consistent with the primary analysis (Supplemental Appendix).

TABLE 2 Baseline Characteristics for the Combined Literature Review and Expanded Multicenter Data Sets

	TAR	Non-TAR	Studies/Registries[a]
Number of grafts	3.2 (3.0-3.4)	3.2 (3.0-3.4)	15
Age, y	63.9 (62.1,65.7)	64.2 (62.3-66.0)	18
% male	70.8 (52.2-84.3)	73.9 (56.6-86.1)	18
% smoking history	47.2 (36.0-58.8)	47.2 (36.3-58.3)	12
% hypertension	71.3 (63.1-78.3)	70.2 (62.8-76.7)	17
% dyslipidemia	61.9 (50.7-72.0)	61.6 (49.8-72.1)	15
% diabetes	37.8 (24.3-53.6)	37.9 (25.0-52.8)	18
% peripheral vascular disease	10.6 (7.8-14.1)	11.5 (8.6-15.2)	14
% previous myocardial infarct	27.1 (17.6-39.4)	26.8 (16.8-40.0)	12
% COPD	9.0 (5.8-13.7)	8.8 (5.8-13.0)	13

Values are median (IQR). Only propensity score–matched patients were included in this meta-analysis of baseline characteristics using inverse variance weighted algorithm. The literature review used in the combined analysis was without 5 studies[4,17-19] that were or could have been duplicated in the expanded multicenter data set.
COPD = chronic obstructive pulmonary disease; other abbreviations as in Table 1.

FIGURE 3 Combined Literature Review and Expanded Multicenter Collaborative Data Set Meta-Analysis



Data from individual publications or registries were pooled using a meta-analysis methodology. Four studies[4,17-19] from the literature review section were removed because they did, or potentially did, include duplicate patients from the expanded multicenter collaborative data set. A combined cohort of 127,565 propensity score–matched or propensity score–adjusted patients allocated to total arterial revascularization or non-total arterial revascularization were compared for late all-cause mortality at 8.3 years (95% CI: 6.2-10.4 years). A HR <1 indicates a survival benefit. Almost all studies found a survival benefit favoring total arterial revascularization. Meta-analysis for the combined cohort found a significant survival advantage for total arterial revascularization by both random-effects and fixed-effect models.

COMBINED LITERATURE REVIEW AND EXPANDED ANALYSIS. The matched results from the expanded data set were combined with studies from the literature review, discarding 4 previously published studies that may have overlapped with the expanded data set (Table 2). The weighted mean duration postoperatively was 8.3 years (95% CI: 6.2-10.4 years). From a total of 127,565 patients, survival was found to significantly favor TAR with HR: 0.78 (95% CI: 0.72-0.85; $P = 0.010$; $I^2 = 54\%$) (Figure 3).

BAYESIAN ANALYSIS. An additional analysis using Bayesian statistical methodology was performed for all 3 considerations, and the findings were consistent with the traditional meta-analysis methodology (Table 3, Supplemental Tables 22 and 23, Figure 4). For the combined analysis, the Bayesian analysis may be expressed alternatively, where there was a >99.9% posterior probability that the treatment effect from total arterial revascularization produced a HR <1.00, and a 99.8% probability that HR was <0.90 (Table 4). The posterior median HR ranged from 0.79 to 0.80 (95% credible interval ranges: 0.71 to 0.87), depending on the prior selection.

TABLE 3 Comparison Between Random Effects Meta-Analysis and Bayesian Methodology

	HR (95% CI)	I^2, %	*P* Value
Literature review			
Random-effects model	0.77 (0.71-0.84)	45	<0.001
Low-moderate risk of bias studies only	0.81 (0.77-0.85)	5	<0.001
Propensity score–matching studies only	0.76 (0.70-0.83)	19	<0.001
Bayesian model[a]	0.77 (0.70-0.84)	NA	NA
Multicenter collaboration			
Random-effects model	0.83 (0.74-0.92)	33	<0.001
Bayesian model[a]	0.82 (0.66-0.96)	NA	NA
Combined analysis			
Random-effects model	0.78 (0.72-0.85)	54	0.010
Bayesian model[b]	0.79 (0.71-0.87)	NA	NA

[a]Bayesian normal-normal hierarchal model, with noninformative priors for μ and τ^2. Additional model results with differing priors are available in the Supplemental Appendix section 4. [b]Bayesian normal-normal hierarchal model, with $\log(\mu) = -0.264$, SD = 0.060 as per Bayesian meta-analysis of the literature review, with the multi-institutional collaboration serving as the likelihood function.

NA = not applicable to the Bayesian model.

DISCUSSION

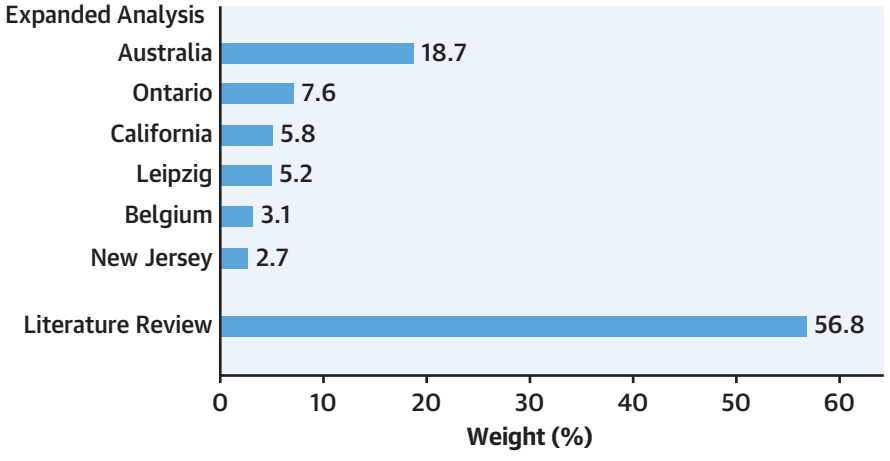
KEY FINDINGS. The key result was that complete avoidance of SVG grafts in CABG, TAR, was associated with significantly decreased long-term mortality compared with the use of SVG (non-TAR) in populations that have undergone propensity score matching or Cox regression adjustments. Survival curve separation occurred early and continued to widen over time. Further, the application of an alternative Bayesian methodology, found very similar effect sizes to the conventional approach, suggesting that the analyses are robust. The Bayesian approach predicted with a very high degree of probability that the use of TAR is associated with improved survival even to an effect size of HR of <0.90.

SIZE OF ANALYSIS. The combined data set included 127,565 matched patients, which is more than 5-fold larger than a previous report.[47] This data set comprised studies from the isolated literature review that had analyzed 100,314 patients but was reduced by exclusion of 4 studies, resulting in 62,427 patients, then expanded by a further 63,288 matched patients from the multicenter registry data.

CONSISTENCY BETWEEN ANALYSES. The HR for mortality for the combined analysis was 0.78, similar to the literature review (0.77) and the expanded multicenter analysis (0.83). Various sensitivity analyses in both cohorts yielded results consistent with the primary analysis. Within the expanded multicenter analysis, despite a wide variation in the rate of TAR between registries, the effect size of the survival benefit for TAR was surprisingly similar. This strengthens rather than weakens the argument that the late mortality can be explained by the well-documented late failure of SVG leading to mortality.

The Bayesian approach is relatively novel in the field of coronary surgery and expresses findings differently. This approach avoids arbitrary classifications of significance or nonsignificance and presents a measure of certainty (probability) to effect sizes

FIGURE 4 Bayesian Analysis: Posterior Mean Weights (Overall Mean Estimate)



The weighted contributions to the posterior treatment effect estimate, with the literature review serving as the primary information in the random-effects Bayesian meta-analysis. The final treatment effect can be considered as a weighted average of all the displayed estimates. The existing literature is most prominent in this analysis.

contained in the 95% credible interval. The Bayesian approach allows the preselection of where the treatment effect is believed to be centered (eg, that HR = 1.00), and the certainty in this belief (a certain belief has a narrower variance surrounding this treatment effect). A Bayesian meta-analysis allows us to directly incorporate prior understandings from the literature into the pooled data and quantify the effect that different prior beliefs have on the understanding of the evidence. The resultant "posterior probability" of the calculated treatment effect is considered more scientifically useful than dichotomizing a *P* value.[24] The observed survival benefit in favor of TAR, expressed as a probability, showed a >99.9% probability that the true HR is <1.00 and a 99.8% probability that the true HR is <0.90.

RELEVANCE. This analysis has relevance for most adult cardiac surgeons, and many cardiologists, because CABG still comprises a substantial component of surgical practice, and use of SVG remains routine.

BASIS FOR APPROACH. SVG is well known to develop atherosclerosis over time, and failure of the conduit is common in the late period.[12,48] Although a "no-touch" harvest technique for SVG has been advocated following a small series[49] and a larger series,[50] a recent large propensity score–matched analysis found no difference in survival.[51] The ischemic consequences of graft failure would logically lead to a recurrence of symptoms, heart failure, or death.[11,52] Therefore, it would be expected that reliance on SVG could lead to higher mortality rates due to graft failure over time. Conversely, the internal mammary artery is known to be resistant to progressive atherosclerosis and failure,[53,54] and there is some evidence that this may be true for other arterial conduits.[5,8,9,55] Therefore, it may be logical to consider SVG as a more important predictor of long-term outcome than the increased use of arterial conduits as it represents the most likely conduit to fail.

SELECTION BIAS. A retrospective analysis cannot control for all confounding variables irrespective of the quality of statistical matching methods. Although the rate of TAR varied considerably, the HR remained surprisingly similar in most series. Yet selection bias must occur, and not all variables can be controlled for or even adequately measured such as surgeon competence, surgeon skill, acuity of surgical intervention, and many more. Reversion to "familiar techniques" under emergency circumstances is also common and can vary—many surgeons may be more comfortable harvesting SVG in preference, whereas some are more comfortable harvesting the RA in preference. Emergency surgery scenarios, however, represent a small proportion of the total sample size (1.8%-2.8%).

TABLE 4 Bayesian Analysis of Combined Matched Data Set (n = 127,565)

Prior Belief for τ^2	Posterior Median HR (95% Credible Interval)	Posterior Probability for True HR, %		
		HR <1.00	HR <0.90	HR <0.80
Uniform	0.789 (0.714-0.869)	100	99.8	60.6
Half-normal	0.790 (0.715-0.870)	100	99.8	60.0
Tibshirani[58]	0.795 (0.720-0.873)	100	99.8	54.7

The combined data set includes the literature review without 4 papers[4,17-19] that were or could have been duplicated in the expanded multicenter data set. The interpretation of these data is that there is close to certainty that total arterial revascularization (TAR) is responsible for the observed improved survival, that there is a 99.8% probability that TAR is responsible for a moderate survival effect size (HR <0.90), and a 55% to 61% probability that TAR is responsible for a relatively large survival effect size (HR <0.80).

IMPLICATIONS OF STUDY FINDINGS. A nonrandomized study is hypothesis generating and suggests that a RCT comparing TAR with CABG inclusive of 1 or more SVG is justified. These data support a logical basis for the argument that the elimination of a conduit known to fail over time should lead to reduced adverse outcomes associated with that failure, including death.

Despite perceived increased technical difficulty, danger, time, or lack of evidence of benefit for TAR, it can be achieved in a variety of ways, including bilateral RA from the aorta in combination with the left internal mammary artery and with the use of sequential grafting techniques; use of a composite grafting strategy with either right internal mammary artery or RA as the second conduit[5,19,55,56] or even use of just 2 RA alone including the use of a composite graft.[57] Importantly, most strategies can be achieved with minimal alteration to conventional conduit harvesting and grafting techniques.

STUDY STRENGTHS AND LIMITATIONS. This study is 5-fold larger than any previous report, and the extensive matching of patients should provide some confidence in the overall trend of the effect. The findings of the new original analysis are consistent across jurisdictions with little heterogeneity. Comparisons are adjusted by robust propensity scores and the primary outcome is robust and patient-centered. The addition of a secondary Bayesian alternative statistical approach had findings consistent with the meta-analysis and is reassuring.

A retrospective cohort study cannot account for all patient allocation and treatment variables despite propensity score matching and cannot account for variables such as technical competence of the surgeon. The proportion of patients receiving TAR varied with each jurisdiction, with some infrequently performing TAR, which may introduce bias. The use of

all-cause mortality is a robust patient-centered endpoint variable. Still, it may be less robust when collected during researcher follow-up than by independent national or state-based death index linkage. Further, an assumption when using all-cause mortality is that the noncardiac causes of death and the cardiac causes of death unrelated to coronary graft failure will be evenly distributed between the 2 arms. This cannot be proven without an RCT; however, the large size of this observational data set may reduce such bias.

CONCLUSIONS

Meta-analytical assessment, matched cohort assessment, and Bayesian analysis of large data sets are concordant in showing a long-term survival benefit from TAR vs non-TAR CABG. Given the continuing dominance of non-TAR worldwide, these findings providing the epidemiological justification for a pivotal randomized controlled trial comparing these 2 approaches to CABG.

ACKNOWLEDGMENTS Three state or national registries were involved in the expanded analysis, including the Australia and New Zealand Society of Cardiothoracic Surgery (ANZSCTS), the Ontario registry in Canada (ICES), and the California State registry in the United States, and analyzed within each jurisdiction by local authors.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Prof Alistair Royse, Department of Surgery, The University of Melbourne, PO Box 2135, Royal Melbourne Hospital, Carlton, Victoria 3050, Australia. E-mail: Alistair.Royse@iteachu.com. Twitter: @AlistairRoyse.

REFERENCES

1. Bridgewater B, Keogh B, Kinsman R, Walton P. *Sixth National Adult Cardiac Surgical Database Report 2008: Demonstrating Quality*. Henley-on-Thames, UK: Dendrite Clinical Systems Limited; 2009.

2. Dimitrova KR, Hoffman DM, Geller CM, Dincheva G, Ko W, Tranbaugh RF. Arterial grafts protect the native coronary vessels from atherosclerotic disease progression. *Ann Thorac Surg*. 2012;94:475–481.

3. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(2):e21–e129. https://doi.org/10.1016/j.jacc.2021.09.006

4. Royse A, Pawanis Z, Canty D, et al. The effect on survival from the use of a saphenous vein graft during coronary bypass surgery: a large cohort study. *Eur J Cardiothorac Surg*. 2018;54:1093–1100.

5. 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;72:1332–1340.

6. Rocha RV, Tam DY, Karkhanis R, et al. Multiple arterial grafting is associated with better outcomes for coronary artery bypass grafting patients. *Circulation*. 2018;138:2081–2090.

7. Goldstone AB, Chiu P, Baiocchi M, et al. Second arterial versus venous conduits for multivessel coronary artery bypass surgery in California. *Circulation*. 2018;137:1698–1707.

8. Gaudino M, Lorusso R, Rahouma M, et al. 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. *J Am Heart Assoc*. 2019;8:e010839.

9. Gaudino M, Benedetto U, Fremes S, et al. Radial-artery or saphenous-vein grafts in coronary-artery bypass surgery. *N Engl J Med*. 2018;378:2069–2077.

10. Taggart DP. The role of multiple arterial grafts in CABG: all roads lead to ROMA. *J Am Coll Cardiol*. 2019;74:2249–2253.

11. 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;28:616–626.

12. Goldman S, Zadina K, Moritz T, et al. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study. *J Am Coll Cardiol*. 2004;44:2149–2156.

13. Taggart DP, Benedetto U, Gerry S, et al. Bilateral versus single internal-thoracic-artery grafts at 10 years. *N Engl J Med*. 2019;380:437–446.

14. Taggart DP, Gaudino MF, Gerry S, et al. Effect of total arterial grafting in the Arterial Revascularization Trial. *J Thorac Cardiovasc Surg*. 2022;163:1002–1009.e6.

15. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535. https://doi.org/10.1136/bmj.b2535

16. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev*. 2019;10:ED000142.

17. Rocha RV, Tam DY, Karkhanis R, et al. Long-term outcomes associated with total arterial revascularization vs non-total arterial revascularization. *JAMA Cardiol*. 2020;5:507–514.

18. Grau JB, Ferrari G, Mak AW, et al. Propensity matched analysis of bilateral internal mammary artery versus single left internal mammary artery grafting at 17-year follow-up: validation of a contemporary surgical experience. *Eur J Cardiothorac Surg*. 2012;41:770–775.

19. Glineur D, Etienne PY, Kuschner CE, et al. Bilateral internal mammary artery Y construct with multiple sequential grafting improves survival compared to bilateral internal mammary artery with additional vein grafts: 10-year experience at 2 different institutions. *Eur J Cardiothorac Surg*. 2017;51:368–375.

20. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.

21. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.

22. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.

23. Matthews R. Why should clinicians care about Bayesian methods? *J Stat Plan Inference*. 2001;94:43-58. https://doi.org/10.1016/S0378-3758(00)00232-9

24. Burton PR, Gurrin LC, Campbell MJ. Clinical significance not statistical significance: a simple Bayesian alternative to p values. *J Epidemiol*

Community Health. 1998;52(5):318–323. https://doi.org/10.1136/jech.52.5.318

25. Sutton AJ, Cooper NJ, Abrams KR, Lambert PC, Jones DR. A Bayesian approach to evaluating net clinical benefit allowed for parameter uncertainty. *J Clin Epidemiol*. 2005;58:26–40.

26. Muneretto C, Negri A, Manfredi J, et al. Safety and usefulness of composite grafts for total arterial myocardial revascularization: a prospective randomized evaluation. *J Thorac Cardiovasc Surg*. 2003;125:826–835.

27. Damgaard S, Wetterslev J, Lund JT, et al. One-year results of total arterial revascularization vs. conventional coronary surgery: CARRPO trial. *Eur Heart J*. 2009;30:1005–1011.

28. Muneretto C, Bisleri G, Negri A, et al. Total arterial myocardial revascularization with composite grafts improves results of coronary surgery in elderly: a prospective randomized comparison with conventional coronary artery bypass surgery. *Circulation*. 2003;108(suppl 1):II29–II33.

29. 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;101:1775–1781.

30. Janiec M, Nazari Shafti TZ, Dimberg A, Lagerqvist B, Lindblom RPF. Graft failure and recurrence of symptoms after coronary artery bypass grafting. *Scand Cardiovasc J*. 2018;52:113–119.

31. Locker C, Schaff HV, Dearani JA, et al. Multiple arterial grafts improve late survival of patients undergoing coronary artery bypass graft surgery: analysis of 8622 patients with multivessel disease. *Circulation*. 2012;126:1023–1030.

32. Bisleri G, Di Bacco L, Giroletti L, Muneretto C. Total arterial grafting is associated with improved clinical outcomes compared to conventional myocardial revascularization at 10 years follow-up. *Heart Vessels*. 2017;32:109–116.

33. Chung JW, Kim JB, Jung SH, et al. Mid-term outcomes of total arterial revascularization versus conventional coronary surgery in isolated three-vessel coronary disease. *J Korean Med Sci*. 2012;27:1051–1056.

34. Di Bacco L, Repossini A, Muneretto C, Torkan L, Bisleri G. Long-term outcome of total arterial myocardial revascularization versus conventional coronary artery bypass in diabetic and non-diabetic patients: a propensity-match analysis. *Cardiovasc Revasc Med*. 2020;21:580–587.

35. Dimitrova KR, Hoffman DM, Geller CM, et al. Radial artery grafting in women improves 15-year survival. *J Thorac Cardiovasc Surg*. 2013;146:1467–1473.

36. Formica F, D'Alessandro S, Singh G, et al. The impact of the radial artery or the saphenous vein in addition to the bilateral internal mammary arteries on late survival: a propensity score analysis. *J Thorac Cardiovasc Surg*. 2019;158:141–151.

37. Garatti A, Castelvecchio S, Canziani A, et al. Long-term results of sequential vein coronary artery bypass grafting compared with totally arterial myocardial revascularization: a propensity score-matched follow-up study. *Eur J Cardiothorac Surg*. 2014;46:1006–1013.

38. Hwang HY, Lee Y, Sohn SH, Choi JW, Kim KB. Equivalent 10-year angiographic and long-term clinical outcomes with saphenous vein composite grafts and arterial composite grafts. *J Thorac Cardiovasc Surg*. 2021;162:1535–1543.e4.

39. Jegaden OJL, Farhat F, Jegaden MPO, Hassan AO, Eker A, Lapeze J. Does the addition of a gastroepiploic artery to bilateral internal thoracic artery improve survival? *Semin Thorac Cardiovasc Surg*. 2022;34:92–98.

40. Jeong DS, Kim YH, Lee YT, et al. Revascularization for the right coronary artery territory in off-pump coronary artery bypass surgery. *Ann Thorac Surg*. 2013;96:778–785.

41. Kunihara T, Wendler O, Heinrich K, Nomura R, Schafers HJ. Coronary artery bypass grafting in diabetic patients: complete arterial versus internal thoracic artery and sequential vein grafts-a propensity-score matched analysis. *Thorac Cardiovasc Surg*. 2019;67:428–436.

42. Legare JF, Hassan A, Buth KJ, Sullivan JA. The effect of total arterial grafting on medium-term outcomes following coronary artery bypass grafting. *J Cardiothorac Surg*. 2007;2:44.

43. Medalion B, Mohr R, Ben-Gal Y, et al. Arterial coronary artery bypass grafting is safe and effective in elderly patients. *J Thorac Cardiovasc Surg*. 2015;150:607–612.

44. Nishida H, Tomizawa Y, Endo M, Kurosawa H. Survival benefit of exclusive use of in situ arterial conduits over combined use of arterial and vein grafts for multiple coronary artery bypass grafting. *Circulation*. 2005;112:I299–I303.

45. Raja SG, Navaratnarajah M, Kitchlu CS, George S, Ilsley CD, Amrani M. 10-year follow-up of off-pump multivessel coronary artery bypass grafting. *Asian Cardiovasc Thorac Annals*. 2010;18:260–265.

46. Suzuki T, Asai T, Nota H, Kinoshita T, Fujino S. Impact of total arterial reconstruction on long-term mortality and morbidity: off-pump total arterial reconstruction versus non-total arterial reconstruction. *Ann Thorac Surg*. 2015;100:2244–2249.

47. Rayol SC, Van den Eynde J, Cavalcanti LRP, et al. Total arterial coronary bypass graft surgery is associated with better long-term survival in patients with multivessel coronary artery disease: a systematic review with meta-analysis. *Braz J Cardiovasc Surg*. 2021;36:78–85.

48. Grondin CM, Campeau L, Lesperance J, Enjalbert M, Bourassa MG. Comparison of late changes in internal mammary artery and saphenous vein grafts in two consecutive series of patients 10 years after operation. *Circulation*. 1984;70:I208–I212.

49. Samano N, Geijer H, Liden M, Fremes S, Bodin L, Souza D. The no-touch saphenous vein for coronary artery bypass grafting maintains a patency, after 16 years, comparable to the left internal thoracic artery: a randomized trial. *J Thorac Cardiovasc Surg*. 2015;150:880–888.

50. Tian M, Wang X, Sun H, et al. No-touch versus conventional vein harvesting techniques at 12 months after coronary artery bypass grafting surgery: multicenter randomized, controlled trial. *Circulation*. 2021;144:1120–1129.

51. Weiss MG, Nielsen PH, James S, Thelin S, Modrau IS. Clinical outcomes after surgical revascularization using no-touch versus conventional saphenous vein grafts: mid-term follow-up of propensity score matched cohorts. *Semin Thorac Cardiovasc Surg*. Published online December 5, 2021. https://doi.org/10.1053/j.semtcvs.2021.12.002

52. Adelborg K, Horvath-Puho E, Schmidt M, et al. Thirty-year mortality after coronary artery bypass graft surgery: a Danish nationwide population-based cohort study. *Circ Cardiovasc Qual Outcomes*. 2017;10:e002708.

53. 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;78:2005–2012.

54. 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;130:539–545.

55. Royse AG, Bellomo R, Royse CF, et al. Radial artery vs bilateral mammary composite Y coronary artery grafting: 15-year outcomes. *Ann Thorac Surg*. 2021;111:1945–1953.

56. Paterson HS, Naidoo R, Byth K, Chen C, Denniss AR. Full myocardial revascularization with bilateral internal mammary artery Y grafts. *Ann Cardiothorac Surg*. 2013;2:444–452.

57. Royse AG, Boggett S, Abraham V, Royse CF. RARAY operation: operative description and early results for achieving total arterial coronary revascularisation. *Heart Lung Circ*. 2020;29:1873–1879.

58. Tibshirani R. Noninformative priors for one parameter of many. *Biometrika*. 1989;76:604–608.

KEY WORDS CABG, meta-analysis, mortality, SVG, TAR, total arterial revascularization

APPENDIX For an expanded Methods section, as well as supplemental figures and tables, please see the online version of this paper.