Unmeasured Confounders in Observational Studies Comparing Bilateral Versus Single Internal Thoracic Artery for Coronary Artery Bypass Grafting: A Meta-Analysis

Mario Gaudino, MD; Antonino Di Franco, MD; Mohamed Rahouma, MD; Derrick Y. Tam, MD; Mario Iannaccone, MD; Saswata Deb, MD; Fabrizio D'Ascenzo, MD; Ahmed A. Abouarab, MD; Leonard N. Girardi, MD; David P. Taggart, PhD; Stephen E. Fremes, MD

***Background*—**Observational studies suggest a survival advantage with bilateral single internal thoracic artery (BITA) versus single internal thoracic artery grafting for coronary surgery, whereas this conclusion is not supported by randomized trials. We hypothesized that this inconsistency is attributed to unmeasured confounders intrinsic to observational studies. To test our hypothesis, we performed a meta-analysis of the observational literature comparing BITA and single internal thoracic artery, deriving incident rate ratio for mortality at end of follow-up and at 1 year. We postulated that BITA would not affect 1-year survival based on the natural history of coronary artery bypass occlusion, so that a difference between groups at 1 year could not be attributed to the intervention.

***Methods and Results*—**We searched MEDLINE and Pubmed to identify all observational studies comparing the outcome of BITA versus single internal thoracic artery. One-year and long-term mortality for BITA and single internal thoracic artery were compared in the propensity-score–matched (PSM) series, that is, the form of observational evidence less prone to confounders. Thirty-eight observational studies (174 205 total patients) were selected for final comparison. In the 12 propensity-score–matched series (34 019 patients), the mortality reduction for BITA was similar at 1 year and at the end of follow-up (incident rate ratio, 0.70; 95% confidence interval, 0.60–0.82 versus 0.77; 95% confidence interval, 0.70–0.85; *P* for subgroup difference=0.43).

***Conclusions*—**Unmeasured confounders, rather than biological superiority, may explain the survival advantage of BITA in observational series. **(*J Am Heart Assoc*. 2018;7:e008010. DOI: 10.1161/JAHA.117.008010.)**

Key Words: bypass graft • myocardial revascularization • surgery

A clear contradiction between observational and randomized studies exists in the literature on the effect of multiple internal thoracic artery grafts in patients undergoing coronary artery bypass surgery.

From the Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York, NY (M.G., A.D.F., M.R., A.A.A., L.N.G.); Schulich Heart Centre, Sunnybrook Health Science, University of Toronto, Toronto, Ontario, Canada (D.Y.T., S.D., S.E.F.); Department of Cardiology, Città della Scienza e della Salute, University of Turin, Torino, Italy (M.I., F.D'.); University of Oxford, Oxford, United Kingdom (D.P.T.).

Accompanying Data S1, Tables S1 through S5, and Figures S1 through S5 are available at http://jaha.ahajournals.org/content/7/1/e008010/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Mario Gaudino, MD, Department of Cardiothoracic Surgery, Weill Cornell Medicine, 525 E 68th St, New York, NY 10065. E-mail: mfg9004@med.cornell.edu

Received November 4, 2017; accepted November 17, 2017.

In the 1980s, it was recognized that in coronary artery bypass surgery patients long-term survival was enhanced when the left anterior descending (LAD) was grafted with a left internal thoracic artery, rather than a saphenous vein graft (SVG).[1] By extension, the use of bilateral internal thoracic arteries (BITAs) should further increase postoperative survival, compared with the use of a single internal thoracic artery (SITA).[2] This difference is generally attributed to greater and more-durable patency of the internal thoracic artery compared with the SVG, as well as increased late SVG atherosclerosis.[3]

In the past 25 years, a very large amount of observational data, including 6 meta-analyses,[4–9] have supported this concept. On this basis, the use of BITA is a class IIA recommendation in patients with a long anticipated life expectancy by current guidelines and professional society position papers.[10–12]

The randomized studies, however, reported different results. To date, there have been 4 randomized controlled trials (RCTs) comparing BITA and SITA.[13–16] In these studies,

Clinical Perspective

What Is New?

- Our findings suggest that factors not related to the conduit patency, such as the patients' general status or quality of the target vessels, play a role in determining the outcome of observational studies and that a selection bias is present even in propensity-score–matched analyses.

What Are the Clinical Implications?

- Our findings elicit concerns regarding the ability of the propensity-matching process to overcome selection bias and assure comparability between groups.
- The long-term clinical outcomes data from the ART (Arterial Revascularization Trial) trial and new randomized studies are needed to clarify the effect of bilateral internal thoracic artery grafting in patients undergoing coronary bypass surgery.

survival has been similar following BITA and SITA grafting. In the largest of the RCTs, the ART (Arterial Revascularization Trial), mortality was 8.7% after BITA grafting and 8.4% following SITA at 5 years.[16]

There are several possible explanations for the discrepant findings between observational and RCT evidence. The RCTs may not have sufficient sample size or follow-up to detect a mortality difference compared with observational series. In the ART trial, a relatively higher proportion of crossovers in the patients randomized to BITA, as well as the allowed use of a radial artery in the SITA group, may have diluted the treatment effect.

The other possible explanation, however, is that the benefit observed in the observational studies for BITA grafting is largely related to unmeasured confounders.

The objective of this study is to perform a meta-analysis of the observational literature comparing survival following BITA and SITA grafting. To evaluate whether unmeasured confounders rather than biological superiority explained the BITA effect, we chose to compare both 1-year as well as late survival in the BITA and SITA cohorts. We postulated that BITA would not affect 1-year survival based on the natural history of SVG occlusion. The latter analysis was restricted to propensity-score–matched studies, because PSM is considered the best method to minimize confounding in observational series.

Methods

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Search Strategy and Study Selection

This systematic review was conducted in accord to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[17]

Pubmed and OVID's version of MEDLINE was searched from January 1972 to August 2017 for publications comparing BITA versus SITA grafting on all-cause mortality. The following keywords were combined with the Boolean operator "or": "bilateral internal mammary," "bilateral internal thoracic," "total arterial revascularization," and "multiple arterial revascularization." The full search strategy can be found in Data S1. All citations were screened for study inclusion independently by 2 investigators (A.D.F. and M.G.). Any disagreements were discussed and resolved by consensus. In addition, the bibliography of all studies and meta-analyses was searched to identify further publications.

Inclusion criteria for analysis were:

1. Observational study (unadjusted and adjusted studies were eligible).
2. Sample size of at least 100 patients in each group.
3. Follow-up duration longer than 30 days.
4. Written in English language.

We excluded studies that were: RCTs, not performed in humans, review articles, case reports, editorials, and expert opinions. To ensure that the analysis was strictly limited to a comparison of BITA versus SITA, we excluded studies where an additional arterial graft was used in 1 of the 2 groups and it was not possible to abstract the exact information for the isolated BITA and SITA series. In case of overlapping between studies or multiple publications from the same center, only the publication with the largest sample size was considered.

The quality of included studies was assessed using the Newcastle–Ottawa Scale for observational studies by 2 investigators independently (A.D.F. and M.G.).[18] The highest possible score is 9 stars; <6 stars was considered low quality whereas ≥6 stars was considered high quality.

Data Abstraction

Two investigators (A.D.F. and M.G.) independently abstracted the following: study demographics (study period, country, and centers involved, sample size), study design methods, completeness of follow-up, and follow-up duration. In addition, the following patient characteristics in the unmatched and matched groups were also obtained: age, female sex, diabetes mellitus, left ventricular ejection fraction, and chronic obstructive pulmonary disease. Continuous variables were expressed as median (25th, 75th percentile) or as mean±SD. Categorical variables are reported as frequency (%).

For all-cause mortality, crude event rates, unadjusted and adjusted hazard ratios (HRs) for BITA versus SITA grafting, and their respective 95% confidence intervals (CIs) and log *P*-rank values were abstracted.

Outcome Analyses

The primary outcome was all-cause mortality. Long-term all-cause mortality for BITA and SITA patients was compared in all the studies.

Subgroup analyses for the primary outcome were performed as follows:

1. Studies in the general population versus studies in specific subgroups of patients (ie, diabetics, elderly patients as defined by the individual studies, patients with renal failure, urgent/emergent cases, and patients with low ejection fraction).
2. Unadjusted versus adjusted studies (including regression-adjusted and PSM) in the general population.
3. Regression-adjusted versus PSM studies in the general population.

To assess for possible treatment allocation bias in the observational studies, we chose to compare 1-year mortality between matched treatment groups. The 1-year interval was chosen because the patency rate of SVGs at 1 year remains high and a survival difference related to difference in patency between arterial and venous conduits is unlikely.[19] PSM is a robust method used to balance against confounding by indication in observational studies[20]; for this reason, we compared all-cause mortality for BITA and SITA at 1 year in the PSM studies only.

Analytical Plan

Long-term all-cause mortality between BITA and SITA patients was compared in all studies initially. Comparisons were then performed in the general population studies after exclusion of studies restricted to specific patient subgroups (diabetes mellitus, elderly as defined in the individual studies, renal failure, urgent/emergent, and reduced left ventricular ejection fraction) and in the individual specific patient subgroups. Next, separate comparisons were made between BITA and SITA in the unadjusted and adjusted series (covariate adjusted and PSM combined). Last, comparisons were performed in the covariate adjusted and PSM series separately.

One-year mortality between BITA and SITA patients was compared in PSM studies only.

Statistical Analysis

The generic inverse variance method[21] was used to pool the natural logarithm of the incident rate ratio (IRR) across studies to account for potentially different follow-up durations between the groups. We estimated the IRR through several means depending on the available study data. When HRs were provided, we took the natural logarithm of the HR; the SE was derived from the 95% CI or log rank *P* value.[22] When Kaplan–Meier curves were present, we estimated the number of events from the curves to calculate the IRR, as previously described.[23] The SE was estimated from the number of events in each arm.[22] When event rates were not readily available, they were extracted from Kaplan–Meier curves using GetData Graph Digitizer software (version 2.26; http://getdata-graph-digitizer.com/) according to a previously described method.[24]

A random-effects model was used for statistical survival pooling, computing risk estimates with 95% CIs. Funnel plots were used to assess publication bias by graphical inspection.[25] Hypothesis testing for equivalence was set at the 2-tailed 0.01 level. Hypothesis testing for statistical heterogeneity was set at the 2-tailed 0.10 level and was based on the Cochran Q test, with I^2 values of 0% to 25%, 26% to 50%, and 51% to 100% representing low, moderate, and high heterogeneity, respectively.[26]

Metaregression analysis examining the following variables—age, sex, diabetes mellitus, and left ventricular ejection fraction—was performed. In addition, a “leave-one-out” analysis and a cumulative meta-analysis were performed in all studies ordered by year of publication.

All analyses were performed using CMA software (version 3; Biostat, Englewood, NJ).

Results

Selected Studies

From 2921 titles, 149 pertinent studies were included for full-text review. We excluded 111 studies that did not meet inclusion criteria. Further details of the study flow are shown in Figure S1. A total of 38 observational studies were selected for the quantitative analysis. Eight nonadjusted, 9 covariate-adjusted, and 21 PSM studies were included (see Table 1).[27–64] Twenty-eight studies (162 989 patients) were performed in the general population, whereas 10 (11 216 patients) were performed in specific subgroups of patients (diabetics: 3 studies [1533 patients]; elderly: 4 studies [6033 patients]; renal failure patients: 1 study [1203 patients]; urgent/emergent cases: 1 study [652 patients]; and patients with low ejection fraction: 1 study [1795 patients]). An overview of the studies is summarized in Tables 1 and 2[27–64] (variables included for PSM are summarized in Table S1).

The selected studies reported on 174 205 patients (BITA: 32 206; SITA: 141 999) for final comparisons.

Overall, the BITA and SITA groups presented different preoperative risk-factor distribution (mean age, BITA versus

DOI: 10.1161/JAHA.117.008010

Table 1. Characteristics of the Studies Included in the Primary Analysis

Study	Year	Center	Study Period	Setting	Type of Study	Adjustment Performed
Ashraf[27]	1994	Manchester Royal Infirmary, Manchester, UK	1989–1992	Isolated primary CABG	Retrospective	NS
Benedetto[28]	2014	Harefield Hospital, London, UK	2001–2013	Isolated primary CABG	Retrospective	PSM
Berreklouw[29]	2001	Catharina Hospital, Eindhoven, The Netherlands	1985–1990	Isolated primary CABG	Retrospective	MCPHR
Bonacchi[30]	2006	University of Florence, Italy	1997–2003	Non-elective CABG in unstable angina patients	Retrospective	MCPHR
Buxton[31]	1998	Austin and Repatriation Medical Center, University of Melbourne, Victoria, Australia	1985–1995	Isolated primary CABG	Retrospective	MCPHR
Calafiore[32]	2004	University Hospital, Torino, Italy and "G D'Annunzio" University, Chieti, Italy	1986–1999	Isolated primary CABG in patients <75 years old	Retrospective	PSM
Carrier[33]	2009	Montreal Heart Institute, Montreal, Quebec, Canada	1995–2007	Isolated primary CABG	Retrospective	MCPHR
Dalén[34]	2014	Nationwide population-based cohort study (Sweden)	1997–2008	Isolated primary CABG	Retrospective	PSM
Danzer[35]	2001	University Hospital, Geneva, Switzerland	1983–1989	Isolated primary CABG	Retrospective	NA
Dewar[36]	1995	Vancouver Hospital and Health Sciences Centre, University of British Columbia, Vancouver, Canada	1984–1992	Isolated primary CABG	Retrospective	Univariate regression
Endo[37]	2001	Tokyo Women's Medical University, Tokyo, Japan	1985–1998	Isolated primary CABG	Retrospective	MCPHR
Gansera 2004[38]	2004	Klinikum Bogenhausen, Munich, Germany	1997–1999	Isolated primary CABG	Retrospective	NA
Gansera 2017[39]	2017	Klinikum Bogenhausen, Munich, Germany	2000–2011	Isolated CABG in diabetic patients, <65 years old	Retrospective	PSM
Grau[40]	2015	The Valley Columbia Heart Center, Columbia University College of Physicians and Surgeons, Ridgewood, NJ, USA	1994–2013	Isolated CABG	Retrospective	PSM
Hirotani[41]	2003	Tokyo Saiseikai Central Hospital, Minato-Ku, Tokyo, Japan	1991–2003	Isolated primary CABG in diabetic patients	Retrospective	NA
Itoh[42]	2016	Saitama Medical Center, Jichi Medical University, Saitama, Japan	1990–2014	Isolated CABG in patients ≥ 75 years old	Retrospective	PSM
Johnson[43]	1989	Milwaukee Heart Surgery Associates, S.C., and St. Mary's Hospital, Milwaukee, WI, USA	1972–1986	Isolated CABG	Retrospective	NA (patients matched with the general US population)
Jones[44]	2000	Baylor College of Medicine and Veterans Affairs Medical center, Houston, TX, USA	1986–1996	Isolated primary CABG in patients >65 years old	Retrospective	NA

Continued

DOI: 10.1161/JAHA.117.008010

Table 1. Continued

Study	Year	Center	Study Period	Setting	Type of Study	Adjustment Performed
Joo[45]	2012	Yonsei Cardiovascular Hospital, Seoul, Republic of Korea	2000–2009	Isolated OPCAB	Retrospective	PSM
Kelly[46]	2012	Queen Elizabeth II Health Sciences Center, Halifax, Nova Scotia, Canada	1995–2007	Isolated primary CABG	Retrospective	Non-parsimonious MCPHR including PS quintiles
Kieser[47]	2011	The Province of Alberta, Canada	1995–2008	Isolated primary CABG	Retrospective	MCPHR
Kinoshita[48]	2015	Shiga University of Medical Science, Otsu, Japan	2002–2014	Isolated CABG-patients stratified by GFR	Retrospective	PSM
Kurlansky[49]	2010	Florida Heart Research Institute, Miami, FL, USA	1972–1994	Isolated CABG	Retrospective	PSM
Locker[50]	2012	Mayo Clinic, Rochester, MN, USA	1993–2009	Isolated primary CABG	Retrospective	PSM and MCPHR
Lytle[51]	2004	The Cleveland Clinic Foundation, Cleveland, OH, USA	1971–1989	Isolated primary CABG	Retrospective	PSM
Medalion[52]	2015	Tel Aviv Sourasky Medical Center, Tel Aviv, Israel	1996–2008	isolated CABG in patients ≥70 years old	Retrospective	PSM
Mohammadi[53]	2014	Quebec Heart and Lung Institute, Quebec City, Canada	1991–2011	Isolated primary CABG in patients with EF ≤40%	Retrospective	PSM
Nasso[54]	2012	Multicenter	2003–2008	Isolated primary CABG	Retrospective	PSM
Naunheim[55]	1992	St. Louis University Medical Center, St. Louis, MS, USA	1972–1975	Isolated CABG	Retrospective	NA
Navia[56]	2016	Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina	1996–2014	Isolated CABG	Retrospective	PSM
Parsa[57]	2013	Duke University Medical Center, Durham, NC, USA	1984–2009	Isolated CABG	Prospective	MCPHR
Pettinari[58]	2015	Ziekenhuis Oost Limburg, Genk, Belgium and University Hospitals Leuven, Leuven, Belgium	1972–2006	Isolated CABG in patients ≥70 years old	Retrospective	PSM
Pick[59]	1997	Mayo Clinic, Rochester, MN, USA	1983–1986	Isolated CABG	Retrospective	MCPHR
Rosenblum[60]	2016	Emory University School of Medicine, Atlanta, GA, USA	2003–2013	Isolated primary CABG	Retrospective	PSM
Schwann[61]	2016	Multicenter	1987–2011	Isolated CABG	Retrospective	PSM
Stevens[62]	2004	Montreal Heart Institute, Montreal, Quebec, Canada	1985–1995	Isolated primary CABG	Retrospective	MCPHR including PS
Tarelli[63]	2001	Varese Hospital, Varese, Italy	1988–1990	Isolated CABG	Retrospective	NA
Toumpoulis[64]	2006	St. Luke's–Roosevelt Hospital Center at Columbia University, NY, USA	1992–2002	Isolated CABG in diabetic patients	Retrospective	MCPHR in PS-matched patients

CABG indicates coronary artery bypass grafting; MCPHR, multivariable Cox proportional hazards regression; NA, not applicable; NR, not reported; NS, not specified; OPCAB, off-pump coronary artery bypass; PS, propensity score; PSM, propensity-score matching.

Table 2. Overview of the Studies Included in the Primary Analysis

Study	Overall Population, n	UNM BITA, n	UNM SITA, n	PSM BITA, n	PSM SITA, n	Mean/Median Follow-up (Y)	Completeness of Follow-up
Ashraf[27]	300	150	150	NA	NA	Median (IQR) BITA: 1.9 (1.3–2.6) Median (IQR) SITA: 2.3 (1.7–3)	NR
Benedetto[28]	4195	750	3445	750	750	4.8±3.2 (PSM sample)	100%
Berreklouw[29]	482	NA	NA	249	233	BITA: 9.7±2.7 SITA: 10.1±2.4	94%
Bonacchi[30]	652	NA	NA	320	332	5.6±1.4	99.7%
Buxton[31]	2853	1296	1557	NA	NA	4.3	95.9%
Calafiore[32]	1602	1026	576	570	570	Overall: 7.3±4.8 BITA: 7.1±5.0 SITA: 7.5±4.7	100%
Carrier[33]	6655	Statin+: 1166 Statin−: 69	Statin+: 4835 Statin−: 585	NA	NA	10	99%
Dalén[34]	49 702	559	49 143	558	558	7.5	100%
Danzer[35]	521	382	139	NA	NA	10	97.5%
Dewar[36]	1142	377	765	NA	NA	4	NR
Endo[37]	1131	443	688	NA	NA	6.2	99.3%
Gansera 2004[38]	1378	716	662	NA	NA	5.3	NR
Gansera 2017[39]	250	NA	NA	125	125	9.3±3.5	100%
Grau[40]	6666	1544	5122	1006	1006	Overall: 10.5±5 BITA: 10.9±5 SITA: 10.1±5	100%
Hirotani[41]	303	179	124	NA	NA	NR	95%
Itoh[42]	400	107	293	98	196	9.0±5.8	95.6%
Johnson[43]	2014	576	1438	NA	NA	NR	100%
Jones[44]	510	172	338	NA	NA	5.0±3.1	100%
Joo[45]	1749	392	1357	366	366	Overall: 7.0±2.0 BITA: 6.9±2.1 SITA: 7.1±2.7	98.1%
Kelly[46]	7633	1079	6554	NA	NA	BITA: 5.4 SITA: 4.6	NR
Kieser[47]	5067	1038	4029	NA	NA	Overall: 7 BITA: 6.4±3.2 SITA: 7.1±3.4	NR
Kinoshita[48]	1203	750	453	412	412	PSM BITA: 5.6±3.3 PSM SITA: 4.9±3.2	99%
Kurlansky[49]	4584	2215	2369	Quintiles	Quintiles	Overall: 11.5 BITA: 12.7 SITA: 11.1	BITA=96.7% SITA=98.3%
Locker[50]	8295	BITA only: 271 BITA/SVG: 589	7435	NR	NR	7.6±4.6	100%
Lytle[51]	10 124	2001	8123	1152	1152	BITA: 16.2±2.4 SITA: 16.3±2.5	100%
Medalion[52]	1627	1045	582	NA	NA	8.2±4.5	98%
Mohammadi[53]	1795	129	1666	111	111	Overall PSM: 8.0±5.3 PSM BITA: 8.6±5.1 PSM SITA: 7.7±5.5	92.7%

Continued

Table 2. Continued

Study	Overall Population, n	UNM BITA, n	UNM SITA, n	PSM BITA, n	PSM SITA, n	Mean/Median Follow-up (Y)	Completeness of Follow-up
Nasso[54]	8054	4088	3966	3584	3584	3.1	98%
Naunheim[55]	365	100	265	100	100	NR	96.5%
Navia[56]	2486	2098	388	485	NR	Median: 5.5 (IQR: 2.6–8.8)	95%
Parsa[57]	17 609	728	16 881	NA	NA	NR	100%
Pettinari[58]	3496	1328	2168	892	892	3.1	100%
Pick[59]	321	NA	NA	160	161	9.8±2.8	100%
Rosenblum[60]	8254	873	7381	306	306	Median: 2.8 (IQR: 1.1–4.9)	100%
Schwann[61]	5125	641	4484	551	551	NR	100%
Stevens[62]	4382	1835	2547	NA	NA	Overall: 11±3 BITA: 8±2 SITA: 12±3	98%
Tarelli[63]	300	150	150	NA	NA	Overall: 9.2 BITA: 9.2±2.8 SITA: 9.1±2.5	100%
Toumpoulis[64]	980	NA	NA	490	490	4.7±3.0	99.1%

BITA indicates bilateral internal thoracic arteries; IQR, interquartile range; NA, not applicable; NR, not reported; PSM, propensity-score matched; SITA, single internal thoracic artery; SVG, saphenous vein graft.

SITA: 60 versus 64.1 years; female sex, BITA versus SITA: 16% versus 20.8%; diabetes mellitus, BITA versus SITA: 32.2% versus 40.5%; chronic obstructive pulmonary disease, BITA versus SITA: 9.6% versus 11.8%; Table S2).

Long-Term All-Cause Mortality

Mean follow-up time across the 38 studies was 7.25 years (range, 2.1–16.3). The overall mortality rate at the end of follow-up was 28.03±18.4% in the BITA versus 39.96±23.5% in the SITA series.

Use of BITA was associated with a statistically significant reduction of mortality at the end of follow-up when compared with SITA (IRR, 0.74; 95% CI, 0.69–0.80; $P<0.001$; $I^2=71\%$; Figure 1A[27–64] and Figure S2). This finding was consistent across the general population and all the specific patient subgroups and all the study designs (Figures S3 through S5) and was not influenced by age, sex, diabetes mellitus, and ejection fraction (Figure 2).

One-Year All-Cause Mortality in the PSM Populations

Mean follow-up time of the 12 PSM studies was 7.41±4.4 years, and the number of patients included was 34 019. Use of BITA was associated with a similar reduction of mortality at 1-year and at the end of follow-up (IRR, 0.70; 95% CI, 0.60–0.82 at 1 year versus IRR, 0.77; 95% CI, 0.70–0.85 at the end of follow-up; *P* for subgroup differences=0.43; Figure 3)* (details of the statistical analysis for the PSM studies included in this analysis are summarized in Table S3). These findings were robust in a leave-one-out analysis (Figure 4).†

Publication Bias and Internal Validity Appraisal

Study quality was high across all studies included in the primary analysis (Table S4). Overall heterogeneity was high both at 1-year analysis in the PSM studies ($I^2=51\%$) and at end of follow-up in the overall studies analysis ($I^2=71\%$). Publication bias was low, as assessed by funnel plots, for all-cause mortality in the primary analysis (Figure 5).

An overview of the results of all the analyses is provided in Table S5.

Discussion

For almost 25 years, the concept that the use of BITA is associated with improved survival after coronary artery bypass surgery has been accepted in the cardiovascular community. This concept is almost completely based on observational studies.

To date, at least 60 English-language observational studies comparing the clinical outcome of BITA and SITA patients

*References 28, 32, 34, 40, 45, 46, 49, 51, 54, 60–62.
†References 28, 32, 34, 40, 45, 46, 49, 51, 54, 60–62.

A

Study name	Point (raw)	Lower limit	Upper limit	Z-Value	p-Value
Ashraf 1994[27]	1.211	0.024	61.009	0.096	0.924
Benedetto 2014[28]	0.610	0.382	0.975	-2.067	0.039
Berreklouw 2001[29]	0.780	0.490	1.241	-1.050	0.294
Bonacchi 2006[30]	0.670	0.194	2.310	-0.634	0.526
Buxton 1998[31]	0.483	0.406	0.574	-8.219	0.000
Calafiore 2004[32]	0.778	0.548	1.105	-1.402	0.161
Carier (Statin +) 2009[33]	0.925	0.681	1.256	-0.499	0.618
Carrier (Statin -) 2009[33]	0.646	0.511	0.817	-3.651	0.000
Dalen 2014[34]	0.950	0.871	1.036	-1.158	0.247
Danzer 2001[35]	0.572	0.293	1.118	-1.635	0.102
Dewar 1995[36]	1.300	0.912	1.853	1.451	0.147
Endo 2001[37]	0.950	0.669	1.348	-0.287	0.774
Gansera 2004[38]	0.571	0.380	0.860	-2.684	0.007
Gansera 2016[39]	0.484	0.333	0.703	-3.801	0.000
Grau 2015[40]	0.707	0.536	0.933	-2.452	0.014
Hirotani 2003[41]	1.200	0.473	3.047	0.383	0.701
Itoh 2016[42]	0.654	0.433	0.986	-2.029	0.042
Johnson 1989[43]	0.767	0.640	0.919	-2.876	0.004
Jones 2000[44]	0.750	0.577	0.974	-2.153	0.031
Joo 2012[45]	0.933	0.636	1.369	-0.355	0.723
Kelly 2012[46]	0.818	0.672	0.996	-2.001	0.045
Kieser 2011[47]	0.460	0.371	0.571	-7.046	0.000
Kinoshita 2015[48]	0.570	0.379	0.858	-2.697	0.007
Kurlansky 2010[49]	0.792	0.742	0.844	-7.085	0.000
Locker (BITA only) 2012[50]	0.800	0.551	1.162	-1.172	0.241
Locker (BITA/SV) 2012[50]	0.730	0.568	0.937	-2.466	0.014
Lytle 2004[51]	0.805	0.721	0.898	-3.882	0.000
Medalion 2015[52]	0.826	0.712	0.959	-2.515	0.012
Mohammadi 2014[53]	0.700	0.388	1.262	-1.186	0.236
Nasso 2012[54]	0.699	0.612	0.800	-5.227	0.000
Naunheim 1992[55]	0.881	0.566	1.370	-0.562	0.574
Navia 2016[56]	0.535	0.437	0.656	-6.048	0.000
Parsa 2013[57]	0.950	0.833	1.084	-0.763	0.445
Pettinari 2015[58]	0.787	0.643	0.964	-2.311	0.021
Pick 1997[59]	0.820	0.503	1.335	-0.799	0.424
Rosenblum 2016[60]	0.743	0.403	1.369	-0.953	0.341
Schwann 2016[61]	0.606	0.471	0.780	-3.891	0.000
Stevens 2004[62]	0.650	0.529	0.799	-4.103	0.000
Tarelli 2001[63]	1.012	0.587	1.744	0.044	0.965
Toumpoulis 2006[64]	0.890	0.692	1.144	-0.909	0.363
	0.740	0.689	0.795	-8.262	0.000

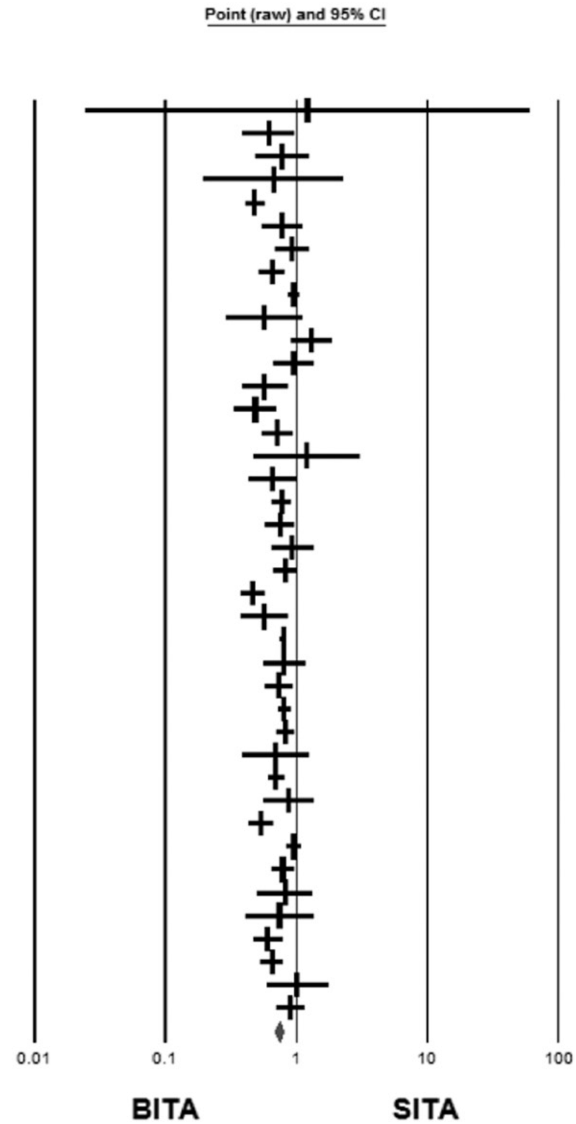


Figure 1. A, Forest plot comparing the effect of the use of BITA vs SITA on end of follow-up mortality across all the included studies (38 studies; 174 205 patients). B, Cumulative analysis of all the included studies using random-effect model (38 studies; 174 205 patients). BITA indicates bilateral internal thoracic artery; CI, confidence interval; SITA, single internal thoracic artery. Incident rate ratio (IRR) is used.

have been published (Figure S1). The overwhelming majority of these have shown better outcomes in the BITA treatment group. Several reports have also suggested that the advantages of BITA grafting could be extended to females,[65] diabetics,[66] and patients with chronic renal insufficiency.[48] Over time, this evidence has been summarized in 6 meta-analyses.[4–9] All of them showed a significant and similar survival advantage, as measured by the HR, for the use of BITA (see Table 3).[4–9]

Our analysis pools data from 38 of these studies and 174 205 patients and confirms the previous findings (Table 3).[4–9] We used IRRs instead of HR or relative risk ratio to account for potential differences in follow-up duration within studies and between studies. We confirmed better long-term survival for BITA compared with SITA (IRR, 0.74; 95% CI, 0.69–0.80; $P<0.001$; Figure 1A).[27–64] This difference was evident independently from the patient population included and the methodology used (Figures S3 through S5). The benefit was uncertain from 1989 to 2000, was consistently significant at the 0.05 level starting in 2001, and crossed the 0.01 and 0.001 levels in 2004 (Figure 1B).[27–64]

Basing on these data, the current US[10] and European[11] Guidelines encourage the use of a second arterial graft in patients with a long life expectancy, and last year the Society of Thoracic Surgeons published a position paper strongly encouraging a wider use of arterial grafts.[12]

B

Study name	Cumulative statistics				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Johnson 1989 [43]	0.767	0.640	0.919	-2.876	0.004
Naunheim 1992 [55]	0.782	0.662	0.925	-2.875	0.004
Ashraf 1994 [27]	0.783	0.663	0.925	-2.869	0.004
Dewar 1995 [36]	0.936	0.687	1.276	-0.417	0.677
Pick 1997 [59]	0.906	0.714	1.150	-0.813	0.416
Buxton 1998 [31]	0.794	0.563	1.120	-1.316	0.188
Jones 2000 [44]	0.781	0.591	1.032	-1.737	0.082
Danzer 2001 [35]	0.760	0.586	0.985	-2.075	0.038
Berreklouw 2001 [29]	0.761	0.601	0.964	-2.266	0.023
Tarelli 2001 [63]	0.779	0.622	0.976	-2.173	0.030
Endo 2001 [37]	0.795	0.645	0.981	-2.138	0.033
Hirotani 2003 [41]	0.807	0.657	0.991	-2.042	0.041
Gansera 2004 [38]	0.783	0.646	0.949	-2.490	0.013
Lytle 2004 [51]	0.781	0.666	0.915	-3.051	0.002
Calafiore 2004 [32]	0.779	0.672	0.904	-3.291	0.001
Stevens 2004 [62]	0.764	0.667	0.876	-3.873	0.000
Bonacchi 2006 [30]	0.763	0.667	0.872	-3.972	0.000
Toumpoulis 2006 [64]	0.771	0.680	0.875	-4.027	0.000
Carier (Statin +) 2009 [33]	0.780	0.691	0.881	-4.015	0.000
Carrier (Statin -) 2009 [33]	0.769	0.686	0.862	-4.504	0.000
Kurlansky 2010 [49]	0.766	0.697	0.843	-5.482	0.000
Kieser 2011 [47]	0.745	0.671	0.828	-5.507	0.000
Locker (BITA only) 2012 [50]	0.747	0.675	0.827	-5.646	0.000
Locker (BITA/SV) 2012 [50]	0.746	0.677	0.821	-5.964	0.000
Nasso 2012 [54]	0.741	0.678	0.810	-6.569	0.000
Kelly 2012 [46]	0.744	0.684	0.811	-6.779	0.000
Joo 2012 [45]	0.749	0.689	0.815	-6.748	0.000
Parsa 2013 [57]	0.761	0.700	0.827	-6.427	0.000
Dalen 2014 [34]	0.772	0.710	0.839	-6.114	0.000
Benedetto 2014 [28]	0.768	0.707	0.834	-6.304	0.000
Mohammadi 2014 [53]	0.767	0.707	0.832	-6.416	0.000
Kinoshita 2015 [48]	0.762	0.703	0.825	-6.644	0.000
Grau 2015 [40]	0.760	0.702	0.822	-6.877	0.000
Medalion 2015 [52]	0.763	0.708	0.822	-7.099	0.000
Pettinari 2015 [58]	0.764	0.710	0.821	-7.313	0.000
Navia 2016 [56]	0.754	0.700	0.811	-7.522	0.000
Gansera 2016 [39]	0.746	0.693	0.804	-7.744	0.000
Itoh 2016 [42]	0.744	0.692	0.801	-7.916	0.000
Schwann 2016 [61]	0.740	0.688	0.795	-8.184	0.000
Rosenblum 2016 [60]	0.740	0.689	0.795	-8.262	0.000
	0.740	0.689	0.795	-8.262	0.000

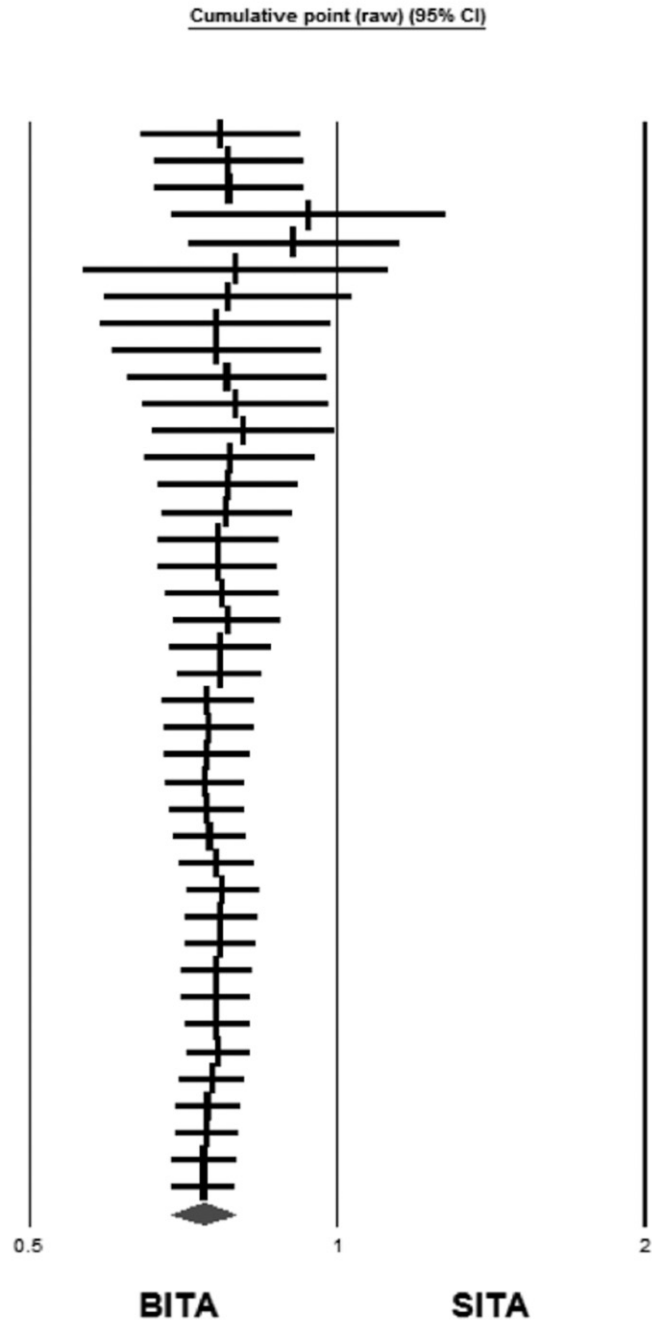


Figure 1. Continued

It must, however, be noted that the results of the observational studies have not been confirmed in the randomized comparisons. The 4 RCTs that have compared BITA and SITA to date have all failed to show a survival difference between the 2 revascularization strategies.[13–16] Two of the RCTs were small, with less than 100 patients in each arm, and had limited follow-up, so that they were probably underpowered to detect moderate differences.[13,14] Another study was moderate in size (Stand-in-Y,[15] 800 patients) and the most recent, the ART trial,[16] included more than 3000 patients.

The Stand-in-Y Mammary study compared the outcomes of 800 patients randomized to receive BITA using 2 different configurations: SITA and radial artery or SITA and saphenous vein.[15] At a mean follow-up of 24.1±9.8 months, no difference in survival was found between the BITA and SITA groups (P=0.62; odds ratio, 0.63; 95% CI, 0.27–1.47), although

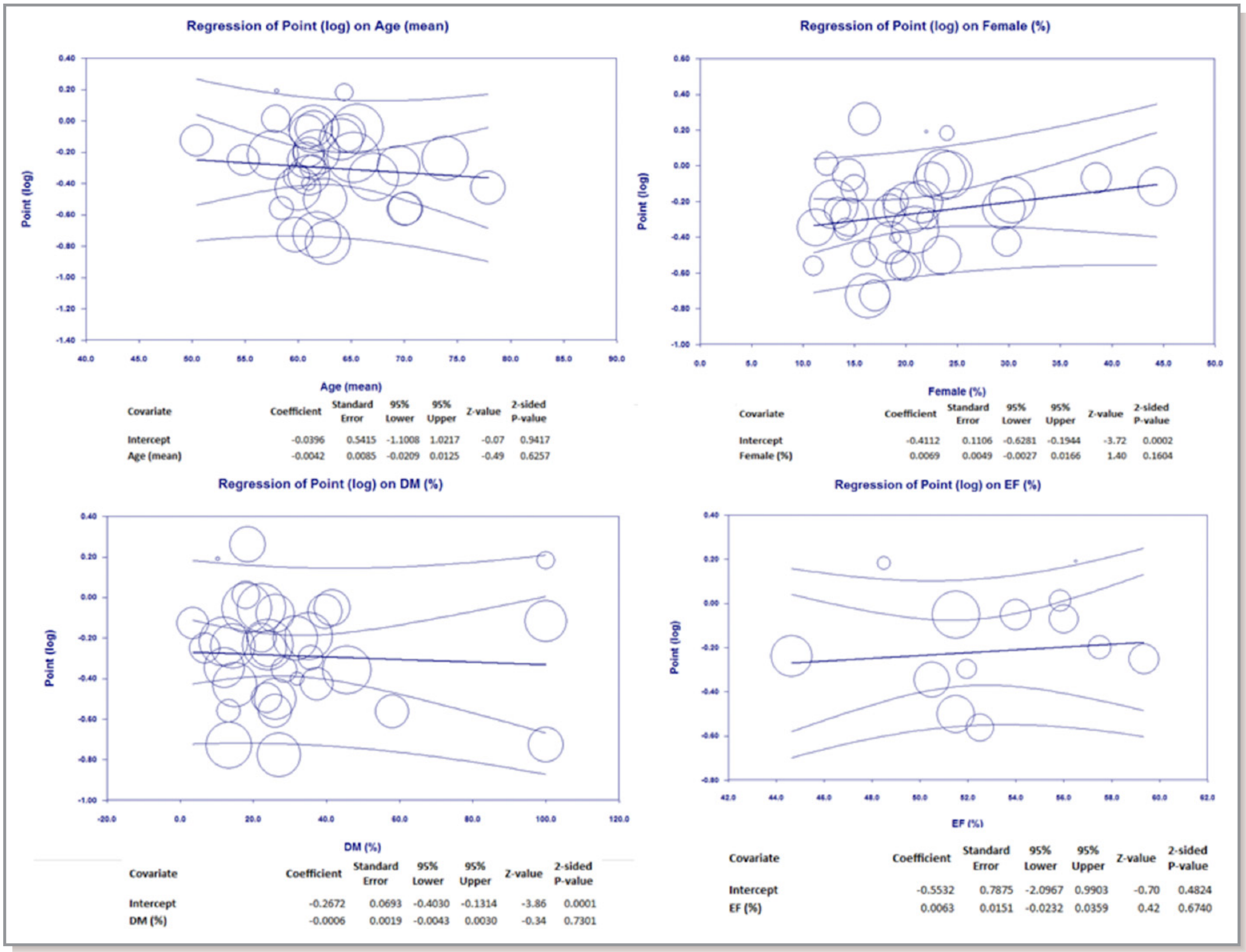


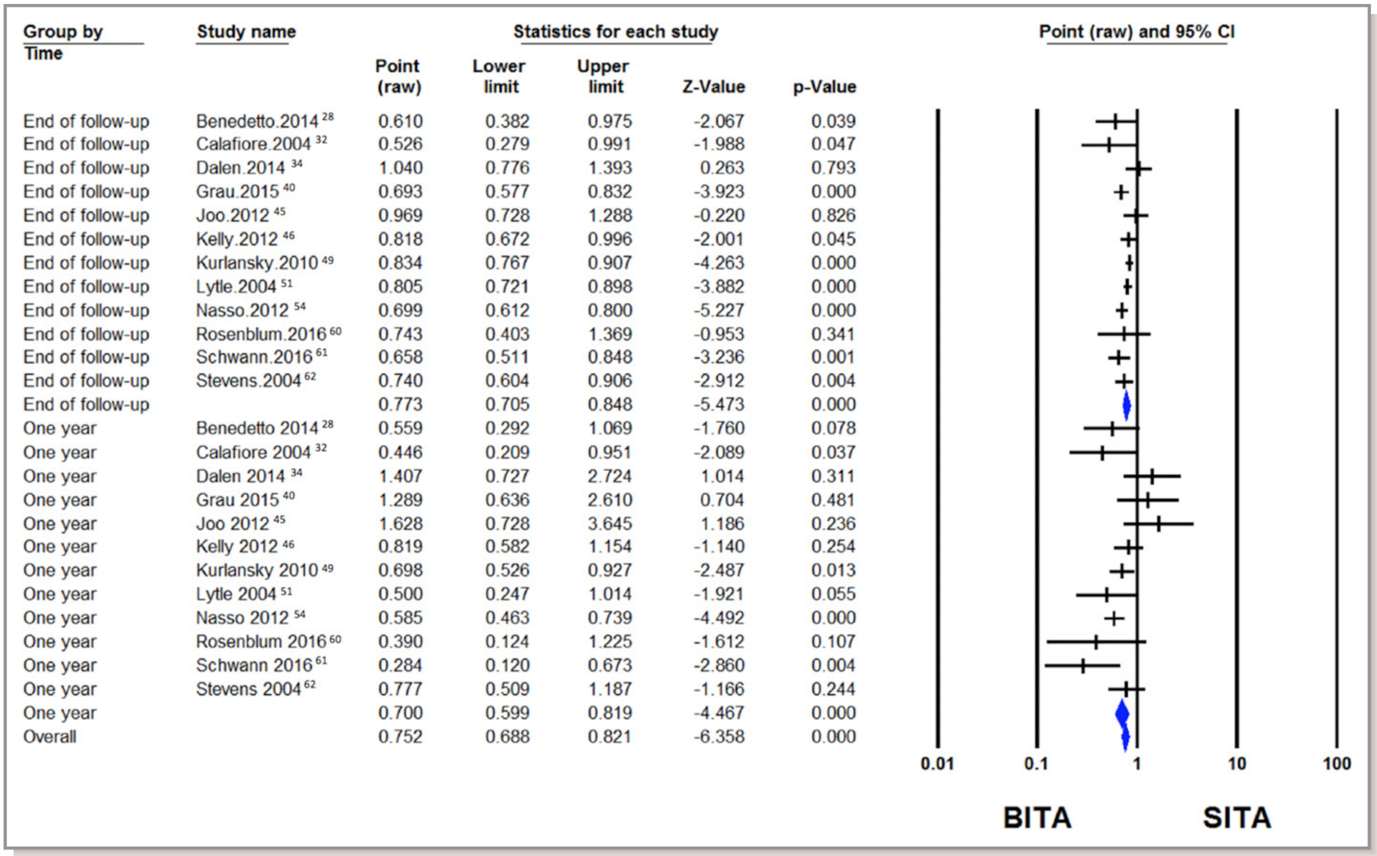
Figure 2. Results of the metaregression analyses. Univariate metaregression analysis showed that the effect of BITA was not influenced by age (slope *P* value=0.625; intercept *P* value=0.941), sex (slope *P* value=0.160; intercept *P* value=0.0002), diabetes mellitus (slope *P* value=0.730; intercept *P* value=0.0001), and ejection fraction (slope *P* value=0.674; intercept *P* value=0.482). Similarly, multivariate metaregression analysis showed that the effect of BITA was not influenced by age (slope *P* value=0.270), sex (slope *P* value=0.412), diabetes mellitus (slope *P* value=0.848), and ejection fraction (slope *P* value=0.644) with intercept *P* value=0.487 (plot not shown). BITA indicates bilateral internal thoracic artery; DM, diabetes mellitus; EF, ejection fraction.

patients with arterial grafts had better cardiac event–free survival (Wilcoxon test, $P<0.0001$).

The ART trial randomized 3102 patients to receive 1 or 2 internal thoracic arteries.[16] The primary end point is overall survival, and the study was designed to be able to detect a 20% reduction in the primary end point at 10 years. At a planned 5-year interim analysis, no difference in survival (91.3% in the BITA group and 91.6% in the SITA group; HR, 1.04; CI, 0.81–1.32) or in the composite of mortality, myocardial infarction, and/or stroke (12.2% BITA versus 12.7% SITA; HR, 0.96; CI, 0.79–1.17) was found between groups.

Several methodological flaws in the design of the RCTs can partially explain the variance between the results of the randomized and observational studies. All the RCTs were limited to mid-term follow-up, and it is known the attrition rate of saphenous grafts remains low at 5 years[19]; it is possible that a difference between the groups would have become apparent with further follow-up. There are additional considerations specifically regarding the ART study that may explain a negative result. A sizeable proportion (23%) of patients randomized to SITA also received a radial artery as an additional arterial graft. There was a high rate of crossover in the group allocated to BITA (16.4%). There was very high compliance with optimal medical therapy in both groups (90% of patients on aspirin, beta-blockers, and statins). Finally, there was a treatment age interaction that approached statistical significance, favoring BITA in patients aged <70 years whereas BITA appeared harmful in patients aged >70.

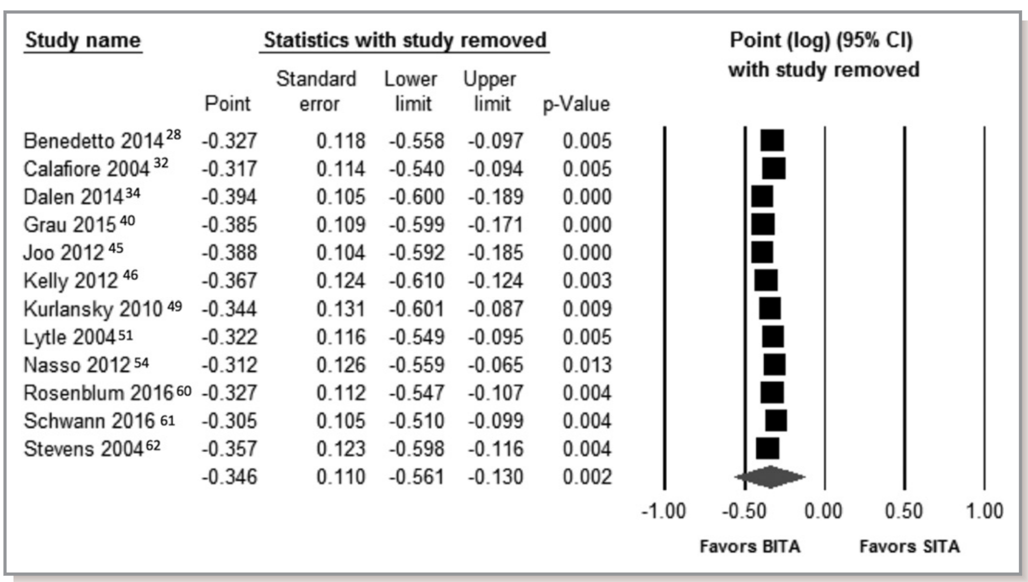
There are, however, biological reasons in support of the results of the RCTs. A second arterial conduit to a non-LAD



Group by Time	Study name	Point (raw)	Lower limit	Upper limit	Z-Value	p-Value
End of follow-up	Benedetto.2014[28]	0.610	0.382	0.975	-2.067	0.039
End of follow-up	Calafiore.2004[32]	0.526	0.279	0.991	-1.988	0.047
End of follow-up	Dalen.2014[34]	1.040	0.776	1.393	0.263	0.793
End of follow-up	Grau.2015[40]	0.693	0.577	0.832	-3.923	0.000
End of follow-up	Joo.2012[45]	0.969	0.728	1.288	-0.220	0.826
End of follow-up	Kelly.2012[46]	0.818	0.672	0.996	-2.001	0.045
End of follow-up	Kurlansky.2010[49]	0.834	0.767	0.907	-4.263	0.000
End of follow-up	Lytle.2004[51]	0.805	0.721	0.898	-3.882	0.000
End of follow-up	Nasso.2012[54]	0.699	0.612	0.800	-5.227	0.000
End of follow-up	Rosenblum.2016[60]	0.743	0.403	1.369	-0.953	0.341
End of follow-up	Schwann.2016[61]	0.658	0.511	0.848	-3.236	0.001
End of follow-up	Stevens.2004[62]	0.740	0.604	0.906	-2.912	0.004
End of follow-up		0.773	0.705	0.848	-5.473	0.000
One year	Benedetto 2014[28]	0.559	0.292	1.069	-1.760	0.078
One year	Calafiore 2004[32]	0.446	0.209	0.951	-2.089	0.037
One year	Dalen 2014[34]	1.407	0.727	2.724	1.014	0.311
One year	Grau 2015[40]	1.289	0.636	2.610	0.704	0.481
One year	Joo 2012[45]	1.628	0.728	3.645	1.186	0.236
One year	Kelly 2012[46]	0.819	0.582	1.154	-1.140	0.254
One year	Kurlansky 2010[49]	0.698	0.526	0.927	-2.487	0.013
One year	Lytle 2004[51]	0.500	0.247	1.014	-1.921	0.055
One year	Nasso 2012[54]	0.585	0.463	0.739	-4.492	0.000
One year	Rosenblum 2016[60]	0.390	0.124	1.225	-1.612	0.107
One year	Schwann 2016[61]	0.284	0.120	0.673	-2.860	0.004
One year	Stevens 2004[62]	0.777	0.509	1.187	-1.166	0.244
One year		0.700	0.599	0.819	-4.467	0.000
Overall		0.752	0.688	0.821	-6.358	0.000

Figure 3. Forest plot comparing the effect of the use of BITA vs SITA on end of follow-up (top) and 1-year (bottom) mortality in PSM studies in the general population (12 studies; 34 019 patients). BITA indicates bilateral internal thoracic artery; CI, confidence interval; PSM, propensity-score matched; SITA, single internal thoracic artery. Incident rate ratio (IRR) is used.

target has less potential to impact on overall survival than the single left internal thoracic artery to the LAD. Solid evidence suggests, in fact, that in coronary artery bypass surgery, patient survival is mainly determined by the status of the LAD and that grafts to non-LAD vessels are more likely to affect other cardiac end points (myocardial infarction, angina recurrence, and need



Study name	Point	Standard error	Lower limit	Upper limit	p-Value
Benedetto 2014[28]	-0.327	0.118	-0.558	-0.097	0.005
Calafiore 2004[32]	-0.317	0.114	-0.540	-0.094	0.005
Dalen 2014[34]	-0.394	0.105	-0.600	-0.189	0.000
Grau 2015[40]	-0.385	0.109	-0.599	-0.171	0.000
Joo 2012[45]	-0.388	0.104	-0.592	-0.185	0.000
Kelly 2012[46]	-0.367	0.124	-0.610	-0.124	0.003
Kurlansky 2010[49]	-0.344	0.131	-0.601	-0.087	0.009
Lytle 2004[51]	-0.322	0.116	-0.549	-0.095	0.005
Nasso 2012[54]	-0.312	0.126	-0.559	-0.065	0.013
Rosenblum 2016[60]	-0.327	0.112	-0.547	-0.107	0.004
Schwann 2016[61]	-0.305	0.105	-0.510	-0.099	0.004
Stevens 2004[62]	-0.357	0.123	-0.598	-0.116	0.004
	-0.346	0.110	-0.561	-0.130	0.002

Figure 4. Leave-one-out analysis for 1-year mortality among PSM studies (12 studies). BITA indicates bilateral internal thoracic artery; CI, confidence interval; PSM, propensity-score matched; SITA, single internal thoracic artery. Incident rate ratio (IRR) is used.

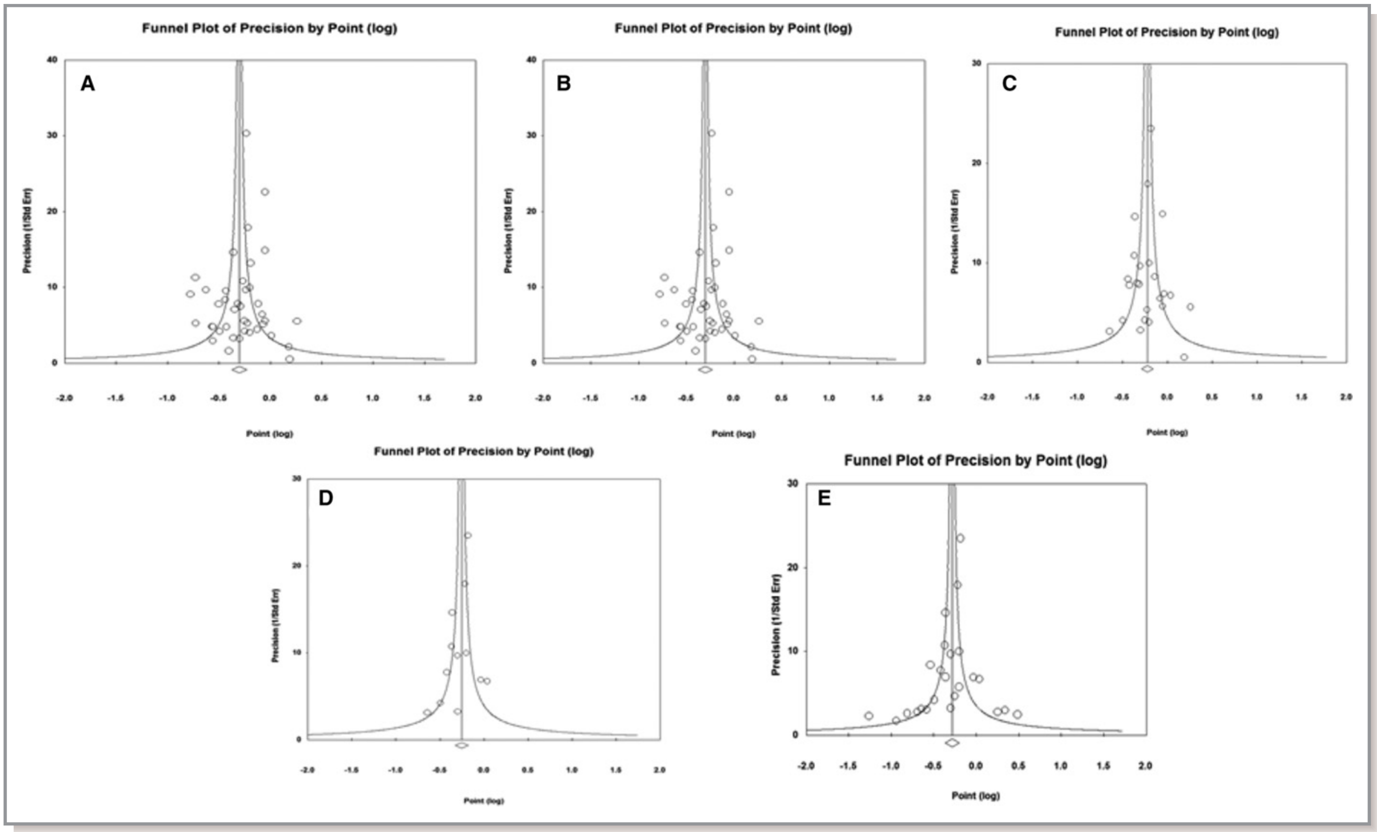


Figure 5. Publication bias as assessed by funnel plots for all-cause mortality in the primary analysis. A, All included studies. B, Studies performed in the general population vs studies performed in specific subpopulations. C, Unadjusted studies vs adjusted studies. D, PSM studies vs adjusted non-PSM studies. E, PSM studies at 1-year follow-up vs PSM studies at end of follow-up. PSM indicates propensity-score matched.

for revascularization), but not overall survival.[27–29] The LAD also can provide collaterals to other coronaries (commonly the right coronary); a persistently patent internal thoracic artery graft to the LAD can therefore supply not only the anterior wall, but, through collaterals, viable myocardium in other territories. Last, patency of grafts to the LAD generally exceed the patency of grafts to non-LAD vessels.[3]

Our hypothesis, however, is that the difference in results between the RCTs and the observational evidence is attributed to unmeasured confounders and not to the difference in revascularization strategy.

In order to test this hypothesis, we repeated the BITA versus SITA comparison at 1 year, when the attrition rate of the SVGs is still low and a survival difference attributable to a difference in graft patency is unlikely.

Because PSM studies are considered the observational studies less prone to confounders, we decided to limit the 1-year analysis to PSM studies only.

Table 3. Published Meta-Analyses of the Observational Evidence on the BITA vs SITA Comparison

First Author, Year	Studies Included in Survival Analysis, n	Patients Included in Survival Analysis, n	Type of Observational Studies Included	Patient Populations Excluded by Inclusion Criteria	HR in Favor of BITA
Taggart, 2001[5]	7	15 962	All	None	0.81 [95% CI 0.70–0.94]
Rizzoli, 2002[4]	7	15 299	All	High-risk patients, emergencies, diabetics	0.79 [95% CI 0.66–0.91]
Weiss, 2013[7]	27	79 063	All	None	0.78 [95% CI 0.72–0.84]
Takagi, 2014[6]	20	70 897	Adjusted	None	0.80 [95% CI 0.77–0.84]
Yi, 2014[8]	9	15 583	Adjusted	None	0.79 [95% CI 0.75–0.84]
Buttar, 2017[9]	29	89 399	All	None	0.78 [95% CI 0.72–0.84]

BITA indicates bilateral internal thoracic artery; HR, hazard ratio; PSM, propensity-score matched; UNM, unmatched.

In fact, PSM series constitute a large amount of the current evidence in the surgical fields.[20] The PSM process is thought to be able to minimize differences in the preoperative risk profile of the patients, and PSM studies are often quoted as the best level of evidence after RCTs.[20]

We found that the relative survival advantage attributed to the BITA group at 1 year was similar to that observed at late follow-up (Figure 3).[‡]

This finding suggests that factors not related to the conduit patency, such as the patients' general status or quality of the target vessels, played a role in determining the outcome and that unmatched biases are present even in PSM studies.

The use of the BITA increases the complexity and invasiveness of the procedure. It is likely that surgeons tend to reserve this operation for the patients perceived as healthier and with longer life expectancy from a cardiac and a general health perspective. A bias may also exist in terms of the graftability and location of the target vessels. This type of "eye-balling" or clinical acumen based on the individual surgeon's experience is very difficult to quantify; the statistics can only be adjusted for the measured, and not for the unmeasured, confounders. Our findings elicit concerns on the ability of the propensity-matching process to overcome treatment allocation biases in observational studies and assure comparability between groups.

Limitations

This analysis shares the common limitations of meta-analysis of observational data, although the funnel plots do not indicate important publication bias.

In addition, the different studies included different surgical techniques (on- versus off-pump) and grafting strategies (single versus composite grafts) as well as different definitions and matching algorithms, so that the homogeneity of the included population cannot be regarded as optimal.

In most of the series, the 1-year IRR was not specified in the original study and had to be derived using the described statistical methods.

Upon careful review of the methods of the PSM studies, we could not confer that the original studies adjusted the variance estimates appropriately for the matched nature of the data in the original studies (Table S3). That said, the HRs would still be correct, and the leave-one-out analysis was consistent with the overall findings.

Finally, given that we included only articles in English, a language bias cannot be excluded, although there are no plausible biological reasons to support it.

[‡]References 28, 32, 34, 40, 45, 46, 49, 51, 54, 60–62.

Conclusions

In conclusion, the present meta-analysis challenges the benefit traditionally attributed to BITA grafting. The fact that, even in the PSM series, BITA patients exhibit a significant survival advantage at 1-year follow-up suggests that unmeasured confounders may account for the reported survival benefit of BITA in the observational series.

In addition, our results suggest that even our best statistical methods to minimize baseline demographic differences in observational studies have major limitations.

Later reporting of the clinical outcomes of ART and new randomized studies are needed to clarify the effect of BITA grafting in patients undergoing CABG.

Sources of Funding

Prof Fremes is partially supported by the Bernard S. Goldman Chair in Cardiovascular Surgery.

Disclosures

Prof Fremes is supported, in part, by the Bernard S. Goldman Chair in Cardiovascular Surgery. The remaining authors have no disclosures to report.

References

1. Loop FD, Lytle BW, Cosgrove DM, Stewart RW, Goormastic M, Williams GW, Golding LA, Gill CC, Taylor PC, Sheldon WC. Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. *N Engl J Med*. 1986;314:1–6.
2. Lytle BW, Blackstone EH, Loop FD, Houghtaling PL, Arnold JH, Akhrass R, McCarthy PM, Cosgrove DM. Two internal thoracic artery grafts are better than one. *J Thorac Cardiovasc Surg*. 1999;117:855–872.
3. Tatoulis J, Buxton BF, Fuller JA. Patencies of 2127 arterial to coronary conduits over 15 years. *Ann Thorac Surg*. 2004;77:93–101.
4. Rizzoli G, Schiavon L, Bellini P. Does the use of bilateral internal mammary artery (IMA) grafts provide incremental benefit relative to the use of a single IMA graft? A meta-analysis approach. *Eur J Cardiothorac Surg*. 2002;22:781–786.
5. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. *Lancet*. 2001;358:870–875.
6. Takagi H, Goto S, Watanabe T, Mizuno Y, Kawai N, Umemoto T. A meta-analysis of adjusted hazard ratios from 20 observational studies of bilateral versus single internal thoracic artery coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2014;148:1282–1290.
7. Weiss AJ, Zhao S, Tian DH, Taggart DP, Yan TD. A meta-analysis comparing bilateral internal mammary artery with left internal mammary artery for coronary artery bypass grafting. *Ann Cardiothorac Surg*. 2013;2:390–400.
8. 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.
9. Buttar SN, Yan TD, Taggart DP, Tian DH. Long-term and short-term outcomes of using bilateral internal mammary artery grafting versus left internal mammary artery grafting: a meta-analysis. *Heart*. 2017;103:1419–1426.
10. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, Cigarroa JE, Disesa VJ, Hiratzka LF, Hutter AM, Jessen ME, Keeley EC, Lahey SJ, Lange RA, London MJ, Mack MJ, Patel MR, Puskas JD, Sabik JF, Selnes O, Shahian DM, Trost JC, Winniford MD. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/

American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124:e652–e735.

11. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35:2541–2619.
12. Aldea GS, Bakaeen FG, Pal J, Fremes S, Head SJ, Sabik J, Rosengart T, Kappetein AP, Thourani VH, Firestone S, Mitchell JD; Society of Thoracic Surgeons. The Society of Thoracic Surgeons clinical practice guidelines on arterial conduits for coronary artery bypass grafting. *Ann Thorac Surg*. 2016;101:801–809.
13. Myers WO, Berg R, Ray JF, Douglas-Jones JW, Maki HS, Ulmer RH, Chaitman BR, Reinhart RA. All-artery multigraft coronary artery bypass grafting with only internal thoracic arteries possible and safe: a randomized trial. *Surgery*. 2000;128:650–659.
14. Gaudino M, Cellini C, Pragliola C, Trani C, Burzotta F, Schiavoni G, Nasso G, Possati G. Arterial versus venous bypass grafts in patients with in-stent restenosis. *Circulation*. 2005;112:I265–I269.
15. Nasso G, Coppola R, Bonifazi R, Piancone F, Bozzetti G, Speziale G. Arterial revascularization in primary coronary artery bypass grafting: direct comparison of 4 strategies—results of the Stand-in-Y Mammary Study. *J Thorac Cardiovasc Surg*. 2009;137:1093–1100.
16. Taggart DP, Altman DG, Gray AM, Lees B, Gerry S, Benedetto U, Flather M. Randomized trial of bilateral versus single internal-thoracic-artery grafts. *N Engl J Med*. 2016;375:2540–2549.
17. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
18. Wells G, Shea B, O'Connel D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [Internet]. 2011. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed September 15, 2017.
19. Benedetto U, Raja SG, Albanese A, Amrani M, Biondi-Zoccai G, Frati G. Searching for the second best graft for coronary artery bypass surgery: a network meta-analysis of randomized controlled trials†. *Eur J Cardiothorac Surg*. 2015;47:59–65; discussion, 65.
20. Lonjon G, Boutron I, Trinquart L, Ahmad N, Aim F, Nizard R, Ravaud P. Comparison of treatment effect estimates from prospective nonrandomized studies with propensity score analysis and randomized controlled trials of surgical procedures. *Ann Surg*. 2014;259:18–25.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
22. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med*. 1998;17:2815–2834.
23. Yanagawa B, Verma S, Jüni P, Tam DY, Mazine A, Puskas JD, Friedrich JO. A systematic review and meta-analysis of in situ versus composite bilateral internal thoracic artery grafting. *J Thorac Cardiovasc Surg*. 2017;153:1108–1116.e16.
24. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*. 2007;8:16.
25. Rothstein HR, Sutton AJ, Borenstein M. *Publication Bias in Meta-Analysis: Prevention, Assessment and Adjustments*. Chichester, UK: John Wiley & Sons Ltd; 2005.
26. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
27. Ashraf SS, Shaukat N, Akhtar K, Love H, Shaw J, Rowlands DJ, Keenan D. A comparison of early mortality and morbidity after single and bilateral internal mammary artery grafting with the free right internal mammary artery. *Br Heart J*. 1994;72:321–326.
28. Benedetto U, Amrani M, Gaer J, Bahrami T, de Robertis F, Simon AR, Raja SG; Harefield Cardiac Outcomes Research Group. The influence of bilateral internal mammary arteries on short- and long-term outcomes: a propensity score matching in accordance with current recommendations. *J Thorac Cardiovasc Surg*. 2014;148:2699–2705.
29. Berreklouw E, Rademakers PP, Koster JM, van Leur L, van der Wielen BJ, Westers P. Better ischemic event-free survival after two internal thoracic artery grafts: 13 years of follow-up. *Ann Thorac Surg*. 2001;72: 1535–1541.
30. Bonacchi M, Maiani M, Prifti E, Di Eusanio G, Di Eusanio M, Leacche M. Urgent/emergent surgical revascularization in unstable angina: influence of different type of conduits. *J Cardiovasc Surg (Torino)*. 2006;47:201–210.
31. Buxton BF, Komeda M, Fuller JA, Gordon I. Bilateral internal thoracic artery grafting may improve outcome of coronary artery surgery. Risk-adjusted survival. *Circulation*. 1998;98:II1–II6.
32. Calafiore AM, Di Giammarco G, Teodori G, Di Mauro M, Iacò AL, Bivona A, Contini M, Vitolla G. Late results of first myocardial revascularization in multiple vessel disease: single versus bilateral internal mammary artery with or without saphenous vein grafts. *Eur J Cardiothorac Surg*. 2004;26:542–548.
33. Carrier M, Cossette M, Pellerin M, Hébert Y, Bouchard D, Cartier R, Demers P, Jeanmart H, Pagé P, Perrault LP. Statin treatment equalizes long-term survival between patients with single and bilateral internal thoracic artery grafts. *Ann Thorac Surg*. 2009;88:789–795; discussion, 795.
34. Dalén M, Ivert T, Holzmann MJ, Sartipy U. Bilateral versus single internal mammary coronary artery bypass grafting in Sweden from 1997-2008. *PLoS One*. 2014;9:e86929.
35. Danzer D, Christenson JT, Kalangos A, Khatchatourian G, Bednarkiewicz M, Faidutti B. Impact of double internal thoracic artery grafts on long-term outcomes in coronary artery bypass grafting. *Tex Heart Inst J*. 2001;28:89–95.
36. Dewar LR, Jamieson WR, Janusz MT, Adeli-Sardo M, Germann E, MacNab JS, Tyers GF. Unilateral versus bilateral internal mammary revascularization. Survival and event-free performance. *Circulation*. 1995;92:II8–II13.
37. Endo M, Nishida H, Tomizawa Y, Kasanuki H. Benefit of bilateral over single internal mammary artery grafts for multiple coronary artery bypass grafting. *Circulation*. 2001;104:2164–2170.
38. Gansera B, Loef A, Angelis I, Gillrath G, Schmidtler F, Kemkes BM. Double thoracic artery—halved mid-term mortality? A 5-year follow-up of 716 patients receiving bilateral ITA versus 662 patients with single ITA. *Z Kardiol*. 2004;93:878–883.
39. Gansera B, Delalic A, Eszlari E, Eichinger W. 14-year results of bilateral versus single internal thoracic artery grafts for left-sided myocardial revascularization in young diabetic patients. *Thorac Cardiovasc Surg*. 2017;65:272–277.
40. Grau JB, Johnson CK, Kuschner CE, Ferrari G, Shaw RE, Brizzio ME, Zapolanski A. Impact of pump status and conduit choice in coronary artery bypass: a 15-year follow-up study in 1412 propensity-matched patients. *J Thorac Cardiovasc Surg*. 2015;149:1027–1033.e2.
41. Hirotani T, Nakamichi T, Munakata M, Takeuchi S. Risks and benefits of bilateral internal thoracic artery grafting in diabetic patients. *Ann Thorac Surg*. 2003;76:2017–2022.
42. Itoh S, Kimura N, Adachi H, Yamaguchi A. Is bilateral internal mammary arterial grafting beneficial for patients aged 75 years or older? *Circ J*. 2016;80:1756–1763.
43. Johnson WD, Brenowitz JB, Kayser KL. Factors influencing long-term (10-year to 15-year) survival after a successful coronary artery bypass operation. *Ann Thorac Surg*. 1989;48:19–24; discussion, 24–25.
44. Jones JW, Schmidt SE, Miller CC, Beall AC, Baldwin JC. Bilateral internal thoracic artery operations in the elderly. *J Cardiovasc Surg (Torino)*. 2000;41:165–170.
45. Joo HC, Youn YN, Yi G, Chang BC, Yoo KJ. Off-pump bilateral internal thoracic artery grafting in right internal thoracic artery to right coronary system. *Ann Thorac Surg*. 2012;94:717–724.
46. Kelly R, Buth KJ, Légaré JF. Bilateral internal thoracic artery grafting is superior to other forms of multiple arterial grafting in providing survival benefit after coronary bypass surgery. *J Thorac Cardiovasc Surg*. 2012;144:1408–1415.
47. Kieser TM, Lewin AM, Graham MM, Martin B-J, Galbraith PD, Rabi DM, Norris CM, Faris PD, Knudtson ML, Ghali WA; APPROACH Investigators. Outcomes associated with bilateral internal thoracic artery grafting: the importance of age. *Ann Thorac Surg*. 2011;92:1269–1275; discussion, 1275–1276.
48. Kinoshita T, Asai T, Suzuki T. Off-pump bilateral skeletonized internal thoracic artery grafting in patients with chronic kidney disease. *J Thorac Cardiovasc Surg*. 2015;150:315–321.e3.
49. Kurlansky PA, Traad EA, Dorman MJ, Galbut DL, Zucker M, Ebra G. Thirty-year follow-up defines survival benefit for second internal mammary artery in propensity-matched groups. *Ann Thorac Surg*. 2010;90:101–108.
50. Locker C, Schaff HV, Dearani JA, Joyce LD, Park SJ, Burkhart HM, Suri RM, Greason KL, Stulak JM, Li Z, Daly RC. 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.
51. 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; discussion, 2012–2014.

52. Medalion B, Mohr R, Ben-Gal Y, Nesher N, Kramer A, Eliyahu S, Pevni D. Arterial coronary artery bypass grafting is safe and effective in elderly patients. *J Thorac Cardiovasc Surg*. 2015;150:607–612.

53. Mohammadi S, Kalavrouziotis D, Cresce G, Dagenais F, Dumont E, Charbonneau E, Voisine P. Bilateral internal thoracic artery use in patients with low ejection fraction: is there any additional long-term benefit? *Eur J Cardiothorac Surg*. 2014;46:425–431; discussion, 431.

54. Nasso G, Popoff G, Lamarra M, Romano V, Coppola R, Bartolomucci F, Giglio MD, Romeo F, Tavazzi L, Speziale G. Impact of arterial revascularization in patients undergoing coronary bypass. *J Card Surg*. 2012;27:427–433.

55. Naunheim KS, Barner HB, Fiore AC. 1990: results of internal thoracic artery grafting over 15 years: single versus double grafts. 1992 update. *Ann Thorac Surg*. 1992;53:716–718.

56. Navia DO, Vrancic M, Piccinini F, Camporrotondo M, Dorsa A, Espinoza J, Benzadon M, Camou J. Myocardial revascularization exclusively with bilateral internal thoracic arteries in T-graft configuration: effects on late survival. *Ann Thorac Surg*. 2016;101:1775–1781.

57. Parsa CJ, Shaw LK, Rankin JS, Daneshmand MA, Gaca JG, Milano CA, Glower DD, Smith PK. Twenty-five-year outcomes after multiple internal thoracic artery bypass. *J Thorac Cardiovasc Surg*. 2013;145:970–975.

58. Pettinari M, Sergeant P, Meuris B. Bilateral internal thoracic artery grafting increases long-term survival in elderly patients. *Eur J Cardiothorac Surg*. 2015;47:703–709.

59. Pick AW, Orszulak TA, Anderson BJ, Schaff HV. Single versus bilateral internal mammary artery grafts: 10-year outcome analysis. *Ann Thorac Surg*. 1997;64:599–605.

60. Rosenblum JM, Harskamp RE, Hoedemaker N, Walker P, Liberman HA, de Winter RJ, Vassiliades TA, Puskas JD, Halkos ME. Hybrid coronary revascularization versus coronary artery bypass surgery with bilateral or single internal mammary artery grafts. *J Thorac Cardiovasc Surg*. 2016;151:1081–1089.

61. Schwann TA, Hashim SW, Badour S, Obeid M, Engoren M, Tranbaugh RF, Bonnell MR, Habib RH. Equipoise between radial artery and right internal thoracic artery as the second arterial conduit in left internal thoracic artery-based coronary artery bypass graft surgery: a multi-institutional study. *Eur J Cardiothorac Surg*. 2016;49:188–195.

62. Stevens LM, Carrier M, Perrault LP, Hébert Y, Cartier R, Bouchard D, Fortier A, El-Hamamsy I, Pellerin M. Single versus bilateral internal thoracic artery grafts with concomitant saphenous vein grafts for multivessel coronary artery bypass grafting: effects on mortality and event-free survival. *J Thorac Cardiovasc Surg*. 2004;127:1408–1415.

63. Tarelli G, Mantovani V, Maugeri R, Chelazzi P, Vanoli D, Grossi C, Ornaghi D, Panisi P, Sala A. Comparison between single and double internal mammary artery grafts: results over ten years. *Ital Heart J*. 2001;2:423–427.

64. Toumpoulis IK, Anagnostopoulos CE, Balaram S, Swistel DG, Ashton RC, DeRose JJ. Does bilateral internal thoracic artery grafting increase long-term survival of diabetic patients? *Ann Thorac Surg*. 2006;81:599–606; discussion, 606–607.

65. Gansera B, Gillrath G, Lieber M, Angelis I, Schmidtler F, Kemkes BM. Are men treated better than women? Outcome of male versus female patients after CABG using bilateral internal thoracic arteries. *Thorac Cardiovasc Surg*. 2004;52:261–267.

66. Raza S, Sabik JF, Masabni K, Ainkaran P, Lytle BW, Blackstone EH. Surgical revascularization techniques that minimize surgical risk and maximize late survival after coronary artery bypass grafting in patients with diabetes mellitus. *J Thorac Cardiovasc Surg*. 2014;148:1257–1264; discussion, 1264–1266.

SUPPLEMENTAL MATERIAL

Data S1
Database: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® <1946-Present>
Search Strategy:
----
1 bilateral internal mammary.mp. (331)
2 bilateral internal thoracic.mp. (434)
3 1 or 2 (756)
4 exp Internal Mammary-Coronary Artery Anastomosis/ (2248)
5 3 or 4 (2765)
6 limit 5 to english language (2396)
7 limit 6 to case reports (576)
8 6 not 7 (1820)
9 limit 8 to "review" (127)
10 8 not 9 (1693)
11 total arterial revascularization.mp. (153)
12 multiple arterial revascularization.mp. (8)
13 11 or 12 (160)
14 (arterial revascularization adj6 coronary).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (95)
15 13 or 14 (224)
16 (multiple arterial adj6 coronary).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (39)
17 (total arterial adj6 coronary).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (87)
18 15 or 16 or 17 (311)
19 limit 18 to (english language and humans) (247)
20 limit 19 to (case reports or comment or editorial or "review") (71)
21 19 not 20 (176)
22 10 or 21 (1822)

****

Table S1. Pre-treatment variables included for propensity score-matching.

Study	Variables
Benedetto[1]	Age, sex, NYHA class, MI, PCI, smoking, COPD, CVA, PVD, AF, LMD, number of vessels diseased, LVEF <50%, BMI ≥30, creatinine ≥200 mmol/L, DM, preoperative IABP, urgent/emergent, resident performing procedure, CPB
Calafiore[2]	COPD, no. of anastomoses, DM, extra-cardiac vasculopathy, EF ≤35%, sex, urgency, age, CHF, CRF, previous MI, unstable angina, ventricular arrhythmias
Dalen[3]	NR
Gansera 2016[4]	Age, sex, number of grafts, EF, elective, urgent/emergent operations, preoperative MI, preoperative PCI or preoperative stent
Grau[5]	Sex, age, BMI, DM, history of smoking and current smoking status, hypertension, CVA, no. of diseased coronary vessels, PVD, NYHA class IV, stroke, COPD, previous MI, renal failure, LMD, LVEF, creatinine, cardiogenic shock presentation, prior cardiac surgery, urgency status
Itoh[6]	Sex, DM, use of insulin, obesity, hypertension, dyslipidemia, PAD, CRF, CVA, previous MI, LVEF <40%, involvement of the left main coronary trunk, triple-vessel disease, double-vessel disease, urgent/emergency surgery
Joo[7]	Age, sex, DM, peripheral occlusive disease, prior PCI, CRF, recent MI, 3-vessel disease, LVEF, low LVEF (<35%)
Kelly[8]	Age, sex, BMI, smoking history, DM, renal failure, hypertension, PVD, cardiovascular disease, COPD, LVEF <40%, CHF, recent MI (less than 7 days), prior PCI, urgency of surgery, left main/triple vessel disease, surgeon
Kinoshita[9]	Age, age group, sex, BMI, BSA, DM, HbA1C, oral hypoglycemic agents, insulin, GFR, dialysis, hypertension, COPD, PAD, CVA, LVEF <40%, previous PCI, MI, CHF, NYHA class III or IV, LV diastolic dimensions, LV systolic dimensions, LVEF, no. of target coronary arteries
Kurlansky[10]	NR
Locker[11]	Age, sex, BSA, LVEF, hypertension, DM, chronic lung disease, renal failure, PVD, previous MI, CVA
Lytle[12]	Sex, age, BMI, previous MI, severe LV dysfunction, HF symptoms, no. of vessels with ≥50% stenosis, % stenosis in the left main trunk, stenosis ≥50% in the LAD system, stenosis ≥50% in the Cx system, stenosis ≥50% in the RCA system, NYHA class, family history of CAD, hypertension, DM, history of smoking, COPD, PVD, cholesterol, surgeon, date of operation
Medalion[13]	Age, sex, DM, hyperlipidemia, PVD, emergency surgery, critical preoperative state, recent MI, acute MI, repeat operation, renal insufficiency, CHF, COPD, unstable angina, LMD, no. of diseased vessels, LVEF
Mohammadi[14]	Age, sex, hypertension, COPD, DM, insulin-dependent DM, PVD or cerebral vascular disease (or both), previous stroke, BMI ≥30 kg/m^2, renal failure, creatinine value, previous MI, LMD, NYHA, surgical acuity, Parsonnet score, smoking status, previous PCI
Nasso[15]	NR
Navia[16]	Age, sex, DM, hypertension, dyslipidemia, smoking habit, family history, elective operation, on-pump operation, LV dysfunction (moderate/severe), LMD, three-vessel disease, redo operation, previous MI, previous PCI, PVD, carotid artery disease, abdominal aortic aneurysm, COPD, cerebrovascular disease, previous renal dysfunction
Pettinari[17]	OPCAB, surgeon, age, preoperative creatinine, sex, length, weight, BMI, preoperative dialysis, carotid stenosis, simultaneous carotid surgery, presence of carotid occlusion, history of stroke, PVD, shock or CPR, acute MI, urgency, recent myocardial infarction, perioperative AF, DM, COPD, FEV1, coronary vessel diseased, degree LM stenosis, redo, mild aortic stenosis, mild mitral insufficiency, EF, BBB, LV hypertrophy, experience, end diastolic pressure
Rosenblum[18]	Age, sex, race, height, weight, BMI, current smoker, DM, cerebrovascular disease, chronic lung disease, dyslipidemia, hypertension, PVD, renal failure, GFR, hemoglobin, previous MI, HF, LVEF, isolated LMD, left main plus other vessel, three-vessel disease, aspirin use, beta blocker use, STS predicted risk for mortality, STS risk morbidity/mortality, year of procedure
Schwann[19]	Age, EF, vessel disease, no. of grafts, completeness of revascularization index, sex, obesity, DM, insulin-dependent DM, DM and obesity, DM or obesity, hypertension, hypercholesterolemia, COPD, smoker, previous MI, PVD, previous surgery, LMD, no. of diseased vessels, no. of grafts, deep sternal infection, bleeding post-operation

Stevens[20]	Age, sex, DM, hypertension, unstable angina, prior MI, preoperative PCI, perioperative need for IABP, CHF, PVD, obesity, dyslipidemia, COPD, no. of coronary artery bypass grafts
Toumpoulis[21]	EuroSCORE, age, sex, race, vessels involved, unstable angina, previous MI, transmural MI, more than one previous MI, previous cardiac operation, CCS angina class, urgency of the operation, hemodynamic instability, shock, EF categories, current CHF, past CHF, PVD, BMI categories, hypertension, COPD, calcified aorta, renal failure, preoperative dialysis, hepatic failure, immune deficiency, preoperative IABP, IV NTG, LV hypertrophy, malignant ventricular arrhythmia, thrombolysis prior surgery, previous PCI, smoking previous year

AF, preoperative atrial fibrillation; BITA, bilateral thoracic arteries; BMI, body mass index; BSA, body surface area; CBP, cardio-pulmonary bypass; CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CPR, cardio-pulmonary resuscitation; Cr, creatinine; CRF, chronic renal failure; CVA, previous cerebrovascular accident; Cx, circumflex coronary artery; DIA, diagonal coronary artery; DM, diabetes mellitus; EF, ejection fraction; FEV1, Forced expiratory volume in the 1st second; IABP, intra-aortic balloon pump; ITA, internal thoracic artery; IVNTG, intravenous nitroglycerine; LAD, left anterior descending; LMD, left main disease; LV, left ventricle; MI, myocardial infarction; NYHA, New York Heart Association; NR, not reported; OPCAB, off-pump coronary artery bypass grafting; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCA, right coronary artery; STS, Society of Thoracic Surgeons.

Table S2. Risk factor distribution in the populations of the studies included in the primary analysis.

Study	Age (y) Mean±SD	Female (%)	DM (%)	EF	COPD (%)
Ashraf[22]					
BITA	57 (median)	23	10	55% (median)	NR
SITA	59 (median)	21	10.7	58% (median)	NR
Benedetto[1]					
BITA	NR (Ranges)	10.8	15.9	EF<50% in 13.2%	7.7
SITA	NR (Ranges)	21.2	31.5	EF<50% in 22.1%	10.6
Berreklouw[23]					
BITA	53.7	10.4	6	NR	NR
SITA	56	16.3	7.4	NR	NR
Bonacchi[24]					
BITA	59 ± 14	18	30	EF<35% in 19%	14
SITA	63 ± 11	20	34	EF<35% in 21%	16
Buxton[25]					
BITA	58.6 ± 9	10.6	6.8	EF<50% in 4.9%	NR
SITA	64.9 ± 9	22	19.9	EF<50% in 24.2%	NR
Calafiore[2]					

BITA	60.7 ± 8.3	19.3	24.2	59.4 ± 13.1	2.8
SITA	60.8 ± 9.0	17.5	24.2	59.3 ± 13.8	3
Carrier[26]					
BITA	61 ± 9	16	21	NR	NR
SITA	68 ± 8	29	31	NR	NR
Dalen[3]					
BITA	64.4 ± 11.1	25.9	13.7	EF<30% in 4.3%	4.3
SITA	66.7 ± 9.2	21	22.8	EF<30% in 3.2%	4.6
Danzer[27]					
BITA	59.8 ± 8.8	12	13.6	EF<40% in 13.6	NR
SITA	57.1 ± 8.5	10.1	13	EF<40% in 13	NR
Dewar[28]					
BITA	NR	15.4	17.7	NR	NR
SITA	NR	16.6	19.3	NR	NR
Endo[29]					
BITA	61 (median)	9.7	42.9	54% (median)	NR
SITA	62 (median)	19.2	40.3	54% (median)	NR
Gansera 2004[30]					

BITA	69.2 (median)	16	26	NR	NR
SITA	71 (median)	23	25.9	NR	NR
Gansera 2016[4]					
BITA	59.3 ± 5.3	17	100	NR	NR
SITA	60.1 ± 5.3	17	100	NR	NR
Grau[5]					
BITA	60 ± 9	10.4	11	51 ± 11	5.1
SITA	62 ± 9	12.1	13.3	50 ± 12	5.9
Hirotani[31]					
BITA	64.8 ± 7.8	23	100	48.2 ± 15.1	NR
SITA	63.9 ± 8.9	25	100	48.8 ± 16.4	NR
Itoh[6]					
BITA	77.6 ± 2.5	23.4	37.4	EF<40% in 10.3%	NR
SITA	78.2 ± 2.8	36.2	37.3	EF<40% in 7.2%	NR
Johnson[32]					
BITA	NR	NR	NR	NR	NR
SITA	NR	NR	NR	NR	NR
Jones[33]					

BITA	69.2	19.2	NR	EF<50% in 38.9%	NR
SITA	69.7	9.8	NR	EF<50% in 39.6%	NR
Joo[7]					
BITA	60.4 ± 9.1	39.8	38.3	57 ± 11%	7.4
SITA	61.3 ± 7.5	37.2	40.8	55 ± 11%	6.7
Kelly[8]					
BITA	58.4 ± 10.0	18	26	EF<40% in 7%	11
SITA	65.0 ± 10.1	25	37	EF<40% in 12%	14
Kieser[34]					
BITA	58 ± 9.1	NR	27.8	EF<20% in 0.4%	NR
SITA	67.6 ± 9.5	NR	26.2	EF<20% in 0.4%	NR
Kinoshita[9]					
BITA	69 ± 8	16	61	52 ± 14%	19
SITA	71 ± 9	24	55	53 ± 14%	22
Kurlansky[10]					
BITA	62.9 ± 10.0	14.9	20.8	EF<30% in 3.9%	NR
SITA	67.5 ± 9.4	25.7	27.3	EF<30% in 6.2%	NR
Locker[11]					

BITA	NR	NR	NR	NR	NR
SITA	68 ± 9	24.8	33.5	NR	11.7
Lytle[12]					
BITA	57.5 ± 8.1	12	12	NR	NR
SITA	57.8 ± 8.3	14	12	NR	NR
Medalion[13]					
BITA	NR (ranges)	27	32.2	EF≤30% in 8.2%	5.5
SITA	NR (ranges)	33.7	38.3	EF≤30% in 7.7%	12.9
Mohammadi[14]					
BITA	54.6 ± 9.5	9.3	14	EF≤30% in 30.2%	12.4
SITA	65.2 ± 9.6	19	42.9	EF≤30% in 34.5%	19.2
Nasso[15]					
BITA	67.3 ± 9.3	20.4	42.8	EF<30% in 10.2%	9.9
SITA	66.9 ± 9.1	21.4	48.4	EF<30% in 10.1%	10.1
Naunheim[35]					
BITA	49.6 ± 7.9	17	4	NR	NR
SITA	51.3 ± 6.6	13	3	NR	NR
Navia[16]					

BITA	63.7 ± 9.1	9.8	25.9	NR	4.2
SITA	NR	NR	NR	NR	NR
Parsa[36]					
BITA	59 (median)	19.8	14.7	51% (median)	3.9
SITA	64 (median)	28.5	29.9	52% (median)	8.2
Pettinari[17]					
BITA	73.2 ± 2.8	26.1	12.6	44.3 ± 32.2	16.3
SITA	74.5 ± 3.5	32.9	16.2	45.0 ± 30.9	21.4
Pick[37]					
BITA	60	18	17.5	58%	NR
SITA	62	20	27	57%	NR
Rosenblum[18]					
BITA	59.0 ± 10.1	15.5	27.6	52.2 ± 11.0	1.8
SITA	63.8 ± 10.6	28.7	43.8	51.7 ± 12.4	6.3
Schwann[19]					
BITA	59.8 ± 10.2	12	15	54 ± 11	6.4
SITA	65.3 ± 10.4	35	37	49 ± 12	22
Stevens[20]					

BITA	57 ± 9	12	12	NR	4
SITA	63 ± 9	25	18	NR	6
Tarelli[38]					
BITA	56.5 ± 8.2	7.3	11.3	57.2 ± 13.6	NR
SITA	59.3 ± 8.3	17.3	24.7	54.5 ± 13.5	NR
Toumpoulis[21]					
BITA	63.6 ± 9.9	44.9	100	EF<30% in 20.6%	15.5
SITA	64.5 ± 9.4	43.9	100	EF<30% in 19.2%	17.3

COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EF, ejection fraction; NR, not reported; SD, standard deviation.

Table S3. Details of statistical analysis for the propensity score matched studies included in the 1-year analysis.

Study	Year	PSM methods	Cox regression adjusted for matched sample	Statistical Software
Benedetto[1]	2014	Greedy 1:1 matching	Yes	R
Calafiore[2]	2004	Stepwise logistic regression (nearest neighbor matching)	No	SPSS
Dalen[3]	2014	Logistic regression and nearest neighbor matching without replacement	Yes	STATA
Grau[5]	2015	Nearest-neighbor matching algorithm with greedy 5-1 digit matching	No	NS
Joo[7]	2012	Logistic regression model, 1:1 ratio	No	SPSS
Kelly[8]	2012	NR	No	SAS
Kurlansky[10]	2010	Rosenbaum optimal matching algorithm using Mahalanobis distance within	No	NCSS

		propensity score calipers		
Lytle[12]	2004	NR	NS	NS
Nasso[15]	2012	1:1 matching with maximum allowable difference: 0.1	No	NS
Rosenblum[18]	2016	Logistic regression	No	SPSS
Schwann[19]	2016	Logistic regression	Yes	SPSS
Stevens[20]	2004	NR	Yes	SAS

NR, not reported; NS, not specified.

Table S4. Newcastle-Ottawa Scale for the studies included in the primary analysis.

Study	Selection	Comparability	Outcome/Exposure
Ashraf[22]	****	**	**
Benedetto[1]	****	**	***
Berreklouw[23]	****	**	***
Bonacchi[24]	****	**	***
Buxton[25]	****	**	***
Calafiore[2]	****	**	***
Carrier[26]	****	**	***
Dalen[3]	****	**	***
Danzer[27]	****		**
Dewar[28]	****	**	*
Endo[29]	****	**	***
Gansera 2004[30]	****		**
Gansera 2016[4]	****	**	**
Grau[5]	****	**	***
Hirotani[31]	****	*	**
Itoh[6]	****	**	***
Johnson[32]	****		***
Jones[33]	****	*	***
Joo[7]	****	**	***
Kelly[8]	****	**	**
Kieser[34]	****	**	**
Kinoshita[9]	****	**	***
Kurlansky[10]	****	**	***
Locker[11]	****	**	***
Lytle[12]	****	**	***
Medalion[13]	****	**	***
Mohammadi[14]	****	**	***
Nasso[15]	****	**	***
Naunheim[35]	****	**	***
Navia[16]	****	**	***
Parsa[36]	****	**	***
Pettinari[17]	****	**	***
Pick[37]	****	**	***
Rosenblum[18]	****	**	***
Schwann[19]	****	**	**
Stevens[20]	****	**	***
Tarelli[38]	****		***
Toumpoulis[21]	****	**	***

Table S5. Overview of the results

Outcomes summary	Studies	Effect Estimate IRR [95%CI]	Heterogeneity	Overall effect	Favors
All studies	38	0.74(0.69-0.80)	I^2=71%, p< 0.00001	Z=8.26, p< 0.00001	BITA
All studies, excluding those performed in specific subpopulations	28	0.74(0.68-0.80)	I^2=77%, p< 0.00001	Z=6.94, p< 0.00001	BITA
Studies performed in specific subpopulations	10	0.73(0.63-0.86)	I^2=24%, p= 0.22	Z=4.88, p< 0.00001	BITA
Unadjusted studies	6	0.68(0.58-0.80)	I^2=56%, p= 0.04	Z=3.52, p= 0.0004	BITA
Adjusted studies	22	0.79(0.74-0.85)	I^2=54%, p= 0.001	Z=5.59, p< 0.00001	BITA
Adjusted non-PSM studies	10	0.84(0.76-0.93)	I^2=38%, p= 0.09	Z=3.09, p= 0.002	BITA
PSM studies (end of follow-up)	12	0.77(0.70-0.85)	I^2=37%, p= 0.09	Z=6.82, p< 0.00001	BITA
PSM studies (1-year follow-up)	12	0.70(0.60-0.82)	I^2=51%, p= 0.02	Z=3.14, p= 0.002	BITA

BITA, bilateral internal thoracic artery; CI, confidence interval; IRR, incidence rate ratio; PSM, propensity score matching

Figure S1. Flow chart for study selection.

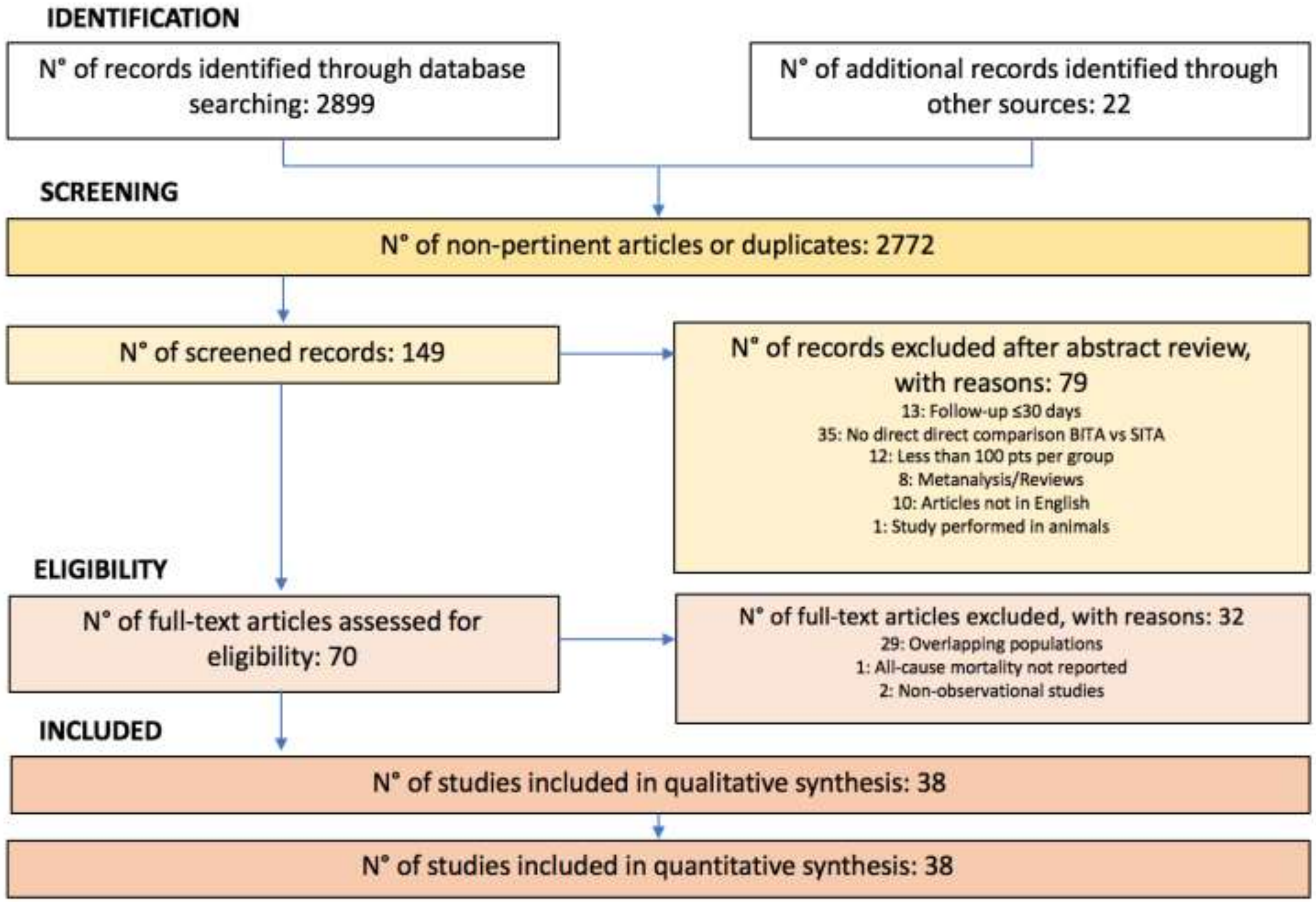


Figure S2. Leave-one-out analysis for the end of follow-up mortality among all the studies included in the primary analiysis (38 studies). Incident rate ratio (IRR) is used.

Study name	Statistics with study removed			
	Point	Lower limit	Upper limit	p-Value
Ashraf 1994[22]	-0.302	-0.373	-0.230	0.000
Benedetto 2014[1]	-0.298	-0.371	-0.226	0.000
Berreklouw 2001[23]	-0.302	-0.375	-0.230	0.000
Bonacchi 2006[24]	-0.301	-0.373	-0.229	0.000
Buxton 1998[25]	-0.284	-0.350	-0.217	0.000
Calafiore 2004[2]	-0.303	-0.375	-0.230	0.000
Carier (Statin +) 2009[26]	-0.307	-0.380	-0.235	0.000
Carrier (Statin -) 2009[26]	-0.297	-0.370	-0.224	0.000
Dalen 2014[3]	-0.313	-0.384	-0.243	0.000
Danzer 2001[27]	-0.299	-0.371	-0.227	0.000
Dewar 1995[28]	-0.314	-0.384	-0.243	0.000
Endo 2001[29]	-0.307	-0.380	-0.235	0.000
Gansera 2004[30]	-0.297	-0.369	-0.224	0.000
Gansera 2016[4]	-0.292	-0.364	-0.221	0.000
Grau 2015[5]	-0.300	-0.373	-0.227	0.000
Hirotani 2003[31]	-0.304	-0.376	-0.232	0.000
Itoh 2016[6]	-0.299	-0.372	-0.227	0.000
Johnson 1989[32]	-0.303	-0.377	-0.229	0.000
Jones 2000[33]	-0.302	-0.375	-0.229	0.000
Joo 2012[7]	-0.306	-0.379	-0.234	0.000
Kelly 2012[8]	-0.305	-0.379	-0.231	0.000
Kieser 2011[34]	-0.284	-0.352	-0.217	0.000
Kinoshita 2015[9]	-0.296	-0.369	-0.224	0.000
Kurlansky 2010[10]	-0.305	-0.384	-0.225	0.000
Locker (BITA only) 2012[11]	-0.303	-0.376	-0.230	0.000
Locker (BITA/SV) 2012[11]	-0.301	-0.374	-0.228	0.000
Lytle 2004[12]	-0.305	-0.381	-0.230	0.000
Medalion 2015[13]	-0.306	-0.380	-0.232	0.000
Mohammadi 2014[14]	-0.301	-0.373	-0.229	0.000
Nasso 2012[15]	-0.299	-0.373	-0.225	0.000
Naunheim 1992[35]	-0.304	-0.377	-0.232	0.000
Navia 2016[16]	-0.290	-0.360	-0.219	0.000
Parsa 2013[36]	-0.312	-0.384	-0.240	0.000
Pettinari 2015[17]	-0.304	-0.377	-0.230	0.000
Pick 1997[37]	-0.303	-0.375	-0.231	0.000
Rosenblum 2016[18]	-0.301	-0.374	-0.229	0.000
Schwann 2016[19]	-0.295	-0.368	-0.223	0.000
Stevens 2004[20]	-0.297	-0.370	-0.224	0.000
Tarelli 2001[38]	-0.305	-0.378	-0.233	0.000
Toumpoulis 2006[21]	-0.307	-0.380	-0.234	0.000
	-0.301	-0.373	-0.230	0.000

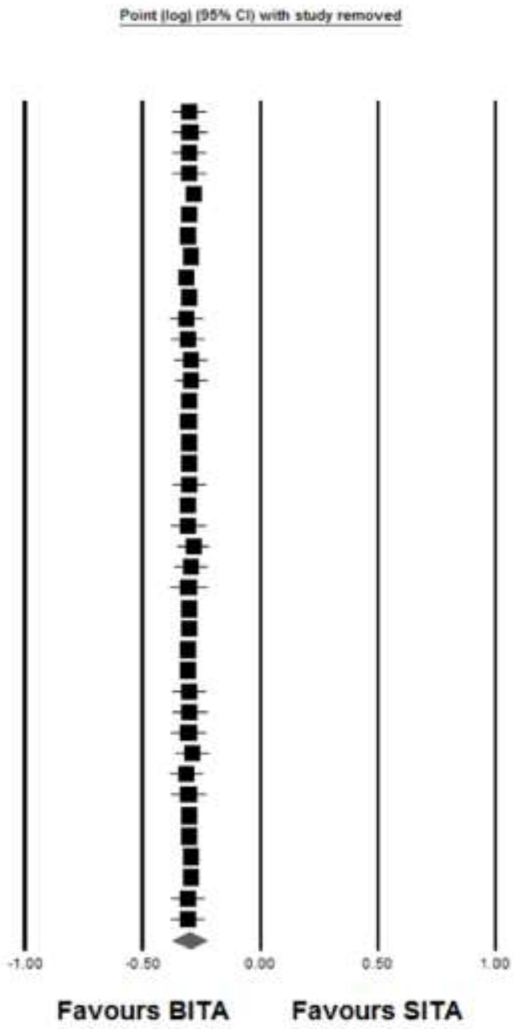


Figure S3. Forest plots comparing the effect of the use of BITA vs SITA on end of follow-up mortality after the exclusion of studies performed in specific subpopulations (28 studies; 162,989 patients, top) and in those studies performed in specific subpopulations (10 studies; 11,216 patients, bottom). (BITA, bilateral internal thoracic artery; CI, confidence interval; SITA, single internal thoracic artery). Incident rate ratio (IRR) is used.

Group by Population	Study name	Statistics for each study				
		Point (raw)	Lower limit	Upper limit	Z-Value	p-Value
General	Ashraf 1994 [22]	1.211	0.024	61.009	0.096	0.924
General	Benedetto 2014 [1]	0.610	0.382	0.975	-2.067	0.039
General	Berreklouw 2001 [23]	0.780	0.490	1.241	-1.050	0.294
General	Buxton 1998 [25]	0.483	0.406	0.574	-8.219	0.000
General	Calafiore 2004 [2]	0.778	0.548	1.106	-1.402	0.161
General	Carrier (Statin +) 2009 [26]	0.925	0.681	1.256	-0.499	0.618
General	Carrier (Statin -) 2009 [26]	0.646	0.511	0.817	-3.651	0.000
General	Dalen 2014 [3]	0.950	0.871	1.036	-1.158	0.247
General	Danzer 2001 [27]	0.572	0.293	1.118	-1.635	0.102
General	Dewar 1995 [28]	1.300	0.912	1.853	1.451	0.147
General	Endo 2001 [29]	0.950	0.669	1.348	-0.287	0.774
General	Gansera 2004 [30]	0.571	0.380	0.860	-2.684	0.007
General	Grau 2015 [5]	0.707	0.536	0.933	-2.452	0.014
General	Johnson 1989 [32]	0.767	0.640	0.919	-2.876	0.004
General	Joo 2012 [7]	0.933	0.636	1.369	-0.355	0.723
General	Kelly 2012 [8]	0.818	0.672	0.996	-2.001	0.045
General	Kieser 2011 [34]	0.460	0.371	0.571	-7.046	0.000
General	Kurlansky 2010 [10]	0.792	0.742	0.844	-7.085	0.000
General	Locker (BITA only) 2012 [11]	0.800	0.551	1.162	-1.172	0.241
General	Locker (BITA/SV) 2012 [11]	0.730	0.568	0.937	-2.466	0.014
General	Lytle 2004 [12]	0.805	0.721	0.898	-3.882	0.000
General	Nasso 2012 [13]	0.699	0.612	0.800	-5.227	0.000
General	Naunheim 1992 [35]	0.881	0.566	1.370	-0.562	0.574
General	Navia 2016 [16]	0.535	0.437	0.656	-6.048	0.000
General	Parsa 2013 [36]	0.950	0.833	1.084	-0.763	0.445
General	Pick 1997 [37]	0.820	0.503	1.336	-0.799	0.424
General	Rosenblum 2016 [18]	0.743	0.403	1.369	-0.953	0.341
General	Schwann 2016 [19]	0.606	0.471	0.780	-3.891	0.000
General	Stevens 2004 [20]	0.650	0.529	0.799	-4.103	0.000
General	Tarelli 2001 [38]	1.012	0.587	1.744	0.044	0.965
General		0.742	0.683	0.805	-7.159	0.000
Specific	Bonacchi 2006 [24]	0.670	0.194	2.310	-0.634	0.526
Specific	Gansera 2016 [4]	0.484	0.333	0.703	-3.801	0.000
Specific	Hirotani 2003 [31]	1.200	0.473	3.047	0.383	0.701
Specific	Itoh 2016 [6]	0.654	0.433	0.986	-2.029	0.042
Specific	Jones 2000 [33]	0.750	0.577	0.974	-2.153	0.031
Specific	Kinoshita 2015 [9]	0.570	0.379	0.858	-2.697	0.007
Specific	Medalion 2015 [39]	0.826	0.712	0.959	-2.515	0.012
Specific	Mohammadi 2014 [14]	0.700	0.388	1.262	-1.186	0.236
Specific	Pettinari 2015 [17]	0.787	0.643	0.964	-2.311	0.021
Specific	Toumpoulis 2006 [21]	0.890	0.692	1.144	-0.909	0.363
Specific		0.733	0.625	0.858	-3.850	0.000
Overall		0.740	0.688	0.796	-8.128	0.000

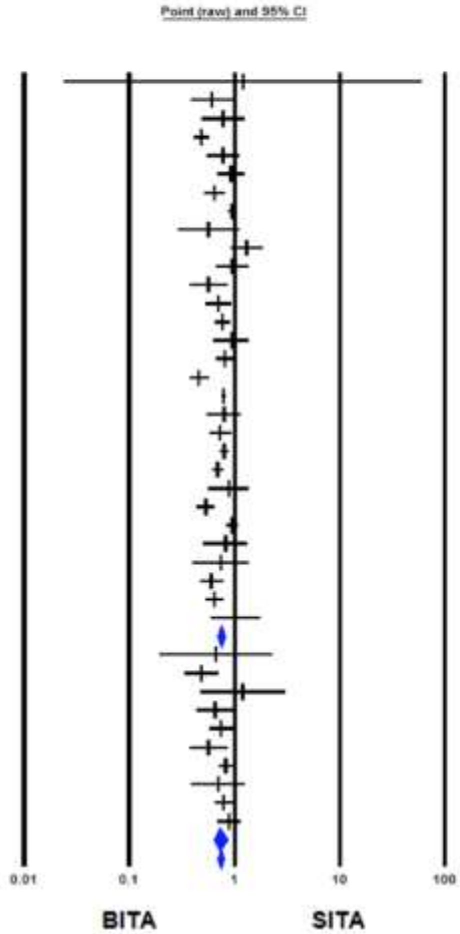


Figure S4. Forest plots comparing the effect of the use of BITA vs SITA on end of follow-up mortality in adjusted (22 studies; 155, 925 patients, top) and unadjusted (6 studies; 7064 patients, bottom) studies in the general population. (BITA, bilateral internal thoracic artery; CI, confidence interval; SITA, single internal thoracic artery). Incident rate ratio (IRR) is used.

Group by Adjustment	Study name	Statistics for each study			
		Point (raw)	Lower limit	Upper limit	p-Value
Adjusted	Ashraf 1994[22]	1.211	0.024	61.009	0.924
Adjusted	Benedetto 2014[1]	0.610	0.382	0.975	0.039
Adjusted	Berreklouw 2001[23]	0.780	0.490	1.241	0.294
Adjusted	Buxton 1998[25]	0.714	0.558	0.914	0.007
Adjusted	Calafiore 2004[2]	0.526	0.279	0.991	0.047
Adjusted	Carier (Statin +) 2009[26]	0.925	0.681	1.256	0.618
Adjusted	Carrier (Statin -) 2009[26]	0.646	0.511	0.817	0.000
Adjusted	Dalen 2014[3]	0.950	0.871	1.036	0.247
Adjusted	Dewar 1995[28]	1.300	0.912	1.853	0.147
Adjusted	Endo 2001[29]	0.950	0.669	1.348	0.774
Adjusted	Grau 2015[5]	0.707	0.536	0.933	0.014
Adjusted	Joo 2012[7]	0.933	0.636	1.369	0.723
Adjusted	Kelly 2012[8]	0.818	0.672	0.996	0.045
Adjusted	Kieser 2011[34]	0.870	0.692	1.093	0.232
Adjusted	Kurlansky 2010[10]	0.792	0.742	0.844	0.000
Adjusted	Locker (BITA only) 2012[11]	0.800	0.551	1.162	0.241
Adjusted	Locker (BITA/SV) 2012[11]	0.730	0.568	0.937	0.014
Adjusted	Lytle 2004[12]	0.805	0.721	0.898	0.000
Adjusted	Nasso 2012[15]	0.699	0.612	0.800	0.000
Adjusted	Parsa 2013[36]	0.950	0.833	1.084	0.445
Adjusted	Pick 1997[37]	0.820	0.503	1.335	0.424
Adjusted	Rosenblum 2016[18]	0.743	0.403	1.369	0.341
Adjusted	Schwann 2016[19]	0.606	0.471	0.780	0.000
Adjusted	Stevens 2004[20]	0.650	0.529	0.799	0.000
Adjusted		0.794	0.740	0.852	0.000
Unadjusted	Danzer 2001[27]	0.572	0.293	1.118	0.102
Unadjusted	Gansera 2004[30]	0.571	0.380	0.860	0.007
Unadjusted	Johnson 1989[32]	0.767	0.640	0.919	0.004
Unadjusted	Naunheim 1992[35]	0.881	0.566	1.370	0.574
Unadjusted	Navia 2016[16]	0.535	0.437	0.656	0.000
Unadjusted	Tarelli 2001[38]	1.012	0.587	1.744	0.965
Unadjusted		0.678	0.575	0.799	0.000
Overall		0.747	0.643	0.869	0.000

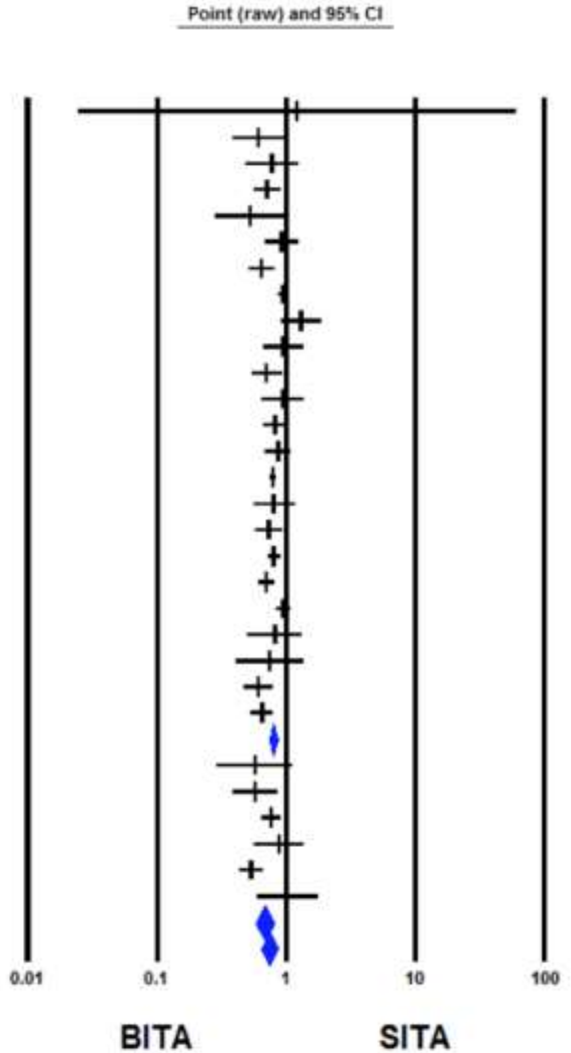
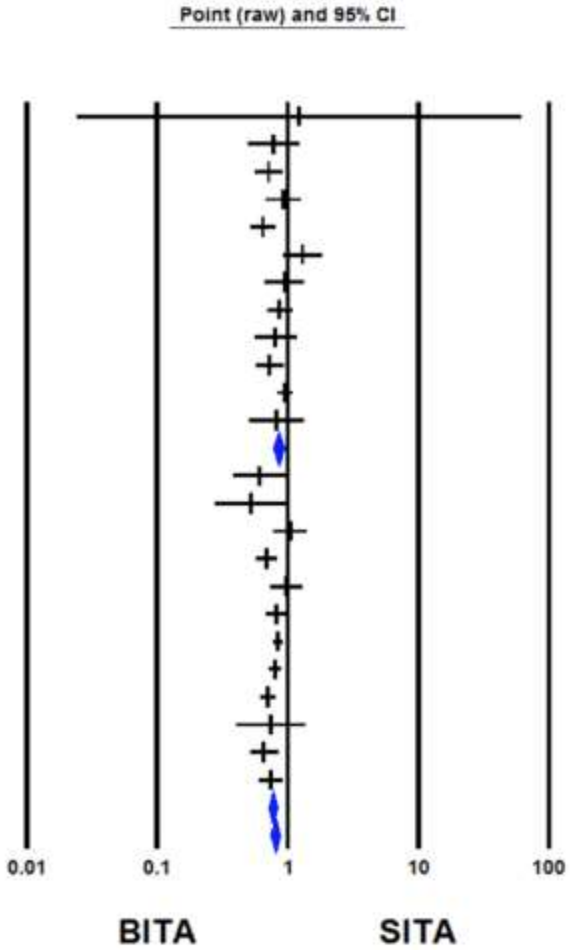


Figure S5. Forest plots comparing the effect of the use of BITA vs SITA on end of follow-up mortality in adjusted-non PSM studies (10 studies; 43,855 patients, top) and PSM studies (12 studies; 34,019 patients, bottom) in the general population. (BITA, bilateral internal thoracic artery; CI, confidence interval; PSM, propensity score matched; SITA, single internal thoracic artery). Incident rate ratio (IRR) is used.

Group by PSM / Adjusted	Study name	Statistics for each study: Point (raw)	Lower limit	Upper limit	Z-Value	p-Value
Adjusted (non-PSM)	Ashraf 1994[22]	1.211	0.024	61.009	0.096	0.924
Adjusted (non-PSM)	Berreklouw 2001[23]	0.780	0.490	1.241	-1.050	0.294
Adjusted (non-PSM)	Buxton 1998[25]	0.714	0.558	0.914	-2.679	0.007
Adjusted (non-PSM)	Carier (Statin +) 2009[26]	0.925	0.681	1.256	-0.499	0.618
Adjusted (non-PSM)	Carrier (Statin -) 2009[26]	0.646	0.511	0.817	-3.651	0.000
Adjusted (non-PSM)	Dewar 1995[28]	1.300	0.912	1.853	1.451	0.147
Adjusted (non-PSM)	Endo 2001[29]	0.950	0.669	1.348	-0.287	0.774
Adjusted (non-PSM)	Kieser 2011[30]	0.870	0.692	1.093	-1.195	0.232
Adjusted (non-PSM)	Locker (BITA only) 2012[31]	0.800	0.551	1.162	-1.172	0.241
Adjusted (non-PSM)	Locker (BITA/SV) 2012[31]	0.730	0.568	0.937	-2.466	0.014
Adjusted (non-PSM)	Parsa 2013[36]	0.950	0.833	1.084	-0.763	0.445
Adjusted (non-PSM)	Pick 1997[37]	0.820	0.503	1.335	-0.799	0.424
Adjusted (non-PSM)		0.843	0.764	0.930	-3.407	0.001
PSM	Benedetto 2014[1]	0.610	0.382	0.975	-2.067	0.039
PSM	Calafiore 2004[2]	0.526	0.279	0.991	-1.988	0.047
PSM	Dalen 2014[3]	1.040	0.776	1.393	0.263	0.793
PSM	Grau 2015[5]	0.693	0.577	0.832	-3.923	0.000
PSM	Joo 2012[7]	0.969	0.728	1.288	-0.220	0.826
PSM	Kelly 2012[8]	0.818	0.672	0.996	-2.001	0.045
PSM	Kurlansky 2010[10]	0.834	0.767	0.907	-4.263	0.000
PSM	Lytle 2004[12]	0.805	0.721	0.898	-3.882	0.000
PSM	Nasso 2012[15]	0.699	0.612	0.800	-5.227	0.000
PSM	Rosenblum 2016[18]	0.743	0.403	1.369	-0.953	0.341
PSM	Schwann 2016[19]	0.658	0.511	0.848	-3.236	0.001
PSM	Stevens 2004[20]	0.740	0.604	0.906	-2.912	0.004
PSM		0.775	0.716	0.839	-6.277	0.000
Overall		0.804	0.741	0.873	-5.211	0.000



Supplemental References:

1. Benedetto U, Amrani M, Gaer J, Bahrami T, de Robertis F, Simon AR, Raja SG, Harefield Cardiac Outcomes Research Group. The influence of bilateral internal mammary arteries on short- and long-term outcomes: a propensity score matching in accordance with current recommendations. *J Thorac Cardiovasc Surg*. 2014;148:2699–2705.

2. Calafiore AM, Di Giammarco G, Teodori G, Di Mauro M, Iacò AL, Bivona A, Contini M, Vitolla G. Late results of first myocardial revascularization in multiple vessel disease: single versus bilateral internal mammary artery with or without saphenous vein grafts. *Eur J Cardio-Thorac Surg*. 2004;26:542–548.

3. Dalén M, Ivert T, Holzmann MJ, Sartipy U. Bilateral versus single internal mammary coronary artery bypass grafting in Sweden from 1997-2008. *PloS One*. 2014;9:e86929.

4. Gansera B, Delalic A, Eszlari E, Eichinger W. 14-Year Results of Bilateral versus Single Internal Thoracic Artery Grafts for Left-Sided Myocardial Revascularization in Young Diabetic Patients. *Thorac Cardiovasc Surg*. 2017;65:272–277. Epub 2016 Nov 17.

5. Grau JB, Johnson CK, Kuschner CE, Ferrari G, Shaw RE, Brizzio ME, Zapolanski A. Impact of pump status and conduit choice in coronary artery bypass: A 15-year follow-up study in 1412 propensity-matched patients. *J Thorac Cardiovasc Surg*. 2015;149:1027–1033.e2.

6. Itoh S, Kimura N, Adachi H, Yamaguchi A. Is Bilateral Internal Mammary Arterial Grafting Beneficial for Patients Aged 75 Years or Older? *Circ J*. 2016;80:1756–1763.

7. Joo H-C, Youn Y-N, Yi G, Chang B-C, Yoo K-J. Off-pump bilateral internal thoracic artery grafting in right internal thoracic artery to right coronary system. *Ann Thorac Surg*. 2012;94:717–724.

8. Kelly R, Buth KJ, Légaré J-F. Bilateral internal thoracic artery grafting is superior to other forms of multiple arterial grafting in providing survival benefit after coronary bypass surgery. *J Thorac Cardiovasc Surg*. 2012;144:1408–1415.

9. Kinoshita T, Asai T, Suzuki T. Off-pump bilateral skeletonized internal thoracic artery grafting in patients with chronic kidney disease. *J Thorac Cardiovasc Surg*. 2015;150:315–321.e3.

10. Kurlansky PA, Traad EA, Dorman MJ, Galbut DL, Zucker M, Ebra G. Thirty-year follow-up defines survival benefit for second internal mammary artery in propensity-matched groups. *Ann Thorac Surg*. 2010;90:101–108.

11. Locker C, Schaff HV, Dearani JA, Joyce LD, Park SJ, Burkhart HM, Suri RM, Greason KL, Stulak JM, Li Z, Daly RC. 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.

12. 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; discussion 2012–2014.

13. Medalion B, Mohr R, Ben-Gal Y, Nesher N, Kramer A, Eliyahu S, Pevni D. Arterial coronary artery bypass grafting is safe and effective in elderly patients. *J Thorac Cardiovasc Surg*. 2015;150:607–612.

14. Mohammadi S, Kalavrouziotis D, Cresce G, Dagenais F, Dumont E, Charbonneau E, Voisine P. Bilateral internal thoracic artery use in patients with low ejection fraction: is there any additional long-term benefit? *Eur J Cardio-Thorac Surg*. 2014;46:425–431; discussion 431.

15. Nasso G, Popoff G, Lamarra M, Romano V, Coppola R, Bartolomucci F, Giglio MD, Romeo F, Tavazzi L, Speziale G. Impact of arterial revascularization in patients undergoing coronary bypass. *J Card Surg*. 2012;27:427–433.

16. Navia DO, Vrancic M, Piccinini F, Camporrotondo M, Dorsa A, Espinoza J, Benzadon M, Camou J. Myocardial Revascularization Exclusively With Bilateral Internal Thoracic Arteries in T-Graft Configuration: Effects on Late Survival. *Ann Thorac Surg*. 2016;101:1775–1781.

17. Pettinari M, Sergeant P, Meuris B. Bilateral internal thoracic artery grafting increases long-term survival in elderly patients. *Eur J Cardio-Thorac Surg*. 2015;47:703–709.

18. Rosenblum JM, Harskamp RE, Hoedemaker N, Walker P, Liberman HA, de Winter RJ, Vassiliades TA, Puskas JD, Halkos ME. Hybrid coronary revascularization versus coronary artery bypass surgery with bilateral or single internal mammary artery grafts. *J Thorac Cardiovasc Surg*. 2016;151:1081–1089.

19. Schwann TA, Hashim SW, Badour S, Obeid M, Engoren M, Tranbaugh RF, Bonnell MR, Habib RH. Equipoise between radial artery and right internal thoracic artery as the second arterial conduit in left internal thoracic artery-based coronary artery bypass graft surgery: a multi-institutional study†. *Eur J Cardio-Thorac Surg*. 2016;49:188–195.

20. Stevens LM, Carrier M, Perrault LP, Hébert Y, Cartier R, Bouchard D, Fortier A, El-Hamamsy I, Pellerin M. Single versus bilateral internal thoracic artery grafts with concomitant saphenous vein grafts for multivessel coronary artery bypass grafting: effects on mortality and event-free survival. *J Thorac Cardiovasc Surg*. 2004;127:1408–1415.

21. Toumpoulis IK, Anagnostopoulos CE, Balaram S, Swistel DG, Ashton RC, DeRose JJ. Does bilateral internal thoracic artery grafting increase long-term survival of diabetic patients? *Ann Thorac Surg*. 2006;81:599–606; discussion 606–607.

22. Ashraf SS, Shaukat N, Akhtar K, Love H, Shaw J, Rowlands DJ, Keenan D. A comparison of early mortality and morbidity after single and bilateral internal mammary artery grafting with the free right internal mammary artery. *Br Heart J*. 1994;72:321–326.

23. Berreklouw E, Rademakers PP, Koster JM, van Leur L, van der Wielen BJ, Westers P. Better ischemic event-free survival after two internal thoracic artery grafts: 13 years of follow-up. *Ann Thorac Surg*. 2001;72:1535–1541.

24. Bonacchi M, Maiani M, Prifti E, Di Eusanio G, Di Eusanio M, Leacche M. Urgent/emergent

surgical revascularization in unstable angina: influence of different type of conduits. *J Cardiovasc Surg (Torino)*. 2006;47:201–210.

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

26. Carrier M, Cossette M, Pellerin M, Hébert Y, Bouchard D, Cartier R, Demers P, Jeanmart H, Pagé P, Perrault LP. Statin treatment equalizes long-term survival between patients with single and bilateral internal thoracic artery grafts. *Ann Thorac Surg*. 2009;88:789–795; discussion 795.

27. Danzer D, Christenson JT, Kalangos A, Khatchatourian G, Bednarkiewicz M, Faidutti B. Impact of double internal thoracic artery grafts on long-term outcomes in coronary artery bypass grafting. *Tex Heart Inst J*. 2001;28:89–95.

28. Dewar LR, Jamieson WR, Janusz MT, Adeli-Sardo M, Germann E, MacNab JS, Tyers GF. Unilateral versus bilateral internal mammary revascularization. Survival and event-free performance. *Circulation*. 1995;92:II8–13.

29. Endo M, Nishida H, Tomizawa Y, Kasanuki H. Benefit of bilateral over single internal mammary artery grafts for multiple coronary artery bypass grafting. *Circulation*. 2001;104:2164–2170.

30. Gansera B, Gillrath G, Lieber M, Angelis I, Schmidtler F, Kemkes BM. Are men treated better than women? Outcome of male versus female patients after CABG using bilateral internal thoracic arteries. *Thorac Cardiovasc Surg*. 2004;52:261–267.

31. Hirotani T, Nakamichi T, Munakata M, Takeuchi S. Risks and benefits of bilateral internal thoracic artery grafting in diabetic patients. *Ann Thorac Surg*. 2003;76:2017–2022.

32. Johnson WD, Brenowitz JB, Kayser KL. Factors influencing long-term (10-year to 15-year) survival after a successful coronary artery bypass operation. *Ann Thorac Surg*. 1989;48:19–24; discussion 24–25.

33. Jones JW, Schmidt SE, Miller CC, Beall AC, Baldwin JC. Bilateral internal thoracic artery operations in the elderly. *J Cardiovasc Surg (Torino)*. 2000;41:165–170.

34. Kieser TM, Lewin AM, Graham MM, Martin B-J, Galbraith PD, Rabi DM, Norris CM, Faris PD, Knudtson ML, Ghali WA, APPROACH Investigators. Outcomes associated with bilateral internal thoracic artery grafting: the importance of age. *Ann Thorac Surg*. 2011;92:1269–1275; discussion 1275–1276.

35. Naunheim KS, Barner HB, Fiore AC. 1990: Results of internal thoracic artery grafting over 15 years: single versus double grafts. 1992 update. *Ann Thorac Surg*. 1992;53:716–718.

36. Parsa CJ, Shaw LK, Rankin JS, Daneshmand MA, Gaca JG, Milano CA, Glower DD, Smith PK. Twenty-five-year outcomes after multiple internal thoracic artery bypass. *J Thorac Cardiovasc Surg*. 2013;145:970–975.

37. Pick AW, Orszulak TA, Anderson BJ, Schaff HV. Single versus bilateral internal mammary artery

grafts: 10-year outcome analysis. *Ann Thorac Surg*. 1997;64:599–605.

38. Tarelli G, Mantovani V, Maugeri R, Chelazzi P, Vanoli D, Grossi C, Ornaghi D, Panisi P, Sala A. Comparison between single and double internal mammary artery grafts: results over ten years. *Ital Heart J*. 2001;2:423–427.