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Multiple *versus* single arterial grafting in coronary artery bypass grafting: A meta-analysis of randomized controlled trials and propensity score studies

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ABSTRACT

Objectives: We conducted a meta-analysis of randomized controlled trials (RCTs) and propensity score (PS) studies comparing survival and major adverse cardiac and cerebrovascular events (MACCEs) of patients who underwent coronary artery bypass grafting (CABG) with multiple (MAG) *versus* single arterial grafting (SAG).
Methods: MEDLINE, Web of Science and Cochrane Library were used to find relevant literature (1960–2018). Survival at a follow-up ≥1 year, MACCEs and early outcomes were evaluated. Time-to-event outcomes were collected through hazard ratio (HR) along with their variance, and the other endpoints using frequencies from matched sample or adjusted odds ratios. Random effect models were used to compute combined statistical measures and 95% confidence intervals (CI) through generic inverse variance method (time-to-event) or Mantel-Haenszel method (binary events).
Results: Twenty-nine PS cohorts and 8 RCTs comprising 122,832 patients (52,178 MAG and 70,654 SAG) were included in this meta-analysis. MAG was associated with lower early mortality (OR: 0.82, 95%CI: 0.71–0.95, $p = .007$), long-term mortality (HR: 0.76, 95%CI: 0.73–0.78, $p < .001$) and MACCEs (HR: 0.85, 95%CI: 0.79–0.91, $p < .001$). Increased risk of sternal wound complications (SWC) was only observed when the bilateral internal mammary artery configuration was used for MAG (OR MAG BIMA: 1.96, 95%CI: 1.37–2.81, $p < .001$).
Conclusion: Although the BIMA configuration increases the risk of SWC, MAG improves both early and long-term survival as well as MACCEs in CABG.

1. Rationale

Although revascularization with an internal mammary artery graft to the left anterior descending artery is well established [1,2], the survival benefit of adding other arterial conduits to the remaining vessels is still debated since it is based almost exclusively in observational studies [3]. The majority of non-experimental series evidenced a substantial survival benefit from both right internal mammary artery (RIMA) [4–6] and radial artery (RA) [7,8] used as the second conduit compared with single internal mammary artery (SIMA) plus saphenous vein (SV) graft. However, the major randomized controlled trial (RCT) designed to answer the bilateral internal mammary artery (BIMA) *vs.* SIMA question, the Arterial Revascularization Trial (ART), failed to reach a positive result [9]. Not surprisingly, multiple arterial revascularization is not the mainstay at the majority of centres [10], despite most recent US [11] and European guidelines [12] as well as STS [13] recommendations.

One of the main difficulties in implementation of the ART was the relatively high crossover rate from BIMA to SAG thus underlying the difficulty for the surgeons to implement the BIMA grafts in every case. To overcome some of the limitations in ART, the ROMA (Randomized comparison of the clinical Outcome of single *versus* Multiple Arterial grafts) trial [14], currently recruiting, was designed to compare any multiple arterial graft (MAG) configuration *vs.* SAG without imposing to the surgeon which graft configuration should be adopted. The ROMA trial results are expected to be reported in 2030 and therefore there is a need to provide some interim guidance in the choice of arterial grafts. Previous meta-analyses have focused on single MAG configuration [15–17]. Hence, we aim to conduct a meta-analysis which mimics the ROMA

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trial groups, including all MAG configurations in the MAG group (BIMA, SIMA + RA), compared with SAG.

2. Objectives

To perform a meta-analysis of RCTs and PS studies, comparing MAG *versus* SAG topic in patients undergoing CABG. The main outcomes are long-term survival and major adverse cardiac and cerebrovascular events occurrence (MACCEs, death from any cause, stroke, myocardial infarction and/or repeat revascularization). Secondary endpoints include every individual event in the MACCEs composite outcome and early results, namely in-hospital death, sternal wound complications (SWC), repeat revascularization, stroke, myocardial infarction (MI) and re-intervention due to bleeding.

3. Methods

This study follows the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) statement (Table S1) [18]. MOOSE (Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies) [19] items were also consulted and incorporated as adequate.

3.1. Eligibility criteria

The search was limited by date of publication (January 1960–December 2018) and study language (English, Spanish or Portuguese) without geographical restrictions.

We included RCTs that compared clinical outcomes after MAG *vs.* SAG and prospective or retrospective cohort studies using PS methodology which included at least 200 patients. SAG was defined as any single arterial graft whereas MAG was defined as at least two arterial grafts. Supplemental grafts were allowed in both groups, except for additional arterial grafts in SAG. Studies with a follow-up period <1 year, reviews, cross-sectional studies, case-control studies, case series, case reports, abstracts conference presentations, editorials and expert opinions were excluded. Papers addressing outcomes in specific patient subgroups were also excluded. For the case of more than one article reporting the same cohort, we included the one with either longer follow-up or larger sample size, whichever seemed more informative by author consensus.

3.2. Information sources

Literature search was performed using MEDLINE, Web of Science and Cochrane Library databases. An additional manual search was done covering references of both original and review articles on the subject.

3.3. Search strategy

After a free manual search, we defined both MeSH terms (controlled language) and free text terms to express each component of PICO expression: P) Population, coronary artery disease adult patients submitted to CABG procedure; I) Intervention, multiple arterial grafts; C) Comparison, single arterial graft and O) Outcomes, survival, MACCEs and in-hospital endpoints.

The detailed search queries are available at Tables S2 and S3.

3.4. Study records

3.4.1. Data management

Records identified in each database were imported and managed through EndNote Web and Microsoft Excel. Duplicates were automatically removed by software and manually confirmed.

3.4.2. Selection process

Two reviewers (FAS and JPLM) independently screened the titles and abstracts of all citations identified by the searches and compared the screening results for potentially eligible studies. All full texts of potentially eligible studies were retrieved and assessed for inclusion criteria by both reviewers. Discrepancies were settled by author consensus.

3.4.3. Data collection process

Fig. 1 depicts the flow process chart of study selection. Using a standardized form in Microsoft Excel, two reviewers (FAS and JPLM) extracted data into a database. Databases were compared and, in case of discrepancy, studies were double-checked by both reviewers for consistency. Authors of selected studies were not contacted to resolve missing or unclear reporting of data.

3.4.4. Data items

Both clinical and methodological data were gathered from the included studies using all data from text, tables and figures. Clinical definitions were considered as reported by each study and some categories were clustered for homogeneity. Study type, study period, country, overall and per group sample size, type of grafts, preoperative clinical characteristics including cardiovascular risk factors and comorbidities, operative data: off-pump CABG, number of grafts, follow-up duration and immediate and long-term outcomes were systematically collected.

Both the primary endpoint and secondary endpoints were collected through treatment effect estimates derived from PS analysis or directly from intention-to-treat analysis of RCTs: hazard ratios (HR) and its variance for time-to-event analyses and odds ratio (OR) or absolute frequencies for immediate results. PS data items are described in Supplementary Appendix 3. One of these studies [20] provided two distinct cohorts contributing as two articles stated as Schwann 2014a and Schwann 2014b. Also, Benedetto and colleagues [21] provided a comprehensive comparison between MAG and SAG according to pump-status: off-pump subgroup stated as Benedetto 2017a and on-pump stated as Benedetto 2017b. Regarding the study by Schwann et al. [22], which compared two distinct MAG groups (SIMA + RA and BIMA) with SAG, only the BIMA group was selected for comparison since the SIMA + RA group was too small to be also compared with BIMA in matched triplets. Also, although our previous BIMA *vs.* SIMA study [23] did not meet this meta-analysis group definition as 10 patients within the SIMA group had one RA graft, we reanalysed the data excluding those patients. Finally, as patients randomized to SIMA group in the ART trial could receive radial arteries as supplementary grafts, we used data from the subgroup analysis without radial artery [9].

3.4.5. Risk of bias in individual studies

The quality of observational included studies was assessed using the Newcastle-Ottawa Scale, maximum of nine stars [24] and RCTs using Cochrane scale [25].

3.5. Data analysis

Continuous variables are expressed as mean ± standard deviation or median (interquartile range), as reported by authors. Categorical variables are reported as absolute and relative frequency (%) using the overall sample in both PS adjusted and PS stratification studies, using the matched cohort in PS matching (PSM) studies and the weighting cohort according to estimate sample size (ESS) in PS weighting (PSW) studies. SAG group was used as the reference category in all comparisons. The I^2 was calculated for each analysis and heterogeneity was considered low ($I^2 < 49\%$), moderate (I^2 50–74%), or high ($I^2 > 75\%$) [26].

The primary outcomes, long-term survival and freedom from MACCEs, were assessed through adjusted or matched HR, and 95%

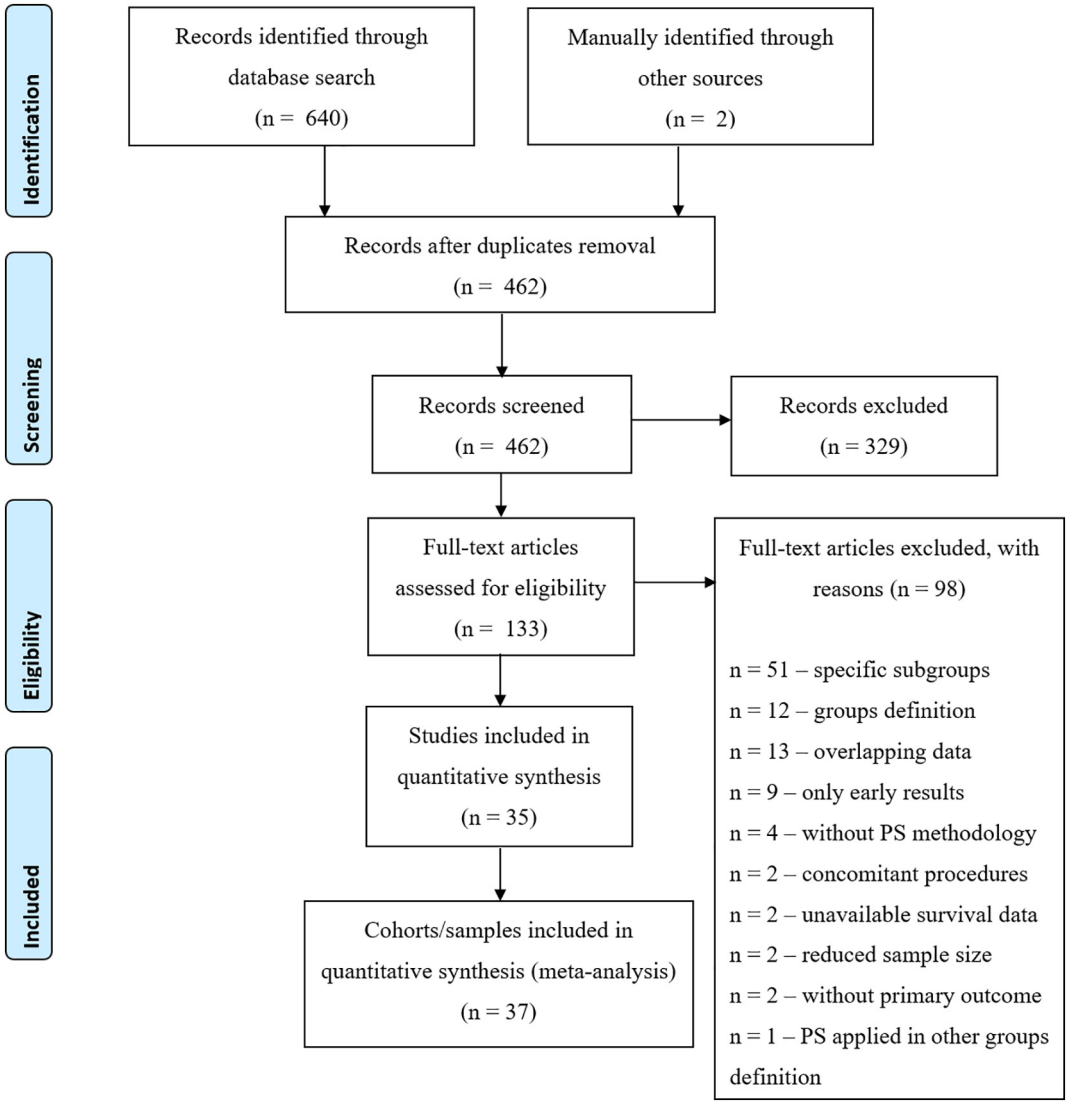

Fig. 1. Flow chart for study selection. PS, propensity score.

confidence interval (CI) collected from the included studies. When not readily provided, HR was estimated from Kaplan Meier curves of PSM, PSW, or PS adjustment (PSA) groups using GetData Digitizer version 2.26.0.20 application software and an R script provided by Guyot et al. [27]. When neither HR nor good-quality curves were available, we calculated the incidence rate ratio (IRR) if the number of events and mean follow-up was provided using *metainc* function of the meta R package [28] or relative risk (RR) if cumulative incidences were provided.

Pooled HR and 95% CI were computed by the generic inverse variance method using a random effect model.

For the secondary endpoints, in PS matched cohorts we collected the number of events per group and calculated odds ratio whereas in PSW or PSA studies we collected the adjusted OR and computed pooled OR using the generic inverse variance method.

Review Manager 5.3, as well as the *meta* [28] and *metafor* [29] packages based on the R environment (version 3.6.0) [30] were used to handle the extracted data.

3.6. Risk of bias across studies

The funnel plots, together with Egger's linear regression method (*metabias* from the *meta* R package), were used to assess publication bias risk [31].

3.7. Subgroup analysis

Three subgroup analyses were performed: 1) according to study type: RCTs *vs.* PS; 2) according to follow-up time: short follow-up (mean/median follow-up <5 years), mid-term follow-up (5 to 10 years) and long-term follow-up (≥10 years); and 3) according to MAG configuration (BIMA, SIMA + RA and BIMA or SIMA + RA).

4. Results

4.1. Selected studies

Fig. 1 presents the study flow diagram. From 642 titles, 180 were duplicates. The remaining 462 were screened by title and abstract and 133 were considered for full-text review. A total of 35 articles (37 cohorts) were considered for quantitative analysis.

4.2. Study characteristics

Table 1 presents the most relevant study characteristics and Table S4 details the pre-operative and operative data.

The selected studies included 8 RCTs [9,32–38] and 29 PS cohorts [6,8,20–23,39–50]. The overall sample included 122,832 patients

(52,178 MAG, 70654 SAG): 5095 from RCTs (2755 MAG, 2340 SAG) and 117,737 from PS cohorts (49,423 MAG, 68314 SAG).

All the included studies reported survival results with mean follow-up time ranging from 1 [32,33,35] to 16 years [49]. Eight studies (12,344 MAG, 13,858 SAG) reported follow-up <5 years, 21 studies (31,002 MAG, 47,266 SAG) between 5 and 10 years, and 8 studies (8832 MAG, 9530 SAG) ≥ 10 years. In 16 studies MAG consisted of either BIMA or SIMA + RA (33,741 MAG, 49099 SAG), in 12 of BIMA (11,858 MAG, 14,967 SAG) and the remaining 9 of SIMA + RA (6579 MAG, 6588 SAG).

After applying PS methodologies, similar pre-operative characteristics were found between MAG and SAG in observational studies.

4.3. Risk of bias within studies

The Newcastle-Ottawa Scale and Cochrane Risk Bias confirmed good quality of the majority of included studies (Table S5).

4.4. Primary analysis

4.4.1. Long-term survival

Although several studies did not report the adjusted HR, it was derived from curves [6,20,40,41,43,49] or by IRR [32,33,35–38] or RR estimation [58]. Overall, MAG significantly improved survival when compared to SAG (pooled HR: 0.76, 95%CI: 0.73–0.78, p < .001, Fig. 2). A low grade of heterogeneity was found (I^2 = 18%, p = .18) mainly at the expense of observational studies (I^2 = 12% *vs.* I^2 = 0% for RCTs). No publication bias was detected (p = .60, Fig. S1A).

As for the prespecified subgroup analyses, a significant difference was found regarding study type (p = .005) showing high heterogeneity across subgroup results (I^2 = 88%). Although no significant differences were found across follow-up subgroups, studies with longer follow-up, over 10 years, presented the larger effect size, pooled HR: 0.74, 95%CI: 0.67–0.81, while studies with follow-up between 5 and 10 years provided more precise estimates (pooled HR: 0.77, 95%CI:0.74–0.79, Fig. S2) which can be partly ascribed to larger sample size. Also, MAG with BIMA configuration provided a larger, but less precise effect size (pooled HR: 0.74, 95%CI: 0.68–0.81, Fig. S3).

4.4.2. Long-term MACCEs

Although 16 studies reported long-term MACCEs (different definitions of MACCEs adopted are given in Table S6), data in 2 RCTs [35,36] was not suitable to be pooled and ART did not provide subgroup analysis for secondary endpoints. For Stand-in-Y trial [37], available data to pool just included SIMA + RA strategy, thus the aggregate estimate included 13 studies with 58,019 patients (28,530 MAG, 29489 SAG). We observed a significant 15% risk reduction in MAG (pooled HR: 0.85, 95%CI: 0.79–0.91, p < .001, Fig. 3) with moderate grade heterogeneity (I^2 = 58%, p = .005), mainly due to observational studies (I^2 = 67% *vs.* I^2 = 1% in RCTs), and no publication bias (p = .56, Fig. S1B).

No significant differences were found regarding the type of study (p = .37) or length of follow-up (p = .62, Fig. S4) subgroup analyses. Still, a higher effect size was found for the longer follow-up subgroup (>10-years pooled HR: 0.80, 95%CI: 0.70–0.90).

Stratifying according to MAG configuration was based on 2 studies for BIMA and another 2 for SIMA + RA configurations while the remaining 9 studies allowed both configurations. No subgroup differences were found (p = .44; Fig. S5).

4.5. Secondary endpoints

Long-term stroke, myocardial infarction and re-revascularization are presented in Supplementary Appendix 1.

4.5.1. Early mortality

Thirty-two studies reported early mortality as defined in Table S6. Four were excluded from analysis: 1 RCT reported zero events [38], ART did not provide this data for the subgroup analysis [9] and 2 PS studies [6] did not report adjusted values. Although only 1 out of 28 included studies showed significant benefit in early mortality [21], the pooled estimate showed 18% risk reduction for MAG (OR: 0.82, 95%CI: 0.71–0.95, p = .007, Fig. S8). We found neither significant heterogeneity (I^2 = 0%) nor publication bias (p = .58, Fig. S11A).

4.5.2. Sternal wound complications

From 26 studies that quantified SWC according to Table S6 definitions, 8 were excluded: 2 for encompassing the in-hospital period [32,44], 1 because no events were reported [46], 4 PS studies due to lack of adjusted data [6,48] and ART which did not report this outcome for the no RA analysis [9]. MAG showed 50% increased risk for SWC (OR: 1.50, 95%CI: 1.12–2.01, p = .006, Fig. S9), but this was entirely attributable to the BIMA configuration as confirmed in the prespecified subgroup analysis (p = .002 for subgroup differences, OR BIMA: 1.96, 95% CI: 1.37–2.81). A low grade of heterogeneity was found (I^2 = 45%) more marked within the BIMA subgroup (I^2 = 25% *vs.* I^2 = 0% within the other two subgroups). No publication bias was detected (p = .15, Fig. S11B).

Other early results, including re-revascularization, stroke, MI and re-intervention due to bleeding, are presented in Supplementary Appendix 2.

5. Discussion

Though observational studies have consistently supported the use of MAG compared with SAG showing better survival for multivessel coronary artery disease, and despite the noticeable difference in angiographic patency between arterial and vein grafts on follow-up [61], surprisingly the largest RCT addressing this issue to date, ART, had neutral outcomes. Raising substantial debate between practitioners that favour one approach over the other, various issues in RCT implementation have been proposed as reasonable explanations for the neutral results. Indeed, the *as treated* analysis of ART also supports lower 10-year mortality and MACCEs with MAG. The ROMA trial was designed as a multicentre international event-driven RCT powered to detect differences in MACCEs and finally address the issue of MAG *vs.* SAG as CABG standard of care [14]. To the best of our knowledge, this is the first meta-analysis of PS observational and RCT studies performed to date comparing patients submitted to CABG with MAG *vs.* SAG, regardless of the technique used. We pooled data from 122,832 patients enrolled in PS -matched, −adjusted, −weighted or –stratified observational cohort studies and previous RCTs.

Interpretation of individual studies is limited by lack of randomization, small sample size for estimating survival outcome (all but one RCT < 1000 patients), short length of follow-up (14% PS cohorts and 50% RCTs < 5 years) and representativeness of general real-world practice. Although we limited observational study inclusion solely to studies that employed PS, mitigating some of the drawbacks of observational studies by offering a quasi-randomized selection of patients [62], we must still acknowledge that unmeasured confounders are not a straightforward topic [63].

Nevertheless, the weight of observational studies remained the main contributor to the outcomes of this meta-analysis (weight in long-term survival outcome: 95.8% for PS and 4.2% for RCTs). Even if treatment effect in both RCTs and PS studies shows the same trend towards a benefit from MAG, a significant difference across the type of study subgroup was uncovered, supporting the need for ROMA trial to address this issue. As previously reported by Dahabreh and colleagues [64], it would be expected that PS studies will show an extreme magnitude of the treatment effect when compared to RCTs. This could be attributed to a differential publication bias. While small or neutral effects from observational studies are unlikely to be accepted for publication or even submitted, similar results from RCTs have a higher likelihood of being

Table 1
Overview of propensity score studies and randomized controlled trials included in the quantitative synthesis.

Study/Year	Region	Type of study	MAG Definition	Total (n)	SAG (n)	SAG matched (n)	MAG (n)	MAG matched (n)	Study period	Follow-up
Benedetto 2013	UK	PSM	SIMA + RA	9005	8069	809	936	809	March 1996 to May 2012	5 to 10 years
Benedetto 2014	UK	PSM	BIMA	4195	3445	750	750	750	April 2001–May 2013	<5 years
Benedetto 2017a	UK	PSW	BIMA or SIMA + RA	6230	4412	ESS: 2567	1818	ESS: 739	1996- April 2015	5 to 10 years
Benedetto 2017b	UK	PSW	BIMA or SIMA + RA	6402	5194	ESS: 3972	1208	ESS: 388	1996- April 2015	5 to 10 years
Bisleri 2017	Italy	PSM	BIMA or SIMA + RA (TA)	973	587	151	386	151	March 1999–May 2004	5 to 10 years
Buxton 2014	Australia	PSM	BIMA or SIMA + RA (TA)	3774	786	384	2988	384	January 1995–2010	>10 years
DeSimone 2018	UK	PSM/PSA/PSW	BIMA	47,984	46,502	1297	1482	1297	1992–2014	>10 years
Garatti 2014	Italy	PSM	BIMA or SIMA + RA (TA)	2306	2097	243	209	209	January 1994–December 1996	>10 years
Goldstone 2018	USA	PSM	BIMA or SIMA + RA	59,432	53,566	5813	5866	5813	January 2006–July 2011	5 to 10 years
Grau 2012	USA	PSM	BIMA	6313	4854	928	1459	928	January 1994–December 2010	5 to 10 years
Guru 2006	Canada	PSM	BIMA or SIMA + RA	53,727	47,214	5491	6513	5491	September 1991–March 2002	5 to 10 years
Kurlansky 2010	USA	PSM/PSS	BIMA	4584	2369	2197	2215	2197	February 1972–May 1994	>10 years
Lin 2013	USA	PSM	SIMA + RA	1248	NR	260	NR	260	January 1997–December 2001	5 to 10 years
Locker 2012	USA	PSM	BIMA or SIMA + RA	8622	7435	1153	1187	1153	January 1993–December 2009	5 to 10 years
Luthra 2018	UK	PSM	BIMA or SIMA + RA	3995	2757	1226	1238	1226	October 2004–March 2014	5 to 10 years
Lytle 2004	USA	PSM	BIMA	10,124	8123	1152	2001	1152	1971–1989	>10 years
Parasca 2015	Multicentre (17 countries)	PSM	BIMA or SIMA + RA	1419	963	432	456	432	March 2005–April 2008	5 to 10 years
Pu 2017	Canada	PSW/PSM	BIMA or SIMA + RA	20,076	14,496	4842	5580	4842	January 2000–December 2014	5 to 10 years
Puskas 2012	Georgia	PSA	BIMA	3527	2715	NA	812	NA	January 2002–December 2010	<5 years
Raja 2010	England	PSA	BIMA or SIMA + RA (TA)	1386	806	NA	580	NA	September 1998–September 2008	5 to 10 years
Rocha 2018	Canada	PSM	BIMA or SIMA + RA	50,230	38,951	8629	11,279	8629	October 2008–March 2016	<5 years
Saraiva 2018	Portugal	PSW	BIMA	2414	1478	ESS: 1992	936	ESS: 1460	January 2004–December 2013	5 to 10 years
Schwann 2014a	USA	PSM	SIMA + RA	4908	2547	1799	2361	1799	1996–2006	5 to 10 years
Schwann 2014b	USA	PSM	SIMA + RA	4944	2974	995	1970	995	1995–2011	5 to 10 years
Schwann 2016	USA	PSM/PSM + PSA	BIMA	5125	4484	551	641	551	1987–2011	>10 years
Shi 2016	Australia	PSM	SIMA + RA	4006	786	507	3220	507	1995–2010	5 to 10 years
Stevens 2004	Canada	PSS	BIMA	4382	2498	NA	1808	NA	March 1985 – April 1995	>10 years
Tranbaugh 2015	USA	PSM/PSA	SIMA + RA	4945	2975	1023	1970	1023	January 1995–June 2011	5 to 10 years
Zacharias 2004	USA	PSM	SIMA + RA	3161	1869	925	1292	925	January 1996–December 2002	<5 years
Damgaard 2009	Denmark	RCT	SIMA + RA	331	170	NA	161	NA	February 2002–February 2005	<5 years
Goldman 2011	USA	RCT	SIMA + RA	733	367	NA	366	NA	February 2003–February 2008	<5 years
Kim 2018	South Korea	RCT	BIMA	224	112	NA	112	NA	September 2008–October 2011	5 to 10 years
Muneretto 2003	Italy	RCT	BIMA or SIMA + RA (TA)	200	100	NA	100	NA	1999–2001	<5 years
Myers 2000	USA	RCT	BIMA (TA)	162	81	NA	81	NA	January 1990–December 1994	5 to 10 years
Nasso 2009	Italy	RCT	BIMA or SIMA + RA	803	202	NA	601	NA	January 2003–April 2006	<5 years
Petrovic 2015	Serbia	RCT	SIMA + RA	200	100	NA	100	NA	March 2001–November 2003	5 to 10 years
Taggart 2019	Multicentre (7 countries)	RCT	BIMA	2442	1208	NA	1234	NA	June 2004–December 2007	>10 years

BIMA, bilateral internal mammary artery; ESS – estimated sample size; MAG – multiple arterial graft; NA – not applicable; NR – not reported; PSA – propensity score adjustment; PSM – propensity score matching; PSS – propensity score stratification; PSW – propensity score weighting; RA – radial artery; RCT – randomized controlled trial; SAG – single arterial graft; SIMA – single internal mammary artery; TA – total arterial.

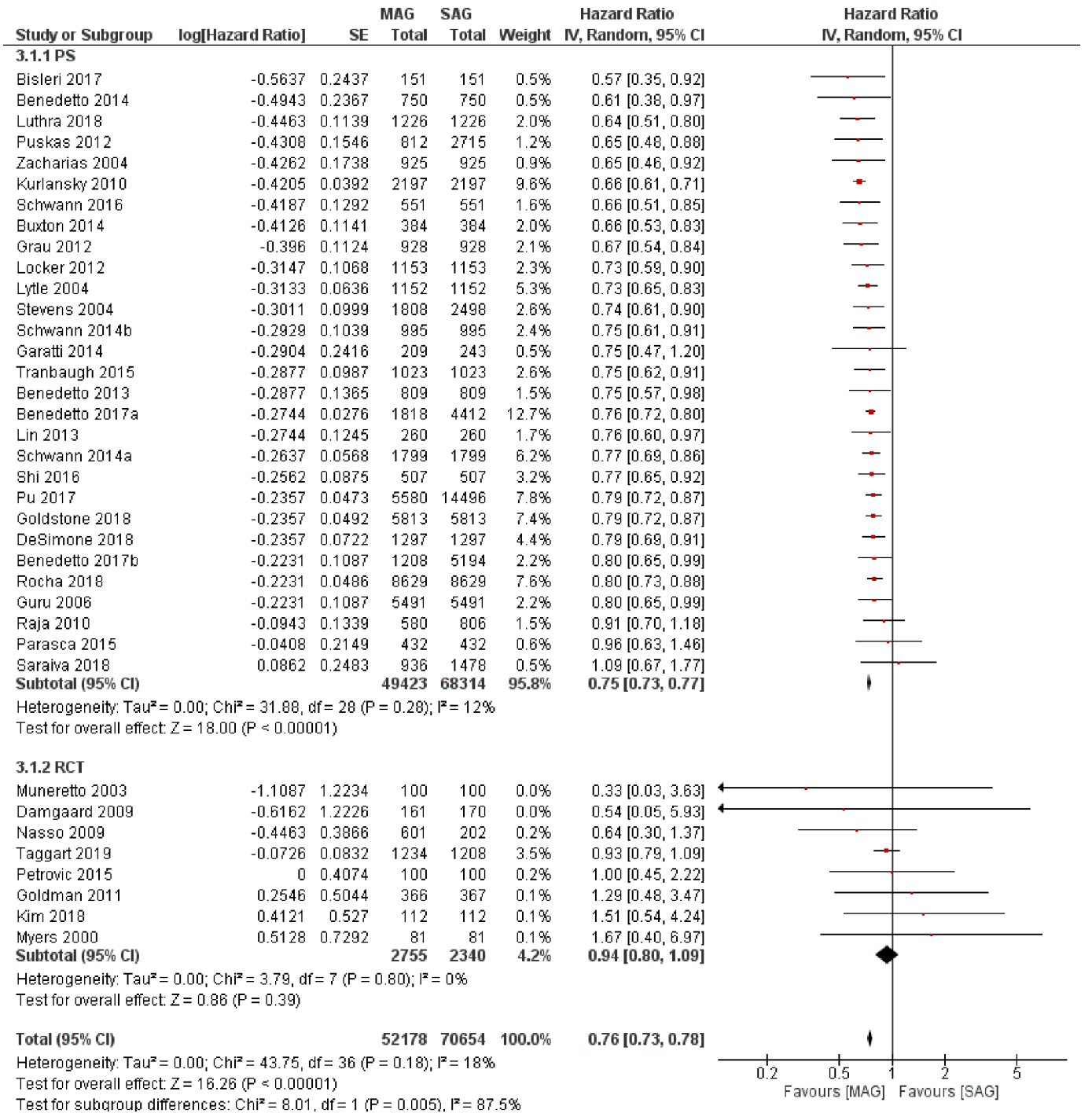

Fig. 2. Forest plot comparing the effect of multiple arterial (MAG) *versus* single arterial grafting (SAG) on late mortality after coronary artery bypass grafting across individual studies and through pooled estimates. IV, inverse variance; PS, propensity score; RCT, randomized controlled trial; SE, standard error.

submitted and accepted for publication [65]. The highly selective samples for RCTs could also contribute for subgroup differences.

Previous RCTs addressing MAG *vs.* SAG are underpowered for long-term survival estimation, having angiographic primary outcomes and short follow-up. The Stand-in-Y trial [37] randomized 815 patients to one of 4 strategies, 3 of them constituting MAG, and although no survival advantage was reported in any study group, a significant benefit in MACCEs for the 3 MAG groups comparing with SAG (appropriate data to pool not available) was reported. These results emphasize the limited power for this study to report survival differences for the short 2-years of follow-up, the wide-ranging confidence interval, and its reduced weight for the pooled survival result (0.2%). Indeed, sample size estimation was done using historical data for the expected rate of graft failure outcome. CARRPO [32] and Goldman et al. [33] trials' sample size were also estimated accounting for 5- and 1-year graft patency outcomes, respectively, and both presented results for 1-year survival (3 and 16 deaths, each) totalizing a 0% and 0.1% of weighting for this meta-analysis. Differential crossover rates were reported in several trials: CARRPO [32], Goldman [33], Myers [36] and ART [9] trials crossover from arterial to conventional group were 7%, 9%, 4% and 14% of patients,

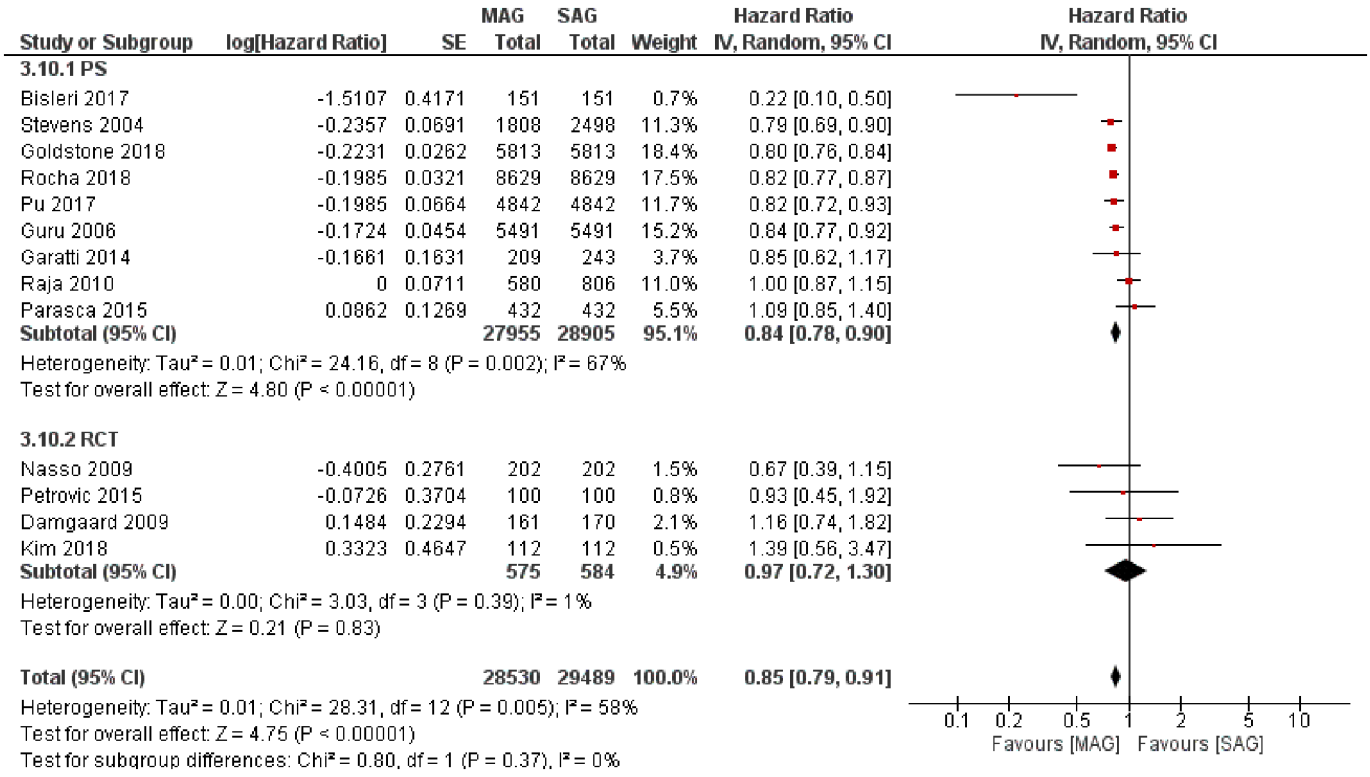

Fig. 3. Forest plot comparing the effect of multiple arterial (MAG) *versus* single arterial grafting (SAG) on long-term incidence of major adverse cardiac and cerebrovascular events (MACCEs) after coronary artery bypass grafting across individual studies and through pooled estimates. IV, inverse variance; PS, propensity score; RCT, randomized controlled trial; SE, standard error.

respectively, representing higher rates than the reverse crossover from conventional to arterial group (2%, 1%, 1% and 4%). Besides that, within CARRPO and Myers trials the arterial group included 8 out of 161 and 8 out of 81 patients, respectively, with only one arterial conduit. Even if SAVE RITA (SAphenous Vein *versus* Right Internal Thoracic Artery as a Y-Composite Graft trial) [34] and Petrovic and colleagues [38] reported 5- and 8-years clinical outcomes, the former was designed to 1-year angiographic patency and the latter had randomized only 200 patients, without a prespecified assumption. ART is the only included RCT that was specifically designed for 10-year death from any-cause and its results contributed to 3.5% of the pooled result.

Besides the lack of level 1 evidence, MAG is not the mainstay in CABG due to higher complexity of surgical technique, concerns about SWC and early "quality metrics", increasing number of elderly high-risk patients, lack of surgical experience or simply inertial hurdles [66, 67]. These hurdles became noticeably clear in ART considering its differential crossover rates and the modification of effect according to surgeon volume. Indeed, surgical centre experience partly dictates long-term outcomes from BIMA grafting [67].

Our results corroborate the concerns regarding SWC: there was a nearly 2-fold increase in the risk of SWC in MAG with BIMA grafting configuration, which was not the case with other configurations. Nevertheless, MAG was associated with reduced mortality on long-term follow-up (24% and 26% risk reduction overall and in studies over 10-years of follow-up, respectively), as well as with reduced MACCEs incidence (20% risk reduction on follow-up over 10 years) and even with lower rates of early mortality (18% risk reduction) thereby clearly offsetting the drawback of SWC in the BIMA subset of MAG patients. Conforming to these results, recent meta-analyses have shown a survival benefit of BIMA over SIMA grafting [15] and SIMA + RA over SIMA [17].

Concerning graft configurations in MAG, Benedetto and colleagues published a meta-analysis of PS matched studies that reported superiority of BIMA configuration over SIMA + RA in long-term survival, freedom from repeat revascularization and similar early mortality and SWC when skeletonized harvesting was used [70]. Cumulative evidence regarding skeletonized harvesting supports lack of increased risks of SWC [71, 72], and this is the recommended harvesting technique by ESC guidelines mainly in groups at high risk of SWC, such as diabetic patients [73]. We found reports on type of ITA harvesting in 5 out of 7 studies considered in our SWC results of BIMA *vs.* SAG [22,36,39]. The heterogeneity amongst studies precludes considerations on the role of skeletonized harvesting.

5.1. Study limitations

The present meta-analysis has limitations: i) diversity of study design, patient's selection and PS models; ii) heterogeneity regarding endpoint definitions; iii) although adjusted outcomes were analysed, selection bias in observational studies might have contributed to better results since usually younger and healthier patients are selected for MAG and "eye-balling" from surgeon experience [63], cannot be measured; iv) RCTs were scarce and had shorter follow-up periods; and, finally, v) the role of comorbidities and specific patient subgroups were not assessed and which subgroup of patients is more likely to benefit from MAG is still to be determined.

6. Conclusion

Pooling data of RCTs and PS studies comparing MAG *vs.* SAG CABG, showed a benefit of MAG in long-term survival and MACCEs, as well as early survival, although the BIMA configuration raised the risk of SWC.

Author Contribution

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.08.001.

References

[1] F.D. Loop, B.W. Lytle, D.M. Cosgrove, et al., Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events, N. Engl. J. Med. 314 (1) (1986) 1–6.
[2] M.J. Boylan, B.W. Lytle, F.D. Loop, et al., Surgical treatment of isolated left anterior descending coronary stenosis. Comparison of left internal mammary artery and venous autograft at 18 to 20 years of follow-up, J. Thorac. Cardiovasc. Surg. 107 (3) (1994) 657–662.
[3] M. Gaudino, F.G. Bakaeen, U. Benedetto, et al., Arterial grafts for coronary bypass: a critical review after the publication of ART and RADIAL, Circulation. 140 (15) (2019) 1273–1284.
[4] M.J. Dorman, P.A. Kurlansky, E.A. Traad, D.L. Galbut, M. Zucker, G. Ebra, Bilateral internal mammary artery grafting enhances survival in diabetic patients: a 30-year follow-up of propensity score-matched cohorts, Circulation. 126 (25) (2012) 2935–2942.
[5] D.L. Galbut, P.A. Kurlansky, E.A. Traad, M.J. Dorman, M. Zucker, G. Ebra, Bilateral internal thoracic artery grafting improves long-term survival in patients with reduced ejection fraction: a propensity-matched study with 30-year follow-up, J. Thorac. Cardiovasc. Surg. 143 (4) (2012), 844–53.e4.
[6] P.A. Kurlansky, E.A. Traad, M.J. Dorman, D.L. Galbut, M. Zucker, G. Ebra, Thirty-year follow-up defines survival benefit for second internal mammary artery in propensity-matched groups, Ann. Thorac. Surg. 90 (1) (2010) 101–108.
[7] T.A. Schwann, L. Al-Shaar, R.F. Tranbaugh, et al., Multi versus single arterial coronary bypass graft surgery across the ejection fraction spectrum, Ann. Thorac. Surg. 100 (3) (2015) 810–817.
[8] U. Benedetto, M. Codispoti, Age cutoff for the loss of survival benefit from use of radial artery in coronary artery bypass grafting, J. Thorac. Cardiovasc. Surg. 146 (5) (2013) 1078–1084.
[9] D.P. Taggart, U. Benedetto, S. Gerry, et al., Bilateral versus single internal-thoracic-artery grafts at 10 years, N. Engl. J. Med. 380 (5) (2019) 437–446.
[10] S.J. Head, J. Borgermann, R.L. Osnabrugge, et al., Coronary artery bypass grafting: part 2-optimizing outcomes and future prospects, Eur. Heart J. 34 (37) (2013) 2873–2886.
[11] L.D. Hillis, P.K. Smith, J.L. Anderson, et al., 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, J. Am. Coll. Cardiol. 58 (24) (2011) e123–e210.
[12] F.-J. Neumann, M. Sousa-Uva, A. Ahlsson, et al., 2018 ESC/EACTS guidelines on myocardial revascularization, Eur. Heart J. 40 (2) (2018) 87–165.
[13] G.S. Aldea, F.G. Bakaeen, J. Pal, et al., The society of thoracic surgeons clinical practice guidelines on arterial conduits for coronary artery bypass grafting, Ann. Thorac. Surg. 101 (2) (2016) 801–809.
[14] M. Gaudino, J.H. Alexander, F.G. Bakaeen, et al., Randomized comparison of the clinical outcome of single versus multiple arterial grafts: the ROMA trial-rationale and study protocol, Eur. J. Cardiothorac. Surg. 52 (6) (2017) 1031–1040.
[15] S.N. Buttar, T.D. Yan, D.P. Taggart, D.H. Tian, Long-term and short-term outcomes of using bilateral internal mammary artery grafting versus left internal mammary artery grafting: a meta-analysis, Heart. 103 (18) (2017) 1419–1426.
[16] M. Gaudino, M. Rahouma, A. Abouarab, et al., Radial artery versus saphenous vein as the second conduit for coronary artery bypass surgery: a meta-analysis, J. Thorac. Cardiovasc. Surg. 157 (5) (2019), 1819–25.e10.
[17] M. Gaudino, R. Lorusso, M. Rahouma, et al., Radial artery versus right internal thoracic artery versus saphenous vein as the second conduit for coronary artery bypass surgery: a network Meta-analysis of clinical outcomes, J. Am. Heart Assoc. 8 (2) (2019), e010839.
[18] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, J. Clin. Epidemiol. 62 (10) (2009) 1006–1012.
[19] D.F. Stroup, J.A. Berlin, S.C. Morton, et al., Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group, Jama. 283 (15) (2000) 2008–2012.
[20] T.A. Schwann, R.F. Tranbaugh, K.R. Dimitrova, et al., Time-varying survival benefit of radial artery versus vein grafting: a multiinstitutional analysis, Ann. Thorac. Surg. 97 (4) (2014) 1328–1334.
[21] U. Benedetto, M. Caputo, G. Mariscalco, et al., Impact of multiple arterial grafts in off-pump and on-pump coronary artery bypass surgery, J. Thorac. Cardiovasc. Surg. 153 (2) (2017), 300–9.e6.
[22] T.A. Schwann, S.W. Hashim, S. Badour, et al., 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 studydagger, Eur. J. Cardiothorac. Surg. 49 (1) (2016) 188–195.
[23] F.A. Saraiva, N. Girerd, R.J. Cerqueira, et al., Survival after bilateral internal mammary artery in coronary artery bypass grafting: are women at risk? Int. J. Cardiol. 270 (2018) 89–95.
[24] G.A.S.B. Wells, D. O'Connell, J. Peterson, V. Welch, P. Tugwell, The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis, 3rd Symposium on Systematic Reviews: Beyond the Basics, 2000, July 3–5.
[25] J.P. Higgins, J. Savović, M.J. Page, R.G. Elbers, J.A. Sterne, Cochrane handbook for systematic reviews of interventions version 6.0, updated Chapter 8: Assessing Risk of Bias in a Randomized Trial, Cochrane, July 2019 , editor 2019 Available from https://training.cochrane.org/handbook/current/chapter-08#section-8-9.
[26] J.P. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, BMJ (Clin. Res. Ed.). 327 (7414) (2003) 557–560.
[27] P. Guyot, A.E. Ades, M.J.N.M. Ouwens, N.J. Welton, Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves, BMC Med. Res. Methodol. 12 (1) (2012) 9.
[28] G. Schwarzer, Meta: an R package for meta-analysis, R News 7 (3) (2007) 40–45.
[29] W. Viechtbauer, Conducting meta-analyses in R with the metafor package, J. Stat. Softw. 36 (3) (2010).
[30] R Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, 2019.
[31] M. Egger, G. Davey Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test, BMJ (Clin. Res. Ed.). 315 (7109) (1997) 629–634.
[32] S. Damgaard, J. Wetterslev, J.T. Lund, et al., One-year results of total arterial revascularization vs. conventional coronary surgery: CARRPO trial, Eur. Heart J. 30 (8) (2009) 1005–1011.
[33] S. Goldman, G.K. Sethi, W. Holman, et al., Radial artery grafts vs. saphenous vein grafts in coronary artery bypass surgery: a randomized trial, Jama. 305 (2) (2011) 167–174.
[34] M.S. Kim, H.Y. Hwang, J.S. Kim, S.J. Oh, M.J. Jang, K.B. Kim, Saphenous vein versus right internal thoracic artery as a Y-composite graft: five-year angiographic and clinical results of a randomized trial, J. Thorac. Cardiovasc. Surg. 156 (4) (2018), 1424–33.e1.
[35] C. Muneretto, A. Negri, J. Manfredi, et al., Safety and usefulness of composite grafts for total arterial myocardial revascularization: a prospective randomized evaluation, J. Thorac. Cardiovasc. Surg. 125 (4) (2003) 826–835.
[36] W.O. Myers, R. Berg, J.F. Ray, et al., All-artery multigraft coronary artery bypass grafting with only internal thoracic arteries possible and safe: a randomized trial, Surgery 128 (4) (2000) 650–659.
[37] G. Nasso, R. Coppola, R. Bonifazi, F. Piancone, G. Bozzetti, G. Speziale, 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. 137 (5) (2009) 1093–1100.
[38] I. Petrovic, D. Nezic, M. Peric, et al., Radial artery vs. saphenous vein graft used as the second conduit for surgical myocardial revascularization: long-term clinical follow-up, J. Cardiothorac. Surg. 10 (2015) 127.
[39] U. Benedetto, M. Amrani, J. Gaer, et al., 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. 148 (6) (2014) 2699–2705.
[40] G. Bisleri, L. Di Bacco, D. Turturiello, et al., Improved outcomes of total arterial myocardial revascularization in elderly patients at long-term follow-up: a propensity-matched analysis, Ann. Thorac. Surg. 103 (2) (2017) 517–525.
[41] B.F. Buxton, W.Y. Shi, J. Tatoulis, J.A. Fuller, A. Rosalion, P.A. Hayward, Total arterial revascularization with internal thoracic and radial artery grafts in triple-vessel coronary artery disease is associated with improved survival, J. Thorac. Cardiovasc. Surg. 148 (4) (2014) 1238–1243.

[42] J.P. DeSimone, D.J. Malenka, P.W. Weldner, et al., Coronary revascularization with single versus bilateral mammary arteries: is it time to change? Ann. Thorac. Surg. 106 (2) (2018) 466–472.
[43] A. Garatti, S. Castelvecchio, A. Canziani, et al., Long-term results of sequential vein coronary artery bypass grafting compared with totally arterial myocardial revascularization: a propensity score-matched follow-up studydagger, Eur. J. Cardiothorac. Surg. 46 (6) (2014) 1006–1013.
[44] A.B. Goldstone, P. Chiu, M. Baiocchi, et al., Second arterial versus venous conduits for multivessel coronary artery bypass surgery in California, Circulation 137 (16) (2018) 1698–1707.
[45] V. Guru, S.E. Fremes, J.V. Tu, How many arterial grafts are enough? A population-based study of midterm outcomes, J. Thorac. Cardiovasc. Surg. 131 (5) (2006) 1021–1028.
[46] J. Lin, W. Cheng, L.S. Czer, et al., Coronary artery bypass graft surgery using the radial artery as a secondary conduit improves patient survival, J. Am. Heart Assoc. 2 (4) (2013), e000266.
[47] C. Locker, H.V. Schaff, J.A. Dearani, et al., Multiple arterial grafts improve late survival of patients undergoing coronary artery bypass graft surgery: analysis of 8622 patients with multivessel disease, Circulation 126 (9) (2012) 1023–1030.
[48] S. Luthra, M.M. Leiva-Juarez, A. John, M. Matuszewski, I.S. Morgan, J.S. Billing, A second arterial conduit to the circumflex circulation significantly improves survival after coronary artery bypass surgery, Eur. J. Cardiothorac. Surg. 53 (2) (2018) 455–462.
[49] B.W. Lytle, E.H. Blackstone, J.F. Sabik, P. Houghtaling, F.D. Loop, D.M. Cosgrove, The effect of bilateral internal thoracic artery grafting on survival during 20 postoperative years, Ann. Thorac. Surg. 78 (6) (2004) 2005–2012.
[50] A. Pu, L. Ding, J. Shin, et al., Long-term outcomes of multiple arterial coronary artery bypass grafting: a population-based study of patients in British Columbia, Canada, JAMA Cardiol. 2 (11) (2017) 1187–1196.