Meta-Analysis Comparing Multiple Arterial Grafts Versus Single Arterial Graft for Coronary-Artery Bypass Grafting

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Observational studies and randomized controlled trials (RCTs) have shown conflicting outcomes for multiple arterial graft (MAG) coronary artery bypass graft surgery compared with single arterial grafts (SAGs). The predominant evidence supporting the use of MAGs is observational. The aim of this meta-analysis of RCTs is to compare outcomes following MAG and SAG. We searched multiple databases for RCTs comparing MAG versus SAG. The clinical outcomes studied were all-cause mortality, cardiac mortality, myocardial infarction (MI), revascularization, stroke, sternal wound complications, and major bleeding. We used hazard ratio (HR), relative risk (RR), and corresponding 95% confidence interval (CI) for measuring outcomes. Ten RCTs (6392 patients) were included. The average follow-up in the studies was 4.2 years. The average age of the patients in the studies ranged from 56.3 years to 74.6. No significant difference was seen between MAG and SAG groups for all-cause mortality (11.8% vs 12.7%, HR 0.94, 95% CI 0.81 to 1.09, p 0.36), cardiac mortality (4.1% vs 4.5%, HR 0.96 95% CI 0.74 to 1.26, p 0.77), MI (3.5% vs 5.1%, HR 0.87 95% CI 0.67 to 1.12, p 0.28), and major bleeding (3.3% vs 4.9%, RR 0.85 95% CI 0.64 to 1.13, p 0.26). Repeat revascularization in MAG showed a lower RR than SAG when one of the confounding studies was excluded (RR 0.63, 95% CI 0.4 to 0.99, p 0.04). The incidence of stroke was lower in MAG than SAG (2.9% vs 3.9%, RR 0.74 95% CI 0.56 to 0.98, p 0.03). MAG had higher incidence of sternal wound complications than SAG (2.9% vs 1.7%, RR 1.75 95% CI 1.19 to 2.55, p 0.004). In conclusion, MAG does not have a survival advantage compared with SAG but is better in revascularization and risk of stroke. This benefit may be set off by a higher incidence of sternal wound complications in MAG. **(Am J Cardiol 2020;130:46−55)**

The predominant evidence supporting the use of multiple arterial grafts (MAGs) is observational. In a study of 1.5 million coronary artery bypass graft (CABG) surgeries from The Society of Thoracic Surgeons National Database (2004 to 2015), the rates of use of both internal mammary arteries and radial arteries were 4.9% and 6.5%, respectively.[1] This poor adoption rate of MAG is due to MAG being technically more difficult, requiring longer operative time and the potential risk of complications including sternal infections. Secondly, there remains an ambiguity regarding the superiority of MAG as compared with single arterial grafts (SAG) in randomized controlled trials (RCTs).[2] The aim of this study was to perform a meta-analysis of the RCTs comparing the clinical outcomes of MAG and SAG.

Methods

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplementary Table 1).[3] The search strategy is provided in Figure 1 and the supplementary file. The database was searched from inception to December 2019.

The inclusion criterial for our study were: Age ≥18 years; randomized controlled trials in any language, that evaluated the outcomes of MAG vs SAG; and follow-up of at least 1 year.

Data extraction was independently performed by 2 groups of authors (3 in each group) and differences in opinion were resolved with mutual discussion and adjudication by a senior author. Demographic data and study characteristics were extracted. The clinical outcomes studied were all-

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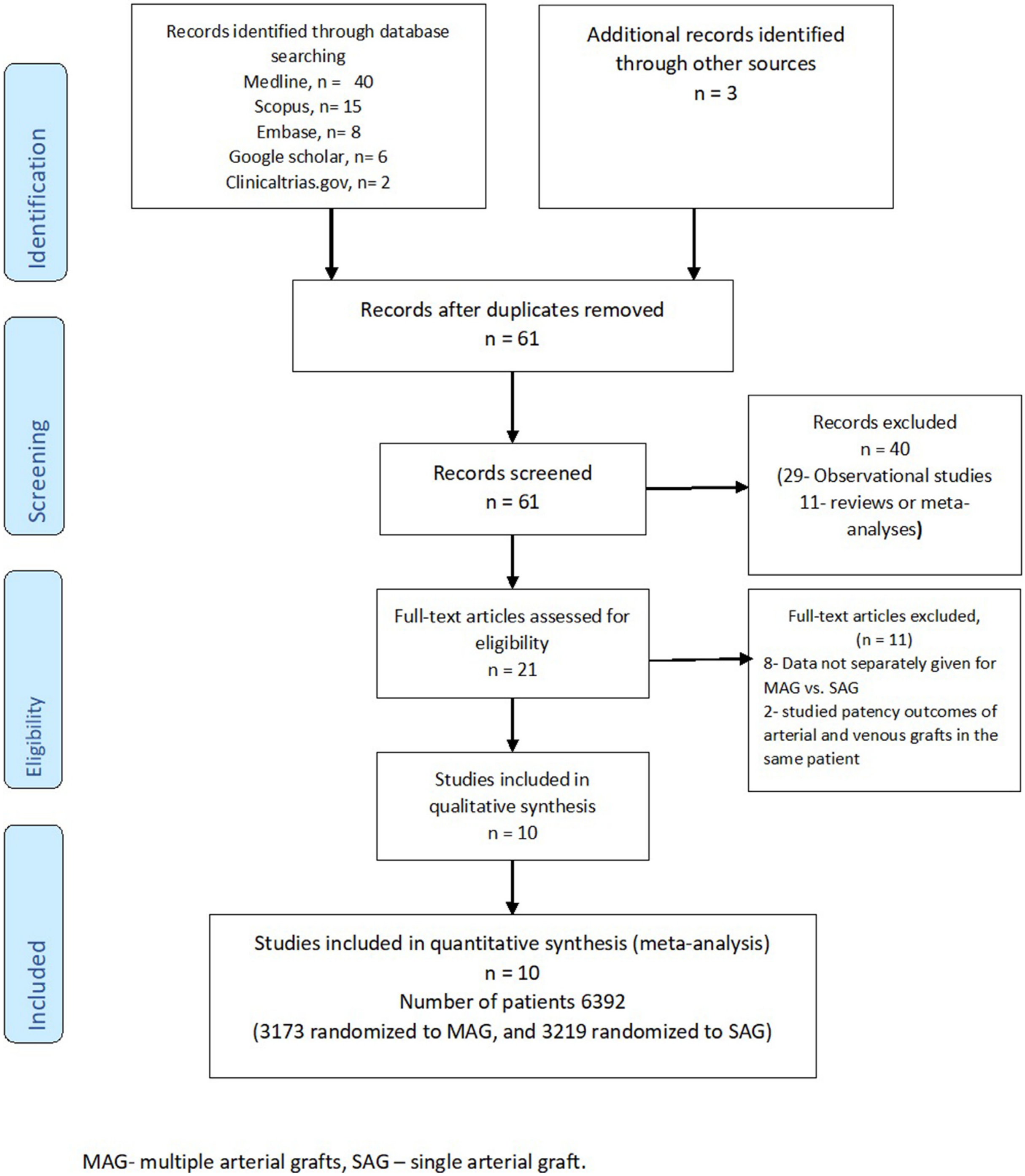

Figure 1. PRISMA flow diagram.

cause mortality, cardiac mortality, myocardial infarction (MI), stroke, repeat revascularization, sternal wound complications, and major bleeding. Outcomes were assessed at maximum follow-up.

The studies were divided into 3 subgroups based on the arterial grafts used in the MAG group: (1) RITA (right internal thoracic artery) MAG: The first arterial graft was LITA (left internal thoracic artery) and second arterial graft used was RITA. (2) RA (radial artery) MAG: The first arterial graft was LITA and second arterial graft used was RA. (3) RITA/RA MAG: The first arterial graft was LITA or RITA while the second arterial graft used was either LITA, RITA, or RA. All utilized saphenous venous grafts (SVGs) in addition to and after the arterial grafts were used. The SAG group always had 1 arterial graft (LITA) to LAD and additional venous grafts to other coronary vessels.

The quality of RCTs was assessed by the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).[4]

Pooled hazard ratios (HR) or relative risk (RR) were calculated for the outcomes using generic inverse variance method. HR takes account of the total number of events, and also of the timing of each event and differences in follow-up. If HR was not provided for an individual study, an online calculator was used to calculate the hazard ratio.[5] In this calculator the log-rank test is used to calculate the X^2 statistics, the p value, and the confidence intervals. The standard error for the log of the HR was estimated from the log-rank p value. A random-effects model was used if the outcome showed significant heterogeneity. A fixed Effects model was used if the outcome did not show significant heterogeneity. Heterogeneity was assessed using the Higgins I^2 statistic. Publication bias was assessed using Egger's regression test and visually by asymmetry in funnel plots. Sensitivity analysis was done by leave-one-out method. Meta-regression was not performed as the number of studies used for each outcome was less than 10 and most outcomes were homogenous. All tests were 2-tailed with a p value of less than 0.05 considered statistically significant. Statistical analyses were performed using Review Manager Version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014), R version 3.6.2 and the Meta-Essentials tool (Erasmus research institute of management).

Results

Ten RCTs were included in the meta-analysis (Figure 1).[6−15] The studies included 6,392 patients (3173 randomized to MAG, and 3219 randomized to SAG). The average age of the patients ranged from 56.3 years to 74.6. In the MAG group 19.4% patients were women, while in the SAG group 17.1% were women (Table 1). The number of vessels grafted were similar between the comparison groups in the studies. Of the 3,173 patients randomized to MAG, 1,846 received RITA in addition to LITA, 657 received RA in addition to LITA, and 670 received either RA or RITA in addition to LITA. LITA to LAD was used in almost all the patients except in the study by Nasso et al where 202 patients in the MAG group had RITA to LAD. Seven hundred eight patients (11%) had off pump CABG with comparable distribution in the MAG and SAG patients.

There was no significant heterogeneity evident in the measurement of clinical outcomes (Figures 2−7), except for repeat revascularization (I^2 56%, p 0.02, Figure 8). This heterogeneity was contributed by difference in the subgroups (I^2 85%, p 0.001). A random-effect model was used for repeat revascularization.

Risk-of-bias assessment (supplementary Table 2) demonstrated "low risk" of overall bias for 3 studies and "some concerns" for 3 trials.[12,13] The RCT by Taggart et al [8] was judged to have a high risk of bias due to deviation from effect of assignment to and adhering to intervention. Fourteen percent of the patients who had been randomly assigned to the bilateral ITA-graft group actually underwent single ITA grafting, and 22% of those who had been randomly assigned to the single-ITA group also received a second arterial graft in the form of a radial-artery graft (and thus classified as MAG). No other RCT had such high cross-over. Therefore, we performed a primary meta-analysis of intention to treat data where intention to treat data from Taggart et al was used. A secondary meta-analysis was completed for the as-treated data where as-treated data from Taggart et al was used.

The funnel plots (supplementary Figures 16 to 22) did not show any asymmetry except for major bleeding complications.

In the intention to treat analysis (Figure 2), all-cause mortality was similar between the MAG and SAG groups (11.8% vs 12.7%, HR 0.94, 95% confidence interval [CI] 0.81 to 1.09, p 0.49). On subgroup analysis, no difference in mortality was seen. The outcome did not change significantly in leave-one-out sensitivity analysis (supplementary Table 3). The outcome persisted to be statistically nonsignificant on repeating the analysis with a random effect model (HR 0.91, 95% CI 0.70 to 1.19, p 0.49, I^2 20, supplementary Figure 1).

In the as treated analysis (supplementary Figure 2), all-cause mortality was significantly lower in MAG group compared with SAG group (11.2% vs 13.8%, HR 0.81 95% CI 0.70 to 0.94, p 0.006, I^2 14%). In leave-one-out sensitivity analysis (supplementary Table 4), the pooled all-cause mortality changed to not significant (HR 0.83, 95% CI 0.58 to 1.20, p 0.33, I^2 28 %) when the trial by Taggart et al was excluded. Thus, the result was significantly influenced by this trial. No other trial significantly affected the outcome. The outcome was statistically nonsignificant on repeating the analysis with a random effect model (HR 0.83, 95% CI 0.65 to 1.05, p 0.12, I^2 14, supplementary Figure 3).

For cardiac mortality only intention-to-treat data was available. Cardiac mortality was similar in the MAG and SAG groups (4.1% vs 4.5%, HR 0.96 95% CI 0.74 to 1.26, p 0.77, I^2 0, Figure 3). On subgroup analysis, no significant difference was seen between the subgroups (p 0.75, I^2 0). The pooled outcome did not change significantly in leave-one-out sensitivity analysis (supplementary Table 3) and on repeating the analysis with a random effect model (HR 0.96, 95% CI 0.74 to 1.26, p 0.77, I^2 0, supplementary Figure 4).

In the intention to treat analysis, incidence of MI after CABG did not show significant difference between MAG and SAG groups (3.5% vs 5.1%, HR 0.87 95% CI 0.67 to 1.12, p 0.28, I^2 0, Figure 4). The outcome did not change significantly in leave-one-out sensitivity analysis (supplementary Table 3) and on repeating the analysis with a random effect model (supplementary Table 3). Repeat analysis of the as-treated data did not show significantly different results (supplementary Figures 6 and 7).

There was no statistically significant difference for repeat revascularization between MAG and SAG (6.8% vs 8.1%, RR 0.71 95%CI 0.47 to 1.06, p 0.10, I^2 56, Figure 8). On subgroup analysis, no significant difference was seen between RITA MAG and SAG (9.5% vs 8.8%, RR 1.02 95% CI 0.84 to 1.24, p 0.82), and RA MAG versus SAG (4.4% vs 5.7%, RR 0.72 95% CI 0.38 to 1.37, p 0.32). Revascularization incidence was significantly low in the RITA/RA group compared with SAG (2% vs 7.8%, RR 0.29 95% CI 0.15 to 0.56, p 0.0003). In leave-one-out sensitivity analysis, the pooled outcome of repeat revascularization achieved statistical significance with MAG having a lower RR than SAG when the study by Goldman et al was

Table 1
Baseline characteristics of the studies included in the systematic review and meta-analysis

Study, year	Country	Group	N	Mean age Years ± SD	Women	Cardiopulmonary bypass on pump	SH	DM	HLP	ACS presentation	Prior PCI*	Follow up, Years
		RITA MAG vs. SAG CABG										
Myers, 2000[6]	USA	MAG	81	62.6	18 (22.2)	+	46 (57%)	11 (14%)	55 (68%)	24 (30%)	-	5
		SAG	81	62.8	20 (24.6)	+	38 (47%)	12 (15%)	44 (54%)	20 (25%)	-	
Thujis, 2018 (EXCEL) [7]	USA	MAG	217	64.5 ± 9.3	31 (14.3)	Off-pump:74 (34.1).	146 (67%)	33 (15%)	147 (68%)	-	-	3
		SAG	688	66.1 ± 9.5	167 (24.3)	Off-pump:197 (28.6)	523 (76%)	198 (30%)	477 (70%)	-	-	
Taggart, 2019 (ART) [8]	Multiple	MAG	1548	63.7± 8.7	230 (14.9)	Off pump: 132 (8.5)	1193 (77.1%)	371 (23.9%)	1457 (94.2%)	-	242 (15.6%)	10
		SAG	1554	63.5 ± 9.1	216 (13.9)	Off pump:135 (8.7)	1217 (78.3%)	363 (23.3%)	1448 (93.2%)	-	248 (16%)	
		RA MAG group vs SAG										
Buxton 2003 [9]	Australia	MAG	73	72.9 ± 10.6	10 (14)	+	39 (59%)	27 (37%)	N/A	0	-	5
		SAG	80	73.2 ± 9.2	13 (16)	+	50 (66%)	37 (46%)	N/A	0	-	
Collins 2008[10]	UK	MAG	82	58 ± 6	3 (4)	+	46 (56%)	15 (18%)	63 (77%)	0	-	5
		SAG	60	59 ± 7	2 (3)	+	32 (53%)	10 (17%)	52 (87%)	0	-	
Goldman, 2011 [11]	USA	MAG	367	61 ± 8	5 (1)	Off pump=17(13)	289 (79%)	154 (42%)	N/A	0	15 (4%)	1
		SAG	366	62 ± 8	1 (0.3)	Off pump=48 (13)	287 (79%)	153 (42%)	N/A	0	11 (3%)	
Song, 2012[12]	Korea	MAG	35	72.7 ± 3.2	18 (51.4)	0	23 (65.7%)	15 (42.9%)	17 (48.6%)	0	8 (22.9%)	1
		SAG	25	74.6 ± 3.8	11 (44)		21 (84%)	13 (52%)	11 (44%)	0	11 (44%)	
Petrovic, 2015[13]	Serbia	MAG	100	56.3 ± 6.1	27 (27)	+	92 (92%)	39 (39%)	75 (75%)	0	-	8
		RITA/RA MAG vs. SAG	100	57.1 ± 6.5	27 (27)		89 (89%)	43 (43%)	74 (74%)	0	-	
Gaudino, 2005[14]	USA	MAG	80	-	-	+	-	-	-	-	80 (100%)	5
		SAG	40	-	-		-	-	-	-	40 (100%)	
Nasso, 2008[15]	USA	MAG	201	69.2 ± 3.9	88 (44)	+	-	(38%)	-	-	-	2
		MAG	198	68.4 ± 4.6	85 (43)			(38%)			-	
		MAG	202	70.5 ± 3.1	87 (43)			(36%)			-	
		SAG	202	69.7 ± 3.5	85 (42)			(38%)			-	

* No prior CABG was reported in the patients.
(+) indicates present, (0) indicates absent and a (−) indicates "no information available" or "not applicable."
Numbers are n (%).
Abbreviations: ACS = acute coronary syndrome; CABG = coronary artery bypass graft surgery; CPB = cardiopulmonary bypass; Cx = circumflex coronary artery; DM = diabetes mellitus; HLP = hyperlipidemia; LAD = left anterior descending coronary artery; LITA = left internal thoracic artery; LM = left main coronary artery; MAG = multiple arterial grafts; N = number; OM = obtuse marginal coronary artery; PCI = percutaneous coronary intervention; RA = radial artery; RITA = right internal thoracic artery; SAG = single arterial graft; SD = standard deviation; SH = systemic hypertension; SVG = saphenous vein graft; UK = United Kingdom; USA = United States of America.

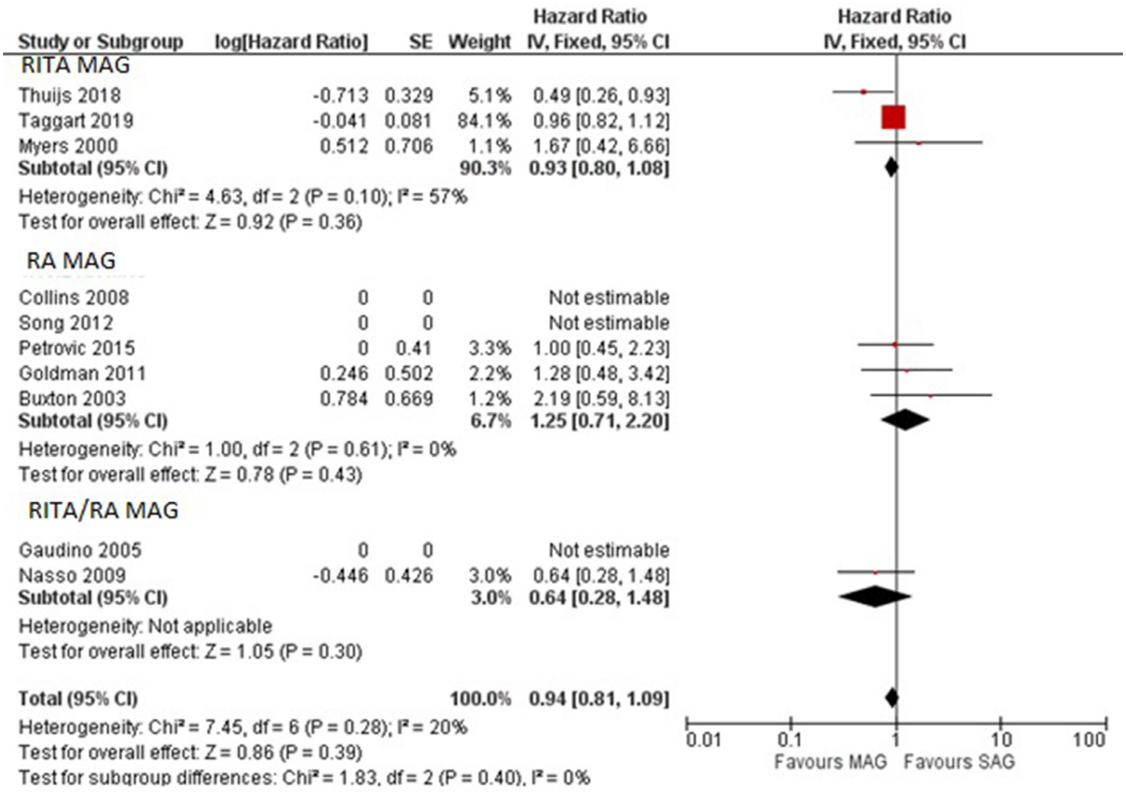

Figure 2. Forrest plot for all-cause mortality using intention to treat data. Horizontal lines represent 95% confidence intervals (CI). The rectangles represent the point estimate, and the size of the rectangle is proportional to the weight given to each study in the meta-analysis. The diamond represents the summary estimate (size of the diamond = 95% CI). The vertical line represents the reference of no increased risk. SE = standard error.

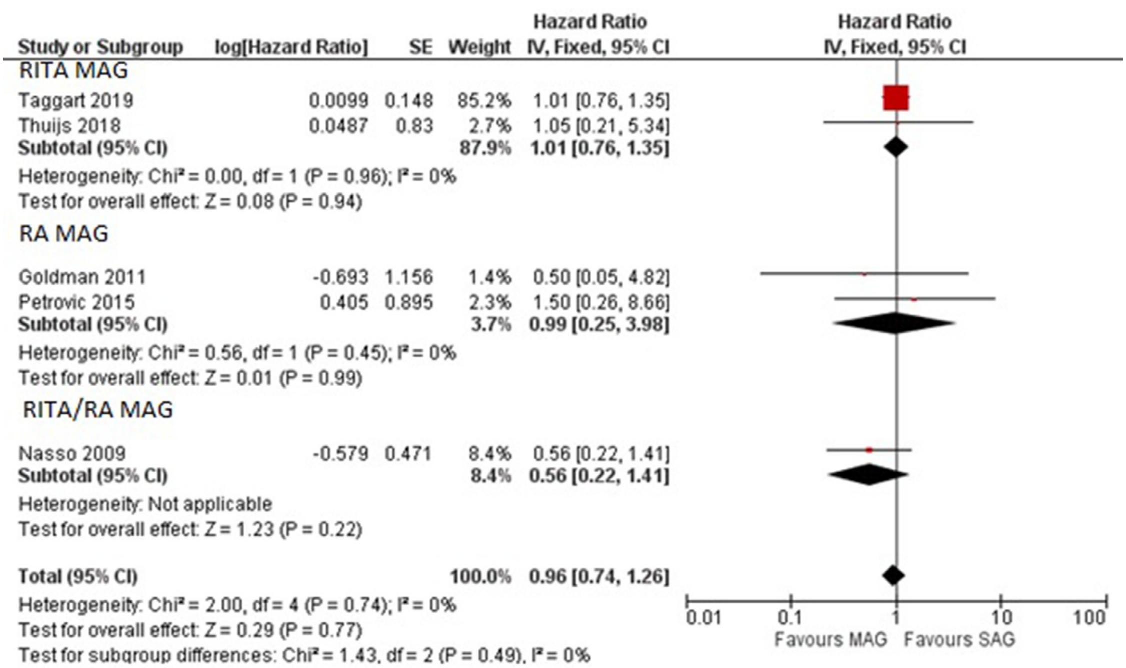

Figure 3. Forrest plot for cardiac mortality using intention to treat data.

excluded (RR 0.63, 95% CI 0.4 to 1, p 0.05, I^2 58, supplementary Table 3). On repeating the analysis with a fixed effect model the outcome continued to be statistically nonsignificant (supplementary Figure 8).

In the as-treated analysis, similar results were noted (supplementary Figures 9 and 10, supplementary Table 4).

Data about stroke after CABG was available in 7 of the 10 included studies (2,598 MAG patients and 2,999

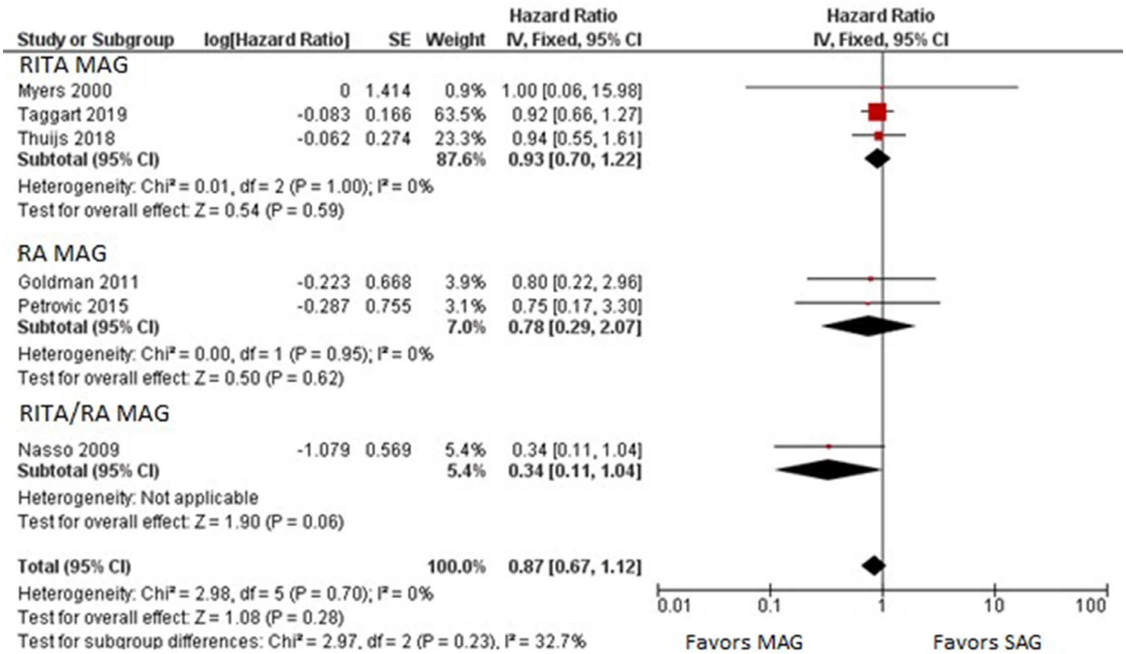

Figure 4. Forrest plot for myocardial infarction using intention to treat data.

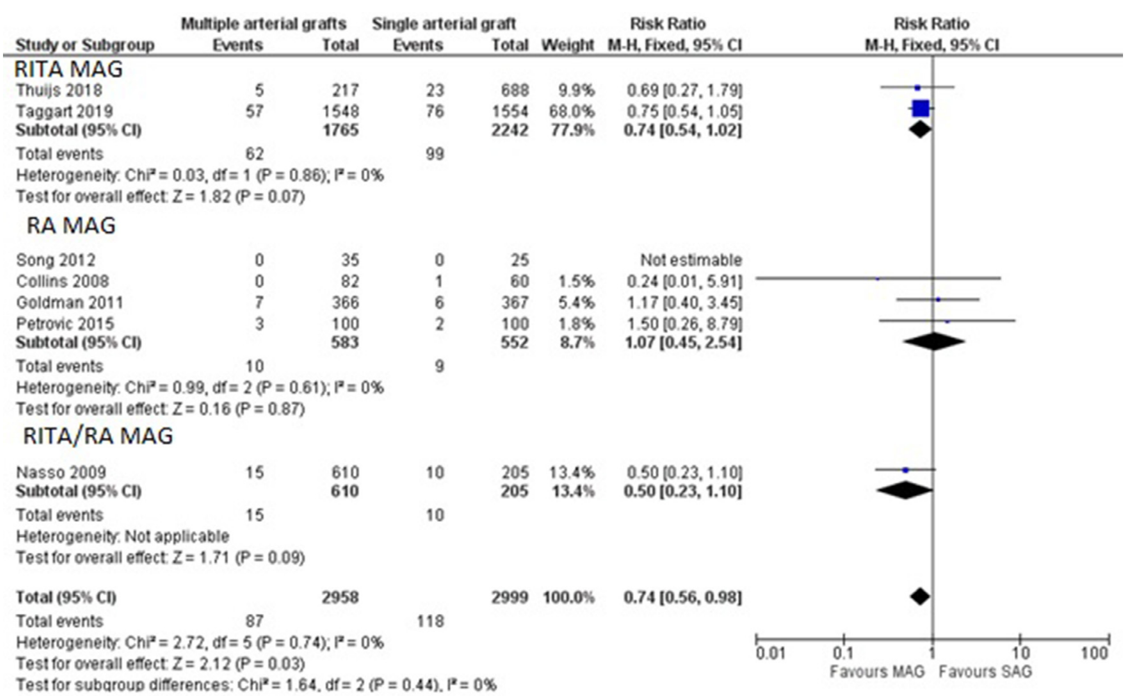

Figure 5. Forrest plot for stroke using intention to treat data.

SAG). The stroke incidence was assessed for the perioperative period. In the intention to treat analysis, the incidence of stroke was found to be lower in the MAG group compared with SAG group, and the result was statistically significant (2.9% vs 3.9%, RR 0.74 95% CI 0.56 to 0.98, p 0.03, I^2 0, Figure 5). In leave-one-out sensitivity analysis, the pooled outcome of stroke lost statistical significance when the studies by Thujis (RR 0.75, 95% CI 0.56 to 1.01, p 0.06, I^2 0), Taggart (RR 0.72, 95% CI 0.44 to 1.17, p 0.18, I^2 0), and Nasso (RR 0.79, 95% CI 0.58 to 1.06, p 0.11, I^2 0) were excluded (supplementary Table 3). There was no significant change in the outcome when the analysis was repeated by a random effect model (RR 0.74, 95% CI 0.56 to 0.98, p 0.03, I^2 0, supplementary Figure 11).

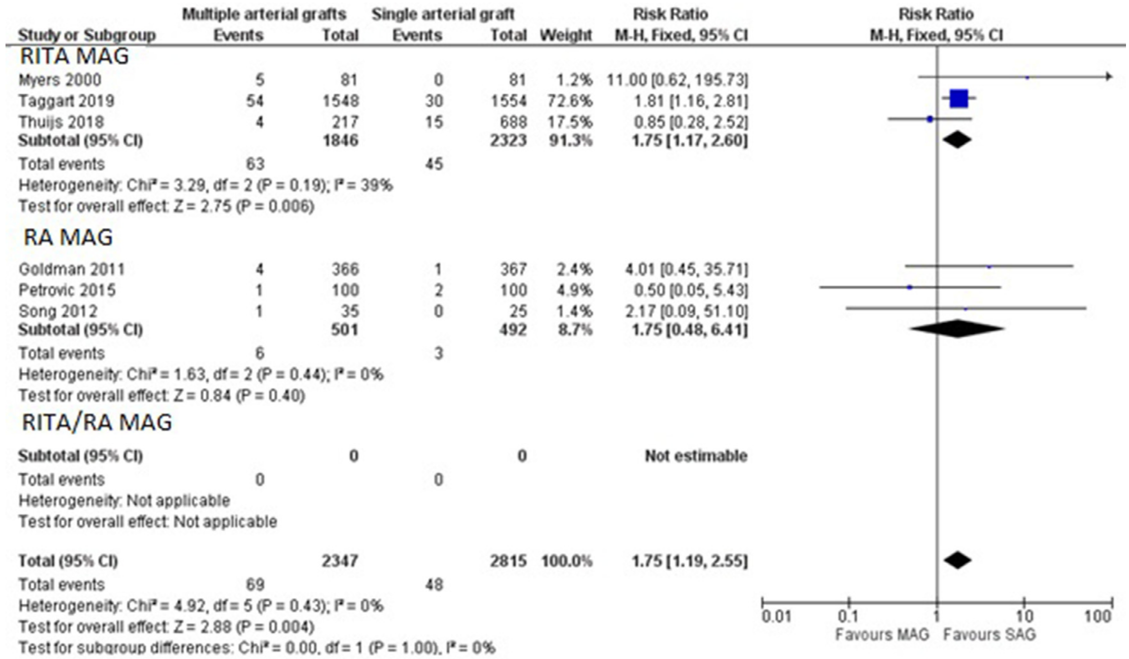

Figure 6. Forrest plot for sternal wound complications using intention to treat data.

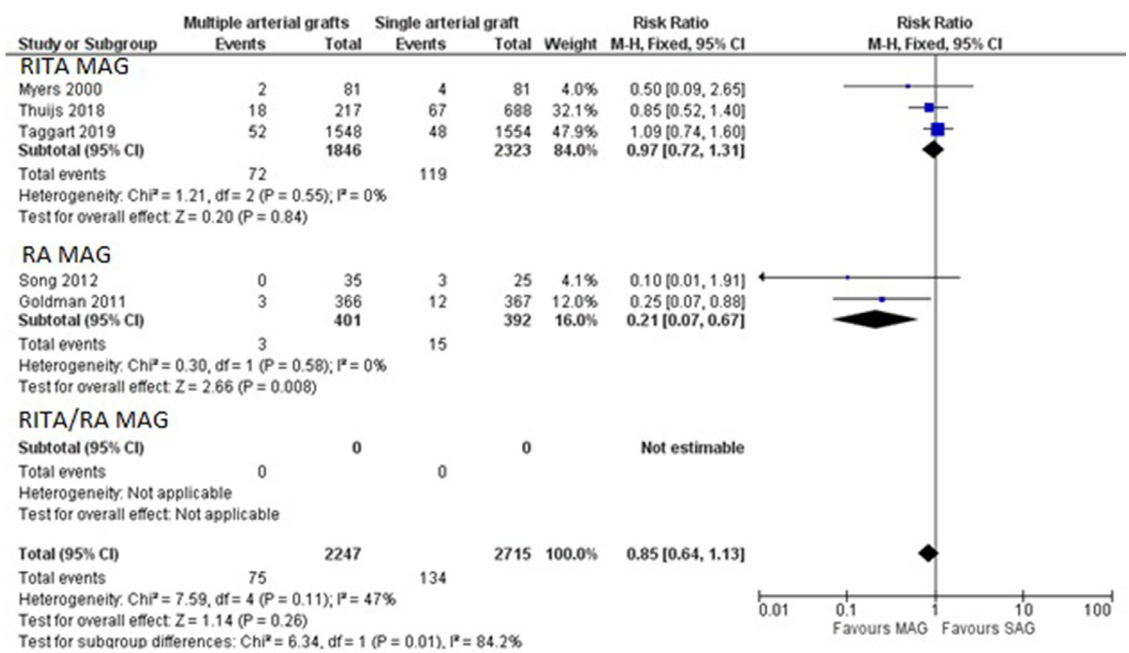

Figure 7. Forrest plot for major bleeding complications using intention to treat data.

Similar results were seen in the as treated analysis. (supplementary Figures 12 and 13).

For major bleeding only intention-to-treat data was available. MAG and SAG groups did not show any significant difference in the incidence of major bleeding (3.3% vs 4.9%, RR 0.85 95% CI 0.64 to 1.13, p 0.26, I^2 47, Figure 7).

MAG group showed a statistically significant higher incidence of sternal wound complications compared with SAG (2.9% vs 1.7%, RR 1.75 95% CI 1.19 to 2.55, p 0.004, I^2 0, Figure 6). On subgroup analysis, RITA MAG sub-group showed a statistically significant higher incidence of this complication compared with SAG (3.4% vs 1.9%, RR 1.75 95% CI 1.17 to 2.60, p 0.006, I^2 39). In the leave-one-out sensitivity analysis, excluding the study by Taggart et al caused the outcome to lose statistical significance (RR 1.58, 95% CI 0.75 to 3.35, p 0.23, supplementary Table 3).

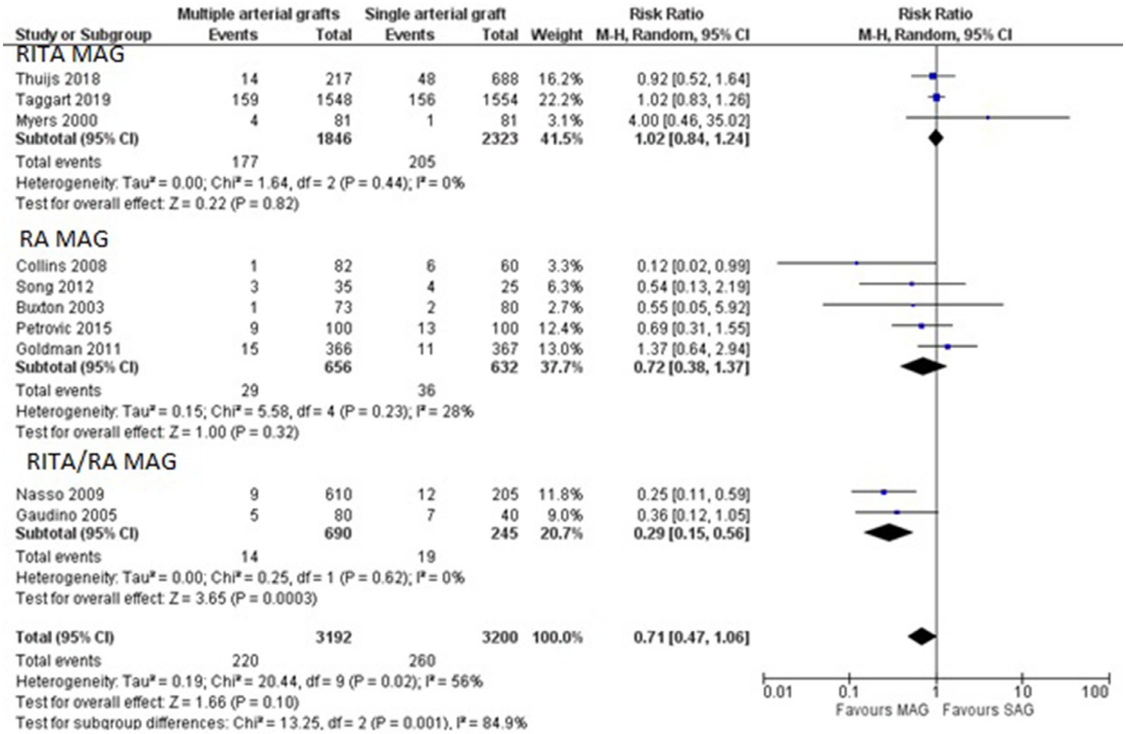

Figure 8. Forrest plot for repeat revascularization using intention to treat data.

Discussion

In this meta-analysis of 10 RCTs (6,392 patients), comparing the intention-to-treat outcomes of MAG vs SAG, no significant difference was seen for all-cause mortality, cardiac mortality, MI, repeat revascularization and major bleeding complications. MAG group had a lower risk of stroke and higher risk of sternal wound complications.

Our results for mortality outcomes are different than prior non-randomized studies. Meta-analyses of observational studies have shown mortality benefit for MAG compared with SAG.[16−21] This superiority is thought to be due to greater patency rates of the durable arterial grafts compared with SVGs.[22] However, a meta-analysis of observational studies concluded that unmeasured confounders, rather than biological superiority, may explain the survival advantage of BITA in observational series.[23] Surgeons may reserve the more invasive BITA operation for healthier patients and those with longer life expectancy. This approach by surgeons is not matched in databases and thus difficult to match in algorithms.[24] MAG group in observational studies has been measured to have younger patients and lower percentage of female patients, diabetics, peripheral vascular disease, and extensive coronary artery disease.[25] We found similar all-cause mortality and cardiac mortality for MAG and SAG groups. The reason could be that an arterial graft (most commonly LITA) is anastomosed to the most important vessel (commonly LAD). The occlusion of a graft to a coronary artery other than the LAD may not have a survival effect.[26] Our results are similar to the patient level meta-analysis done by the RADIAL investigators.[27] This meta-analysis of 6 RCTS comparing RA MAG versus SAG also found similar all-cause mortality for the 2 (7.5% vs 8.4%, HR 0.90, 95% CI 0.59 to 1.41, p 0.68). However, the composite outcome of death, MI, or repeat revascularization was better in the RA MAG group in this study. The follow-up in our meta-analysis ranged from 1 to 10 years. It is possible that longer follow-up may yield a survival advantage for MAG, although the ART trial with the longest follow-up in our study did not show mortality difference.[8] In ART trial there was a high cross-over. Thus, we repeated the meta-analysis with the as-treated data from the ART trial. In the as-treated analysis, MAG showed survival advantage over SAG. However, this analysis is not based on randomization assignment and shares limitations of the observational studies. If the ART trial was excluded from the meta-analysis, the mortality outcome continued to be similar between MAG and SAG.

Myocardial infarction was similar in MAG and SAG. Our result is different from the RADIAL meta-analysis.[27] In RADIAL, RA MAG had lower MI than SAG (HR, 0.72; 95% CI, 0.53 to 0.99; p = 0.04). However, as pointed out by the RADIAL authors, this study had a much smaller sample size for a common procedure like CABG (RA MAG 534, SAG 502 patients). In comparison, our meta-analysis had a much larger sample size for this outcome (2,922 MAG patients, 2,995 SAG). Also, our study included RITA and RA MAG patients while RADIAL included only RA MAG patients.

In our study, repeat revascularization with MAG was lower than SAG when the study by Goldman et al was excluded (RR 0.63, 95% CI 0.4 to 0.99, p 0.04). Goldman et al had used more than 70% proximal stenosis as the entry criterion for the study vessel to receive a RA graft which possibly contributed to higher rates of repeat revascularization in the MAG group in this study.[11] To minimize competitive flow, the RA is currently grafted to coronary arteries that have stenosis of 90% or more of the vessel diameter.[2] Similar results were seen in a New York registry study (HR 0.80, 95% CI 0.74 to 0.87, p < 0.001)[28] and RADIAL meta-analysis (HR 0.50, 95% CI 0.40 to 0.63, p < 0.001).[27] Increased repeat revascularization rate in SAG is related to lower patency of SVGs.

The RR of having stroke was significantly low in MAG compared with SAG in both intention-to-treat and as-treated analysis. In sensitivity analysis, the trials with RITA MAG contributed significantly to the outcome. Similar result was seen in the meta-analysis of observational studies done by Buttar et al where RITA MAG showed fewer cerebrovascular accidents compared with SAG (1.3% vs 2.9%; p = 0.0003). Lesser aortic manipulation could be related to lower stroke rates in MAG.[29]

In our study, MAG group had a higher RR of sternal wound complications. This higher RR was seen only in RITA MAG subgroup. Sternal wound complications have been considered the Achilles' heel for the use of RITA MAG.[2] The higher incidence of sternal wound complications in RITA MAG is due to higher sternal devascularization and has been seen in a large meta-analysis of observational studies as well.[30] Use of skeletonized bilateral internal mammaries has been suggested to reduce the rate of sternal wound complications.[30]

The follow up in the RCTs ranged from 1 to 10 years. It is possible that the studies with a shorter follow-up could have shown a survival advantage in the MAG group if they were followed for a longer period. However, survival advantage was not seen individually in the RCTs that had longer follow-up. ART trial had a significant cross-over between MAG and SAG groups. This resulted in different mortality outcomes in the intention-to-treat and as-treated analysis. However, we repeated the meta-analysis after excluding ART trial, and MAG versus SAG did not show survival differences.

In conclusion, MAG does not have a survival advantage over SAG but has better revascularization and stroke outcomes in randomized data. This benefit may be offset by a higher incidence of sternal wound complications in MAG. Till further evidence is available we suggest that the decision to use MAG or SAG should be individualized by taking the revascularization, stroke, and wound complication rates in to consideration.

Author Contribution

Khalid Changal, MD: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Resources; Software; Validation; Roles/Writing - original draft; Writing - review & editing. Saqib Masroor, MD: Conceptualization; Methodology; Project administration; Supervision; Validation; Writing - review & editing, Corresponding author. Ahmed Elzanaty, MD: Data curation; Methodology; Writing - review & editing. Mitra Patel, MD: Data curation; Formal analysis; Validation; Visualization; Writing - review & editing. Tanveer Mir, MD: Data curation; Investigation; Writing - review & editing. Shayan Khan, MD: Data curation; Investigation; Writing - review & editing. Salik Nazir[a]: Data curation; Formal analysis; Validation; Visualization; Writing - review & editing. Ronak Soni, MD: Data curation; Investigation; Writing - review & editing. Carson Oostra, MD: Data curation; Investigation; Writing - review & editing. Sadik Khuder, Ph.D.: Data curation; Formal analysis; Methodology. Ehab Eltahawy, MD, MPH: Conceptualization; Methodology; Project administration; Resources; Software; Validation; Roles/Writing - original draft; Writing - review & editing. Senior Author.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.06.012.

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