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Are two really always better than one? Results, concerns and controversies in the use of bilateral internal thoracic arteries for coronary artery bypass grafting in the elderly: A systematic review and meta-analysis

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HIGHLIGHTS

- Data discussing benefit of bilateral internal thoracic artery grafting in elderly is limited.
- These patients are at higher risk of deep sternal wound infection.
- It is unclear whether this technique improves long-term survival in the elderly patient cohort.

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ABSTRACT

Introduction: Bilateral internal thoracic artery grafting appears to be the preferred method to achieve durable long-term coronary artery revascularization. However, data reporting the benefit of this technique in the elderly is very conflicting.

Method: We performed a systematic review of available literature (till November 2014) using multiple databases to identify studies comparing clinical events in patients undergoing coronary artery bypass grafting using either a single or double internal thoracic artery in the elderly. While early mortality was the primary end-point of inclusion, other adverse events compared were sternal wound infection (deep and superficial), stroke and peri-operative myocardial infarction. Individual and pooled odd's ratios were calculated using the Mantel–Haenzel method (random effect model); sensitivity analysis was performed. Results are presented using 95% confidence intervals.

Result: Nine retrospective studies (4479 BITA, 7733 LITA patients) fulfilled search criteria. Deep sternal wound infection was significantly higher after BITA harvest [OR 1.86 (1.3–2.5); $I^2 = 0\%$; $p < 0.01$]. Early mortality (BITA 3.6% vs SITA 3.1%; $p = 0.86$), stroke [OR 0.7(0.4–1.1); $p = 0.1$], and peri-operative myocardial infarction (BITA 4.3% vs SITA 2.3%; $p = 0.1$) were comparable in both cohorts. Long-term survival favored the BITA cohort in two propensity matched studies.

Conclusion: The incidence of deep sternal wound infection may be significantly higher after the harvest of both internal thoracic arteries in the elderly. While other post-operative adverse events are comparable, data regarding the long-term survival advantage in this cohort is conflicting. Hence, the use of both internal thoracic arteries in this age group needs to be invidualized.

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1. Introduction

Superiority of arterial conduit for coronary artery bypass grafting (CABG) is now well established [1]. Recent evidence has demonstrated that the use of both internal thoracic arteries is highly beneficial for long-term survival [2].With a worldwide increase in life expectancy, we are now performing CABG on older patients. These people are frail and have a higher incidence of diabetes, renal dysfunction, pulmonary disease and aggressive atherosclerosis. Conflicting data is present in the literature as regards the use of bilateral internal thoracic artery (BITA) in elderly patients undergoing CABG. In spite of the proven benefit of BITA use in CABG, a recent article reported significant underutilization of this strategy [3]. Hesitancy for use of both arteries stems from concerns regarding sternal wound infection, increased technical complexity and the possible use of the right internal thoracic artery as a free graft.

2. Material and methods

2.1. Search strategy

Medline, Web of Science, the Cochrane Database of Systematic Reviews and CINAHL (November 2014) were queried to identify original articles comparing clinical events in adult human elderly subjects undergoing coronary artery bypass grafting using a single and bilateral internal thoracic artery. The detailed search strategy for CINAHL is as follows:

(MH "Mammary Arteries") AND (MH "Coronary Artery Bypass/MT") AND (MH "Treatment Outcomes") AND (single OR bilateral) AND (elderly OR advanced age)

Primary end-point included in this study was early mortality/in-hospital mortality. Secondary end-points compared were sternal wound infection, stroke, and respiratory failure and hospital length of stay. Two authors (SEA, SVD) independently reviewed all abstracts for potential inclusion; they then reviewed retrieved full-text articles. Dispute was resolved by consensus.

The reference sections of included studies were also scanned to ensure completeness of the review process. As we limited our study to published peer-reviewed literature, conference abstracts were not reviewed for possible inclusion. This is in line with the Cochrane Collaboration recommendations (Cochrane database of systematic reviews). The systematic review has been performed and reported as per the PRISMA guidelines and the checklist is presented (on-line supplement) [4]. The synopsis of the review is not available online.

2.2. Definition of end-points

The definition of the clinical end-points is as per the individual study. Early mortality was defined as death within 30 days of surgery or during the same hospital admission. Deep sternal wound infection was defined as any infection involving the sternal bone, mediastinal tissue, sternal dehiscence or non-union, infection limited to the soft tissue without sternal instability was considered as superficial sternal infection.

2.3. Statistical analysis

Statistical analysis was performed using Stata 12.0 (StataCorp, Station, Texas). Categorical data is presented using Odds Ratio (OR) with 95% confidence intervals calculated implementing inverse variance weighting using the random effect model. The BITA

Table 1
Demographic data of the patients before surgery.

	Elmistekawy et al. 2011		Pettinari et al. 2014		Jones et al. 2000		Hassanein et al. 2010		Sahar et al. 2007		Hirotani et al. 2003		Kinoshita et al. 2012	
Country	Canada		Belgium		USA, TX		Germany		Israel		Japan		Japan	
Type of Study	PCS		PCS		PCS		RCS		RCS		RCS		PCS	
Cohort	SITA	BITA	SITA(Matched)	BITA(Matched)	SITA	BITA	SITA	BITA	SITA(Matched)	BITA(Matched)	SITA	BITA	SITA	BITA
Number of patients	3581	359	892	892	338	172	389	415	68	68	108	138	217	217
Age (years)	72 ± 5.0	71 ± 5.0	73 ± 3.13	73 ± 2.94	69.7	69.2	72	71.8	74 ± 4.2	74 ± 3.8	70 ± 4.8	71 ± 4.1	76 ± 5	76 ± 4
Males (%)	74.1	76.6	72.5	71.9	90.2	80.8	73.1	73.5	66.2	76.5	72	66	49	53
Diabetes (%)	34.2	32.7	14	13.1	NA	NA	28.5	31.5	36.7	36.7	45	54	48	44
Hypertension (%)	72	78.5	NA	NA	NA	NA	80.98	88.95	57.4	60.3	NA	NA	72	71
Previous MI (%)	26.9	27	2.48	1.62	6.8	9.8	NA	NA	66.2	50	75	77	47	44
PVD (%)	21.3	22.3	35.1	35	NA	NA	NA	NA	17.6	20.6	NA	NA	23	21
BMI	27.9 ± 4.5	27.3 ± 4.1	NA	NA	NA	NA	27.365	27.97	NA	NA	NA	NA	22 ± 3	23 ± 3

Abbreviations: BITA: Bilateral Internal Mammary Artery, BMI: Body Mass Index, NA: Not Available, MI: Myocardial Infarction, PCS: Prospective Cohort Study, PVD: Peripheral Vascular Disease, RCS: Retrospective Cohort Study, SITA: Single Internal Mammary Artery.

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cohort is the experimental group; hence any OR (+95% CI) <1 favors that cohort and vice versa. Publication bias has been assessed visually using the funnel plot and statistically evaluated using the Begg–Mazumdar test. Heterogeneity is assessed from the Egger's I^2; a value of 25%, 50% and 75% were implemented as low, moderate and high heterogeneity respectively. Sensitivity analyses were performed to investigate heterogeneity where necessary.

3. Results

3.1. Study characteristics

From an initial search result of 740 titles, we obtained nine studies that compared clinical results of SITA and BITA use for CABG in the elderly [5–13]. All the studies are retrospective database reviews of single institutions. From nine studies, only three [6,12,13] implement propensity matching. Apart from these studies, we were able to identify five more articles [14–18] that reported the long-term survival of BITA use stratified by patient age. These however, did not present data regarding results of the use of single internal thoracic artery for CABG and hence are not included in our meta-analysis. Table 1 present the pre-operative demographics of studies included in our meta-analysis. Elmistekawy et al. [5] reported that the mean age (yrs) of the LITA cohort (72.2 ± 5) was higher than the BITA group (71.2 ± 5). Importantly, both cohorts were comparable with regards to the incidence of diabetes mellitus. Fig. 1 demonstrates the PRISMA flow diagram.

3.2. Technique of ITA harvest

Among the nine studies discussed in our meta-analysis, Hirotani [8] and Gansera [6] implemented pedicled harvest with care to preserve sternal blood flow, while three studies [7,9,13] implemented skeletonized ITA harvest.

3.3. Sternal wound infection

The incidence of deep sternal wound infection was 2.4% and 1.3% in the BITA and SITA cohorts respectively. A pooled analysis of eight studies (10,745 patients) [5–8,13] demonstrates that BITA harvest is

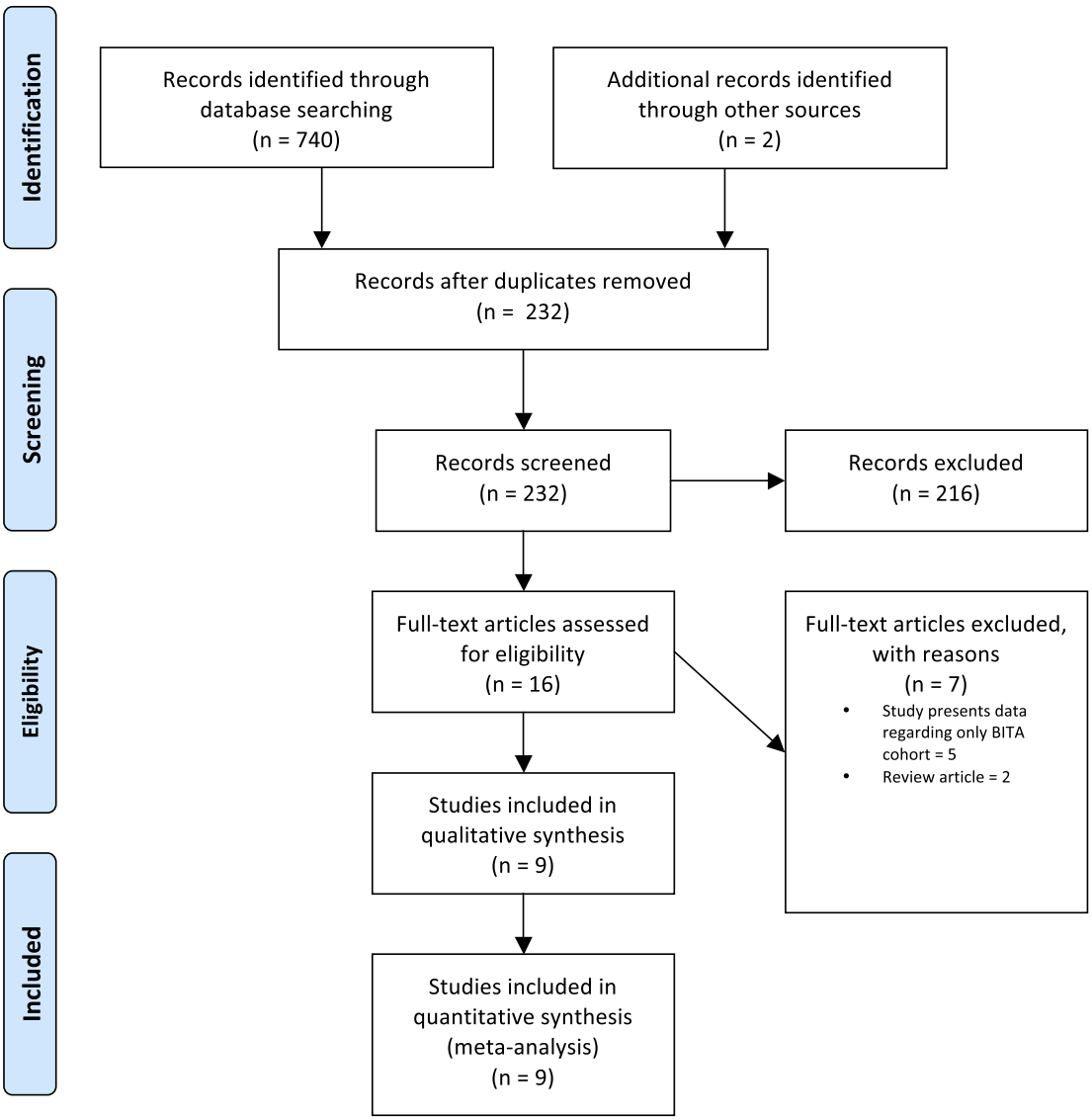

Fig. 1. PRISMA 2009 flow diagram. *From*: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. http://dx.doi.org/10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org.

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clearly associated with a higher risk of DSWI [OR 1.86(1.35–2.57); $I^2 = 0\%$; $p < 0.0001$] (Fig. 1A). The funnel plot demonstrates lack of publication bias (Fig. 1B) ($p = 0.80$). Sensitivity analysis performed by removal of Pettinari et al. [12] (study contributing maximal weightage to the initial result) confirmed that SITA cohort has a significantly lower incidence of DSWI. Elmistekawy [5] reported that re-admission rates ($p < 0.01$), debridement rates ($p = 0.04$) and bacteremia ($p < 0.001$) were higher in the BITA cohort, although they did not directly increase early mortality in the BITA cohort (Fig. 2A/B).

3.4. Superficial sternal wound infection

Superficial sternal wound infection was reported in three studies. The pooled analysis demonstrated a significant benefit for the SITA cohort [OR 1.97(1.23–3.15); $p = 0.004$]. This was due to the strong influence of Elmistekawy et al. [5]. Sensitivity analysis after removing this study reported comparable incidence of SSWI in both groups (Fig. 3).

3.5. Early (30 day) mortality [5–11]

The peri-operative mortality was 3.6% and 3.1% in the BITA and LITA cohorts respectively. Pooled analysis demonstrated that early mortality was comparable in both cohorts [OR 0.98 (0.78–1.22); $I^2 = 45\%$; $p = 0.86$]. The moderate heterogeneity in the analysis ($I^2 = 45\%$) is due to Galbut et al. [10] who reported significantly better survival in the BITA cohort. Begg–Mazumdar test demonstrates that there is a lack of publication bias in the results ($p = 0.216$) (Fig. 4).

3.6. Respiratory failure [5,7,11]

Respiratory failure was comparable in both cohorts [OR 1.21(0.89–1.65); $p = 0.20$; $I^2 = 74\%$]. The heterogeneity in the analysis was as a result of Jones et al. [11]; excluding this study reduced the heterogeneity to 9% without any significant difference in the overall pooled estimate.

3.7. Peri-operative myocardial infarction [5,7,8,11]

The incidence of peri-operative myocardial infarction was reported by six studies; the pooled incidence was 2.4% and 4.3% in the SITA and BITA cohorts respectively. Pooled evidence demonstrates that the occurrence of peri-operative MI is comparable in both cohorts [OR 0.74 (0.49–1.13); $p = 0.17$; $I^2 = 0\%$] (Fig. 5).

3.8. Stroke [5,7–9,11,12]

The early stroke rate was presented by seven studies (7854patients) included in the systematic review. The stroke rate was lower in the BITA cohort (1.1% vs 1.6%). However, pooled analysis did not

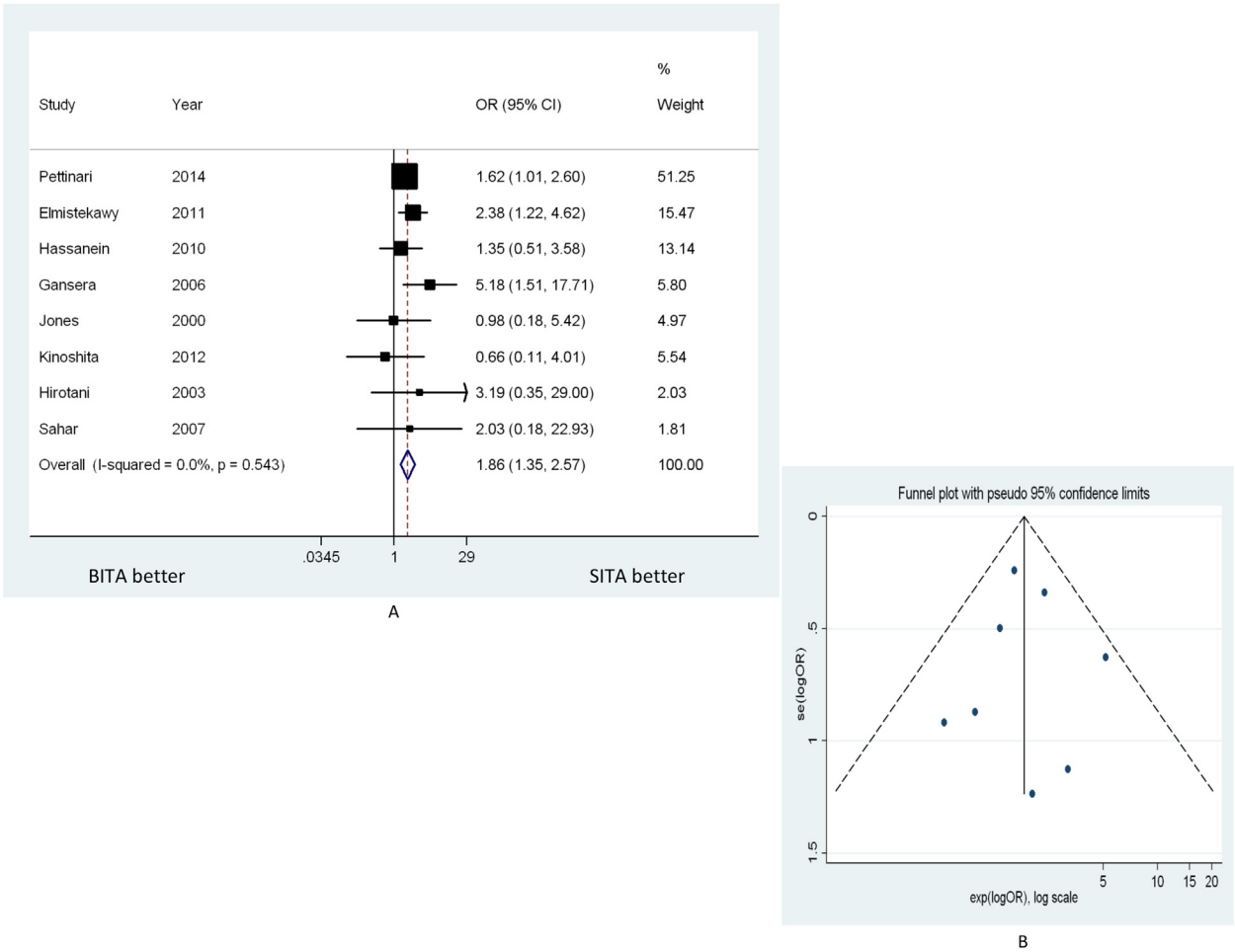

Fig. 2. A: Pooled analysis of eight studies demonstrates that deep sternal wound infection is much higher with BITA harvest in the elderly. B: A symmetrical funnel plot demonstrates that the result lacks possible publication bias. Begg–Mazumdar test; p-value = 0.80.

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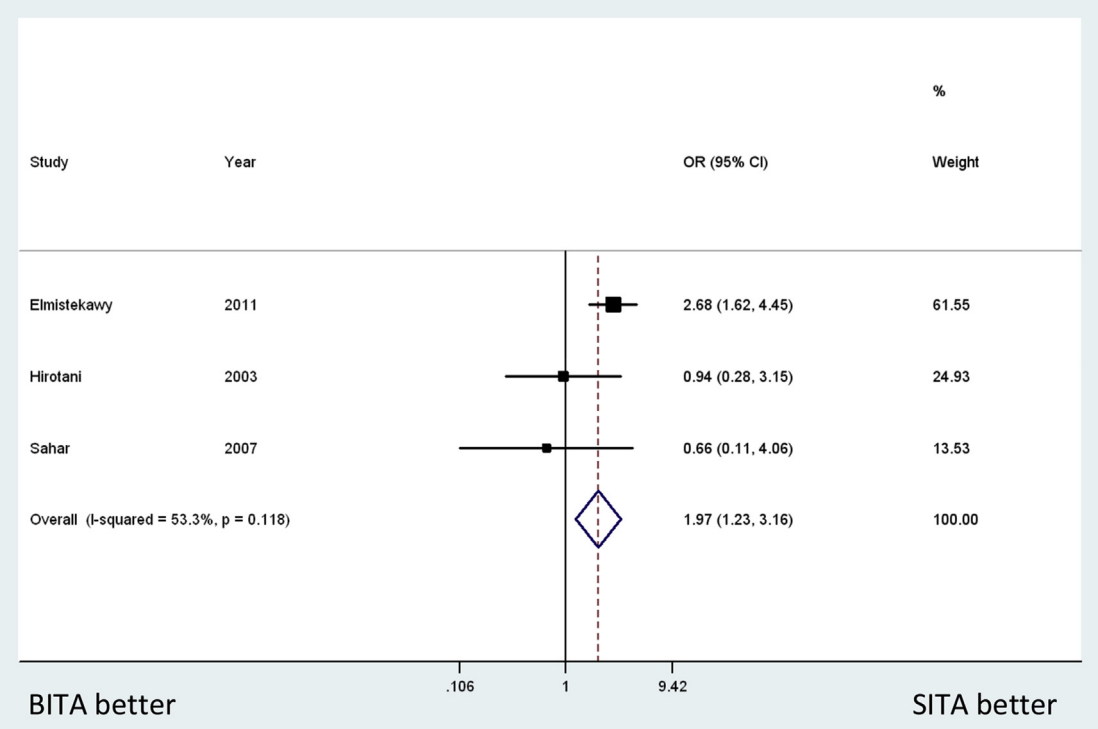

Fig. 3. Superficial sternal wound infection is higher with BITA harvest. However, sensitivity analysis demonstrates that incidence may be comparable.

demonstrate a statistically significant benefit with the use of both internal thoracic arteries [OR 0.70(0.43–1.12); p = 0.14; I^2 = 0%] (Fig. 6).

3.9. Late results

Survival at 8–10 yrs was reported in four studies [8,10,12,13]. All agree that survival after BITA use is superior to the use of a single

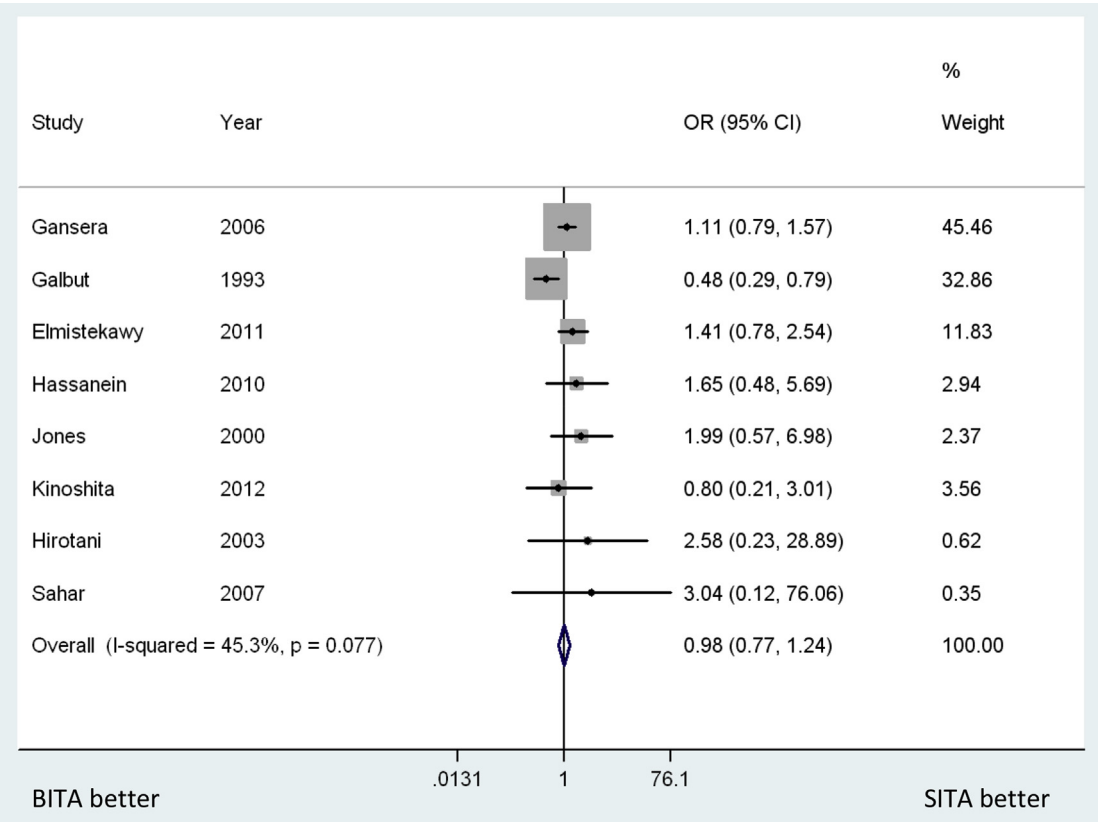

Fig. 4. Early mortality is comparable between BITA and SITA cohorts.

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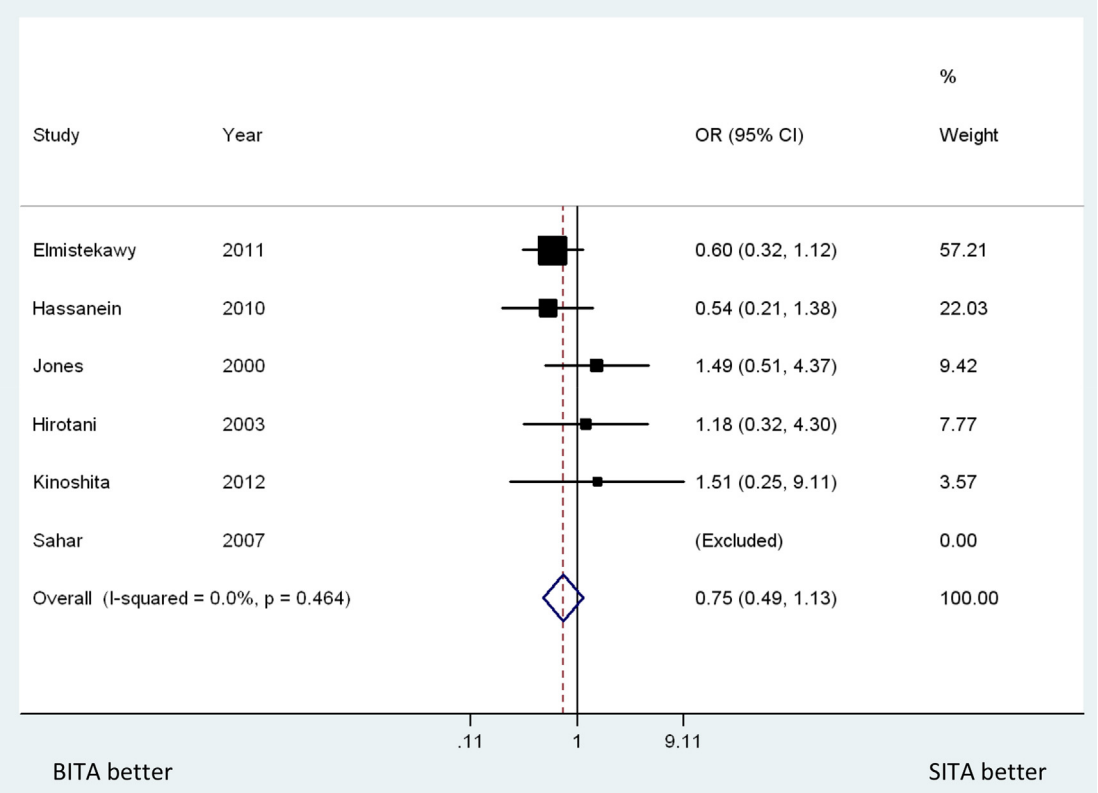

Fig. 5. Peri-operative myocardial infarction is comparable in both cohort.

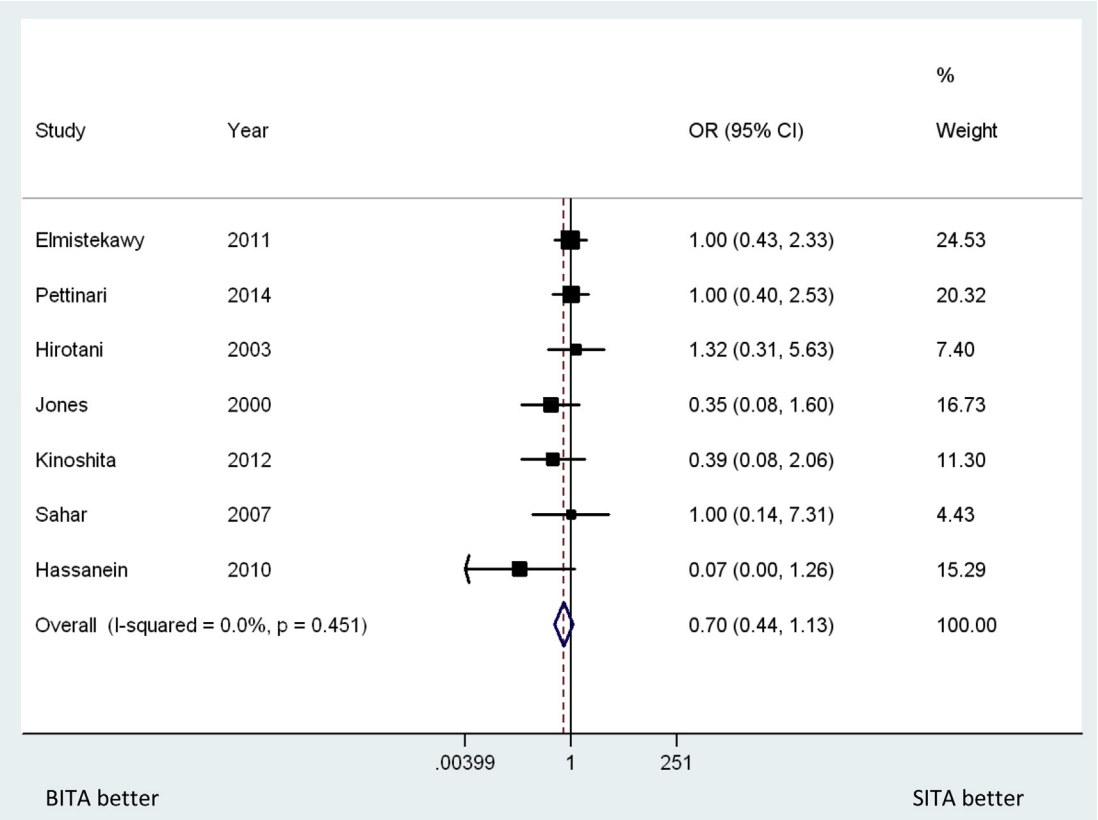

Fig. 6. Stoke rates were comparable between BITA and SITA cohorts.

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Table 2
Summary of findings table outlining the pooled results of our meta-analysis.

Clinical end-point	Studies included in analysis	OR (95% CI)	p-value	Heterogeneity (I^2%)
Early mortality	8	0.98 (0.78–1.22)	0.86	45
Deep sternal wound infection	8	1.86 (1.34–2.57)	<0.001	0
Superficial sternal wound infection	3	1.97 (1.23–3.15)	0.004	53
Myocardial infarction	5	0.74 (0.49–1.13)	0.17	0
Stroke	7	0.70 (0.43–1.12)	0.14	0

internal thoracic artery. The two recent studies among these are propensity matched [12,13]. Additionally, one study [13] reported significantly lower re-intervention in the BITA cohort (2.8% vs 10.1%) and better cardiac event-free survival with the use of both internal thoracic arteries. A large retrospective study spanning a decade and 1977 patients undergoing BITA use, reported that this did not help improve survival in patients above 66 yrs [15]. Two recent analyses with BITA use report that this does not positively impact survival at the age of seventy [14,18]

The Summary of finding table (Table 2) outlines the pooled OR with 95% CI, number of studies contributing to the analysis with sample size, heterogeneity and sensitivity analysis performed.

4. Discussion

Coronary artery bypass is often the commonest procedure performed by adult cardiovascular surgeons. From the initial “all-vein” procedure, Dr. Loop conclusively established the importance of the internal thoracic artery graft almost 25 years ago. However, even after two decades, we still have not reached a consensus regarding the “best” operation for coronary revascularization.

A recent article from the Mayo Clinic has appropriately demonstrated the importance of total arterial grafting to improve survival after CABG [19]. A large meta-analysis of nine studies (5 propensity matched; 15,583 patients) demonstrated that BITA use was associated with significantly superior survival at the end of 10 years (Hazard ratio for mortality 0.79; 95% confidence interval 0.75–0.84) [5,20]. However, when we consider patients above the age of 65 years, the available data is more conflicting.

The internal thoracic artery has been traditionally harvested along with it's venae comitante as a pedicle. This technique however may result significant reduction in sternal blood flow. When both internal thoracic arteries are being used for CABG, surgeons have implemented a skeletonized method. In this modification, only the artery is carefully dissected off the chest wall clipping and dividing it's branches. This technique has been found to preserve sternal blood flow [21]. Deep sternal wound infection (DSWI) continues to be a major concern when BITA harvest is considered, especially in diabetic patients. A recent meta-analysis of eleven studies (126,235 patients) reviewed the incidence of sternal wound infection in diabetic patients undergoing skeletonized and pedicled ITA harvest. While pedicled BITA harvest clearly increases the risk of DSWI, skeletonized BITA harvest can be safely performed in diabetic patients [22]. Our present analysis demonstrates that DSWI is an important problem in BITA harvest in the elderly. Authors [23,24] have demonstrated that DSWI is associated with increased mortality after cardiac surgery. A recent institutional database review implicated obesity, female gender and diabetes (especially in combination) as likely risk factors for DSWI after BITA harvest [25].

The ART trial [26] is the first randomized study that compares outcome of single and bilateral internal thoracic artery grafting for CABG. While the primary end-point is ten years, only one-year survival has been reported. After pooling all patients irrespective of age, this study has also demonstrated that sternal wound infection is higher [RR 3.54(1.54–6.83)] after BITA harvest in diabetic patients. While data on the long-term results are awaited, it would be beneficial for the research group to investigate the effect of patient age on the early results of the trial.

We have demonstrated that early mortality is comparable in both cohorts. Hence the increased complexity of skeletonized harvest and surgical techniques does not appreciably increase the risk of the procedure. Peri-operative myocardial infarction and post-operative respiratory failure is also similar among cohorts. While we have demonstrated that stroke is comparable in both cohorts, the use of BITA would theoretically increase the possibility of using off-pump CABG and the “no-touch” aorta techniques. The use of the no-touch method has been demonstrated to reduce the incidence of stroke, especially in the hostile aorta [27]. A recent ad-hoc analysis of data from the ART study did not demonstrate any difference in stroke rates between conventional and off-pump CABG [28].

Additional data lacking is the incidence of recurrent angina, need for repeat re-intervention and cardiac event-free survival. These aspects clearly point out the lack of robust evidence on this important subject. Our meta-analysis unfortunately does not allow us to determine predictors of poor survival in the elderly undergoing bilateral internal thoracic artery grafting. This information would provide us with a better understanding of when the use of both internal thoracic arteries would be beneficial in this age group.

4.1. Strengths and limitations

We acknowledge that our systematic review has some limitations. Firstly, it is pooled analysis of retrospective studies. Variation in surgical technique or ITA harvest methods would vary among institutions and even within the same hospital. However, in the absence of data from a randomized controlled study, a meta-analysis such as ours provides evidence less prone to type 1 error. We have also performed a sensitivity analysis and tests to assess for publication bias for each important end-point.

5. Conclusions

BITA use in the elderly may lead to a significantly higher incidence of deep sternal wound infection. The late survival advantage of using both internal thoracic arteries in this cohort is not equivocal. Hence given the present evidence, we would suggest selective use of bilateral internal thoracic artery grafting in the elderly patients undergoing coronary artery bypass grafting.

Ethical approval

None required.

Funding

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Conflict of interest

None.

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