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Coronary artery bypass grafting using bilateral internal thoracic arteries in patients with diabetes and obesity: A systematic review and meta-analysis

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ABSTRACT

Background: Patients with diabetes and obesity are at higher risk of adverse long-term outcomes following coronary artery bypass grafting. The use of bilateral internal thoracic arteries (BITA) can potentially offer survival benefit in higher risk patients compared to single internal thoracic artery (SITA), but BITA is not routinely used due to lack of clear evidence of efficacy and concerns over sternal wound complications.

Methods: Medline, Embase and the Cochrane Library were searched for studies comparing the efficacy and safety of BITA and SITA grafting in patients with diabetes and obesity. Meta-analysis of mortality and sternal wound complications was performed.

Results: We identified eight observational and ten propensity matched studies, and one RCT, comparing BITA and SITA which included patients with diabetes (n = 19,589); two propensity matched studies and one RCT which included patients with obesity (n = 6,972); mean follow up was 10.5 and 11.3 years respectively. Meta-analysis demonstrated a mortality reduction for BITA compared to SITA in patients with diabetes (risk ratio [RR] 0.79; 95% confidence interval [CI] 0.70–0.90; p = 0.0003). In patients with obesity there was a non-significant reduction in mortality in the BITA group (RR 0.73, 95% CI 0.47–1.12; p = 0.15). There was a significantly higher rate of sternal wound complications following BITA observed in patients with diabetes (RR 1.53, 95% CI 1.23–1.90; p = 0.0001) and obesity (RR 2.24, 95% CI 1.63–3.07; p < 0.00001).

Conclusions: BITA is associated with better long-term survival in patients with diabetes. The effects of BITA grafting in patients with obesity are uncertain. BITA is associated with higher rates of sternal wound complications compared to SITA in both patients with diabetes and obesity.

1. Introduction

Coronary artery disease (CAD) is one of the main causes of mortality and morbidity globally [1]. Coronary artery bypass graft (CABG) surgery is an effective method of coronary revascularisation in patients with symptomatic advanced coronary artery disease including patients with diabetes, left ventricular dysfunction and left main coronary disease [2–5]. Conventional CABG involves use of the left internal thoracic artery (LITA) with additional vein grafts as required. There is growing evidence that greater use of arterial grafts including the right internal thoracic artery (RITA) and the radial artery may offer superior outcomes compared to the conventional CABG approach but evidence from randomised controlled trials is lacking. The Arterial Revascularisation Trial (ART) compared all-cause mortality at ten years in 3102 patients randomised to single (SITA) versus bilateral internal thoracic (BITA) and found no overall clear benefit from BITA grafting [6]. Secondary analysis from ART suggests potentially greater benefits of BITA grafting in patients with diabetes (about 25% of the trial population) although the

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risk of sternal wound complications is also higher in patients with diabetes who undergo BITA grafting. Many patients with diabetes are also obese, and the rate of obesity is increasing in CABG patients even without diabetes [7,8]. To understand the latest aggregate evidence for BITA compared to SITA grafting in patients with diabetes and those with obesity we conducted a systematic review of the literature with a *meta*-analysis of all-cause mortality and sternal wound complications.

2. Methods

This review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) recommendations. We selected randomised controlled trials and observational studies comparing isolated BITA grafting and isolated SITA grafting in patients with diabetes or obesity as defined by BMI $\geq$ 30 kg/m^2. Eligible studies reported data on mortality and sternal wound complications with the minimum length of follow-up of 2 years. We searched Medline, Embase and Cochrane Database of Systematic Reviews for completed, peer-reviewed manuscripts and conference abstracts. Text words and Medical Subject Headings (MeSH) were used as search terms; truncation and 'wildcard' approach were utilised, and combined searches were performed using Boolean operators such as 'AND' and 'OR' (Supplementary Table 1). Quality assessment of the included observational studies was carried out using the Newcastle–Ottawa scale for observational studies. A random-effects model was used to carry out the primary analysis stratified by study with a pooled p value of < 0.05 to indicate statistical significance. Heterogeneity was assessed using the I^2 statistic. To determine the impact of publication bias, a funnel plot of included studies was constructed. All searches, data extraction and management, quality assessments and analyses were independently performed by two reviewers (MS and MD) and disagreements were resolved by discussion and consensus.

When studies did not include numerical data for outcomes of interest, all-cause mortality was extracted from Kaplan-Meier curves using an online plot digitizer software [9]. The extracted data was used to derive the number of patients with events/number available for analysis in the BITA and SITA groups respectively which was used to generate risk ratios (RR) with 95% confidence intervals (CI) per study. Data synthesis was performed in Review Manager software (version 5.1.2; Cochrane Collaboration, Oxford, United Kingdom). Subgroup analyses of studies reporting unmatched observational data, propensity score matched data and randomised trial results were carried out. A sensitivity analysis was carried out excluding medium and/or high risk of bias studies to check for consistency of results.

3. Results

3.1. Results of the search

A total of 297 potentially relevant studies were identified in the initial search (Fig. 1) of which 21 (7%) met the eligibility criteria. Nineteen studies (8 observational, 10 propensity matched and 1 RCT)

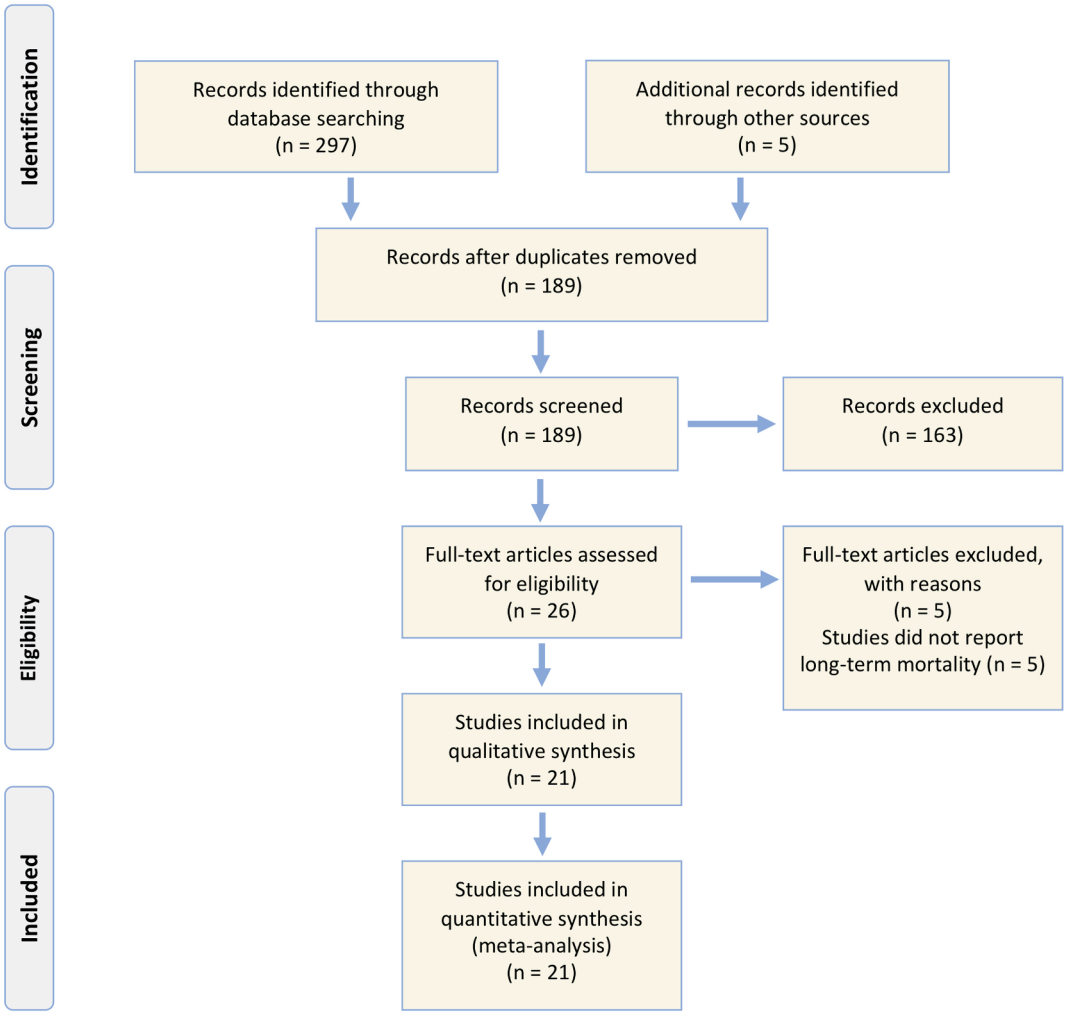

Fig. 1. PRISMA flow chart for literature search.

[6,10–27] involving 19,589 patients compared BITA versus SITA in patients with diabetes with a mean follow up of 10.5 years and 3 studies (2 propensity matched and 1 RCT) [6,28,29] with 6,972 patients with obesity with a mean follow up of 11.3 years (Supplementary Table 2a and 2b).

Baseline characteristics are summarized in Supplementary Table 3a and 3b. In the diabetes studies the BITA group, compared to SITA, included younger patients, fewer women, lower mean BMI, more hyperlipidaemia, and more non-insulin-dependent diabetes mellitus (NIDDM). The BITA group received more grafts and fewer perioperative (pooled preoperative, intraoperative and postoperative) intra-aortic balloon pumps; BITA was associated with longer bypass and cross-clamp time, likely as a result of higher number of anastomoses needed compared to SITA [30,31]. Among the diabetic patients SITA was associated with higher odds of skeletonised grafting compared to BITA. In the obesity studies patients in the BITA group were younger, had lower BMI, higher mean ejection fraction, and less peripheral vascular disease (Supplementary Table 3b). The methodology and variables used in propensity score matched analyses are presented in Supplementary Table 4a and 4b.

3.2. Quality assessment

Quality assessment of studies is shown in Supplementary Table 5a and 5b**.** All studies demonstrated high methodologic quality except one [14] due to missing data.

3.3. Long-term mortality following BITA versus SITA in patients with diabetes

Pooled analysis demonstrated that, overall, BITA grafting was associated with lower long-term all-cause mortality compared to SITA grafting in patients with diabetes (RR 0.79; 95% CI 0.70–0.90; $Z = 3.62$, $p = 0.0003$; $I^2 = 88\%$). Based on the I^2 statistic there is potential for heterogeneity of results between studies (Fig. 2**, panel a**). The potential benefit of BITA compared to SITA in diabetes was greatest in unmatched studies, less in the propensity matched studies and least in the RCT.

3.4. Long-term mortality following BITA versus SITA in patients with obesity

Pooled analysis of studies evaluating outcomes in patients with obesity similarly demonstrated that overall BITA grafting might be associated with lower long-term all-cause mortality compared to SITA grafting (RR 0.73, 95% CI 0.47–1.12; $Z = 1.43$, $p = 0.15$; $I^2 = 78\%$). The overall effect was non-significant and there was again potential for heterogeneity (Fig. 2**, panel b**).

3.5. Sternal wound complications following BITA versus SITA in patients with diabetes

The rate of sternal wound complications in patients with diabetes undergoing BITA grafting (3.74%) was significantly higher compared to those undergoing SITA grafting (2.06%) (RR 1.53, 95% CI 1.23–1.90; $Z = 3.86$, $p = 0.0001$; $I^2 = 4\%$), and there was no detectable heterogeneity (Fig. 3**, panel a**).

3.6. Sternal wound complications following BITA versus SITA in patients with obesity

The overall incidence of sternal wound complications in patients with obesity undergoing BITA grafting was similarly significantly higher compared to those undergoing SITA grafting (5.67% versus 2.74%) (RR 2.24, 95% CI 1.63–3.07; $Z = 5.0$, $p < 0.00001$; $I^2 = 0\%$), and there was no detectable heterogeneity (Fig. 3**, panel b**). The absolute rates appeared higher than those with diabetes.

3.7. Publication bias assessment

Visual inspection of the funnel plots of diabetes studies does not suggest a high risk of publication bias, as there was no clear evidence for funnel plot asymmetry (Supplementary Fig. 1). There were too few obesity studies to construct informative funnel plots.

4. Discussion

4.1. Summary of main findings

We found that BITA grafting was associated with significantly better long-term survival in patients with diabetes compared to SITA but most of the favourable evidence comes from observational studies. ART was the only large RCT comparing BITA and SITA with about a quarter of patients enrolled with diabetes and did not show any clear evidence of benefit for BITA. As expected, BITA was associated with higher sternal wound complications in patients with diabetes compared to SITA and this finding was consistent across observational studies and the RCT. BITA grafting showed a potential mortality reduction in patients with obesity compared to SITA but only two studies were identified and this finding was not significant. Similar to the findings in patients with diabetes, BITA was associated with higher sternal wound complication rate in patients with obesity compared to SITA.

Patients with diabetes undergoing CABG usually have complex CAD, co-morbidities such as renal impairment and heart failure which puts them at higher risk of mortality, and diabetes itself is associated with accelerated atherosclerosis [32]. Patients with diabetes are at a higher risk of vein graft failure due to intimal degeneration and impairment of the endothelial function and loss of vasomotor function [33–35]. The introduction of the left internal thoracic artery as a routine conduit for CABG has provided a more reliable graft for the left ventricle and improved long-term outcomes in patients with and without diabetes. The LITA has better longevity and resistance to atherosclerosis, intimal hyperplasia, medial calcification and less spasticity than vein grafts and these findings have also been extended to the right internal thoracic artery (RITA) [36–38]. Patency rates of the LITA have been shown to be ~ 90% at ten years and similar results have been found for the RITA [39–43]. As patients with diabetes are at an increased risk of developing cardiovascular and arteriopathic complications compared to patients without diabetes, BITA compared to SITA grafting may provide additional survival benefit in patients with diabetes.

Observational studies have demonstrated potential benefits of BITA grafting in patients with diabetes [44–46]. Our review was able to demonstrate via stratified analysis that the treatment effect associated with BITA use appears greater in unmatched observational studies, less pronounced in the propensity score matched observational studies, and finally non-significant in the RCT. This pattern of effects is consistent with the potential for biased comparisons in unmatched or matched observational studies [47]. For example, in the diabetes analysis of observational studies BITA patients were younger by about 2.5 years and in the obesity analysis BITA patients had lower BMI. Both of these factors could provide an advantage for the BITA group.

In a secondary analysis of ART addition of a RITA and/or radial artery to the LITA (multiple arterial grafts) was associated with improved mortality outcomes in patients with diabetes compared to LITA graft alone with vein grafts being used as needed in both multiple and single arterial graft groups [48]. The ongoing randomised ROMA trial is comparing multiple arterial grafts with standard LITA CABG in patients aged ≤ 70 years and will provide further information on the efficacy and safety of multiple arterial grafts in a general CABG population and subgroups with diabetes and obesity [49].

Pre-operatively, the potential survival advantage of BITA grafting in patients with diabetes ought to be weighed against the higher rates of sternal wound complications. Our review found that patients with diabetes experienced more sternal wound complications following BITA

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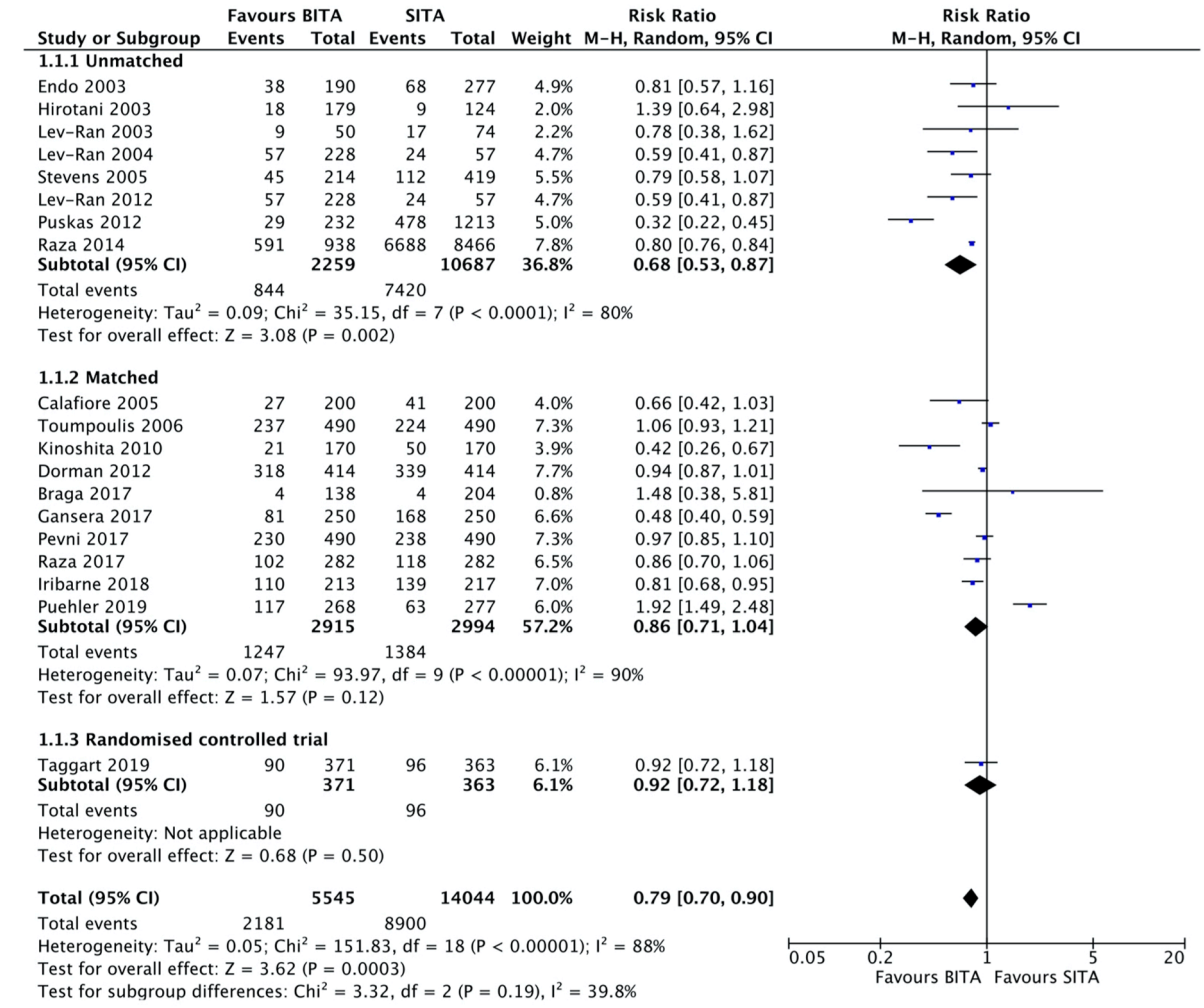

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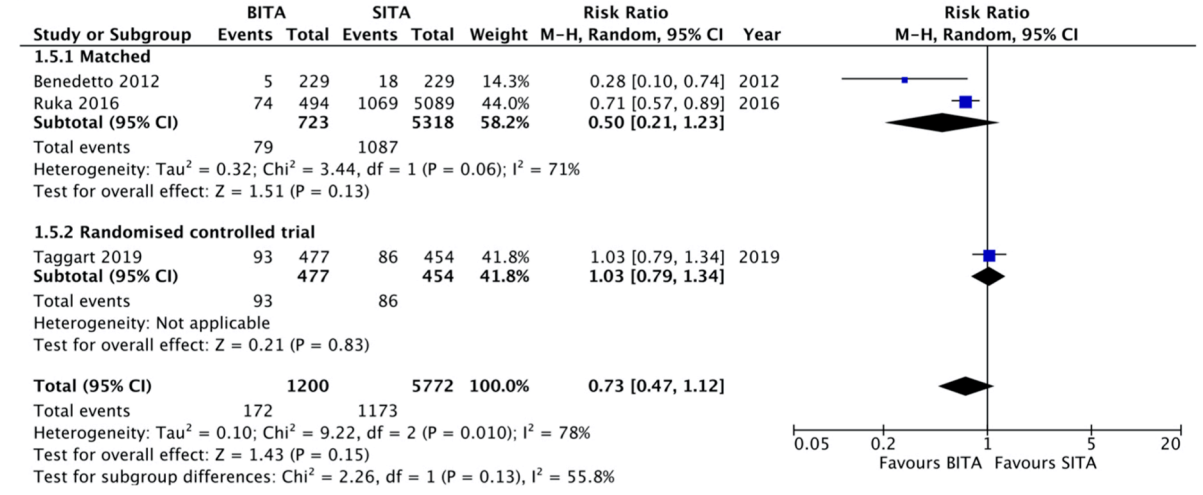
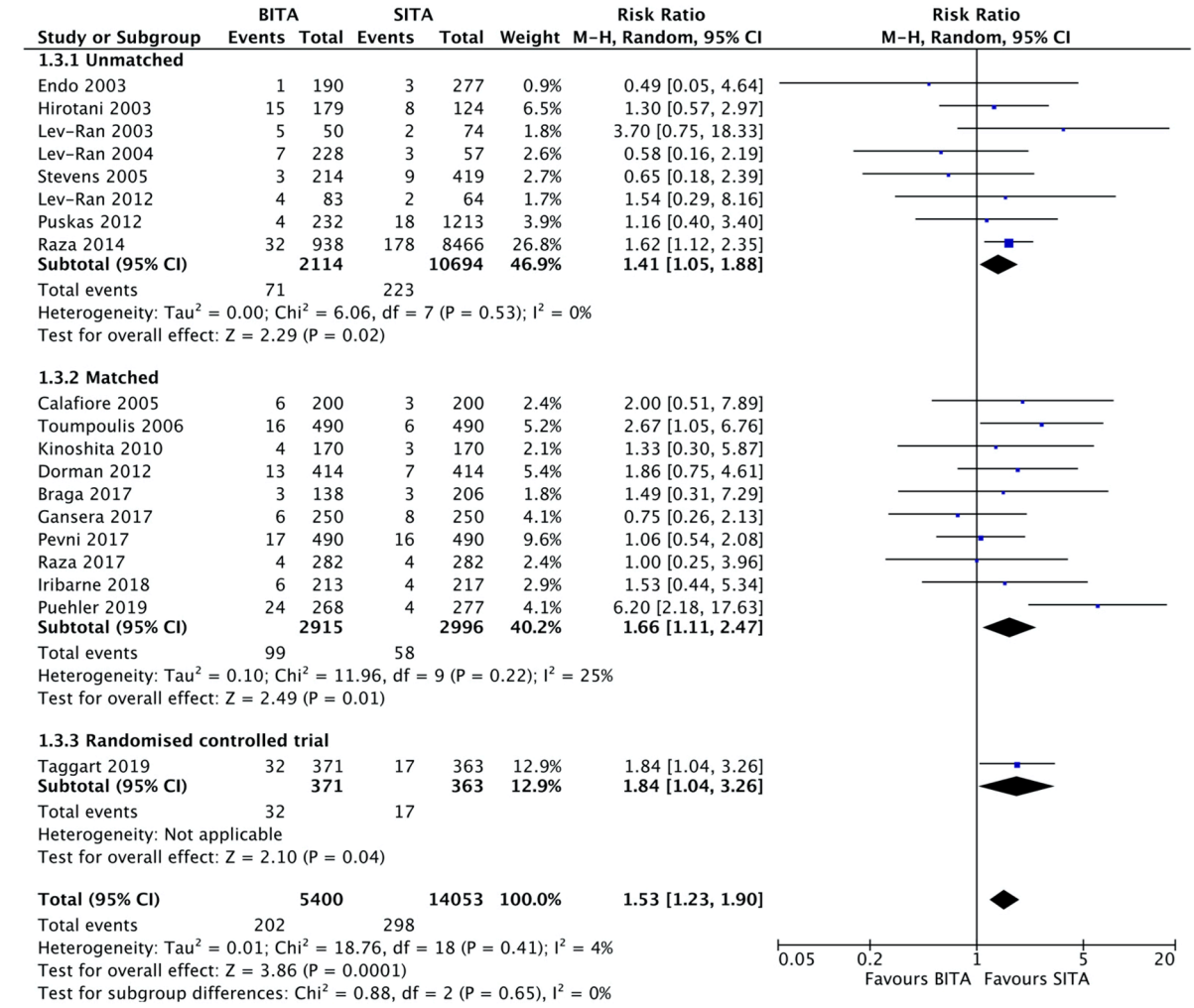


Fig. 2. Forest plot demonstrating effects of BITA grafting compared to SITA grafting on long-term all-cause mortality in patients with diabetes (panel a) and patients with obesity (panel b). *BITA – bilateral internal thoracic artery; SITA – single internal thoracic artery; M–H - Mantel-Haenszel; CI – confidence interval.*

a



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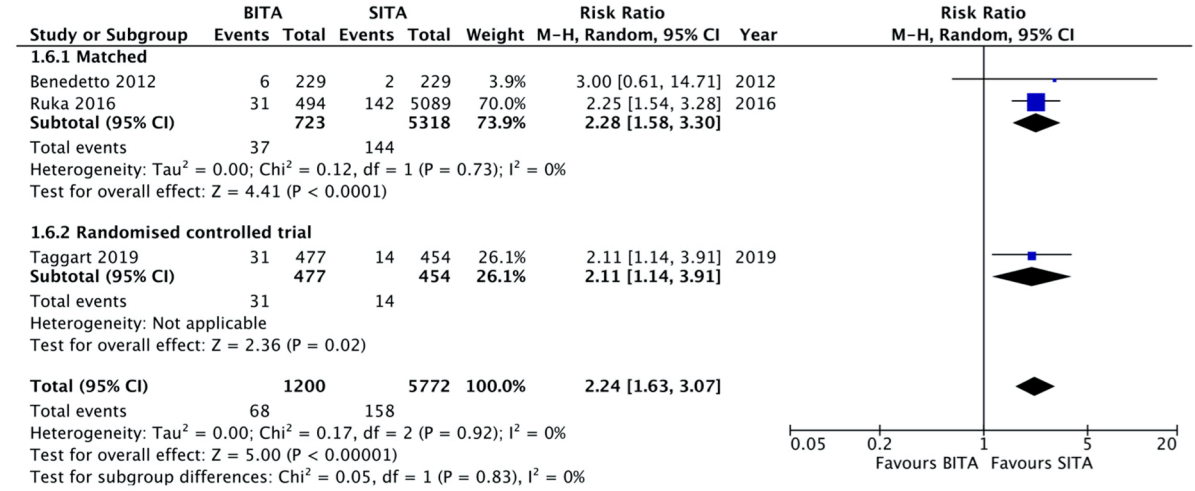

Fig. 3. Forest plot demonstrating effects of BITA grafting compared to SITA grafting on sternal wound complications in patients with diabetes (panel a) and patients with obesity (panel b). *BITA – bilateral internal thoracic artery; SITA – single internal thoracic artery; M–H - Mantel-Haenszel; CI – confidence interval.*

grafting compared to SITA grafting. Excess sternal wound problems have always been a concern for the wider adoption of BITA grafting especially in patients with diabetes. Use of BITA increases the risk of sternal ischaemia leading to poor healing and higher rates of infection and these risks are higher in patients with diabetes compared to those without diabetes. Patients with diabetes are inherently more prone to developing sternal wound complications due to unreliable control of blood sugar levels perioperatively that interferes with platelet function and immune response that in turn slows down healing [50]. Tight glucose control in the weeks leading up to the surgery as well as in the perioperative phase via continuous intravenous infusion of insulin has been shown to improve sternal wound outcomes in patients with diabetes [51,52].

A *meta*-analysis of 32 observational studies by Dai et al including 128,109 patients with diabetes has shown that BITA compared to SITA grafting is associated with higher rates of sternal wound complications (RR 0.65, 95% CI 0.52–0.81), which was partially alleviated by the use of skeletonisation technique bringing the risk of sternal wound complications closer to the level associated with SITA grafting (RR 0.84, 95% CI 0.54–1.31) [53]. Regardless of the harvesting technique used, the rate of sternal wound complications in patients with diabetes following BITA is higher than SITA.

Negative pressure wound therapy (NPWT) may also reduce the risk of sternal wound infections (SWI), although this may be most apparent in the prevention of deep SWI, specifically. It has been estimated that NPWT has an approximate number needed to treat of 22.2 to prevent one case of SWI. NPWT can be expensive, particularly if applied indiscriminately; however, its use in selected high-risk patients may be considered to prevent the development of SWI and the associated cost of prolonged hospital stays and mortality [54].

Topical antibiotic application to both cut edges of the sternum has been recommended in patients undergoing a median sternotomy. Topical vancomycin (in addition to pre-operative IV antibiotics and tight glycaemic control) has been shown to significantly reduce the risk of SWI [55]. Similarly, gentamicin sponges have also been demonstrated to reduce (both superficial and deep) SWI [56].

The use of intra-nasal mupirocin in patients with positive nasal cultures or PCR assay for Staphylococcus species has been recommended as studies have shown a reduction in SWI in treated carriers of Staphylococcal colonisation [57]. The same effect has not been demonstrated in patients who test negative for Staphylococcus colonisation and so mupirocin ought to be reserved for those who are colonised or in patients whose culture / PCR results are not obtained or available prior to CABG.

While the rate of sternal wound complications is higher in BITA grafting, there is not enough evidence to suggest that it adversely affects mortality; in fact, despite the elevated risk of sternal wound complications among those patients with diabetes who receive BITA grafts, our review suggests a long-term survival benefit. Although BITA grafting may not be appropriate for all patients with diabetes, this potential survival benefit ought to carry substantial weight, particularly if the previously discussed methods to reduce the rate of sternal wound complications can be employed. In those with a relatively shorter life expectancy (due to other lifespan-limiting conditions), the rate of sternal wound complications may perhaps be weighed more heavily in the preoperative discussion with the patient.

The higher rate of sternal wound complications is associated with a higher economic burden which has been demonstrated in the ART trial where at one year follow up mean costs were approximately 9% higher in BITA than SITA patients, due to longer time in theatre, longer in-hospital stay, and sternal wound problems during follow-up [58].

Like with diabetes, patients with obesity are at an increased risk of accelerated atherosclerosis in the graft vessels. Wee et al have shown that higher BMI is associated with more rapid progression of atherosclerotic disease after CABG utilising vein grafts [59]. It is plausible that this forms part of a reason why BITA grafting could be more beneficial than SITA grafting in patients with obesity, as arterial grafts are capable to withstand larger circulating volumes in patients with obesity and are more resistant to atherosclerotic changes [42,59] and demonstrate high patency rates at 10 years follow-up [40,60,61]. The inherent structural characteristics of the ITAs such as lower intercellular junction permeability, fewer fenestrations, greater antithrombotic mediators, and greater concentration of nitric oxide in the endothelial tissue make it less susceptible to atherosclerosis as these characteristics help prevent excessive transfer of lipoproteins into the arterial wall tissue [62–68]. These properties may preferentially benefit patients with obesity who generally have higher lipid levels than patients without obesity.

Obesity has been perceived as a relative contraindication for BITA grafting in the past, as there is potential for higher sternal complication rate. Some reports suggest a higher risk [69] while others show no apparent difference between the rates of sternal wound complication in BITA compared to SITA grafting in patients with obesity [70–72]. This evidence is limited by the lack of RCTs available. Patients with obesity are thought to be more vulnerable to sternal wound complications due to the difficulty of dissection through the excess adipose tissue as well as potential insulin resistance that leads to slower healing [73]. A secondary analysis of the ART looking at the role of skeletonisation involving 631 patients with obesity showed that a pedicled compared to skeletonised BITA approach was associated with higher incidence of sternal wound complications (OR, 2.07; 95% CI, 1.09–3.90); the same pattern was evident in the diabetic subgroup, however the analysis was underpowered to draw definitive conclusions [74]. Skeletonisation of the internal arterial grafts and the use of haemostatic clips and scissors to divide the collateral circulation helps to preserve perfusion to the surrounding tissue via the intercostal and muscular branches and could reduce the risk of infection [62].

4.2. Limitations

The main limitation of this analysis is that most of the studies were observational with all the inherent biases of trying to estimate treatment benefits. These biases may arise from confounded comparisons, different concomitant treatments, missing data, retrospective studies and surgeon experience. Propensity matching is a method to try and control for differences in populations receiving BITA and SITA, however even after matching for key variables there may be residual bias that remains undetected. Funnel plotting did not reveal a high risk of publication bias, however observational studies with outcomes of interest are still more likely to be published than similar studies with “null” findings. At present the evidence base for effects of BITA graft surgery in patients with obesity is modest.

5. Conclusions

Diabetes and obesity are closely associated with coronary artery disease and global prevalence is growing. BITA is associated with better long-term survival in patients with diabetes, but most of the supportive data comes from observational studies. The effects of BITA grafting in patients with obesity is uncertain but preliminary evidence looks favourable. BITA is associated with higher rates of sternal wound complications compared to SITA in both patients with diabetes and obesity. Further randomised controlled trials of BITA grafting in patients with diabetes and obesity would help define the balance of efficacy and safety in these high-risk populations and develop strategies to reduce sternal wound complications.

6. Registration number of clinical studies

Not applicable.

CRediT authorship contribution statement

Maria Stefil: Conceptualization, Methodology, Software,

Investigation, Formal analysis, Visualization, Writing – original draft. **Matthew Dixon:** Data curation, Validation, Writing – original draft. **Umberto Benedetto:** Writing – review & editing. **Mario Gaudino:** Writing – review & editing. **Belinda Lees:** Writing – review & editing. **Alastair Gray:** Writing – review & editing. **Stephen Gerry:** Writing – review & editing. **David Taggart:** Writing – review & editing. **Marcus Flather:** Conceptualization, Methodology, Writing – review & editing, Project administration, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2023.101235.

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