Abstract:

Introduction:

Arterial grafting improves long term survival in patients undergoing coronary artery bypass grafting (CABG). However, it`s benefit in diabetic patients is still unclear. Thus, we performed a systematic review to determine the impact of diabetes mellitus (DM) on long-term survival of various grafting strategies.

Methods:

Multiple databases were searched (Inception – August 2019) to identify peer-reviewed studies analyzing the impact of DM on long-term survival after CABG. We compared grafting strategies by pooling individual hazard ratios (HR) with inverse variance random effects model. Results are reported at 95% confidence level.

Results:

Three studies compared total arterial revascularization (TAR) with non-TAR. Survival was 90 %, 88% at 5 and 10 years respectively in the TAR cohort compared to 78 % and 74 % in the non-TAR cohort [HR 1.22(1.06-1.4); p = 0.008]. Pooling four studies, reported survival in bilateral Internal Thoracic Artery (BITA) group was 84%, 64%, 37%, and 26% at 5, 10, 15, and 20 years, respectively compared to 78%, 55%, 30%, and 21% in left Internal Thoracic Artery (LITA) cohort. Survival in LITA/RA cohort (1088 patients) was 88 %, 69 % and 50 % at 5, 10, and 15 years, respectively. Corresponding survival was 83 %, 65 % and 39 % with LITA/SVG group (1078 patients) [HR 1.3(1.1 – 1.5); p = 0.006].

Conclusion:

Among patients with diabetes mellitus, compared with the saphenous vein, use of the radial artery as a second conduit improves long-term survival. We believe that this strategy should be widely considered in patients with diabetes mellitus undergoing coronary artery bypass grafting.

**Background:**

Patients with diabetes mellitus often have diffuse multi-vessel coronary artery disease 1. Coronary artery bypass grafting (CABG) is now unequivocally the treatment of choice for CAD in patients with diabetes mellitus (DM). However, diabetes mellitus itself, is an independent predictor of poorer long-term survival after CABG 2. Observational studies report the long-term survival benefit of bilateral internal thoracic artery (BITA) grafting in CABG 3. However, among patients with DM, BITA grafting may be associated with increased risk for sternal wound infection. Thus, data regarding its benefit among diabetic patients is sparse. Even more unclear is long-term survival for diabetic patients undergoing CABG with the use of other arterial conduits like the radial artery (RA), saphenous vein (SVG) and less frequently, the right gastroepiploic artery (RGEA). We, hence, conducted a systematic review to analyze and compare long-term survival among diabetic patients undergoing CABG with differing grafting strategies

**Methods:**

Literature Search:

We performed a systematic literature search (Inception – August 2019) using multiple databases (Pubmed, Ovid, Embase, Web of Science and Cochrane Database of Systematic Reviews) to identify English language peer-reviewed publications that compared long-term outcome (defined as a minimum of 10 years) for at least two different grafting strategies for CABG in adult patients with diabetes mellitus. We queried the databases with keywords “diabetes mellitus,” “coronary artery bypass grafting,” “internal mammary artery,” “internal thoracic artery,” “radial artery,” “bilateral internal thoracic artery,” “bilateral internal mammary artery,” either singly or in combination (Supplement).

Briefly, our inclusion criteria were as follows: (1) study compares long-term clinical outcome of patients with diabetes mellitus (2) study reports results of propensity adjusted data; and (3) study compares least two different conduit strategies for CABG. Search strategy (Online supplement) was devised and conducted by our librarian (MN). Review of titles and full-text articles was conducted by three authors (CC, SEA, SVD) in a blinded manner. Disputes were resolved by consensus. Case reports, editorials, other systematic reviews and studies that did not present propensity-matched results were excluded. References and citations from included articles were manually searched to ensure the completeness of the systematic review process.

As a review study, it was exempt from Institutional Board approval and waived of the need for patient consent.

Abstraction of Data:

Our primary aim was to compare long-term survival between groups. Grafting strategies available from the data and hence compared were as follows: total arterial revascularization (TAR), non-total arterial revascularization (non-TAR), bilateral internal thoracic artery group (BITA), left internal thoracic artery group (LITA), a combination of the left internal thoracic artery + radial artery (LITA/RA) and left internal thoracic artery + saphenous vein (LITA/SVG). We collected reported hazard ratios (HR) from each study. When hazard ratios were not directly available, the Guyot method, reportedly the most accurate method, was used to obtain study estimates 4-6. This method requires analysts to initially extract information from the published Kaplan-Meier curves. Using the Digitizelt proprietary software program (<https://www.digitizeit.de/>), we obtained co-ordinates for each individual study arm on both x and y axes. Apart from one study 7, all others also provided the study number of patients at risk at specific time intervals during the study period. Using an algorithm reported by Guyot et al. 5, we were able to reliably obtain (1) time of follow-up for each patient, and (2) whether the patient experienced the event of interest for each individual patient in the study. Censoring was non-informatively distributed equally for each time interval. Once hazard ratios were available from each study, they were combined to compare conduit strategies. Pooled meta-analysis was performed in an inverse variance framework with a random effects model. Extracted data from each study was then pooled together; survival estimates for each grafting strategy were the non-parametric Kaplan-Meier method. Sensitivity analysis was conducted as follows: (1) when a single study had a disproportionately high weight to the result, we repeated this analysis excluding this study. (2) we fit a clustered flexible parametric survival model to the extracted patient level data 8. This model was fit on the hazard scale.

Heterogeneity between studies was assessed with I2; standard cut-offs were implemented to report the degree of heterogeneity. Given the small number of studies for each pooled conduit strategy (n < 10), publication bias could not be assessed. Study quality was evaluated with the Newcastle Ottawa Scale that is recommended for observational studies.

Statistical analysis was performed with R 3.6.1 (The R foundation for Statistical Computing, Austria). Details regarding methods employed for individual patient level data extraction from the published Kaplan-Meier curves are provided in the supplement. We adhered to the meta-analysis of observational studies in epidemiology (MOOSE) guidelines.

**Results:**

From 860 titles, we reviewed the full-text of 54 papers. We eventually included 10 studies 7,9-17 in our systematic review (Supplement, Figure 1). One study 18 was excluded as it performed multi-variable Cox regression without propensity matching. Four studies 7,11,13,17 compared outcome of bilateral internal thoracic arterial grafting (BITA group) and single internal thoracic artery supplemented with either a radial artery or saphenous vein for other grafts (LITA group). Three studies 9,12,14 compared patients operated with a total arterial revascularization (TAR group) strategy and those receiving at least one vein graft (non-TAR group). Three studies 10,15,16 compared survival between patients receiving the left internal thoracic artery and radial artery (LITA/RA group) and left internal thoracic artery with saphenous vein grafts (LITA/SVG group). Tables 1, 2, and 3 present a brief overview of patient clinical characteristics according to the grafting strategy implemented in each study. All papers were high quality observational studies, scoring at least 7/10 on the Newcastle scale.

TAR vs. non-TAR groups (Figure 1):

Three studies 9,12,14 compared patients having a TAR or non-TAR strategy (2551 patients -TAR vs. 2501 patients - non-TAR; 27,912 patient-years follow-up). Observed survival was 90.5 ± 1.4% at 5 years and 88.7 ± 1.6 % at 10 years in the TAR cohort. In the non-TAR cohort, at the same time points, estimated survival was 78.5 ± 3% and 74.2 ± 3.6 %. (Figure 1). Survival in the TAR cohort was significantly higher [HR 0.80 (0.71 – 0.91); p = 0.0007]. ]. This pooled outcome did not demonstrate any inter-study heterogeneity (I2 = 0%). Parametric modelling reported very similar hazard ratios [HR 0.80 (0.71 – 0.90); p = 0.0008].

BITA vs LITA groups (Figure 2):

Four studies 7,11,13,17 (1,399 BITA and 1,403 LITA patients) compared survival between patients receiving a single (LITA) and bilateral (BITA) internal thoracic artery. Among these, Raza et al 11 studied patients who had radial artery as the second conduit with the single internal thoracic artery; other studies did not specify details regarding other conduits used along with the LITA. Survival in the BITA group was 84%, 64%, 37%, and 26% at 5, 10, 15, and 20 years, respectively. At the same time intervals of follow-up, corresponding survival in the LITA cohort was 78%, 55%, 30%, and 21%, respectively. There was no heterogeneity (I2 = 0%) in the reported results. Sensitivity analysis removing Dorman et al17 confirmed the overall pooled results. Parametric modelling confirmed our initial results [HR 0.75 (0.85 – 0.66)].

LITA/RA vs. LITA/SVG groups (Figure 3A/3B):

Three studies 10,15,16 (1088 LITA/RA vs 1078 LITA/SVG) patients were pooled for this analysis. Survival in the LITA/RA cohort was 88.8 (86.7 – 90.7) %, 69.2 (66.2 – 72.2) % and 50.2 (46.7 – 54) % at the end of 5, 10, and 15 years, respectively. In the LITA/SVG group, corresponding survival estimates were 83.3 (81.5 – 86) %, 65.2 (62.2 – 68.4) % and 39.8 (36.4 – 43.5) %, respectively (log-rank test p-value < 0.001). On Kaplan Meier analysis, median survival in the LITA/RA and LITA/SVG groups was 15.5 and 12.5 years, respectively. Hazard for mortality was thus significantly higher in the LITA/SVG group [HR = 1.32 (1.17 – 1.50); p-value = 0.0006]. The instantaneous hazard was high in the post-operative period, after which it reduced and then again increased throughout the follow-up duration. The result was devoid of heterogeneity (I2 = 0%). Parametric modelling used as sensitivity analysis confirmed our pooled result.

**Discussion:**

We pooled reconstructed data from the Kaplan Meier curves of propensity-matched studies that reported long-term survival with various grafting strategies in diabetic patients undergoing CABG. We demonstrate that long-term survival is excellent with total arterial revascularization and the use of bilateral internal thoracic artery grafts, even among diabetics. But more importantly, we observed that the use of the radial artery as a second arterial conduit also improved survival when compared with patients receiving conventional internal thoracic artery + saphenous vein grafts.

Diabetes mellitus is highly prevalent among patients suffering from atherosclerotic coronary artery disease 19. In the present era, almost half of the patients undergoing CABG have pre-existing DM; it is also an important predictor for increased long-term mortality post-surgery 2. Diabetes mellitus is known to impact both early (< 1 year) and late saphenous vein graft failure 20. Compared with vein grafts, arterial conduits appear to be resistant to atherosclerotic disease. They also seem to reduce progression of native disease in the coronary arteries; a possible mechanism leading to improved patient survival with arterial grafting 21. Many observational studies have reported benefit with BITA grafting in the long term 22. The as-treated analysis of the Arterial Revascularization Trial (ART) demonstrate the long-term benefit of BITA grafts at the end of 10 years 23.However, only around 5 % patients receive BITA grafting in the United States 24. Increased technical complexity, concern for sternal non-healing and lack of incentive are often listed as possible factors contributing to these low rates of BITA adoption 25. Recent reports of programmatic specialization for coronary surgery are welcome initiatives that will increase arterial grafting 26.

Clinical Implications:

Our meta-analysis again underlines the message that BITA grafting improves long-term survival; even in diabetic patients. But, we feel that the most important message from our study is the long-term survival advantage of the radial artery over the saphenous vein in diabetic patients. The radial artery can be safely harvested by trained physician assistants. Minimally invasive radial artery harvest is possible with excellent conduit quality 27. The radial artery can be grafted proximally either to the aorta or to the internal thoracic artery as a T- or Y- graft with comparable long-term patency rates 28. Thus it is an easily harvested, reliable, conduit. Hence, we hope that our study will promote increased use of the radial artery among surgeons when treating diabetic patients.

**Strength and Limitations:**

We present here limitations of our study. We have pooled observational data. In spite of selecting results from only propensity-matched studies, it is possible that residual confounding may impact results. Given that we pool observational studies, we have adopted a random effect model to account for unexplained between study variance. However, we believe that our study also has unique strengths that validate our results. By extracting reconstructed patient data where hazard ratios are not reported, we have adopted the most accurate method for obtaining study level estimates. Sensitivity analysis with parametric frailty modelling was conducted for each end-point. This demonstrates that our results were valid independent of the proportional hazards assumption. Our study is also the largest systematic review to date which focuses specifically on long-term outcome between various grafting strategies in diabetic patients.

**Conclusion:**

Among patients with diabetes mellitus, compared with the saphenous vein, use of the radial artery as a second conduit improves long-term survival. We believe that this strategy should be widely considered in patients with diabetes mellitus undergoing coronary artery bypass grafting.

Legends:

Figure 1.

Long-term survival in diabetic patients with total arterial revascularization was associated with lower overall hazard for mortality during follow-up {HR 0.8(0.71 – 0.9)}.Long-term survival in diabetic patients undergoing coronary artery bypass surgery with a total arterial revascularization was observed at 90.5 +/- 1.4% and 88.7 +/- 1.6 % at the end of 5 and 10 years respectively. The corresponding estimates in patients who received at least one vein graft was 78.5 +/- 3%, 74.2 +/- 3.6 % at similar time periods (log rank test p-value = 0.01).

Figure 2.

We compared 2802 patients who underwent either bilateral internal thoracic artery grafting (BITA) or single internal thoracic artery (LITA) coronary artery bypass. BITA cohort survival was 84%, 64%, 37% and 26% at 5, 10, 15 and 20 years respectively; corresponding survival in the LITA group was 78%, 55%, 30% and 21% respectively (log rank test p-value < 0.001).

Figure 3A.

In our meta-analysis, 1088 patients who underwent coronary artery bypass surgery (CABG) with a single internal thoracic artery and radial artery (LITA/RA) were compared against 1078 patients who received a single internal thoracic artery and saphenous vein grafts (LITA/SVG) from three propensity-matched studies. We demonstrate that survival with LITA/RA is superior to LITA/SVG in diabetic patients undergoing CABG[HR 0.72(0.62 – 0.84)].

Figure 3B. Overall hazard for mortality is lower with use of a radial artery (LITA/RA group) rather than a saphenous vein (LITA/SVG group) as a second conduit with the internal thoracic artery. The instantaneous hazard was high in both groups in the immediate postoperative period and then gradually increased during the study period.

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