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The effect on survival from the use of a saphenous vein graft during coronary bypass surgery: a large cohort study†

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Abstract

OBJECTIVES: Saphenous vein graft (SVG) remains the predominant conduit used in coronary surgery. The internal mammary artery has higher later term patency and confers superior survival. Current debate focuses on the increased use of arterial conduits rather than eradication of venous conduits.

METHODS: Patient data extracted from the Australian and New Zealand Society of Cardiothoracic Surgeons database from 2001–2013 were linked to the national death registry held by the Australian Institute of Health and Welfare for all-cause mortality with censor date 7 October 2014. The dataset was divided according to use of SVG rather than the arterial conduit. Analyses of SVG $\geq$1 or SVG = 1 were compared to SVG = 0. Additionally, groups of 3, 4 or 5 grafts were subjected to multiple analyses testing the mortality hazard with increasing use of SVG. Propensity score matched analyses were conducted using 24 variables.

RESULTS: Of 51 113 primary coronary surgery patients, unmatched survival at up to 12.5 years was significantly lower for SVG $\geq$1, n = 33 359, mortality hazard ratio (HR) 1.24 [95% confidence interval (CI) 1.18–1.30], P < 0.001; and for SVG = 1, mortality HR 1.19 (95% CI 1.12–1.26), P < 0.001. Similar results were present for the propensity score matched groups; SVG $\geq$1, n = 14 355 pairs, HR 1.22 (95% CI 1.15–1.30), P < 0.001; and for SVG = 1, n = 12 316 pairs, HR 1.22 (95% CI 1.14–1.30), P < 0.001. All matched analyses within restricted graft groups had increasing HR with increased number of SVG used.

CONCLUSIONS: Any use of SVGs is independently associated with reduced survival after coronary artery bypass surgery.

Keywords: TAR • SVG • Total arterial revascularization • Survival

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INTRODUCTION

For coronary artery bypass surgery (CABG), up to 95% of patients worldwide receive at least 1 saphenous vein graft (SVG) in addition to the use of the left internal mammary artery anastomosed to the left anterior descending artery (LAD) [1, 2]. SVG is known to progressively occlude over time, and even if patent, it becomes progressively diseased. This is in contrast to the long-term disease-free patency of the left internal mammary artery [3] and other arterial conduits [4–6]. If graft occlusion is associated with mortality after CABG, then use of conduits, which are known to fail in the long term, may contribute to reduced survival. Because venous conduits are predicted to fail in the long term and arterial conduits are not, this makes the concept of using all arteries and no venous conduits a possible approach to improve long-term survival after CABG.

The patency for SVG varies widely in the literature from 59% to 89% at <3 years [4, 7] and 67–81% at 5–10 years [3, 5, 6, 8] and after 10 years at approximately 50–63% [9–13]. Conversely, long-term angiographic results of arterial grafts show high long-term patency and absence of intraluminal disease in 90–95% of left internal mammary artery [8]. The 5-year outcome of the Arterial

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Revascularisation Trial (ART) of single versus bilateral internal mammary artery grafting did not show improvement in outcomes with the use of a second internal mammary artery graft [14]. However, SVGs were used in both groups, and if SVG failure is the primary mechanism for reduced late outcomes, then the ART findings may be confounded by SVG use and with similar findings in large registries [15]. Further, the investigators allowed the use of radial artery (RA) interchangeably with SVG, possibly under the belief that this novel conduit was not better—or not worse—than the SVG. This was not further clarified in their subsequent subset analysis [16].

An evidence gap in our current understanding of late outcomes after CABG is whether any graft failure is associated with worse late survival. This is a different concept to ensuring that the LAD is protected by an arterial conduit with very high late patency. Our hypothesis is that, irrespective of the number of arterial grafts, the use of any SVG (which has known poor long term patency)—or even a single SVG—may confer worse late outcomes compared to the complete avoidance of SVG referred to as total arterial revascularization (TAR).

For context, the European Cardiac Society and European Association of Cardio-thoracic Surgeons 2014 ECS/EACTS guidelines recommend internal mammary artery to the LAD Class I, Level of Evidence (LOE) B; with bilateral internal mammary grafting if <70 years Class IIa, LOE B; use of RA only to high-grade coronary stenosis Class I, LOE B or when there was poor-quality SVG Class 1, LOE C; and TAR may be considered if there was reasonable life expectancy Class IIa, LOE B [17]; with most of these recommendations citing relatively few references.

MATERIALS AND METHODS

This retrospective study was approved by the Melbourne Health Human Research Ethics committee (2011.164) as a quality assurance project not requiring written consent with additional ethics approvals (EC2012-2-23; EO2014-2-85).

Dataset

Data of patients who underwent operations from 2001 to 2013 were used from the Australian and New Zealand Society of Cardiothoracic Surgery (ANZSCTS) database. Participating institutions record all cardiac surgery cases in the registry. From all records, patients were excluded according to Fig. 1. All-cause mortality was determined by an enquiry with the national death registry from the Australian Institute of Health and Welfare (AIHW), a federal government organization with censor date of 7 October 2014 (see Supplementary Materials). Survival was calculated to the date of death or censor. The grafting strategy was determined by the individual surgeon consistent with their institutional practice. For arterial conduits, no separate consideration was made as to type of conduit, methods of conduit usage, surgeon or institution.

Analysis of the overall effect of a saphenous vein graft

Analysis was performed based on the distal anastomosis (graft) and survival analysed per patient. Patients were grouped according to the use of SVG as follows (Fig. 1):

a. SVG = 0, or TAR irrespective of the number of grafts;
b. SVG≥1, any use of SVG irrespective of the number of arterial grafts;
c. SVG = 1, specifically restricted to 1 SVG, irrespective of the number of arterial grafts;
d. Propensity score matched (PSM) analysis for (a) and (b) and (a) and (c).

Analysis of the effect of an increasing number of saphenous vein grafts

The dataset was then further analysed within each of 3-, 4- or 5-graft cohorts to account for similarities in the extent of the coronary disease and to examine the effect of increasing numbers of SVGs (Fig. 2). Within each group, subgroups of increasing SVG use were separately subjected to propensity score matching and mortality analysis as well as for SVG ≥ 1 for each of these groups. All analyses were compared to SVG = 0.

Statistics

Continuous variables are reported as mean ± standard deviation and analysed using unpaired Student's *t*-test in the unmatched group, while paired *t*-test was used in the matched group. Categorical variables were expressed as frequency and percentage, and they were compared between groups by χ^2 test or Fisher's exact test in unmatched samples, while McNemar's test was performed after matching for complete paired samples. To analyse the difference of survival distribution and the magnitude of hazard between the 2 groups of interest, Kaplan–Meier graphs according to Klein and Moeschberger [18] or the Cox proportional hazards model, including univariable predictors of mortality that were significant at univariable analysis with 2-tailed *P* values <0.10, were performed with or without stratification by matched pair. For both unmatched and matched analyses, sensitivity test and proportionality test were conducted with no temporal effects found and HRs being proportional (see Supplementary Materials). The frequency of missing data for the fields being analysed was small, mostly 0–0.2%, with details listed in the Supplementary Material, Tables S1–S3. No imputation was used.

We performed 16 propensity score matchings with the use of 24 variables in all analyses to account for the possible selection bias at the time of surgery. The primary 2 PSM analyses were performed to examine the global survival function for patients with SVG ≥ 1 and for SVG = 1 (Figs 1, 3 and 4 and Supplementary Material, Tables S1 and S2), and grafting details in Supplementary Material, Tables S3 and S4. Fourteen of the PSM analyses were performed to analyse individual grafting strategies within groups of 3, 4 or 5 grafts (Figs 2, 5 and 6). Details of the unmatched and matched groups are listed in Supplementary Material, Tables S5–S7, with further explanation regarding the size of the matched groups in the statistics section of Supplementary Materials. These variables included emergency surgery, preoperative renal failure or dialysis, acute myocardial infarction and preoperative use of intra-aortic balloon pump. Matched pairs of patients were created by random selection of each patient in the 2 groups with similar propensity score in the designated calliper (0.05 SD of logit of propensity score). 'Greedy' matching with ratio of 1:1 and without replacement was employed to make sure each group had numerical balance. Strict matching on patient characteristics was also performed, except for gender where exact matching was used. Standardized mean differences as described by Austin [19] and *P* values were calculated to assess the balance of the covariates after

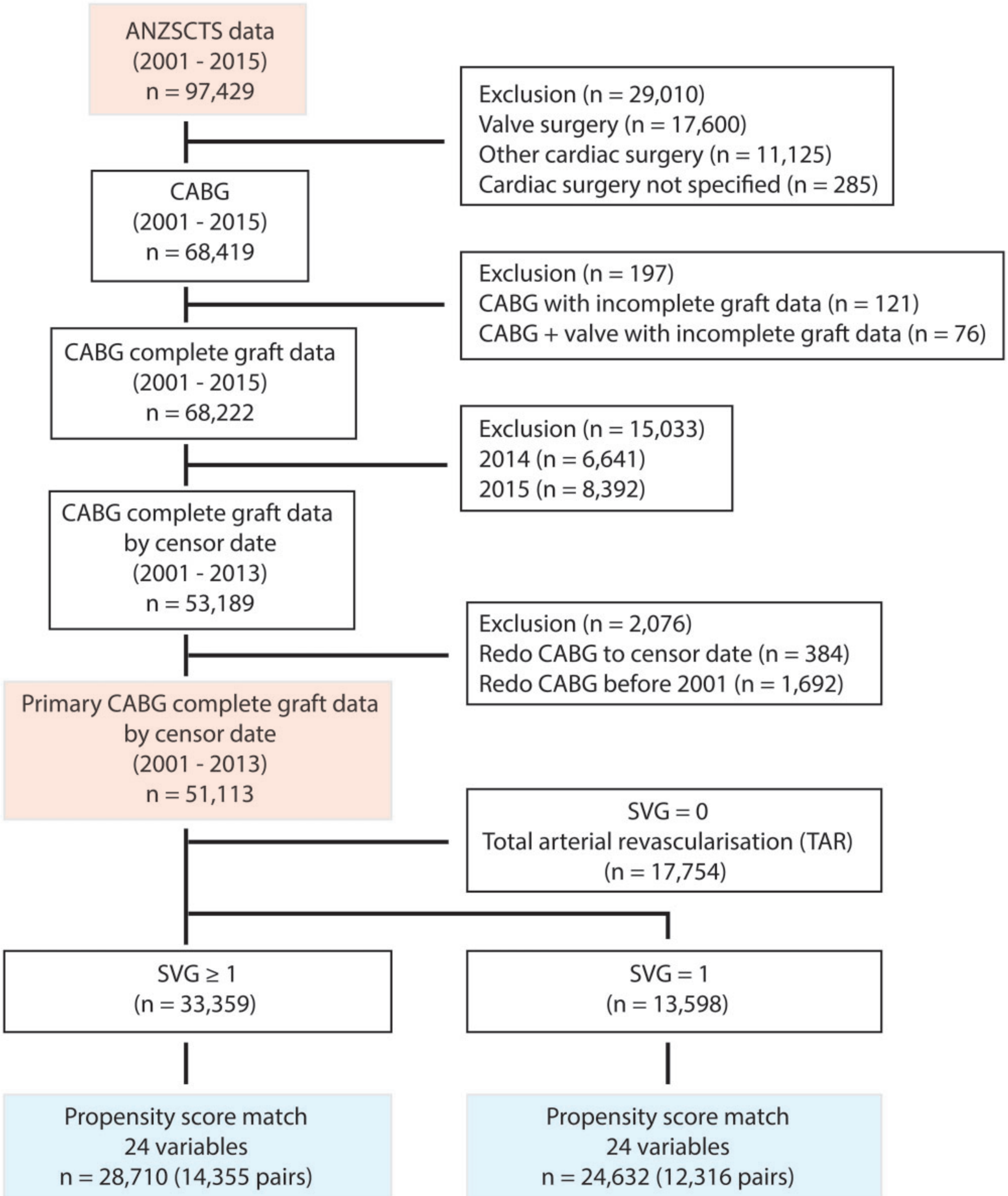

Figure 1: CONSORT flow diagram for selection of primary CABG. ANZSCTS: Australia and New Zealand Society of Cardiothoracic Surgeons; CABG: coronary bypass surgery; SVG: saphenous vein graft; TAR: total arterial revascularization. Refer Supplementary Material, Tables S1–S3.

the matching process. A standardized difference of 10% or less was considered to represent a high degree of matching, and 10–25% was considered to indicate a moderate level of matching. In addition, overall multivariate balance [20] and relative multivariate imbalance [21] were calculated using SPSS (IBM SPSS Statistics for Windows, Version 23.0) to assess the propensity score model.

RESULTS

Of the 97 429 patients in the dataset, there were 51 113 patients with primary CABG within the study period, of which 17 754 had no use of any vein graft, SVG = 0 (TAR) and 33 359 had SVG ≥ 1 graft with a subset of 13598 patients who received SVG. PSM

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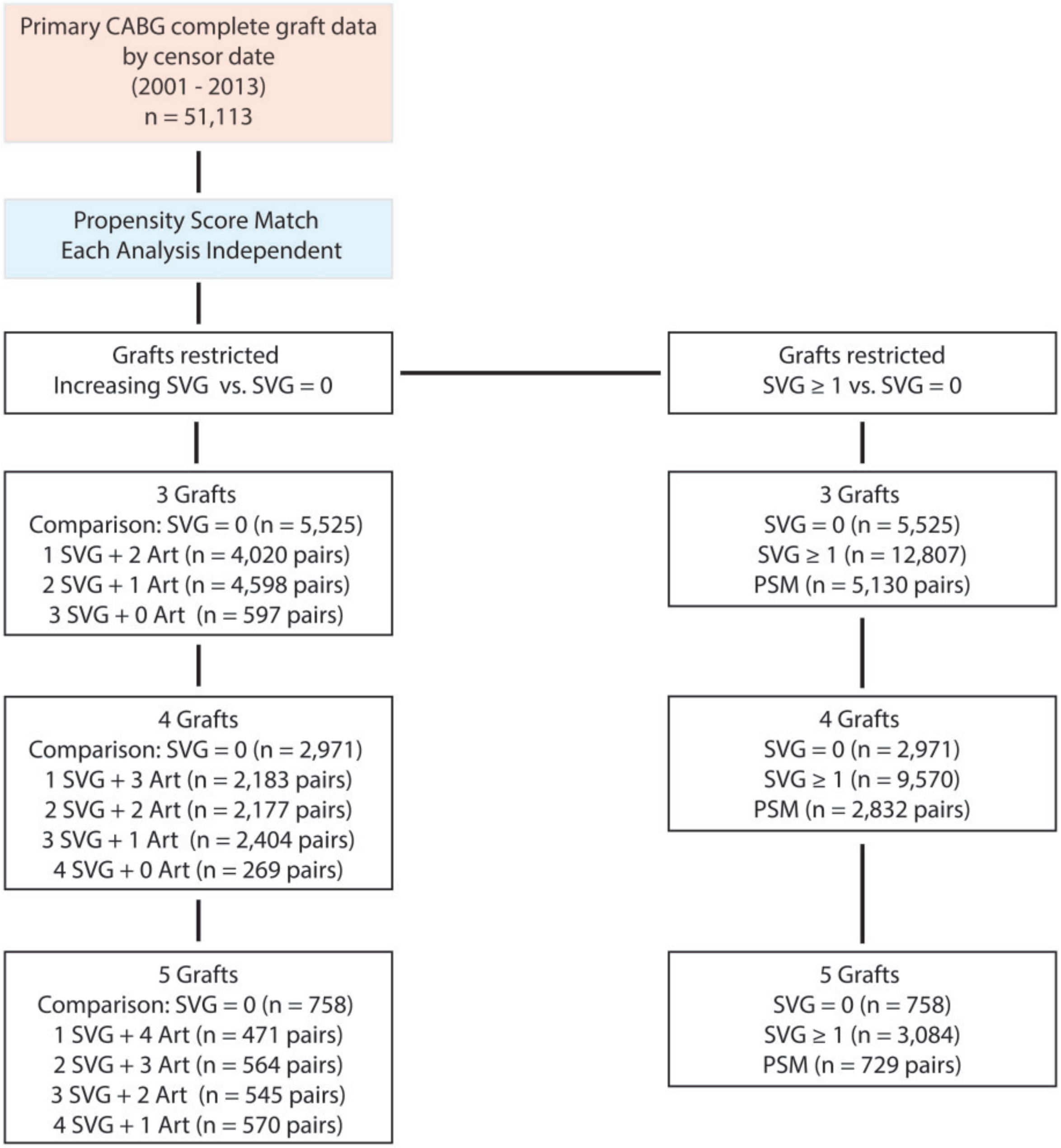

Figure 2: Flow diagram examining incremental SVG hazard with restricted number of grafts. CABG: coronary bypass surgery; PSM: propensity score match; SVG: saphenous vein graft. Refer to unmatched group size (Supplementary Material, Table S5); theoretical maximum of PSM size (Supplementary Material, Table S6) and actual matched cohort size (Supplementary Material, Table S7).

analyses were performed using 24 variables for SVG ≥ 1 (*n* = 28 710; 14 355 pairs) or SVG = 1 (*n* = 24 632; 12 316 pairs) (Fig. 1).

Significant differences between the unmatched groups were found: SVG = 0 vs SVG ≥ 1; age 65.6 ± 10.9 vs 67.9 ± 10.3, $P < 0.001$; number of grafts 2.6 ± 1.2 vs 3.3 ± 1.1, $P < 0.001$; and number of arterial grafts 2.6 ± 1.2 vs 1.4 ± 0.9 (range 1–8). There were 1.9 ± 0.9 (range 1–7) SVGs in the SVG ≥ 1 group (Supplementary Material, Table S1). For the remaining variables, there were generally small differences in magnitude, but which were statistically significantly different as a result of the large sample size. Similar findings were present in the SVG = 1 group (Supplementary Material, Table S2). Unmatched survival was significantly worse in SVG ≥ 1 at up to 12.5 years postoperative, $P < 0.001$ (Supplementary Material, Fig. S1) and in SVG = 1, $P < 0.001$ (Supplementary Material, Fig. S2). The HR for mortality calculated with the Cox method using 24 variables for SVG ≥ 1 was 1.24 (95% CI 1.18–1.30); and for SVG = 1 was 1.19 (95% CI 1.12–1.26).

Following propensity score matching in primary CABG patients, there remained no significant differences between the matched SVG = 0 and SVG ≥ 1 (Supplementary Material, Table S1) or SVG = 1 groups (Supplementary Material, Table S2). Survival was worse for SVG ≥ 1 [HR 1.22 (95% CI 1.15–1.30), $P < 0.001$; Fig. 3] or SVG = 1 [HR 1.22 (95% CI 1.14–1.30), $P < 0.001$; Fig. 4].

The grafting and conduit details for unmatched and 24-variable PSM groups where SVG ≥ 1 was used are shown in Supplementary Material, Table S3. The RA was used for about half of the grafts in the SVG = 0 group; and in the SVG ≥ 1 group,

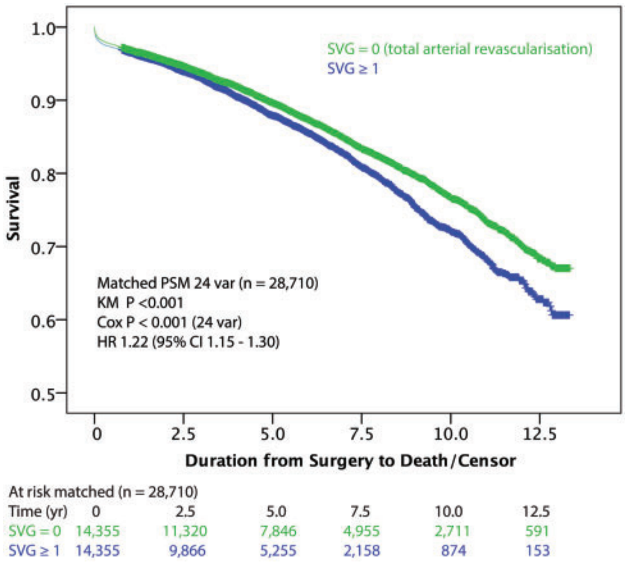

Figure 3: Survival plot SVG ≥ 1 vs SVG = 0, matched (*n* = 28 710). Cox: Cox proportional hazards analysis; HR: hazard ratio; KM: Kaplan–Meier; PSM: propensity score matched; SVG: saphenous vein graft; var: number of variables included in the analysis; 95% CI: 95% confidence interval.

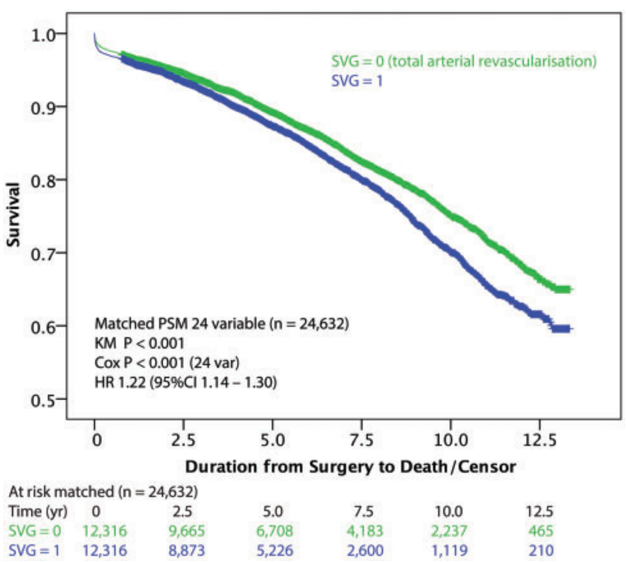

Figure 4: Survival plot for SVG = 1 vs SVG = 0, matched (*n* = 24 632). Cox: Cox proportional hazards analysis; HR: hazard ratio; KM: Kaplan–Meier; PSM: propensity score matched; SVG: saphenous vein graft; var: number of variables included in the analysis; 95% CI: 95% confidence interval.

RA was used in a quarter of the arterial grafts and about one-tenth of all grafts. Arterial conduits were used for 43% of the grafts in the SVG ≥ 1 group. There were 3763 (7%) patients of the entire cohort who received exclusive SVG and 11% in the SVG ≥ 1 group. Total venous revascularization data are provided in Supplementary Material, Table S4.

Within each of 3, 4 or 5 graft groups, an increase in the mortality HR was observed with increased use of SVG when compared to a PSM SVG = 0 group (Fig. 5). All analyses favoured SVG = 0, with only 2 of 11 crossing unity, and the remainder being significant. For the separate consideration of SVG ≥ 1 vs SVG = 0, each matched analysis significantly favoured SVG = 0 (Fig. 6). In all cases, with increased number of grafts and numbers of SVG, the mortality HR increased. In the unmatched overall analysis, survival was incrementally worse with increasing use of SVGs (Supplementary Material, Fig. S3).

A stratified log-rank test for SVG ≥ 1 and SVG = 0 analyses, pooled and paired over strata, for both PSM pairs had $P < 0.001$ for all analyses, indicating that the results were not different from those already reported (see Supplementary Materials).

DISCUSSION

Key findings

The key finding of our study is that any use of SVGs (even a single graft) resulted in reduced survival and that the HR was consistent between unmatched (Supplementary Material, Figs S1 and S2) and matched (Figs 3 and 4) analyses from 1.19 to 1.24. In the SVG = 1 group, the majority of grafts were arterial (1.7 ± 1.1 grafts) (Supplementary Material, Table S2). Thus, use of 1 or more SVGs, irrespective of any other consideration in primary CABG, was associated with an increased mortality HR of 19–24% in this dataset.

The second key finding is that improved survival with no use of vein (SVG = 0) occurred irrespective of the number, type or configuration of arterial grafts. Specifically, all arterial conduits were considered equal for the purposes of this analysis. Since bilateral IMA was uncommon, there was a substantial contribution from RA in the SVG = 0 group. This is not particularly surprising, given that there was a substantial contribution from hospitals based in the State of Victoria (Melbourne, Australia) during this time frame where heavy reliance on arterial conduits including the RA was common [5, 6, 22]. For surgeons, the reversal of emphasis away from the arterial conduit to a focus on the venous conduit is difficult to accept where there is a predominant reliance on the use of SVG in CABG.

The third key finding is that greater use of SVG was associated with a higher hazard for mortality. This was examined in multiple ways. The unmatched analysis (Supplementary Material, Fig. S3) found incrementally increased mortality hazard with increasing number of SVGs used. To address a potential grafting selection bias, whereby SVG could potentially be avoided in patients with less extensive coronary disease, we formed groups according to the number of coronary grafts (3, 4 or 5). The extent of coronary disease within each group was considered to be equivalent and thus comparable. Within each group, separate PSM analyses were then conducted according to the logical arrangement of increasing numbers of SVGs (Fig. 5). We found that there was a consistent finding in all analyses favouring SVG = 0 with only 2 of 11 analyses crossing unity and all the remainder being significant. Further, there was an increasing HR with increased use of SVG suggesting incrementally worse survival with each additional SVG conduit. Finally, we performed the SVG ≥ 1 vs SVG = 0 analysis for these grafting groups, and again the findings significantly favoured SVG = 0 in all cases, and the HR increased with additional number of grafts suggesting that patients receiving larger numbers of grafts would also be receiving greater numbers of SVG conduits leading to higher hazard (Fig. 6).

Relationships to previous studies and current practice

Current practice for TAR approximates 5% in the USA [1] and 10% in the UK [2]. Arterial conduits were used more frequently in the

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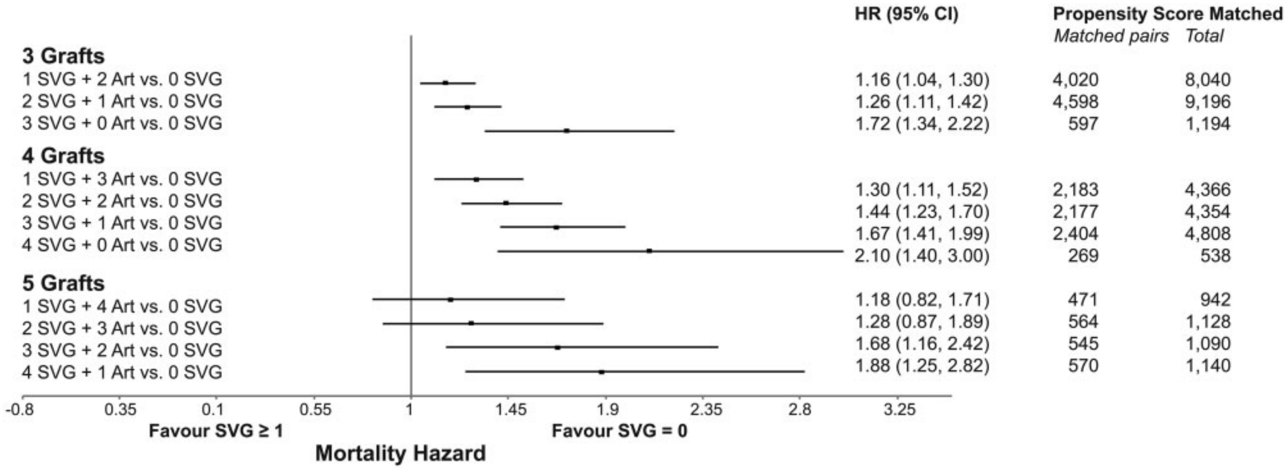

Figure 5: Mortality hazard from increasing SVG use with restricted number of grafts. Art: arterial conduit; HR: mortality hazard ratio; SVG: saphenous vein graft; 95% CI: 95% confidence interval of the HR. *Note:* The maximum number of SVG = 0 group available for matching is detailed in Supplementary Material, Tables S5–S7.

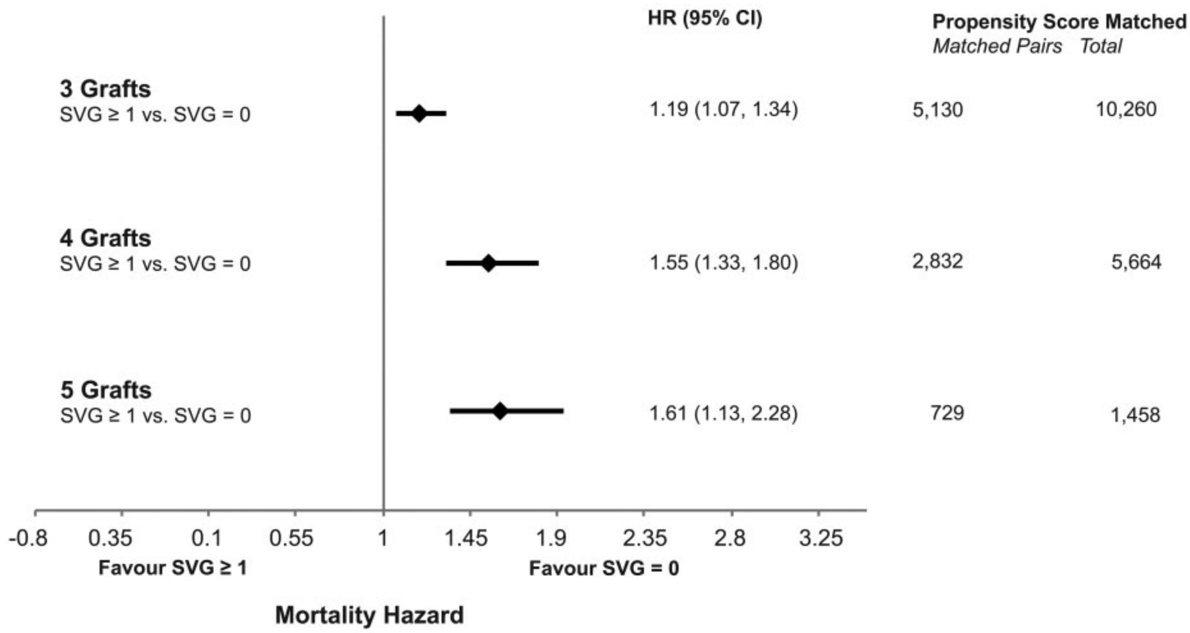

Figure 6: Mortality hazard from SVG ≥ 1 with restricted number of grafts. HR: mortality hazard ratio; SVG: saphenous vein graft; 95% CI: 95% confidence interval of the HR. *Note:* The maximum number of SVG = 0 group available for matching is detailed in Supplementary Material, Tables S5–S7.

SVG ≥ 1 group compared to real world practice with 43% of all anastomoses being with arterial conduits and 36% of patients received more than 1 arterial graft. RA was used in a quarter of the arterial grafts in the SVG ≥ 1 group and 10% of anastomoses in this group.

Our study informs an important evidence gap in the literature surrounding arterial grafts. Two studies [15, 16] have not shown improvement in outcomes with an addition of a second arterial graft. Conversely, Goldstone *et al.* [23] and Gaudino *et al.* [24] showed that additional arterial grafts improved outcomes. The fundamental flaw in most studies is that SVG is used in both groups being analysed. If the use of any SVG has a larger effect on reduced survival than the use of additional arterial grafts, then the potential benefit of increased use of arterial grafts could be confounded by the use of SVG.

Most surgeons use SVG which may be related to a variety of factors including the perceived risk of deep sternal wound infection with bilateral IMA use [25, 26], a lack of belief that more arterial conduits will actually improve the outcome, the belief that there is a 'safe period' for the use of SVG such that the patient may die of other causes before SVG fails, a reluctance to engage in more complex reconstruction techniques such as Y grafting or sequential grafting, and a convenient argument that wider use of arterial grafts will take more time to perform which cannot be afforded. Furthermore, personal preference may play a role: surgeons may be relunctant to use the RA as a graft as they may find it difficult to use, more prone to spasms than other grafts, or more likely to fail due to competitive flow if anastomosed to non-critically stenosed coronary arteries. Our data demonstrate that TAR, which involved the use of the RA in about half of the anastomoses, had a lower hazard for mortality, and this held true even if one single SVG was the difference between groups. The 24-variable PSM group, which still showed improved survival despite including patients considered at high risk for poor outcome, supports the safety and feasibility of RA use.

To alter a surgeon's grafting practice from being predominantly SVG-based to predominantly arterial-based is relatively simple. Without any significant change to the technique of anastomotic construction, an RA or additional IMA could be used as a substitute for SVG. Thus, bilateral IMA and bilateral RA would account for 4–5 grafts, which is sufficient for the majority of CABG cases. Further extension of arterial grafting to achieve universal TAR may require reliance on sequential grafting methods or composite Y grafts [27, 28], both of which are techniques relatively easily learned by coronary surgeons. The transition to TAR represents a relatively brief learning curve for most surgeons, which is evident in Australian and particularly Melbourne practice, and counteracts a concern that avoidance of SVG could lead to incomplete revascularization.

Study implications

The key inference from this study is that any use of SVG could lead to adverse survival. Whilst confronting to most surgeons, our findings are logical since the failure of SVG in the long term is both common and progressive [4, 6, 8, 13], as graft failure leads to failure of the revascularization treatment overall. These data challenge the common belief that if the left IMA is grafted to the LAD, then 1 or 2 failed SVG grafts may lead to the recurrence of angina, but not death.

Most randomized studies comparing percutaneous coronary intervention and CABG involve patients receiving ≥1 SVGs. It is possible that CABG utilizing TAR may show an increased difference in outcome compared to percutaneous coronary intervention.

Strengths and Limitations

The principle strength of this study is the large sample size, in which we were able to consider any use of SVG (SVG ≥ 1) and to additionally restricted SVG use to just one single graft (SVG = 1) irrespective of the number of arterial grafts. The existing literature predicts this approach to be counterintuitive due to the view that it is the arterial grafts that are more important in determining long-term survival. The large sample size also allowed for matching with an extended set of variables which, although sometimes infrequent, may have significant influences on adverse outcome. We also used a very small calliper, which would also improve the matching of the groups. Although this cohort has significantly higher rates of arterial revascularization compared to real world practice, which is characteristic of many Melbourne hospitals, the inclusion of interstate centres provided for large numbers of patients using SVG, rendering the sample well balanced as to the use of all conduits. It is noteworthy that the unmatched analyses were not markedly different from the matched analyses, and this is considered to reflect in the large sample size. An additional strength is the multiple PSM analysis of increasing usage of SVG within groups of patients restricted to a defined number of grafts. Increasing HR was noted in all these analyses.

Our study is limited by it being a retrospective cohort study and not a randomized prospective study. We have attempted to mitigate inclusion bias by performing propensity matched analyses. Specifically, the 24-variable PSM analysis includes the majority of patients and surgical presentations that would occur in real world practice. Performance bias was mitigated by a very large sample size although the earlier part of the dataset contained more patients from Victorian hospitals, which were early adopters of TAR and extensive use of RA. The cause of death is not reliably coded in the Australian Death Registry, and so all-cause mortality rather than cardiac-specific mortality was used, although a potential maldistribution in cause of death between groups is unlikely with such a large sample size and propensity matching. Whilst a prospective randomized trial remains the ideal study design, the time to replicate a large-scale trial remains problematic. To date, no trial has yet considered the primary end point of SVG = 0; rather, the emphasis has been on the usage of an arterial conduit—the opposite of what these data suggest—which is that the emphasis should be on the usage of a venous conduit.

CONCLUSION

Any use of SVG is independently associated with reduced survival after CABG.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: none declared.

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EDITORIAL COMMENT

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Is the non-use of a saphenous vein graft the true question in coronary surgery?

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In this issue of the *European Journal of Cardiothoracic Surgery*, Royse *et al*. [1] present further analysis of total arterial revascularization (TAR) using the database of the Society of Cardiothoracic Surgeons of New Zealand and Australia. Specifically, the authors compared the long-term outcomes of coronary artery bypass grafting (CABG) based on the number of saphenous vein grafts (SVGs) and not according to the number of arterial grafts (AGs) or the specific arterial revascularization strategy used. The authors made extensive use of propensity matching techniques and concluded that any use of SVG, independently from all the other aspects of the grafting strategy, is associated with a significant reduction in long-term survival.

In observational studies and meta-analyses, the use of 3 AGs and TAR has been associated with better long-term survival compared to the use of 2 or 1 AGs and saphenous veins [2, 3]. These earlier studies did encompass some of the patients also included in the cohort of the present analysis. However, it is, to our knowledge, the first time that the survival analysis is stratified by the number of SVGs, independently by the number of AGs and by any other surgical variables.

The analysis has, however, some limitations: the authors did not match or perform hierarchal modelling for institutions or surgeons. It is conceivable that more experienced centres and operators used TAR more often, and this opens the door to a