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ORIGINAL ARTICLE

Total arterial coronary artery bypass grafting in patients with preoperative anemia

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Abstract

Objectives: Blood transfusions after coronary artery bypass grafting (CABG) has been associated to adverse outcomes, especially in anemic patients. However, little is known about the influence of the modality of revascularization. Total arterial revascularization (TAR) was shown to reduce postoperative transfusion when compared to saphenous vein-based (SV)-CABG (LIMA plus one/more SV grafts). We, therefore, aimed to investigate the impact of TAR-CABG versus SV-CABG on blood products use and perioperative outcomes in patients with preoperative anemia, normally at higher risk for postoperative transfusions.

Methods: From a cohort of 936 patients with mild preoperative anemia undergoing primary elective on-pump CABG, 166 matched pairs of patients undergoing either TAR- or SV-CABG were obtained. Anemia was defined as hemoglobin level <13 g/dl for men and <12 g/dl for women. The primary endpoint was the evaluation of red packed cells (RPC) use over the entire hospital stay.

Results: TAR patients showed significantly reduced RPC usage compared with SV (mean difference 0.45 units). TAR patients had a reduced intubation time (mean difference 7.6 h) and were discharged 1.24 days earlier than SV patients. Pneumonia and acute kidney injury were doubled among SV patients. Adjusted regression showed that TAR technique is a predictor of reduced RPC unit use regardless of age and EuroSCORE II (odds ratio: 0.63, $p < .01$).

Conclusion: Patients with preoperative anemia might benefit from TAR regardless of age or calculated operative risk. TAR-CABG was associated to reduced postoperative use of blood products and postoperative length of stay in comparison with SV-CABG in this subset of patients.

KEYWORDS

anemia, coronary artery bypass graft, coronary artery disease, total arterial revascularization

1 | INTRODUCTION

Preoperative anemia and perioperative transfusions are independent predictors of early adverse events^{1–4} and decreased long-term survival^{5–7} after cardiac surgery. The severity of preoperative anemia^{5,8–12} and amount of transfusions of red blood cells (RBCs) have been previously associated to poorer short^{13–15} and long-term outcomes.⁵

Total arterial revascularization-coronary artery bypass grafting (TAR-CABG), beside the suggested benefits in terms of graft patency,^{16–19} long-term survival, and freedom from cardiac events,^{20–28} has been previously associated to reduced blood products consumption when compared to revascularization using saphenous vein (SV)-CABG grafts.^{29,30} In fact, SV harvesting may be a source of concealed bleeding frequently passing unnoticed and might explain this finding.^{29,31}

This provided a rationale to analyze the impact of TAR-CABG versus SV-CABG on blood products use and perioperative outcomes in patients with preoperative anemia, who are the ones mostly more prone to receive blood transfusion and susceptible to postoperative complications.

2 | PATIENTS AND METHODS

An overall cohort of 2188 patients underwent primary elective isolated on-pump CABG for multivessel coronary artery disease (CAD) at the Golden Jubilee National Hospital, Glasgow, UK, from April 2019 to June 2021. Among them, 936 patients with preoperative anemia were the subjects of the present analysis. Patients who underwent urgent or

emergency surgery, repeat cardiac surgery, or any associated procedure were excluded from the analysis (Figure 1).

No patient was receiving dual antiplatelet therapy or oral anticoagulants before surgery and no preoperative transfusions were required in this series. All patients underwent complete revascularization for multivessel CAD according to “anatomical” definition (i.e., all stenotic vessels were revascularized). Antiplatelet treatment with aspirin was continued in all patients until the day before surgery and restarted on intensive care unit (ICU) arrival, according to institution protocol.

In all patients, skeletonized mammary artery harvesting was performed with electrocautery and clips as per center routine practice. Pleura was opened and drained to accommodate the course of the mammary artery. TAR-CABG entailed the use of bilateral internal thoracic arteries (BITA). In this group, the radial artery was used in 24 patients as extra conduit next to the BITA to achieve TAR.

In the SV-CABG group, the left internal thoracic artery was always used to bypass the left anterior descending artery, while the other coronary arteries were bypassed using a SV graft. SV was harvested with open technique in all patients by experienced surgical care practitioners, as per center routine. Cardioplegia and operative strategies were chosen according to the surgeon's preference and tailored to achieve complete revascularization. All perfusionists used the same protocols as per center routine. No retrograde autologous priming and no minimal invasive extracorporeal circulation are used in our center. Crystalloid priming (1.5 L) was used in all adult patients. During cardiopulmonary bypass, hematocrit was maintained between

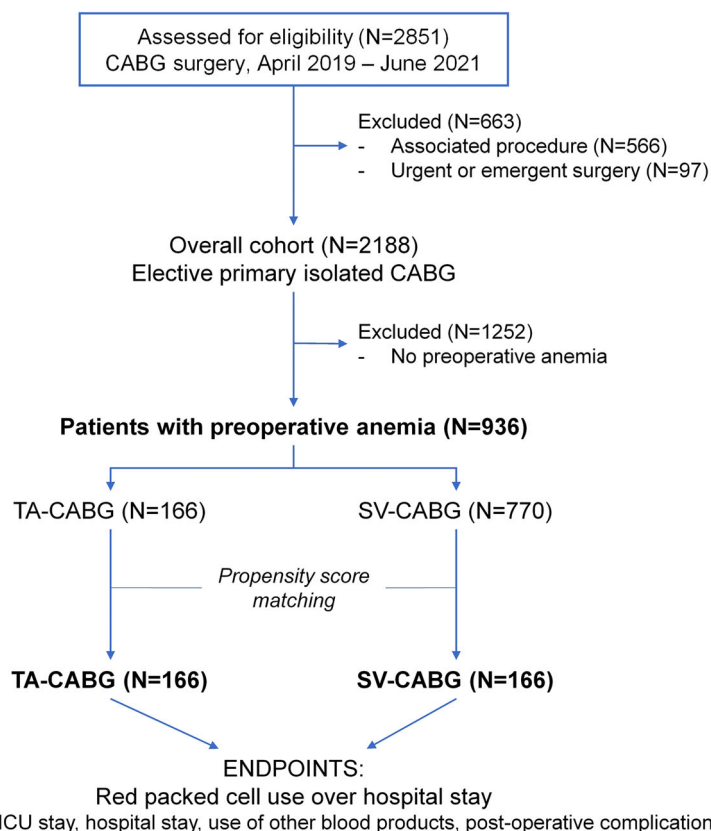


FIGURE 1 Study flowchart. CABG, coronary artery bypass grafting; ICU, intensive care unit; SV-CABG, saphenous vein-CABG; TA-CABG, total arterial-CABG

22% and 26% and pump flows were kept at 2.0–2.5 L/min/m² to keep a mean arterial pressure of 50–70 mmHg. Flow monitoring was routinely confirmed by arterial or venous blood gases. Pre-, intra-, and postoperative data were prospectively collected into our institutional database. The local Ethical Committee (Golden Jubilee National Hospital) approved the study protocol.

2.1 | Definitions and endpoints

The primary endpoint of this study was the RBC transfusion use during the index hospitalization.

Secondary endpoints included all-cause 30-day mortality, length of ICU stay, length of hospital stay, use of other blood products, such as platelets (PLT) and fresh frozen plasma (FFP), postoperative acute kidney injury (AKI), atrial fibrillation, myocardial infarction, stroke, respiratory complications, and wound complications.

Anemia was defined according to the World Health Organization (WHO) definition criteria, that is, hemoglobin level <13 g/dl for men and <12 g/dl for women. Severity of anemia was defined according to Munoz et al.³² Transfusion threshold was hemoglobin <9 g/dl, in presence of signs or symptoms of reduced tissue oxygenation.³³ Judgment on clinical need for transfusion and hypoperfusion was made on the basis of a comprehensive multimodal evaluation including clinical, hemodynamic, and laboratory parameters. AKI was defined as a 50% increase in serum creatinine from baseline over the first postoperative 48 h. Respiratory complications were defined as pneumonia, need for reintubation, need for positive pressure ventilation, and pleural effusion requiring drainage. Wound complications were defined as any wound leak or infection requiring antibiotic, wound revision and/or vacuum assisted therapy. Postoperative chest drainage output was estimated at 12 h from the end of the procedure.³⁴ Chest drains were removed when the drainage output became serosanguineous and of less than 20 ml for 6 consecutive hours. Total chest drain output was considered unreliable for our purposes as circumstances as delayed removal (e.g., pneumothorax) could have introduced bias. Transfusion requirement was preferred as more representative of the impact on clinical management and providing a more informative parameter for perioperative bleeding. Leg wound drain output was not calculable as drainage of saphenous wound site is not a routine practice at our institution.

2.2 | Statistical analysis

Patients' cohort was matched using 1-to-1 propensity score matching using the nearest neighbor method a caliper width of 0.2. The logistic regression for estimation of the propensity score included the following covariates: age, body mass index, EuroSCORE II, left main disease, preoperative hemoglobin, and number of diseased vessels (i.e., number of distal grafts) (Table S1). This model was associated with a C-statistic of .835. Preoperative characteristics and results of

the unmatched study population are shown in Tables S2 and S3. In-text results are shown for the matched population. Categorical variables are expressed as frequencies and percentages and compared with χ^2 test. Normality criteria were checked for continuous variables, which are expressed as means and standard deviations, and compared using unpaired or paired Student *t*-test for matched pairs; otherwise, nonparametric Wilcoxon ranksum test has been used and variables are expressed as median and interquartile range. A zero-inflated Poisson regression was used for RBC transfused units considering the excess zeros in this variable. McNemar's test for matched pairs was used to assess the difference in proportion of binary outcomes between the two surgical groups. A *p* < .05 was considered statistically significant. Statistical analysis was performed with STATA version 13 for Windows.

3 | RESULTS

Propensity score matching yielded 166 patients' pairs with similar baseline and operative characteristics (Table 1). Intraoperative details are shown on Table 2. TAR-CABG was associated with significantly reduced use of RBC transfusion, to a mean reduction of about one RBC unit per patient (Table 3). No statistical differences were found with regard to PLT or FFP usage, although a trend for reduced use of these products was found in the TAR-CABG group (Table 3).

Univariable and multivariable regression analyses confirmed these findings and showed that the number of transfused RBC units was reduced using the TAR-CABG technique even when adjusted for age, EuroSCORE II, or postoperative bleeding (adjusted odds ratio [OR]: 0.63, 95% confidence interval [CI]: 0.48–0.82, *p* = .001, Table 4).

Table 5 shows the 30-day results in the matched groups. Thirty-day mortality was similar both groups (1.2%). No statistical difference was observed in chest drain output (*p* = .18), or in major postoperative complications for either group (Table 5). No wound leakage or wound infection complications related to radial artery harvesting site were observed. In contrast, leg wound leak at discharge was observed in 3.0% of SV patients and leg wound infection in 1.2% of patients. Superficial and deep sternal wound infections and sternal dehiscence were similar in the matched groups. Time to extubation was halved in the TAR-CABG group, with a mean difference of 7.6 h (*p* = .02). Results showed an improvement trend in ICU stay, once again favoring the TAR-CABG group. TAR-CABG patients were discharged from hospital 1.2 days earlier than SV patients (*p* = .03). The combined outcome including the cumulative postoperative complications/events rate was in favor of TAR-CABG (60.8% vs. 77.1%, *p* < .01).

4 | DISCUSSION

This study suggests that in anemic patients, normally prone to receive more frequently blood transfusion, TAR-CABG is associated with reduced use of RBC when compared to SV-CABG. These results were

TABLE 1 Baseline characteristics after propensity score matching

	TAR-CABG, N = 166	SV-CABG, N = 166	p	Standardized difference
Age (years)	62.6 ± 10.6	63.1 ± 9.8	.66	0.045
Male sex	131 (78.9%)	126 (75.9%)	.51	-0.072
Hypertension	132 (79.5%)	126 (75.9%)	.43	-0.087
Diabetes, not insulin dependent	58 (34.9%)	64 (38.5%)	.49	0.075
Diabetes, insulin dependent	18 (10.8%)	18 (10.8%)	1.00	0.000
Smoking habit	108 (65.1%)	109 (65.6%)	.91	0.012
Chronic obstructive pulmonary disease	46 (27.7%)	37 (22.3%)	.25	-0.078
Previous myocardial infarction	95 (57.2%)	94 (56.6%)	.91	-0.012
Previous percutaneous coronary intervention	23 (13.8%)	21 (12.6%)	.75	-0.035
Body mass index (kg/m ²)	30.0 ± 5.4	30.1 ± 4.9	.85	0.020
Preoperative left ventricular function			.82	-0.065
Good (LVEF > 50%)	118 (71.1%)	122 (73.5%)		
Moderate (LVEF 31%–50%)	40 (24.1%)	38 (22.9%)		
Poor (LVEF < 30%)	8 (4.8%)	6 (3.6%)		
NYHA Class 3–4	25 (15.1%)	26 (15.7%)	.88	-0.068
CCS Class 3–4	35 (21.1%)	29 (17.5%)	.40	-0.049
Hemoglobin (g/L)	10.5 (9.0–12.0)	10.4 (8.8–12.2)	.55	-0.067
Creatinine (mg/ml)	0.95 (0.75–1.12)	0.97 (0.74–1.15)	.67	-0.082
Left main stenosis	31 (18.7%)	33 (19.9%)	.78	0.030
EuroSCORE II (%)	4.32 (3.95–4.70)	4.65 (4.20–4.83)	.68	0.055

Abbreviations: CCS, Canadian Cardiovascular Society; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SV-CABG, saphenous vein-based-coronary artery bypass grafting; TAR-CABG, total arterial revascularization-CABG.

independent on baseline clinical characteristics as age and EuroSCORE II, or postoperative bleeding. The TAR-CABG group also experienced a significant reduction in intubation time and length of hospital stay in comparison with the SV-CABG group. We found no significant differences in terms of early mortality or occurrence of major cardiovascular events, while the cumulative incidence of postoperative complications was trending in favor of the TAR-CABG group.

Our results are in line with previous studies pointing out the impact of transfusion burden on cardiovascular outcomes after cardiac surgery. A recent study by Crawford et al.¹⁵ has shown that transfusion of even one unit of RBC after CABG is associated short-term mortality (OR: 3.3, CI 1.4–7.7, $p < .01$) and significantly longer length of stay. Similarly, in a recent investigation by Padmanabhan et al.⁵ transfusion of more than 2 RBC units was associated with

increased mortality after cardiac surgery (OR: 1.3, CI: 1.03–1.65, $p = .027$). However, in this study, there was no interaction between preoperative anemia or blood transfusion on long-term mortality. These results were echoed by Tauriainen et al.³⁵ in a propensity matched analysis including 2760 patients adjusted for baseline characteristics, operative factors, perioperative bleeding, and the amount of transfused blood products. While anemia was not associated with an increased risk of adverse events, blood transfusion in the subgroup of anemic patients was considered a determinant of poorer late survival. A large registry study³⁶ including 33,411 patients after cardiac surgery investigated the relation between preoperative hematocrit and RBC transfusions. In this study, both preoperative anemia and blood transfusions were independently associated with worse outcomes, with RBC transfusion having the major impact (postoperative mortality OR: 4.3, $p < .0001$; renal failure OR: 6.3,

TABLE 2 Intraoperative data

	TAR-CABG, N = 166	SV-CABG, N = 166	p
Number of distal anastomoses			.147
2	40 (24.1%)	28 (16.9%)	
3	73 (44.0%)	91 (54.8%)	
4	47 (28.3%)	45 (27.1%)	
5	4 (2.4%)	2 (1.2%)	
6	2 (1.2%)	0 (0.0%)	
Cardiopulmonary bypass time, min	64 (53–75)	66 (55–77)	.25
Aortic cross clamp time, min	52 (44–60)	54 (46–62)	.26
Duration of surgery, hours	3.7 (3.0–4.2)	3.8 (3.1–4.4)	.49

Note: Number of grafts refers to the number of total distal anastomoses performed.

Abbreviations: SV-CABG, saphenous vein-based-coronary artery bypass grafting; TAR-CABG, total arterial revascularization-CABG.

TABLE 3 Bleeding related outcomes

	TAR-CABG, N = 166	SV-CABG, N = 166	p
RBC, transfused patients	54 (32.5%)	65 (39.2%)	.21
RBC, transfused units	0 (0–1) 0.68 ± 1.27	1 (1–1) 1.13 ± 1.78	.03
RBC, units per transfused patient	2 (1–2) 2.09 ± 1.43	2 (2–3) 2.89 ± 1.71	.01
RBC, number of transfused units			
0	112 (67.5%)	101 (60.8%)	
1	24 (14.4%)	14 (8.4%)	
2	18 (10.8%)	20 (12.0%)	
3	2 (1.2%)	11 (6.6%)	
4	6 (3.6%)	11 (6.6%)	
5	2 (1.2%)	0 (0.0%)	
6	1 (0.6%)	6 (3.6%)	
7	1 (0.6%)	3 (1.8%)	
PLT transfusion	17 (10.2%)	25 (15.1%)	.19
FFP transfusion	14 (8.4%)	18 (10.8%)	.46
Predischarge hemoglobin (g/L)	9.5 (8.1–10.9)	9.4 (8.2–10.6)	.17

Abbreviations: FFP, fresh frozen plasma; PLT, platelets; RBC, red blood cells; SV-CABG, saphenous vein-based coronary artery bypass grafting; TAR-CABG, total arterial revascularization-CABG.

TABLE 4 Predictors of red blood cell transfusion after coronary artery bypass grafting (CABG)

Variable	IRR	Standard error	95% CI	p
<i>Univariable model</i>				
TAR-CABG	0.626	0.087	0.477–0.821	.001
Age	1.013	0.007	0.999–1.027	.055
EuroSCORE II	1.016	0.008	0.998–1.033	.070
Postoperative bleeding	1.018	0.009	0.996–1.037	.085
<i>Multivariable model</i>				
TAR-CABG	0.632	0.087	0.482–0.828	.001
Age	1.011	0.007	0.996–1.026	.139
EuroSCORE II	1.009	0.009	0.991–1.028	.334
Postoperative bleeding	1.016	0.009	0.994–1.033	.348

Abbreviations: CI, confidence interval; IRR, incidence-rate ratio; TAR-CABG, total arterial revascularization-CABG.

$p < .0001$; stroke OR: 2.4, $p < .0001$). On the other hand, in a meta-analysis on 114,277 patients including 20.6% patients with preoperative anemia, a nonsignificant association was found between short-term mortality and blood transfusions (OR: 1.35, 95% CI: 0.92–1.98), but no specific comparisons related to the type of operation within the anemic population was performed.³⁷

Despite the body of evidence demonstrating adverse impact of preoperative anemia or blood transfusion on coronary surgical outcomes, a little is known about the influence of the modality of revascularization (i.e., multiple or single arterial grafting).³⁰ This is the first study specifically addressing the relation between preoperative anemia and blood transfusion in TAR-CABG versus SV-CABG.

In the present propensity score matching analysis, TAR-CABG in patients with preoperative anemia was associated with a reduced use of RBC, with a mean of 1 unit saved in respect to SV-CABG. Length of stay was also significantly reduced. We speculate that one possible explanation for these findings is that TAR-CABG does not imply the use of SV conduits and thus avoids the insensible blood loss known to be associated to vein harvesting. Concealed bleeding into the leg wound as well as intraoperative blood loss could lead to a significant hemoglobin drop with a consequent need of RBC transfusions. This mechanism could be further exacerbated by the routine fluid resuscitation protocols administered in the first hours of intensive care, leading to further hemodilution. The hypothesis of insensible leg blood loss has been already suggested by similar findings in previous studies demonstrating increased blood transfusions rate in SV-CABG versus TAR-CABG in nonanemic patients.^{29,30} Furthermore, the nonsignificant difference in postoperative chest drains loss and reoperations for bleeding between the two groups strengthens this concept, excluding any influence of intrathoracic sources of bleeding

TABLE 5 Postoperative complications and length of stay

	TAR-CABG, N = 166	SV-CABG, N = 166	p
Time to extubation (h)	Mean 7.0 7 (5–9)	Mean 14.6 12 (10–16)	.02
Intensive care unit stay (h)	Mean 32 32 (20–45)	Mean 38 38 (15–60)	.52
Bleeding at 12 h from chest tubes (ml)	Mean 385 360 (320–430)	Mean 410 350 (290–450)	.18
Reoperation for bleeding	4 (2.4%)	2 (1.2%)	.68
Inotropes	20 (12.0%)	25 (15.1%)	.55
Postoperative atrial fibrillation	37 (22.3%)	35 (21.1%)	.91
Postoperative stroke	0 (0.0%)	2 (1.2%)	.50
Pneumonia	3 (1.8%)	6 (3.6%)	.51
Positive pressure ventilation	14 (8.4%)	16 (9.6%)	.85
Pleural effusion	11 (6.6%)	12 (7.2%)	1.00
Reintubation	0 (0.0%)	1 (0.6%)	1.00
Postoperative acute kidney injury	4 (2.4%)	8 (4.8%)	.39
Need for dialysis	1 (0.6%)	2 (1.2%)	1.00
Intra-aortic balloon pump	0 (0.0%)	1 (0.6%)	1.00
Myocardial infarction	0 (0.0%)	0 (0.0%)	1.00
Radial wound complications	0 (0.0%)	0 (0.0%)	1.00
Leg wound leak	0 (0.0%)	5 (3.0%)	.06
Leg wound infection	0 (0.0%)	2 (1.2%)	.50
Sternal wound leak	3 (1.8%)	2 (1.2%)	1.00
Deep sternal wound infection	2 (1.2%)	5 (3.0%)	.45
Sternal dehiscence	0 (0.0%)	2 (1.2%)	.50
Length of postoperative stay (days)	6 (5–6) Mean 6.5	7 (7–8) Mean 7.7	.03
30-Days mortality	2 (1.2%)	2 (1.2%)	1.00

Abbreviations: SV-CABG: saphenous vein-coronary artery bypass grafting; TAR-CABG, total arterial revascularization-CABG.

related to the CABG procedure or to the surgical manipulation for BITA harvesting.

Total arterial CABG might, therefore, decrease transfusion requirements by avoiding the insensible blood loss associated to vein harvesting. Also, TAR-CABG resulted in reduced length of stay

and overall complications without a significant impact on sternal wound problems rate. Nevertheless, a causative link between the avoidance of SV harvesting and the reduced blood products consumption cannot be established in this study because of its retrospective nature and the lack of data on blood loss from the leg wound. Therefore, these results should be only considered as hypothesis generating.

Lastly, we might hypothesize that the reduced usage of blood products and the quicker mobilization related to the absence of leg wound could have decreased the burden on lung parenchyma, allowing a quicker respiratory recovery from surgery and justifying the reduced intubation time and length of hospital stay in the TAR-CABG group.

Interestingly, despite sternal wound infection are among the most feared complications of TAR-CABG, problems related to SV harvesting remain often neglected, as normally do not require aggressive inpatient treatment.^{38–40} In this study, TAR-CABG was not associated to higher rate of sternal wound complications. Conversely, a cumulative incidence of 4% of leg wound complications was detected in the SV-CABG group. Despite this rate is below the one currently reported in the literature (reaching up to 18%),⁴¹ leg wound management might demand for a significant exploitation of resources for health systems.⁴²

Beside the caveat of its retrospective nature, this study reinforces the safety of TAR-CABG in the subset of preoperative anemic patients and introduces an additional potential advantage in terms of early postoperative recovery and reduced blood transfusion-related costs. However, both randomized and real-life registry data are required to elucidate these points.

4.1 | Limitations

This study included patients who underwent surgery using different techniques and graft choice, according to surgeon's preference. Off-pump surgery is performed in selected cases in our institution and, therefore, these patients were not included in this analysis. We acknowledge that those differences might translate into confounding variables in the evaluation of the outcomes since they are not included in the propensity score model. However, we deliberately did not include intraoperative parameters in the propensity score model because our aim was to realize a “pre-theatre” matching algorithm, tailored to the preoperative evaluation. Furthermore, in the propensity score model, the use of EuroSCORE II was preferred over single risk factors because resulted in a greater metabis reduction compared to a nonparsimonious approach.

Second, anemia was defined according to WHO guidelines and the most recent literature.³² A specific consensus statement on perioperative anemia in cardiac surgery is not available yet but could have better described the scenario in this study. Also, a “liberal” transfusion threshold policy has been adopted in our institution and application of a more restrictive cutoff for blood administration might have produced different results.⁴³ However, the fact that all the

patients were from a single center and received transfusions according to a univocal institutional "liberal" transfusion policy should flatten the potential bias. Moreover, despite its importance, no precise assessment of the etiology of preoperative anemia was available.

Third, minimally invasive or endoscopic harvesting for SV or arterial conduits were not evaluated as are not routinely performed in our center. Despite the recent interest and apparent benefits,^{44,45} whether using these techniques would have reduced blood consumption in the SV-CABG remains unknown. In fact, previous studies comparing endoscopic SV harvesting to open SV harvesting have demonstrated no significant difference in the incidence of RBC transfusions⁴⁶ or hematoma formation.⁴⁷

Another potential source of bias might be related to the difference in the surgical profiles of the harvesters of the conduits with SV normally harvested by more junior surgeons. In our center vein harvesting is performed by experienced surgical care practitioners and the rate of SV harvest site-related complications in this study is well in line with the data currently reported in the literature.⁴¹ Also, no differences in harvesting-related complications or blood transfusions were observed between thigh and calf SV harvesting. Despite an effect of the learning curve could be reliably excluded in these settings, the experience of the harvester might also have played a role. A learning curve analysis and a correlation with the surgical experience of the harvester should be explored and this point would deserve further investigations in the future. To this regard, the study might also open to additional considerations in the teaching and training of junior surgeons. Vein harvesting represents a phase that is not of secondary importance and the amount of blood loss from the harvesting site could be significant to the point of being at least partially responsible for blood transfusion postoperatively. Surgeons should be cognizant of this possibility.

Lastly, a significant limitation of the study regards the lack of leg drain blood loss measurement. Leg drains placement is not a routine practice in our and other centers and is often not even required. A potential ad hoc study involving ethical approval and patient consent to study a nonconventional procedure should be conducted. Beside this, the aim of the study is to provide a "real-life" picture of the actual issues related to the postoperative management and outcomes of patients with preoperative anemia undergoing on-pump CABG, and the use of blood product on the basis of a standardized transfusion policy seemed to be the more informative data to be used.

5 | CONCLUSION

Beside the caveats of its retrospective nature, this study indicates that patients with preoperative anemia might benefit from TAR-CABG regardless of age or estimated operative risk. TAR-CABG was associated to reduced postoperative use of blood products and length of stay compared with SV-CABG and might be a valid option even in this subset of patients.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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