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Exploring the role of prophylactic levosimendan in coronary surgery

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【**Abstract**】 **Background:** The role of prophylactic levosimendan in coronary surgery has not been established conclusively. **Methods:** Postoperative outcomes of 139 patients (mean age, 68.2±9.6 years) having preoperative left ventricular ejection fraction (LVEF) ≤40% and undergoing isolated coronary surgery (2013–2017) were reviewed retrospectively. In 42 (30.2%) patients (L-group), an intravenous infusion of levosimendan was started 24 hours before operation. The remaining 97 (69.8%) patients were the control group (C-group). A comparison between the two groups regarding outcome of surgery was performed also after propensity matching. **Results:** Although the risk profile in L-patients was higher than in C-patients (median European System for Cardiac Operative Risk Evaluation II, 10.5% *vs.* 6.5%, P=0.013) due to higher prevalence of New York Heart Association class III–IV, LVEF ≤30%, and preoperative intra-aortic balloon pump, in-hospital mortality was equivalent (4.8% *vs.* 3.1%, P=0.48). However, low cardiac output, multiple blood transfusion, and any major complication early after surgery were more frequent in L-patients. After one-to-one propensity matching, which resulted in 15 pairs with similar baseline characteristics the use of levosimendan was associated with a trend towards an increased blood use (P=0.077), a higher frequency of any major complication (P=0.053), and lower peak serum levels of cardiac troponin I (P=0.088). No intergroup differences concerning mid-term survival or outcomes were found even for matched patients. **Conclusion:** When compared with traditional inotropes alone, prophylactic use of levosimendan showed clear benefits/drawbacks neither concerning immediate nor mid-term outcomes after coronary surgery. There could be any advantage in terms of myocardial preservation.

【**Key words**】 Coronary artery bypass grafting (CABG); left ventricular dysfunction; levosimendan; morbidity/mortality; prophylaxis

Introduction

Levosimendan (Simdax®; Orion Corporation, Espoo, Finland) is a calcium sensitizer and potassium channel opener that is currently used for the prevention and treatment of the low cardiac output syndrome in situations where conventional therapy is not sufficient, and in cases where inotropic support is considered appropriate[1]. To date, however, no definite consensus has been obtained regarding its use in clinical practice, despite excellent observational studies, randomized controlled trials and corresponding meta-analyses[2-10].

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While some authors emphasize the benefits[1,3,9,10], other investigators remark the uselessness with respect to traditional inotropic agents[2,4-8]. This uncertainty pertains to cardiac surgery as well, where levosimendan is being used either before operation to prevent low cardiac output syndrome in high-risk patients with left ventricular dysfunction [left ventricular ejection fraction (LVEF) ≤35% (or 40%)][1,4-9], or after surgery to treat the still overt syndrome[2-3].

The aim of this retrospective study was to explore immediate and mid-term outcomes of a limited series of patients having left ventricular dysfunction and undergoing isolated coronary artery bypass grafting (CABG) at one-single cardiac surgery center. Outcomes of patients treated with levosimendan before surgery with prophylactic purposes were compared with outcomes of patients who did not receive levosimendan.

We present the following article in accordance with the STROBE reporting checklist (available at https://www.thecjts.cn/article/view/10.3877/cma.j.issn.2095-8773.2022.01.01/rc).

Patients and methods

From 2013 throughout 2017, 670 consecutive patients with multivessel coronary artery disease underwent isolated CABG at the Division of Cardiac Surgery of the University Hospital of Trieste, Italy. Of these, 139 (20.7%, mean age, 68.2±9.6 years) suffered from left ventricular dysfunction (defined as LVEF ≤40%) and were enrolled in the present study; their baseline characteristics, operative data and postoperative complications were prospectively recorded in a computerized database. In 42 (30.2%) patients (L-group), an intravenous infusion of levosimendan was started on at a dose of 0.2 g per kilogram of body weight per minute for 1 h, and the dose was then reduced to 0.1 g/kg/min for another 23 h; the remaining 97 (69.8%) patients were the control group (C-group). The adoption of concomitant medications, including other inotropes (epinephrine and dobutamine) and vasopressors (norepinephrine), or intra-aortic balloon pump (IABP)[11] was left to the decision of treating physicians. The use of a pulmonary artery catheter for hemodynamic monitoring was encouraged but not required (*Tables 1-3*).

The role of baseline characteristics, operative data and some postoperative complication was explored, for L and C-group separately, in patients who experienced a significant LVEF improvement after surgery (defined as % increase of LVEF >30%) and in patients who had no improvement (defined as no LVEF increase, or % increase of LVEF <10%).

Surgical technique

Surgery was carried out via a median sternotomy either with cardiopulmonary bypass, with or without cross-clamping the aorta or off-pump technique. When a period of myocardial ischaemia was used, myocardial protection was achieved with multidose cold blood cardioplegia, which was delivered in both antegrade and retrograde mode. Off-pump and on-pump beating heart techniques were adopted only in the presence of a diseased (atherosclerotic) ascending aorta, which was demonstrated by epiaortic ultrasonography scan. Bilateral or single internal thoracic artery (ITA) grafts, or saphenous vein grafts alone were used. Both ITAs were harvested as skeletonized conduits with low-intensity bipolar coagulation forceps. In bilateral ITA patients, when both ITAs were used as *in situ* grafts, the right ITA was almost invariably directed to the left anterior descending coronary artery, and the left ITA to the posterolateral cardiac wall. When the two ITAs were used as composite Y-graft, the right ITA was transected proximally and used as a free graft from the *in situ* left ITA. In single ITA patients, either the *in situ* left or (exceptionally) right ITA was directed to the left anterior descending coronary artery. In both groups, additional coronary bypasses were performed with one or more saphenous vein grafts[14].

Unless otherwise stated, the definitions and cut-off values of preoperative variables were those used for the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II)[12]. The risk profile of each patient was established preoperatively according to EuroSCORE II. The definitions of postoperative complications were in accordance with the internationally agreed definitions of complications after cardiac surgery[13].

Follow-up

An up-to-date clinical follow-up was obtained by a telephone interview with the patients or their family. The occurrence of at least one postoperative major adverse cardiac or cerebrovascular event (MACCE)—defined as any of the following complications from surgery to follow-up: sudden death, recurrent angina, myocardial infarction, congestive heart failure needing hospital readmission, percutaneous coronary intervention and other invasive cardiac procedures, reoperation, pulmonary embolism and cerebrovascular accidents – was recorded. For this study, follow-up was closed on December 30, 2017.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ufficio Studi Clinici ed Epidemiologici dell'Azienda sanitaria universitaria Giuliano Isontina (October 23, 2018 – odg 5.18) and individual consent for this retrospective analysis was waived.

Table 1 Baseline characteristics of patients and risk profiles

Characteristic	Overall series			Matched pairs		
	L-group (n=42)	C-group (n=97)	P	L-group (n=15)	C-group (n=15)	P
Age			0.95			0.89
<60 years	10 (23.8)	22 (22.7)		4 (26.7)	3 (20.0)	
60–70 years	12 (28.6)	26 (26.8)		6 (40.0)	6 (40.0)	
≥70 years	20 (47.6)	49 (50.5)		5 (33.3)	6 (40.0)	
Female	1 (2.4)	10 (10.3)	0.21	1 (6.7)	1 (6.7)	1
Hypertension treated with drugs	33 (78.6)	83 (85.6)	0.44	12 (80.0)	13 (86.7)	1
Body mass index >30 kg/m^2	8 (19.0)	21 (21.6)	0.91	2 (13.3)	2 (13.3)	1
Diabetes			0.26			0.8
No history	16 (38.1)	51 (52.6)		6 (40.0)	5 (33.3)	
Insulin-dependent diabetes	4 (9.5)	9 (9.3)		1 (6.7)	2 (13.3)	
Non-insulin-dependent diabetes	22 (52.4)	37 (38.1)		8 (53.3)	8 (53.3)	
Poor mobility	0	2 (2.1)	0.89	0	0	–
Chronic lung disease	7 (16.7)	10 (10.3)	0.44	3 (20.0)	2 (13.3)	1
eGFR*			0.39			0.86
>85 mL/min	13 (31.0)	40 (41.2)		5 (33.3)	4 (26.7)	
50–85 mL/min	17 (40.5)	38 (39.2)		8 (53.3)	8 (53.3)	
≤50 mL/min	12 (28.6)	19 (19.6)		2 (13.3)	3 (20.0)	
Extracardiac arteriopathy	16 (38.1)	37 (38.1)	0.85	7 (46.7)	7 (46.7)	1
NYHA class			0.0018			0.79
I	10 (23.8)	54 (55.7)		4 (26.7)	6 (40.0)	
II	3 (7.1)	9 (9.3)		1 (6.7)	1 (6.7)	
III	12 (28.6)	18 (18.6)		4 (26.7)	2 (13.3)	
IV	17 (40.5)	16 (16.5)		6 (40.0)	6 (40.0)	
CCS class 4	25 (59.5)	61 (62.9)	0.85	8 (53.3)	8 (53.3)	1
Recent myocardial infarction			0.93			0.87
No history	26 (61.9)	58 (59.8)		10 (66.7)	8 (53.3)	
Within 7–90 days	10 (23.8)	21 (21.6)		3 (20.0)	5 (33.3)	
Within 1–7 days	4 (9.5)	13 (13.4)		1 (6.7)	1 (6.7)	
Within 24 h	2 (4.8)	5 (5.2)		1 (6.7)	1 (6.7)	
Coronary artery disease			0.65			1
Two-vessel	9 (21.4)	16 (16.5)		2 (13.3)	2 (13.3)	
Three-vessel	33 (78.6)	81 (83.5)		13 (86.7)	13 (86.7)	
Left main coronary artery disease	21 (50.0)	40 (41.2)	0.44	6 (40.0)	5 (33.3)	1

Table 1 (*continued*)

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Characteristic	Overall series			Matched pairs		
	L-group (n=42)	C-group (n=97)	P	L-group (n=15)	C-group (n=15)	P
LVEF			<0.0001			1
31–40%	14 (33.3)	86 (88.7)		9 (60.0)	10 (66.7)	
21–30%	25 (59.5)	10 (10.3)		6 (40.0)	5 (33.3)	
<21%	3 (7.1)	1 (1.0)		0	0	
Cardiac reoperation	0	1 (1.0)	0.67	0	0	–
Critical preoperative state	23 (54.8)	36 (37.1)	0.081	6 (40.0)	5 (33.3)	1
VT, VF or aborted sudden death	4 (9.5)	5 (5.2)	0.56	1 (6.7)	1 (6.7)	1
Use of adrenergic agents	1 (2.4)	14 (14.4)	0.071	1 (6.7)	2 (13.3)	1
Use of IABP	22 (52.4)	22 (22.7)	0.0011	3 (20.0)	4 (26.7)	1
Acute renal failure (diuresis <10 mL/h)	1 (2.4)	2 (2.1)	0.61	0	0	–
Surgical priority			0.35			1
Elective	9 (21.4)	12 (12.4)		2 (13.3)	2 (13.3)	
Urgent	31 (73.8)	73 (75.3)		12 (80.0)	12 (80.0)	
Emergency	1 (2.4)	7 (7.2)		0	0	
Salvage	1 (2.4)	5 (5.2)		1 (6.7)	1 (6.7)	
Expected operative risk (by EuroSCORE II)[12], %	10.5 (6.4–25.8)	6.5 (2.6–13)	0.013	8.6 (4.8–12)	6.2 (4.9–9)	0.8

Continuous variables with normal distribution were expressed as mean ± SD and those without normal distribution as median and the range between the first and the third quartile. Discrete variables were expressed as frequencies and percentages. Unless otherwise stated, the definitions and cut-off values of the preoperative variables were those used for EuroSCORE II. *, the creatinine clearance rate, calculated according to the Cockcroft-Gault formula, was used for approximating the GFR. CCS, Canadian Cardiovascular Society; eGFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SD, standard deviation; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 2 Operative data

Data	Overall series			Matched pairs		
	L-group (n=42)	C-group (n=97)	P	L-group (n=15)	C-group (n=15)	P
No. of coronary anastomoses	3.9±1	3.7±1.1	0.27	3.9±0.8	4.1±1	0.61
Grafts			0.31			1
Bilateral ITA	40 (95.2)	84 (86.6)		15 (100.0)	14 (93.3)	
Single ITA	2 (4.8)	12 (12.4)		0	1 (6.7)	
SVGs alone	0	1 (1)		0	0	
SVG use	39 (92.9)	84 (86.6)	0.39	15 (100.0)	14 (93.3)	1
Surgical technique			0.35			0.34
Off-pump	2 (4.8)	10 (10.3)		0	1 (6.7)	
On-pump	40 (95.2)	85 (87.6)		15 (100.0)	13 (86.7)	
On-pump beating heart	0	2 (2.1)		0	1 (6.7)	
Cross-clamp time, min	86.7±22.5	86.4±38.9	0.96	85.7±16.5	90.1±23.6	0.73
Cardiopulmonary bypass						
Time, min	111.5±28.8	110.1±42.4	0.85	111.4±27	113.6±32.4	0.98
Rapid starting	4 (9.5)	8 (8.2)	1	3 (20.0)	0	0.22
Prolonged (>30 min) weaning	3 (7.1)	14 (14.4)	0.23	2 (13.3)	3 (20.0)	1
Length of the operation, min	292.2±45.2	273.9±54.9	0.058	295.2±46.2	279.5±51.2	0.37

Continuous variables were expressed as mean ± SD. Discrete variables were expressed as frequencies and percentages. ITA, internal thoracic artery; SD, standard deviation; SVG, saphenous vein graft.

Table 3 In-hospital outcomes

Complication	Overall series			Matched series		
	L-group	C-group	P	L-group	C-group	P
	n=42	n=97		n=15	n=15	
In-hospital death	2 (4.8)	3 (3.1)	0.48	1 (6.7)	0	1
30-day death	2 (4.8)	1 (1.0)	0.22	1 (6.7)	0	1
Neurological dysfunction	6 (14.3)	6 (6.2)	0.18	2 (13.3)	2 (13.3)	1
Transitory	4 (9.5)	8 (8.2)	0.93	1 (6.7)	1 (6.7)	1
Permanent	3 (7.1)	2 (2.1)	0.33	1 (6.7)	1 (6.7)	1
Prolonged (>48 h) invasive ventilation	11 (26.2)	18 (18.6)	0.31	3 (20.0)	1 (6.7)	0.6
Atrial fibrillation, new-onset	15/40‡ (37.5)	35/92‡ (38.0)	0.89	6/15‡ (40.0)	8/15‡ (53.3)	0.46
VT, VF or aborted sudden death	3 (7.1)	1 (1.0)	0.082	1 (6.7)	0	1
Myocardial infarction	2 (4.8)	3 (3.1)	0.48	0	1 (6.7)	1
Low cardiac output	19 (45.2)	15 (15.5)	<0.0002	5 (33.3)	1 (6.7)	0.17
Prolonged (>12 h) use of adrenergic agent	36 (85.7)	86 (88.7)	0.62	15 (100.0)	14 (93.3)	1
Use of norepinephrine	39 (92.9)	79 (81.4)	0.084	15 (100.0)	11 (73.3)	0.11
Intraoperative use of IABP	4 (9.5)	3 (3.1)	0.24	2 (13.3)	0	0.48
Use of VA-ECMO	1 (2.4)	2 (2.1)	1	1 (6.7)	0	1
Acute kidney injury	6 (14.3)	6 (6.2)	0.18	2 (13.3)	1 (6.7)	1
Renal replacement therapy	5 (11.9)	4 (4.1)	0.13	1 (6.7)	0	1
Mesenteric ischemia	1 (2.4)	0	0.3	1 (6.7)	0	1
Multiorgan failure	2 (4.8)	4 (4.1)	1	2 (13.3)	0	0.48
48-h chest tube output/BSA, mL/m^2	537 (287–863)	451 (256–827)	0.4	383 (286–620)	561 (304–1002)	0.25
No. of transfused patients	21 (50.0)	31 (32.0)	0.068	8 (53.3)	4 (26.7)	0.26
No. of transfused RBC units per patient	0.5 (0–3)	0 (0–1)	0.064	1 (0–2.5)	0 (0–0.5)	0.077
Multiple transfusion (>2 RBC units)	11 (26.2)	12 (12.4)	0.044	4 (26.7)	0	0.11
Mediastinal re-exploration	6 (14.3)	6 (6.2)	0.18	2 (13.3)	0	0.48
Deep sternal wound infection§	4 (9.5)	6 (6.2)	0.72	1 (6.7)	1 (6.7)	1
Any major complication#	27 (64.3)	35 (36.1)	0.0039	8 (53.3)	2 (13.3)	0.053
In-hospital stay, days	14 (11–25)	13 (9–18)	0.051	15 (11–27.5)	13 (9–15.5)	0.19
Intensive care unit stay, days	4 (3–7)	3 (2–5)	0.042	4 (3–6.5)	3 (2–4)	0.34

Continuous variables were expressed as median and the range between the first and the third quartile. Discrete variables were expressed as frequencies and percentages. Unless otherwise stated, the definitions of the postoperative complications were in accordance with the internationally agreed definitions of complications after cardiac surgery[13]. ‡, patients having stable sinus rhythm; §, deep sternal wound infection; #, in-hospital death, permanent neurological dysfunction, prolonged invasive ventilation, myocardial infarction, low cardiac output, acute kidney injury, mesenteric ischemia, multiorgan failure, multiple transfusion, mediastinal re-exploration, and deep sternal wound infection. BSA, body surface area; IABP, intra-aortic balloon pump; RBC, red blood cells; VA-ECMO, venous-arterial extracorporeal membrane oxygenator; VF, ventricular fibrillation; VT, ventricular tachycardia,

Statistical methods

Continuous variables with normal distribution were expressed as mean ± standard deviation and those without normal distribution as median and the range between the first and the third quartile. Discrete variables were expressed as frequencies and percentages. Independent predictors of all-cause death, cardiac or cerebrovascular deaths, and MACCEs were found with the Cox proportional-hazards regression analysis. Crude rates, EuroSCORE II and multiple covariates-adjusted-risk estimates of all-cause death, cardiac or cerebrovascular deaths, and MACCEs according to the use of levosimendan were calculated. Study patients were divided in two groups according to the prophylactic use of levosimendan. Statistical comparison of baseline patient characteristics, operative data and postoperative complications was performed using the Chi-square or the Fisher's exact test for categorical variables, and the Student's *t*-test or the Mann-Whitney *U*-test for continuous variables. Since the study groups significantly differed in a number of preoperative characteristics, a multivariable analysis was performed using the backward stepwise logistic regression. The area under the receiver-operating characteristic curve, with 95% confidence interval (CI), was used to represent the regression probabilities. To estimate the probability of being assigned either to the one or the other group, a propensity score (PS) was calculated in a nonparsimonious way including the following preoperative patient characteristics: age, hypertension, body mass index, diabetes on insulin, diabetes on oral agent, poor mobility, chronic lung disease, glomerular filtration rate estimated according to the Cockcroft-Gault formula, extracardiac arteriopathy, New York Heart Association (NYHA) functional class, Canadian Cardiovascular Society class 4 of angina, recent myocardial infarction, left main coronary artery disease, number of diseased coronary vessels, LVEF, prior cardiac surgery, critical preoperative state, life-threatening ventricular arrhythmias, IABP use, cardiac reoperation, surgical priority and EuroSCORE II. One-to-one PS matching was performed employing the nearest neighbour method and a caliper of 0.2 of the standard deviation of the logit of the PS. To evaluate the balance between the matched groups, the Wilcoxon rank and the Student's *t*-test for paired samples for continuous variables, the McNemar test for dichotomous variables, and the analysis of the standardized differences after matching were used. Standardized difference <10% was considered an acceptable imbalance between the treatment groups. The same tests were adopted to evaluate differences in operative data and postoperative complications of matched groups. Non-parametric estimates and curves of freedom from all-cause death, cardiac or cerebrovascular deaths, MACCEs, and new cardiovascular invasive procedures were generated with the Kaplan-Meier method, both for overall and matched series. Comparison between survival curves was made by the log-rank test. All tests were two-sided and P value <0.05 was set for statistical significance. Statistical analysis was performed by the SPSS program for Windows, version 13.0 (SPSS, Inc., Chicago, IL, USA).

Results

There were 5 (3.6%) in-hospital deaths (30-day mortality, 2.2%); 62 (44.6%) patients experienced at least one major complication during hospital course (*Table 3*). Four patients were lost to follow-up (follow-up rate, 97.1%). During the follow-up period (mean, 2.2±1.5 years, cumulative, 287.7 years-patient), there were 17 (12.6%) all-cause deaths, 8 (5.9%) cardiac or cerebrovascular deaths, 33 (24.4%) MACCEs, and 19 (14.1%) new cardiovascular invasive procedures [implantation of pacemaker, implantable cardioverter-defibrillator or cardiac resynchronization therapy device =12, diagnostic coronary (computed tomography) angiography =4, percutaneous coronary intervention =1, percutaneous treatment of mitral regurgitation =1, treatment of abdominal aortic aneurysm with endovascular prosthesis =2, ascending aortic replacement =1]. The 4-year non-parametric estimates of freedom from all-cause death, cardiac or cerebrovascular deaths, MACCEs, and new cardiovascular invasive procedures were 78.1% (95% CI, 72.7–83.5%), 92.1% (95% CI, 89.3–94.9%), 67.6% (95% CI, 62.6–72.6%), and 79.5% (95% CI, 75–84%), respectively. Independent predictors of all-cause death, cardiac or cerebrovascular deaths, and MACCEs were reported in Table S1.

C- vs. L-patients: the overall series

All patients tolerated preoperative infusion of levosimendan well. The patient risk profile in L-group was higher than in C-group (median EuroSCORE II, 10.5% *vs.* 6.5%, P=0.013) owing to the greater prevalence of NYHA class III–IV, LVEF ≤30% and preoperative use of IABP (*Table 1*). There were no significant differences between the groups regarding operative data (*Table 2*). In-hospital mortality was equivalent (4.8% *vs.* 3.1%, P=0.48). Low cardiac

output, multiple blood transfusion and any major complication early after surgery were more frequent in L-patients; consequently and consistently, both hospital and intensive care unit stay were longer (P=0.051 and 0.042, respectively) (*Table 3*). No intergroup differences concerning mid-term survival or outcomes were found (*Figure 1A*,*1C*,*1E*). Crude rates and adjusted-risk estimates of survival and freedom from MACCEs according to the use of levosimendan were calculated (*Table 4*).

C- vs. L-patients: the matched pairs

Based on the logistic regression analysis that was carried out for propensity matching of patients, chronic lung disease, NYHA class III–IV and LVEF ≤30% were more frequent in L-group, whereas female sex, hypertension treated with drugs and emergency/salvage surgical priority were more common in C-group (Table S2). A PS was estimated by logistic regression and its area under receiver-operating characteristic curve was of 0.948 (95% CI: 0.897–0.979). One-to-one matching resulted in 15 pairs with similar baseline characteristics and risk profile (*Table 1*). Operative management was equivalent (*Table 2*). The use of levosimendan was associated with a trend towards an increased use of transfused units of red blood cells and a higher frequency of any major complication, though such a difference did not reach statistical significance (P=0.077 and 0.053, respectively; *Table 3*). No intergroup differences concerning mid-term survival or outcomes were found even for matched patients (*Figure 1B*,*1D*,*1F*).

Peak serum levels of cardiac troponin I were lower in L-group than in C-group (median, 2.6 *vs.* 5.5 g/L), though the difference was not quite significant (P=0.088). From preoperative echocardiographic evaluation to assessment early before hospital discharge, LVEF increased from 31.7%±4.6% to 38.1%±9.8% in L-group (P=0.021), and from 33.7%±4.1% to 42.5%±9.5% in C-group (P=0.0013); however, there was no significant difference between the corresponding % increases (median, 15.6% *vs.* 25%, P=0.8).

C- vs. L-patients: change in LVEF after surgery

A total of 129 (92.8%) patients underwent hospital discharge having no signs of new myocardial infarction. Early after surgery, the median % increase of LVEF was of 23.7% for L-group (38 patients) and 25% for C-group (91 patients) (P=0.66). A % increase of LVEF >30% was experienced after surgery in 42.1% of L-patients and in 41.8% of C-patients; 36.8% of L-patients and 25.3% of C-patients had a % increase of LVEF <10%, or no increase (P=0.28). According to the multivariable analyses, while extracardiac arteriopathy [odds ratio (OR) =3.93, 95% CI: 1–15.4, P=0.049], left main coronary artery disease (OR =5.62, 95% CI: 1.24–25.4, P=0.025) and blood transfusion (OR =5.85, 95% CI: 1.46–23.4, P=0.013) were predictors of significant LVEF augmentation post-surgery for C-patients, old age was predictor of failure of significant LVEF improvement for L-patients (OR =1.16, 95% CI: 1.03–1.3, P=0.013) (Tables S3).

Discussion

The most relevant finding of the present study was that, after propensity matching, both immediate and mid-term outcomes of patients with left ventricular dysfunction who received prophylactic levosimendan before isolated CABG were equivalent to those of corresponding patients who did not receive it. Although the use of levosimendan was associated with a trend towards an increased use of blood transfusions and a higher frequency of any major complication, such differences were not quite significant. Actually, in overall series, low cardiac output, multiple blood transfusion and any major complication early after surgery were significantly more frequent in L-patients. However, this poor outcome was mainly due to the higher risk profile of L-patients (higher rates of NYHA class III–IV, LVEF ≤30% and preoperative use of IABP) than C-patients. In effects, although the selection of patients to treat preoperatively with levosimendan was quite random in the first years of the study and due to contingent reasons (availability of the drug, bed availability in intensive care unit, opinion and knowledge of the drug by the treating physicians), there were usually included into L-group patients with chronic lung disease, severe dyspnea and lower LVEF. On the other hand, female sex, the ongoing use of antihypertensive agents and emergency/salvage surgical priority aided inclusion into the control group. This selection bias gives reason of the limited number of matched pairs of the present analysis. However, despite the aforementioned considerations, the increased use of blood transfusions in the patients of the present study who had received levosimendan before surgery deserves to be emphasized. In effects, as phosphodiesterase III inhibitor, levosimendan is an inhibitor of platelet aggregation in vitro, even though this effect has never proven at clinically relevant doses[15]. No significant differences were found, between L- and C-patients, in term of crude rates and adjusted-risk estimates of survival and freedom from MACCEs according to the use of levosimendan even according to the Cox proportional-hazards regression analysis, which was carried out in the overall series.

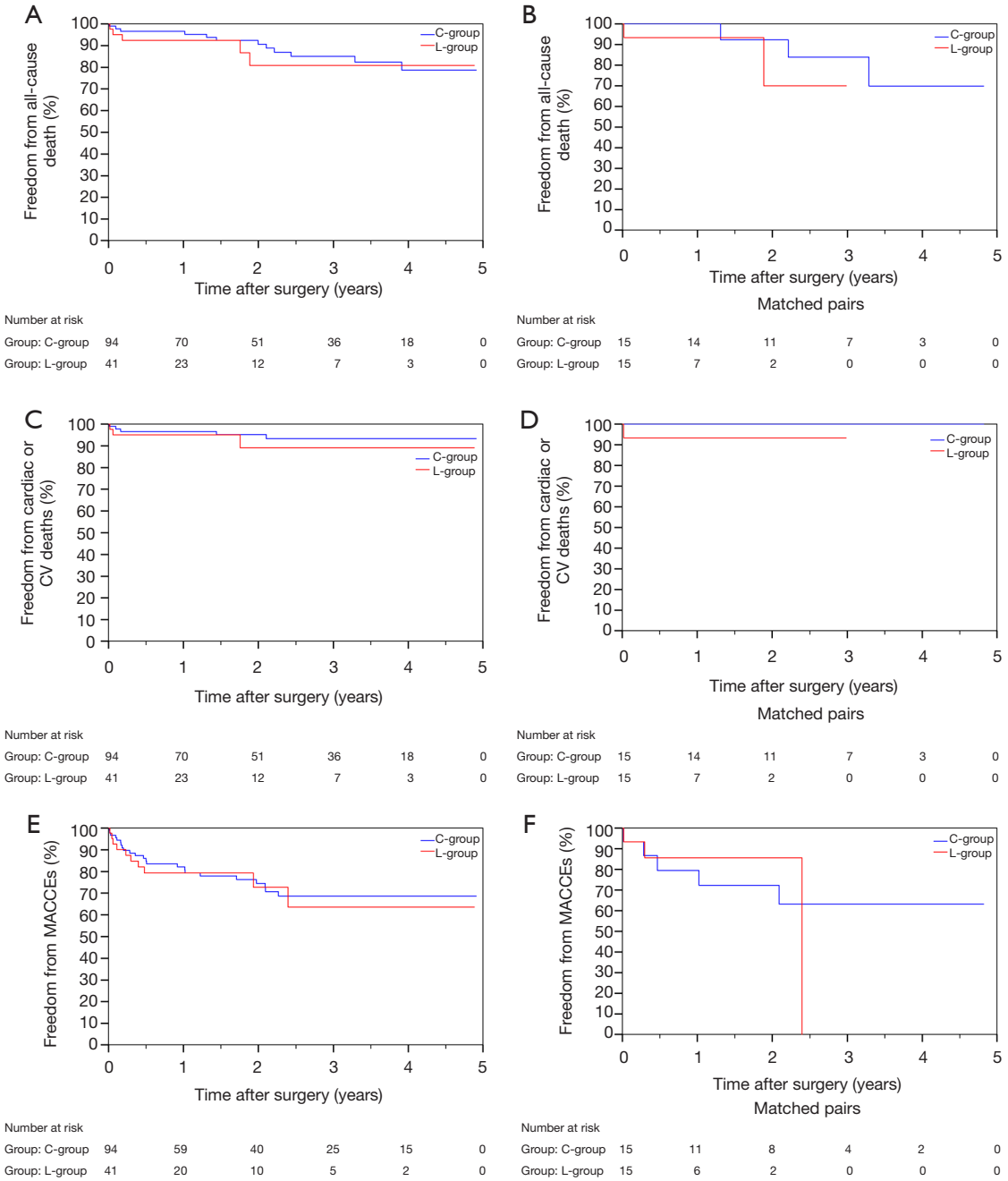

Figure 1 Non-parametric curves of (A,B) freedom from all-cause death, (C,D) cardiac or CV deaths, and (E,F) MACCEs during the follow-up period according to the levosimendan use. The overall (A, C and E) and matched series (B, D and F). Comparison between curves was made by the log-rank test and the P values were 0.54 (A), 0.3 (B), 0.5 (C), 0.32 (D), 0.73 (E), and 0.99 (F). CV, cerebrovascular; MACCEs, major adverse cardiac and cerebrovascular events.

These findings were consistent with more recent evidence in Literature on the prophylactic use of levosimendan in cardiac surgery, primarily before CABG. In a randomized, double-blind, placebo-controlled trial conducted by Cholley *et al.*[4] on 336 patients with LVEF ≤40% undergoing isolated coronary surgery, prophylactic levosimendan (24-hour infusion of 0.1 g/kg/min starting at anesthetic induction) compared with placebo did not result in a significant difference in the composite end-point of prolonged catecholamine infusion, use of left ventricular mechanical assist device, or renal replacement therapy. According to the multicenter, randomized, placebo-controlled trial performed by Mehta and the LEVO-CTS

Investigators[5] on 849 cardiac surgery patients with LVEF of 35% or less, prophylactic levosimendan (the dosage was the same adopted in the present study) did not result in a rate of the short-term composite endpoint of death, renal-replacement therapy, perioperative myocardial infarction, or use of a mechanical cardiac assist device that was lower than the rate with placebo. Based on the results of a retrospective analysis carried out by Grieshaber *et al.*[6] on 246 cardiac surgery patients (82 had received 12.5 mg of levosimendan at induction of anesthesia), levosimendan showed a positive effect on postoperative renal function but no significant benefits in terms of immediate and three-year survival; in addition, there was a higher risk of new-onset atrial fibrillation. In a prospective, double-blind, pilot study, which was performed by Anastasiadis *et al.*[7] on 32 coronary surgery patients with LVEF ≤40%, and where the subjects were randomized to receive either a continuous infusion of levosimendan at a dose of 0.1 g/kg/min for 24 h (without a loading dose) or a placebo, a significant increase (P=0.001) in LVEF was shown after surgery only in the levosimendan group. Finally, in a prospective randomized trial by Lomivorotov *et al.*[8] on 90 coronary surgery patients who received either prophylactic IABP one day before surgery, or a prophylactic IABP one day before surgery plus a levosimendan infusion at a dose of 0.1 g/kg/min with an initial bolus (12 g/kg for 10 min) after anesthesia induction, or a levosimendan infusion alone (with the same dosage), lower serum levels of cardiac troponin I were measured when levosimendan had been administered (P=0.048); however, there were no intergroup differences in the need for inotropic support, the rate of complications and mortality. While a significant (and comparable) LVEF improvement was shown for both groups of patients of the present study, lower peak serum levels of cardiac troponin I were documented in the levosimendan group (P=0.08). However, this hypothetical, reduced injury to myocardial cells, which has been still shown for human hepatocytes by Brunner *et al.*[16] translated in no real benefits in terms of outcomes after surgery.

Table 4 Crude rates and adjusted risk estimates of all-cause death, cardiac or CV deaths, and MACCEs during the follow-up period according to the levosimendan use (n=135)*

Event	L-group (n=41)	C-group (n=94)	HR	95% CI	P
All-cause death					
Crude	5 (12.2%)	12 (12.8%)	0.95	0.31–2.89	0.92
Multiple covariates-adjusted†			0.76	0.16–3.57	0.73
EuroSCORE II-adjusted[12]			1.31	0.453.8	0.62
Cardiac or CV deaths					
Crude	3 (7.3%)	5 (5.3%)	1.41	0.32–6.18	0.7
Multiple covariates-adjusted†			0.84	0.07–10.3	0.89
EuroSCORE II-adjusted[12]			1.42	0.336.14	0.64
MACCEs					
Crude	10 (25%)	23 (24.5%)	1	0.42–2.34	1
Multiple covariates-adjusted†			0.85	0.3–2.41	0.77
EuroSCORE II-adjusted[12]			1.12	0.53–2.37	0.76

*, four patients were lost to follow-up; †, age, female sex, diabetes, chronic lung disease. eGFR, extracardiac arteriopathy, LVEF. CI, confidence interval; CV, cerebrovascular; eGFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACCEs, major adverse cardiac and cerebrovascular events.

According to the supplementary analysis of this study, in C- and L-patients there were different predictors of significant LVEF improvement after surgery, namely there were two different patterns of left ventricular functional change following coronary revascularization. While old age was the only risk factor for failure in improving LVEF after surgery for L-patients, in C-group, there was a significant LVEF improvement for patients with left main coronary artery disease, extracardiac arteriopathy, and perioperative blood transfusion, i.e.,

for patients having a great amount, preoperatively, of hibernating myocardium (extracardiac arteriopathy such as carotid artery disease is often a surrogate variable of left main coronary artery disease), and perioperative optimization of hemoglobin. However, the present authors do not have further elements either to support these results or to give reason of such a different performance between C- and L-patients.

The present study has several limitations which deserve to be acknowledged. First, this is a single-centre retrospective study where the patients have been evaluated at different times after surgery, and only on a mid-term basis. Second, the study includes a limited number of patients with left ventricular dysfunction. Precisely to address this issue, less restrictive definition criteria for left ventricular dysfunction (LVEF ≤40% rather than ≤35%) were adopted. Besides, because the patients who had had prophylactic levosimendan were at higher risk profile than patients who did not receive it, the propensity matching generated a very limited number of matched pairs. Fourth, a possible selection bias could persist even after the propensity matching, though it appears well-conducted. Fifth, because dobutamine and/or epinephrine (and/or IABP) were used for many patients of both groups, both early before and after surgery, the comparison was between levosimendan plus adrenergic agent (and/or IABP) and adrenergic agent (and/or IABP) alone. Sixth, following the authors' institutional policy, which does not provide for perioperative use of phosphodiesterase III inhibitor for short-term treatment of cardiac failure no comparison was possible between calcium sensitizer and any one of phosphodiesterase III inhibitor. Actually, even for these drugs that mimic sympathetic stimulation and that increase cardiac output, there is no conclusive evidence on possible benefits in cardiac surgery patients[17]. Finally, the lack of details both on the quality check of grafts (using transit-time flowmetry or epicardial ultrasound) and on their late patency (coronary angiography). Consequently, the results obtained can in no way be considered conclusive and should be verified in larger patient populations by means of randomized controlled trials that include angiographic evaluations.

In conclusion, according to the results of this study, when compared with traditional inotropes alone, prophylactic use of levosimendan showed clear benefits/drawbacks neither concerning immediate nor mid-term outcomes after coronary surgery. There could be any advantage in terms of myocardial preservation. However, this fact could not be demonstrated by the present analysis.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ufficio Studi Clinici ed Epidemiologici dell'Azienda sanitaria universitaria Giuliano Isontina (October 23, 2018 – odg 5.18) and individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 The Cox proportional-hazards regression for all-cause death, cardiac or CV deaths, and MACCEs during the follow-up period

Characteristic	All-cause death			Cardiac or CV deaths			MACCEs		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age	–	–	–	–	–	–	–	–	–
Female	4.91	1.28–18.8	0.021	11.6	2.32–58.2	0.003	–	–	–
Diabetes	–	–	–	–	–	–	–	–	–
Chronic lung disease	3.25	1.03–10.3	0.046	5.45	1.09–27.3	0.04	–	–	–
eGFR‡	0.97	0.95–0.99	0.012	0.97	0.94–1	0.083	0.98	0.97–0.99	0.003
Extracardiac arteriopathy	3.59	1.24–10.4	0.019	–	–	–	–	–	–
LVEF	0.95	0.87–1.03	0.2	–	–	–	–	–	–

Continuous variables with normal distribution were expressed as mean ± SD and those without normal distribution as median and the range between the first and the third quartile. Discrete variables were expressed as frequencies and percentages. Unless otherwise stated, the definitions and cut-off values of the preoperative variables were those used for EuroSCORE II[12]. ‡, the creatinine clearance rate, calculated according to the Cockcroft-Gault formula, was used for approximating the GFR. CI, confidence interval; CV, cerebrovascular; eGFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACCEs, major adverse cardiac and cerebrovascular events; SD, standard deviation.

Table S2 The one-to-one propensity score matched analysis: Multivariable, backward stepwise, binary logistic regression

Characteristic	β	SE	P	OR	95% CI
Age	–	–	–	–	–
Female	–4.7	2.052	0.022	0.01	0–0.51
Hypertension on drug treatment	–2.116	0.914	0.021	0.12	0.02–0.72
Diabetes on Insulin	2.435	1.271	0.055	11.4	0.95–138
Diabetes on oral agent	1.16	0.783	0.138	3.19	0.69–14.8
Chronic lung disease	2.92	1.016	0.0041	18.5	2.53–136
eGFR 50–85 mL/min†	–	–	–	–	–
eGFR ≤50 mL/min†	–	–	–	–	–
Extracardiac arteriopathy	–	–	–	–	–
NYHA class II	2.418	1.482	0.1	11.2	0.61–205
NYHA class III	2.997	1.047	0.0042	20	2.57–156
NYHA class IV	3.887	1.007	0.0001	48.8	6.77–351
CCS class 4	–	–	–	–	–
Recent myocardial infarction	1.237	0.766	0.11	3.44	0.77–15.4
Three-vessel coronary artery disease	–	–	–	–	–
Left main coronary artery disease	1.15	0.744	0.12	3.16	0.73–13.6
LVEF 21–30%	4.952	1.013	<0.0001	142	19.4–1,030
LVEF <21%	5.732	1.973	0.0037	309	6.46–14,756
Critical preoperative state	–1.232	0.937	0.19	0.29	0.05–1.83
Preoperative IABP	1.872	0.954	0.05	6.05	1–42.2
Urgent surgical priority	–	–	–	–	–
Emergency surgical priority	–6.565	2.333	0.0049	0	0–0.14
Salvage surgical priority	–4.924	1.724	0.0043	0.01	0–0.21
EuroSCORE II[12]	–	–	–	–	–
B_0	–4.805				

Unless otherwise stated, the definitions and cut-off values of the preoperative variables were those used for EuroSCORE II[12]. †, the creatinine clearance rate, calculated according to the Cockcroft-Gault formula, was used for approximating the GFR. CCS, Canadian Cardiovascular Society; CI, confidence interval; eGFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OR, odds ratio; SE, standard error.

Table S3 Baseline characteristics of patients and risk profiles (n=129)

Characteristic	L-group, n=38			C-group, n=91		
	LVEF increase >30% (n=16)	LVEF increase <10% (n=14)	P	LVEF increase >30% (n=38)	LVEF increase <10% (n=23)	P
Age, years			0.034			0.99
<60	7 (43.7)	1 (7.1)		8 (21.1)	5 (21.7)	
60–70	6 (37.5)	5 (35.7)		12 (31.6)	7 (30.4)	
≥70	3 (18.7)	8 (57.1)		18 (47.4)	11 (47.8)	
Female	0	0	–	4 (10.5)	3 (13.0)	1
Anemia	7 (43.7)	9 (64.3)	0.26	22 (57.9)	13 (56.5)	0.92
Hypertension on drug treatement	11 (68.7)	14 (100.0)	0.045	32 (84.2)	18 (78.3)	0.73
Body mass index >30 kg/m^2	4 (25.0)	2 (14.3)	0.66	9 (23.7)	3 (13.0)	0.35
Diabetes			0.23			0.83
No history	5 (31.2)	6 (42.9)		19 (50.0)	12 (52.2)	
On insulin	3 (18.7)	0		2 (5.3)	2 (8.7)	
On oral agent	8 (50.0)	8 (57.1)		17 (44.7)	9 (39.1)	
Chronic lung disease	1 (6.2)	4 (28.6)	0.16	5 (13.2)	3 (13.0)	1
eGFR[§], mL/min			0.12			0.46
>85	9 (56.2)	3 (21.4)		17 (44.7)	7 (30.4)	
50–85	4 (25.0)	8 (57.1)		15 (39.5)	10 (43.5)	
≤50	3 (18.7)	3 (21.4)		6 (15.8)	6 (26.1)	
Extracardiac arteriopathy	5 (31.2)	5 (35.7)	1	18 (47.4)	4 (17.4)	0.018
NYHA class			0.75			0.3
I	4 (25.0)	4 (28.6)		19 (50)	15 (65.2)	
II	1 (6.2)	2 (14.3)		5 (13.2)	0	
III	5 (31.2)	5 (35.7)		7 (18.4)	4 (17.4)	
IV	6 (37.5)	3 (21.4)		7 (18.4)	4 (17.4)	
CCS class 4	9 (56.2)	7 (50.0)	0.73	26 (68.4)	12 (52.2)	0.2
Recent myocardial infarction			0.66			0.63
No history	9 (56.2)	10 (71.4)		23 (60.5)	14 (60.9)	
Within 7–90 days	4 (25.0)	2 (14.3)		9 (23.7)	5 (21.7)	
Within 1–7 days	2 (12.5)	2 (14.3)		4 (10.5)	4 (17.4)	
Within 24 h	1 (6.2)	0		2 (5.3)	0	
Coronary artery disease			0.74			1
Two-vessel	3 (18.7)	2 (14.3)		6 (15.8)	3 (13.0)	
Three-vessel	13 (81.2)	12 (85.7)		32 (84.2)	20 (87.0)	
Left main coronary artery disease	6 (37.5)	7 (50)	0.49	15 (39.5)	3 (13.0)	0.028

Table S3 (*continued*)

Table S3 (*continued*)

Characteristic	L-group, n=38			C-group, n=91		
	LVEF increase >30% (n=16)	LVEF increase <10% (n=14)	P	LVEF increase >30% (n=38)	LVEF increase <10% (n=23)	P
LVEF, %			0.49			0.73
31–40	6 (37.5)	3 (21.4)		34 (89.5)	21 (91.3)	
21–30	8 (50.0)	10 (71.4)		3 (7.9)	2 (8.7)	
<21	2 (12.5)	1 (7.1)		1 (2.6)	0	
Cardiac reoperation	0	0	–	1 (2.6)	0	1
Critical preoperative state	12 (75)	8 (57.1)	0.44	12 (31.6)	5 (21.7)	0.41
Use of adrenergic agents	3 (18.7)	2 (14.3)	1	5 (13.2)	2 (8.7)	0.7
Use of IABP	9 (56.2)	8 (57.1)	1	7 (18.4)	3 (13)	0.73
Acute renal failure (diuresis <10 mL/h)	1 (6.2)	0	1	2 (5.3)	0	0.52
Surgical priority			0.38			0.81
Elective	2 (12.5)	4 (28.6)		5 (13.2)	3 (13)	
Urgent	13 (81.2)	10 (71.4)		29 (76.3)	19 (82.6)	
Emergency	0	0		3 (7.9)	1 (4.3)	
Salvage	1 (6.2)	0		1 (2.6)	0	
EuroSCORE II[12], %	10.5 (8–25.3)	8.5 (4.5–16.7)	0.53	6 (2.9–10.6)	6.6 (2.1–9.8)	0.43
Operative data						
No. of coronary anastomoses	4.1±1	3.8±1.1	0.38	3.6±1	4.1±1.2	0.064
Off-pump technique	0	2 (14.3)	0.21	4 (10.5)	0	0.16
Cross-clamp time, min	89.4±21.5	86.4±23.6	0.73	94±53.8	80.1±21.2	0.24
Postoperative complication						
Prolonged (>12 h) use of adrenergic agent	16 (100.0)	12 (85.7)	0.2	33 (86.8)	23 (100.0)	0.15
Use of norepinephrine	16 (100.0)	12 (85.7)	0.2	31 (81.6)	21 (91.3)	0.46
Intraoperative use of IABP	2 (12.5)	1 (7.1)	1	1 (2.6)	1 (4.3)	1
Acute kidney injury	0	1 (7.1)	0.47	4 (10.5)	0	0.16
No. of transfused patients	8 (50.0)	6 (42.9)	0.7	17 (44.7)	4 (17.4)	0.029
No. of transfused units of RBCs per patient	0.5 (0–1.5)	0 (0–1.5)	0.76	0 (0–2)	0 (0–0)	0.022
Multiple transfusion (>2 RBC units)	4 (25)	3 (21.4)	1	6 (15.8)	0	0.075

The patients who underwent hospital discharge without signs of new myocardial infarction. Continuous variables with normal distribution were expressed as mean ± SD and those without normal distribution as median and the range between the first and the third quartile. Discrete variables were expressed as frequencies and percentages. Unless otherwise stated, the definitions and cut-off values of the preoperative variables were those used for EuroSCORE II. [§], the creatinine clearance rate, calculated according to the Cockcroft-Gault formula, was used for approximating the GFR. CCS, Canadian Cardiovascular Society; eGFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RBCs, packed red blood cells; SD, standard deviation; VF, ventricular fibrillation; VT, ventricular tachycardia Coefficients and Standard Errors.