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Lack of protective role of HDL-C in patients with coronary artery disease undergoing elective coronary artery bypass grafting

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Aims Primary prevention studies have confirmed that high-density lipoprotein cholesterol (HDL-C) levels are strongly associated with reduced cardiovascular events. However, recent evidence suggests that HDL-C functionality may be impaired under certain conditions. In the present study, we hypothesize that HDL-C may lose their protective role in the secondary prevention of coronary artery disease (CAD).

Methods and results A consecutive series of 1548 patients undergoing isolated first-time elective CABG at one institution between 2004 and 2009 was studied. According to the ATPIII criteria, pre-operative HDL-C values were used to identify patients with high (Group A) vs. low HDL-C (Group B). To eliminate biased estimates, a propensity score model was built and two cohorts of 1:1 optimally matched patients were obtained. Cumulative survival and major adverse cardiovascular events (MACE) were analysed by means of Kaplan–Meier method. Cox proportional-hazards regression models were used to identify independent predictors of MACE and death. Propensity matching identified two cohorts of 502 patients each. At a median follow-up time of 32 months, there were 44 out of 502 (8.8%) deaths in Group A and 36 out of 502 deaths in Group B (7.2%, HR 1.19; $P = 0.42$). MACE occurred in 165 out of 502 (32.9%) in Group A and 120 out of 502 (23.9%) in Group B ($P = 0.04$). Regression analysis showed that pre-operative HDL-C levels were not associated with reduced but rather increased MACE occurrence during follow-up (HR 1.43, $P = 0.11$).

Conclusion Higher HDL-C levels are not associated with reduced risk of vascular events in CAD patients undergoing CABG. Our findings may support efforts to improve HDL-C functionality instead of increasing their levels.

Keywords Dysfunctional HDL-C • Coronary artery bypass grafting • Secondary prevention • Cardiovascular mortality

Introduction

Over the last few years, epidemiological studies have shown that low high-density lipoprotein cholesterol (HDL-C) levels are associated with an increased risk of coronary artery disease (CAD) and cardiovascular events.[1,2] Indeed, low HDL-C remains an independent predictor of cardiovascular risk even in CAD patients with LDL cholesterol levels < 70 mg/dL on statin therapy.[3] Experimental studies suggest that atheroprotective effects of HDL-C is based on reverse cholesterol transport[4,5] as well as anti-inflammatory properties.[6] This led to the perspective that raising the levels of HDL-C represents a potential therapeutic strategy to reduce cardiovascular risk.[7] However, recent translational studies strongly suggest that vascular effects of HDL-C can be highly heterogeneous in different

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Table 1 Baseline characteristics after propensity matching[a]

	Group A High HDL-C	Group B Low HDL-C	*P*-value
Number of patients	502	502	N/A
Age, years	70 ± 8	70 ± 9	0.72
Gender, male, *n* (%)	388 (77.3)	386 (76.9)	0.55
Body mass index, kg/m^2	28.6 ± 4.1	28.5 ± 4.9	0.88
Hypertension, *n* (%)	476 (94.8)	477 (95.0)	0.59
Diabetes, *n* (%)	220 (43.8)	222 (44.2)	0.91
COPD, *n* (%)	178 (35.5)	181 (36.1)	0.64
History of smoking, *n* (%)	286 (56.9)	285 (56.8)	0.82
Current smoking, *n* (%)	45 (8.9)	43 (8.6)	0.77
Pre-operative LVEF, %	52 ± 10	51 ± 11	0.64
Pre-operative GFR, mL min^{-1}·1.73 m^{-2}	68 ± 12	68 ± 14	0.94
Pre-operative NYHA class ≥ 3, *n* (%)	156 (31.1)	159 (31.7)	0.63
Pre-operative CCS class ≥ 3, *n* (%)	307 (61.2)	304 (60.6)	0.52
Recent MI, *n* (%)	162 (32.3)	160 (31.9)	0.65
Previous stroke, *n* (%)	28 (5.6)	24 (5.0)	0.43
Pre-operative medications			
ACE-inhibitors	340 (67.8)	341 (67.9)	0.78
ARBs	170 (33.9)	171 (34.1)	0.74
BBs	355 (70.7)	352 (70.1)	0.63
Statins	326 (64.9)	327 (65.1)	0.59
Ezetimibe	12 (2.4)	9 (1.8)	0.37
Fibrates	37 (7.4)	30 (5.9)	0.22
Diuretics	11 (11)	12 (12)	0.88
Insulin	124 (24.7)	126 (25.1)	0.69
Metformin	116 (23.1)	118 (23.5)	0.74
Sulfolynureas	31 (6.2)	32 (6.4)	0.82
LDL cholesterol, mg/dL	124.3 ± 39.6	122.9 ± 45.3	0.55
HDL-C, mg/dL	52.6 ± 18.7	36.4 ± 12.3	<0.0001
Triglycerides, mg/dL	132 (66–193)[b]	188 (100–266)[b]	<0.0001
Logistic EuroSCORE II, %	1.6 (0.4–5.1)[c]	1.7 (0.4–5.3)[c]	0.66
CPB time, min	86 ± 22	87 ± 24	0.41
X-Clamp time, min	58 ± 19	59 ± 21	0.57
Distal anastomoses, mean	2.7 ± 0.9	2.8 ± 0.4	0.71

Continuous variables are expressed as mean ± standard deviation, categorical variables as percentages.
GFR, glomerular filtration rate; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; LVEF, left-ventricular ejection fraction; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BB, β-blockers; CPB, cardio-pulmonary bypass; X-Clamp, aortic cross-clamp.
[a]Goodness-of-fit: *c* statistic 0.79, $P = 0.0001$.
[b]Values shown are medians and interquartile ranges.
[c]Values shown are medians and their 95% confidence intervals.

clinical conditions.[8,9] HDL-C isolated from patients with CAD showed less anti-inflammatory activity than HDL-C derived from healthy controls.[6] Furthermore, the capacity of HDL-C to stimulate endothelial NO production and endothelial repair is substantially reduced in patients with CAD and diabetes.[10] The mechanisms underlying this phenomenon remain to be fully elucidated but likely include increased lipid oxidation of HDL-C due to a reduced HDL-C-associated paroxonase-1 activity, an enzyme that protects HDL-C from lipid oxidation, as well as modifications of the protein moiety.[11–13]

On the basis of these observations, the term 'dysfunctional HDL-C' was coined to indicate the loss of their anti-inflammatory and vasoprotective effects.[6] An increase of dysfunctional HDL-C particles may be less beneficial or might even be detrimental in certain clinical settings. This issue needs to be rapidly clarified since therapies that raise HDL-C levels are being investigated for the treatment of CAD patients.[14]

In the present study, we evaluated the protective effect of HDL-C cholesterol in a large prospective cohort of CAD patients undergoing elective coronary artery bypass grafting (CABG).

Our findings clearly show that protective effect of HDL-C cholesterol is lost in secondary prevention of CAD suggesting that HDL-C-raising strategies have to be carefully evaluated not to exert counterproductive effects.

Methods

The study was reviewed and approved by the Institutional Review Board of the University of Rome, and a waiver of consent was granted.

Patients and definitions

A consecutive series of patients undergoing isolated first-time elective CABG at one institution (Department of Cardiac Surgery, Ospedale Sant'Andrea, Rome, Italy) between April 2004 and April 2009 was studied.

All the operations were performed through a full-median sternotomy on cardio-pulmonary bypass (CPB) and cardiac arrest was obtained by means of antegrade cold-blood cardioplegia, repeated every 15 min. The left internal mammary artery was always used to graft the left anterior descending artery and revascularization completed using saphenous vein grafts to the right coronary and left circumflex artery segments.

Major adverse cardiovascular outcomes (MACE) were investigated, including all-cause mortality, myocardial infarction, repeated revascularization (either percutaneous or surgical), and cerebrovascular accidents. Diagnosis of MI was made by clinical symptoms and the presence of new Q waves, new persistent ST segment or T-wave changes (Minnesota codes 1-1-1 to 1-2-7, 4-1, 4-2, 5-1, 5-2, and 9-2), or elevated levels of troponin I. Diagnosis of stroke was made if there was a clinical evidence or a focal/global defect on computed tomography or magnetic resonance imaging.

Data were prospectively collected and recorded in an electronic database and clinical follow-up was completed within routine outpatient clinics. Patients who did not present at the visit were contacted by telephone and all symptoms as well as any complications,

including mortality which occurred during the follow-up period were recorded.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 11.0 (SPSS, Chicago, IL, USA). Variables were checked for normality by means of the Kolmogorov–Smirnov test for normal distribution and normality was accepted when $P \leq 0.05$. Continuous variables are shown as mean with standard deviation. All categorical data were displayed as percentages. Differences in baseline characteristics were compared using the χ^2 test for categorical variables and *t*-test for continuous variables.

According to the ATPIII criteria,[15] pre-operative values were used to identify a group of high HDL-C (>50 mg/dL for women and >40 mg/dL for men) vs. low HDL-C patients. To eliminate covariate differences that might lead to biased estimates, a propensity score model[16] was built and two cohorts of 1:1 optimally matched patients were obtained. The propensity score was computed with logistic regression with the dependent variable being HDL-C class and the independent variables (covariates) being age, gender, body mass index, hypertension, diabetes, smoking status, pre-operative left-ventricular ejection fraction (LVEF), pre-operative glomerular filtration rate (GFR), recent MI, pre-operative angina and dyspnoea degrees (NYHA and CCS classes), pre-operative stroke, medications (ACE-I, ARB, BB, Diuretics, anti-glicemic agents, anti-lipemic agents), CPB time, aortic cross-clamp time, and mean number of distal anastomoses; mixing continuous and binary variable to obtain a semi-saturated model.

Cumulative survival and freedom from MACE at follow-up were analysed by means of the Kaplan–Meier method and compared between groups using a log-rank test.

The survival/freedom from event time of a patient started at the time of surgery and ended at death/event or at last follow-up.

In addition, baseline characteristics showing a significant correlation ($P < 0.05$) with endpoints at univariate analysis were then introduced into two Cox proportional-hazards regression models to identify independent predictors of both mortality and MACE at follow-up. Age was the only continuous variable used, in fact, pre-operative LVEF was dichotomized into LV dysfunction as <0.41, and pre-operative GFR (estimated with the four-variable Modified Diet and Renal Disease equation)[17] was dichotomized into pre-operative renal dysfunction as <61 mL min^{-1}·1.73 m^{-2}.

In addition, a sensitive analysis was performed using the full cohort of patients rather than the propensity matched data. These results are separately shown in the appendix.

Results

Based on ATPIII criteria, 1548 consecutive patients were divided into patients with higher [617 (39.9%)] and with lower pre-operative HDL-C [931 (60.1%)]. Propensity matching identified two cohorts of 502 patients each, with high (Group A) vs. low (Group B) pre-operative HDL-C. *Table 1* depicts baseline characteristics stratified for high or low HDL-C, after propensity matching. As shown, only HDL-C and triglycerides levels were found to differ significantly between the groups, thus allowing a fair comparison of outcomes. In fact, the propensity model showed acceptable goodness-of-fit (*c* statistic 0.79, $P = 0.0001$) and discriminatory ability (χ^2 1.58, significance 0.22). Median logistic EuroSCORE was 1.6 (95%CI 0.4–5.1) for Group A and 1.7 (95%CI 0.4–5.3) for Group B ($P = 0.66$).

Survival analysis

At a median follow-up time of 32 months (mean 29.1 months; 95%CI: 28.6–29.6 months), there were 44 out of 502 (8.8%) deaths among high HDL-C patients and 36 out of 502 deaths among low HDL-C patients (7.2%), hence survival curves (*Figure 1*) were similar between high and low HDL-C groups: 87.0 ± 2.2% for Group A vs. 88.1 ± 2.1% for group B (Model χ^2 0.66; HR 1.19; $P = 0.42$). Furthermore, incidence of MACE was 165 out of 502 (32.9%) in Group A and 120 out of 502 (23.9%) in Group B, showing a statistically significant difference ($P = 0.04$), then confirmed at the Kaplan–Meier analysis (*Figure 2*): freedom from MACE at 3 years was 57.0 ± 2.8% for Group A vs. 67.9 ± 2.6% for Group B (Model χ^2 5.62; HR 1.32; $P = 0.017$).

Risk-factor analysis

A first Cox proportional-hazards regression model (χ^2 14.7, $P < 0.0001$; *Table 2*) was built to identify independent predictors of mortality: age (HR 1.15 per 1-year increase; $P < 0.0001$), diabetes (HR 2.23, $P = 0.0002$), chronic obstructive pulmonary disease (HR 1.74, $P = 0.03$), and pre-operative renal dysfunction (HR 2.11, $P < 0.0001$) were found to be independently correlated with survival. A trend towards worse survival was found among patients with pre-operative LV dysfunction (HR 1.46, $P = 0.09$), although it did not reach statistical significance. Pre-operative HDL-C levels as well were found to have some impact in increasing the risk of death (HR 1.33), but this correlation was not statistically significant ($P = 0.13$).

Independent predictors of MACE were identified by means of a second Cox proportional-hazards regression model (χ^2 23.5, $P < 0.0001$; *Table 3*), which showed age (HR 1.36 per 1-year increase; $P < 0.0001$), diabetes (HR 3.62, $P < 0.0001$), pre-operative renal dysfunction (HR 1.94, $P = 0.03$), pre-operative LV dysfunction (HR

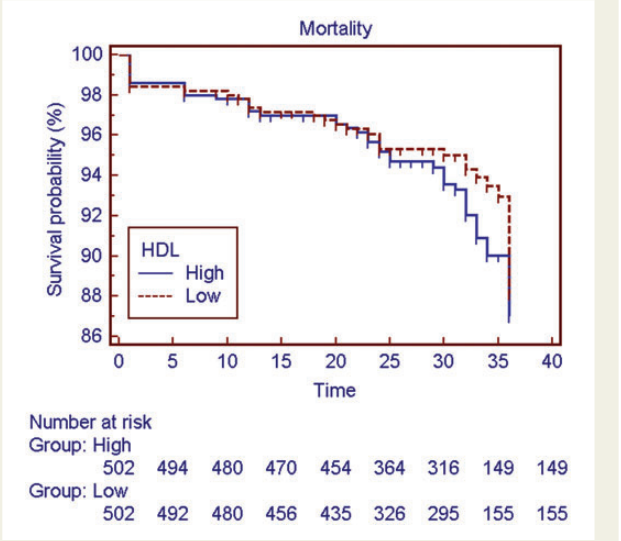

Figure 1 Kaplan–Meier analysis of survival in patients with high and low HDL-C.

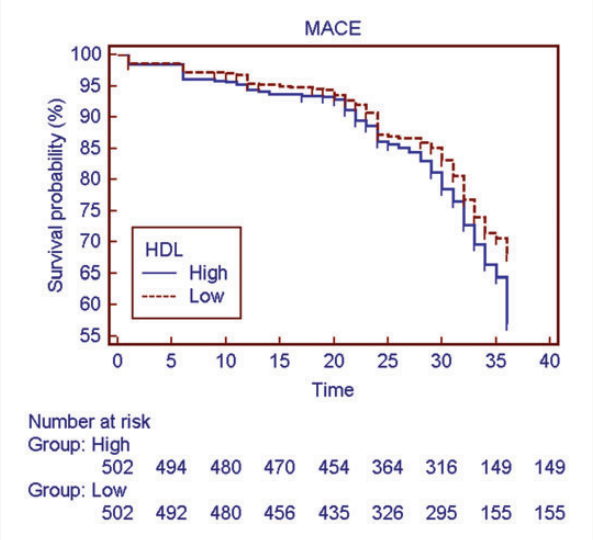

Figure 2 Kaplan–Meier curves showing MACE-free survival in patients with high and low HDL-C.

Table 2 Cox proportional-hazards regression analysis of time to death[a]

	Hazard ratio	95% CI	*P*-value
Age	1.15[b]	1.09–1.42	<0.0001
Diabetes mellitus	2.23	1.52–3.67	0.0002
COPD	1.74	1.53–2.46	0.03
Pre-operative renal dysfunction	2.11	1.62–3.55	<0.0001
Pre-operative LV dysfunction	1.46	0.94–2.11	0.09
High HDL-C	1.33	0.86–1.64	0.13

LV, left ventricular; HDL, high-density lipoprotein; COPD, chronic obstructive pulmonary disease.
[a]Model χ^2 14.7; $P < 0.0001$.
[b]Per 1-year increase.

2.25, $P = 0.003$), and pre-operative stroke (HR 2.18, $P = 0.02$) to be independently correlated with MACE-free survival of patients. Chronic obstructive pulmonary disease did not show any correlation with MACE-free survival (HR 1.07, $P = 0.14$), while pre-operative levels of HDL-C were found to have a negative impact on the occurrence of MACE during the follow-up (HR 1.43), but without reaching statistical significance ($P = 0.11$).

To further characterize the predictive value of HDL-C in our population, an additional univariate analysis was performed among the whole cohort of 1548 patients, before the propensity matching. Variables showing significant association with mortality after uncontrolled univariate analysis were age ($P = 0.0001$), diabetes ($P = 0.0001$), COPD ($P = 0.07$), LVEF ($P = 0.001$), GFR ($P = 0.002$), NYHA class ($P = 0.07$), recent MI ($P = 0.02$), CPB time ($P = 0.01$), and aortic cross-clamp time ($P = 0.01$, Appendix, *Table A1*). Similar results were found using MACE as a dependent variable. In line with our propensity-based regression analysis, univariate analysis could not show any significant association between HDL-C and either mortality or MACE ($\beta = 0.06$, 95% CI: −0.11–0.27, $P = 0.24$). Independent variables significantly associated with death and MACE were then included in the multivariate model (*Table A2*). Age, diabetes, GFR, and LVEF were independently associated with either death or MACE (Appendix, *Table A2*).

Table 3 Cox proportional-hazards regression analysis of time to major adverse cardiovascular event[a]

	Hazard ratio	95% CI	*P*-value
Age	1.36[b]	1.19–1.53	<0.0001
Diabetes mellitus	3.62	1.81–4.25	<0.0001
Chronic obstructive pulmonary disease	1.07	0.88–2.06	0.14
Pre-operative renal dysfunction	1.94	1.62–2.15	0.03
Pre-operative LV dysfunction	2.25	1.67–2.83	0.003
Pre-operative stroke	2.18	1.62–2.96	0.02
High HDL-C	1.43	0.89–2.07	0.11

LV, left ventricular; HDL, high-density lipoprotein.
[a]Model χ^2 23.5; $P < 0.0001$.
[b]Per 1-year increase.

Discussion

The present study demonstrates that the well-known protective role of HDL-C is lost in a large cohort of CAD patients undergoing isolated first-time elective CABG.

Primary prevention studies have previously suggested a pivotal role of HDL-C as a strong inverse predictor of cardiovascular events.[1,2] The HDL-C level in patients receiving statins were indeed predictive of major cardiovascular events across the TNT study cohort.[3] Moreover, even among study subjects with LDL cholesterol levels below 70 mg per decilitre, those in the highest quintile of HDL-C level were at less risk for major cardiovascular events than those in the lowest quintile.[2] Consistently, experimental observations showed unequivocal anti-atherogenic and anti-inflammatory properties of HDL-C isolated from healthy subjects.[6,18] The vasoprotective effect of HDL-C is thought to relate to reverse macrophage cholesterol transport[19] and, more recently, by the notion that HDL-C warrants endothelial homeostasis via the increase in nitric oxide production as well as the inhibition of critical pathways involved in vascular inflammation and endothelial apoptosis.[20] This body of evidence led to consider the opportunity to raise HDL-C levels as a potential therapeutic strategy to reduce cardiovascular risk.[21]

Recent translational studies demonstrated that HDL-C isolated from patients with CAD or diabetes lose their ability to stimulate endothelial NO production and accelerate endothelial repair.[20] The oxidative milieu observed in patients with CAD may lead to a

deregulation of critical enzymes protecting HDL-C from oxidation.[4] However, it is not clear whether modifications of HDL-C structure and functionality translate in a loss of their protective effect in the secondary prevention of cardiovascular disease. This aspect deserves attention since therapies that raise HDL-C levels are in high demand for the secondary prevention of CAD.[14] In the present study, we investigated the possibility that HDL-C may not be protective against future cardiovascular events in CAD patients undergoing surgical revascularization with CABG. To this end, in our study population, pre-operative HDL-C values were used to identify two groups of high and low HDL-C patients according to ATPIII criteria. In order to rule out the confounding effect of covariates, a propensity score model was built and two cohorts of optimally matched 1:1 patients were obtained. Cox proportional-hazard regression models showed that all-cause mortality rate was 8.8 and 7.2% in high and low HDL-C groups (HR 1.33, $P = 0.13$), respectively. More interestingly, a similar trend was observed when considering MACE occurrence. Indeed, pre-operative values of HDL-C were found to directly correlate with cardiovascular events (HR 1.43) but without reaching statistical significance ($P = 0.11$). Moreover, uncontrolled univariate and multivariate analysis performed on the whole population of 1548 patients before propensity matching confirmed the lack of a protective effect of HDL-C ($\beta = 0.06$, 95% CI: −0.11–0.27, $P = 0.24$). These results suggest that the inverse relation between HDL-C and cardiovascular mortality may be overturned in patients with CAD. Indeed, patients with higher HDL-C showed a clear trend towards increased all-cause mortality and cardiovascular event rates. Hence, the present analysis strengthens the notion that raising dysfunctional HDL-C may be potentially detrimental in CAD patients.[22–26] In the present study, the propensity-based analysis explored the relation between HDL-C levels and cardiovascular events ruling out the effect of confounding factors such as age, diabetes, previous cardiovascular events as well as pre-operative renal and LV dysfunction. Logistic EuroSCORE II, CPB time, X-Clamp time, and number of distal anastomoses were also equally distributed among the two groups, thus excluding the impact of different revascularization modalities. Importantly, treatment with statins, ezetimibe, and fibrates did not differently affect HDL-C levels during follow-up.

The main limitation of the present study is the retrospective nature. Despite the use of propensity score analysis to control for selection bias, eventually unidentified confounders may have influenced the results. Moreover, statin use is suboptimal in our population and our findings may not be generalizable to every cohort of CABG patients. However, propensity matching allowed a similar distribution of lipid-lowering agents among patients with high and low HDL-C.

In conclusion, we show here that higher HDL-C levels are not associated with a reduced risk of vascular events in patients with CAD undergoing elective bypass surgery. Our findings suggest that HDL-C functionality may be impaired in patients with CAD and may support efforts to improve HDL-C functionality instead of increasing their levels.

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Conflict of interest: none declared.

Appendix

To deeply investigate the relationship between HDL-cholesterol and outcomes among CABG patients, a sensitive analysis on the whole cohort of patients was performed.

To identify baseline factors correlated to the endpoints investigated, univariate Cox proportional-hazards regression was used. With respect to mortality (*Table A1*), variables showing significant ($P < 0.1$) association were age ($P < 0.0001$), diabetes ($P < 0.0001$), COPD ($P = 0.05$), pre-operative LV dysfunction ($P = 0.003$), pre-operative renal dysfunction ($P = 0.0001$), pre-operative NYHA class ≥ 3 ($P = 0.04$), and pre-operative recent MI ($P = 0.08$). Similar results were found using MACE as dependent variable.

Moreover, a multivariable Cox proportional-hazards regression model was used to identify independent predictors of mortality using all variables showing a significant correlation at univariable analysis ($P < 0.10$).

Multivariable Cox regression analysis (*Table A2*) showed age ($P = 0.0001$), diabetes ($P = 0.01$), LV dysfunction ($P = 0.03$), and renal dysfunction ($P = 0.001$) to be independent predictors of mortality, while age ($P < 0.0001$), diabetes ($P = 0.0001$), COPD ($P = 0.04$),

Table A1 Univariate analysis of correlation between baseline characteristics and mortality among the whole cohort of patients

	HR	95% CI	*P*-value
Age	1.19[a]	1.10–1.55	<0.0001
Male gender	1.22	1.05–1.63	0.12
Body mass index	1.16	−0.53–1.67	0.16
Hypertension	1.36	1.20–1.69	0.14
Diabetes	2.25	1.71–3.42	<0.0001
COPD	1.82	1.54–2.49	0.05
History of smoking	1.63	1.22–2.15	0.16
Current smoking	1.75	1.25–2.51	0.12
Pre-operative LV dysfunction	1.77	1.64–2.37	0.003
Pre-operative renal dysfunction	2.36	1.81–4.10	0.0001
Pre-operative NYHA class ≥ 3	1.74	1.56–1.82	0.04
Pre-operative CCS class ≥ 3	1.32	1.04–1.66	0.45
Recent MI	1.58	1.16–1.92	0.08
Previous stroke	1.51	1.02–2.01	0.22
High HDL-C	1.27	−0.34–1.59	0.18
CPB time	1.26	1.01–1.42	0.11
X-Clamp time	1.22	1.04–1.39	0.13

NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; LV, left ventricular; CPB, cardio-pulmonary bypass; X-Clamp, aortic cross-clamp.
[a]Per 1-year increase.

Table A2 Cox proportional-hazards regression analysis of pre-operative variables for each endpoint

Endpoints	Variables	HR	95% CI	*P*-value
Mortality				
	Age	1.22[a]	1.11–1.63	0.0001
	Diabetes	2.37	1.61–3.82	0.01
	COPD	1.68	1.22–4.17	0.08
	LV dysfunction	1.66	1.88–2.35	0.03
	Renal dysfunction	2.74	1.95–5.13	0.001
	NYHA class ≥ 3	1.57	1.16–2.71	0.09
	Recent MI	1.26	1.05–1.63	0.18
	High HDL-C	1.29	−1.02–1.61	0.26
Major adverse cardiovascular events				
	Age	1.41[a]	1.25–1.76	<0.0001
	Diabetes	2.45	1.73–4.14	0.0001
	COPD	1.71	1.55–4.19	0.04
	LV dysfunction	1.82	1.74–2.66	0.002
	Renal dysfunction	2.16	1.85–3.87	0.001
	NYHA class ≥ 3	1.34	1.19–1.49	0.22
	Recent MI	1.11	1.03–1.46	0.47
	High HDL-C	1.31	−1.02–1.63	0.19

HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; LV, left ventricular.
[a]Per 1-year increase.

LV dysfunction ($P = 0.002$), and renal dysfunction ($P = 0.001$) were found to be independent predictors of MACE.

Both Cox regression models significantly predicted their outcomes (model $\chi^2 = 21.6$; $P < 0.0001$ for mortality model; model $\chi^2 = 24.8$; $P < 0.0001$ for MACE model).

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