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Timing of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker restart after cardiac surgery and postoperative outcomes: a target trial emulation

qilin lu
Affiliated Hospital of Southwest Medical University https://orcid.org/0009-0005-7081-9710
Junning Liu
Affiliated Hospital of Southwest Medical University
Yuhang Luo
Affiliated Hospital of Southwest Medical University
Juyi Wan
Affiliated Hospital of Southwest Medical University
Bin Liao
liaobin@swmu.edu.cn
Affiliated Hospital of Southwest Medical University

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Abstract

Objective

Restarting angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) after cardiac surgery is associated with better in-hospital outcomes, but evidence on when to restart after surgery is lacking. This study takes "restart timing" itself as an intervenable treatment strategy and compares the effects of four restart strategies on postoperative outcomes.

Methods

A target trial emulation was conducted based on the MIMIC-IV 3.1 public critical care database. Inclusion criteria: adult open cardiac surgery, preoperative use of ACEI/ARB, postoperative admission to the intensive care unit (ICU), no ACEI/ARB order in use at ICU admission (t0), and restart before discharge. Four strategies were compared: restart within 24 h, restart within 48 h, restart within 72 h, and restart from 72 h to before discharge. Twelve outcomes were analysed: all-cause death at 30, 90 and 365 days, and 9 in-hospital complication outcomes.

Results

Among 10 939 open cardiac surgeries, 5 496 patients used ACEI/ARB before surgery, and 1 420 patients restarted before discharge (median restart time 53.9 h). The four strategies contained 259, 664, 872 and 548 patients, respectively. There were 51 deaths within 1 year, 24 within 90 days and 12 within 30 days. Weighted mortality in the four strategies was 4.90%, 2.76%, 3.05% and 4.57% at 1 year, 1.57%, 1.32%, 1.78% and 1.80% at 90 days, and 0.40%, 0.59%, 1.13% and 0.79% at 30 days; at the two earlier time points the intervals of all 6 pairwise comparisons included 0. Compared with restart within 48 h, restart within 24 h had higher 1-year mortality (RD +2.14 percentage points, 95%CI 0.05–4.27; relative risk 1.78, 1.02–2.67; hazard ratio 1.70, 1.01–2.55; E-value 2.95), but this comparison was no longer significant after correction for 6 comparisons within the mortality family (q = 0.23). Among the 15 comparisons whose uncorrected confidence intervals did not cross 0, 8 had q values below 0.05, 3 were 0.054–0.060, and 4 were 0.09–0.23. The risk of reintubation with restart within 24 h was lower than in those restarting at other times. The risk of hyperkalaemia and liver injury was highest with restart at 72 h and later. The risk of infection, pulmonary complications and cardiovascular or cerebrovascular complications with restart within 48 h was higher than with restart at 72 h and later.

Conclusions

ACEI/ARB restart timing did not differ across the four strategies with respect to 30-day and 90-day mortality; the association with 1-year mortality was not robust after correction for multiple comparisons; the risk of reintubation with restart within 24 h was lower than in those restarting at other times. The risk of hyperkalaemia and liver injury was highest with restart at 72 h and later. The risk of infection, pulmonary complications and cardiovascular or cerebrovascular complications with restart within 48 h was higher than with restart at 72 h and later.

Introduction

ACEI and ARB reduce the risk of cardiovascular events and death in patients with coronary heart disease, heart failure and chronic kidney disease, and are extremely commonly used in cardiac surgery patients [1][2]. Because of concern about vasoplegia and intractable hypotension after induction of anaesthesia, these drugs are usually withheld on the morning of the day of surgery [3][4]. Whether to restart after surgery has already been answered by previous studies. Some studies show that in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass, compared with those in whom ACEI was stopped after surgery, those who continued treatment had a lower risk of the in-hospital nonfatal ischaemic composite endpoint, and also fewer cardiac and renal events, with no difference seen in in-hospital death; compared with those who received no ACEI at all, those who continued treatment also had a lower risk of cardiovascular events [5]. In 294,505 noncardiac inpatient surgeries in the Veterans Affairs healthcare system, 25% of patients did not restart ACEI within 14 days after surgery, and those who did not restart had a higher 30-day mortality risk [6]. These findings together support the current recommendation that treatment should be restarted rather than abandoned, but these studies did not answer the question of when to restart after surgery, and guidelines give no clear recommendation. When to resume after surgery is a decision made every day after cardiac surgery, yet it has rarely been studied as a treatment strategy in itself.

The question of restart timing is not trivial. Mechanistically, ACEI/ARB dilate the efferent arteriole and lower glomerular filtration pressure [7]; too early restart may aggravate hypotension and renal hypoperfusion during the postoperative vasoplegic phase; while with too late restart, RAAS activity rebounds, angiotensin II rises and sodium and water are retained, which may affect pulmonary fluid distribution and systemic vascular tone; patients with ventricular dysfunction and diabetes lose renin-angiotensin system blockade at the stage of highest sympathetic tone, which may promote postoperative atrial fibrillation, as well as the thrombotic and infectious complications that constitute the main burden of the late hospital stay [8][9]. Among patients in whom restart is decided, whether timing constitutes a factor that needs to be considered. Risks in both directions coexist, making when to restart a question that needs to be quantified in data rather than one that can be inferred.

On this basis, we emulated a hypothetical randomised trial comparing four postoperative ACEI/ARB restart strategies in a large public critical care database [10], comparing the effect of restart timing on outcomes after cardiac surgery.

Methods

Data source and study design

This study is a retrospective target trial emulation, with data from MIMIC-IV 3.1. The database contains de-identified records of ICU and ward inpatients from 2008—2019 at a tertiary academic medical centre in Boston, Massachusetts, USA [10]. This study was written according to the STROBE reporting guideline

for observational studies. The original data collection was approved by the institutional review board of the host institution with a waiver of informed consent; this analysis used only de-identified data and required no separate approval.

Study population

Inclusion criteria: adults aged 18 years and above undergoing cardiac surgery, with only the first eligible hospitalisation taken for each patient; cardiac surgery included isolated coronary artery bypass grafting, isolated valve surgery, isolated thoracic aortic surgery, other cardiac surgery, and combined cardiac surgery. Patients had to have used ACEI/ARB before surgery and to restart ACEI/ARB treatment after surgery.

Exclusion criteria. Patients who did not use ACEI/ARB before surgery were excluded. Patients who did not restart ACEI/ARB during the postoperative hospital stay were excluded.

Study measures

Time zero and treatment strategies: time zero (t0) was taken as the time of postoperative ICU admission instead of the time of surgery end. The four strategies were defined by the interval from t0 to the first postoperative ACEI/ARB order: restart within 24 h was S1, restart within 48 h was S2, restart within 72 h was S3, and restart from 72 h to before discharge was S4. The four strategies are in a nested relation: patients in S1 also belong to S2 and S3.

Outcome measures: a total of 12 outcomes were analysed. All-cause death within 30 days, 90 days and 1 year after t0, of which 1-year all-cause death was the primary outcome; deaths after discharge were ascertained from death registry information linked to the database. Nine postoperative complications, uniformly assessed to 720 h (30 days): hypotension, acute kidney injury KDIGO stage 2 or above, hyperkalaemia, reintubation after first extubation, new-onset atrial fibrillation, liver injury grade 3 or above, infection (sepsis and septic shock, pneumonia, surgical site infection, urinary tract infection, bloodstream infection), pulmonary complications (pneumonia, respiratory failure, acute respiratory distress syndrome, atelectasis, pleural effusion, pneumothorax and pneumomediastinum, pulmonary embolism), cardiovascular or cerebrovascular complications (acute myocardial infarction, ischaemic stroke, cardiogenic shock, cardiac arrest).

Covariates: static covariates: age, sex, body mass index, surgical category (5 categories), emergency or urgent admission, preoperative atrial fibrillation, hypertension, diabetes, estimated glomerular filtration rate, chronic obstructive pulmonary disease, prior myocardial infarction, prior cardiac surgery, preoperative β-blocker, preoperative diuretic, no record of any preoperative medication. Time-varying covariates: lowest haemoglobin, highest lactate, lowest mean arterial pressure, whether vasoactive drugs were used, whether invasive mechanical ventilation was used.

Statistical analysis

Cloning and censoring: each patient was cloned according to the four strategies; those who had not restarted when the assigned strategy window closed (S1 24 h, S2 48 h, S3 72 h; for S4 the observed restart time, if earlier than 72 h) were artificially censored. Death was followed up to 1 year and complications to 720 h or discharge. Censoring weights: the probability of artificial censoring was fitted cell by cell by "strategy × 24 h cell" with a discrete-time logistic model: the denominator contained 15 static covariates (surgical category as 4 indicator variables), 5 time-varying covariates and 3 missing indicators, and the numerator contained only the 15 static covariates. Cumulative multiplication was performed cell by cell (r0, r0·r1, r0·r1·r2, thereafter carrying forward the last value), truncated at the 1st and 99th percentiles within strategy. Estimators: mortality was estimated with weighted Kaplan-Meier; the 6 complications with timestamps with weighted Aalen-Johansen (death and discharge as competing events, reporting 720 h); the 3 ICD composite outcomes with weighted logistic regression (offset as the logarithm of length of hospital stay, including strategy indicators) followed by cohort marginal standardisation. The 6 pairwise comparisons reported absolute risk difference (a positive value indicating higher risk in the former strategy), relative risk and hazard ratio (weighted Cox with time-dependent weights, Breslow ties). Intervals and correction: intervals were taken as the 2.5 and 97.5 percentiles of 500 resamples by patient. Each of the 12 outcomes formed one family, with Benjamini-Hochberg correction applied to the 6 pairwise comparisons within the family; bootstrap P values were continuously corrected as (r + 1)/(B + 1), and "significant" in the text refers to the corrected q value. Sensitivity and diagnostics: additionally performed: unweighted; multiple imputation of body mass index (m = 20, Rubin rules, Barnard-Rubin degrees of freedom); cut-points 12, 36, 48 h; conventional landmark analyses at 24, 48, 72 h; two alternative definitions of the ICD composite outcomes; carry-forward of time-varying covariates to 2 cells; stratification by surgical category. The E-value of the primary comparison was also calculated, proportional hazards were tested with weighted Schoenfeld residuals, standardised mean differences before and after weighting were compared on the risk-set scale, and effective sample size and weight distribution were reported. Analyses used Python 3.11 (NumPy, pandas) and Stata 19.0 (StataCorp, College Station, TX, USA).

Results

Cohort: among 10 939 open cardiac surgeries, 5 496 patients used ACEI/ARB before surgery, and 4 996 had a postoperative ICU. A total of 1 480 restarted during the hospital stay, of whom 1 420 restarted before discharge (flow details in Fig. 1). The 1 420 patients were each cloned according to the four strategies, giving 5 680 clones in total; 3 335 clones were artificially censored within 0–72 h because they did not restart within the assigned strategy window. Mean age was 68.3 years (SD 10.7), 1 001 were men (70.5%), mean body mass index was 29.8 kg/m² (SD 6.1; this variable was missing in 69 patients (4.9%) and was singly imputed with the cohort median 29.1 kg/m²), 516 (36.3%) were emergency or urgent admissions, and 705 (49.6%) had diabetes. Isolated coronary artery bypass grafting accounted for 686 patients (48.3%), isolated valve surgery 347 (24.4%), and combined surgery 320 (22.5%); 1 360

operations (95.8%) were under cardiopulmonary bypass. Mean estimated glomerular filtration rate was 78.7 mL/min/1.73 m² (SD 22.7). Compared with the 0–24 h group, the ≥ 72 h group had more emergency or urgent admissions (38.7% versus 33.6%), chronic obstructive pulmonary disease (12.4% versus 10.0%) and prior myocardial infarction (12.2% versus 8.1%), and patients using vasoactive drugs at t0 were more numerous in the 48–72 h and ≥ 72 h groups (83.7% and 82.8%) than in the 0–24 h group (64.9%). Baseline characteristics are shown in Table 1.

Restart timing: among the 4 178 eligible patients, 259 (6.2%) restarted within 24 h, 665 (15.9%) within 48 h, 876 (21.0%) within 72 h and 1 384 (33.1%) within 168 h; 2 698 (64.6%) never received a postoperative ACEI/ARB order during this hospitalisation (Fig. 2). Within the analysis cohort of 1 420 patients, the corresponding proportions were 18.2%, 46.8% and 61.4%. Median restart time was 53.9 h (IQR 27.9–95.7), and median time from t0 to discharge was 143.2 h.

Table 1
Baseline characteristics of the study cohort, by strategy

Characteristic	Overall (n = 1 420)	0–24 h (n = 259)	24–48 h (n = 405)	48–72 h (n = 208)	≥ 72 h–discharge (n = 548)
Patients, n	1 420	259	405	208	548
Age, years	68.3 (10.7)	68.5 (10.4)	68.7 (9.8)	68.0 (11.1)	67.9 (11.3)
Male sex	1001 (70.5)	177 (68.3)	295 (72.8)	147 (70.7)	382 (69.7)
BMI, kg/m²	29.8 (6.1)	29.5 (6.4)	30.1 (6.3)	29.9 (5.2)	29.6 (6.0)
Urgent or emergency admission	516 (36.3)	87 (33.6)	140 (34.6)	77 (37.0)	212 (38.7)
Preoperative atrial fibrillation	103 (7.3)	21 (8.1)	24 (5.9)	11 (5.3)	47 (8.6)
Hypertension	1316 (92.7)	240 (92.7)	374 (92.3)	198 (95.2)	504 (92.0)
Diabetes	705 (49.6)	135 (52.1)	191 (47.2)	106 (51.0)	273 (49.8)
eGFR, mL/min/1.73 m²	78.7 (22.7)	79.8 (23.4)	79.6 (21.6)	81.5 (21.4)	76.4 (23.5)
COPD	147 (10.4)	26 (10.0)	35 (8.6)	18 (8.7)	68 (12.4)
Prior myocardial infarction	137 (9.6)	21 (8.1)	34 (8.4)	15 (7.2)	67 (12.2)
Prior cardiac surgery	128 (9.0)	20 (7.7)	34 (8.4)	14 (6.7)	60 (10.9)
Beta-blocker	1168 (82.3)	204 (78.8)	345 (85.2)	169 (81.2)	450 (82.1)
Diuretic	770 (54.2)	125 (48.3)	211 (52.1)	106 (51.0)	328 (59.9)
No preoperative order recorded	47 (3.3)	4 (1.5)	13 (3.2)	7 (3.4)	23 (4.2)
Isolated CABG	686 (48.3)	117 (45.2)	214 (52.8)	95 (45.7)	260 (47.4)
Isolated valve	347 (24.4)	77 (29.7)	106 (26.2)	56 (26.9)	108 (19.7)
Isolated thoracic aorta	21 (1.5)	1 (0.4)	5 (1.2)	3 (1.4)	12 (2.2)

Characteristic	Overall (n = 1 420)	0–24 h (n = 259)	24–48 h (n = 405)	48–72 h (n = 208)	≥ 72 h–discharge (n = 548)
Other cardiac open surgery	46 (3.2)	11 (4.2)	5 (1.2)	5 (2.4)	25 (4.6)
Combined cardiac surgery	320 (22.5)	53 (20.5)	75 (18.5)	49 (23.6)	143 (26.1)
Minimum haemoglobin, g/dL	8.6 (1.6)	8.7 (1.6)	8.7 (1.5)	8.7 (1.7)	8.4 (1.5)
Maximum lactate, mmol/L	3.0 (1.5)	2.8 (1.3)	2.8 (1.2)	3.1 (1.3)	3.3 (1.7)
Minimum MAP, mmHg	57.5 (9.5)	58.1 (9.3)	57.9 (8.5)	56.7 (10.6)	57.2 (9.8)
Vasopressor use	1100 (77.5)	168 (64.9)	304 (75.1)	174 (83.7)	454 (82.8)
Mechanical ventilation	1301 (91.6)	239 (92.3)	379 (93.6)	194 (93.3)	489 (89.2)

Values are mean (SD) for continuous variables and n (%) for categorical variables. Groups are mutually exclusive and defined by the interval from ICU admission (t0) to ACEI/ARB restart; they are used here for description only, whereas the four nested strategies used in the primary analysis are shown in Fig. 1. Body mass index was missing in 69 patients (4.9%) and was replaced by the cohort median (29.1 kg/m²) before analysis, so the mean and SD given for that variable describe the imputed distribution. BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; SD, standard deviation.

Primary outcome

There were 51 deaths within 1 year, of which 10 were in hospital and 41 after discharge. Weighted 1-year cumulative mortality across the four strategies was 4.90% (S1), 2.76% (S2), 3.05% (S3) and 4.57% (S4), respectively (**Supplementary Table 1A**, Fig. 3). Of the 6 pairwise comparisons, only S1 versus S2 had an interval excluding 0: 1-year mortality was 2.14 percentage points higher in those restarting within 24 h than in those restarting within 48 h (95%CI 0.05–4.27), with a relative risk of 1.78 (1.02–2.67) and a hazard ratio of 1.70 (1.01–2.55). The corresponding E-values were 2.95 for the relative risk and 2.79 for the hazard ratio, and 1.14 and 1.11 for the respective confidence interval bounds. The intervals of the remaining 5 pairs all included 0 (**Supplementary Table 1B**).

Twelve patients died within 30 days and 24 within 90 days. Weighted 30-day cumulative mortality across the four strategies was 0.40% (S1), 0.59% (S2), 1.13% (S3) and 0.79% (S4), and at 90 days 1.57%, 1.32%, 1.78% and 1.80% (Table 2A). At both time points the intervals of all 6 pairwise comparisons included 0: risk differences ranged from − 0.73 to + 0.34 percentage points at 30 days and from − 0.49 to + 0.26 percentage points at 90 days, and the intervals of the relative risk and hazard ratio also all included 1.

After applying Benjamini-Hochberg correction within the mortality family, the q value of this comparison was 0.23 (uncorrected P value 0.046; the threshold corresponding to the smallest P value in the family was about 0.008).

Secondary outcomes

At 720 h, the weighted risks from S1 to S4 were: hypotension 58.50%, 60.04%, 60.09%, 61.68%; acute kidney injury 4.43%, 5.41%, 5.47%, 6.53%; hyperkalaemia 25.74%, 26.86%, 27.10%, 28.13%; reintubation 0.93%, 2.53%, 2.72%, 3.34%; new-onset atrial fibrillation 21.63%, 23.34%, 22.85%, 24.42%; liver injury 1.70%, 2.44%, 3.24%, 4.39% (**Supplementary Table 2A**); the corresponding event counts were 863, 82, 392, 43, 329 and 47, respectively. The weighted risks of the ICD composite outcomes were: infection 12.91%, 14.98%, 13.99%, 11.90%; pulmonary complications 25.14%, 27.37%, 26.09%, 23.55%; cardiovascular or cerebrovascular complications 14.36%, 15.65%, 15.05%, 13.41%; the event counts for the three were 176, 343 and 196, respectively.

Of the 54 secondary comparisons, 14 had uncorrected confidence intervals excluding 0 (**Supplementary Table 2B**, Fig. 4). The weighted risks of reintubation, hyperkalaemia and liver injury rose sequentially from S1 to S4. The pairs with reintubation intervals excluding 0 were S1 versus S2 (− 1.60 percentage points, 95%CI − 3.32 to −0.15), S1 versus S3 (− 1.79, − 3.28 to −0.38) and S1 versus S4 (− 2.40, − 3.97 to −0.88); for hyperkalaemia, S1 versus S4 (− 2.39, − 4.25 to −0.27); for liver injury, S1 versus S4 (− 2.69, − 4.62 to −0.73) and S2 versus S4 (− 1.95, − 3.56 to −0.21). For infection, pulmonary complications and cardiovascular or cerebrovascular complications the pairs with intervals excluding 0 were: infection S1 versus S2 (− 2.08, − 3.92 to −0.62), S2 versus S4 (+ 3.08, 1.62 to 5.11), S3 versus S4 (+ 2.09, 0.93 to 4.12); pulmonary complications S2 versus S4 (+ 3.82, 1.96 to 6.12), S3 versus S4 (+ 2.54, 1.18 to 4.93), S1 versus S4 (+ 1.59, 0.32 to 8.03); cardiovascular or cerebrovascular complications S2 versus S4 (+ 2.24, 0.66 to 4.26), S3 versus S4 (+ 1.64, 0.44 to 3.08). For hypotension, acute kidney injury and atrial fibrillation no pair had an interval excluding 0.

In the weighted Fine-Gray models, 5 of the 36 subdistribution hazard ratios had intervals excluding 1: hypotension S2 versus S4 1.09 (1.02 to 1.17) and S3 versus S4 1.07 (1.03 to 1.14); atrial fibrillation S2 versus S4 1.21 (1.08 to 1.38); liver injury S1 versus S2 0.51 (0.31 to 0.74) and S1 versus S3 0.56 (0.31 to 0.87).

Results of multiple comparisons

Of the 15 comparisons whose uncorrected intervals excluded 0, 8 had q values below 0.05 (6 were 0.006, 2 were 0.020 and 0.044), all falling in the three families of infection, pulmonary complications and cardiovascular or cerebrovascular complications; 3 had q values of 0.054, 0.054 and 0.060 (reintubation S1 versus S3 and S1 versus S4; liver injury S1 versus S4); the remaining 4 had q values of 0.09 (reintubation S1 versus S2), 0.09 (liver injury S2 versus S4), 0.16 (hyperkalaemia S1 versus S4) and 0.23 (1-year death S1 versus S2).

Sensitivity and diagnostic analyses

After removing the weights entirely, 36 comparisons had intervals excluding 0 (15 with weights). For the 3 ICD composite outcomes, the unweighted risk differences for S2 versus S4 were − 15.16, − 8.14 and − 8.67 for pulmonary complications, infection and cardiovascular or cerebrovascular complications (weighted + 3.82, + 3.08, + 2.24), with the signs all reversed. After multiple imputation of body mass index, point estimates across the 72 comparisons changed by no more than 0.008 percentage points; the 3 comparisons whose intervals excluded 0 in the main analysis (reintubation S1 versus S2, 1-year death S1 versus S2, pulmonary complications S1 versus S4) had intervals including 0 after imputation, no comparison changed direction, and the ratio of between- to within-imputation variance was at most 0.0004. With 12, 36 and 48 h as cut-points, no comparison had an interval excluding 0; the risk difference at the 12 h cut-point was + 1.14 percentage points (95%CI − 3.68 to 17.59), and 21 patients restarted within 12 h. The landmark analyses at 24, 48 and 72 h comprised 21 comparisons, 14 of which had intervals excluding 0, all for complications and all with higher risk in those not yet restarted at the landmark time. The two alternative definitions of the ICD composite outcomes did not change the sign of any comparison; after including the primary diagnosis, the two comparisons for cardiovascular or cerebrovascular complications had intervals including 0 (S2 versus S4 + 1.17, − 0.47 to 3.07; S3 versus S4 + 1.09, − 0.27 to 2.48). With the carry-forward of time-varying covariates relaxed to 2 cells, the file digests of the 48 risk estimates and the 72 risk differences were identical to the main analysis; the 18 within-stratum comparisons by surgical category all had intervals including 0, and the interaction test gave χ^2 = 1.22, 6 degrees of freedom, P = 0.98.

Adherence to the strategies was 18.2% for S1 (259 patients), 46.8% for S2 (664), 61.4% for S3 (872) and 38.6% for S4 (548), with the remaining clones censored when the window closed. The proportional hazards tests for the 6 mortality comparisons gave P values of 0.15 to 0.97 (0.054 for S3 versus S4). The ratio of effective sample size to the number at risk was 0.84 to 1.00, lowest for S2 at 48 h and 72 h (0.84, maximum weight 4.11), and 0.87 for S1 at 24 h (effective sample size 224.8, 258 at risk, maximum weight 2.58) (Fig. 5). Truncated observations accounted for 1.2% to 4.3%. After weighting, the median absolute standardised mean difference across 384 cells fell from 0.0104 to 0.0089, 16 cells exceeded 0.10, and the maximum was 0.141 ("no record of preoperative medication" in S1 at 24 h) (Fig. 6).

Discussion

In this target trial emulation of ACEI/ARB restart timing after cardiac surgery, patients restarting within 24 h had higher 1-year mortality than those restarting within 48 h, with a risk difference of 2.14 percentage points and a relative risk of 1.78. However, this was the only one of the 6 mortality comparisons whose interval excluded 0, its uncorrected P value was 0.046, and it was no longer significant after correction for the 6 comparisons within the mortality family (q = 0.23). Among the 11 secondary outcomes the pattern was not monotonic: the weighted risk of reintubation was lowest in S1, lower than in S2, S3 and S4; hyperkalaemia and liver injury were highest in S4, higher than in S1 (liver

injury also higher than in S2); infection, pulmonary complications and cardiovascular or cerebrovascular complications were highest in S2, with 8 of these comparisons passing correction.

Comparison with existing studies

The existing literature answers another decision. The randomised evidence concerns whether to continue the drug in the days before surgery: a registry-based randomised pilot trial of 121 patients found no difference between continuation and discontinuation 2 days before surgery in vasoactive drug requirement, vasoplegic shock, kidney injury and death, but the sample size was far from sufficient to evaluate clinical endpoints [3]. Large observational studies on continuation versus discontinuation reach conflicting conclusions: in 37 197 veterans undergoing cardiac surgery, continuation of a preoperative renin-angiotensin system blocker, or early initiation after surgery, was associated with lower 30-day and 1-year mortality than discontinuation or non-initiation [4]; in a propensity-matched multicentre analysis of 1 072 patients, maintaining ACEI on the day of surgery was not associated with kidney injury[11]. A consensus document on postoperative blood pressure goes further, pointing out that postoperative withdrawal of β-blockers, ARB and ACEI is itself associated with adverse outcomes [12].

The perioperative management of renin-angiotensin system inhibitors remains controversial at present, and contains two questions that need to be answered separately: the short-term risk of preoperative discontinuation, and the benefit of long-term postoperative use. A multicentre prospective observational study of patients undergoing coronary artery bypass grafting (CABG) under cardiopulmonary bypass suggested that those in whom ACEI was stopped after surgery had more in-hospital nonfatal ischaemic events, whereas in-hospital death and cerebral events did not differ from those who continued treatment [5]. The Stop-or-Not randomised controlled trial, in patients undergoing major noncardiac surgery, compared discontinuation 48 h before surgery with continuation, and the composite endpoint of 28-day all-cause death and major postoperative complications did not differ significantly between the two groups, but intraoperative hypotension was more common in those who continued treatment [13]. Complementing the above short-term perioperative studies, a population-based retrospective cohort study including 15 439 CABG patients focused on the later phase after revascularisation, and found that whether or not heart failure was present, postoperative use of ACEI/ARB was associated with a lower risk of long-term major adverse cardiovascular events (MACE), supporting long-term maintenance of treatment after CABG for secondary prevention [14]. It can be seen that the clinical trade-off of stopping such drugs is specific to the type of surgery, while long-term standardised use after CABG can provide sustained cardiovascular protection.

The 2017 EACTS guidelines on perioperative medication in adult cardiac surgery state: initiation of a short-acting ACEI no earlier than 48 hours after cardiac surgery may be considered, but this is limited to patients with LVEF < 40% and eGFR > 30, with a level of evidence of IIa C [15]. The 2024 guidelines state: early restart of ACEI/ARB, guided by haemodynamics. The guidelines give only qualitative recommendations and no time window; is "early" 24h? 48h? 72h? No one has quantified it [16]. The results of this study are not in contradiction with previous studies, but move the question to another

position. All of the above studies compared "exposed" with "unexposed" at a single time point, mostly preoperatively, and none estimated the effect of "on which day medication is resumed". The only analysis that distinguished continuation, discontinuation and early postoperative initiation still grouped all postoperative initiations together, and found that the earliest group had the best outcomes [4]; our data instead show that the first 24 h may differ from the second 24 h, although this difference is not robust. The difference may also come from case composition: 85% of that veteran cohort underwent coronary artery bypass grafting, whereas nearly half of the patients in this study underwent valve or combined surgery, and in the eligible population of this study, those never restarted accounted for 64.6%, far higher than in cohorts where restart is protocolised.

Understanding the non-monotonic results

Our study data do not show a monotonic relation of "the earlier the better" or "the later the better". The risk of reintubation was lowest in S1 and higher in S2 to S4; hyperkalaemia and liver injury were higher in S4 than in S1 (liver injury in S4 was also higher than in S2); another 3 complications were higher in S2 than in S4, which deferred restart to 72 h and later. There are two mechanisms that can produce this shape. First, the competing risks change over time: on the first day after surgery, circulating angiotensin-converting enzyme activity and vasoactive drug dependence are at their peak, and the haemodynamic cost of restarting is greatest at this time; from the second day onward, the risks brought by persistent vasoplegia, renal hypoperfusion and immobility accumulate continuously. Second, the groups divided by restart time are not the same in aspects that weighting can only partially correct. Those restarting at 72 h and later are by definition people who survived and were still in hospital, and they are also more often emergency admissions with chronic lung disease and prior myocardial infarction, and more often still using vasoactive drugs at t0. This kind of residual imbalance is visible in the balance diagnostics: after weighting there were still 16 cells with an absolute standardised mean difference greater than 0.10. The three items of reintubation, hyperkalaemia and liver injury deserve separate mention, because their direction is consistent with an explicable mechanism, rather than appearing to be caused only by residual confounding. Long absence of renin-angiotensin system blockade is related to sodium and water retention, hyperkalaemia in the presence of impaired renal function, and hepatic congestion, and reintubation may reflect the pulmonary consequence of the same congestion process. However, these are hypotheses rather than conclusions, and the absolute differences are not large: the 2.4 percentage points for reintubation corresponds to about 6 patients in the earliest restart strategy.

Limitations

This study still has limitations: this study is an observational emulation: the strategies were assigned by t0, and the censoring models can only correct for measured covariates, so confounding by indication such as ventricular function, bleeding, reoperation and surgeon habit may exist. The study database is single-centre, blood pressure and vasopressors were recorded only in the ICU, and hypotension after transfer to the ward cannot be identified; renal function is only a single preoperative value, which can hardly reflect intraoperative injury. There were 51 deaths within 1 year in the study cohort, and the mortality comparisons are imprecise; another 3 comparisons had q values of 0.054–0.060, which are

indeterminate. Weighting did not fully balance, 16 cells exceeded 0.10, and the effective sample size in the most heavily weighted stratum fell to 0.84 of the risk set.

Conclusions

This study is a target trial emulation including 1 420 patients restarting ACEI/ARB after cardiac surgery; patients restarting within 24 h had higher 1-year mortality than those restarting within 48 h, but this comparison is not robust after correction for multiple comparisons. The 30-day mortality of the four strategies was 0.40%–1.13% and the 90-day mortality 1.32%–1.80%, and at both time points the intervals of the 6 pairwise comparisons all included 0. Secondary outcomes move in opposite directions depending on the time window taken: reintubation was least frequent in S1 and more frequent in S2 to S4, hyperkalaemia and liver injury were most frequent when deferred to 72 h and later (S4), and restart within 48 h (S2) was associated with more infection, pulmonary and cardiovascular or cerebrovascular complications. The above results come from observational data and are exploratory findings, which are not yet sufficient to provide a basis for any specific restart time point and still require confirmation by prospective studies.

Declarations

Author contributions

Study conception and design: Qilin Lu. Data extraction and data analysis: Junning Liu, Yuhang Luo. Writing the paper: Qilin Lu, Junning Liu, Yuhang Luo. Important revisions: Qilin Lu, Junning Liu, Juyi Wan, Bin Liao. Research Guidance: Juyi Wan, Bin Liao.

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Availability of data and materials

MIMIC-IV (version 3.1) is hosted on PhysioNet (https://physionet.org/content/mimiciv/3.1/). Access requires PhysioNet credentialing, including completion of a training course in human subjects research, and signature of the PhysioNet data use agreement; the data are therefore not redistributed by the authors. The cohort definition scripts and analysis code that produce every estimate reported in this article are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study is a secondary analysis of the MIMIC-IV database (version 3.1). The collection of patient information and the creation of the research resource were reviewed by the Institutional Review Board of the Beth Israel Deaconess Medical Center, which granted a waiver of informed consent and approved the data sharing initiative. All records used in the present analysis were de-identified; the study involved no intervention and no attempt to re-identify any individual, and accordingly no further ethical approval or informed consent was required.

Competing interests

The authors declare no competing interests.

References

1. Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P et al (2000) Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 342(3):145–153
2. Neumann FJ, Sousa-Uva M, Ahlsson A et al (2019) 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 40(2):87–165
3. van Diepen S, Norris CM, Zheng Y et al (2018) Comparison of Angiotensin-Converting Enzyme Inhibitor and Angiotensin Receptor Blocker Management Strategies Before Cardiac Surgery: A Pilot Randomized Controlled Registry Trial. J Am Heart Assoc 7(20):e009917
4. Antoniak DT, Walters RW, Alla VM (2021) Impact of Renin-Angiotensin System Blockers on Mortality in Veterans Undergoing Cardiac Surgery. J Am Heart Assoc 10(10):e019731
5. Drenger B, Fontes ML, Miao Y et al (2012) Patterns of use of perioperative angiotensin-converting enzyme inhibitors in coronary artery bypass graft surgery with cardiopulmonary bypass: effects on in-hospital morbidity and mortality. Circulation 126(3):261–269
6. Mudumbai SC, Takemoto S, Cason BA et al (2014) Thirty-day mortality risk associated with the postoperative nonresumption of angiotensin-converting enzyme inhibitors: a retrospective study of the Veterans Affairs Healthcare System. J Hosp Med 9(5):289–296
7. Schoolwerth AC, Sica DA, Ballermann BJ et al (2001) Renal considerations in angiotensin converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. Circulation 104(16):1985–1991
8. Baeza-Herrera LA, Rojas-Velasco G, Márquez-Murillo MF et al (2019) Atrial fibrillation in cardiac surgery. Arch Cardiol Mex 89(4):348–359 English
9. Khwaja A (2012) KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 120(4):c179–c184
10. Johnson AEW, Bulgarelli L, Shen L et al (2023) MIMIC-IV, a freely accessible electronic health record dataset. Sci Data 10(1):1

11. Guilleminot P, Andrei S, Nguyen M et al (2024) Pre-operative maintenance of angiotensin-converting enzyme inhibitors is not associated with acute kidney injury in cardiac surgery patients with cardio-pulmonary bypass: a propensity-matched multicentric analysis. Front Pharmacol 15:1343647
12. McEvoy MD, Gupta R, Koepke EJ et al (2019) Perioperative Quality Initiative consensus statement on postoperative blood pressure, risk and outcomes for elective surgery. Br J Anaesth 122(5):575–586
13. Legrand M, Falcone J, Cholley B et al (2024) Continuation vs Discontinuation of Renin-Angiotensin System Inhibitors Before Major Noncardiac Surgery: The Stop-or-Not Randomized Clinical Trial. JAMA 332(12):970–978
14. Barry AR, Helisaz H, Safari A et al (2024) Effect of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers After Coronary Artery Bypass Graft Surgery: A Population-Based Cohort Study. J Am Heart Assoc 13(12):e035215
15. Sousa-Uva M, Head SJ, Milojevic M et al (2018) 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery. Eur J Cardiothorac Surg 53(1):5–33
16. ; Authors/Task Force Members, Jeppsson A et al (2024) (Co-Chairperson) (Sweden); Rocca B; (Co-Chairperson) (Italy);. 2024 EACTS Guidelines on perioperative medication in adult cardiac surgery. Eur J Cardiothorac Surg. ;67(1):ezae355

Figures

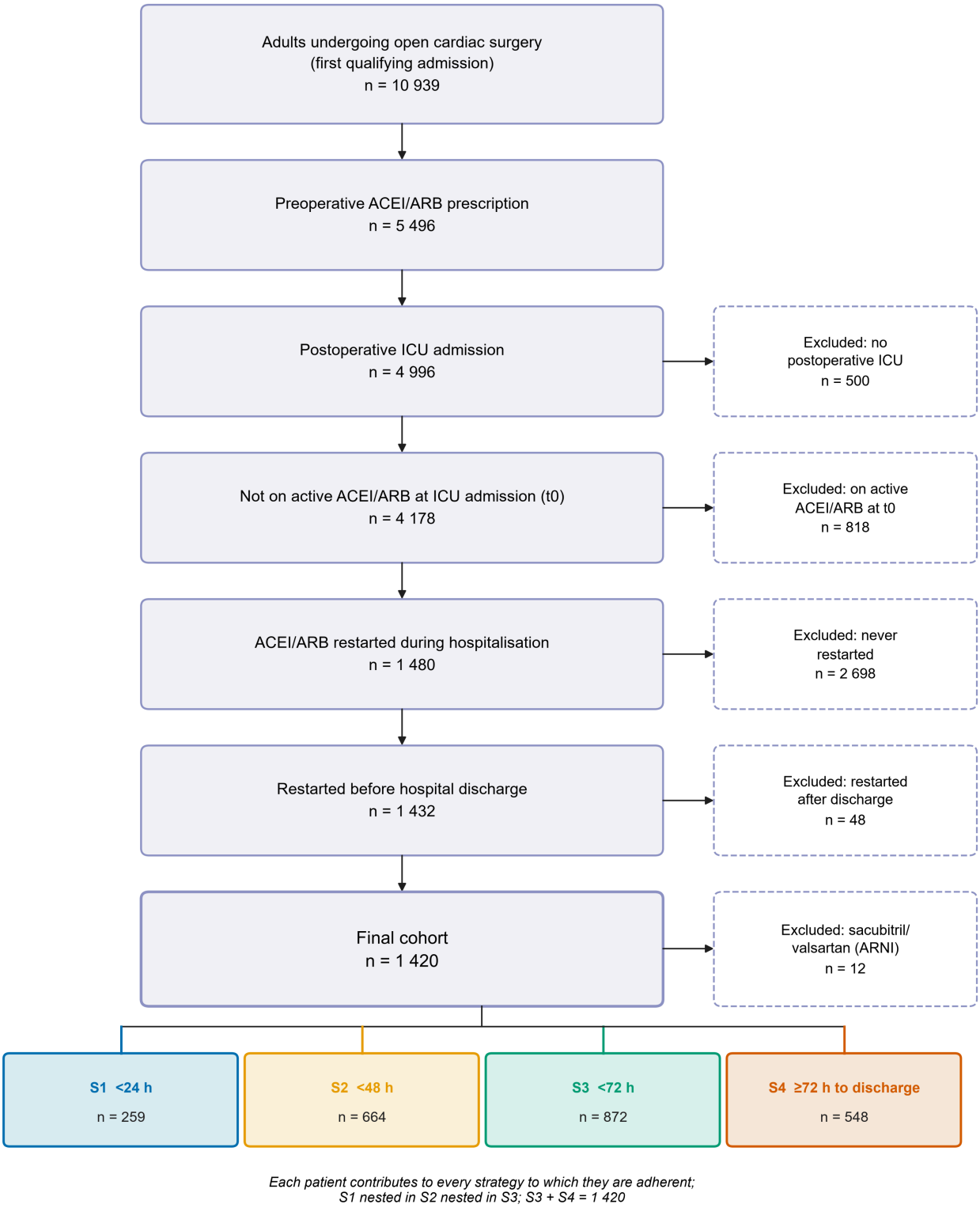


Figure 1

Study flow and treatment strategies

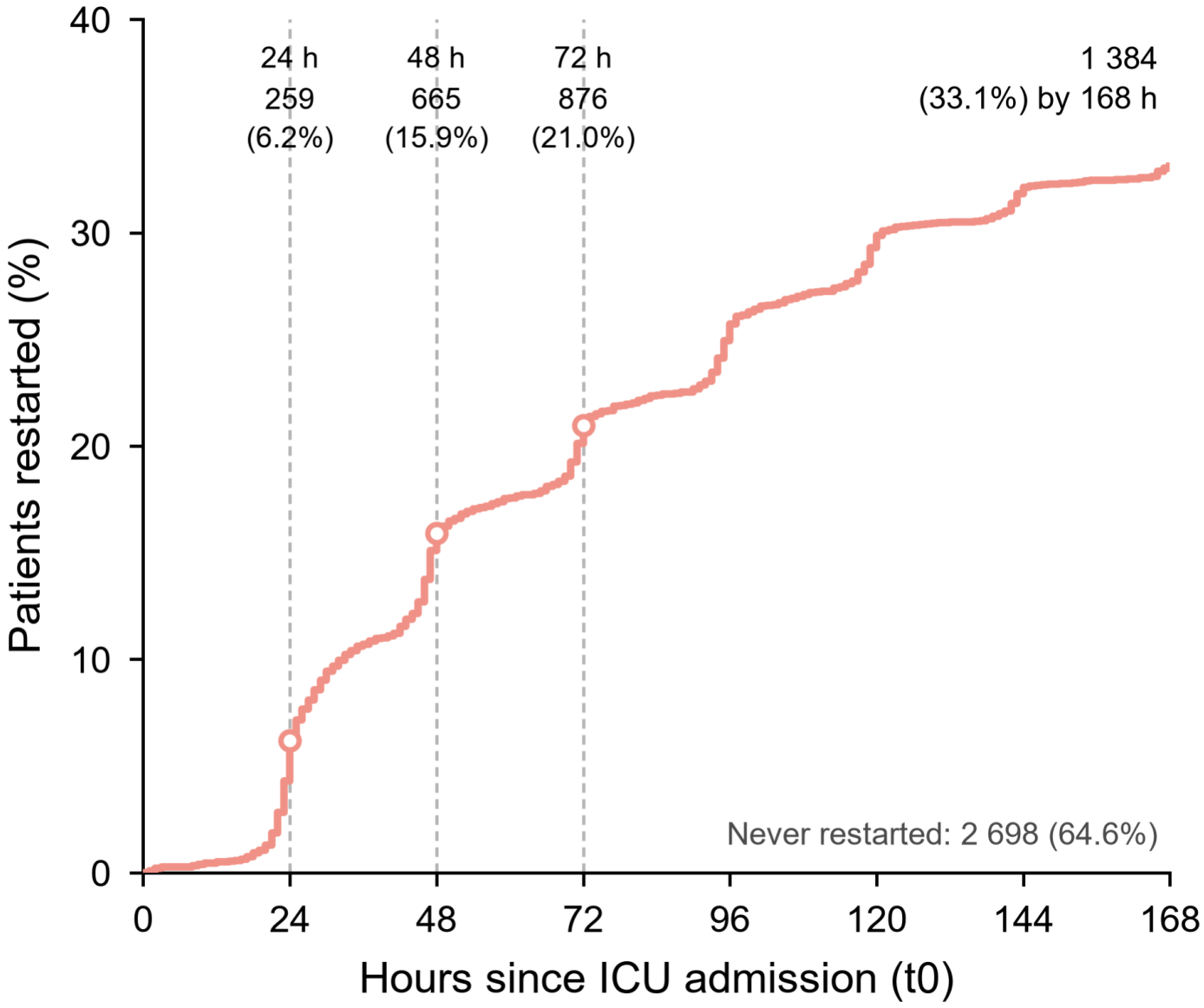


Figure 2

Time from ICU admission to postoperative ACEI/ARB restart

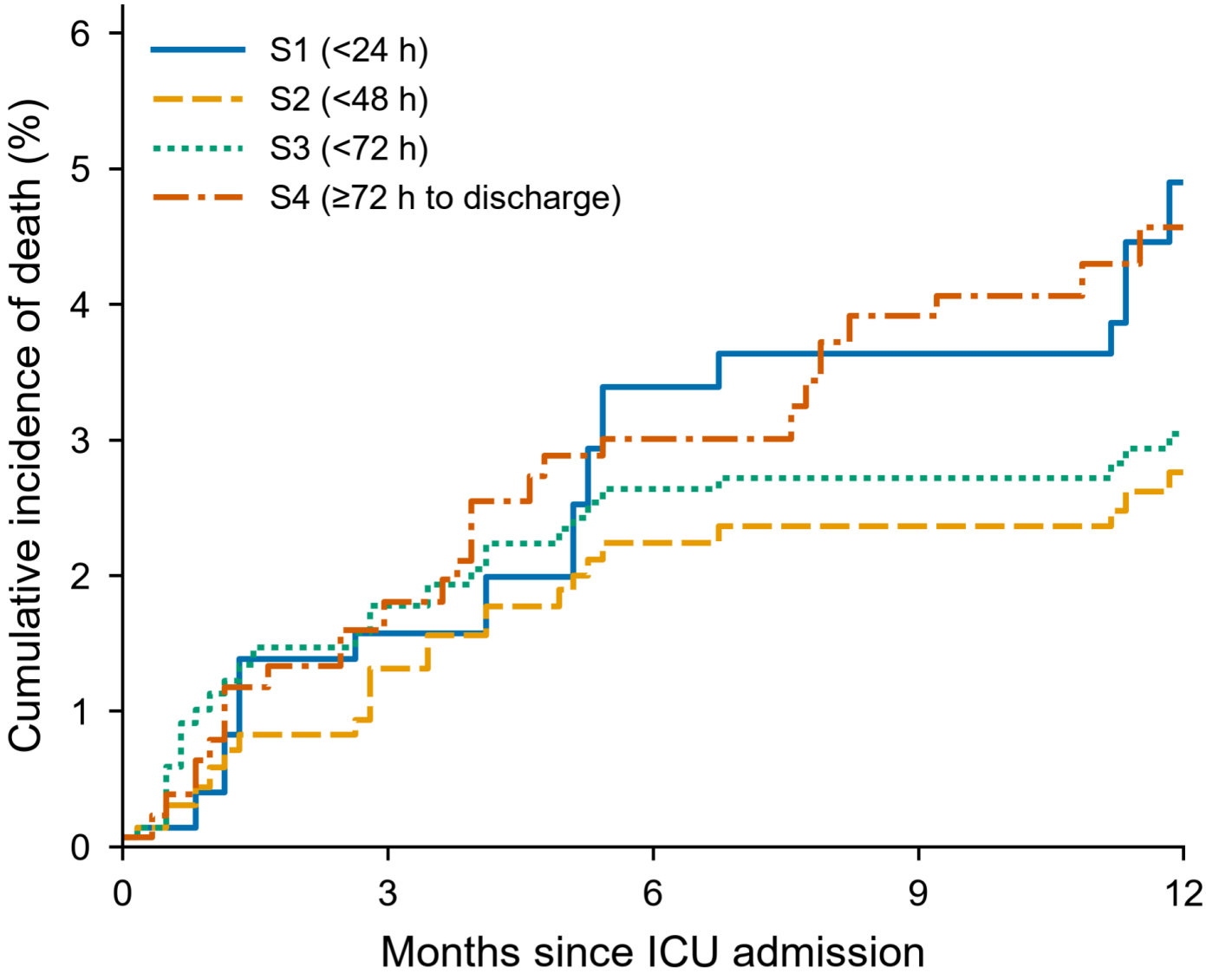


Figure 3

Weighted cumulative incidence of all-cause death

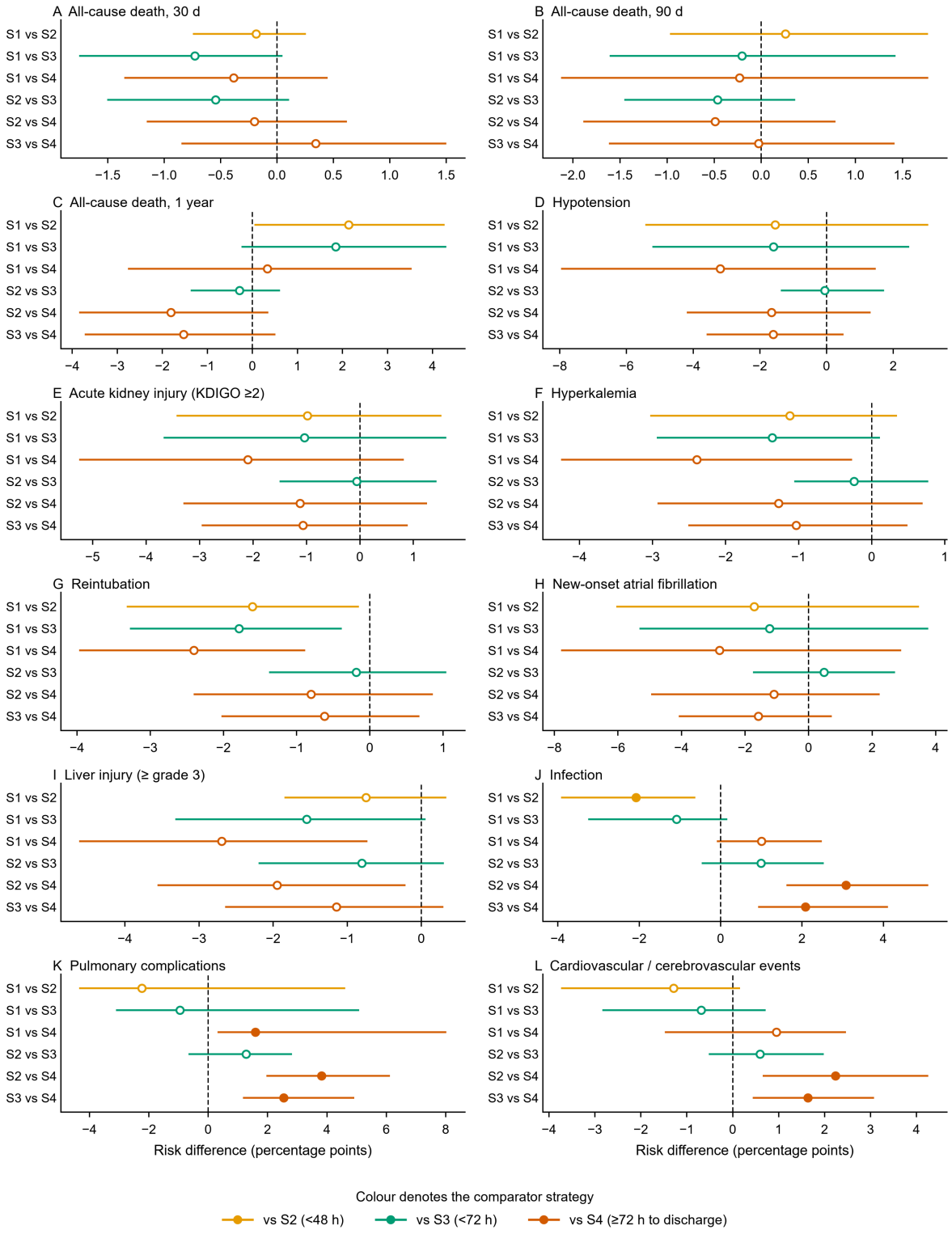


Figure 4

Weighted risk differences for all 12 outcomes and 6 pairwise strategy comparisons

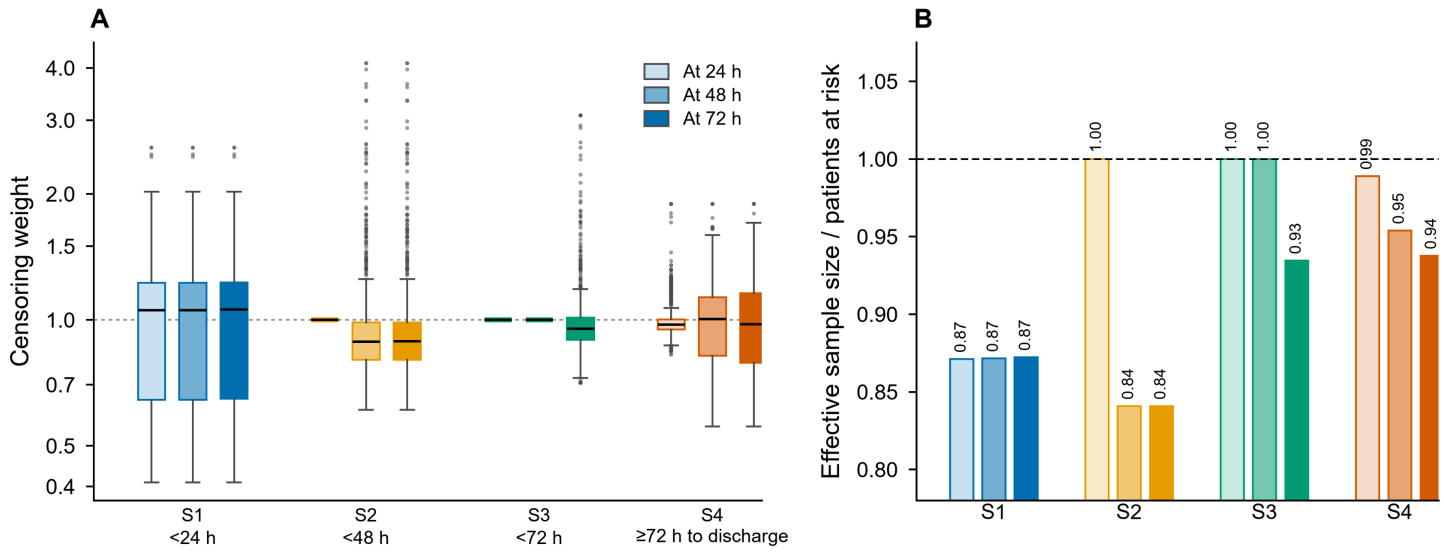


Figure 5

Distribution of censoring weights and effective sample size

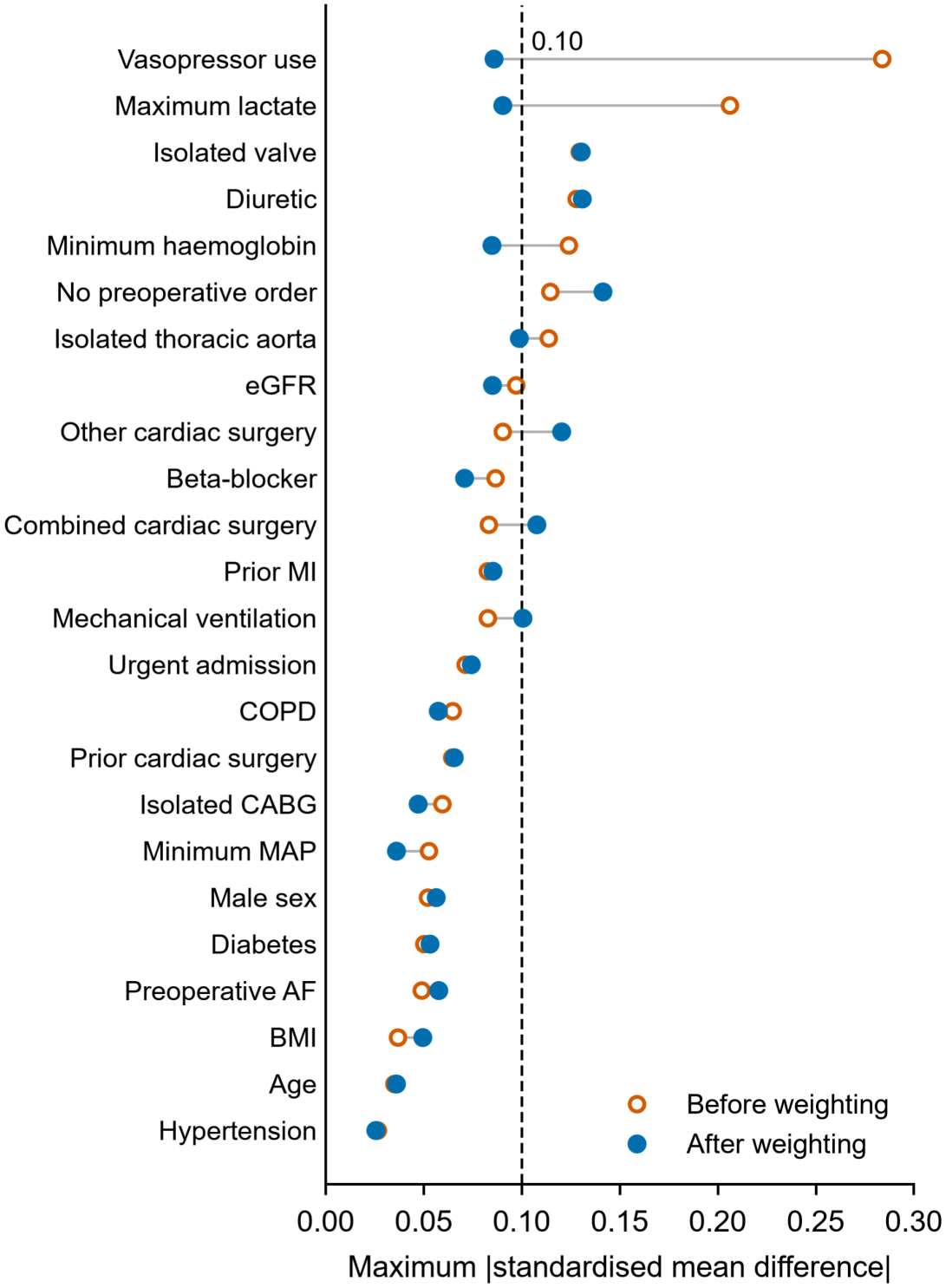


Figure 6

Covariate balance before and after weighting

Supplementary Files

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- SupplementaryMaterials.docx