Proton pump inhibitors versus histamine-2 receptor antagonists for stress ulcer prophylaxis during extracorporeal membrane oxygenation: a propensity score-matched analysis

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ABSTRACT

Purpose Patients receiving extracorporeal membrane oxygenation (ECMO) generally receive proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs) to avoid major gastrointestinal bleeding. Our aim was to compare outcomes between patients receiving PPIs and H2RAs for stress ulcer prophylaxis during ECMO.

Materials and methods We performed a retrospective cohort study using the Japanese Diagnosis Procedure Combination Database, using data recorded from 1 July 2010 to 31 March 2017. We defined patients who received PPIs within 2 days after starting ECMO as the PPIs group and those who received H2RAs within 2 days after starting ECMO as the H2RAs group. We performed propensity score matching to compare outcomes. The primary outcomes were gastrointestinal bleeding requiring endoscopic haemostasis and in-hospital mortality. The secondary outcomes were red blood cell transfusion, hospital-acquired pneumonia and Clostridium difficile infection during hospitalisation.

Results Of 11 328 eligible patients, 9738 received PPIs and 1590 received H2RAs. Propensity score matching created 1556 pairs. No significant differences were seen regarding endoscopic haemostasis (1.2% vs 0.8%; p=0.37), in-hospital mortality (53.0% vs 53.1%; p=0.94), red blood cell transfusion rates (91.4% vs 89.7%; p=0.11), hospital-acquired pneumonia (13.0% vs 12.4%; p=0.59) or C. difficile infection (0.1% vs 0.2%; p=0.32) between the PPIs and H2RAs groups, respectively.

Conclusion We found no differences in the evaluated outcomes between the PPIs and H2RAs groups. Both PPIs and H2RAs are treatment options for stress ulcer prophylaxis in patients undergoing ECMO.

PURPOSE

Extracorporeal membrane oxygenation (ECMO) therapy is widely used for circulatory and respiratory support for critically ill patients. Although the use of ECMO is increasing, in-hospital mortality and bleeding complications among critically ill patients receiving ECMO remain high. Clinically important gastrointestinal bleeding (CIGIB) often results in death because ECMO requires anticoagulants. To avoid CIGIB, patients receiving ECMO generally also receive stress ulcer prophylaxis drugs. The use of ECMO equipment in critically ill patients may result in gastrointestinal ischaemia because ECMO can change the blood flow. Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) are the main stress ulcer prophylactic drugs. The American Society of Health-System Pharmacists’ guidelines recommend using PPIs as the first-line drugs for critically ill patients. A systematic review of randomised controlled trials also showed that PPIs were superior to H2RAs in preventing CIGIB without increasing the risk of adverse effects.

Recently, some studies have thrown doubt on the efficacy of PPIs. In 2014, an observational study reported that PPIs were associated with a higher risk of CIGIB (OR, 2.24 (95% CI 1.81 to 2.76)) compared with H2RAs, in critically ill patients. In 2018, a larger observational study showed that PPIs were associated with a higher risk of CIGIB compared...
with $H_2$RAs in critically ill patients. A recent randomised controlled trial showed no difference in CIGIB between PPIs and $H_2$RAs; however, to our knowledge, no previous study has assessed the superiority of PPIs over $H_2$RAs in patients receiving ECMO.

The aim of the present study was to compare outcomes between PPIs and $H_2$RAs to prevent stress ulcers in patients receiving ECMO using a Japanese National Inpatient Database.

**MATERIALS AND METHODS**

The requirement to obtain patients’ informed consent was waived because of the anonymous nature of the datasets. Patients and the public were not involved in the design or planning of the study.

**Study design and data collection**

This retrospective cohort study was performed using the Japanese Diagnosis Procedure Combination Database, which comprises administrative claims and discharge abstract data from more than 1200 acute-care hospitals in Japan. The database covers approximately 90% of all tertiary-care emergency hospitals and includes the following patient variables: age, sex, weight, height, consciousness level, primary diagnosis, comorbidities at admission, postadmission complications, procedures, prescriptions and discharge status. The main diagnosis, primary diagnosis on admission, comorbidities present on admission and comorbidities diagnosed during each episode of hospitalisation are recorded using the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes, with text data in Japanese. A previous validation study for the database showed a high specificity for the recorded diagnoses and a high sensitivity and specificity for the recorded procedures.

**Study participants**

Data recorded from 1 July 2010 to 31 March 2017 in the database were used in the present study. We studied critically ill patients receiving ECMO and excluded patients (1) who were younger than 18 years of age, (2) who died or were discharged within 2 days of receiving ECMO, (3) who had a history of gastric ulcer or gastritis before stress ulcer prophylaxis, (4) who received sucralfate within 2 days of ECMO, (5) who underwent endoscopic haemostasis before ECMO, (6) who received neither PPIs nor $H_2$RAs, (7) who received both PPIs and $H_2$RAs within 2 days of ECMO (because gastrointestinal bleeding within 2 days of ECMO suggests existence of gastritis before ECMO) and (8) whose reason for receiving ECMO was unspecified. Eligible patients were divided into those who received PPIs within 2 days after starting ECMO (PPIs group) and those who received $H_2$RAs within 2 days after starting ECMO ($H_2$RAs group). We included patients receiving both PPIs and $H_2$RAs after 2 days of ECMO.

Patients who used PPIs first and then used $H_2$RAs were categorised to the PPIs group, and vice versa.

**Variables and outcomes**

For this study, we examined the following patient characteristics: age, sex, Japan Coma Scale (JCS) score, body mass index (kg/m²), Charlson Comorbidity Index score, fiscal year, aetiology (online supplemental table 1), ambulance use, academic hospital, cardiac surgery before ECMO, interventions (mechanical ventilation, continuous renal replacement therapy, chest tube drainage, intra-aortic balloon pumping, defibrillation, chest compression, tracheostomy, arterial pressure monitoring and hypothermia treatment) within 2 days of ECMO, drugs (dopamine, dobutamine, norepinephrine, epinephrine and vasopressin) within 2 days of ECMO and transfusion (red blood cells, fresh-frozen plasma, platelets and albumin) within 2 days of ECMO. The JCS score was categorised into four groups: 0 (alert), 1–3 (dizziness), 10–30 (somnolence) and 100–300 points (coma). JCS scores are well correlated with Glasgow Coma Scale scores, and a JCS score of 100 is equivalent to a Glasgow Coma Scale score of 6–9. Charlson Comorbidity Index scores predict the risk of death by weighting or classifying comorbidities.

Several validation studies for the Charlson Comorbidity Index have been reported. We identified diagnoses of hospital-acquired pneumonia with the ICD-10 codes J152, J159, J180, J181, J189, J209, J690 and J958. We also identified diagnoses of Clostridium difficile infection with the ICD-10 code A047.

The primary outcomes were gastrointestinal bleeding requiring endoscopic haemostasis and in-hospital mortality. The secondary outcomes were red blood cell transfusion, hospital-acquired pneumonia and C. difficile infection during hospitalisation.

**Statistical analysis**

We used propensity score matching to compare the outcomes between the PPIs and $H_2$RAs groups and a multivariable logistic regression model to predict propensity scores for receiving PPIs. Predictor variables included age, sex, fiscal year, admission to a teaching hospital, ambulance use, body mass index at admission, JCS at admission, Charlson Comorbidity Index, reason for ECMO, cardiac surgery before ECMO, interventions (mechanical ventilation, continuous renal replacement therapy, chest tube drainage, intra-aortic balloon pumping, defibrillation, chest compression, tracheostomy, arterial line and hypothermia treatment) within 2 days of ECMO, drugs (dopamine, dobutamine, norepinephrine, epinephrine and vasopressin) within 2 days of ECMO and transfusion (red blood cells, fresh-frozen plasma, platelets and albumin) within 2 days of ECMO.

One-to-one nearest-neighbour matching without replacement was performed for patients’ estimated propensity scores using a caliper width set at 20% of the SD of the propensity scores.
A standardised difference of $-10\%$ to $\leq 10\%$ was considered to denote negligible imbalances in the variables between the propensity score-matched PPIs and H$_2$RAs groups. We performed propensity score matching using the Stata (StataCorp) module PSMATCH2.

We used a generalised estimating equation approach for comparisons of the primary and secondary outcomes, accompanied by cluster-robust standard errors that treated both propensity score-matched pairs and individual hospitals as clusters. ORs and 95% CIs were calculated for the primary and secondary outcomes. These estimates were obtained by generalised estimating equation models with logit link functions, irrespective of outcome types. We performed sensitivity analyses using the variables within 1 day of ECMO instead of the variables within 2 days of ECMO.

We performed sensitivity analyses by the stabilised inverse probability of treatment weighting (IPTW) method to account for differences in baseline covariates between the groups. Stabilised IPTW is a propensity score-based method to adjust for measured potential confounding factors and creates a pseudodataset by preserving the sample size. Stabilised IPTW estimates the average treatment effects over a marginal distribution of measured covariates in the matched cohort.

Continuous variables are presented as medians and IQRs. Categorical variables are presented as numbers and percentages. Baseline characteristics and crude outcomes were compared using the Mann-Whitney test for continuous variables with a skewed distribution and the $\chi^2$ test or Fisher’s exact test for categorical variables between the groups.

The two-sided significance level for all tests was $p<0.05$. All analyses were performed using Stata/MP V.15 (StataCorp).

**Patient and public involvement**

Patients or members of the public were not involved in the design or implementation. Patients and the general public will be informed of the results via publication.

**RESULTS**

A total of 11 328 patients met the inclusion criteria during the study period. Of these, 9738 (86.0%) patients received PPIs and 1590 (14.0%) patients received H$_2$RAs (figure 1). Patients’ characteristics before and after propensity score matching are shown in table 1. Before propensity score matching, the PPIs group had higher proportions of patients with ischaemic heart disease (40.4% in the PPIs group and 34.7% in the H$_2$RAs group) and congestive heart failure (15.8% in the PPIs group and 12.2% in the H$_2$RAs group), whereas the H$_2$RAs group had higher proportions of patients with aortic dissection/aneurysm (5.4% in the PPIs group and 11.4% in the H$_2$RAs group) and trauma/intoxication (3.4% in the PPIs group and 7.0% in the H$_2$RAs group). The PPIs group was more likely to receive continuous renal replacement therapy (32.2% in the PPIs group and 25.4% in the H$_2$RAs group), intra-aortic balloon pumping (65.6% in the PPIs group and 49.1% in the H$_2$RAs group), norepinephrine (77.1% in the PPIs group and 69.9% in the H$_2$RAs group), and epinephrine (61.6% in the PPIs group and 55.6% in the H$_2$RAs group). The H$_2$RAs group was more likely to receive arterial blood pressure lines (84.7% in the PPIs group and 89.2% in the H$_2$RAs group), cardiac surgery (13.1% in the PPIs group and 28.5% in the H$_2$RAs group) and dopamine (56.4% in the PPIs group and 65.7% in the H$_2$RAs group). The proportions of patients receiving PPIs increased annually during the study period compared with the proportions of patients receiving H$_2$RAs. After propensity score matching, patients’ characteristics were well balanced between the two groups.

Crude in-hospital mortality and the proportion of patients receiving red blood cell transfusions were significantly higher in the PPIs group (57.2%) than H$_2$RAs group (52.6%) (table 2). The proportions of patients undergoing endoscopic haemostasis, developing hospital-acquired pneumonia and acquiring C. difficile infection did not differ significantly between the two groups. In the propensity score-matching analysis, no outcomes were significantly different between the groups (table 2).

A generalised estimating equation analysis after propensity score matching showed no significant differences in any outcomes between the PPIs and H$_2$RAs groups (table 3). The results of the sensitivity analyses using the variables within 1 day of ECMO were similar to those using the variables within 2 days (online supplemental table 2). The stabilised IPTW analysis also showed no significant differences in any of the outcomes (table 4).

**DISCUSSION**

The use of PPIs increased annually during our study period; however, our results showed no obvious benefits of PPIs regarding reducing the need for endoscopic haemostasis or in-hospital mortality. In addition, we found no significant differences in the number of transfusions, the proportions of patients developing in-hospital acquired pneumonia or the proportions of patients acquiring C. difficile infection.
### Table 1: Patients' backgrounds in the unmatched and propensity score-matched groups

| Table 1 | Patients' backgrounds in the unmatched and propensity score-matched groups |
|---------|-------------------------------------------------------------------------|
|         | Unmatched group | Propensity score-matched group |
|         | PPIs (n=9738) | H$_2$RAs (n=1590) | SD, % | PPIs (n=1556) | H$_2$RAs (n=1556) | SD, % |
| Age in years | 65 (53 to 73) | 66 (54 to 74) | −1.8 | 65 (54 to 73) | 65 (54 to 74) | −0.4 |
| Sex | Male | 7314 (75.1) | 1151 (72.4) | 6.1 | 1123 (72.2) | 1127 (72.4) | −0.6 |
| Consciousness | Alert (0) | 4623 (47.5) | 797 (50.1) | −5.7 | 770 (49.5) | 778 (50.0) | −1.0 |
| | Dizziness (1–3) | 881 (9.0) | 122 (7.7) | 4.9 | 133 (8.5) | 122 (7.8) | 2.6 |
| | Somnolence (10–30) | 449 (4.6) | 60 (3.8) | 4.1 | 63 (4.0) | 60 (3.9) | 1.0 |
| | Coma (100–300) | 3785 (38.9) | 611 (38.4) | 1.4 | 590 (37.9) | 596 (38.3) | −0.8 |
| Body mass index | <18.5 | 667 (6.8) | 105 (6.6) | 1.1 | 106 (6.8) | 104 (6.7) | 0.5 |
| | 18.5–22.9 | 4982 (51.2) | 842 (53.0) | −3.8 | 838 (53.9) | 823 (52.9) | 1.9 |
| | 23.0–24.9 | 2152 (22.1) | 355 (22.3) | −0.9 | 338 (21.7) | 347 (22.3) | −1.4 |
| | 25.0–29.9 | 661 (6.8) | 88 (5.5) | 5.6 | 88 (5.7) | 86 (5.5) | 0.6 |
| | ≥30.0 | 1276 (13.1) | 200 (12.6) | 1.9 | 186 (12.0) | 196 (12.6) | −2.0 |
| Charlson Comorbidity Index | 0 | 3806 (39.1) | 665 (41.8) | −5.1 | 641 (41.2) | 644 (41.4) | −0.4 |
| | 1 | 3319 (34.1) | 536 (33.7) | 0.6 | 524 (33.7) | 526 (33.8) | −0.3 |
| | 2 | 1524 (15.7) | 237 (14.9) | 1.9 | 257 (16.5) | 235 (15.1) | 3.9 |
| | 3 | 694 (7.1) | 87 (5.5) | 6.6 | 79 (5.1) | 87 (5.6) | −2.3 |
| | >4 | 395 (4.1) | 65 (4.1) | −0.2 | 55 (3.5) | 64 (4.1) | −3.0 |
| Fiscal year | July 2010–Mar 2011 | 519 (5.3) | 200 (12.6) | −25.7 | 226 (14.5) | 188 (12.1) | 7.2 |
| | April 2011–March 2012 | 1036 (10.6) | 284 (17.9) | −20.9 | 322 (20.7) | 277 (17.8) | 7.3 |
| | April 2012–March 2013 | 1230 (12.6) | 298 (18.7) | −17.1 | 289 (18.6) | 291 (18.7) | −0.3 |
| | April 2013–March 2014 | 1506 (15.5) | 218 (13.7) | 4.8 | 213 (13.7) | 218 (14.0) | −0.9 |
| | April 2014–March 2015 | 1708 (17.5) | 232 (14.6) | 8.9 | 215 (13.8) | 226 (14.5) | −2.0 |
| | April 2015–March 2016 | 1851 (19.0) | 196 (12.3) | 18.5 | 163 (10.5) | 195 (12.5) | −6.4 |
| | April 2016–March 2017 | 1888 (19.4) | 162 (10.2) | 26.0 | 128 (8.2) | 161 (10.3) | −7.3 |
| Aetiology | Postcardiac arrest | 1980 (20.3) | 325 (20.4) | 0.3 | 310 (19.9) | 319 (20.5) | −1.4 |
| | Ischaemic heart disease | 3937 (40.4) | 552 (34.7) | 11.5 | 504 (32.4) | 542 (34.8) | −5.2 |
| | Arrhythmia | 529 (5.4) | 78 (4.9) | 2.2 | 75 (4.8) | 76 (4.9) | −0.3 |
| | Congestive heart failure | 1543 (15.8) | 194 (12.2) | 10.4 | 186 (12.0) | 194 (12.5) | −1.6 |
| | Aortic dissection/aneurysm | 528 (5.4) | 182 (11.4) | −22.0 | 194 (12.5) | 175 (11.2) | 3.8 |
| | Pulmonary embolism | 373 (3.8) | 61 (3.8) | −0.1 | 70 (4.5) | 61 (3.9) | 2.9 |
| | Septic shock | 106 (1.1) | 20 (1.3) | −1.6 | 21 (1.3) | 20 (1.3) | 0.6 |
| | ARDS/ARF | 207 (2.1) | 37 (2.3) | −1.0 | 39 (2.5) | 36 (2.3) | 1.3 |
| | Pneumonia | 201 (2.1) | 30 (1.9) | 1.2 | 39 (2.5) | 30 (1.9) | 3.9 |
| | Trauma/intoxication | 334 (3.4) | 111 (7.0) | −16.0 | 118 (7.6) | 103 (6.6) | 3.8 |
| | Ambulance use | 7032 (72.3) | 1063 (67.2) | 11.2 | 1024 (65.8) | 1054 (67.7) | −4.1 |
| | Academic hospital | 8844 (90.8) | 1398 (87.9) | 9.50 | 1366 (87.8) | 1370 (88.0) | −0.8 |
| | Mechanical ventilation started within 2 days of ECMO | 8802 (90.4) | 1397 (87.9) | 8.3 | 1339 (86.1) | 1373 (88.2) | −6.5 |
| | CRRT started within 2 days of ECMO | 3133 (32.2) | 404 (25.4) | 15.0 | 361 (23.2) | 399 (25.6) | −5.7 |

Continued
difficile infection between the groups. The stabilised IPTW analysis also showed no differences between the groups; therefore, our results are robust.

To the best of our knowledge, ours is the first report comparing PPIs and H2RAs for stress ulcer prophylaxis during ECMO. Most previous studies comparing PPIs and H2RAs focused on critically ill patients with heterogeneous backgrounds.3 CIGIB is pronounced in ECMO patients because of the required high doses of heparin and the mechanically high blood flow rates. Thus, complications related to haemorrhage in ECMO are frequent and have a significant negative impact on outcomes.23

Our results showed no significant differences for in-hospital mortality or the proportions of patients requiring endoscopic haemostasis, similar to results in previous randomised controlled trials.24–26 Some previous studies have shown conflicting results regarding the efficacy of PPIs and H2RAs for stress ulcer prophylaxis.7 27 In the present study, we found no significant difference in C. difficile infection rates between patients receiving PPIs versus H2RAs for stress ulcer prophylaxis. Previous studies showed that stress ulcer medical prophylaxis increased the risk of C. difficile infection, but it remains unclear whether the risk of C. difficile infection differs between patients receiving PPIs versus H2RAs.28 29 C. difficile infection and community-acquired pneumonia may occur because of gastric acid suppression. Our results indicate that either PPIs or H2RAs can be used.

In a previous study, endoscopic therapy was feasible and helped to achieve complete bleeding control.

### Table 1 Continued

| Outcome                                | Unmatched group | Propensity score-matched group |
|----------------------------------------|-----------------|--------------------------------|
|                                        | PPIs (n=9738)   | H2RAs (n=1590)                | PPIs (n=1556) | H2RAs (n=1556) |
|                                        | SD, %           | SD, %                         | SD, %         | SD, %           |
| Arterial blood pressure line started within 2 days of ECMO | 8252 (84.7)     | 1419 (89.2)                   | −13.3         | 1395 (89.7)     | 1386 (89.1) | 1.9   |
| Intra-aortic balloon pumping           | 6385 (65.6)     | 780 (49.1)                    | 34.0          | 700 (45.0)      | 773 (49.7) | −9.4  |
| Cardiac surgery followed by ECMO       | 1272 (13.1)     | 453 (28.5)                    | −39.0         | 479 (30.8)      | 432 (27.8) | 6.6   |
| Drugs started within 2 days of ECMO    |                 |                               |               |                 |
| Dopamine                               | 5488 (56.4)     | 1045 (65.7)                   | −20.0         | 1051 (67.5)     | 1023 (65.7) | 3.8   |
| Dobutamine                             | 5501 (56.5)     | 932 (58.6)                    | −3.9          | 907 (58.5)      | 908 (58.4) | −0.1  |
| Norepinephrine                         | 7506 (77.1)     | 1112 (69.9)                   | 16.6          | 1080 (69.4)     | 1095 (70.4) | −2.1  |
| Vasopressin                            | 804 (8.3)       | 110 (6.9)                     | 5.2           | 88 (5.7)        | 109 (7.0) | −5.5  |
| Epinephrine                            | 6002 (61.6)     | 884 (55.6)                    | 12.4          | 84 (54.0)       | 871 (56.0) | −3.9  |
| Transfusion started within 2 days of ECMO |               |                               |               |                 |
| Red blood cells                        | 7854 (80.7)     | 1255 (78.9)                   | 4.2           | 1245 (80.0)     | 1228 (78.9) | 2.7   |
| Fresh-frozen plasma                    | 6191 (63.6)     | 978 (61.5)                    | 4.4           | 937 (60.2)      | 959 (61.6) | −2.9  |
| Platelets                              | 3445 (35.4)     | 610 (38.4)                    | −6.3          | 624 (40.1)      | 597 (38.4) | 3.6   |
| Albumin                                | 6535 (67.1)     | 1047 (65.8)                   | 2.5           | 1012 (65.0)     | 1029 (66.1) | −2.3  |

Data are presented as number (%) except for median (IQR) for age.

ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; H2RAs, histamine-2 receptor antagonists; PPIs, proton pump inhibitors.

### Table 2 Outcomes in the unmatched and propensity score-matched groups

| Outcome                                | Unmatched group | Propensity score-matched group |
|----------------------------------------|-----------------|--------------------------------|
|                                        | PPIs (n=9738)   | H2RAs (n=1590)                | PPIs (n=1556) | H2RAs (n=1556) |
|                                        | P value         | P value                       |               |               |
| Endoscopic haemostasis                 | 112 (1.2)       | 14 (0.9)                      | 0.34          | 18 (1.2)       | 13 (0.8) | 0.37  |
| In-hospital mortality                  | 5573 (57.2)     | 837 (52.6)                    | <0.001        | 824 (53.0)     | 826 (53.1) | 0.94  |
| RBC transfusion                        | 9052 (93.0)     | 1424 (89.6)                   | <0.001        | 1422 (91.4)     | 1396 (89.7) | 0.11  |
| Hospital-acquired pneumonia            | 1363 (14.0)     | 197 (12.4)                    | 0.085         | 203 (13.0)      | 193 (12.4) | 0.59  |
| Clostridium difficile infection         | 26 (0.3)        | 3 (0.2)                       | 0.57          | 1 (0.1)        | 3 (0.2) | 0.32  |

Data are presented as number (%).

H2RAs, histamine-2 receptor antagonists; PPIs, proton pump inhibitors; RBC, red blood cells.
and the data showed that it may contribute to reduced mortality.30 Our study showed no differences in mortality between the groups, which may have occurred because of the similar proportions of patients achieving endoscopic haemostasis.

This study has several limitations. First, information on the type of gastric ulcer and laboratory data such as serum haemoglobin levels were not available in the Diagnosis Procedure Combination Database. Second, the proportion of patients with gastrointestinal bleeding may have been underestimated because we included only patients with severe bleeding requiring endoscopic haemostasis. Third, we could not exclude all patients with previously diagnosed gastric ulcers or gastritis. Finally, this was a retrospective study, and recorded diagnoses were less well validated than those in prospective registries.

### Table 3 Logistic regression analyses of the outcomes fitted using with a generalised estimation equations for the outcomes in the propensity-score-matched population

| Study outcome                  | H2RAs Reference | PPIs Reference | OR (95% CI)    | P value |
|-------------------------------|-----------------|----------------|----------------|---------|
| Endoscopic haemostasis        | H2RAs           | PPIs           | 1.39 (0.65 to 2.99) | 0.40    |
| In-hospital mortality         | H2RAs           | PPIs           | 0.99 (0.79 to 1.25) | 0.96    |
| RBC transfusion rate          | H2RAs           | PPIs           | 1.22 (0.89 to 1.66) | 0.22    |
| Hospital-acquired pneumonia   | H2RAs           | PPIs           | 1.06 (0.84 to 1.34) | 0.63    |
| *Clostridium difficile* infection | H2RAs             | PPIs           | 0.38 (0.03 to 3.19) | 0.34    |

Data are presented as ORs (95% CI). H2RAs, histamine-2 receptor antagonists; PPIs, proton pump inhibitors; RBC, red blood cells.

### Table 4 Logistic regression analyses of fitted with generalised linear model for the outcomes in stabilised inverse probability of treatment weighted population

| Study outcome                  | H2RAs Reference | PPIs Reference | OR (95% CI)    | P value |
|-------------------------------|-----------------|----------------|----------------|---------|
| Endoscopic haemostasis        | H2RAs           | PPIs           | 1.48 (0.74 to 2.99) | 0.27    |
| In-hospital mortality         | H2RAs           | PPIs           | 1.00 (0.85 to 1.17) | 0.98    |
| RBC transfusion rate          | H2RAs           | PPIs           | 1.04 (0.81 to 1.33) | 0.77    |
| Hospital-acquired pneumonia   | H2RAs           | PPIs           | 1.01 (0.82 to 1.25) | 0.92    |
| *Clostridium difficile* infection | H2RAs             | PPIs           | 1.63 (0.47 to 5.67) | 0.44    |

Data are presented as ORs (95% CI). H2RAs, histamine-2 receptor antagonists; PPIs, proton pump inhibitors; RBC, red blood cells.

**CONCLUSIONS**

No significant differences in endoscopic haemostasis or in-hospital mortality were shown between the PPIs and H2RAs groups in this study. Both PPIs and H2RAs are treatment options for stress ulcer prophylaxis in patients receiving ECMO.

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**Data availability statement** Data may be obtained from a third party and are not publicly available.

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