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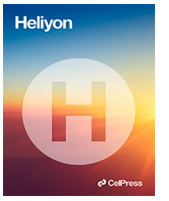

Research article

# Superiority of bivalirudin over heparin anticoagulation therapy for extracorporeal membrane oxygenation? Too early to draw conclusions

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ABSTRACT

*Background:* We aimed to compare the efficacy and safety of bivalirudin versus heparin as the anticoagulant in patients undergoing extracorporeal membrane oxygenation (ECMO).

*Methods:* We conducted a search in PubMed, Embase and the Cochrane Library for all the studies in which bivalirudin was compared to heparin as the anticoagulant for ECMO. Efficacy outcomes were defined as the time to reach therapeutic levels, time within therapeutic range (TTR), thrombotic events, circuit thrombosis, circuit exchanges. Safety outcomes were reported as heparin-induced thrombocytopenia (HIT), major bleeding events, minor bleeding events. Other outcomes included hospital length of stay (LOS), ICU LOS, mortality, 30-day mortality and in-hospital mortality.

*Results:* Ten studies with 1091 patients were included for meta-analysis. A significant reduction in thrombotic events [OR 0.51, 95%CI 0.36,0.73, $p = 0.0002$, $I^2 = 0\%$], major bleeding events [OR 0.31, 95%CI 0.10,0.92, $p = 0.04$, $I^2 = 75\%$] and in-hospital mortality [OR 0.63, 95%CI 0.44,0.89, $p = 0.009$, $I^2 = 0\%$] treated with bivalirudin were found compared with heparin. There were no significant differences between groups regarding the time to reach therapeutic levels [MD 3.53, 95%CI −4.02,11.09, $p = 0.36$, $I^2 = 49\%$], TTR [MD 8.64, 95%CI −1.72,18.65, $p = 0.10$, $I^2 = 77\%$], circuit exchanges [OR 0.92, 95%CI 0.27,3.12, $p = 0.90$, $I^2 = 38\%$], HIT [OR 0.25, 95%CI 0.02,2.52, $p = 0.24$, $I^2 = 0\%$], minor bleeding events [OR 0.93, 95%CI 0.38,2.29, $p = 0.87$, $I^2 = 0\%$], hospital LOS [MD −2.93, 95%CI -9.01,3.15, $p = 0.34$, $I^2 = 45\%$], ICU LOS [MD −4.22, 95% CI -10.07,1.62, $p = 0.16$, $I^2 = 0\%$], mortality [OR 1.84, 95%CI 0.58,5.85, $p = 0.30$, $I^2 = 60\%$] and 30-day mortality [OR 0.75, 95%CI 0.38,1.48, $p = 0.41$, $I^2 = 0\%$].

*Conclusion:* Bivalirudin probably be a potential choice for ECMO anticoagulation. However, based on the included studies' limitation, the superiority of bivalirudin over heparin for anticoagulation in the ECMO population still require further prospective randomized controlled studies before a definite conclusion.

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## 1. Introduction

Extracorporeal membrane oxygenation (ECMO) is widely used for the circulatory and respiratory support [1]. Anticoagulant is an essential component for patients undergoing extracorporeal membrane oxygenation [2]. Thrombosis events and bleeding events are common complications [3]. Heparin remained to be the primary anticoagulant for ECMO in guidelines due to ease of titration and monitoring, ease of reversibility and low cost [4]. Despite these advantages, heparin has its limitations. First, heparin requires the cofactor antithrombin for efficacy [5]. Second, it may cause heparin-induced thrombocytopenia due to platelet dysfunction and its highly antigenic, with mortality as high as 20%–30% [6]. Third, it only inhibits free thrombin.

In recent years, bivalirudin, a direct thrombin inhibitor (DTI), has been used as an alternative for patients requiring ECMO [7]. As a DTI, bivalirudin showed the following advantages. First, bivalirudin does not require the antithrombin for efficacy as it binds directly to thrombin, allowing for more consistent effect. Second, it does not cause the occurrence of HIT. Third, it inhibits both circulating and clot-bound thrombin. Although some studies regarding to the use of bivalirudin as an anticoagulant in ECMO have been published, the reports have been limited. This meta-analysis will review bivalirudin anticoagulation strategies in ECMO patients.

## 2. Materials and methods

### 2.1. Search

We did an electronic search from January 1, 2010 to September 1, 2021 of the following databases: PubMed, Embase, and the Cochrane Library. The keywords “Bivalirudin”, “Heparin” and “Extracorporeal membrane oxygenation” were searched. Two investigators (JG and HJ Y) independently screened the titles and abstracts to ascertain whether each study met the eligibility criteria. The full texts of the identified eligible articles were then evaluated to determine whether they should be included in the analysis. Disagreements between the two reviewers were resolved by consensus.

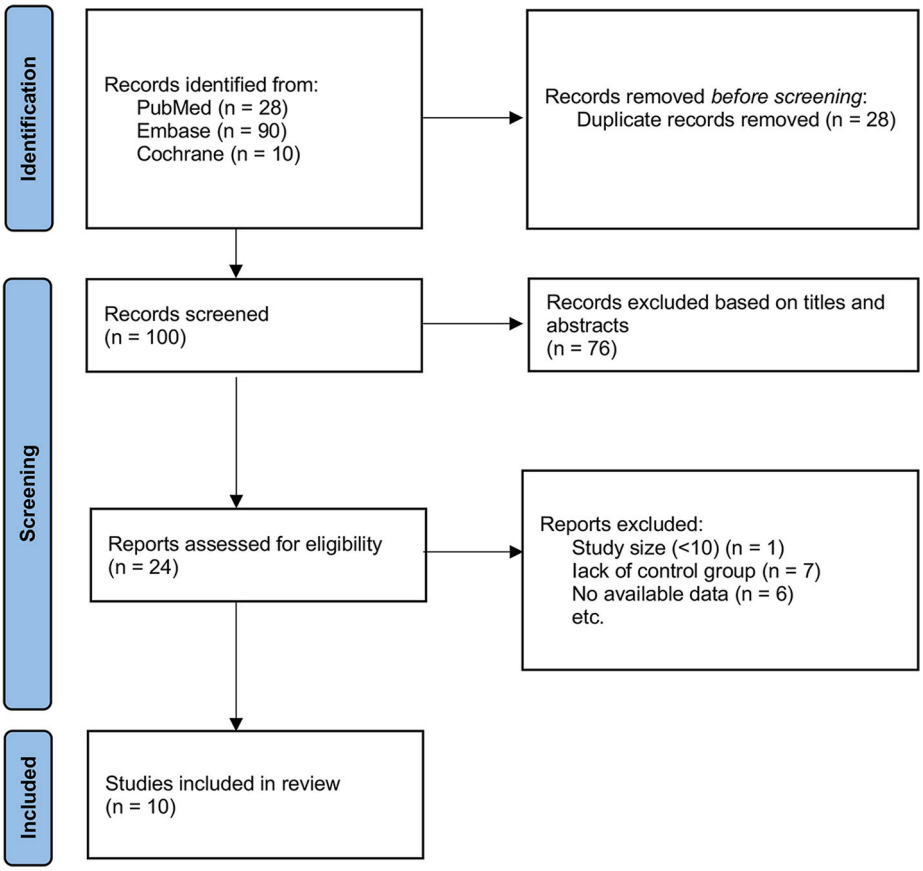


**Fig. 1.** Flow chart of the search process.

### 2.2. Selection criteria

Inclusion criteria: (a) the study was prospectively or retrospectively designed; (b) patients were included who were received either heparin or bivalirudin therapy; We excluded studies that (a) studies reported outcomes with bivalirudin therapy without heparin therapy for comparison; (b) lacked data detailing the outcomes included in our analysis.

### 2.3. Data abstraction and quality appraisal

Surname of the first author, year of publication, country of origin, study period, study design, type, number of patients, study group, control group, targeted ACT/APTT, age, gender, ECMO type and ECMO duration were extracted for each potentially included study. The data extraction was conducted by two independent investigators (JG and HJ Y). Any discrepancy was solved by discussion and intervention of a senior investigator. The validity of included studies was appraised with the Newcastle-Ottawa scale [8].

### 2.4. Data analysis

Treatment effects were expressed as odds ratios (OR) for binary outcomes and mean difference (MD) for quantitative outcomes. Between-study heterogeneity was assessed using $I^2$ statistic and $p$ value. The fixed-effect model was applied if no or low significant heterogeneity was present. To explore heterogeneity, we did subgroup analysis and sensitivity analyses. All statistical analyses were conducted with RevMan software (version 5.3) and Stata software (version 14.0). A two-sided $p$ value$<$0.05 was considered statistically significant.

## 3. Results

### 3.1. Literature search

Literature searches identified 128 potentially relevant citations (28 in PubMed, 90 in Embase, 10 in Cochrane Library), which, after thorough appraisal, yielded a total of 10 eligible studies [9, 10, 11, 12, 13, 14, 15, 16, 17, 18] (Fig. 1).

### 3.2. Demographic characteristics and quality assessment

The characteristic of studies reporting bivalirudin versus heparin as an anticoagulant for ECMO patients were summarized in Table 1 and Table 2. 10 studies reported on 1091 patients treating with bivalirudin or heparin as an anticoagulant for ECMO patients. Bivalirudin was administered in 405 patients while 686 patients were treated with heparin. All studies were published after 2011. All studies were retrospective review. There were 2 studies from Italy, 8 studies from US. The mean/median age and the sex of the patients were extractable in 8 studies with the mean/median age ranging from 12 months to 56.8 years. 589 (61.4%) of the patients were male

**Table 1**
**Characteristics of the studies included**.

| Author | Year | Country | Study period | Study design | Type | No. of patients | Study group | Targeted ACT/APTT |
|---|---|---|---|---|---|---|---|---|
| Ranucci | 2011 | Italy | 2008–2011 | NRCT | Children/ Adults | 21 | Bivalirudin infusion 0.03–0.05 mg/kg/h without bolus | ACT:160–180s, APTT:50–80s |
| Pieri | 2014 | Italy | 2008–2011 | NRCT | Adults | 20 | Bivalirudin infusion 0.025 mg/ kg/h without bolus | 45–60s |
| Berei | 2017 | US | 2012–2015 | NRCT | Adults | 72 | Bivalirudin infusion 0.04 mg/ kg/h without bolus | APTT:low-intensity (45–65s)/high-intensity (60–80s) |
| Macielak | 2019 | US | 2012–2017 | NRCT | Adults | 110 | Bivalirudin infusion 0.01–0.1 mg/kg/h | 60–80s |
| Hamzah | 2020 | US | 2014–2018 | NRCT | Children | 32 | Bivalirudin infusion 0.3mg/kg/ h; if CrCl<60 ml/min, 0.15 mg/ kg/h | 58–78s |
| Kaseer | 2020 | US | 2013–2018 | NRCT | Adults | 52 | Bivalirudin infusion 0.1 mg/kg/ h | 50–90s |
| Machado | 2020 | US | 2015–2019 | NRCT | Children | 32 | Bivalirudin infusion 0.1 mg/kg/ h | na. |
| Rivosecchi | 2021 | US | 2013–2020 | NRCT | Adults | 295 | na. | na. |
| Seelhammer | 2021 | US | 2014–2019 | NRCT | Adults | 333 | Bivalirudin infusion 0.02–0.15 mg/kg/h | 60–80s |
| Seelhammer | 2021 | US | 2014–2019 | NRCT | Children | 89 | Bivalirudin infusion 0.02–0.15 mg/kg/h | 60–80s |
| Kaushik | 2021 | US | 2016–2019 | NRCT | Children | 35 | Bivalirudin infusion 0.5 mg/kg/ h | 60–90s |

na. not available; NRCT non-randomized controlled trial.

**Table 2**
Baseline charateristics of patients.

| Author | Year | Total | B | H | Age | Male Sex, No (%) | Indications for ECMO | V-A ECMO | V–V ECMO | ECMO duration |
|---|---|---|---|---|---|---|---|---|---|---|
| Ranucci | 2011 | 21 | 13 | 8 | 27.9 (27.5) (y) | na. | na. | na. | na. | 119 (71.6) (h) |
| Pieri | 2014 | 20 | 10 | 10 | 56.8 (13.5) (y) | 16 (80.0) | na. | 10 (50) | 10 (50) | na. |
| Berei | 2017 | 72 | 44 | 28 | 55.5 (14.3) (y) | 47 (65.3) | Cardiogenic: 51 (70.8%)<br>Septic shock: 11 (15.3%)<br>Respiratory: 4 (5.6%)<br>Mixed: 6 (8.3%) | 66 (91.7) | 6 (8.3) | na. |
| Macielak | 2019 | 110 | 10 | 100 | 52.0 (14.0) (y) | na. | na. | na. | na. | 7.0 (4.6) (d) |
| Hamzah | 2020 | 32 | 16 | 16 | 12 (0–212) (m) | 14 (44) | na. | 29 (90.6) | 3 (9.4) | 106 (32–419) (h) |
| Kaseer | 2020 | 52 | 19 | 33 | 55 (18–83) (y) | 37 (71.2) | Cardiogenic shock: 15 (28.9%)<br>Respiratory failure: 24 (46.2%)<br>Transplant: 17 (32.7%)<br>Other:1 (1.9%) | 28 (53.8) | 24 (46.2) | 10 (3–70) (d) |
| Machado | 2020 | 32 | 18 | 14 | 37.7 (65.8) (m) | 16 (50) | na. | 30 (93.8) | 1 (3.1) | 161.4 (85.0) (h) |
| Rivosecchi | 2021 | 295 | 133 | 162 | 49 (36–61) (y) | 176 (59.7) | Respiratory failure: 145 (58.3%)<br>Transplant: 108 (36.6%)<br>Thoracic surgery:20 (6.8%)<br>Other:22 (7.5%) | 0 (0) | 295 (100) | 234.4 (311.7) (h) |
| Seelhammer | 2021 | 333 | 110 | 223 | na. | 217 (65.2) | Post cardiotomy: 141 (42.3%)<br>Cardiac: 76 (22.8%)<br>Respiratory: 64 (19.2%)<br>Resuscitation: 47 (14.1%)<br>Transplant:5 (1.5%) | 277 (83.2) | 56 (16.8) | na. |
| Seelhammer | 2021 | 89 | 24 | 65 | na. | 48 (53.9) | Post cardiotomy: 21 (23.6%)<br>Cardiac: 24 (27.0%)<br>Respiratory: 22 (24.7%)<br>ECPR: 22 (24.7%) | 81 (91.0) | 8 (9.0) | na. |
| Kaushik | 2021 | 35 | 8 | 27 | na. | 18 (51.4) | na. | 30 (85.7) | 4 (11.4) | na. |

na. not available; V-A veno-arterial; V-V veno-venous; ECMO extracorporeal membrane B Bivalirudin; H Heparin.

**Table 3**
**Outcomes in the meta-analysis**.

| Outcomes | No. of studies | No. of patients | OR or MD (95%CI) | *P* | Heterogeneity | |
|---|---|---|---|---|---|---|
| | | | | | Q (*p* value) | $I^2$ (%) |
| The time to reach therapeutic levels | 4 | 127 | 3.53 (-4.02,11.09) | 0.36 | 0.12 | 49 |
| TTR | 4 | 249 | 8.64 (-1.72,18.65) | 0.10 | 0.005 | 77 |
| Thrombotic events | 7 | 925 | 0.51 (0.36,0.73) | 0.0002 | 0.74 | 0 |
| Circuit thrombosis | 4 | 399 | 0.48 (0.29,0.78) | 0.003 | 0.71 | 0 |
| Circuit change | 2 | 67 | 0.92 (0.27,3.12) | 0.90 | 0.20 | 38 |
| HIT | 3 | 124 | 0.25 (0.02,2.52) | 0.24 | 0.97 | 0 |
| Major bleeding events | 7 | 538 | 0.31 (0.10,0.92) | 0.04 | 0.0005 | 75 |
| Minor bleeding events | 3 | 127 | 0.93 (0.38,2.29) | 0.87 | 0.59 | 0 |
| Hospital LOS | 5 | 934 | −2.93 (-9.01,3.15) | 0.34 | 0.11 | 45 |
| ICU LOS | 2 | 145 | −4.22 (-10.07,1.62) | 0.16 | 0.95 | 0 |
| Mortality | 2 | 55 | 1.84 (0.58,5.85) | 0.30 | 0.11 | 60 |
| 30-day mortality | 3 | 156 | 0.75 (0.38,1.48) | 0.41 | 0.45 | 0 |
| In-hospital mortality | 4 | 578 | 0.63 (0.44,0.89) | 0.009 | | 0 |

**TTR time within therapeutic range; HIT heparin-induced thrombocytopenia; LOS length of stay**.

(8 studies). 551 patients received veno-arterial (VA) ECMO, and 407 patients received veno-venous (VV) ECMO (8 studies). The mean/median ECMO duration ranged from 106 h to 10 days (Tables 1 and 2). The quality assessment was displayed in eTable S1 (see Table 3).

### 3.3. Primary meta-analysis

#### 3.3.1. The bivalirudin regimens during ECMO

The loading dose of bivalirudin was not administered in our review. The maintenance infusion dosages of bivalirudin ranged from 0.01 mg/kg/h to 0.5 mg/kg/h. APTT and ACT were reported in 8 and 1 studies respectively. The targeted APTT ranged from 45 to 90s while the targeted ACT ranged from 160 to 180s (Table 1).

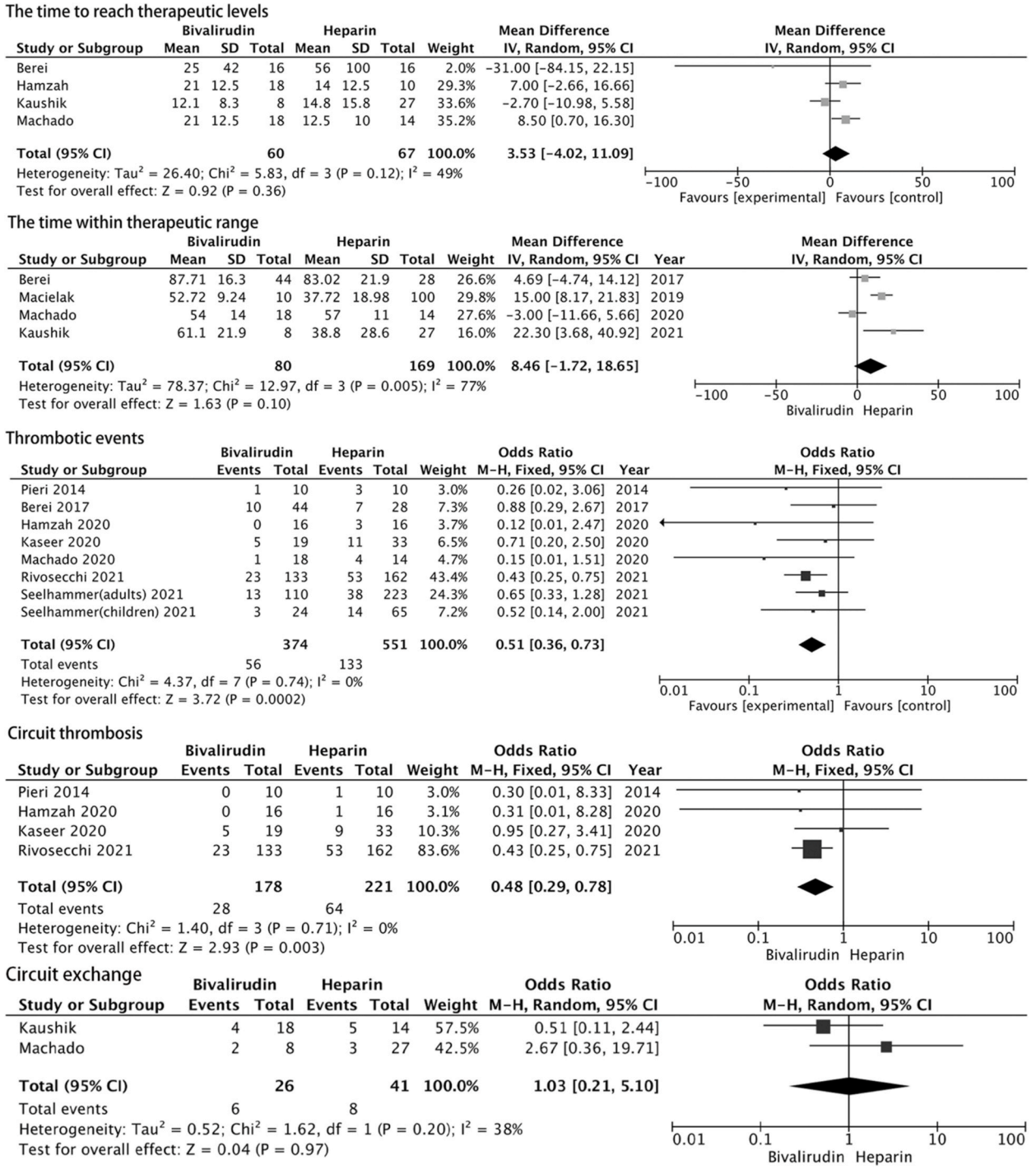


**Fig. 2.** Forest plot for the time to reach therapeutic levels, TTR, thrombotic events, circuit thrombosis and circuit exchanges.

### 3.3.2. The efficacy of bivalirudin versus heparin as ECMO anticoagulant

The time to reach therapeutic levels in patients treated with bivalirudin was similar to those with heparin [MD 3.53, 95%confidence interval (CI)-4.02, 11.09, $p = 0.36$, $I^2 = 49\%$]. There was no statistically significant difference in the time within therapeutic range (TTR) [MD 8.64, 95%CI −1.72,18.65, $p = 0.10$, $I^2 = 77\%$]. A significant reduction in thrombotic events treated with bivalirudin was found compared with heparin [OR 0.51, 95%CI 0.36,0.73, $p = 0.0002$, $I^2 = 0\%$] (The definition of thrombotic events was described in eTable S2). The results remained constant when concerning the circuit thrombosis [OR 0.48, 95%CI 0.29,0.78, $p = 0.003$, $I^2 = 0\%$]. There were 6 (23.1%) circuit exchanges in the bivalirudin group compared with 8 (19.5%) in the heparin group [OR 0.921.03, 95%CI 0.21,5.10, $p = 0.97$, $I^2 = 38\%$] (Fig. 2).

### 3.3.3. The safety of bivalirudin versus heparin as ECMO anticoagulant

There were 2 (3.7%) HIT in the heparin group compared with 0 (0%) in the bivalirudin group, although the result did not reach significant difference [OR 0.25, 95%CI 0.02,2.52, $p = 0.24$, $I^2 = 0\%$]. Taking hemorrhage into consideration, the review showed that the rate of major bleeding events was significantly lower in the bivalirudin group compared with the heparin group [OR 0.31, 95%CI 0.10,0.92, $p = 0.04$, $I^2 = 75\%$] (The definition of major bleeding events was described in eTable S2). There was no statistically significant difference for minor bleeding events in the bivalirudin group versus heparin group [OR 0.93, 95%CI 0.38,2.29, $p = 0.87$, $I^2 = 0\%$] (Fig. 3).

### 3.3.4. Mortality and the hospital length of stay (LOS) associated with ECMO anticoagulant

LOS [MD -2.93, 95%CI -9.01,3.15, $p = 0.34$, $I^2 = 45\%$] and ICU LOS [MD -4.22, 95%CI -10.07,1.62, $p = 0.16$, $I^2 = 0\%$] were not statistically different between the groups. There were similar rate of mortality [OR 1.84, 95%CI 0.58,5.85, $p = 0.30$, $I^2 = 60\%$] and 30-mortality [OR 0.75, 95%CI 0.38,1.48, $p = 0.41$, $I^2 = 0\%$] between bivalirudin and heparin. However, in-hospital mortality was lower in the bivalirudin group compared with heparin group [OR 0.63, 95%CI 0.44,0.89, $p = 0.009$, $I^2 = 0\%$] (Fig. 4).

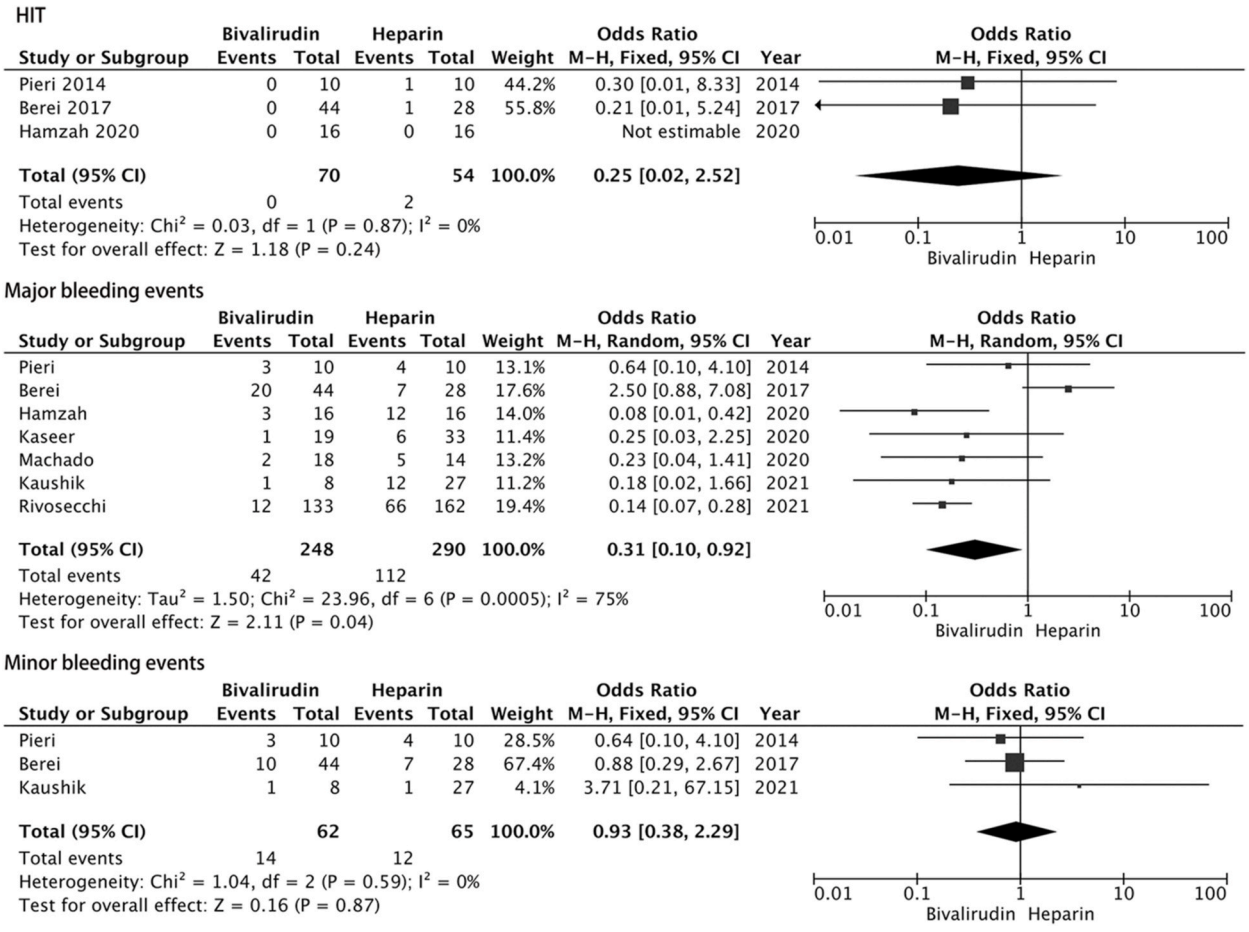


**Fig. 3.** Forest plot for HIT, major bleeding events and minor bleeding events.

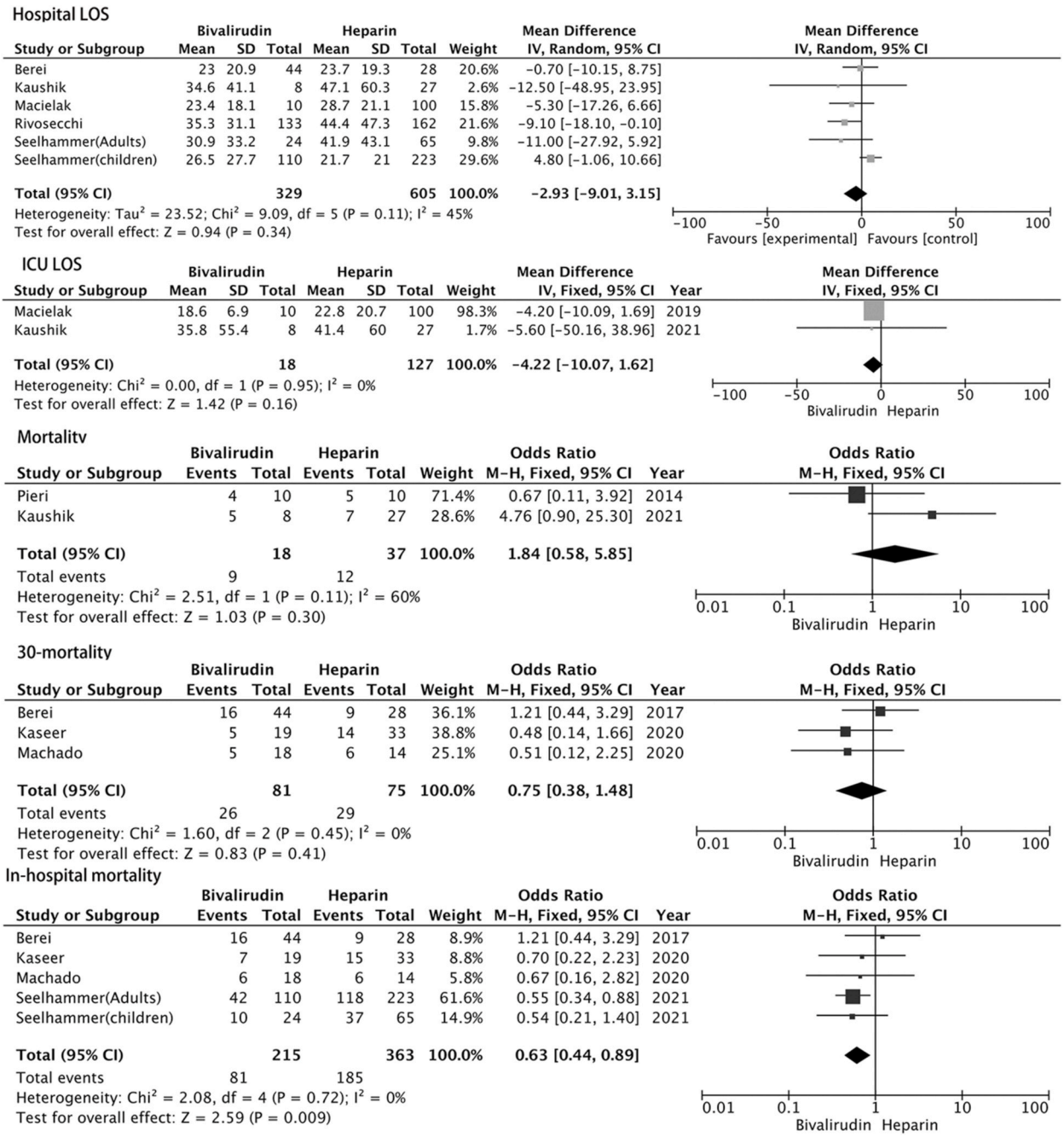


**Fig. 4.** Forest plot for hospital LOS, ICU LOS, mortality, 30-day mortality and in-hospital mortality.

### *3.4. Sensitivity analysis and subgroup analysis*

We performed sensitivity analysis by excluding the enrolled studies at a time from the pooled data. The benefit of bivalirudin over heparin for thrombotic events remained unchanged while the benefit of bivalirudin over heparin was not significant for patients undergoing ECMO for major bleeding events while ruling out the Rivosecchi's study (OR 0.44, 95%CI 0.71–1.14) (eFig. S1). For different type of ECMO, the omission of the Rivosecchi RM et al. [16] (only including patients on VV-ECMO) changed the pooled results, which demonstrated that the benefit of bivalirudin over heparin was not significant (OR 0.44, 95%CI 0.71–1.14) (eFig. S1).

The combined OR was 0.31 (95%CI 0.11,0.91, $p = 0.03$, $I^2 = 0\%$) and 0.55 (95%CI 0.38,0.80, $p = 0.002$, $I^2 = 0\%$) in the subgroup of children and adults for thrombotic events. Similarly, the estimate of OR was 0.14 (95%CI 0.05,0.41, $p = 0.0004$, $I^2 = 0\%$) and 0.39 (95% CI 0.25,0.61, $p < 0.0001$, $I^2 = 83\%$) in the subgroup of children and adults for major bleeding events. Subgroup analysis by

patients' type revealed that studies in children generated lower rate of thrombotic events and major bleeding events compared with adults (eFig. S2). In addition, we have also performed a subgroup analysis based on type of thrombotic events. The findings were still generally robust (eFig. S3).

## 4. Discussion

The major findings from our review suggested that bivalirudin could be a potential anticoagulation in ECMO. A significant reduction in thrombotic events, bleeding events and in-hospital mortality were observed, which were valuable indicators to evaluate the efficacy and safety of bivalirudin as the anticoagulant in patients undergoing ECMO.

The results of bivalirudin demonstrated in percutaneous coronary intervention (PCI) [19,20], balloon aortic valvuloplasty (BAV) [21] and transcatheter aortic valve replacement (TAVR) [22] become the impetus for our meta-analysis. The result of our meta-analysis was that bivalirudin would reduce major bleeding events compared with heparin in ECMO to an extent similar to that observed in PCI and BAV while differed from the results in TAVR procedures, in which bivalirudin did not meet superiority compared with heparin. These results may result from the differences that existed between study patients' population and procedures. In addition, although a statistically significant difference was not reported, lower major bleeding events were observed in bivalirudin group. The lack of statistically significant differences in transcatheter aortic valve replacement (TAVR) may result from sample size limitation. Previous meta-analysis comparing heparin and bivalirudin in PCI demonstrated that bivalirudin was associated with an increased rate of acute stent thrombosis [23], which was contrary to our results. Some comments should be made. Firstly, a confounding effect of glycoprotein IIb/IIIa inhibitors (GPI) use cannot be excluded. Secondly, bivalirudin stopped early before adequate platelet inhibition has been achieved, which resulted in an anti-coagulation free period and increased risk of stent thrombosis. On the contrary, bivalirudin infusion in ECMO was a continuous infusion process without an anti-coagulation free period. This may lead to the different results in two different procedures.

We encountered challenges while developing the optimal antithrombotic regimen during ECMO. To our knowledge, there was no consensus on bolus dosing or infusion dosing of bivalirudin. Bivalirudin was used both with and without in previous studies. The maintenance infusion rates varied significantly between studies, which ranged from 0.01 mg/kg/h to 0.5 mg/kg/h. Previous review found that the maintenance dose ranged from 0.045 to 0.48 mg/kg/h in children and 0.025–0.5 mg/kg/h in adults [24]. It is thus questionable to determine whether the outcomes are from the underdosing or overdosing due to dose variability. However, for dose variability, some comments should be made. Firstly, other studies demonstrated poor correlation with coagulation tests including APTT [25]. Patients' variability and variability of the APTT between laboratories based on reagents may play a role in the variability of maintenance infusion rates. Secondly, approximately 20% of the clearance is provided by the kidneys and as such the maintenance infusion rates of bivalirudin were adjusted based on renal function. Patients with renal dysfunction required lower bivalirudin dose to achieve targeted anticoagulation profile. Further studies were required to assess the correct bivalirudin bolus or infusion dose for ECMO treatment.

The time to reach therapeutic levels and TTR represented directly to the quality of the anticoagulation dose management. Our systematic review did not indicate that bivalirudin exhibited a more consistent APTT control over time compared with heparin. On the contrary, it appeared to have an impact on patient outcomes including thrombotic complications and major bleeding events. Increased bleeding and thrombosis might occur if APTT was more frequently out of the therapeutic range. However, TTR was only reported in four studies in our review. The insignificant result of TTR may be due to small size. Future studies comparing bivalirudin and heparin should attempt to calculate time in the therapeutic range. Thrombosis in ECMO circuit is common. Bivalirudin also demonstrated a lower risk of thrombosis in ECMO circuit compared with heparin group. ECMO is associated with reduction in levels of antithrombin [26]. Heparin requires the cofactor antithrombin for efficacy. Generation of thrombosis in heparin group in the circuit may result from low antithrombin concentration. In addition, bivalirudin binds directly to both free and bound thrombin while heparin binds fibrin-bound poorly, which making bivalirudin have a higher anticoagulation efficiency [27].

Heparin depended on the cofactor antithrombin for efficacy while bivalirudin bound directly to thrombin. Heparin resistance was more frequent in children than in adults due to lower concentration of antithrombin in neonates or critically ill children [28]. Children have deficiencies in anticoagulant hemostasis proteins due to liver immaturity [29]. For these reasons, the disadvantages of using heparin were more pronounced in children. On our subgroup analysis based on the patients' type, bivalirudin remained to be associated with decreased thrombotic events and major bleeding events compared with heparin. In addition, the superiority of bivalirudin over heparin was more evident in children compared with adults.

Our review has several limitations. First, the inherent limitations of our meta-analysis included its retrospective design and relatively small sample size, and the results should be interpreted with caution due to methodological limitation. Second, the dose and the target anticoagulation of bivalirudin and heparin differed in our meta-analysis. It is thus questionable to determine whether the outcomes are from the underdosing or overdosing. Third, other clinical heterogeneities, such as the indications for ECMO and year of cannulation, should be regarded. However, the data sparseness of included studies limited the further subgroup analysis.

In conclusion, the findings of our study demonstrated that bivalirudin probably be a potential choice for ECMO anticoagulation. However, based on the included studies' limitation, the superiority of bivalirudin over heparin for anticoagulation in the ECMO population still require further prospective randomized controlled studies before a definite conclusion.

## Declarations

### *Authors' contributions*

Jie Gu, Hongjie Yu and Dang Lin conceived and designed the experiments. Jie Gu and Hongjie Yu performed the experiments. Jie Gu and Hongjie Yu analyzed and interpreted the data. Jie Gu and Hongjie Yu contributed reagents, materials, analysis tools or data. Jie Gu, Hongjie Yu and Dang Lin wrote the paper. All authors read and approved the final manuscript.

### *Funding*

None.

### *Availability of data and materials*

All data generated and/or analyzed during the current study were included within the published article and its additional flies.

### *Ethics approval and consent to participate*

Not applicable.

### *Consent for publication*

Not applicable.

### *Competing interests*

The authors declared that they have no competing interests.

## Acknowledgements

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## Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e13530.

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