Efficacy and Safety of Bivalirudin Versus Heparin Anticoagulation Therapy for Extracorporeal Membrane Oxygenation: Meta-Analysis

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Research

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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 were included, involving 1091 patients (Bivalirudin was administered in 405 patients while 686 patients were treated with heparin). 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%], Heparin-Induced Thrombocytopenia (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%]. 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). Subgroup analysis by patient's type revealed that studies in children generated lower rate of thrombotic events and major bleeding events compared with adults.

Conclusion

Our meta-analysis suggests that bivalirudin use as the anticoagulant for ECMO are associated with lower thrombotic events, major bleeding events and in-hospital mortality. Meanwhile, the differences are more pronounced in children than adults. However, the results should be interpreted with caution and further larger, randomized trials are needed to confirm the results.

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]. Unfractionated heparin (UFH) remained to be the primary anticoagulant for ECMO in guidelines due to ease of titration and monitoring, ease of reversibility, low cost [4]. Despite these advantages, heparin has its limitations. First, heparin require the cofactor antithrombin III 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 shows the following advantages. First, bivalirudin does not require the antithrombin III 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 data 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.

Materials And Methods

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.

Selection criteria

Inclusion criteria were a) the study was prospectively or retrospectively designed; b) patients were included in the heparin or bivalirudin if they received solely heparin or bivalirudin; We excluded studies that a) reported outcomes with only heparin or only bivalirudin; b) lacked data detailing the outcomes included in our analysis.

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, 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].

Data analysis

Treatment effects were expressed as odds ratios for binary outcomes and mean difference 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 analyses 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.

Results

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 [9-18] (Figure 1).

Demographic characteristics and Quality assessment

The characteristic of studies reporting bivalirudin versus heparin as an anticoagulant for ECMO patients are summarized in Table 1 and Table 2. 10 studies reporting 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 non-randomized clinical trial. There were 2 studies from Italy, 8 studies from American. 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. 551 patients received veno-arterial (VA) ECMO and 407 veno-venous (VV) ECMO. The mean/median ECMO duration ranged from 106 hours to 10 days (Table 1/Table 2). The quality assessment is displayed in eTable 1.

Primary meta-analysis

- **The Bivalirudin regimens during ECMO**

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

- **The efficacy of bivalirudin versus heparin as ECMO anticoagulant**

The time to reach therapeutic levels in patients treated with bivalirudin is similar to those with heparin [MD 3.53, 95%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 were found compared with heparin [OR 0.51, 95%CI 0.36,0.73, p=0.0002, I^2=0%]. 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 on the bivalirudin group compared with 8(19.5%) the heparin group [OR 0.92, 95%CI 0.27,3.12, p=0.90, I^2=38%]. (Figure 2)

- **The Safety of Bivalirudin versus heparin as ECMO anticoagulant**

There were 2(23.1%) HIT on the heparin group compared with 0(0%) 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 systematic review showed that the rate of major bleeding events was significantly higher in the heparin group compared with the bivalirudin group [OR 0.31, 95%CI 0.10,0.92, p=0.04, I^2=75%]. There was no statistically significant difference in 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%]. (Figure 3)

- **Mortality and LOS associated with ECMO anticoagulant**

The hospital length of stay (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 rates 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 higher in the heparin group compared with bivalirudin group [OR 0.63, 95%CI 0.44,0.89, p=0.009, I^2=0%] (Figure 4)

Sensitivity analysis and subgroup analyses

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) (eFigure 1). Subgroup analysis by patient's type revealed that studies in children generated lower rate of thrombotic events and major bleeding events compared with adults (eFigure 2).

Discussion

To our knowledge, our study was the first meta-analysis review which address the efficacy of safety of bivalirudin compared with heparin in patients undergoing ECMO. The major findings from our systematic review of 10 observational studies are as follows: First, bivalirudin bolus or infusion dose varied significantly between studies, which range from 0.01mg/kg/h to 0.5mg/kg/h. Second, compared with heparin, bivalirudin demonstrated efficacy and safety for systematic anticoagulation on extracorporeal membrane oxygenation as established by a decrease in the number of thrombotic complications (circuit thrombosis), bleeding events and hospital mortality. Third, there was no significant differences between groups regarding the time to reach therapeutic levels, TTR, circuit exchanges, HIT, minor bleeding, hospital LOS, ICU LOS, mortality and 30-day mortality.

Challenges we encountered while developing the optimal antithrombotic regimen during ECMO. To our knowledge, there is no consensus on bolus dosing or infusion dosing of bivalirudin. Therapeutic APTT was achieved without the bolus dose in our meta-analysis. The maintenance infusion rates varied significantly between studies, which range from 0.01mg/kg/h to 0.5mg/kg/h, even with similar targeted APTT or ACT. Previous review found that the maintenance dose ranged from 0.045 to

0.48mg/kg/h in children and 0.025 to 0.05 mg/kg/h in adults, which is similar to our results [19]. However, Other studies demonstrated poor correlation with coagulation tests including APTT [20]. Patients' variability and variability of the APTT between laboratories based on reagents may play a role in the dosing strategy. Further studies are required to assess the correct bivalirudin bolus or infusion dose for ECMO treatments.

The time to reach therapeutic levels and TTR represent directly to the quality of the anticoagulation dose management. Our systematic review does not indicate that bivalirudin exhibited a more consistent APTT control over time compared with heparin, which may be primarily due to small sample size. Although bivalirudin does not have significant more consistent APTT value compared with heparin in our study, it appears to have an impact in patient outcomes including thrombotic complications and major bleeding events. However, it should be noticed that the benefit of bivalirudin over heparin was not significant for major bleeding events in sensitivity analysis. First, the definitions for bleeding events varied, which contributed to high heterogeneity among the trials. Second, the meta-analysis might be dominated by a single large study, which led to the insignificant results of major bleeding events while removing the large study. Third, Other cause attributed to this result may be the varied dose of initiation and titration increment dose in different studies.

Heparin depends on the cofactor antithrombin III for efficacy while bivalirudin binds directly to thrombin. Heparin resistance is more frequent in children than in adults due to lower concentration of antithrombin in neonates or critically ill children [21]. Children have deficiencies in anticoagulant hemostasis proteins due to liver immaturity [22]. For these reasons, the disadvantages of using heparin are more pronounced in children. On our subgroup analyses based on the patient's type, bivalirudin remained to be associated with deceased thrombotic events and major bleeding events compared with heparin. Meanwhile, the superiority of bivalirudin over heparin was more evident in children compared with adults.

Our meta-analysis has several limitations. First, potential bias is likely to be greater for observational studies. Therefore, the results should be interpreted with caution due to methodological heterodetic. Second, the definitions of adverse outcomes differed between studies, which should account for the variance between studies. The standardization of definitions for outcomes will allow for a more consistent reporting of outcomes in future clinical investigations.

Conclusions

Overall, Bivalirudin can be used safely and effectively to decease thrombotic complications, bleeding events and in-hospital mortality when compared with heparin for patients undergoing ECMO. Bivalirudin may offer a clinically significant advantages as the anticoagulant of choice. Our findings support the hypothesis, but the pooled results should be interpreted with caution that the results of sensitivity analysis were not consistent. The superiority of bivalirudin over heparin for anticoagulation in the ECMO population requires further prospective randomized controlled studies.

Declarations

Acknowledgements

None.

Authors' contributions

Jie Gu and Hongjie Yu contributed to the conception and design of this review. Jie Gu and Hongjie Yu performed the literature screening. Jie Gu and Hongjie Yu extracted the data and performed the quality assessment. Jie Gu and Hongjie Yu interpreted and synthesized the data. Jie Gu drafted the manuscript. Jie Gu, Hongjie Yu and Dang Lin critically revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated and/or analyzed during the current study are 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 declare that they have no competing interests.

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Tables

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 0.03-0.05mg/kg/h without bolus	ACT:160-180s, APTT:50-80s
Pieri	2014	Italy	2008-2011	NRCT	Adults	20	Bivalirudin infusion 0.025mg/kg/h without bolus	45-60s
Berei	2017	American	2012-2015	NRCT	Adults	72	Bivalirudin infusion 0.04mg/kg/h without bolus	APTT:low-intensity(45-65s)/high-intensity(60-80s)
Macielak	2019	American	2012-2017	NRCT	Adults	110	Bivalirudin infusion 0.01-0.1mg/kg/h	60-80s
Hamzah	2020	American	2014-2018	NRCT	Children	32	Bivalirudin infusion 0.3mg/ kg/h; if CrCl<60ml/min, 0.15mg/kg/h	58-78s
Kaseer	2020	American	2013-2018	NRCT	Adults	52	Bivalirudin infusion 0.1mg/kg/h	50-90s
Machado	2020	American	2015-2019	NRCT	Children	32	Bivalirudin infusion 0.1mg/kg/hr	na.
Rivosecchi	2021	American	2013-2020	NRCT	Adults	295	na.	na.
Seelhammer	2021	American	2014-2019	NRCT	Adults	333	Bivalirudin infusion 0.02-0.15mg/kg/h	60-80s
Seelhammer	2021	American	2014-2019	NRCT	Children	89	Bivalirudin infusion 0.02-0.15mg/kg/h	60-80s
Kaushik	2021	American	2016-2019	NRCT	Children	35	Bivalirudin infusion 0.5mg/kg/h	60–90s

na. not available; NRCT non-randomized controlled trial

Table 2 Baseline Charateristics of Patients

Author	Year	Total	Bivalirudin	Heparin	Age Mean (SD) or Median (IQR)	Male Sex, No (%)	V-A ECMO	V-V ECMO	ECMO duration Mean (SD) or Median (IQR)
Ranucci	2011	21	13	8	27.9(27.5) (y)	na.	na.	na.	119 (71.6) (h)
Pieri	2014	20	10	10	56.8(13.5) (y)	16(80.0)	10(50)	10(50)	na.
Berei	2017	72	44	28	55.5(14.3) (y)	47(65.3)	66(91.7)	6(8.3)	na.
Macielak	2019	110	10	100	52.0(14.0) (y)	na.	na.	na.	7.0(4.6) (d)
Hamzah	2020	32	16	16	12(0-212) (m)	14(44)	29(90.6)	3(9.4)	106(32-419) (h)
Kaseer	2020	52	19	33	55(18-83) (y)	37(71.2)	28(53.8)	24(46.2)	10(3-70) (d)
Machado	2020	32	18	14	37.7(65.8) (m)	16(50)	30(93.8)	1(3.1)	161.4(85.0) (h)
Rivosecchi	2021	295	133	162	49(36-61) (y)	176(59.7)	0(0)	295(100)	234.4(311.7) (h)
Seelhammer	2021	333	110	223	na.	217(65.2)	277(83.2)	56(16.8)	na.
Seelhammer	2021	89	24	65	na.	48(53.9)	81(91.0)	8(9.0)	na.
Kaushik	2021	35	8	27	na.	18(51.4)	30(85.7)	4(11.4)	na.

na. not available; V-A veno-arterial; V-V veno-venous; ECMO extracorporeal membrane

Figures

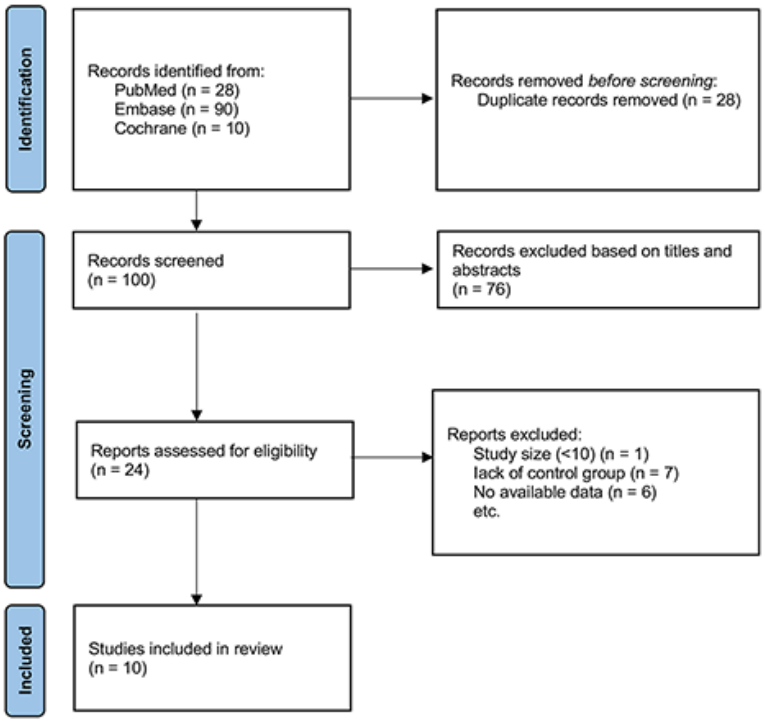

Figure 1

Flow chart of the search process

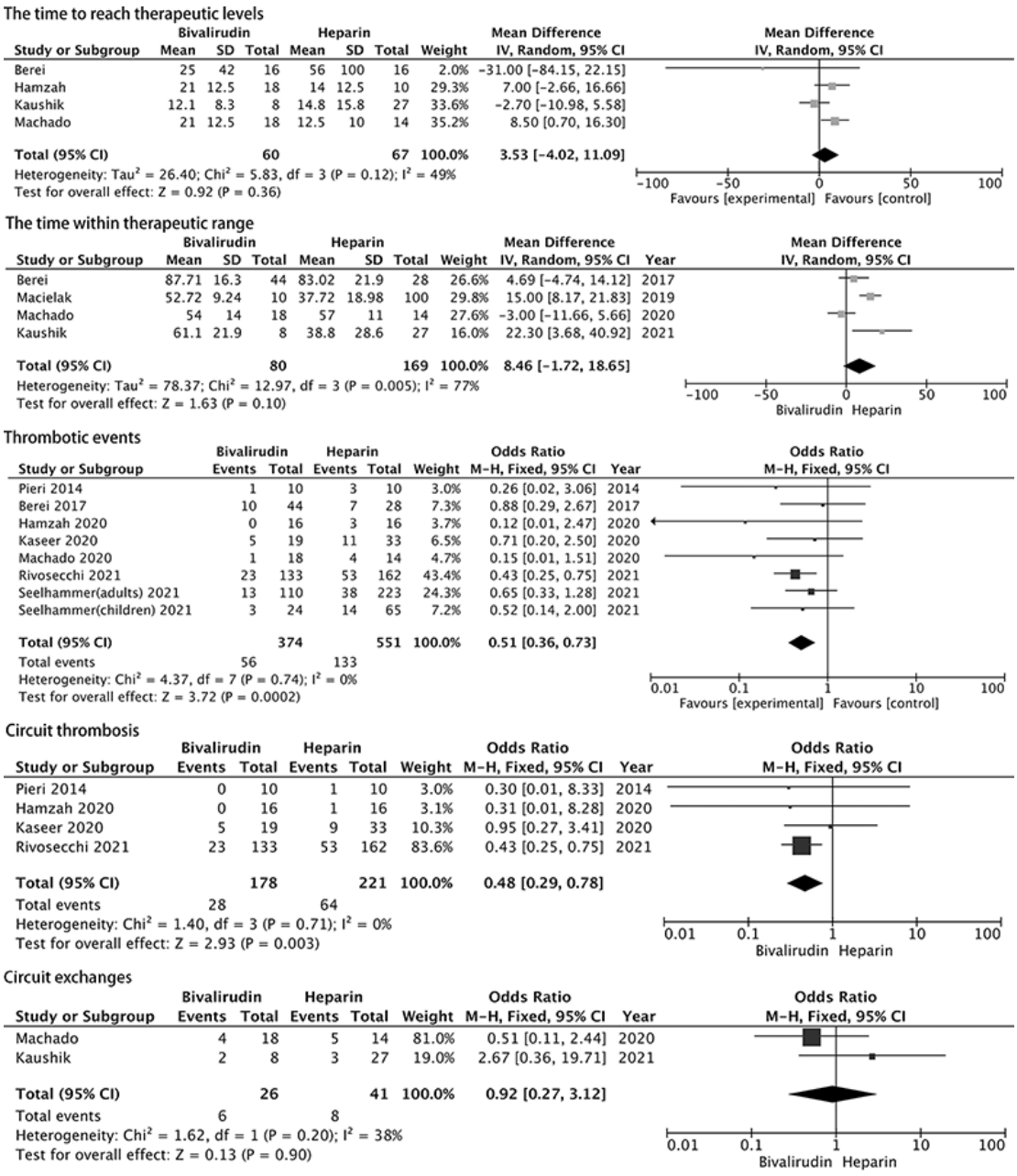

Figure 2

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

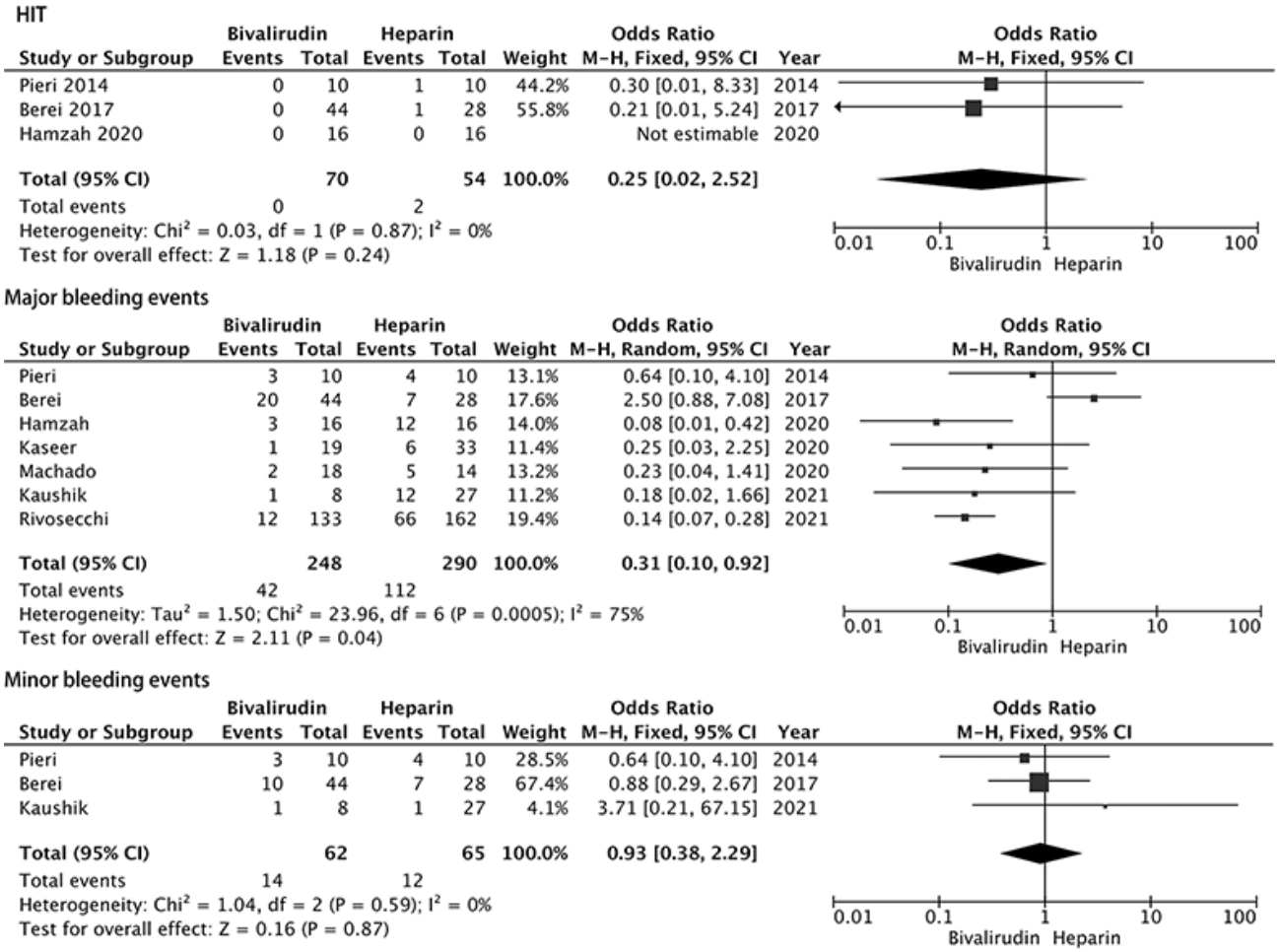

Figure 3

Forest plot for HIT, major bleeding events and minor bleeding events

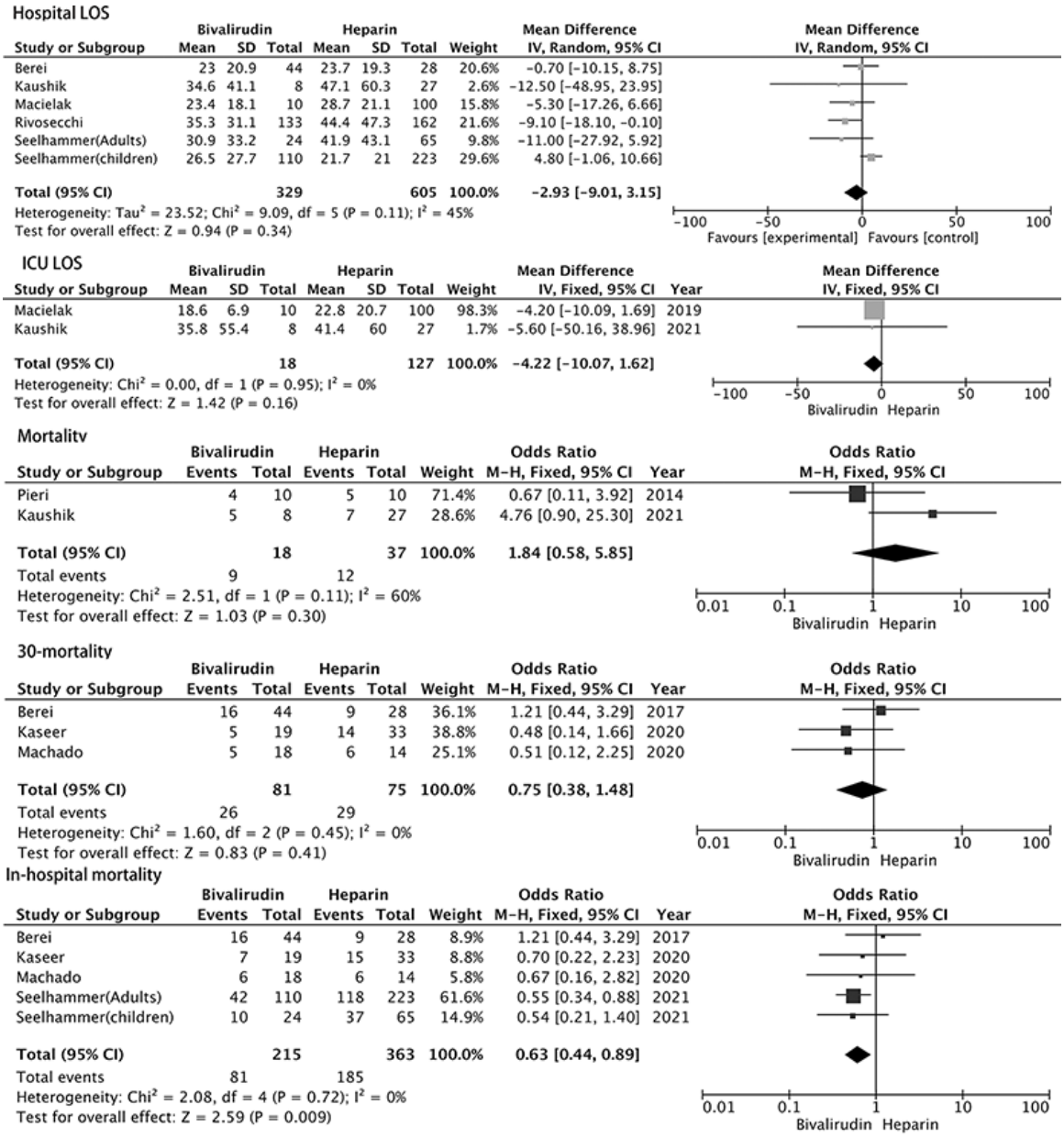

Figure 4

Forest plot for hospital LOS, ICU LOS, mortality, 30-day mortality and in-hospital mortality

Supplementary Files

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- eFigure1sensitivityanalysis.tif
- eFigure2subgroup.tif
- eTable1.docx