The Efficiency and Safety of Bivalirudin versus Heparin in The Anticoagulation Therapy in Extracorporeal Membrane Oxygenation: A Meta-Analysis

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Research

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Abstract

Background: Bivalirudin is a direct thrombin inhibitor (DTI), which can be the alternative of

unfractionated heparin (UFH). The efficiency and safety of bivalirudin versus UFH in the anticoagulation therapy in Extracorporeal membrane oxygenation(ECMO) remains unclear. The purpose of the meta-analysis is to evaluate the efficiency and safety of bivalirudin versus UFH in the anticoagulation therapy in ECMO.

Methods: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed. A systematic literature search for original studies was performed in PubMed, EMBASE and The Cochrane Library to identify all relevant studies published prior to January 13,2021. Studies were reviewed according to eligibility and exclusion criteria. The meta-analysis was used to estimate the efficiency and safety of bivalirudin versus UFH in the anticoagulation therapy in extracorporeal membrane oxygenation.

Results: 6 retrospective studies with 254 patients were eventually included for the quantitative analysis. The results showed that the incidence of major bleeding(I^2=66%, P=0.16, OR=0.43, 95%CI:0.13-1.40), thrombosis(I^2=0%, P=0.09<0.1, OR=0.56, 95%CI:0.29-1.09) and 30-day mortality(I^2=0%, P=0.50, OR=0.90, 95%CI:0.42-1.53) was not statistically significant between the bivalirudin group and the UFH group.

Conclusions: This study suggests that bivalirudin and UFH are associated with similar rates of major bleeding, thrombosis and 30-day mortality in adult and pediatric ECMO support, which is safe, practicable, dependable, and cost-effective in comparison with UFH. Bivalirudin is non-inferior to UFH in the anticoagulation therapy in ECMO.

Background

Extracorporeal membrane oxygenation(ECMO) is an application of life supporting system providing circulatory and/or pulmonary support for the patients suffering from severe, life-threatening diseases[1], such as refractory acute heart failure, ST-segment elevation myocardial infarction(STEMI) and acute respiratory distress syndrome(ARDS). As the medical technology developed, the complications of ECMO are significantly reduced and the survival rate is greatly improved. However, during the treatment of ECMO, coagulation related complications such as bleeding or thrombosis are still the main factors affecting the whole morbidity and mortality.

The exposure of blood to the foreign surface may render the patients at a high risk of thromboembolic events, which can be prevented by the heparinization of blood[2]. For decades, the unfractionated heparin(UFH) is the most common anticoagulant, and is the mainstay antithrombotic in ECMO. Nevertheless, its clinical use may be restricted by the UFH-related complications such as heparin resistance(HR) and heparin-induced thrombocytopenia(HIT). HR is typically caused by the consumptive deficiency of antithrombin III(AT III), and heparin-induced thrombocytopenia(HIT) is a devastating event may occur with heparin exposure[3, 4]. Bivalirudin is a parenteral direct thrombin inhibitor (DTI), which is an oligopeptide analogue of hirudin and independent on AT III inherently. Therefore, bivalirudin is a bivalent DTI that binds specifically to thrombin at two sites without the need for a cofactor[5]. Bivalirudin used to be an alternative anticoagulant option for overcoming the patients with the aforementioned pitfalls. Furthermore, the reversible and transient binding to the thrombin makes it the mainstream anticoagulants in the cardiac catheterization room in this day and age[5]. However, there are no large-scale, randomized clinical trials reporting the incidences of the major bleeding, thrombosis and mortality of bivalirudin versus UFH in the treatment of ECMO to guide the clinicians. Therefore, we believe it worthwhile to carefully conducted a meta-analysis to evaluate the efficiency and safety of bivalirudin versus UFH in the anticoagulation therapy in ECMO. This is a registered meta-analysis on PROSPERO (https://www.crd.york.ac.uk/prospero/) and the registration number is CRD42020214713.

Method

Literature Search

Two authors(S. Liang and J. Zhu) searched on PubMed, EMBASE and The Cochrane Library till January 13, 2021 independently by using heading terms: “heparin” or “unfractioned heparin” and “bivalirudin” and “extracorporeal membrane oxygenation” or “ECMO” or “ECMO treatment” or “ECLS” or “ECLS treatment”.

The articles were included by the following inclusion criteria: (a)the studies compared the incidences of major bleeding and thrombosis between the bivalirudin group and UFH group; (b)the studies were written in English. Studies with insufficient or unspecific data would be excluded.

Data extraction and quality assessment

Data were extracted by the same two independent readers(S. Liang and J. Zhu) who performed the literature search and study selection. Disagreements were solved by a third reader(M. Ma). Y. He was in charge of the whole process. This meta-analysis followed PRISMA guidelines[6].

The two reviewers extracted the following information independently: the first author, the published year, the design of studies(prospective/retrospective), study duration, the total patients and the patients in bivalirudin and UFH group, the dose in bivalirudin and UFH group, and the number of thrombosis, major bleeding and 30-day mortality(per-patient).

The Newcastle-Ottawa Scale(NOS) is used to assess the risk of bias of the observational studies. The NOS score ≥ 6 is considered as a good study. The publication bias is analyzed by Stata version 15.0(The StataCorp LP, Texas City, USA) by drawing funnel plot.

Statistical and Meta-Analysis

The RevMan version 5.3.5(The Cochrane Collaboration, Copenhagen, Denmark) software was properly used in all statistical analyses. Results were compiled using PRISMA.The two reviewers(S. Liang and J. Zhu) collecting the data were not aware of the authors and institutions of included studies. Statistical heterogeneity was assessed using *I* square test. Heterogeneity was interpreted as absent(I^2:0–25%), low(I^2:25.1–50%), moderate(I^2: 50.1–75%), or high(I^2: 75.1–100%). The use of a random effects model was also considered when the number of studies was relatively small, and a random effects model was applied to estimate the continuous outcome data if the *P* value < 0.1 and an I^2 value > 50%, which indicates statistical heterogeneity[7]. Otherwise, a fixed-effects model was used. A *P* value < 0.05 was considered to indicate statistical significance.

Results

Literature Search and Study Selection

The literature search with the above-mentioned criteria produced 115 total findings (91 on EMBASE, 4 on The Cochrane Library, and 20 on PubMed); 80 full texts were retrieved after duplicates removed via automatic software. Then the titles and abstracts of studies were screened, of which 53 were excluded due to the following reasons: systematic reviews (n = 2), reviews (n = 18), case reports (n = 17) and incomplete studies(n = 16). 27 full-text articles were reviewed and 21 were excluded later due to without exact numbers of the events(n = 2) and lack of comparison between UFH and bivalirudin(n = 19). Finally, A total of 6 unique articles[8–13] with 254 patients were included for the quantitative analysis(flow chat of the search according to PRISMA statement is shown in Fig. 1). The basic information of the included studies is shown in Table 1. All articles were published prior to January 13, 2021.

Table 1
Basic Information of the Included Studies

Study	Duration	Total Patients(Pediatric Patients)	VV-/VA-ECMO	Bivalirudin Group		Heparin Group		Indication of ECMO(numbe patients)
				Dose	Number (Pediatric Patients)	Dose	Number (Pediatric Patients)	
Ranucci2011[8] **(Retrospective)**	January 2008-April 2011	21(9)	NR	0.03–0.05 mg/kg/h	13(4)	5–10 IU/kg/h	8(5)	NR
Pieri2012[9] **(Retrospective)**	January 2008-March 2011	20(0)	10/10	0.025 mg/kg/h	10(0)	3 IU/kg/h	10(0)	NR
Ljajikj2017[10] **(Retrospective)**	March 2012-March 2016	57(0)	NR	APTT > 160s: 0.25 mg/kg/h APTT < 160s: 0.5 mg/kg/h	21(0)	NR	36(0)	Left ventricula assist device implantation(
Berei2018[11] **(Retrospective)**	January 2012-September 2015	72(0)	6/66	0.04 mg/kg/h	44(0)	8–12 IU/kg/h	28(0)	STEMI(15) Cardiogenic shock(51) Septic shock(Respiratory shock(4) Mixed shock(
Hamzah2020[12] **(Retrospective)**	October 2014-May 2018	32(32)	3/29	Ccr > 60 ml/min:0.3 mg/kg/h renal impairment:0.15 mg/kg/h	16(16)	open chest:10 IU/kg/h < 12M:18 IU/kg/h 1Y-12Y:16 IU/kg/h > 12Y:14 IU/kg/h	16(16)	heart transplantatic
Kaseer2020[13] **(Retrospective)**	January 2013-September 2018	52(0)	24/28	0.1 mg/kg/h	19(0)	10.4 IU/kg/h	33(0)	Cardiogenic shock(13) Respiratory failure(13) Heart and/or l transplant(9) Others(1)

NR:Not Reported; NOS:Newcastle-Ottawa Scale

Quality Assessment

All of the 6 included articles were retrospective studies. Generally, most of the quality indicators of the NOS were met in these included studies. However, the control group of all the studies did not meet the standard of “community controls” and “no history of diseases” as the controls were from the hospital. Also, as the included studies were all case-control retrospective studies, they were not blinded to the case/control status.

Data Extraction and Meta-Analysis

The basic information and the NOS score of the included studies were shown in Table 1. The meta-analysis indicated that the incidence of major bleeding(I^2 = 66%, P = 0.16, OR = 0.43, 95%CI: 0.13–1.40), thrombosis(I^2 = 0%, P = 0.09 < 0.1, OR = 0.56, 95%CI: 0.29–1.09) and 30-day mortality(I^2 = 0%, P = 0.50, OR = 0.90, 95%CI: 0.42–1.53) was not statistically significant between the bivalirudin group and the UFH group(Fig. 2).

Publication Bias

Funnel plot analysis was made for the incidence of complications with bivalirudin or UFH. The results of major bleeding, 30-day mortality and thrombosis showed a relatively inverted and symmetrical funnel diagram, indicating that publication bias was less likely(Fig. 3).

Discussion

To our knowledge, this is the first meta analysis exploring the efficiency and safety of bivalirudin versus UFH in the anticoagulation therapy in ECMO. Our results include 6 studies with 254 patients to evaluate bivalirudin versus UFH in the anticoagulation therapy in ECMO. 2 studies with 41 patients belonging to the pediatric population, suggested that there is no significant difference in the incidence of major bleeding, thrombosis and 30-day mortality between the bivalirudin group and UFH group. However, it seems that the incidence of major bleeding, thrombosis and 30-day mortality in the bivalirudin group is lower, indicating that the benefit of anti-thromboembolic therapy that altering UFH to bivalirudin may overshadow the pitfalls of major bleeding.

Though HIT is a severe complication of UFH with only an absolute risk of 2.6%[14], the untreated HIT may lead to the risk of thrombosis up to 50%[15]. Bivalirudin, as a DTI, was found at least non-inferior to UFH in our meta-analysis. What is more, though bivalirudin is more expensive than the UFH, as was reported as $1170 per vial in Kaseer et al.[13]’s study, it may actually reduce the total fees such for less frequent monitoring, platelet transfusion, etc. Hamzah et al.[12]’s study to evaluate their experience in pediatric extracorporeal life support with bivalirudin. They found the time to reach goal therapeutic anticoagulation level was shorter and the bleeding events were fewer in the bivalirudin group. Furthermore, they indicated that the total cost of bivalirudin anticoagulation therapy was significantly lower than UFH. As an anticoagulant, UFH can stimulate platelet activation in vivo, whilst bivalirudin can serve as the inhibitor of both thrombin-dependent platelet activation and collagen-induced platelet procoagulant activity[16–17]. Therefore, bivalirudin has better antithrombotic and anticoagulant function than UFH with less platelet activation, which means less platelet consumption. Ranucci et al.[8] also reported that the bivalirudin group lost less blood(P = 0.015), and therefore used fewer amount of platelet concentrates(P = 0.008), fresh frozen plasma(P = 0.02) and purified antithrombin(P = 0.048). It has to be said, the daily cost of ECMO was significantly lower in patients of bivalirudin-group[8].

Bivalirudin was proved efficient and safe in the use of percutaneous coronary intervention(PCI), which can reduce the major bleeding risk in the NSTE-ACS and AMI population[18–21]. The Polish researchers recommended that the population who is taking a PCI therapy with (a)age > 75 years,(b)female gender,(c)BMI < 20 or BMI > 30 kg/m^2,(d)previous gastrointestinal bleeding, previous hemorrhagic stroke,(e)chronic kidney disease (estimated glomerular filtration rate 30–60 mL/min/1.73 m^2),(f)frailty,(g)increased bleeding risk related to other factors, should use bivalirudin[22]. In addition, in the use of percutaneous transcatheter aortic valve interventions(PAVI), there is no significant difference in 30-day all-cause and cardiovascular mortality between the bivalirudin and UFH, whereas the incidence of myocardial infarction is significant lower in the bivalirudin group[23]. But is bivalirudin truly efficient and safe compared with UFH in ECMO? Brown et al.[24] spent 203 days(91 days on heparin and 112 days on bivalirudin) and found that there were total 28 bleeding events and 4 thrombotic events occurring on heparin (0.35 events/ECMO day) whilst 7 bleeding events and 0 thrombotic while on bivalirudin (0.06 events/ECMO day), which is statistically significant (P = 0.0125). However, in most of our included studies, both of major bleeding and thrombosis rate were not statistically significant, and thus a standardized anticoagulation with ECMO is required[25].

High prevalence of renal insufficiency were found in both bivalirudin and UFH group in Ljajikj et al.[10] and Kaseer et al.[13]’s studies. Renal insufficiency is an independent risk factor for major bleeding, which slows down the metabolism of UFH, rendering high activated coagulation time(ACT) level for a long time[26]. Bivalirudin clearence is mainly dependent on renal function but independent of dose and gender[27]. For the patients with normal renal function, the half time of bivalirudin is 25 minutes. The anticoagulant effect of bivalirudin with thrombin was reversible and lasted for a short time, which wears off fast after withdraw, making it more predictable than UFH. However, in the severe renal impairment patients(CrCl:10–29 mL/min) and patients in dialysis, the half time is 57 and 210 minutes respectively[13]. Studies found that the dose of bivalirudin is lower in the patients in order to reach a therapeutic partial thromboplastin time(APTT) than that in the patients of normal renal function, and slightly higher doses in those who were receiving dialysis[28]. For the patients with slightly renal impairment, the dose adjustment is unnecessary; while for those who with moderate to severe renal impairment (eGFR < 60 ml/min/1.73 m^2), it is wise and safe, as the wait for the accumulation of bivalirudin may lead to high risk of bleeding[29]. What is more, the value of APTT reflects the condition of the anticoagulation, the higher the values are, the higher the risk of bleeding is. In Kaseer et al.[13]’s study, they found that the percentage of time APTT within the therapeutic range was higher with bivalirudin(50% vs 85.7%; P = 0.007), which means that bivalirudin consistently maintained APTT within the therapeutic range in comparison to UFH. Bivalirudin appears to be a reliable option for alternative anticoagulation in pediatric ECMO patients who have failed UFH.

From our perspective, to rationally use bivalirudin in ECMO, the baseline value of APTT, the presence of renal insufficiency or renal replacement therapy, the use of other drugs(e.g argatroban), the possibility of bivalirudin resistance and the ways of operation should be all taken into consideration. With less rate of circuit intervention, bivalirudin seems to be a viable option for those who failed by using UFH in systemic anticoagulation in ECMO, though the optimal

monitoring strategy remains to be explored[30]. To monitor bivalirudin therapy, APTT Hepzyme(HPTT), intrinsic coagulation pathways with heparinase(HEPTEM) and measurement of the clotting time(CT) is recommended[31]. Whether the use of bivalirudin in ECMO can reduce thrombosis remains to be discussed in the future.

There are some limitations in our study. First and foremost, the studies included are all retrospective small-size single-center studies, which means the argumentation intensity is not strong enough and only the hypothesis can be generated. Therefore, the large-scale multi-center RCTs are truly requested. What is more, the unspecific results may restrict our subgroup analysis, such as the use of bivalirudin versus UFH in different type of ECMOs(VV or VA), different diseases(STEMI, ARDS, heart transplantation and so forth) and different ages(adult and pediatric), these can be further investigated in the future studies.

Conclusion

Though the incidence of major bleeding, thrombosis and 30-day mortality was not statistically significant between the bivalirudin group and UFH group, the incidence of the aforementioned complications is seemingly lower in the bivalirudin group. Therefore, we can conservatively draw the conclusion that bivalirudin is non-inferior to UFH in the anticoagulation therapy in ECMO.

Abbreviations

CI: Confidential interval; ECMO: Extracorporeal membrane oxygenation; STEMI: ST-segment elevation myocardial infarction; ARDS: acute respiratory distress syndrome; UFH: unfractionated heparin; HIT: heparin-induced thrombocytopenia; DTI:direct thrombin inhibitor; NOS: Newcastle-Ottawa Scale

Declarations

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Availability of data and materials

All data generated or analyzed during this study are from published articles

Author contributions

MM and SL contributed equally to this work. MM, LS, JZ, and YH conceived the study, participated in the design, collected the data, performed statistical analyses and drafted the manuscript. SL and JZ performed statistical analyses and helped to draft the manuscript. LS and JZ collected the data and revised the manuscript critically for important intellectual content. MM and YH collected the data, performed statistical analyses and helped to revise the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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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Figures

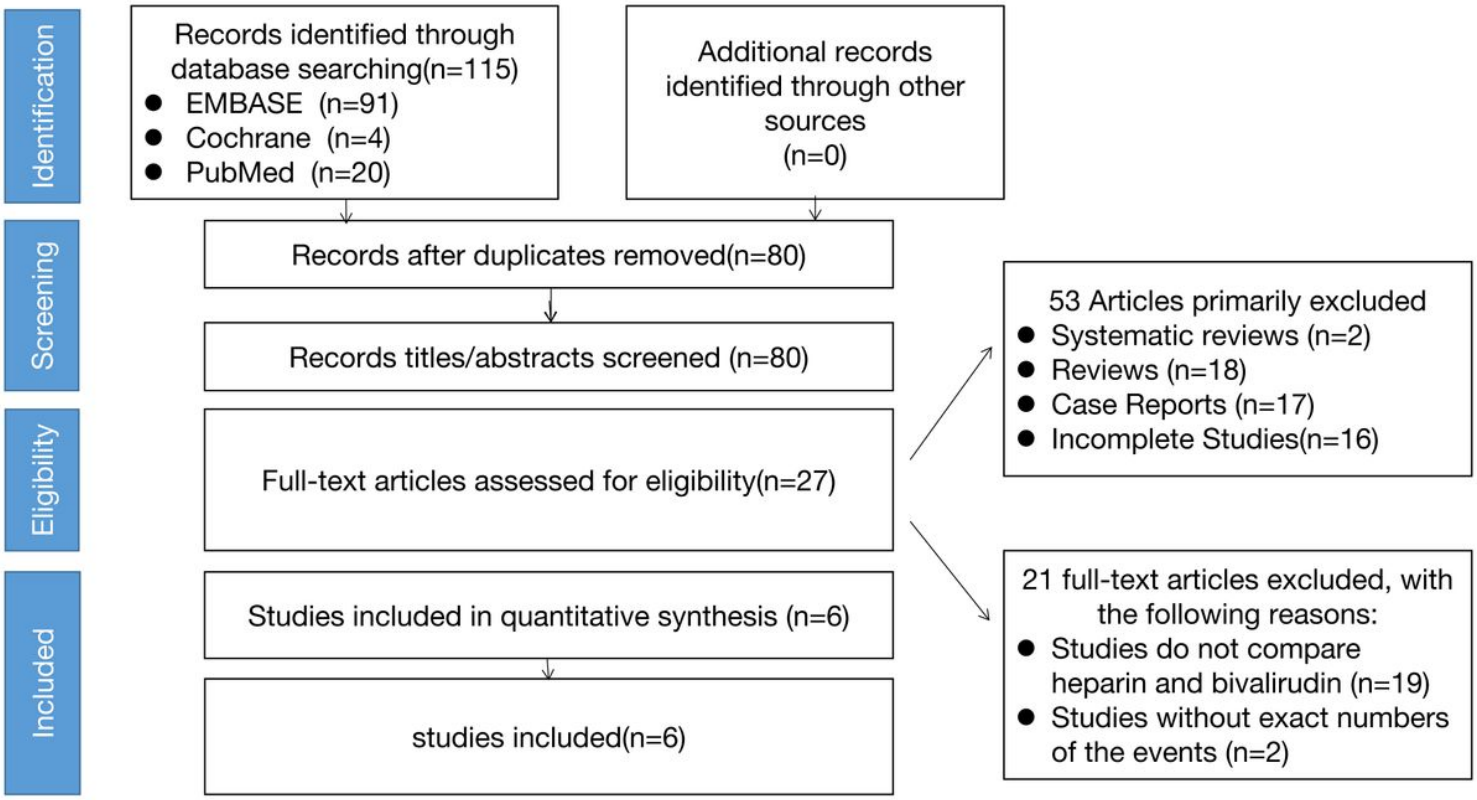

Figure 1

Flow chat of study selection

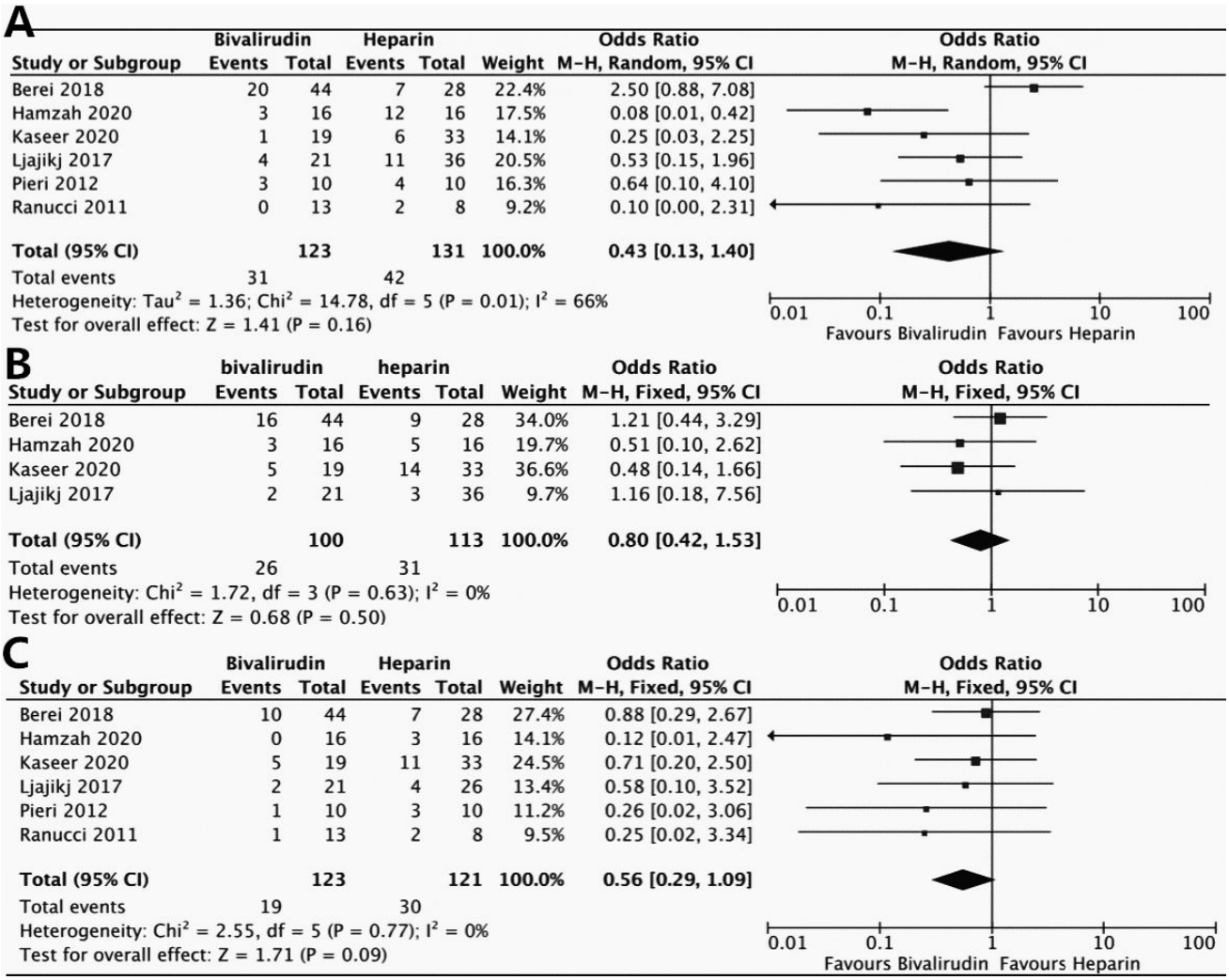

Figure 2

The incidence of events between the bivalirudin group and the heparin group (A: major bleeding; B: 30-day mortality; C: thrombosis)

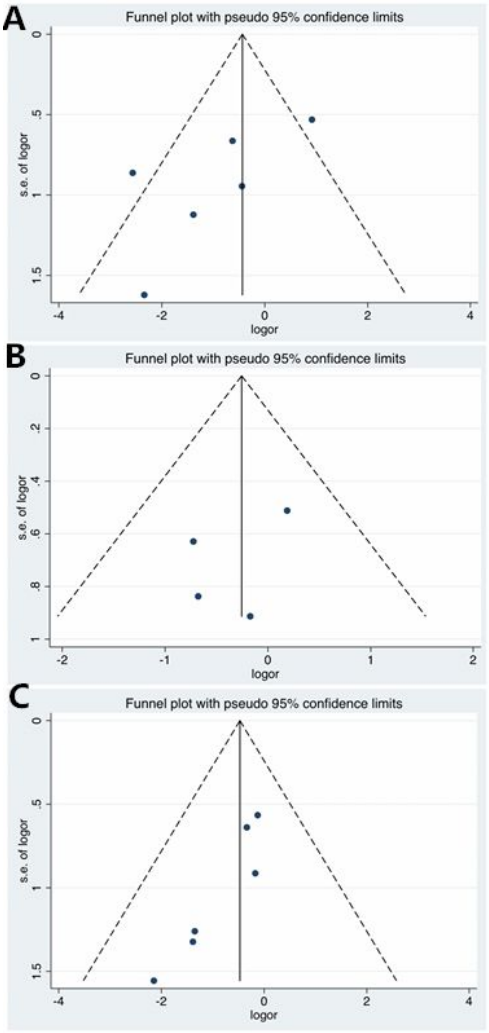

Figure 3

The Funnel plots of events between the bivalirudin group and the heparin group (A: major bleeding; B: 30-day mortality; C: thrombosis)

Supplementary Files

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