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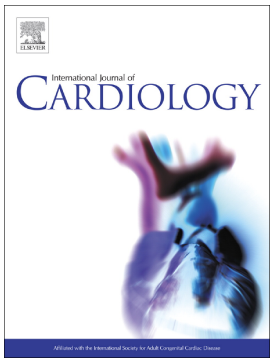

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The effect of Antithrombotic Treatment on Mortality in Patients with Acute Infection: a Meta-Analysis of Randomized Clinical Trials

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

Running Title: Thrombosis and inflammation

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Abstract

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Background and aims

Acute infections cause relevant activation of innate immunity and inflammatory cascade. An excessive response against pathogens has been proved to trigger the pathophysiological process of thrombo-inflammation. Nevertheless, an association between the use of antithrombotic agents and the outcome of critically ill patients with infectious diseases is lacking. The aim of this meta-analysis is to determine the impact of antithrombotic treatment on survival of patients with acute infective disease.

Methods

MEDLINE, Embase, Cinahl, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL) databases were systematically searched from inception to March 2021. We included randomized controlled trials (RCTs) that evaluated any antithrombotic agent in patients with infectious diseases other than COVID-19. Two authors independently performed study selection, data extraction and risk of bias evaluation. The primary outcome was all-cause mortality. Summary estimates for mortality were calculated using the inverse-variance random-effects method.

Results

A total of 16,588 patients participating in 18 RCTs were included, of whom 2141 died. Four trials evaluated therapeutic-dose anticoagulation, 1 trial prophylactic-dose anticoagulation, 4 trials aspirin, and 9 trials other antithrombotic agents. Overall, the use of antithrombotic agents was not associated with all-cause mortality (relative risk 0.96; 95% confidence interval, 0.90-1.03).

Conclusions

The use of antithrombotics is not associated with all-cause mortality in patients with infectious disease other than COVID-19. Complex pathophysiological interplays between inflammatory and thrombotic pathways may explain these results and need further investigation.

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REGISTRATION: PROSPERO, CRD42021241182.

Keywords: Anticoagulants, Antithrombotic Agents, Hemostasis, Infections, Meta-Analysis

1. Introduction

The interplay between innate immunity, platelet activation and inflammatory disease, named immune-thrombosis, has been recognized and described over the past decades.(1–4) It involves the crosstalk between blood neutrophils (releasing a large amount of proinflammatory mediators), aggregated platelets, complement pathway activation and viral and bacterial agents surface proteins.(1–4) Nevertheless, when these processes become excessive and dysregulated, it may lead to the pathophysiological process of thrombo-inflammation(1–4). This is triggered by neutrophils serine protease release further amplified by thrombin generation, anaphylatoxins C3a and C5a, C3b and C5b-9 complex (membrane attack complex, MAC) activation and reactive oxygen species release (ROS).(1–4) In this perspective, a first line non-specific host defence can lead to an overwhelming activation response.

The multiple and pleiotropic mechanisms involved explain why it is challenging finding therapeutic approaches balancing between the beneficial and detrimental effects of immune-thrombosis (Figure 1). Indeed, it is well known that heparin exhibits a wide range of pleiotropic activities, including anti-inflammatory, antiviral (heparin frontiers) and anticoagulant properties.(5–9) Recently, growing evidence rises for a role of unfractionated heparin (UFH) as entry blocking agent via the receptor binding domain (RBD) of the SARS-CoV-2 spike protein(10,11) in competition with the polyanionic polysaccharide heparan sulphate. Also, nebulized UFH has shown its effectiveness in preventing patients from developing severe acute lung injury and pulmonary fibrosis.(12,13) Moreover, UFH

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reduces both the release of IL-6 by inhibiting the expression of NF-κB and its biological activity (impairing IL-6 binding to heparan sulphate on cell surface).(14)

Recent reviews (including the Cochrane review(15)) have explored this topic in COVID-19 disease. However, a comprehensive review, exploring the available evidence making an association between any antithrombotic management and outcome in critically ill patients with severe, overwhelming infectious disease is still lacking. This review aims at evaluating whether any antithrombotic therapy impacts on survival of patients with acute infections.

2. Methods

2.1 Search strategy and eligibility criteria

This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.(16) The study protocol was registered on PROSPERO (CRD42021241182). A literature search on PubMed, Embase, Cinahl, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL) was performed from database inception to March 2021 using terms for “infectious disease”, "critically ill patients”, “aspirin”, “heparin”, “Vitamin-K antagonist”, “anticoagulant” and “mortality”. The detailed search strategy is available in Supplementary Material 1 (S1). Additional relevant articles were identified through citation search of reviewed papers.

Observational studies and randomized clinical trials (RCTs) of adult patients with infectious diseases treated with antithrombotic agents were included in the analysis, with the conclusive report focusing only on RCTs. Studies were excluded if: (1) data concerning overall mortality were not reported, (2) they were abstracts, posters, reviews, case reports, editorials or guidelines, (3) full-text articles weren't available, and (4) there was a sample population duplicate.

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Only papers written in English were considered and no time restrictions were applied. Disagreements about eligibility were solved through discussion with the Senior Author (N.M.).

2.2 Outcomes and Comparators

The overall study objective was to estimate the impact of antithrombotic treatment in hospitalised patients with infectious diseases. The primary outcome was all cause-mortality. Trials and cohort studies were categorized based on the type of antithrombotic treatment used (anticoagulant, antiplatelet, other) and, in case of anticoagulant treatment, on the intensity of anticoagulation (therapeutic or prophylactic). In case of more than two treatment arms, the "weakest" treatment arm was considered as comparator; power of anticoagulation was determined considering both drug class and posology; placebo and no intervention were labelled as the weakest while therapeutic anticoagulation as the strongest.

2.3 Study selection and data extraction

Three authors (G.G., G.A.T., and F.S.) independently screened titles and abstracts, and conducted full text review for eligibility based on our pre-specified criteria. The final list of included studies was assembled after discussion between authors.

For each eligible manuscript, the following data were extracted: setting (whether patients were at the Intensive Care Unit, ICU), disease type, number of enrolling centres, initial and final time of patient accrual and total number of patients enrolled. Moreover, for each treatment arm, further data were extracted: baseline participant characteristics, type of drug, dose, route of administration, treatment length, and mortality. Data extraction was performed independently by three authors (G.G., G.A.T., F.S.).

Final data were tabulated into an electronic spreadsheet.

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2.4 Risk of bias assessment

Risk of bias was assessed for each paper by two authors in duplicate. Data were discussed until final agreement by authors was achieved. Revised Cochrane risk-of-bias tool for randomised trials (RoB 2) was used to assess quality of included studies (17).

2.5 Statistical analysis

The measure of interest was the study-specific hazard ratio (HR) or relative risk (RR) for overall mortality, and the corresponding 95% confidence interval (CI) published in each article. When such information was not directly available, it was calculated based on the numbers of events and total participants in each arm.

Summary estimates were obtained combining study-specific HRs or RRs through random-effects models. Summary as well as study-specific estimates were represented by a forest plot. Heterogeneity among studies was evaluated using the chi-square test and was quantified through the I^2 statistics that represents the percentage of total variability that can be attributed to heterogeneity rather than chance(18,19). As a sensitivity analysis, estimates were also calculated separately from studies providing HRs and RRs.

Subgroup analyses were performed on selected study characteristics including setting, disease, and type of therapy.

Reporting bias was evaluated using a funnel plot(20) and was quantified by the Egger's test(21).

All the statistical analyses were performed using the STATA software (version 14.2; StataCorp, College Station, TX, USA).

3. Results

Out of 11329 articles, 10294 were screened after duplicate removal and 284 full-text articles were sought for retrieval. Sixty additional studies were retrieved through reference

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mining. A total number of 344 papers were assessed for eligibility. After reviewing the full-text manuscript, 60 papers were ultimately included in our meta-analysis. The full screening process is resumed in Figure 2 (PRISMA Flow).

Only the 18 RCTs(22–39) were considered in the primary analysis, but data on observational studies are reported in the Supplementary material (Supplementary Material 2 (S2): complete list of retrieved papers; Supplementary Material 3 (S3): table summarising characteristics of the cohort studies; Supplementary Material 4 (S4): cohort studies meta-analysis; Supplementary Material 5 (S5): pooled estimates for overall mortality according to selected study characteristics in cohort studies).

3.1 RCT

Eighteen RCTs were included in our meta analysis. Characteristics of these studies are summarised in Table 1. Seven RCTs focused on ICU patients, while 11 evaluated non-ICU patients. Sepsis was the main syndrome of interest (11 trials). Other conditions explored were tuberculous meningitis (2 trials), endocarditis (1 trial), peritonitis (1 trial), pneumonia (1 trial) and post-traumatic infection (1 trial). One study focused on infectious diseases in general. Various antithrombotic regimens were examined in these RCTs: therapeutic anticoagulation with low-molecular weight heparin (LMWH) or UFH (4 studies), prophylactic anticoagulation with LMWH (1 study), antiplatelet therapy with aspirin (4 trials), and other antithrombotic agents such ATIII, thrombomodulin and tissue factor pathway inhibitor (9 trials). Comparators for each treatment are shown in Table 1. Median follow-up was 30 days (Interquartile Range 28 – 90). Eleven trials were classified as having low risk of bias; seven trials were classified as having some concerns for bias.

Overall Mortality

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All-cause mortality was 12.7% (1044/8247) in the treatment group and 13.2% (1097/8341) in the control group with a summary HR/RR of 0.96 (95% CI, 0.90-1.03; I^2, 0.0%; Figure 3). The vast majority of studies provided the RR (or data to calculate it); in the sensitivity analysis considering separately RR and HR, the combined estimates did not materially change as compared to the abovementioned. Subgroup analyses were performed and pooled estimates for overall mortality according to selected study characteristics are summarised in Table 2. No statistically significant association between antithrombotic regimens and overall mortality was found.

4. Discussion

The results of this meta-analysis based on 16,588 patients from 18 RCTs showed no association between antithrombotic treatments and mortality. This lack of association was consistent in subgroup analyses according to treatment type or disease setting.

Most of the trials included were focused on the use of other antithrombotic agents, such as antithrombin III and thrombomodulin, with only one trial exploring the role of prophylactic anticoagulation. Regarding disease type, there was only one trial exploring the role of antithrombotic agents in pneumonia and one in endocarditis. Furthermore, COVID-19 RCTs weren't examined in our meta-analysis since their results will be analysed by a focussed ongoing meta-analysis (PROSPERO CRD42020213461).

It is well known that, under certain conditions, thrombosis is an independent line of host defence, being part of the innate immunity to prevent pathogen dissemination through the vascular system(2).

Among the several actors involved, platelets exert an orchestral role: they have the potential activating the haemostatic system throughout the release of inorganic polyphosphates from their dense granules and release various other coagulation interfering mediators (as von Willebrand factor, Platelet-Derived Growth Factor, Platelet factor-4, Platelet-Activating Factor

and thrombin) from their alfa granules; platelets also may contribute to neutrophiles rolling and activation acting by surface p-selectins receptor, have an active role in cytokines and chemokines release from neutrophils throughout CD40L release and finally promote IL-1 activation.(1–4,40) Thrombin generation boosts this process by acting on the tenase complex and by further activating the platelet feedback loop system.(1–4,40) This might explain the important interest in the role of antithrombotic treatment in acute, overwhelming infections complicated by uncontrolled inflammation.

Nevertheless, the large number of thrombosis-related host molecules produced during infectious disorders can explain why hyperactive and unbalanced network of mediators released during more advanced stages of an acute infection is detrimental to the host by uncontrolled immunothrombosis activation. Therefore our results are consistent with the idea that thromboprophylaxis (i.e. mild antithrombotic antagonism) associated to specific antimicrobic agents in the early stage of an infectious disorder are probably the best treatment without exasperating an antagonism of the haemostatic system which is based on balanced relationships.

This explains even because an overall effect of antithrombotic treatments on mortality of patients with acute infections seems unlikely. However, despite the results of our meta-analysis, we believe that the role of antithrombotic treatments in acute infectious diseases needs to be further explored since evidence from RCTs is scarce and some antithrombotic agents were under-represented in clinical trials. Moreover, given the well-known interplay between inflammation, coagulation and platelets aggregation it is mandatory to deeply elucidate if any antithrombotic agent could be beneficial in terms of mortality reduction.

4.1 Limitations

To date, this was the first meta-analysis exploring the overall effect of antithrombotic treatments on mortality of patients with acute infections. However, our study has several

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limitations. First of all, the RCTs available in the non-COVID setting were limited and with heterogenous antithrombotic treatments. We explored all the available studies and pooled results of all the observational studies retrieved is reported in the Supplementary material (S4 and S5). However, the heterogeneity measured strongly limits the possibility of drawing correct inferences from cohort studies. Secondly, we excluded COVID disease, because considered a peculiar disorder being investigated in an ongoing meta-analysis. Third we did not consider secondary endpoints such as bleeding and thromboembolic events, because the RCTs analysed were not consistent about these outcome reporting.

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Conflicts of Interest

None declared.

Author Contributions

Gianluca Gazzaniga: Investigation, Data curation, Writing - Original Draft, Visualization. **Giovanni Amedeo Tavecchia:** Investigation, Data curation, Writing - Original Draft, Visualization. **Francesca Bravi:** Data curation, Formal analysis, Writing - Review & Editing. **Francesca Scavelli:** Investigation, Data curation, Writing - Original Draft. **Giovanna Travi:** Writing - Review & Editing **Gianluca Campo:** Writing - Review & Editing, Supervision. **Christophe Vandenbriele:** Writing - Review & Editing, Visualization, Supervision. **Tobias Tritschler:** Writing - Review & Editing, Supervision. **Jonathan A.C. Sterne:** Writing - Review & Editing, Supervision. **Srinivas Murthy:** Writing - Review &

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Editing, Supervision. **Nuccia Morici:** Conceptualization, Methodology, Investigation, Data curation, Writing - Review & Editing, Project administration.

All the authors gave final approval of the version to be published

Acknowledgement

Figure 1 and Figure 2 were created with BioRender.com (https://biorender.com/)

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Table 1) Characteristics of included RCTs

Author	*Study population*	*Follow-up duration (days)*	*Setting*	*Disease*	*Intervention*	*Drug*	*Comparator*	*RoB 2*
Fourrier et al. (1993)(22)	35	28	Not ICU	Sepsis	Other	ATIII	Placebo	Some concerns
Gardlund et al. (1996)(23)	11693	60	Not ICU	Infectious diseases	Prophylactic anticoagulation	LMWH	No intervention	Some concerns
Baudo et al. (1998)(24)	100	30	ICU	Sepsis	Other	ATIII	Placebo	Low
Eisele et al. (1998)(25)	42	30	ICU	Sepsis	Other	ATIII	Placebo	Some concerns
Schorr et al. (2000)(26)	50	90	Not ICU	Peritonitis	Other	ATIII	Placebo	Some concerns
Abraham et al. (2001)(27)	210	28	ICU	Sepsis	Other	rTFPI	Placebo	Low
Warren et al. (2001)(28)	2314	28	ICU	Sepsis	Other	ATIII	No intervention	Low
Chan et al. (2003)(29)	115	35	Not ICU	Endocarditis	Antiplatelet	Aspirin	Placebo	Low
Jaimes et al. (2009)(30)	319	28	Not ICU	Sepsis	Therapeutic anticoagulation	UFH	No intervention	Low
Misra et al. (2010)(31)	118	90	Not ICU	TB meningitis	Antiplatelet	Aspirin	No intervention	Low
Aikawa et al. (2011)(32)	80	28	Not ICU	Sepsis	Other	TM-alfa	Therapeutic anticoagulation	Low
Oz et al. (2013)(33)	185	30	Not ICU	Pneumonia	Antiplatelet	Aspirin	Placebo	Some concerns
Li et al. (2015)(34)	36	90	ICU	Post traumatic infection	Therapeutic anticoagulation	LMWH	Prophylactic anticoagulation	Some concerns
Hagiwara et al. (2016)(35)	92	90	Not ICU	Sepsis	Other	rhTM	No intervention	Low
Yang et al. (2016)(36)	224	Ns	ICU	Sepsis	Therapeutic anticoagulation	UFH	No intervention	Low
Mai et al. (2018)(37)	81	60	Not ICU	TB meningitis	Antiplatelet	Aspirin	Placebo	Some concerns
Peetermans et al. (2018)(38)	94	90	Not ICU	Sepsis	Therapeutic anticoagulation	DOAC	Prophylactic anticoagulation	Low
Vincent et al. (2019)(39)	800	28	ICU	Sepsis	Other	rhTM	Placebo	Low

ICU Intensive Care Unit; ATIII Antithrombin III; LMWH Low Molecular Weight Heparin; ns: not specified; rTFPI recombinant Tissue factor pathway inhibitor; UFH Unfractionated Heparin; TB Tuberculosis; TM-alfa Thrombomodulin Alfa; rhTM recombinant human soluble thrombomodulin; DOAC Direct Oral Anticoagulant

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Table 2) Pooled estimates for overall mortality according to selected study characteristics in RCT studies

Category	N of studies	N of patients	Estimate	Heterogeneity within subgroup	Heterogeneity between subgroups
Setting					
ICU	7	3726	0.98 (0.90-1.07)	0.739	0.480
Not ICU	11	12901	0.92 (0.80-1.05)	0.408	
Disease					
Sepsis	11	4310	0.98 (0.90-1.06)	0.747	0.441
Endocarditis	1	115	0.58 (0.16-2.19)	-	
Pneumonia	1	185	0.34 (0.08-2.35)	-	
Other infectious diseases	5	12017	0.87 (0.65-1.17)	0.344	
Intervention					
Therapeutic anticoagulant (vs no intervention or prophylactic anticoagulant)	4	673	1.08 (0.87-1.33)	0.917	0.536
Prophylactic anticoagulant (vs no intervention)	1	11603	0.94 (0.80-1.09)	-	
Aspirin (vs no intervention or placebo)	4	538	0.44 (0.24-0.81)	0.878	
Other antithrombotic agent (vs no intervention, placebo, or therapeutic heparin)	9	3723	0.96 (0.89-1.05)	0.690	

ICU Intensive Care Unit; COVID 19 Coronavirus Disease 19

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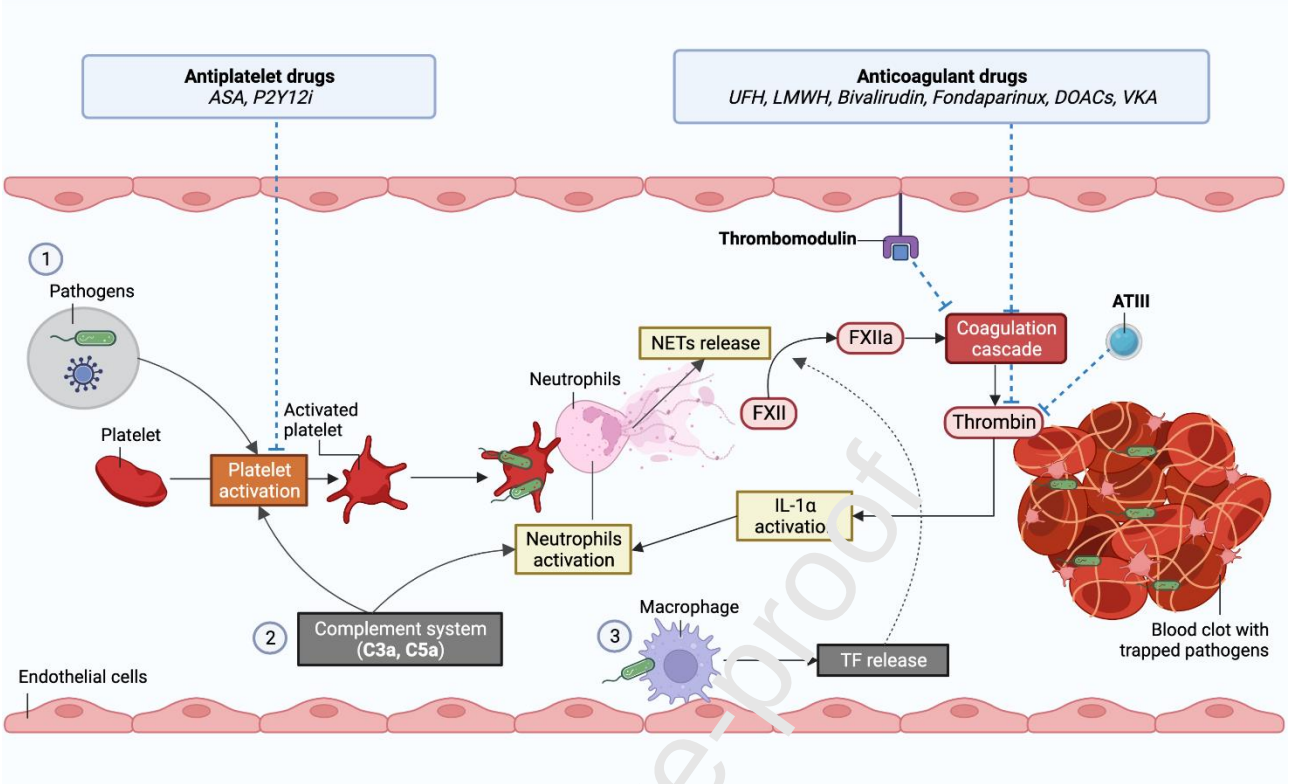
Figure 1) Interplay between immunity, platelet aggregation and coagulation cascade



Immunothrombosis is triggered by pathogens invasion into the bloodstream (1), complement system activation (2), and tissue factor (TF) release by macrophages (3). Neutrophils activation, induced by activated platelets and complements system, promotes neutrophil extracellular traps (NETs) release which catalyse the activation of factor XII (FXII) to FXIIa. Initiation of coagulation cascade leads to thrombin generation and blood clots formation with pathogens trapping. Moreover, thrombin boosts the process by activating interleukin 1-alpha (IL1a) thus leading to further neutrophils activation. ASA acetylsalicylic acid; P2Y12i P2Y12 inhibitors; UFH unfractionated heparin; LMWH low molecular weight heparin; DOACs direct oral anticoagulants; VKA vitamin K antagonist; ATIII antithrombin III.

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Figure 2) PRISMA flow: diagram of trials' selection process

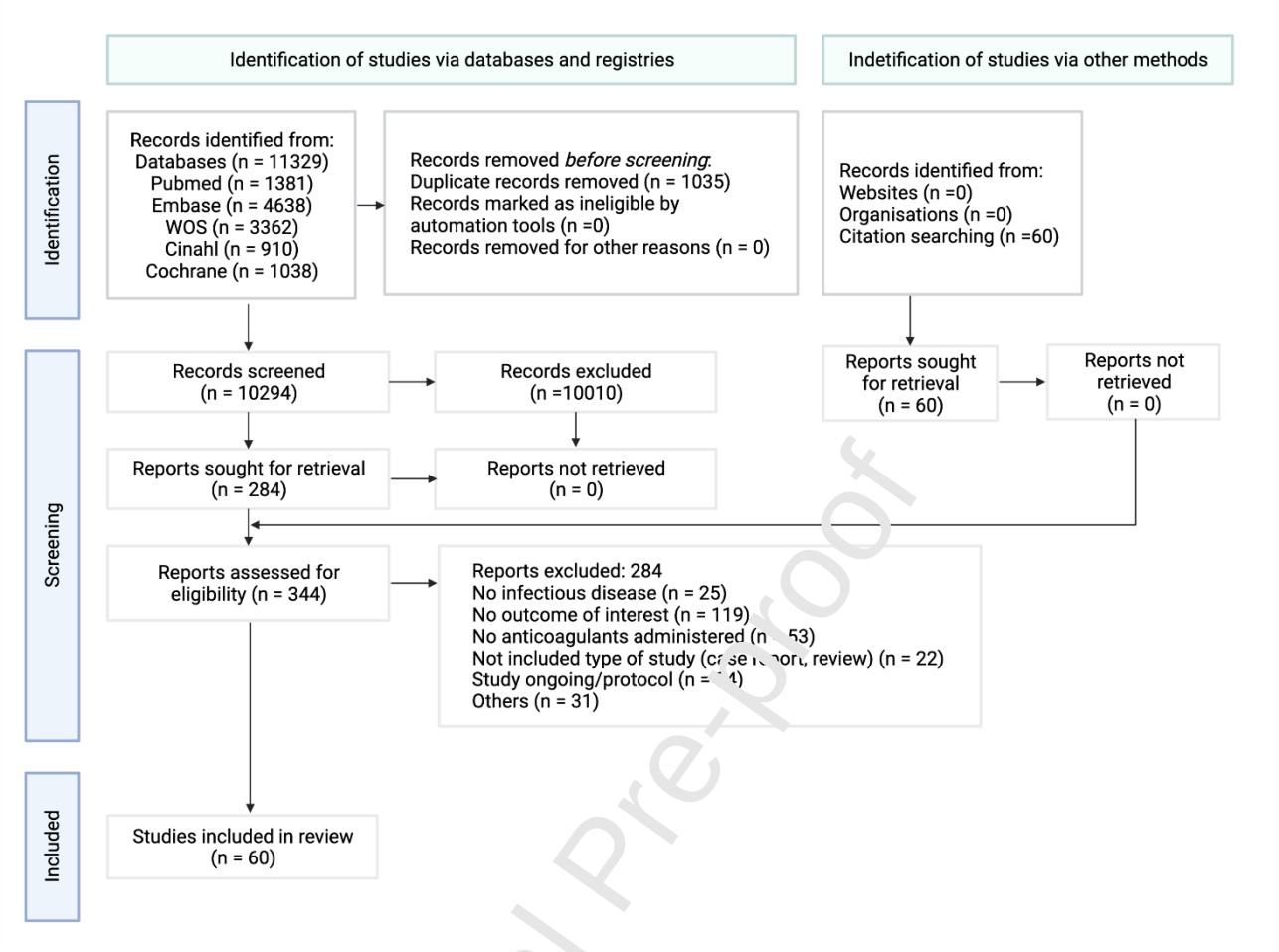

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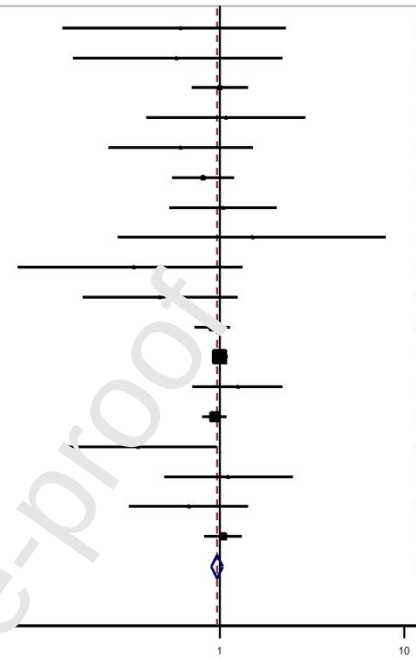
Figure 3) Association byetween antithrombotic treatments and all-cause mortality in patients enrolled in RCTs with infectious disease

Author	Events treatment group	N treatment group	Events control group	N control group	Setting	Disease	Intervention	HR or RR (95% CI)	% Weight
Mai et al. 2018	1	40	4	41	not ICU	other infectious diseases	antiplatelet	0.61 (0.14, 2.28)	0.24
Chan et al. 2003	4	60	6	55	not ICU	endocarditis	antiplatelet	0.58 (0.16, 2.19)	0.28
Baudo et al. 1998	27	49	28	51	ICU	sepsis	other therapeutic anticoagulant	1.00 (0.70, 1.43)	3.73
Schorr et al. 2000	6	24	6	26	not ICU	other infectious diseases	other therapeutic anticoagulant	1.08 (0.40, 2.90)	0.48
Eisele et al. 1998	5	20	9	22	ICU	sepsis	other therapeutic anticoagulant	0.61 (0.25, 1.52)	0.58
Abraham et al. 2001	43	141	26	69	ICU	sepsis	other therapeutic anticoagulant	0.81 (0.55, 1.20)	3.12
Hagiwara et al. 2016	13	47	12	45	not ICU	sepsis	other therapeutic anticoagulant	1.04 (0.53, 2.03)	1.05
Li et al. 2015	3	18	2	18	ICU	other infectious diseases	therapeutic anticoagulant	1.50 (0.28, 7.93)	0.17
Oz et al. 2013	3	91	9	94	not ICU	pneumonia	antiplatelet	0.34 (0.08, 1.33)	0.24
Fourrier et al. 1993	4	17	9	18	not ICU	sepsis	other therapeutic anticoagulant	0.47 (0.18, 1.25)	0.51
Vincent et al. 2019	106	395	119	405	ICU	sepsis	other therapeutic anticoagulant	0.91 (0.73, 1.14)	9.57
Warren et al. 2001	450	1157	448	1157	ICU	sepsis	other therapeutic anticoagulant	1.00 (0.91, 1.11)	48.16
Yang et al. 2016	24	119	17	105	ICU	sepsis	therapeutic anticoagulant	1.25 (0.71, 2.19)	1.50
Gardlund et al. 1996	304	5776	333	5917	not ICU	other infectious diseases	prophylactic anticoagulant	0.94 (0.80, 1.09)	19.87
Misra et al. 2010	10	59	23	59	not ICU	other infectious diseases	antiplatelet	0.36 (0.14, 0.96)	0.51
Peetermans et al. 2018	10	47	9	47	not ICU	sepsis	therapeutic anticoagulant	1.11 (0.50, 2.48)	0.74
Aikawa et al. 2011	9	42	12	38	not ICU	sepsis	other therapeutic anticoagulant	0.68 (0.32, 1.43)	0.85
Jaimes et al. 2009	22	159	25	160	not ICU	sepsis	therapeutic anticoagulant	1.04 (0.82, 1.32)	8.39
Overall (I-squared = 0.0%, p = 0.636)								0.96 (0.90, 1.03)	100.00



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Highlights

- There are complex interplays between inflammatory and thrombotic pathways.
- Antithrombotics are not associated with mortality in patients with infections.
- Exasperating an antagonism of the haemostatic system should not be recommended.

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