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Terapia Antitrombótica para pacientes hospitalizados por COVID-19: Uma Overview de Revisões Sistemáticas de Ensaios Clínicos Randomizados e Metanálises

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Karina Fernanda Barros Carlos

Terapia Antitrombótica para pacientes hospitalizados por COVID-19: Uma Overview de Revisões Sistemáticas de Ensaios Clínicos Randomizados e Metanálises

Este Trabalho Conclusão de Curso foi julgado adequado para obtenção do Título de "Médico" e aprovado em sua forma final pelo Curso de Graduação em Medicina da Universidade Federal de Santa Catarina.

Florianópolis, 07 de junho de 2022.

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DEDICATÓRIA

Este trabalho é dedicado às mais de 500.000 pessoas que perdemos para a COVID-19, mais especialmente dedicado ao Sr. José Ramon Franco, o homem que criou uma das pessoas mais importantes da minha vida.

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RESUMO

Objetivo: Sumarizar e analisar evidências de revisões sistemáticas sobre o uso de agentes antitrombóticos em pacientes hospitalizados pela COVID-19 além de avaliar eficácia dos regimes de doses terapêuticas de antitrombóticos.
Método: Revisões sistemáticas baseadas em ERCs com metanálise acerca do uso de antitrombóticos em pacientes hospitalizados por COVID-19. Foram incluídas nesta Overview. Estudos publicados entre novembro de 2019 e fevereiro de 2022, procurados nas bases de dados Pubmed/MEDLINE, Embase, Cochrane Library, Scopus, LILACS e nas plataformas Epistemonikos, OMS COVID-19 e Google Acadêmico. Os desfechos de interesse foram morte e eventos tromboembólicos, para avaliação de eficácia, e sangramento, como desfecho de segurança. Uma nova metanálise foi conduzida tendo como base os dados dos ERCs originais presentes nas revisões para os desfechos de interesse com: (1) os dados retirados nos estudos primários; (2) os dados de cada revisão sistemática. As sobreposições de estudos (overlap) inerentes ao modelo de estudo foram corrigidas.
Resultados: Três revisões sistemáticas envolvendo um total de 8 ECRs e 5.404 pacientes foram incluídas. Em pacientes não críticos, não há evidência de redução de todas as causas de morte (RR = 0,83; IC 95% 0,61 A 1,13) comparando a dose terapêutica e a dose profilática de anticoagulação, mas menor risco de eventos tromboembólicos (RR = 0,39; IC 95% 0,25 a 0,62) sem aumento do risco de sangramento maior (RR= 1,60, IC 95% 0,85 a 3,03). Em pacientes críticos, houve evidência de benefício com anticoagulação de dose terapêutica para redução de eventos tromboembólicos (RR 0,63; IC 95% 0,44 a 0,90) sem aumento de sangramento maior (RR 1,88; IC 95% 0,97 a 3,64) e nenhuma evidência de benefício no desfecho óbito por todas as causas (RR= 1,03; IC 95% 0,89 a 1,20).
Conclusão: O uso de dose terapêutica de anticoagulação reduz as taxas de eventos trombóticos em pacientes críticos e não críticos com COVID-19, embora não haja evidência de redução na mortalidade. Não houve significância no aumento do sangramento em pacientes críticos e não críticos. A administração da dose terapêutica deve ser criteriosa e individualizada.

Palavras-chave: Antitrombóticos, Anticoagulação, Trombose, COVID-19, Revisão de revisões sistemáticas, Overview.

ABSTRACT

Objective: Summarize and reanalyze evidence from systematic reviews on the use of antithrombotic agents in patients hospitalized with COVID-19 and evaluate the effectiveness of regimens of therapeutic doses of antithrombotics.

Methods: Systematic reviews based on RCTs with meta-analysis, using antithrombotics in patients hospitalized with COVID-19 were included in this Overview. Studies published between November 2019 and February 2022, searched in Pubmed/MEDLINE, Embase, Cochrane library, Scopus, LILACS databases, and in Epistemonikos, WHO COVID-19, and Google Scholar platforms. The outcomes of interest were death and thromboembolic events, for efficacy assessment, and bleeding as a safety outcome. A new meta-analysis was conducted based on data from the original RCTs present in the reviews for the outcomes of interest with: (1) data drawn from primary studies; (2) data from each systematic review. The overlapping inherent to the Overview model was corrected.

Results: Three systematic reviews involving a total of 8 RCTs and 5404 patients were included. In non-critically ill patients, there is no evidence of a reduction in all-cause death (RR= 0.83; 95%CI 0.61 to 1.13) comparing therapeutic-dose with prophylactic-dose of anticoagulation but was shown lower rates of thromboembolic events (RR= 0.39; 95%CI 0.25 to 0.62) without an increased risk of major bleeding (RR= 1.60, 95%CI 0.85 to 3.03). In critically ill patients, there was evidence of benefit with therapeutic dose anticoagulation for a reduction in thromboembolic events (RR 0.63; 95%CI 0.44 to 0.90) without increased major bleeding (RR 1.88; 95%CI 0.97 to 3.64) and no evidence of benefit in the all-cause death outcome (RR= 1.03; 95%CI 0.89 to 1.20).

Conclusion: Therapeutic dose of anticoagulation reduces the rates of thrombotic events in critical and non-critical patients with COVID-19, although there is no evidence of a reduction in mortality. There was no significance in the increase in bleeding in critical and non-critical patients. The administration of the therapeutic dose must be judicious and individualized.

Keywords: Antithrombotics, Anticoagulation, Thrombosis, COVID-19, Review of Systematic Reviews, Overview, meta-analyses.

FIGURAS

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TABELAS

LISTA DE ABREVIATURAS E SIGLAS

ACTION - *Therapeutic versus Prophylactic Anticoagulation for Patients Admitted to Hospital with COVID-19 and Elevated D-dimer Concentration*

ACTIV-4a - *Accelerating COVID-19 Therapeutic Interventions and Vaccines-4 Antithrombotics Inpatient Platform Trial*

AMSTAR - *A MeaSurement Tool to Assess systematic Reviews*

AOD - Anticoagulantes Orais Diretos

ATTAC – *Antithrombotic Therapy to Ameliorate Complications of COVID-19*

AVC - Acidente vascular cerebral

CAC - *Coagulopathy Associated with COVID-19*

CCA - *Corrected Covered Area*

CENTRAL – *The Cochrane Central Register of Controlled Trials*

CI – *Confidence Interval*

COVID-19 - *Coronavirus disease 2019*

DIC - *Disseminated Intravascular Coagulation*

DOAC - *Direct Dral Anticoagulants*

DVT – *Deep Venous Thrombosis*

ECA - Enzima Conversora da Angiotensina

ECR – Ensaio Clínico Randomizado

EMBASE – Base de Dados Eletrônica da Editora Elsevier

FDP - *Fibrin Degradation Products*

GRADE - *Grading of Recommendations Assessment, Development and Evaluation*

HBPM - Heparinas de baixo peso molecular

HEP-COVID – *Systemic Anticoagulation With Full Dose Low Molecular Weight Heparin Versus Prophylactic or Intermediate Dose LMWH in High Risk COVID-19 Patients*

HESACOVID - *Therapeutic Versus Prophylactic Anticoagulation for Severe COVID-19: A Randomized Phase II Clinical Trial*

HNF - Heparinas não fracionadas

I^2 – Teste de Inconsistência de Higgins

IAM Infarto Agudo do Miocárdio

ICU – *Intensive Care Unit*

IL – 1 - *Interleukin 1*

IL-6 - *Interleukin 6*

INSPIRATION - *Effect of Intermediate-Dose Versus Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit*

LILACS – Literatura Científica e Técnica da América Latina e Caribe

LMWH - *Low-Molecular Weight Heparin*

MEDLINE – *Medical Literature Analysis and Retrieval System Online*

M-H = *Mantel-Haenszel*

MI - *Miocardial Infarction*

Multiplatform - *ATTAC, REMAP-CAP and ACTIVE-4a*

NF-Kb - *Nuclear Factor kappa* B

NNH – *Number Needed to Harm*

NNT – *Number Needed to Treat*

OMS Organização Mundial da Saúde

OR – Razão de Chance

PDF - Produto da degradação da fibrina

PE - *Pulmonary Embolism*

PRISMA - *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*

PROSPERO – *International Prospective Register of Ongoing Systematic Reviews*

PubMed – Serviço da Biblioteca Nacional de Medicina dos Estados Unidos para acesso gratuito ao Medline

RAR - *Response-Adapted Randomization*

RAPID - *A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation Versus Standard Care as a Rapid Response to the COVID-19 Pandemic*

RCT - *Randomized Controlled Trial*

REMAP-CAP - *Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia*

RevMan - *Review Manager*

RoB 2 – *Risk of Bias 2*

RR - *Relative Risk*

RR – Risco Relativo

RS - Revisão sistemática

SC - *Subcutaneous*

SR - *Systematic Reviews*

TEP - Tromboembolismo pulmonar

TNF-α – *Tumor Necrosis Factor*

TVP - Trombose venosa profunda

UFH - *Unfractionated Heparin*

UTI - Unidade de terapia intensiva

WHO - *World Health Organization*

SUMÁRIO

ANEXO – MATERIAL SUPLEMENTAR

NORMAS ADOTADAS

Este trabalho de conclusão de curso, escrito em forma de artigo, foi elaborado segundo as normas da revista Blood.

Categoria: Artigo regular.

This undergraduate thesis, written in the form of an article, was prepared according to the rules of a regular article in the Blood.

Category: Regular article.

Antithrombotic therapy in patients hospitalized for COVID-19: An Overview of Systematic Reviews

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ABSTRACT

Patients hospitalized with COVID-19 are at greater risk of developing thromboembolic events. Despite the fact that two years have passed since the beginning of the pandemic and the efforts made by the scientific community to treat this condition, it has not yet been possible to establish an adequate anticoagulation strategy based on the severity of the disease. This overview aimed to summarize and reanalyze the evidence from systematic reviews of RCTs regarding the use of antithrombotics in patients hospitalized with COVID-19. Studies published between November 2019 and February 2022, in Pubmed/MEDLINE, Embase, Cochrane library, Scopus, LILACS databases, and in gray literature were analyzed with interest in the outcomes all-cause of death, thromboembolic events, and bleeding. Three systematic reviews comprising 8 RCTs and 5404 patients were included. Therapeutic dose anticoagulation in non-critically ill patients had lower rates of thrombotic events (RR= 0.39; 95%CI 0.25 to 0.62) without reducing risk of all-cause death (RR= 0.83; 95%CI 0.61 to 1.13) and no significant increase risk of major bleeding (RR= 1.60, 95%CI 0.85 to 3.03). In critically ill patients, therapeutic dose anticoagulation reduced thromboembolic events (RR 0.63; 95CI 0.44 to 0.90) without increased major bleeding (RR 1.92; 95%CI 1.00 to 3.69) and no benefit in all-cause death (RR= 0.98; 95%CI 0.84 to 1.14). A therapeutic dose of anticoagulation has no impact on reducing mortality in hospitalized patients with COVID-19 regardless of disease severity.

KEY POINTS

- Therapeutic dose of anticoagulation has no impact on reducing mortality in hospitalized patients with COVID-19.
- Prophylactic dose remains an anticoagulation recommendation for patients hospitalized for COVID-19.

INTRODUCTION

Despite the large number of people affected and the vast amount of studies on the subject, COVID-19 continues to be a big enigma for everyone. Thromboembolic events are one of the major complications of the disease. These events occur mostly in the microcirculation, and capillary-alveolar interaction in addition to macrocirculation.[1]

Initial post-mortem studies[2-4] that was later on followed by observational studies, and more recently, randomized studies demonstrated a high incidence of venous thromboembolic events, such as pulmonary embolism (PE) and deep venous thrombosis (DVT) and arterial thromboembolic events, stroke and myocardial infarction (MI), in hospitalized patients. Even though these events can occur at any stage of the infection, a higher incidence has been described in critically-ill patients hospitalized in the intensive care units (ICU).[2,5]

The thrombotic alterations are associated with the interaction of the virus with the immune and inflammatory system, coagulation pathways, and direct endothelial damage. Meaning that all three elements of Virchow's triad are involved (endothelial injury, hypercoagulability, and venous stasis) and may act simultaneously in the pathophysiology of thrombosis.[6, 7]

Sars-CoV-2 enters cells by binding its protein S to the host's angiotensin-converting enzyme 2 (ACE2), expressed in greater amounts in the membrane of type II pulmonary alveolar cells, bronchial and nasal secretory cells, endothelial cells, heart, brain, kidneys, and intestine. Viral S and N proteins modulate the signaling of the transcription factor NF-κB and the secretion of pro-inflammatory cytokines such as IL-6, IL-1 β, and TNF-α released by infected macrophages and monocytes. This inflammatory response can culminate in a cytokine storm associated with the disease severity.[8,9] The inflammatory process results in the activation of vascular endothelial cells with the release of platelets and von Willebrand factor, and by direct injury, causing endothelitis.[6] In addition to these mechanisms, the activation of other coagulation factors has also been described fibrinogen, factors VIII, increased platelet reactivity and changes in antithrombin, protein S and C. Increase in D-dimers considered a marker of disease severity[9], and fibrin degradation products (FDP).[6, 10]

Inflammatory activation leads to hemodynamic changes with increased stasis and alterations in flow and shear stress response[11]. The prothrombotic condition is worsened by bed restriction, mechanical ventilation, and/or the use of other invasive devices.[12]

Given these points, it is possible to understand the high incidence of thrombosis in patients with COVID-19, and its peculiar characteristics, which worsen lung damage and

contribute to multiple organ failure and a significant increase in mortality, a fact that motivated a intense search for adequate anticoagulant therapies.[1,3]

Due to the urgency imposed by the pandemic, for some time observational studies guided the recommendations for anticoagulation in hospitalized patients with COVID-19.[13] Recently, randomized controlled clinical trials (RCTs) began to have their results published demonstrating the risks and benefits of different antithrombotic regimens in these patients.[14]

However, there is no consensus regarding the optimal dose for subgroups of ICU and ward patients. The objective of this study is to evaluate and reanalyze the evidence regarding the use of different antithrombotic regimens (intermediate-dose x therapeutic-dose and prophylactic-dose) for critical and non-critical patients. This is a tertiary review study (Overview) of systematic reviews (SR) with meta-analysis.

METHOD

This Overview was registered in PROSPERO: CRD42021261257. The report in this Overview follows the PRISMA checklist, the recommendations of the Cochrane Collaboration manual[15], and the Overview guidelines[16].

Search Strategy and Databases

A search for SR based on RCTs comparing antithrombotic therapeutic regimens published between November 2019 and February 2022 was conducted. The databases included were Pubmed/MEDLINE, Embase, Cochrane library, Scopus, LILACS databases, Epistemonikos, WHO COVID-19, and Google Scholar platforms, without language restriction. The search strategy is detailed in the supplementary material.

Inclusion and Exclusion Criteria

Systematic reviews with meta-analysis were included based on RCTs with at least one active arm of antithrombotic drug therapy, regardless of regimen or dosage.

Studies involving the pediatric population and those under 18 years of age, pregnant women, studies involving non-pharmacological antithrombotic methods, and SRs of observational studies or reviews whose methodology did not meet the methodological criteria of the systematic review model were excluded.

Outcomes

The outcomes of interest evaluated in this Overview were mortality and thromboembolic events as evaluators of efficacy, and bleeding as evaluators of safety during the hospital stay.

Data extraction

Data extraction was performed in pairs (KC and VF) using the COVIDENCE tool. Discrepancies were resolved by consensus or, if necessary, by a third researcher (AH). The data extracted from each review were publication date, country, number of RCTs included, name of RCTs, total sample size, design of RCTs included, antithrombotic used, dose, outcomes and results obtained.

Data synthesis

Systematic reviews were summarized in tabular and narrative form (Table 1). The main findings brought by each SR were also outlined, as well as evaluations, limitations, and eventual disagreements identified during the critical evaluation process.

Evaluation of primary studies

The RCTs were extracted from systematic reviews. A thorough reading was performed, and data from the RCTs were compiled and tabulated for benchmarking. Data extracted directly from the primary studies are shown in Table 2.

Overlapping

The RCTs that recur in reviews (overlapping) and their percentage of importance in each review are available in Table 4. (supplementary material) The rate of overlap within the SRs it's presented in Table 5 (supplementary material) through the calculation of the corrected covered area (CCA). If the overlapping varies between 0 and 5% it means slight overlap; moderate if between 6 – 10%; high if between 11 and 15%, and very high overlap if greater than 15%.[17]

Quality and Risk of bias assessment

The AMSTAR 2[18] SR methodological quality assessment tool was independently performed by peers (KC and VF). Discrepancies in assessments were resolved by consensus or by a third reviewer (AH).

RoB2 was used for risk of bias assessment for each SR and RCT. The generated graph is available in Figures 2 – 4 and Supplementary Figures. (supplementary material – S1 – S6)

Quality of evidence

The GRADE approach was used as a tool for assessing the level of evidence and rating the strength of clinical practice recommendations for the interventions evaluated in this Overview. GRADE has 4 levels of certainty of evidence: very low, low, moderate, and high, and this classification is based on the elements: risk of bias (methodological limitations), imprecision, inconsistency, indirect evidence, and publication bias.[19]

Statistical analysis

Meta-analyses using RevMan 5.4 were conducted for the outcomes of interest and presented as forest plots for data from the primary studies (RCTs) and data from systematic reviews. A confidence interval (CI) of 95% was considered for this study and the significance level was set at 5%. Effect estimates were expressed as relative risk (RR). For Sholzberg et al.[20] the odds ratio analysis was converted into relative risk.[15]

The statistical heterogeneity of the revisions was evaluated by the p-value of the Higgins inconsistency statistic (I^2) and the Cochran's Q test based on I^2. Heterogeneity was considered low if $I^2 < 25\%$, moderate if I^2 between 25 - 50% and high if $I^2 > 50\%$. For statistically significant heterogeneity, the combined effect estimate was determined with a random-effects model. For heterogeneity below 50% (low and moderate), a fixed-effects model was used[15].

We performed a sensitivity analysis by sequentially removing every single study from the pooled effect estimates to verify how a single study affected our overall findings. The same method was performed for individual analysis of escalated-dose, intermediate-dose, and therapeutic-dose.[23-30]

RESULTS

The literature search was carried out in March 2022, resulting in 1450 citations, of which 618 were duplicates. The remaining 832 had their titles and abstracts analyzed. 139 were selected for full-text reading, leading to the exclusion of 133 articles that did not include the intervention, randomization, meta-analysis or analysis for the outcomes of interest. Finally, three systematic reviews[20-22] with meta-analysis met all eligibility criteria and were included in

the present Overview, comprising a total of 8 RCTs[23-30] and 5404 patients. Figure 1 summarizes the screening process in the PRISMA flowchart for the selection of studies.[31]

Data compiled from systematic reviews are described in Table 1. For analysis purposes, the intermediate and therapeutic-doses were called escalated-dose.

Included Systematic Reviews

Reis, 2021[21]

Reis et al.[21], included 8 RCTs and 5580 patients[23–30] evaluating the safety and efficacy of intermediate and therapeutic doses of anticoagulation, without restriction of anticoagulant types, for hospitalized patients with COVID-19. The reviewers applied the World Health Organization Clinical Progression Scale[32] to conduct analyzes of moderately ill (WHO 4 - 5) and critically ill (WHO 6 - 9) patients. Primary studies whose differentiation between these groups could not be established were allocated to a third group called 'moderate to severe disease' (WHO 4 - 9).

Their analysis demonstrates that in any thrombotic event or death, intermediate-dose anticoagulation has no effect in critically ill COVID-19 patients (RR 1.03, 95% CI 0.86 to 1.24). There was no benefit from using therapeutic-dose anticoagulation to decrease any thrombotic event or death in non-critically ill patients (RR 0.64, 95% CI 0.38 to 1.07) and little or no effect in critically ill patients (RR 0.98, 95% CI 0.86 to 1.12). The risk of major bleedings may increase independent of disease severity (RR 1.78, 95% CI 1.15 to 2.74).

Table 1: Details of Systematic Reviews included

Review ID	Country	Date assessed as up to date	Number of included RCTs	Number of participants	Intervention	Control or comparison intervention	Outcomes for which data assessed	Review limitations
Reis, 2021	Germany	November 29, 2021.	8	5580*/ 5404	Intermediate- and therapeutic-dose anticoagulation	Standard thromboprophylaxis	All-cause mortality, worsening of clinical status (intubation or death /mechanical ventilation or death), improvement of clinical status, any thrombotic event , any thrombotic event or death, major bleedings	Heterogeneity of study settings, populations, and therapeutic approaches; No standard for defining disease severity in primary studies. Risk of publication and reporting bias
Sholzberg, 2021	Canada	October 8, 2021	5	2982	Therapeutic-dose anticoagulation	Standard thromboprophylaxis	All-cause death, death or invasive mechanical ventilation, death or organ support, death or major thrombotic event, death or any thrombotic event, major thrombotic events, major bleeding[1], ventilator-free days alive, and organ support–free days alive.	Trial-level rather than individual-level data. Only 5 trials were included. Risk of publication bias
Ortega-Paz, 2021	Spain	August 25, 2021	7	5154	Intermediate- and therapeutic-dose anticoagulation (escalated dose)	Standard thromboprophylaxis	all-cause death, major bleeding, VTE, MI, stroke, systemic arterial embolism, any bleeding and minor bleeding	Trial-level rather than individual-level data, limited size of specific groups. Combined trials using different types and doses of anticoagulants. Risk of ecological bias, publication and reporting bias

RCT: randomized controlled trial; VTE: venous thromboembolism; PE: pulmonary embolism; MI myocardial infarction. [1] Major bleeding as defined by the ISTH.
* The number of patients declared in the review is 5580 patients. The sum of patients in the primary studies is 5404 patients.

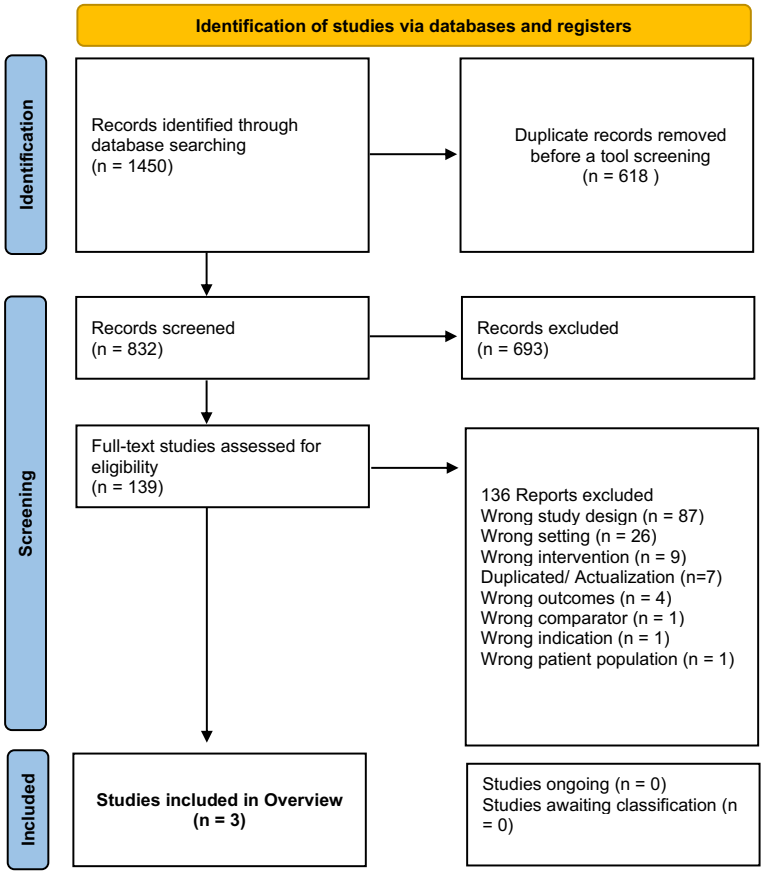

Figure 1. PRISMA flow chart.[31]

Sholzberg, 2021[20]

Sholzberg et al.[20] conducted a systematic review that included only studies involving heparins (UFH or LMWH) with 4055 patients. The authors evaluated therapeutic-dose of heparin and prophylactic-dose in non-critically and critically ill patients hospitalized due to COVID-19.

Multiplatform non-critically ill patients[23], RAPID[30], and HEP-COVID[25], were analyzed with benefit in the use of therapeutic-dose for non-critically ill patients in the outcomes death or mechanical ventilation (OR=0.64, 95%CI 0.60 to 0.98), death or organic support (OR=0.77, 95%CI 0.63 to 0.93), death or major thrombotic event (OR=0.64, 95%CI 0.48 to 0.86) and a significant increase in ventilation-free days alive (OR=1.30, 95%CI 1.05 to 1.61) and organ support-free days alive (OR=1.29, 95%CI 1.07 to 1.57) without a significant increase in major bleeding (OR=1.45, 95%CI 0.77 to 2.70), but without effectiveness in all-cause death (OR=0.76, 95%CI 0.57 to 1.02). A total of 1492 patients receiving a therapeutic-dose of anticoagulation and 1369 receiving a prophylactic-dose were analyzed.

In critically ill analysis, with 589 patients receiving a therapeutic-dose, and 612 receiving a prophylactic-dose, they used a multiplatform of critically ill patients[28], HESACOVID[26] and HEP-COVID[25], there was no evidence of benefit in the use of a therapeutic-dose of heparin to all-cause death (OR=1.17, 95%CI 0.89 to 1.54), major thrombotic events outcome (OR=1.04, 95%CI 0.80 to 1.36) with no increased risk of major bleeding (OR=1.62, 95%CI 0.83 to 3.21), and without benefit in organ support-free days alive (OR=0.83, 95%CI 0.67 to 1.03).

Ortega-Paz, 2021[22]

The manuscript included 7 RCTs[23, 24, 26-29] with a total of 5154 patients comparing prophylactic dose of anticoagulation with escalated-dose (intermediate and therapeutic-dose) in non-critically and critically ill patients with COVID-19.

The review performed subgroup analysis (critical and non-critical) and overall analysis to estimate specific treatment effect according to clinical status. There was no evidence of benefit for all-cause death in critically ill patients (RR= 1.03, 95%CI, 0.91 to 1.18) (28, 30-32), in moderate patients (RR = 0.80, 95%CI 0.40 to 01.61) (21,27,28). The review found no significant increase in bleeding risk when comparing escalating dose and therapeutic dose for critically ill patients (RR = 1.60, 95%CI 0.91, 2.84) and non-critically ill patients (RR=1.86, 95%CI 1.04 to 3.33).

The reviews separately evaluated DVT, MI, stroke and systemic arterial embolism events, having only demonstrated a reduction in rates of VTE in critical and non-critical patients using escalated-dose anticoagulation (RR = 0.55, 95% CI 0.41 to 0.74).

The number of treated patients needed to prevent all-cause death was 119 and to prevent VTE was 46. The number needed to harm was 102, 32 and 16 for major, minor and any bleeding, respectively.

Quality analysis of systematic reviews:

The quality of the reviews ranged from low to very low in AMSTAR2[18] evaluation. Reis, 2021[21] and Sholzberg, 2021[20] were classified as critically low since, in more than one critical domain, they presented elements that were partially present. Ortega-Paz, 2021[22] was evaluated with low quality, as it did not cover some non-critical domains of the tool. (See supplementary material)

Analysis of systematic reviews

The results of studies[20-22] extracted from the reviews in their meta-analyses were compiled and reanalyzed. There was statistical evidence of benefit from the use of the therapeutic anticoagulation regimen on all-cause death (RR = 0.75, 95% CI, 0.58 to 0.97) [20-22] and thromboembolic events (RR = 0.39, 95% CI, 0.25 to 0.62) [20-22] for non-critically ill patients without increasing risk of major bleeding (RR= 1.60, 95%CI, 0.85 to 3.03) [20-22]. In critically ill patients, there was evidence of benefit with therapeutic dose anticoagulation for the outcome of thromboembolic events (RR = 0.59; 95%CI, 0.40 to 0.88) [20-22] without increased major bleeding rates (RR, 1.88, 95% CI; 0.97, 3.64) [20-22] and no evidence of benefit in the death outcome (RR, 0.98; 95% CI; 0.84, 1.14). [20-22]

Overlapping

The primary studies that are repeated in each review are shown in Table 2. The corrected area coverage calculation[17] showed an overlap of 75% between the three reviews, 85% between the studies Reis et al.[21] and Sholzberg et al.[20], 62% between Reis et al.[21] and Ortega-Paz et al.[22] and 62% between Sholzberg et al.[20] and Ortega-Paz et al.[22] All results demonstrate very high overlap from primary studies. (supplementary material)

Risk of Bias Analysis

Through the Cochrane Risk of Bias tool[15], a high risk of bias was identified for some domains of the 8 primary studies[23 - 30], included in three reviews[20-22], present in this Overview.

The primary studies with the largest number of patients (Multiplatform)[23,24] use the response-adapted randomization method (RAR). This method may present inefficiency in estimating the treatment effect, difficulty invalidly analyzing results, and potential for selection bias for ongoing results.[33] Due to this random model, these studies were assessed as having a high risk of bias for these domains. All other RCTs had an electronic 1:1 randomization system and received a low risk of bias.

Perepu et al.[28] stated that more than 85% of their screened patients did not meet the eligibility criteria due to failure in screening due to lack of laboratory evidence of coagulopathy, renal failure or clinical indication of therapeutic dose anticoagulation and for this reason they were evaluated with high risk of bias.

RAPID[30] was classified as having a high risk of bias for the reporting bias domain because in their study the sample size proposed in the protocol for assessing the mortality outcome was not reached.

Re-analyses of the primary studies

Inconsistencies were observed between the data presented by the review[20 - 22] and the RCTs[23 -30] so their data were collected, summarized, and statistically re-analyzed for comparison.

The ACTION[29] was not included in these analyzes because its published results do not differentiate between non-critically ill (94%, n= 578) and critically ill (6%, n= 36) patients present in each group (therapeutic and prophylactic dose).

HEP-COVID[25] authors forwarded outcome data for all causes of death and thrombotic events of critically ill and non-critically ill patients separately for analysis in this Overview.

The INSPIRATION[27] and Perepu et al.[28] used intermediate-dose versus prophylactic dose of anticoagulation only in critically ill patients.

The intermediate dose was defined as a dose between therapeutic and prophylactic doses. It is described in supplementary material.

Critically ill patients

Escaleted-dose

Escalated-dose compared to prophylactic-dose in critically ill patients was not associated with a reduction in all-cause death (RR= 1.03; 95%CI 0.91 to 1.16; 5 RCT, 1936 patients)[24-28] and in thrombotic events (RR= 0.74; 95%CI 0.54 to 1.00; 5 RCT, 1927 patients) [24-28]. There was evidence of an increased risk of major bleeding (RR= 1.77; 95%CI 1.02 to 3.09) 5 RCT, 1929 patients. [24-28] (Figures 2 – 4)

Therapeutic dose:

Compared to prophylactic-dose, therapeutic-dose anticoagulation was associated with reduction in thrombotic events (RR= 0.63; 95%CI 0.44 to 0.90, 3 RCT 1192 patients)[18, 25, 26], without benefit in all-cause death (RR= 1.03; 95%CI 0.91 to 1.16; 3 RCT, 1936 patients) [18, 25, 26] and without increasing risk of major bleeding (RR= 1.88; 95%CI 0.97 to 3.64; 3 RCT, 1194 patients). [18, 25, 26] (supplementary material, Figures S1 – S3).

Intermediate-dose

Intermediate-dose compared to prophylactic dose anticoagulation in critically ill patients was not associated with a reduction in all-cause death (RR= 1.01; 95%CI 0.84 to 1.21; 2 RCT, 735 patients) [27, 28] and in the thrombotic event (RR= 1.18; 95%CI 0.64 to 2.17; 2 RCT,

735 patients) [27, 28]. No evidence of increased risk of major bleeding was demonstrated (RR= 1.53; 95%CI 0.55 to 4.26; 2 RCT, 735 patients).[27,28] (supplementary material, Figures S4 – S6).

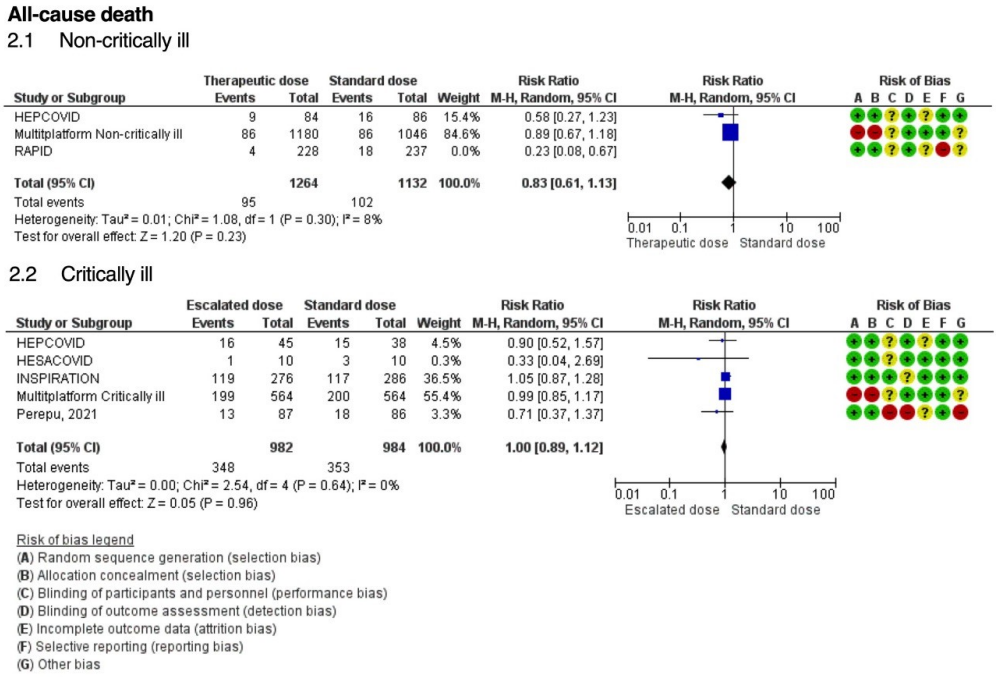

Figure 2. First efficacy outcome all-cause death forest-plot. Escalate-dose versus prophylactic-dose, non-critically ill (2.1) versus critically ill (2.2). CI = confidence intervals; M-H = Mantel-Haenszel;

Non-critically ill

Therapeutic dose:

In non-critically ill patients, compared to prophylactic-dose anticoagulation, therapeutic-dose anticoagulation was not associated with reduction of all-cause death (RR= 0.83; 95%CI 0.61 to 1.13; 2 RCT, 2396 patients)[23, 25] but with a reduction in thrombotic events (RR= 0.39; 95%CI 0.25 to 0.62; 3 RCT 2861 patients)[23, 25, 30], without an increased risk of major bleeding (RR= 1.60; 95%CI 0.85 to 3.03; 3 RC, 2861 patients). [23, 25, 30] RAPID[30] was excluded from the analysis on all-cause of death outcome for adjustment of heterogeneity, without change in effect. (supplementary material, Figures S1 – S3).

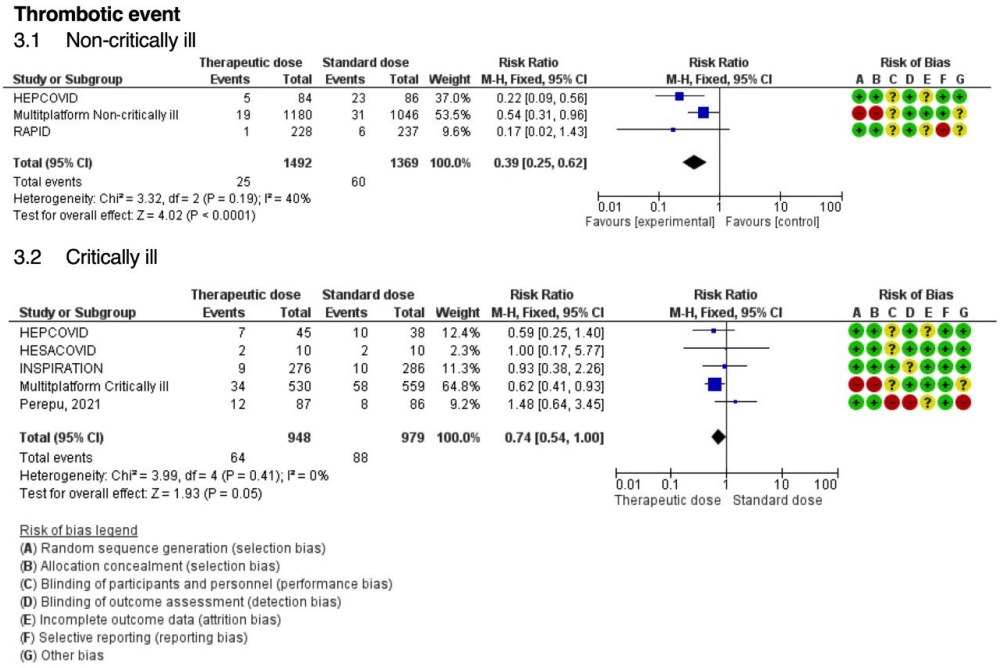

Figure 3. Second efficacy outcome thrombotic events forest-plot. Escalate-dose versus prophylactic-dose, non-critically ill (3.1) versus critically ill (3.2). CI = confidence intervals; M-H = Mantel-Haenszel;

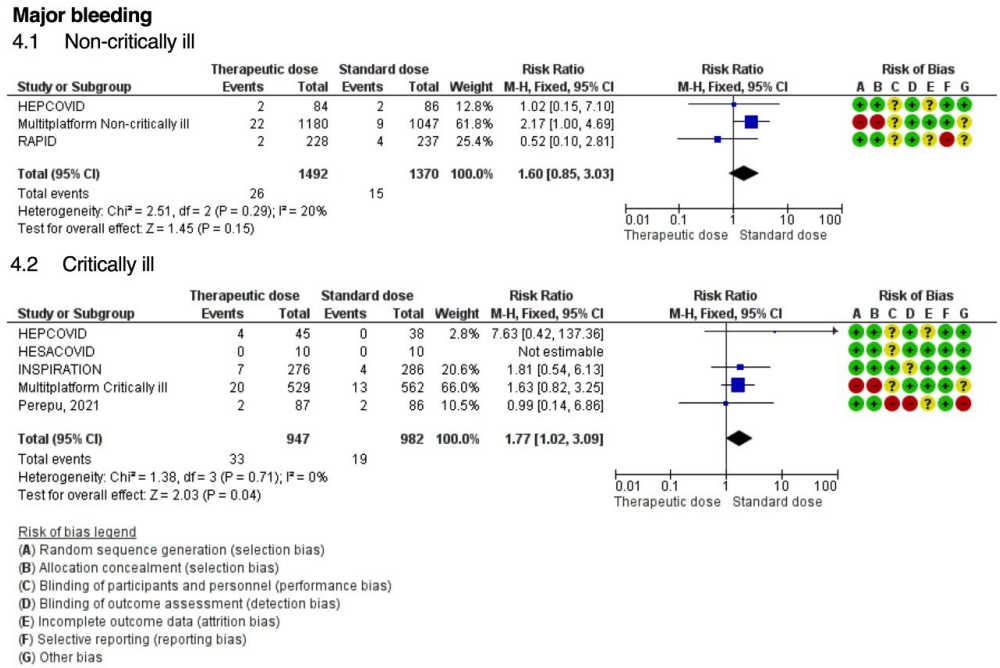

Figure 4. Safety outcome major bleeding forest-plot. Escalate-dose versus prophylactic-dose, non-critically ill (4.1) versus critically ill (4.2). CI = confidence intervals; M-H = Mantel-Haenszel;

Table 2. Overlapping of primary studies

Study Reference	Reis, 2021	Sholzberg, 2021	Ortega-Paz, 2021	Analyzed Patients	Location	Study Design	Clinical status	Intervention	Comparator	Outcomes	Follow-up Duration
INSPIRATION	X		X	562	Iran	RCT, open-label, multicenter	Critically ill	Intermediate-dose anticoagulation (enoxaparin 1mg/kg OD sc); weight and CrCl ajusted	Standard prophylaxis with enoxaparin 40mg OD, weight and CrCl ajusted	Mortality (28 and 90-day), any venous thrombotic events, any venous thrombotic events or death, major bleeding	30 -90 days
Perepu - 2021	X		X	176	USA	RCT, multi-center, open-lable	Critically ill	Intermediate-dose anticoagulation (enoxaparin 1mg/kg OD sc) weight and CrCl ajusted	Standard prophylaxis (enoxaparin 40mg OD sc), weight and CrCl ajusted	Mortality, any venous thrombotic events, major bleeding	30 days or, until hospital discharge or extended beyond
HESACOVID	X	X	X	20	Brazil	RCT, open-label, single center	Critically ill	Therapeutic-dose anticoagulation (enoxaparin 1 mg/kg sc BID)	Standard thromboprophylaxis (enoxaparin 40 mg OD;); weight and CrCI adjusted	Mortality, in-hospital mortality, any thrombotic event	14 days
ACTION	X		X	614	Brazil	RCT, multi-center, open-label	Non-critically ill (94%) and critically ill (6%)	Therapeutic-dose anticoagulation (rivaroxaban 20 mg OD) - 280 patients, 90%	Standard thromboprophylaxis (enoxaparin 40 mg sc OD) weight and CrCI adjusted	Mortality, survival until hospital discharge, any thrombotic event, any thrombotic event or death, major bleeding	30 days or until hospital discharge
RAPID 2021	X	X	X	465	Brazil, Canada, Saudi Arabia, and others	RCT, multi-center, open-label	Non-critically ill	Therapeutic-dose anticoagulation (Enoxaparin 1 mg/kg sc BID) weight and CrCI adjusted	Standard thromboprophylaxis (enoxaparin 40 mg OD), weight and CrCl adjusted	All-cause mortality, venous thrombotic events, major bleeding	28 days
Multiplataform Non-critically ill	X	X	X	2219	Brazil, Canada, UK, USA, and others	RCT, open-label, Bayesian, adaptive, multiplatform	Non-critically ill	Therapeutic-dose anticoagulation with heparinoids*, weight and CrCl adjusted	Standard low- or intermediate-dose thromboprophylaxis*	In-hospital mortality, intubation, or death, discharged without receiving organ support, any thrombotic event, any thrombotic event or death, major bleeding	21, 28 days

(Continuation - Table 2. Overlapping of primary studies)

Study Reference	Reis, 2021	Sholzberg, 2021	Ortega-Paz, 2021	Analyzed Patients	Location	Study Design	Clinical status	Intervention	Comparator	Outcomes	Follow-up Duration
Multiplatform Critically ill	X	X	X	1098	Brazil, Canada, UK, USA, and others	RCT, open-label, Bayesian, adaptive, multiplatform	Critically ill	Therapeutic-dose anticoagulation with heparinoids*, weight and CrCl adjusted	Standard low- or intermediate-dose thromboprophylaxis *	In-hospital mortality, any thrombotic event, any thrombotic event or death, major bleeding	21, 28 days
HEP - COVID 2021	X	X		253	USA	RCT, multi-center, open-label	Non-critically ill (67.2%) and critically ill (32.8%)	Therapeutic-dose anticoagulation (enoxaparin 1 mg/kg sc BID, or 40 mg sc OD/BID) weight and CrCI adjusted	Standard thromboprophylaxis (enoxaparin 40 mg sc OD/BID) weight and CrCI adjusted	VTE, ATE, or death from any cause, major bleeding	30 ± 2 or until hospital discharge

Abbreviations: USA: United States of América, UK: United Kingdom , RCT: Randomized Controlled Trial , OD: once daily, SC: subcutaneous, BID: twice daily CrCl: creatinine clearance, VTE: venous thromboembolism , ATE: arterial thromboembolism

* List with drugs and doses used by the available trial table nine

Table 3. GRADE evidence: COVID-19 hospitalized critically and non-critically ill patients

Certainty assessment							Summary of findings				
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**		**Effect**		**Certainty**
							Escaleted-dose anticoagulation	**Prophylatic - dose anticoagulation**	**Relative(95% CI)**	**Absolute(95% CI)**	
All-cause death (follow-up: mean 28 days; assessed with: Critically ill)											
5	randomised trials	serious a,b	not serious	not serious	not serious 1,a	publication bias strongly suspected strong association b	348/982 (35.4%)	353/984 (35.9%)	**RR 1.02 (0.91 to 1.15)**	**7 more per 1.000 (from 32 fewer to 54 more)**	⊕⊕⊕◯ Moderate
All-cause death (follow-up: mean 28 days; assessed with: Non-critically ill)											
3	randomised trials	serious a,b	not serious	not serious	not serious	publication bias strongly suspected strong association b	90/1492 (6.0%)	120/1369 (8.8%)	**RR 0.75 (0.58 to 0.97)**	**22 fewer per 1.000 (from 37 fewer to 3 fewer)**	⊕⊕⊕◯ Moderate
Thrombotic event (assessed with: Critically ill)											
5	randomised trials	serious a	not serious	not serious	not serious	publication bias strongly suspected strong association b	64/948 (6.8%)	88/979 (9.0%)	**RR 0.74 (0.54 to 1.00)**	**23 fewer per 1.000 (from 41 fewer to 0 fewer)**	⊕⊕⊕◯ Moderate
Thrombotic event (assessed with: Non-critically ill)											
3	randomised trials	serious a	not serious	not serious	not serious	publication bias strongly suspected strong association b	25/1492 (1.7%)	60/1369 (4.4%)	**RR 0.39 (0.25 to 0.62)**	**27 fewer per 1.000 (from 33 fewer to 17 fewer)**	⊕⊕⊕◯ Moderate
Major Bleeding (follow-up: mean 28 days; assessed with: Critically ill)											
5	randomised trials	serious a,b	not serious	not serious	not serious	publication bias strongly suspected strong association b	33/947 (3.5%)	19/982 (1.9%)	**RR 1.80 (1.04 to 3.12)**	**15 more per 1.000 (from 1 more to 41 more)**	⊕⊕⊕◯ Moderate

Table 3. GRADE evidence: COVID-19 hospitalized critically and non-critically ill patients

Certainty assessment							Summary of findings				
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**		**Effect**		**Certainty**
							Escaleted-dose anticoagulation	**Prophylatic - dose anticoagulation**	**Relative(95% CI)**	**Absolute(95% CI)**	
Major bleeding (follow-up: mean 28 days; assessed with: Non-critically ill)											
3	randomised trials	serious a,b	not serious	not serious	not serious	publication bias strongly suspected strong association b	26/1492 (1.7%)	15/1370 (1.1%)	**RR 1.61 (0.85 to 3.07)**	**7 more per 1.000 (from 2 fewer to 23 more)**	⨁⨁⨁◯ Moderate

Abbreviations: CI: confidence intervals, RR: risck ratio.

a.The primary studies with the highest number of patients (Multiplatform) use the response-adapted randomization method (RAR). This method presents problems such as: (1) bias from temporal trends, (2) inefficiency in treatment effect estimation, (3) volatility in sample-size distributions that can cause a nontrivial proportion of trials to assign more patients to an inferior arm, (4) difficulty of validly analyzing results, and (5) the potential for selection bias.

b. It is a topic of great interest in the scientific community, with uncertain risk of publication bias

Grading of Recommendations Assessment, Development and Evaluation (GRADE)

The certainty of evidence and recommendations[19] rating was downregulated for all outcomes due to serious risks of bias, imprecision, and high heterogeneity in RCTs analyzed, it is available in Table 3.

DISCUSSION

We conducted an Overview with three systematic reviews[20 - 22] including eight RCTs[23-30] to summarize and analyze different anticoagulation regimes in critically and non-critically ill hospitalized patients with COVID-19 to the outcomes of all-cause death, thrombotic events, and major bleeding.

Heparin anticoagulants, and direct oral anticoagulants (supplementary material, Table 8), in the intermediate and therapeutic dose regimens compared to the standard prophylactic dose of anticoagulation were evaluated with the intention of establishing an optimal regimen for the management of these patients.

Escalated-dose refers only to critically ill patients as studies have tested the efficacy of intermediate-dose only in patients hospitalized in intensive care units. Studies that evaluated non-critically ill[23, 25, 30] patients used only a therapeutic dose of anticoagulation. In addition, we conducted analyzes for these groups intermediate-dose, therapeutic-dose, and their junction escalate-dose, separately.

We chose to carry out this Overview despite the high overlap index because the systematic reviews analyzed differed from each other and provided data that were inconsistent with the primary studies (RCTs). In our PROSPERO protocol, we did not anticipate performing an analysis of the primary studies because we did not expect to find discrepancies between the data from the reviews and the RCTs. This reanalysis therefore necessary and contributed to the demonstration of the real effect of the analyzed doses on the evaluated outcomes.

Our findings did not show superiority in the use of higher doses of anticoagulation (scaling, therapeutic, or intermediate doses) for the all-cause death outcome, for any group of patients, critically and non-critically ill. The incidence of all-cause death in critically ill patients was 36% (216/589) in the escalated-dose (intermediate and therapeutic doses) and 35% (218/612) in the prophylactic-dose group. In non-critically ill patients, the incidence of all-cause death was 6% (99/1492) and 8% (120/1369) in the therapeutic dose and prophylactic-dose anticoagulation groups respectively.

We evaluated the 'all-cause death' as an outcome of treatment efficacy. Our analysis showed no benefit in the use of therapeutic-dose for non-critically ill and critically ill patients

when compared to prophylactic-dose of anticoagulation in all-cause death outcome, as demonstrated in the included reviews and in the evaluated RCTs. These results can be explained by the complex and multifactorial physiopathology of the disease and their severity.[1]

COVID-19 presents a great challenge precisely due to the diversity of presentations and effects produced by the viral infection and although thromboembolic events are known to impact the outcomes associated with mortality and survival, antithrombotic therapy alone does not prevent deaths associated with other causes.[3, 5, 11-13]

Retrospective observational studies conducted early in the pandemic have suggested the potential benefit of therapeutic dose anticoagulation in patients with COVID-19[34]. Parisi et al.[13] performed a meta-analysis of observational studies with 25,719 hospitalized patients with COVID-19 that demonstrated more than 50% reduction in in-hospital mortality, mainly in ICU patients, using anticoagulants. Despite the authors conclusion, observational studies do not generate evidence of interventions. The findings related to reduced mortality were not confirmed after conducting RCTs for any of the critically and non-critically ill patients as shown in our analyses.[23-30]

For the second efficacy outcome assessed by our Overview, we analyzed 'thrombotic events'. Thrombotic events in critically ill patients occurred in 6% (64/948) of those receiving a therapeutic dose, and 8% (88/979) in a prophylactic dose group. In non-critically ill patients the incidence was 1% (25/1492) in the therapeutic-dose and 4% (60/1369) in the prophylactic-dose group hospitalized due to COVID-19.

Patients infected with SARS-Cov-2 may develop COVID-19-associated coagulopathy (CAC), a condition that reflects the combination of endothelial and acute phase changes that result in an increased risk of developing thromboembolic complications.[1,35] SARS-CoV-2 infection induces robust gene expression and functional changes in platelets, causing platelet hyperreactivity that may contribute to the pathophysiology of COVID-19, inducing inflammation and endotheliopathy.[35] These events are caused by several mechanisms, pathways of cellular activation, involvement of immune cells, and pro-inflammatory factors, in addition to the already known risks for the development of thrombotic events associated with immobility in hospitalization.[10, 12, 35-37] For this reason, high-dose anticoagulants were thought to have a positive impact on venous and arterial thromboembolic events.[23,24]

It would be reasonable to believe that the findings favorable to the therapeutic dose of heparin administered at a less critical stage of the disease could be associated with recent in-vitro findings based on the interaction of heparin with viral protein spike 1 (S1), blocking the virus from entering cells.[38] This effect would be dose-dependent (at levels of 100 μg/mL),

which suggests that higher doses of heparin could produce better effects on outcomes. The heparin could inhibit 70% of the invasion of Vero cells by SARS-CoV-2[38]. In addition, heparin has well-known anticoagulant and anti-inflammatory effects. This drug has historic effectiveness to avoid thrombotic events in hospitalized patients and reversible effect, making it safe to use in medical practice.[36]

The major concern associated with increasing anticoagulation doses as a prevention strategy was the presumed risk of increased bleeding in these patients. Carrying out increased doses of antithrombotics could cause fatal bleeding in already frail patients admitted to the ICU[24] and, especially, increase the risk of bleeding in a group of patients who would theoretically have no risk (not critically ill).[23]

Our Overview assessed 'major bleeding' as a safety outcome for antithrombotic use. The incidence of major bleeding occurred in 3% (33/974) of critically ill patients receiving a therapeutic dose and 1% (19/982) of those receiving a prophylactic dose of anticoagulation. Major bleeding occurred in 1% (26/1492) of non-critically ill patients receiving a therapeutic dose and 1% (15/1370) of those receiving a standard prophylactic-dose.

The low bleeding rates found in our study were also verified by Reis et al.[21] and Sholzberg et al.[20] for both subgroups of patients. Ortega-Paz et al.[26] found an association between an increased risk of major bleeding for patients receiving an escalated-dose of anticoagulation.

According to our analyzed outcomes, there would be a benefit in the use of anticoagulants at full dose for critically and non-critically ill patients only to reduce thromboembolic events, without increasing the risk of major bleeding. However, there are considerations to be made.

Our Overview did not evaluate the data from the ACTION[29] because it was not possible to understand why the authors included 6% of critical patients in their data, without justification. Even small, this percentage could have an impact on the results of the evaluation of the effect of doses and outcomes. In their analyses, Ortega-Paz et al.[22] maintained the study without considering those critical patients contained in the non-critical groups. Reis et al.[21] managed this issue by allocating these patients to one group denominated 'moderate to severe disease' using the WHO Progression Scale.[32]

Reis et al.[21] used the same device to evaluate the study HEP-COVID[25] including in the same group 'moderate to severe disease' because they did not have critically ill patient data separate from non-critical patients in the intervention and comparison arms. Our Overview

performed this analysis separately because the HEP-COVID[25] authors have provided us with this data.

The multiplatform critically ill patients (ATTAC, REMAP-CAP and ACTIVE-4a)[24] whose primary outcomes of interest were probability of support organ-free days and survival to hospital discharge did not find superiority in the anticoagulation therapeutic regimen when compared to standard thromboprophylaxis. The study was discontinued when they met a pre-specified futility criterion. Although our study did not consider these outcomes in our evaluation.

Though, the non-critically ill multiplatform (ATTAC, REMAP-CAP and ACTIVE-4a)[23] demonstrated superiority in the use of a therapeutic dose to these group of patients with heparin by an increased probability of survival to hospital discharge and organ-support free days.

Some considerations need to be made in relation to the multiplatform trials, [23,24] which, despite being robust in terms of the number of patients, have important limitations. Two studies of multiplatform (ATTAC and REMAP-CAP) used the RAR as a randomization method. This method may promote the risk of selection bias for ongoing results.[33] Although the manuscript is called "Therapeutic Anticoagulation with Heparin in Non-critically Ill Patients with COVID-19"[27], about 12 patients allocated to the usual care arm pharmacological thromboprophylaxis used DOAC. There were also 91 patients who used sub-dose anticoagulation allocated in the therapeutic dose arm of the study in non-critically ill patients.[23]

All primary studies were open label design, which may have introduced bias.[23 - 30] Finally, although the urgency imposed by the COVID-19 pandemic has established a huge challenge to the development of science and research in this exceptional context, it is necessary to reinforce the importance of methodological rigor in the quality of scientific production. The search for publication promoted by the scientific community cannot impact the quality of evidence provided by these studies, especially with regard to such a challenging disease

The results of more RCTs on anticoagulation in patients with COVID-19 are being eagerly awaited.[14] Soon we hope to have better evidence to support answers about the optimal anticoagulation regimen for each patient group. We suggest the development of high quality RCTs to individualize indications of an optimal anticoagulation strategy based on the severity disease.

Limitations

Our Overview has several limitations. Our analyzes were at the tertiary level rather than individual-level data. Carrying out analysis at the level of studies implies not considering the particularities of the presentation of COVID-19. The studies evaluated in this Overview were of low or very low quality according to the AMSTAR2 evaluation.[18] The primary studies on which our analyzes are based have significant risks of bias. Because it is an Overview, our findings invariably show overlapping data. We strive to correct these overlapping, but this limitation remains inherent in the study. We cannot exclude the possibility of risk of publication bias associated with our study as an intervention for COVID-19 represents a great opportunity for health technology manufacturers and pharmaceutical industries, in addition to being associated with social pressure for responses and results in the management of this disease.[39]

CONCLUSION

Therapeutic-dose of anticoagulation appears to reduce rates of thrombotic events in critically and non-critically ill patients with COVID-19 although, there is no evidence of a reduction in mortality. There was no significance in the increase of bleeding in critically and non-critically ill patients. This study did not assess aspects in which the therapeutic-dose did not show benefit for critically ill patients. The recommendation for this group of patients should take into account more than prevention of thrombotic events.

Autorship

Contribution: K.C. and V.F. performed the search, data extraction, quality and Risk of bias assessment, and analyses and wrote the first draft. A.H. and M.K. interpreted the results. D. C. critically revised the manuscript. All authors critically revised the manuscript and approved the final version.

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ANEXO 1 - PROSPERO

Antithrombotic therapy in patients hospitalized for COVID-19: An Overview of Reviews

Review Question

Conduct an overview of systematic reviews (SRs) and critically assess the evidence and reanalyze data on the efficacy and safety of antithrombotic therapy in hospitalized patients with COVID-19 based on the scope of the Cochrane Overviews of Reviews protocol "address different approaches to apply the same intervention for the same condition or population".[1] Our PICOT is:

P: patients hospitalized for COVID-19

I: antithrombotic therapy

C: No therapy and/or standard of care therapy.

O: Mortality, thrombotic event and bleeding.

T: time to death or hospital discharge.

Searches

The following electronic databases will be used to the surch: MEDLINE/PubMed, EMBASE, Cochrane Library, Scopus, LILACS, Epistemonikos. OMS COVID-19 database. Manual searches in databases such as Google academic and other sources will be performed looking for gray literature. The search will be carried out in February 2022. Searches will be limited to systematic reviews published between 2020 and 2022. We will not limit language in our searches.

Types of study to be included

We will include only systematic reviews (with or without meta-analyses) of randomized controlled trials (RCTs) with at least one active arm of antithrombotic therapy[1]. We choose to include all relevant Cochrane and non-Cochrane systematic reviews to cover the search and select as many relevant articles as possible. Systematic reviews on observational studies, case-controlled, other quasi-experimental studies will be excluded.

[1] Antithrombotic therapy: anticoagulant agents, antiplatelet agents, fibrinolytic agents.

Condition or domain being studied

The literature has shown the involvement of numerous physiological reactions linked to homeostatic processes that are directly and indirectly caused by the new coronavirus infection (COVID-19), especially with regard to the coagulation cascade. Patients hospitalized with moderate to severe conditions of COVID-19 are at increased risk for the development of thrombotic conditions. Thrombotic events, of different natures, which occurred in these patients, led to an intense search for effective protocols for antithrombotic therapies. A little over a year after the beginning of the current COVID-19 pandemic, there is great heterogeneity in the protocols established by the various medical societies regarding the use of antithrombotic therapies, especially regarding the dose for the prevention of thrombotic events.

Participants/population

Inclusion criteria

- Adults (18 years and over) diagnosed with COVID-19.
- Only systematic reviews (with or without meta-analyses) of randomized controlled trials (RCTs) with at least one active arm of antithrombotic therapy (anticoagulant agents, antiplatelet agents, fibrinolytic agents).
- Year of publication between 2020 to 2021.

Exclusion criteria

- Under 18 years old/
- Pregnant women
- Studies that address non-pharmacological anticoagulation.
- Systematic reviews of observational studies.
- Systematic reviews that do not follow methodological guidelines compatible with this type of study.

Intervention(s), exposure(s)

Pharmacological antithrombotic therapy.

Comparator(s)/control

Placebo and Standard of care.

Context

Only studies conducted after the onset of the COVID-19 pandemic.

Main outcome:

Mortality

Additional outcome(s)

ANEXO 2 - ESTRATÉGIA DE BUSCA - EMBASE

"2019 nCoV" or "2019nCoV" or "2019 ncov" or "2019 novel coronavirus" or "2019 Novel Coronavirus Disease" or "2019 novel coronavirus disease" or "2019 Novel Coronavirus Infection" or "2019 novel coronavirus infection" or "2019 nCoV Disease" or "2019 nCoV Infection" or "B coronavirus" or "beta coronavirus" or "betacoronavirus" or "Deltacoronavirus" or "Delta coronavírus" or "delta coronavirus" or "COVID19" or "COVID 19" or "COVID 19 Pandemic" or "COVID19 Virus Disease" or "COVID19 Virus Infection" or "COVID19 pandemic" or "COVID19 virus" or "COVID 19 virus" or "coronavirus" or "corona virus" or "Coronavirus" or "Coronavirus*" or "corona viruses" or "coronaviruses" or "Coronavirus Disease 2019" or "Coronavirus Disease 19" or "coronavirus disease19" or "coronavirus disease 2019" or "coronavirus disease 2019 virus" or "ncov 2019" or "new coronavirus" or "novel coronavirus" or "novel corona virus" or "SARS Coronavirus 2 Infection" or "SARS CoV 2 Infection" or "SARSCoV2" or "SARSCoV 2" or "SARS CoV 2" or "SARS CoV2" or "SARS CoV 2" or "SARS2" or "Severe Acute Respiratory Syndrome" or "severe acute respiratory syndrome coronavirus" or "severe acute respiratory syndrome coronavirus 2" or "Wuhan" or "Wuhan coronavirus" or "Wuhan seafood market pneumonia virus"

"Antithrombotic" or "antithrombotic*" or "Antithrombocytic agent" or "Antithrombocytic drug" or "Antithrombocytic medication" or "Antithrombocytic therapy" or "Antiplatelet drug" or "Antiplatelet medication" or "Antiplatelet agent" or "Antiplatelet Therapy" or "antiplatelet*" or "anti-platelet*" or "Platelet Aggregation Inhibitors" or "platelet* inhibit*" or "Glycoprotein inhibitor" or "Glycoprotein IIb/IIIa inhibitors" or "Abciximab" or "Eptifibatide" or "Orbofiban" or "Roxifiban" or "Sibrafiban" or "Tirofiban" or "ADP receptor" or "P2Y12 inhibitors" or "Thienopyridines" or "Clopidogrel" or "clopidogrel*" or "plasugrel" or "Ticlopidine" or "Nucleotide analogs" or "nucleoside analogs" or "cangrelor" or "Elinogrel" or "Ticagrelor" or "Prostaglandin analogue" or "PGI2" or "Beraprost" or "Iloprost" or "Prostacyclin" or "Treprostinil" or "Thromboxane inhibitors" or "Thromboxane synthase inhibitors" or "Dipyridamole" or "aspirin" or "aspirin*" or "acetylsalicylic acid" or "acetyl salicylic acid*" or "acetylsalicylic acid" or "Picotamide" or "Terbogrel" or "Terutroban" or "Phosphodiesterase inhibitors" or "Cilostazol" or "Dipyridamole" or "Triflusal" or "Cloricromen" or "Ditazole" or "Vorapaxar"

"Anticoagulants" or "anticoagulant agent" or "blood clotting inhibitor" "anticoagul*" or "Anticoagulant agent" or "Anticoagulant Drug" or "anticoagulant$" or "Anticoagulant*" "anticoagulants" or "Anticoagulation Agent" or "anticoagulant therapy" or "Vitamin K antagonists" or "vitamin k antagonist" or "VKA" or "Coumarins" or "Coumarin" or "Coumarin Derivative*" or "coumarin$" or "coumarin*" or "Coumatetralyl" or "Dicoumarol" or "Ethyl biscoumacetate" or "Phenprocoumon" or "Warfarin" or "warfarin*" or "1,3 indandiones" or "Clorindione" or "Diphenadione" or "Phenindione" or "Tioclomarol"

"Factor Xa inhibitor" or "blood clotting factor 10 inhibitor" or "Heparin" or "alpha Heparin" "Heparin" or "heparin$" or "heparin*" or "Glycosaminoglycans " or "antithrombin" or "Heparin derivative" or "Unfractionated heparin" or "UFH" or "UH" or "Direct oral anticoagulants" or "DOAC" or "oral anticoagulants" or "Low molecular weight heparin" or "Heparin Low Molecular Weight" or "LMWH" or "bemiparin" or "Certoparin" or "Dalteparin" or "Enoxaparin" or "enoxaparin*" or "Nadroparin" or "Parnaparin" or "Reviparin" or "Tinzaparin" or "Oligosaccharides" or "Fondaparinux" or "Idraparinux" or "Heparinoids" or "Danaparoid" or "Dermatan sulfate" or "dermatan sulfate derivative" or "sulodexide" or "Direct Xa inhibitors" or "Apixaban" or "Betrixaban" or "Darexaban" or "Edoxaban" or "Otamixaban" or "Rivaroxaban"

"Direct Thrombin IIa inhibitors" or "Thrombin inhibitor" or "Direct Antithrombin*" or "Direct Thrombin Inhibitor" or "Hirudin" or "Bivalirudin" or "Desirudin" or "Argatroban" or "Dabigatran" or "Efegatran" or "Inogatran" or "Indirect Thrombin Inhibitor*" or "Antithrombin III" or "Defibrotide" or "Ramatroban" or "REG1"

"Thrombolytic drug*" or "Thrombolytic medication*" or "Thrombolytic agent*" or "Fibrinolytic*" or "Fibrinolytic therapy" or "Plasminogen activators" or "r-tPA" or "alteplase" or "Reteplase" or "Tenecteplase" or "UPA" or "Saruplase" or "Urokinase" or "Anistreplase" or "Monteplase" or "Streptokinase" or "Brinase" or "Fibrinolysin" or "klexane" or "Clexane" or "Thrombin inhibitor" or "thrombocyt*" or "Thrombocyte aggregation"

ANEXO 3 - FIGURAS

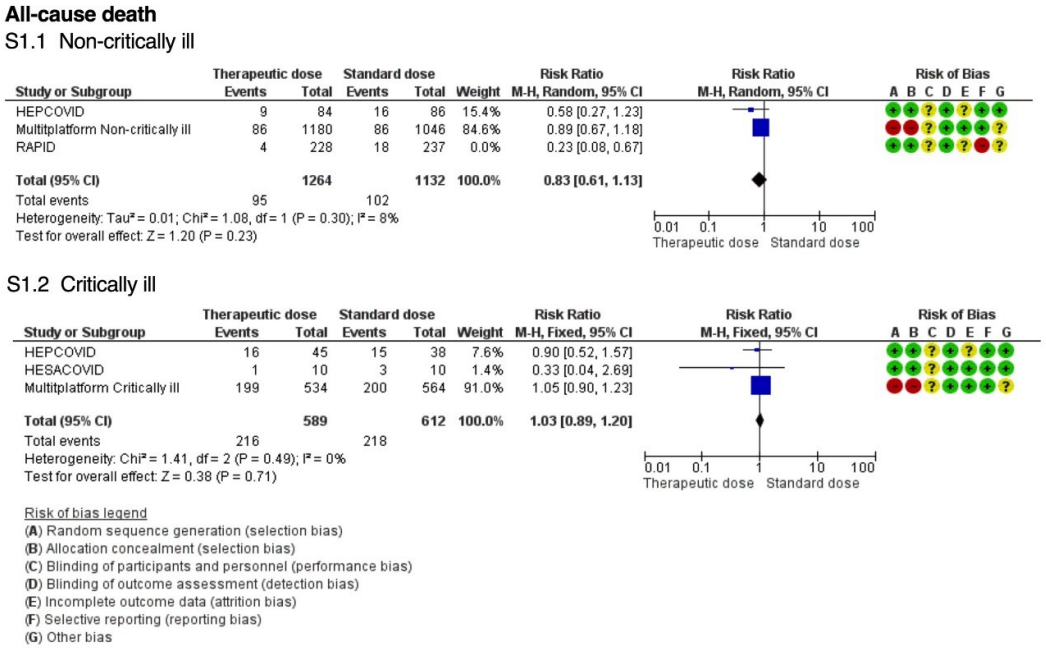

Figure S1. First efficacy outcome all-cause death forest-plot. Therapeutic-dose versus prophylactic-dose, critically ill (S1.1) versus non-critically ill (S1.2). CI = confidence intervals; M-H = Mantel-Haenszel.

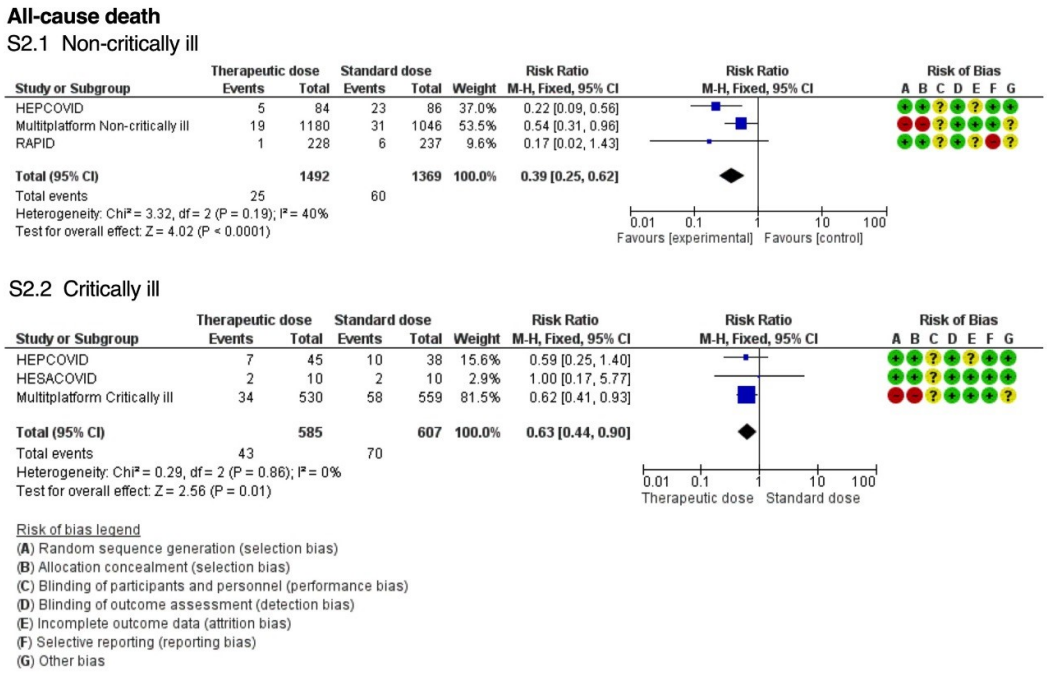

Figure S2. Second efficacy outcome thrombotic events forest-plot. Therapeutic-dose versus prophylactic-dose, critically ill (S2.1) versus non-critically ill (S2.2). CI = confidence intervals; M-H = Mantel-Haenszel.

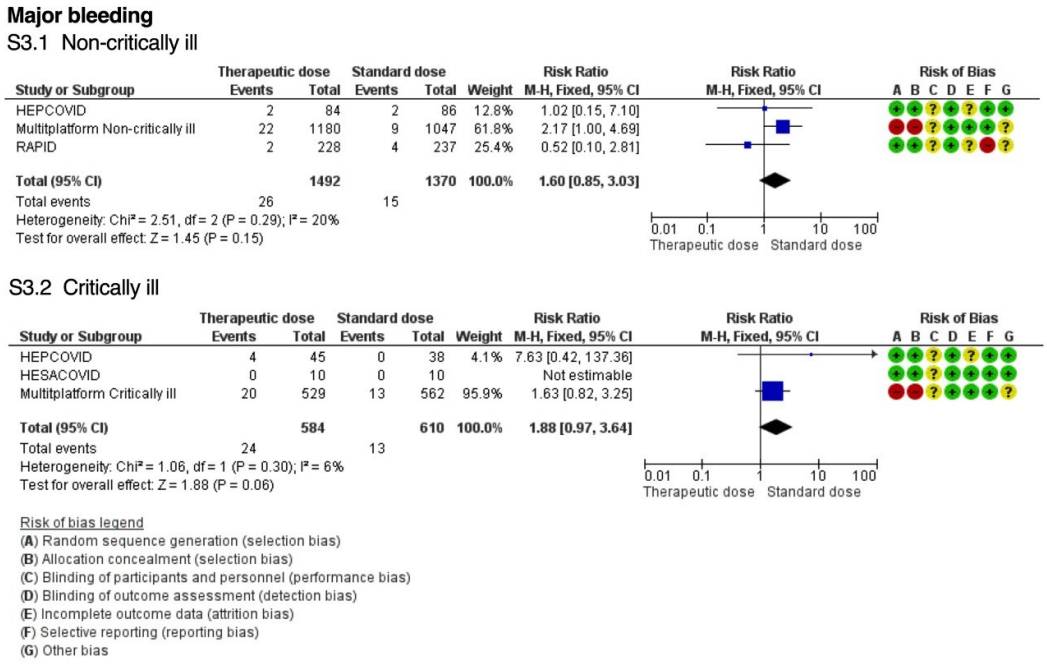

Figure S3. Safety outcome major bleeding forest-plot. Therapeutic-dose versus prophylactic-dose, critically ill (S3.1) versus non-critically ill (S3.2). CI = confidence intervals; M-H = Mantel-Haenszel.

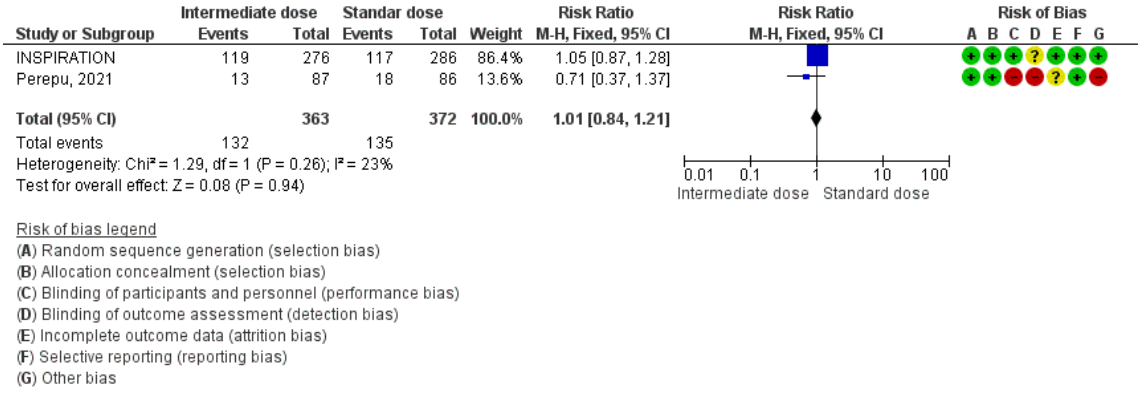

Figure S4. First efficacy outcome all-cause death forest-plot. Intermediate-dose versus prophylactic-dose, critically ill patients. CI = confidence intervals; M-H = Mantel-Haenszel.

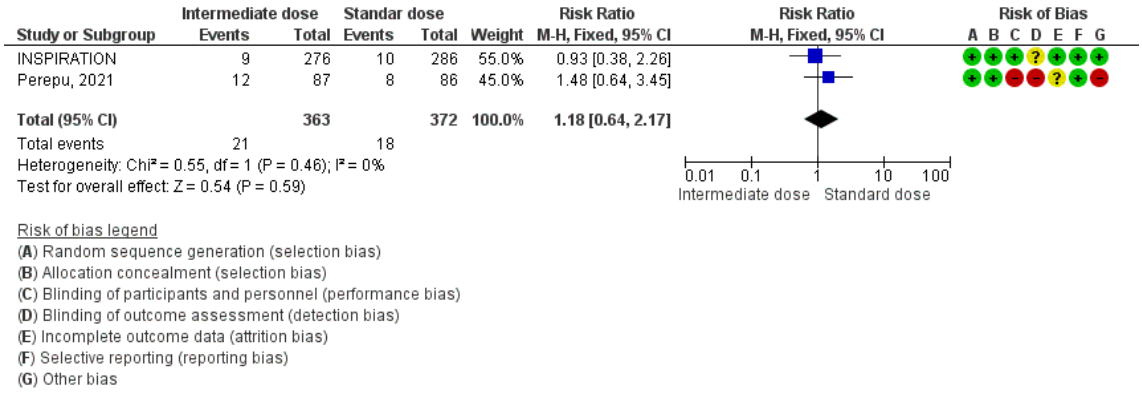

Figure S5. Second efficacy outcome thrombotic events forest-plot. Intermediate-dose versus prophylactic-dose, critically ill patients. CI = confidence intervals; M-H = Mantel-Haenszel.

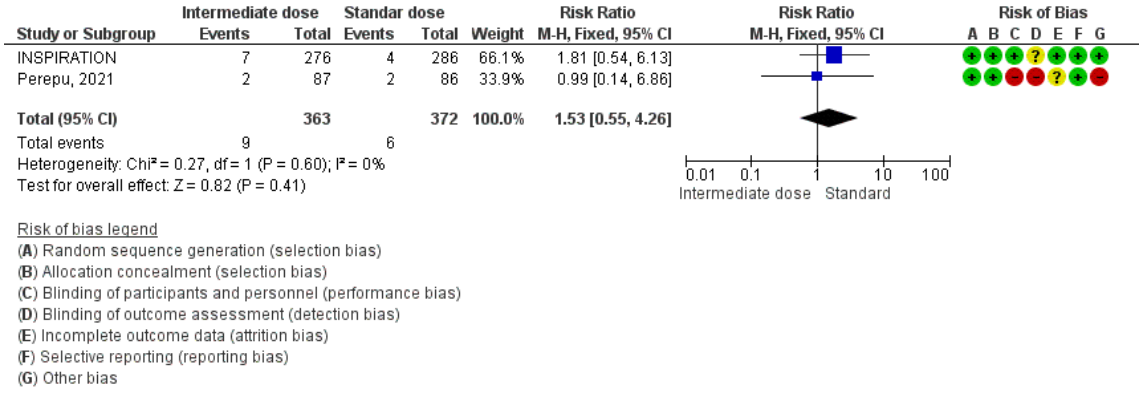

Figure S6. Safety outcome major bleeding forest-plot. Intermediate-dose versus prophylactic-dose, critically ill patients. CI = confidence intervals; M-H = Mantel-Haenszel.

ANEXO 3 - TABELAS

Supplementary table 1. Importance of primary studies in each review (in percentage).

Study Reference	Reis, 2021	Ortega-Paz, 2021	Sholzberg, 2021	Analyzed Patients
HEP - COVID	4,68%		6,24%	253
INSPIRATION	10,40%	10,91%		562
Perepu - 2021	3,20%	3,36%		173
HESACOVID	0,37%	0,39%	0,49%	20
ACTION	11,36%	11,92%		614
RAPID 2021	8,60%	9,03%	11,47%	465
Multiplataform Non-critically ill	41,06%	43,08%	54,72%	2219
Multiplataform Critically ill	20,32%	21,32%	27,08%	1098
	5404	**5151**	**4055**	**5404**

Supplementary table 2. Corrected Covered Area (CCA)

	Reviews	N of lines	N of Reviews	rate	porcentagem
	N	r	c		
Overall	20	8	3	0,75	75%
Review 1 vs 2	15	8	2	0,87	87%
Review 1 vs 3	13	8	2	0, 62	62%
Review 2 vs 3	12	7	2	0,62	62%

Abbreviations: N: number.
Corrected covered área = N-r / r.c – r. N:

Supplementary table 3: AMSTAR2

	Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Confidence in results
KC	**Reis,2021**	Yes	Yes	Yes	Partial Yes	Yes	Yes	Partial Yes	Partial Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Critically low
	Sholzberg,2021	Yes	No	Yes	Partial Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No	Yes	Critically low
	Ortega-Paz,2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
	Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
VF	**Reis,2021**	Yes	Yes	Yes	Partial Yes	Yes	Yes	Yes	Partial Yes	No	No	Yes	Yes	Yes	No	No	Yes	Critically low
	Sholzberg,2021	Yes	No	Yes	Partial Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No	Yes	Critically low
	Ortega-Paz,2021	Yes	Yes	Yes	Partial Yes	Yes	Yes	Yes	Partial Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	Critically low
	Critical domains: 2, 4, 7, 9, 11, 13, 15.																	

Supplementary table 4: Therapeutic, intermediate, or standard doses of anticoagulation regimens used in included studys
Therapeutic-dose anticoagulation:
Enoxaparin 1 mg/kg SC twice daily
Dalteparin 100 U/kg twice daily minus 10% (rounding factor) OR starting at 200 U/kg once daily minus 10% (rounding factor)
Tinzaparin: 175 anti-Xa units/kg SC once daily minus 10% (rounding factor)
UFH continuous IV administration per local protocol
DOAC rivaroxaban (20 mg or 15 mg daily) for stable patients *
Intermediate-dose anticoagulation:
Enoxaparin 1 mg/kg SC once daily
Dalteparin 5.000 units SC twice daily
Tinzaparin 4,500 units SC twice daily
UFH 7,500 units three times daily or 10,000 units SC twice daily
Prophylactic-dose anticoagulation:
Enoxaparin 40 mg SC once daily
Dalteparin 5.000 units SC once daily
Tinzaparin up to and including (a) 75 anti-Xa units/kg + 20% (rounding factor) once daily or (b) 4,500 units once daily (whichever is higher)
UFH 10 000 units SC three times a day
Abbreviations: UFH: unfractionated heparin, SC: subcutaneous , IV: intravenous.
If indicated, all doses were adjusted by creatinine clearance and body mass index .
* ACTION (27) was the only trial using rivaroxaban 20 mg as a therapeutic-dose anticoagulation.

Supplementary table 5: Data for meta-analysis - RCTs								
Death - Critically ill								
	Multiplatform trial NC	**Multiplatform trial C**	**ACTION**	**HESACOVID**	**Perepu**	**INSPIRATION**	**HEPCOVID**	**RAPID**
Therapeutic-dose	-	199/ 534	-	1/10	-	-	16/45	-
Intermediate-dose	-	-	-	-	13/87	119/276	-	-
Prophylatic-dose	-	200 / 564	-	3/10	18/86	117/286	15/38	-
Days	-	21 | 28 | HD	-	28d	30	30	30	-
Death - Non critically ill								
	Multiplatform trial NC	**Multiplatform trial C**	**ACTION**	**HESACOVID**	**Perepu**	**INSPIRATION**	**HEPCOVID**	**RAPID**
Therapeutic-dose	86 / 1180	-	-	-	-	-	9/84	4 /228
Intermediate-dose	-	-	-	-	-	-	-	-
Prophylatic-dose	86 / 1046	-	-	-	-	-	16/86	18 / 237
Days	21 | 28 | HD	-	-	-	-	-	30	28
Thrombotic events - Critically ill								
	Multiplatform trial NC	**Multiplatform trial C**	**ACTION**	**HESACOVID**	**Perepu**	**INSPIRATION**	**HEPCOVID**	**RAPID**
Therapeutic-dose	-	34 / 530	-	2/10	-	-	7/45	-
Intermediate-dose	-	-	-	-	12/87	9/276	-	-
Prophylatic-dose	-	58 / 559	-	2/10	8/86	10/286	10/38	-
Days	-	21 | 28 | HD	-	28d	30	30d	30	-
Thrombotic events - Non Critically ill								
	Multiplatform trial NC	**Multiplatform trial C**	**ACTION**	**HESACOVID**	**Perepu**	**INSPIRATION**	**HEPCOVID**	**RAPID**
Therapeutic-dose	19/1180	-	-	-	-	-	5/84	1/228
Intermediate-dose	-	-	-	-	-	-	-	-
Prophylatic-dose	31/1046	-	-	-	-	-	23/86	6 / 237
Days	21 | 28 | HD	-	-	-	-	-	30	28d
Major bleeding - Critically ill								
	Multiplatform trial NC	**Multiplatform trial C**	**ACTION**	**HESACOVID**	**Perepu**	**INSPIRATION**	**HEPCOVID**	**RAPID**
Therapeutic-dose	-	20/ 529	-	0/10	-	-	4/45	-
Intermediate-dose	-	-	-	-	2/87	7/276		-
Prophylatic-dose	-	13 / 562	-	0/10	2/86	4/286	0/38	-
Days	-	21 | 28 | HD	-	28d	30d	30d	30	-
Major Bleeding - Non-critically ill								
	Multiplatform trial NC	**Multiplatform trial C**	**ACTION**	**HESACOVID**	**Perepu**	**INSPIRATION**	**HEPCOVID**	**RAPID**
Therapeutic-dose	22 / 1180	-	-	-	-	-	2/84	2/228
Intermediate-dose	-	-	-	-	-	-		-

Prophylatic-dose	9 / 1047	-	-	-	-	-	2/86	4/ 237
Days	21 | 28	-	-	-	-	-	30	28
Death - Non-Critically / Critically ill								
	Multiplatform trial NC	**Multiplatform trial C**	**ACTION**	**HESACOVID**	**Perepu**	**INSPIRATION**	**HEPCOVID**	**RAPID**
Therapeutic-dose	-	-	35 / 310	-	-	-	-	-
Intermediate-dose	-	-	-	-	-	-	-	-
Prophylatic-dose	-	-	23 / 304	-	-	-	-	-
Days	-	-	30	-	-	-	-	-
Thrombotic events - Non-Critically/ Critically ill								
	Multiplatform trial NC	**Multiplatform trial C**	**ACTION**	**HESACOVID**	**Perepu**	**INSPIRATION**	**HEPCOVID**	**RAPID**
Therapeutic-dose	-	-	23 /310	-	-	-	-	-
Intermediate-dose	-	-	-	-	-	-	-	-
Prophylatic-dose	-	-	30 / 304	-	-	-	-	-
Days	-	-	30	-	-	-	-	-
Major Bleeding - Non-Critically/ Critically ill								
	Multiplatform trial NC	**Multiplatform trial C**	**ACTION**	**HESACOVID**	**Perepu**	**INSPIRATION**	**HEPCOVID**	**RAPID**
Therapeutic-dose	-	-	10 / 310	-	-	-	-	-
Intermediate-dose	-	-	-	-	-	-	-	-
Prophylatic-dose	-	-	4 / 304	-	-	-	-	-
Days	-	-	30	-	-	-	-	-

Supplementary table 6. Request data - HEPCOVID

Outcomes	ICU (N=83)		Non-ICU (N=170)	
	Therapeutic dose (N=45)	Standard dose (N=38)	Therapeutic dose (N=84)	Standard dose (N=86)
All-cause Mortality During 30 days	16/45	15/38	9/84	**16/86**
Symptomatic Pulmonary Embolism (All PE assumed to be symptomatic) During 30 days	2/45	3/38	2/84	**7/86**
Symptomatic Deep Vein Thrombosis During 30 days	5/45	6/38	2/84	**13/86**
Asymptomatic proximal DVT	0	0	2/84	**3/86**
Symptomatic Venous Thromboembolism (symptomatic DVT, PE, SPVT, CST, other VTE) During 30 days	7/45	10/38	3/84	**20/86**
All VTE	7/45	10/38	5/84	**23/86**
Major Bleeding During 30 days	**4/45**	**0/38**	**2/84**	**2/86**
Intracranial Hemorrhage* During 30 days	0/45	0/38	0/84	**0/86**
Ischemic Stroke During 30 days	0/45	0/38	1/84	**1/86**
ST-elevation Myocardial Infarction? During 30 days	0/45	0/38	0/84	**0/86**
Non-ST elevation Myocardial Infarction	0/45	1/38	0/84	**2/86**
ICU Admission (as outcome)? During 30 days			6/84	**9/86**
Invasive Mechanical Ventilation During 30 days	10/38	8/35	7/84	**13/86**

Multi-organ failure† During 30 days	6/43	2/35	5/84	**4/86**
ECMO During 30 days	1/45	1/38	0/84	**0/86**
Limb Amputation# During 30 days	2/45	0/38	0/84	**0/86**
Other ATE (SYSEMB, INTRC_THR)	0/45	0/38	1/84	**0/86**
Length of Hospital Admission	15 (8, 24)	13 (7, 20)	7 (4, 12)	**8 (5, 12)**
Length of ICU Admission	Median (25th, 75th)	Median (25th, 75th)		

* Or 'Hemorrhagic Stroke'; † Provide definition; # 'Major adverse limb event'

Supplementary table 6 : Tools used in this Overview	
PROSPERO	PROSPERO é uma base internacional de registro prospectivo de revisões sistemáticas em saúde e assistência social, bem-estar, saúde pública, educação, crime, justiça e desenvolvimento internacional, onde há um resultado relacionado à saúde. / *PROSPERO is an international database of prospectively registered systematic reviews in health and social care, welfare, public health, education, crime, justice, and international development, where there is a health related outcome.*
COVIDENCE	A plataforma Covidence é um gerenciador de revisões sistemáticas desenvolvido e administrado por uma organização (COVIDENCE) sem fins lucrativos dedicada à síntese de evidências de qualidade e sua contribuição para a tomada de decisões baseadas em evidênc ias. É uma ferramenta usada por mais de 200 das principais universidades, hospitais e sociedades do mundo. / *The Covidence platform is a systematic review manager developed and administered by a non-profit organization (COVIDENCE) dedicated to the synthesis of quality evidence and its contribution to evidence-based decision making. It is a tool used by over 200 of the world's leading universities, hospitals and societies.*
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) ou literalmente traduzido por 'Itens de relatório preferidos para revisões sistemáticas e meta-análises' é um conjunto mínimo de itens baseado em evidências para relato em revisões sistemáticas e meta-análises que concentra-se principalmente no relatório de revisões avaliando os efeitos das intervenções, embora também possa ser usado como base para r elatar revisões sistemáticas com outros objetivos que não a avaliação de intervenções (por exemplo, avaliação de etiologia, prevalência, diagnóstico ou prognóstico). / *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) is a minimal evidence-based set of items for reporting in systematic reviews and meta-analyses that primarily focuses on reporting of reviews assessing the effects of interventions, although it can also be used as a basis for reporting systematic reviews for purposes other than assessment of interventions (eg, assessment of etiology, prevalence, diagnosis or prognosis).*
GRADE	Grading of Recommendations Assessment, Development and Evaluation (GRADE) é uma colaboração informal de pessoas com interesse em abordar as deficiências dos sistemas de classificação nos cuidados de saúde. O grupo de trabalho desenvolveu uma abordagem comum , sensata e transparente para classificar a qualidade (ou certeza) das evidências e a força das recomendações. Muitas organizações internacionais contribuíram para o desenvolvimento da abordagem GRADE, que agora é considerada o padrão no desenvolvimento de diretrizes. / The Grading of Recommendations Assessment, Development *and Evaluation (short GRADE) working group began in the year 2000 as an informal collaboration of people with an interest in addressing the shortcomings of grading systems in health care. The working group has developed a common, sensible and transparent approach to grading quality (or certainty) of evidence and strength of recommendations. Many international organizations have provided input into the development of the GRADE approach which is now considered the standard in guideline development.*

AMSTAR2	A MeaSurement Tool to Assess systematic Reviews (AMSTAR) ou ferramenta de medição para avaliar revisões sistemáticas cujo objetivo é criar instrumentos válidos, confiáveis e utilizáveis que ajudem os usuários a diferenciar as revisões sistemáticas, com foco em sua qualidade metodológica e consenso de especialistas facilitando assim o desenvolvimento de revisões de alta qualidade. O desenvolvimento não aleatório adicional do AMSTAR para permitir a avaliação sistemática de estudos randomizados de intervenções randomizadas foi chamado de AMSTAR2 / *A MeaSurement Tool to Assess systematic Reviews (AMSTAR) aims to create valid methods, with a focus on users to be used as the main objective, high-quality development methods, as well as high-quality development tools, as well as high-quality development tools. Additional non-randomized development of AMSTAR to allow systematic evaluation of randomized trials of randomized interventions was called AMSTAR2.*
RoB2	A ferramenta RoB 2.0 fornece uma estrutura para considerar o risco de viés nos achados de qualquer tipo de estudo randomizado. A avaliação é estruturada em uma série de domínios através dos quais o viés pode ser introduzido em um estudo. // *The RoB 2.0 tool provides a framework for considering the risk of bias in the findings of any type of randomized trial. The assessment is structured into a series of domains through which bias might be introduced into a trial.*