Full *versus* prophylactic-intermediate doses of anticoagulants in COVID-19: a meta-analysis

Coronavirus disease-19 (COVID-19) is a serious pandemic associated with an elevated risk of venous and arterial thrombosis.[1] There is no consensus on the anticoagulant approach to be implemented to reduce the thrombotic risk; thus, most international guidelines recommend standard thromboprophylaxis with use of intermediate doses restricted to high-risk and critically ill patients.[2] Therapeutic dosage superiority of anticoagulants in reducing thrombosis in moderately but not severely ill patients or uncertain cost-benefit of full-intermediate anticoagulation *versus* prophylactic doses were reported by previous meta-analyses.[3,4] Therefore, we decided to perform a new, updated meta-analysis of randomized clinical trials comparing the effects of full anticoagulation (FA) *versus* prophylactic-intermediate anticoagulation (PIA) on death and thrombotic-related events in COVID-19 patients.

Eligibility criteria

Types of studies: randomized clinical trial studies that assessed the effect of therapeutic *versus* prophylactic anticoagulant therapy in COVID-19 hospitalized patients. No language, publication date, or publication status restrictions were imposed. We conducted all analyses according to the intention-to-treat principle. For trials with a factorial design, we based main results on 2-way analyses, that is, all trial participants receiving FA were compared with all those treated with PIA dose.

Information sources

The studies were identified by searching electronic databases. This search was applied to Pubmed, ISI Web of Science, SCOPUS and Cochrane database. The last search was run on November 14, 2021. Reference lists of all studies included in the present meta-analysis were screened for potential additional eligible studies.

Search

Two investigators independently searched in the electronic databases combining the following text terms and MeSH terms: "COVID-19"[All Fields] OR "COVID-19"[MeSH Terms] OR "SARS-CoV-2"[All Fields] OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[All Fields] OR "NCOV"[All Fields] OR "2019 NCOV"[All Fields] AND ("thrombosis"[MeSH Terms] OR "thrombosis"[All Fields])) AND ("anticoagulants"[Pharmacological Action] OR "anticoagulants"[MeSH Terms] OR "anticoagulants"[All Fields] OR "anticoagulant"[All Fields]) AND "humans"[MeSH Terms]Studies. We limited our search to human studies.

Study selection

Two authors independently reviewed the titles and abstracts generated by the search. Studies were excluded if the title and/or abstract showed that the papers did not meet the selection criteria of our meta-analysis. Studies not including a control group and animal studies were excluded. Case reports, editorials, commentaries, letters, review articles, guidelines were also excluded from the analysis. We defined the following exclusion criteria: (i) studies that included only the intermediate anticoagulation; (ii) studies unrelated to our topic; (iii) studies without randomization assignment of the treatment. A flowchart of the selection studies is reported in the *Online Supplementary Figure S1*.

Main analysis

We evaluated the effect of FA *versus* PIA dose in COVID-19 hospitalized patients. Our primary outcome was to compare the effect of these treatments on death and thrombotic events. Our secondary endpoints were the comparison of these treatments on death, arterial and venous thrombotic events, arterial thrombotic events and VTE; the safety endpoint was to evaluate the effect on major bleedings. This meta-analysis was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Statement issued in 2009.

Statistical analysis

We allocated the results of each trial as dichotomous frequency data. Risk ratios (RR) and 95% confidence intervals (CI) were calculated. Data were pooled and compared with a random-effect model. We calculated the number needed to treat (NNT) and the number needed to harmful (NNH) as the reciprocal of the absolute risk reduction (ARR).

Statistical heterogeneity was calculated by the I2. Presence of publication bias was explored using funnel plots of effect size against standard error and Egger's test. The software Comprehensive Meta Analysis (version 2.2.064, USA, 2011) and R (version 3.1.2, Vienna, 2014) supported the analysis.

Seven studies[5-11] evaluated the effect of FA *versus* PIA. The relevant parameters of each study are reported in the Table 1. Antiplatelet drugs were more frequently used in patients treated with FA (11.9%) *versus* PIA (10.6%). A heterogeneous definition of the severity of COVID-19 infection was found among the studies. Briefly, we considered

Table 1. Characteristics of the studies.

Study	Definition of disease state at baseline	Disease state at baseline	Primary Endpoints	Males %	Age in years	Anticoagulant therapeutic dose	Antiplatelets and corticosteroid	Prophylactic/ intermediate dose	Duration	Major Bleeding
Action[5]	Moderate disease was defined by an oxygen saturation <94%, pulmonary infiltrates >50%, or a partial pressure of oxygen to fractional concentration of oxygen in inspired air ratio <300. Severe disease was defined as respiratory failure, hemodynamic instability, or multiple organ dysfunction. Mild disease includes cases not meeting the criteria for moderate or severe disease.	-311 Patients treated with therapeutic doses (Mild: 10%, Moderate: 83%, Severe: 8%). -304 Patients treated with prophylactic doses (Mild: 13%, Moderate: 82%, Severe: 5%).	Death,duration of hospitalization or of supplemental oxygen support	60	56	Rivaroxaban (20 mg once daily) for patients with a stable condition or enoxaparin (1 mg/kg twice daily) for patients with an unstable condition	Antiplatelets: Therapeutic: 25/310 (8.1%) Prophylactic 30/304 (9.9%) Corticosteroids: Therapeutic: 257/310 (83%), Prophylactic 253/304 (83%)	Standard in-hospital enoxaparin or UFH	30 days	Defined according to ISTH* criteria
HEP-COVID[6]	The study included patients with D-dimer criterion greater than 4 times the upper limit of normal or a sepsis-induced coagulopathy score ≥4. The study considered severe patients those hospitalized in ICU and not severe the “Non-ICU stratum”.	Severe(N=84) and Not Severe(N=45) patients were treated with therapeutic doses. Severe(N=86) and Not Severe(N=38) patients were treated with prophylactic doses.	VTE, arterial thrombotic events or death	53	66	Enoxaparin at a dose of 1 mg/kg s.c. twice daily if CrCl was 30 mL/min/1.73m^2 or greater or 0.5 mg/kg twice daily if CrCl was 15-29 mL/min/1.73m^2	Antiplatelets: Therapeutic: 40/129 (31.0%), Prophylactic 24/124 (19.4) Corticosteroids: Therapeutic: 111/127 (87.4), Prophylactic 93/123 (75.6)	Heparin regimens could include UFH, up to 22 500 IU s.c. (twice or thrice daily); enoxaparin, 30 mg or 40 mg s.c. once or twice daily (weight-based enoxaparin 0.5mg/kg subcutaneously twice daily was permitted; or dalteparin, 2500 IU or 5000 IU s.c. daily	30 days	Defined according to the ISTH criteria
RAPID[7]	Moderate illness was defined as admission to hospital ward level of care (not to ICU), not already mechanically ventilated, and not imminently requiring mechanical ventilation or critical care. D-dimer levels were required to be above the upper limit of normal with an oxygen saturation ≤93% on room air, or ≥2 times the upper limit of normal irrespective of oxygen saturation.	Not Severe (N=465)	Composite of ICU admission, non-invasive or invasive mechanical ventilation.	56	60	Patients allocated to therapeutic heparin receive therapeutic doses of LMWH or UFH as used for the treatment of venous thromboembolism.	Antiplatelets: Therapeutic 24/228 (10%), Prophylactic 29/237 (12%) Corticosteroids: Therapeutic 161 (70.6 %), Prophylactic 162 (68.4%)	Patients allocated to prophylactic heparin received dose capped prophylactic s.c. heparin (LMWH or UFH) adjusted for body mass index and creatinine clearance.	28 days	Defined according to the ISTH criteria.

Continued on following page.

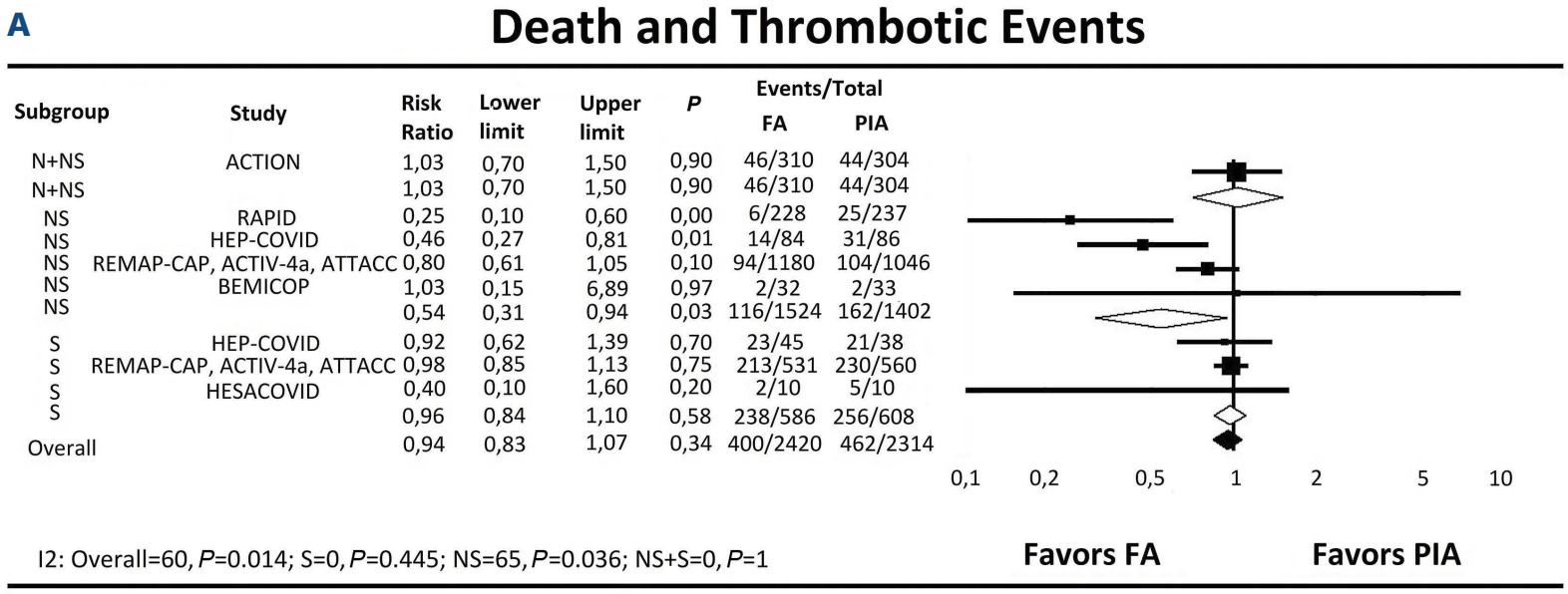
Study	Definition of disease state at baseline	Disease state at baseline	Primary Endpoints	Males %	Age in years	Anticoagulant therapeutic dose	Antiplatelets and corticosteroid	Prophylactic/ intermediate dose	Duration	Major Bleeding
ATTACC, ACTIV-4a, and REMAP-CAP Investigators [8]	Moderate disease was defined as hospitalization for Covid-19 without the need for ICU-level care. ICU-level care was defined as the use of respiratory or cardiovascular organ support in an ICU.	Not Severe (N=2,231)	Organ support–free days	59	59	Therapeutic dose anticoagulation with UFH or LMWH	Antiplatelets: Therapeutic: 148/1140 (13.0), Prophylactic 111/1013 (11.0) Corticosteroids: Therapeutic:479/791 (60.6) Prophylactic 415/656 (63.3)	Usual-care pharmacologic thromboprophylaxis	21 days	Defined according to the ISTH criteria.
ATTACC, ACTIV-4a, and REMAP-CAP Investigators [9]	Severe Covid-19 was defined as Covid-19 that led to receipt of ICU-level respiratory or cardiovascular organ support in an ICU.	Severe (N=1,103)	Organ support–free days	70	61	Therapeutic-dose anticoagulation with UFH or LMWH	Antiplatelets: Therapeutic 37/485 (7.6), Prophylactic 38/494 (7.7) Corticosteroids: Therapeutic: 426/522 (81.6), Prophylactic 458/555 (82.5)	Usual-care pharmacologic thromboprophylaxis	21 days	Defined according to the ISTH criteria.
HESA-COVID[10]	Severe clinical presentation with respiratory failure requiring mechanical ventilation, D-dimer levels greater than 1000 µg/L	Severe (N=20)	The variation in gas exchange over time	80	56	Enoxaparin s.c. with the dose according to age and adjusted daily by the creatinine clearance	Antiplatelets: Therapeutic 0/10 (0), Prophylactic 0/10 (0). Corticosteroids: Therapeutic: 7/70 (70), Prophylactic: 7/70 (70)	The standard thromboprophylaxis group was allocated to receive s.c., UFH at a dose of 5000 IU TID (if weight<120 kg) and 7500 IU TID (if weight>120 kg) or enoxaparin at a dose of 40 mg OD (if weight<120 kg) and 40 mg BID (if weight>120 Kg).	14 days	Defined according to the TIMI** criteria
BEMICOP[11]	positive COVID-19 diagnosis CURB≤2, baseline blood oxygen saturation ≥90%	Not severe (N=65)	Thrombotic Events	62	63	Bamiparin 115 IU/Kg once daily adjusted for body weight.	Antiplatelet drug was an exclusion criterium Corticosteroids: Therapeutic: 30/33 (90) Prophylactic: 32/32 (100)	Bamiparin 3,500 IU once daily	10 days	Defined according to the ISTH criteria.

* International Society on Thrombosis and Hemostasis (ISTH) criteria: fatal bleeding; symptomatic bleeding in a critical area or organ; hemoglobin level <2 g/dL or more; bleeding leading to transfusion of 2 or more units of whole blood or red cells.** TIMI criteria: defined as: any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI), clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in hematocrit, fatal bleeding. s.c.: subcutaneously; LMWH: low molecular weight heparin; UFH: unfractionated heparin. ICU: intensive care unit.

as severe patients those: hospitalized at admission in an intensive care unit (ICU), or with respiratory failure requiring mechanical ventilation or organ support as high flow oxygen, extracorporeal life support, vasopressors, or inotropes. Comparison between subgroups with severe and non-severe disease was prespecified analysis. Funnel plots are reported in the *Online Supplementary Figure S2*.

No difference was observed between the rates of death and thrombotic events (as composite outcome) in patients treated with FA (16.5%) *versus* PIA (19.9%) in seven studies including 4,734 patients (Figure 1A). Subgroup analysis according to severity showed a lower rate of this composite outcome in patients treated with FA as compared to those treated with PIA in non-severe (RR=0.53,

A



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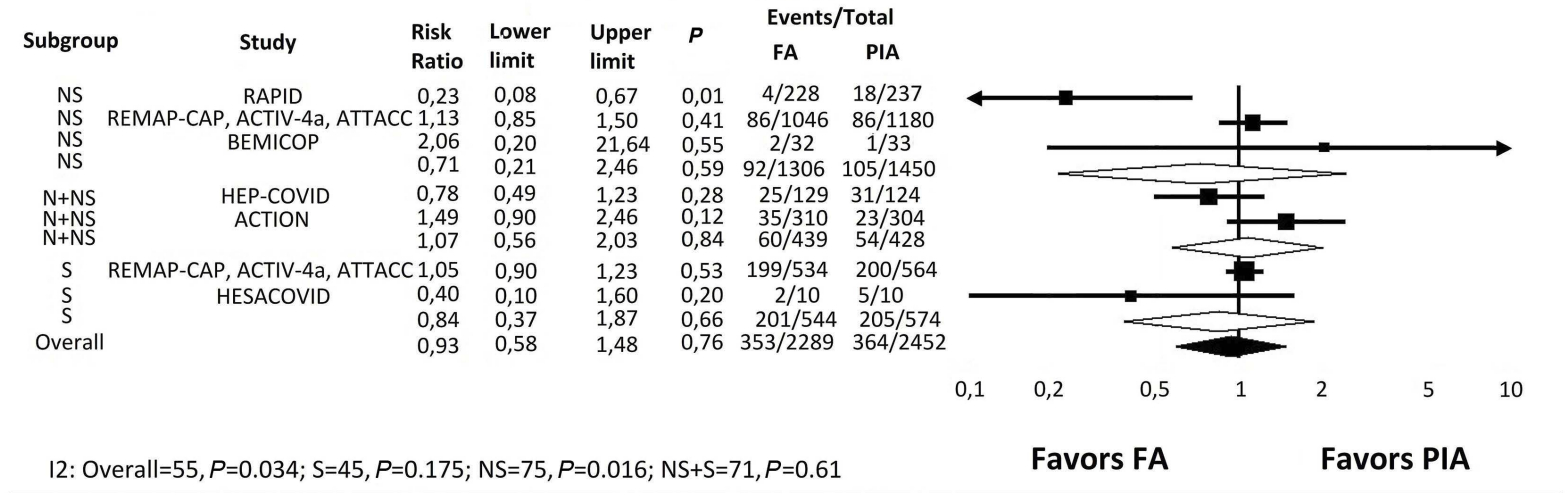

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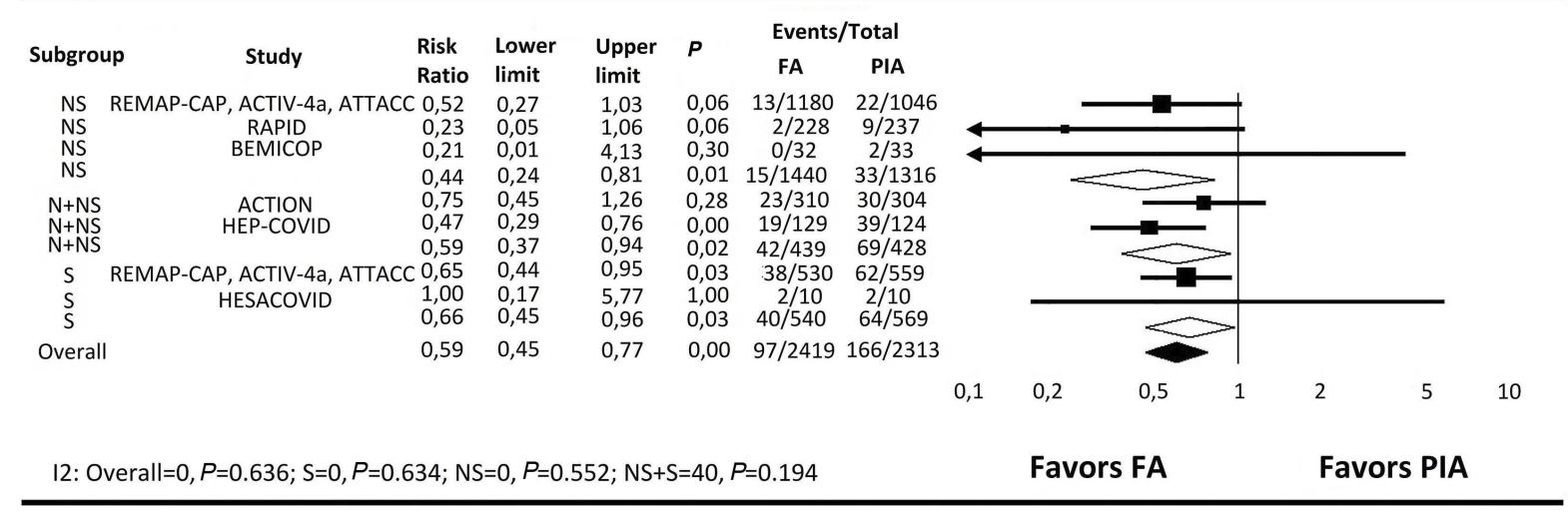


Figure 1. Forrest plots of death and thrombotic events. (A) Forest plots for death and thrombotic events according to the subgroups for full anticoagulation (FA) and prophylactic-intermediate anticoagulation (PIA) doses. (B) Forest plots for death according to the subgroups for FA and PIA doses. (C) Forest plots for arterial and venous and thrombotic events according to the subgroups for FA and PIA doses.

95% CI: 0.30-0.94), but not in severe patients (Figure 1A). No difference was observed between the rates of death in patients treated with FA (15.4%) and PIA (14.8%) in seven studies including 4,741 patients (Figure 1B).

In seven studies including 4,732 patients a difference was observed between the rates of arterial and venous thrombotic events in patients treated with FA (4.0%) compared to those treated with PIA (7.2%, RR=0.58, 95% CI: 0.45-0.76), both in severe and non-severe patients (Figure 1C).

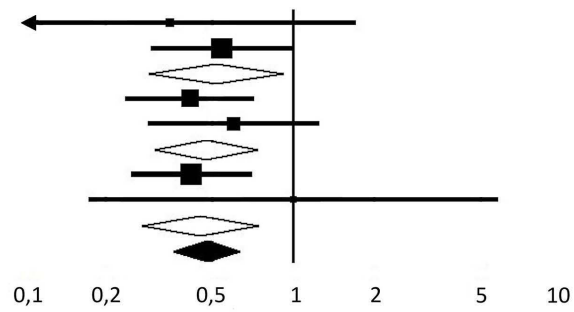
In six studies (n=4,667 patients) a difference was observed between the rate of venous thrombotic events (VTE) in FA (2.7%) *versus* PIA patients (5.9%, RR=0.47, 95% CI: 0.35-0.63), both in severe and non-severe patients (Figure 2A).

No significant difference was observed between the rates of arterial thrombotic events in three studies including 1,332 patients treated with FA or PIA (Figure 2B).

A

Venous Thrombotic Events

Subgroup	Study	Risk Ratio	Lower limit	Upper limit	*P*	Events/Total FA	Events/Total PIA
NS	RAPID	0,35	0,07	1,70	0,19	2/228	6/237
NS	REMAP-CAP, ACTIV-4a, ATTACC	0,55	0,29	1,01	0,05	16/1180	26/1046
NS		0,51	0,29	0,91	0,02	18/1408	32/1283
N+NS	HEP-COVID	0,41	0,24	0,72	0,00	15/129	35/124
N+NS	ACTION	0,60	0,29	1,25	0,17	11/310	18/304
N+NS		0,47	0,30	0,73	0,00	26/439	53/428
S	REMAP-CAP, ACTIV-4a, ATTACC	0,42	0,25	0,70	0,00	19/530	48/559
S	HESACOVID	1,00	0,17	5,77	1,00	2/10	2/10
S		0,45	0,27	0,74	0,00	21/540	50/569
Overall		0,47	0,36	0,63	0,00	65/2387	135/2280

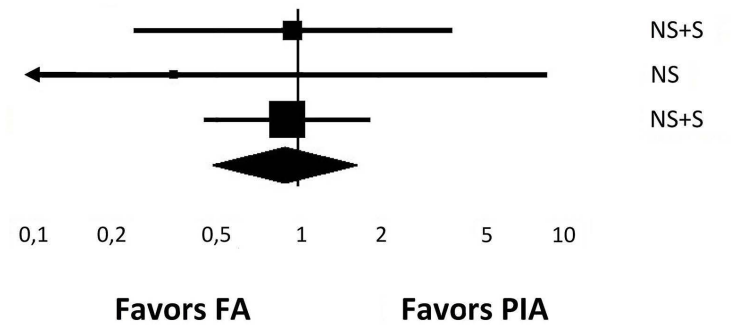


I2: Overall=0, *P*=0.861; S=0, *P*=0.349; NS=0, *P*=0.602; NS+S=0, *P*=0.424

B

Arterial Thrombotic Events

Study	Risk Ratio	Lower limit	Upper limit	*P*	Events/Total FA	Events/Total PIA	Subgroup
HEPCOVID	0,961	0,246	3,759	0,955	4/129	4/124	NS+S
RAPID	0,346	0,014	8,460	0,516	0/228	1/237	NS
ACTION	0,915	0,450	1,863	0,807	14/310	15/304	NS+S
	0,891	0,480	1,655	0,716	18/667	20/665	



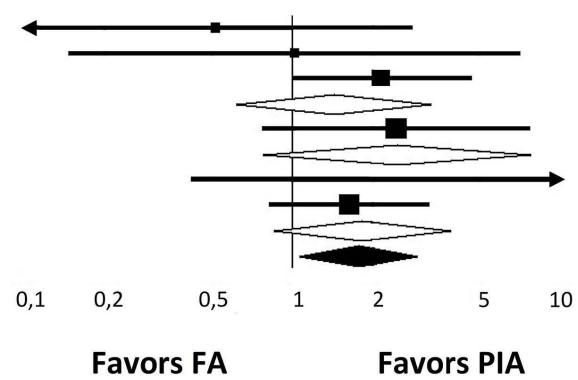
I2 Overall: 0 *P*=0.838

C

Major Bleedings

Subgroup	Study	Risk Ratio	Lower limit	Upper limit	*P*	Events/Total FA	Events/Total PIA
NS	RAPID	0,52	0,10	2,81	0,45	2/228	4/237
NS	HEP-COVID	1,02	0,15	7,10	0,98	2/84	2/86
NS	REMAP-CAP, ACTIV-4a, ATTACC	2,17	1,00	4,69	0,05	22/1180	9/1047
NS		1,43	0,62	3,29	0,40	26/1492	15/1370
N+NS	ACTION	2,45	0,78	7,73	0,13	10/310	4/304
N+NS		2,45	0,78	7,73	0,13	10/310	4/304
S	HEP-COVID	7,63	0,42	137,3	0,17	4/45	0/38
S	REMAP-CAP, ACTIV-4a, ATTACC	1,63	0,82	3,25	0,16	20/529	13/562
S		1,81	0,85	3,88	0,12	24/574	13/600
Overall		1,76	1,06	2,92	0,03	60/2376	32/2274

Overall



I2: Overall=0, *P*=0.558; S=3, *P*=0.309; NS=20, *P*=0.285; NS+S=0, *P*=1

Figure 2. Forrest Plots of thrombotic events and bleeding. (A) Forest plots for venous thrombotic events according to the subgroups for full anticoagulation (FA) and prophylactic-intermediate anticoagulation (PIA) doses. (B) Forest plots for arterial thrombotic events. (C) Forest plots for major bleeding events according to the subgroups for FA and PIA doses.

Six studies, including 4,650 patients, reported major bleeding rates. Major bleeding was observed with an higher rate in FA (2.5%) *versus* PIA patients (1.4%, Figure 2C).

Number needed to treat (NNT) and number needed to harm (NNH) values for major bleedings and several outcomes are reported in the *Online Supplementary Figure S3*, in all studies and according to severity.

The study suggests a beneficial effects of FA towards venous thrombosis compared to PIA COVID-19 patients. Even if the risk of major bleeding is higher in FA-treated patients, the overall cost benefit of treatments is in favor of FA.

It is, so far, unclear whether FA is superior to lower doses of anticoagulants such as PIA on the incidence of death, arterial and venous thrombosis, and major bleeding in COVID-19 patients. The results of the present study show that, in comparison with PIA, FA did not affect the rate of death or arterial thrombosis but reduced the incidence of venous thrombosis interdependently of the clinical presentation, ie., either severe or non-severe disease. As expected, the rate of major bleeding was higher in patients on FA. Concomitant treatment with antiplatelet drugs may be an important confounder as we would expect a higher risk of bleeding in patients under full anticoagulation[12] but lack of clinical information on this specific subgroup precludes definite conclusion.

The study has implications and limitations. Even if the full anticoagulation did not reduce the risk of death, the positive impact on VTE is of clinical relevance for the management and the potentially harmful long term effects of VTE; in accordance with this, for VTE and major bleeding the NTT and NNH are 31 and 90 respectively and NTT/NNH 0.34. This finding adds more to the previous meta-analyses[3,4] as the bleeding risk seems to be lower and the cost-benefit in favor of full anticoagulation in either moderate or severely ill patients. Clinical outcomes were restricted to 30-day followup, thereby it is unclear the impact of several anticoagulant regimens on clinical outcomes, death included, during long term followup.

In conclusion, the results of this meta-analysis suggest the potential usefulness of FA to reduce VTE in COVID-19 patients with either severe or non-severe disease. Further RCT with large sample size are needed to support this finding.

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Disclosures

No conflicts of interest to disclose.

Contributions

FV and LL developed the study concept and design; data: PP, ADC, LL and FV analyzed and interpreted data; FV and LL wrote the initial draft; PP, ADC and GAC critically revised the manuscript for important intellectual content; ADC and LL performed the statistical analysis.

Data-sharing statement

All the data used to support the results of this study are available from the corresponding author upon request.

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