

## Updated meta-analysis of randomized controlled trials on the safety and efficacy of different prophylactic anticoagulation dosing regimens in non-critically ill hospitalized patients with COVID-19

We thank Prof. Čulić and colleagues for their interest in our meta-analysis on the safety and efficacy of different prophylactic anticoagulation dosing regimens in coronavirus disease 2019 (COVID-19) patients.<sup>1</sup> Throughout the COVID-19 pandemic, the high rate of thromboembolic events among COVID-19 patients has been a topic of extensive and ongoing research.<sup>2,3</sup> Several randomized controlled trials (RCTs) have tested different anticoagulation regimens for preventing thromboembolic events.<sup>1</sup> However, the results of the RCTs have not been univocal, and the majority of these lack statistical power for individual hard endpoints such as death. For these reasons, we pooled the data on the safety and efficacy of prophylactic anticoagulation at escalated dose vs. standard dose in critically and non-critically ill hospitalized patients with COVID-19. This meta-analysis did not find any mortality benefit of an escalated dose over the standard dose of prophylactic anticoagulation. Moreover, there was a reduction of venous thromboembolism (VTE) counterbalanced by increased major bleeding in patients treated with escalated-dose prophylactic anticoagulation compared with those treated with a standard dose.<sup>1</sup> As the evidence has constantly been evolving after the publication of our meta-analysis (14 September 2021), further RCTs have become available in the setting of non-critically ill hospitalized patients.<sup>4-6</sup> The HEP-COVID trial, published on 7 October 2021, is the most relevant.<sup>4</sup> We agree with the authors that in non-critically ill hospitalized patients, the data reported by the HEP-COVID and the ATTACC, ACTIV-4a, and REMAP-CAP trials may suggest improved outcomes with an escalated dose of prophylactic anticoagulation compared with the standard dose.4,7 Briefly, HEP-COVID showed a reduction of the primary endpoint (composite of arterial or venous thromboembolic events and all-cause death) driven by a reduction of venous and arterial thromboembolism in the non-intensive care unit (ICU) stratum,<sup>4</sup> while the ATTACC, ACTIV-4a, and REMAP-CAP trials showed a reduction of organ supportfree days, favouring escalated-dose prophylactic anticoagulation.<sup>7</sup> Thus, whether escalateddose prophylactic anticoagulation compared with standard-dose could reduce an individual hard endpoint such as death remains to be proven. To address this issue, we updated our previous analysis focusing on non-critically ill hospitalized patients by including the three RCTs reported meanwhile. This updated version was performed using the same methodology of our previous report (PROSPERO registration CRD42021257203).<sup>1</sup>

Our updated analyses included a total of 3808 patients, 3306 patients from the previous report; 253 from HEP-COVID<sup>4</sup> using low-molecular-weight heparin or unfractionated heparin; 66 from the BEMICOP study<sup>5</sup> using bemiparin; and 183 from X-COVID<sup>6</sup> using enoxaparin. Among non-critically ill hospitalized patients, the incidence of all-cause death was 8.0% (157/1962) in the escalated-dose and 8.7% (160/1838) in the standard-dose prophylactic anticoagulation group. The incidence of major bleeding was 2.1% (41/1971) and 1.1% (20/1837) in the escalated-dose and standard-dose anticoagulation groups, respectively. Compared with standard-dose prophylactic anticoagulation, escalated-dose prophylactic anticoagulation was not associated with a reduction of all-cause death [relative risk (RR) 0.92, 95% confidence interval (CI) 0.58-1.46,  $l^2 = 63\%$ ] but was associated with an increase in major bleeding (RR 1.92, 95% CI 1.13-3.28,  $l^2 = 0\%$  (Figure 1). The number needed to treat (NNT) for all-cause death was 141, while the number needed to harm for major bleeding was 101. The incidence of VTE was 1.6% (29/1809) with the escalated-dose and 3.4% (57/1679) with the standard-dose prophylactic anticoagulation. An escalated-dose regimen was associated with lower rates of VTE events compared with the standard dose (RR 0.48, 95% CI 0.31–0.75,  $l^2 = 0\%$ ) (Figure 1). The NNT for VTE was 56.

In conclusion, this updated version of our meta-analysis found results that were

consistent with those previously reported. In non-critically ill hospitalized patients with COVID-19, compared with standard-dose prophylactic anticoagulation, the escalated dose was not associated with a reduction in all-cause death but with an increase in major bleeding and a reduction in VTE. Therefore, the risks may outweigh the benefits. Overall, the currently available evidence does not support indiscriminate use of escalated-dose prophylactic anticoagulation in non-critically ill hospitalized patients with COVID-19. However, the selective use of therapeutic-dose heparin for patients who have a D-dimer above the upper limit of normal, require low-flow oxygen, and have no increased bleeding risk may be an option according to the updated National Institute of Health recommendations.<sup>8</sup>

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Conflict of interest: D.J.A. declares that he has received consulting fees or honoraria from Abbott, Amgen, Aralez, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol Myers Squibb, Chiesi, Daiichi Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, PhaseBio, PLx Pharma, Pfizer, Sanofi, and The Medicines Company; has received payments for participation in review activities from CeloNova and St Jude Medical; and also that his institution has received research grants from Amgen. AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi Sankyo, Eisai, Eli Lilly, Gilead, Idorsia, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, Renal Guard Solutions, and the Scott R. MacKenzie Foundation. The other authors have nothing to declare.

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Study or Subgroup         Escalated-dose         Strandard-dose           ACTION COALITION         35         310         23         304         24.5%           BEMICOP Study         2         33         1         33         3.5%           HEP-COVID         25         129         31         124         25.5%           RAPID         4         228         18         23.7         12.1%           REMAP-CAP, ACTIV-4a, ATTACC non-critically ill         86         1171         86         1048         30.3%           X-COVID         5         91         1         92         4.1%           Total events         157         160         160         1838         100.0%           Heterogeneity: Tau <sup>2</sup> = 0.16; Chi <sup>2</sup> = 13.44, df = 5 (P = 0.02); l <sup>2</sup> = 63%         Total         Weight           ACTION COALITION         10         310         4         304         19.7%           BEMICOP Study         0         33         0         33         14         12.7%           RAPID         2         2.24         9.9%         3.7         16.1%         19.7%           BEMICOP Study         0         33         0         33         33         14.7% <th colspan="3">All-cause aeath</th>	All-cause aeath		
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ACTION COALITION 35 310 23 304 24.5% BEMICOP Study 2 33 1 33 3.5% HEP-COVID 25 129 31 124 25.5% RAPID 4 228 18 237 12.1% REMAP-CAP, ACTIV-4a, ATTACC non-critically ill 86 1171 86 1048 30.3% X-COVID 5 91 1 92 4.1% Total events 157 160 Heterogeneity: Tau <sup>2</sup> = 0.16; Chi <sup>2</sup> = 13.44, df = 5 (P = 0.02); l <sup>2</sup> = 63% Test for overall effect: Z = 0.37 (P = 0.71) <b>Study or Subgroup</b> Escalated-dose 160 44 30 4 19.7% BEMICOP Study 0 33 0 33 HEP-COVID 6 129 2 124 9.9% RAPID RCMAP-CAP, ACTIV-4a, ATTACC non-critically ill 22 1180 9 1047 46.4% X-COVID 1 91 1 92 4.8% Total events 41 20 HEP-COVID 1 1 91 1 92 4.8% Total events 41 20 Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); l <sup>2</sup> = 0% Total events 41 20 Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); l <sup>2</sup> = 0% Total events 41 20 Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); l <sup>2</sup> = 0% Total events 41 20 Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); l <sup>2</sup> = 0% Total events 41 20 Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); l <sup>2</sup> = 0% Total events 41 20 Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); l <sup>2</sup> = 0% Total events 41 20 Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); l <sup>2</sup> = 0% Total events 41 20 Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); l <sup>2</sup> = 0% Total events 41 20 Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); l <sup>2</sup> = 0% Total events 41 20 Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); l <sup>2</sup> = 0% Total events 41 20 Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); l <sup>2</sup> = 0% Total events 41 20 Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); l <sup>2</sup> = 0% Total events 41 20 Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); l <sup>2</sup> = 0% Total events 41 20 Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); l <sup>2</sup> = 0% Total events 41 20 Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); l <sup>2</sup> = 0% Total events 41 20 Heterogeneity: Chi <sup>2</sup> = 3.04, df =	IV, Random, 95% CI	IV, Random, 95% CI	
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HEP-COVID       25       129       31       124       25.3         RAPID       4       228       18       237       12.19         REMAP-CAP, ACTIV-4a, ATTACC non-critically ill       86       1171       86       1048       30.39         K-COVID       5       91       1       92       4.19         Total (95% CI)       1962       1838       100.0%         Total events       157       160         Heterogeneity: Tau <sup>2</sup> = 0.16; Chi <sup>2</sup> = 13.44, df = 5 (P = 0.02); I <sup>2</sup> = 63%       5tandard-dose         Study or Subgroup       Events       Total       Events       Total         ACTION COALITION       10       310       4       304       19.7%         Study or Subgroup       Events       Total       Events       Total       Weight         ACTION COALITION       10       310       4       304       19.7%         StemicOP study       0       33       0       33       9       19.1%         RAPID       2       228       4       237       19.1%         REMAP-CAP, ACTIV-4a, ATTACC non-critically ill       22       180       9       1047       46.4%         K-COVID       191       19	2.00 [0.19, 21.00]		
CAPID       4       2.37       12.17       18       104.8       30.3%         K-COVID       5       91       1       92       4.1%         Total (95% CI)       1962       183.8       100.0%         Total veents       157       160         Heterogeneity: Tau <sup>2</sup> = 0.16; Chi <sup>2</sup> = 13.44, df = 5 (P = 0.02); l <sup>2</sup> = 63%       5       160 <b>Escalated-dose</b> 5 <b>Exelated-dose</b> 5 <b>Exelated-dose</b> 5 <b>Study or Subgroup Escalated-dose</b> 5 <b>Events</b> Total       Weight         A 30.3%         Ageign to be standard-dose <b>Events</b> Total       Weight         A 30.4       4       30.4       19.7%         Ageign colspan="2"> <b>Total</b> Weight         A 30.4       6       12.9       2       12.4       9.9%         A 30.4       6       12.9       2       12.4       9.9%         Ageign colspan="2"> <b>Events</b> Total (95% CI)       1       91       1       92       4.8%	0.78 [0.49, 1.23]		
Charles - CAP, ACTIV-4a, ATTACC INDIFICITIONALITY III       30       11/1       30       10/43       30.33.9         Total (95% CI)       1962       1838       100.0%         Total events       157       160         Heterogeneity: Tau <sup>2</sup> = 0.16; Chi <sup>2</sup> = 13.44, df = 5 (P = 0.02); I <sup>2</sup> = 63%       Standard-dose         Standy or Subgroup       Escalated-dose       Standard-dose         Standy or Subgroup       Colspan="2">Colspan="2"       Colspan="2"	0.23 [0.08, 0.67]		
Total (95% CI)       1962       1838       100.0%         Total events       157       160       160         Meterogeneity: Tau <sup>2</sup> = 0.16; Chi <sup>2</sup> = 13.44, df = 5 (P = 0.02); l <sup>2</sup> = 63%         Total events       Total Standard-dose         Standard-dose         Standard-dose         Escalated-dose       Standard-dose         Events       Total       Weight         ACTION COALITION         ACTION COALITION         BEMICOP Study       0       310       31         Events       Total       Weight         ACTION COALITION       10       33         BEMICOP Study       0       33         Total (95% CI)       1971       1837       100.0%         Total (95% CI)       1971       1837       100.0%         Study or Subgroup       Events       Total       Events       Total       Weight         ACTIV-4a, ATTACC non-critical	5.05 [0.60, 42.43]		
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BEINICUP Study         0         33         0         33         0         33           REPCOVID         6         129         2         124         9.9%           RAPID         2         228         4         237         19.1%           REMAP-CAP, ACTIV-4a, ATTACC non-critically ill         2         1180         9         1047         46.4%           X-COVID         1         91         1         92         4.8%           Total (95% CI)         1971         1837         100.0%           Total events         41         20	2.45 [0.78, 7.73]		
APPID       0       129       2       124       9.3%         REMAP-CAP, ACTIV-4a, ATTACC non-critically ill       22       1180       9       1047       46.4%         X-COVID       1       91       1       92       4.8%         Total (95% Cl)       1971       1837       100.0%         Total events       41       20         Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); l <sup>2</sup> = 0%       41       20         Study or Subgroup       Escalated-dose       Standard-dose         Study or Subgroup       Events       Total       804       30.8%         RAPID       2       22.8       7       237       11.6%         REMAP-CAP, ACTIV-4a, ATTACC non-critically ill       16       1180       26       10.46       46.7%         X-COVID       0       91       6       92       10.9%         Total (95% Cl)       1809       1679       100.0%	Not estimable		
KRIMAP-CAP, ACTIV-4a, ATTACC non-critically ill       22       1180       9       1047       46.4%         X-COVID       1       91       1       92       4.8%         Total (95% CI)       1971       1837       100.0%         Total events       41       20         Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); l <sup>2</sup> = 0%       41       20 <b>Escalated-dose</b> Standard-dose         Study or Subgroup       Escalated-dose         Actrion Coalition         11       310       18       30.4         ACTION COALITION       11       310       18       30.4         RAPID       2       22       22       7       237       11.6%         REMAP-CAP, ACTIV-4a, ATTACC non-critically ill       16       1180       26       1046       46.7%         X-COVID       0       91       6       92       10.9%			
X-COVID     1     91     1     92     4.8%       Total (95% Cl)     1971     1837     100.0%       Total events     41     20       Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); l <sup>2</sup> = 0%     20     Version       Study or Subgroup     Escalated-dose     Standard-dose       KACTION COALITION     11     310     18     30.4       RAPID     2     22     22     7     237       REMAP-CAP, ACTIV-4a, ATTACC non-critically ill     16     1180     26     1046     46.7%       X-COVID     1809     1679     100.0%	2.17 [1.00, 4.69]		
Example Coll         1971         1837         100.0%           Total events         41         20	1.01 [0.06, 15.92]		
Total events     41     20       Heterogeneity: Chi <sup>2</sup> = 3.04, df = 4 (P = 0.55); I <sup>2</sup> = 0%     Total     Escalated-dose     Events       Study or Subgroup     Events     Total     Events     Total     Weight       ACTION COALITION     11     310     18     30.4     30.8%       RAPID     2     22.28     7     237     11.6%       REMAP-CAP, ACTIV-4a, ATTACC non-critically ill     16     1180     26     1046     46.7%       X-COVID     1809     1679     100.0%	1.92 [1.13, 3.28]	•	
Escalated-dose       Standard-dose         Study or Subgroup       Escalated-dose       Standard-dose         Events       Total       Weight         ACTION COALITION       11       310       18       30.4       30.8%         RAPID       2       22.28       7       23.7       11.6%         REMAP-CAP, ACTIV-4a, ATTACC non-critically ill       16       1180       26       1046       46.7%         X-COVID       0       91       6       92       10.9%         Total (95% CI)       1809       1679       100.0%			
Escalated-dose       Study or Subgroup       Escalated-dose       Events       Total       Weight         ACTION COALITION       11       310       18       304       30.8%         RAPID       2       2228       7       237       11.6%         X-COVID       0       91       6       92       10.9%         Total (95% CI)       1809       1679       100.0%	6.01		
Escalated-dose         Standard-dose         Events         Total         Weight           ACTION COALITION         11         310         18         30.4         30.8           RAPID         2         228         7         237         11.6%           REMAP-CAP, ACTIV-4a, ATTACC non-critically ill         16         1180         26         1046         46.7%           X-COVID         0         91         6         92         10.9%           Total (95% CI)         1809         1679         100.0%	0.01	Favours escalated-dose Favours standard-dose	
Study or Subgroup         Escalated Events         -Cose Total         StandardEvents         Total         Weight           ACTION COALITION RAPID         11         310         18         30.4         30.8           REMAP-CAP, ACTIV-4a, ATTACC non-critically ill X-COVID         16         1180         26         1046         46.7%           Total (95% CI)         1809         91         6         92         10.9%			
Statisticity         Events         Total         Events	Risk Ratio		
RAPID         21         510         304         30.0           RAPID         2         228         7         237         11.6%           REMAP-CAP, ACTIV-4a, ATTACC non-critically ill         16         1180         26         1046         46.7%           X-COVID         0         91         6         92         10.9%           Total (95% CI)         1809         1679         100.0%	0.60 [0.29, 1.25]		
REMAP-CAP, ACTIV-4a, ATTACC non-critically ill         16         1180         26         1046         46.7%           X-COVID         0         91         6         92         10.9%           Total (95% CI)         1809         1679         100.0%	0.30 [0.06, 1.41]		
X-COVID         0         91         6         92         10.9%           Total (95% CI)         1809         1679         100.0%	0.55 [0.29, 1.01]		
Total (95% CI) 1809 1679 100.0%	0.08 [0.00, 1.36]		
	0.48 [0.31, 0.75]	•	
Total events 29 57		-	
Heterogeneity: $Chi^2 = 2.42$ , $df = 3$ (P = 0.49); $l^2 = 0\%$	0.01		

**Figure 1** Forest plots of escalated-dose vs. standard-dose prophylactic anticoagulation in non-critically ill hospitalized patients with COVID-19 for all-cause death, major bleeding, and venous thromboembolism. CI, confidence interval; IV, inverse variance; M–H, Mantel–Haenszel; and VTE, venous thromboembolism.

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# Luis Ortega-Paz<sup>1</sup>, Mattia Galli<sup>2</sup> and Dominick J Angiolillo (D<sup>1,\*</sup>

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<sup>1</sup>Division of Cardiology, University of Florida College of Medicine, 5th floor, ACC Building, 655 West 8th Street, Jacksonville, FL 32209, USA; and <sup>2</sup>Catholic University of the Sacred Heart, Rome, Italy \* Corresponding author. Tel: +1-904-244-3378, Fax: +1-904-244-3102, E-mail: dominick.angiolillo@jax.ufl.edu

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