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Use of anticoagulants in patients with COVID-19: an update of a living systematic review and meta-analysis

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TO THE EDITOR:

This is an update of a living systematic review and meta-analysis by Batista et al.[1] We performed a search for articles published in the period between January of 2020 and December of 2022. We retrieved 431 articles, but only 14 remained. Of those 14 studies, nine had previously been evaluated.[1] Therefore, a total of five studies were included in the present update. Of those, two included hospitalized adult patients (one being an open-label randomized clinical trial—RCT—including 186 hospitalized patients with moderate COVID-19 and one being an open-label RCT including 159 patients admitted to the ICU) and three were RCTs including COVID-19 outpatients (one being a double-blind RCT and two being open-label RCTs) Because of the heterogeneity of intervention designs, three RCTs of COVID-19 outpatients were not included in the present update. Ramacciotti et al.[2] investigated extended post-discharge anticoagulation for COVID-19 patients. For the analysis of hospitalized COVID-19 patients, eight RCTs[3-10] were included in the present update, with 2,695 patients in the therapeutic-dose group (full anticoagulation) and 2,553 patients in the standard-of-care (SOC) group. There was no significant reduction in the 30-day mortality rate in patients with moderate to severe COVID-19 (risk difference [RD], −0.00; 95% CI, −0.03 to 0.02; p = 0.77; I^2 = 60%), the quality of evidence being very low. When patients with moderate COVID-19[3,4,6,7,9] or severe COVID-19[5,10] were analyzed separately, no significant difference was found between full anticoagulation and SOC in those with moderate COVID-19 (RD, −0.01; 95% CI, −0.05 to 0.03; p =0.77; I^2 = 76%), the quality of evidence being very low. Two studies assessed patients with severe COVID-19,[5,10] showing no significant difference in the mortality rate between the two groups (RD, 0.01; 95% CI, −0.04 to 0.06; p = 0.66; I^2 = 0%); the quality of evidence was very low.

Thrombotic events were assessed in seven studies,[3,5-10] with a total of 2,621 patients in the therapeutic-dose group and 2,511 patients in the SOC group. There was a significant (3%) reduction in thrombotic events at 30 days in the therapeutic-dose group in comparison with the SOC group (RD, −0.03; 95% CI, −0.05 to −0.01; p = 0.009; I^2 = 73%), the number needed to treat (NNT) being = 33 and the quality of evidence being low. This result remained significant when the severity of COVID-19 was evaluated. For patients with moderate COVID-19, three studies[6,7,9] demonstrated a 2% reduction in RD (95% CI, −0.04 to −0.00; p = 0.06; I^2 = 55%), the NNT being = 50 and the quality of evidence being low. For patients with severe COVID-19, two studies[5,10] demonstrated a significant (3%) reduction in thrombotic events after 30 days (95% CI, −0.06 to −0.01; p = 0.02; I^2 = 33%), the NNT being = 33 and the quality of evidence being moderate.

Major bleeding within 30 days was reported in seven studies,[3,5-10] with a total sample of 5,132 patients. There was no significant difference in major bleeding between patients receiving full coagulation and those receiving SOC (RD, 0.01; 95% CI, −0.01 to 0.03; p = 0.2; I^2 = 61%), the quality of evidence being very low. When patients with moderate COVID-19 were analyzed, no significant difference was found between the two groups (RD, 0.01; 95% CI, −0.01 to 0.03; p = 0.45; I^2 = 71%), the quality of evidence being very low. For patients with severe COVID-19, three RCTs[5,8,10] showed no significant differences in major bleeding between the two groups (RD, 0.01; 95% CI, −0.02 to 0.05; p = 0.46; I^2 = 51%), the quality of evidence being very low.

A total of 1,023 outpatients with COVID-19 were analyzed in three RCTs,[11-13] with 506 outpatients in the prophylactic-dose group and 517 outpatients in the SOC group. As can be seen in Figure 1A, no significant difference was found between the groups regarding the 30-day mortality rate (RD, 0.00; 95% CI, −0.01 to 0.01; p = 0.61; I^2 = 0%), the quality of evidence being very low. As can be seen in Figure 1B, there was no significant difference between the groups regarding thrombotic events (RD, 0.00; 95% CI, −0.01 to 0.01; p = 0.51; I^2 = 0%), the quality of evidence being moderate. As can be seen in Figure 1C, there was no significant difference between the groups regarding all-cause hospitalization (RD, 0.00; 95% CI, −0.02 to 0.03; p = 0.86; I^2 = 0%), the quality of evidence being very low. Major bleeding was assessed in two studies,[11,12] with a total of 401 patients in the prophylactic-dose group and 403 patients in the SOC group. As can be seen in Figure 1D, there was no significant difference between the groups regarding

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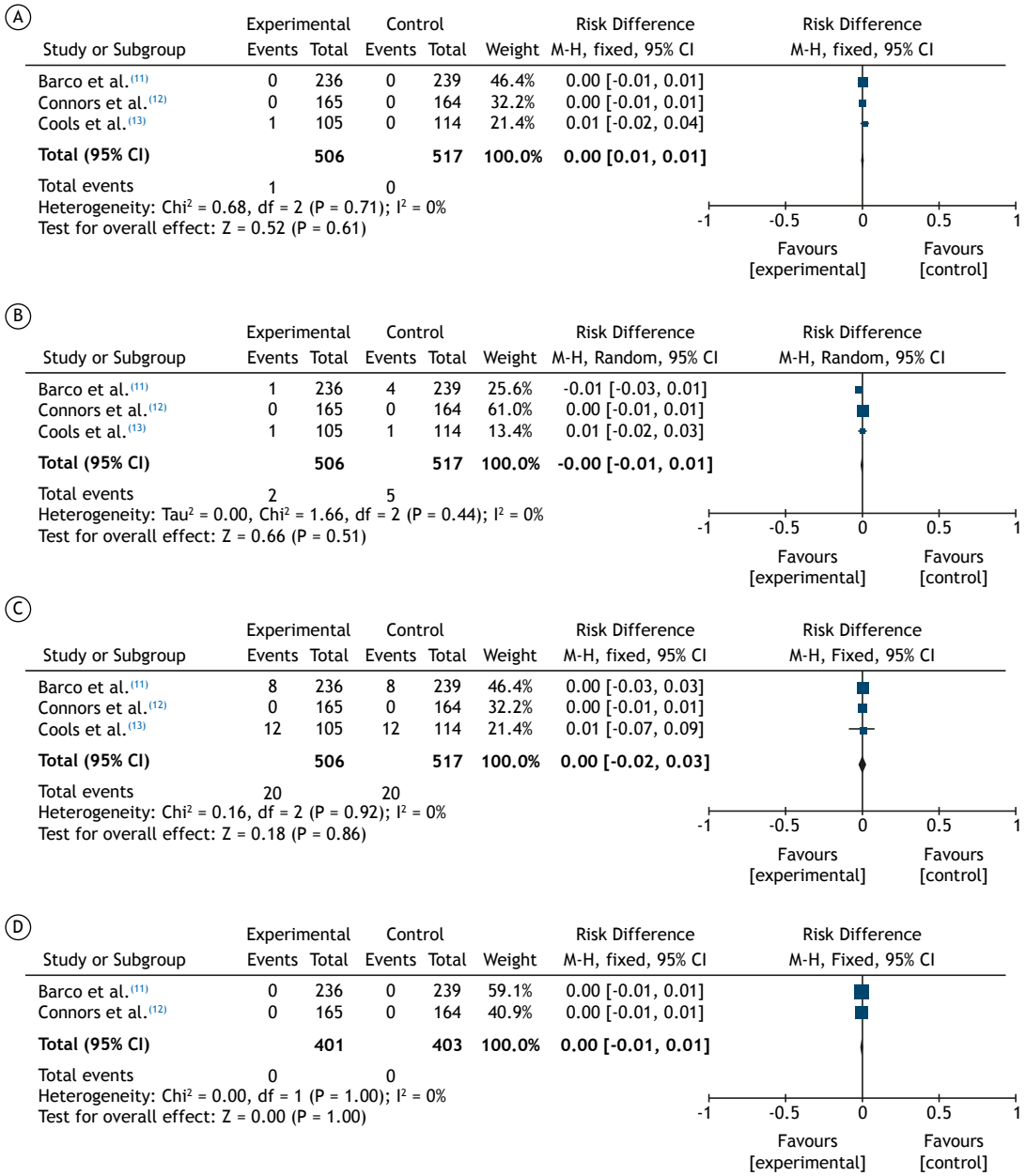

Figure 1. Forest plot of comparison: Prophylactic anticoagulation vs. standard of care/placebo—randomized clinical trials, outcome: A: mortality at 30 days, B: venous thromboembolism at 30 days, C: all-cause hospitalization, D: major bleeding at 30 days. M-H: Mantel-Haenszel (method); and df: degrees of freedom.

major bleeding (RD, 0.00; 95% CI, −0.01 to 0.01; p = 1.0; I^2 = 0%), the quality of evidence being low.

In conclusion, new evidence from RCTs of hospitalized COVID-19 patients shows that full anticoagulation can reduce the risk of thrombotic events with low risk of major bleeding. However, this evidence is highly heterogeneous and of low or very low quality and therefore should not be used for all hospitalized COVID-19 patients. For COVID-19 outpatients, our current findings are consistent with our previous results showing that there is no evidence to support the use of prophylactic anticoagulation in this population.

AUTHOR CONTRIBUTIONS

SET, HAB, IF, and WMB: study concept and design. WMB, SET, DRB, and IF: data collection and interpretation; and statistical analysis. WMB, DRB, and SET: drafting of the manuscript. SET, HAB, AN, AS, and WMB: critical revision of the manuscript for important intellectual content and final approval of the submitted version.

CONFLICTS OF INTEREST

None declared.

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