Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial

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Background

- Thrombotic events complicate COVID-19 at higher rates than previously observed in other comparable clinical situations.
- Prophylactic use of parenteral anticoagulants during hospitalization is recommended, and there is emerging consensus about the role of in-hospital heparin as primary thromboprophylaxis.
- However, there is no consensus on the use of extended thromboprophylaxis beyond the hospital stay.

AIM of the study

- To assess if in patients hospitalized with COVID-19, prophylaxis with rivaroxaban 10 mg/day for 35 days after discharge would improve clinical outcomes, including major and fatal thromboembolic events.

Methods

- Open-label, multicentre, randomised trial conducted at 14 centres in Brazil.
- Patients hospitalised with COVID-19 at increased risk for venous thromboembolism (IMPROVE VTE score of ≥4 or 2–3 with a D-dimer >500 ng/mL) were randomly assigned (1:1) to receive, at hospital discharge, rivaroxaban 10 mg/day or no anticoagulation for 35 days.
- Primary efficacy outcome: a composite of symptomatic or fatal venous thromboembolism, asymptomatic venous thromboembolism on bilateral lower-limb venous ultrasound and CT pulmonary angiogram, symptomatic arterial thromboembolism, and cardiovascular death at day 35.
- Primary safety outcome: major bleeding.

Results (I)

- 320 patients.
- All patients received thromboprophylaxis with standard doses of heparin during hospitalization.
- Baseline characteristics were balanced between groups.
- The mean age was 57,1 years, 127 (40%) were women, and the mean body-mass index was 29·7 kg/m² .
- 165 (52%) patients were in the intensive care unit while hospitalized.
- 197 (62%) patients had an IMPROVE score of 2–3 and elevated D-dimer levels and 121 (38%) had a score of 4 or more.

Results (II)

- The primary efficacy outcome occurred in five (3%) of 159 patients assigned to rivaroxaban and 15 (9%) of 159 patients assigned to no anticoagulation (relative risk 0,33, 95% CI 0·12–0·90; p=0,0293).
- The primary efficacy outcome was driven mainly by pulmonary embolism in the control group.
- No major bleeding occurred in either study group.

	Rivaroxaban (n=159)	Control (n=159)
Age, years	57·8 (14·8)	56·4 (15·6)
Age ≥75 years	18 (11%)	15 (9%)
Sex		
Female	62 (39%)	65 (41%)
Male	97 (61%)	94 (59%)
Body-mass index, kg/m²	29·6 (5·6)	29·9 (6·0)
Creatinine clearance		
30 to <50 mL/min	6/158 (4%)	5/157 (3%)
≥50 mL/min	152/158 (96%)	152/157 (97%)
Duration of index hospitalisation, days	8 (5·5; 12)	8 (6; 12)
ICU or CCU stay	86 (54%)	79 (50%)
In-hospital enoxaparin 40 mg use	136 (86%)	137 (86%)
In-hospital unfractionated heparin use	23 (14%)	22 (14%)
IMPROVE VTE score		
2–3	98 (62%)	99 (62%)
≥4	61 (38%)	60 (38%)
D-dimer level above ULN during index hospitalisation	106/115 (92%)	108/118 (92%)
Antiplatelet use	8 (5%)	8 (5%)

Data are mean (SD), n (%), median (IQR), or n/N (%). CCU=cardiac care unit. ICU=intensive care unit. IMPROVE VTE=International Medical Prevention Registry on Venous Thromboembolism venous thromboembolism. ULN=upper limit of normal.

Table 1: **Baseline characteristics (intention-to-treat analysis)**

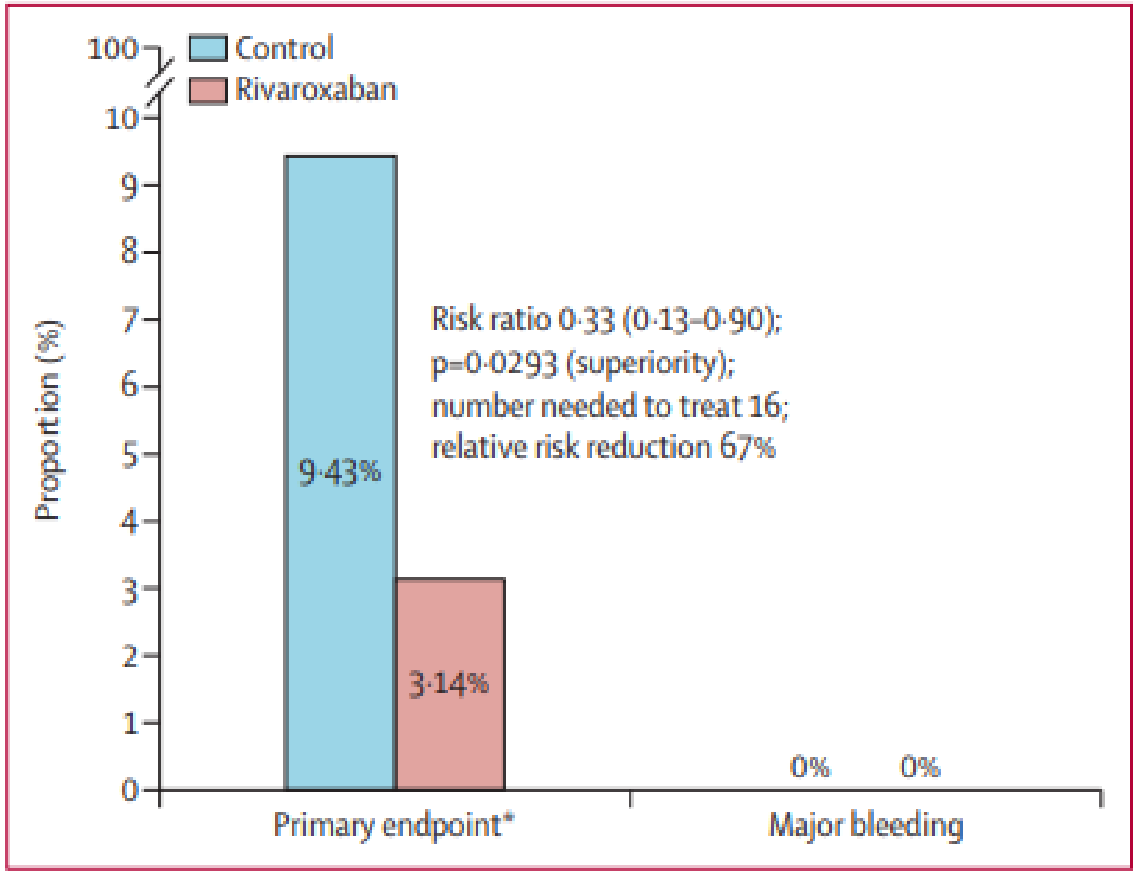

Figure 2: **Primary efficacy and safety outcomes**

The primary endpoint was a composite of symptomatic or fatal venous thromboembolism, asymptomatic venous thromboembolism detected by bilateral lower limb venous Doppler ultrasound and CT pulmonary angiogram, symptomatic arterial thromboembolism (myocardial infarction, non-haemorrhagic stroke, and major adverse limb event), and cardiovascular death at day 35.

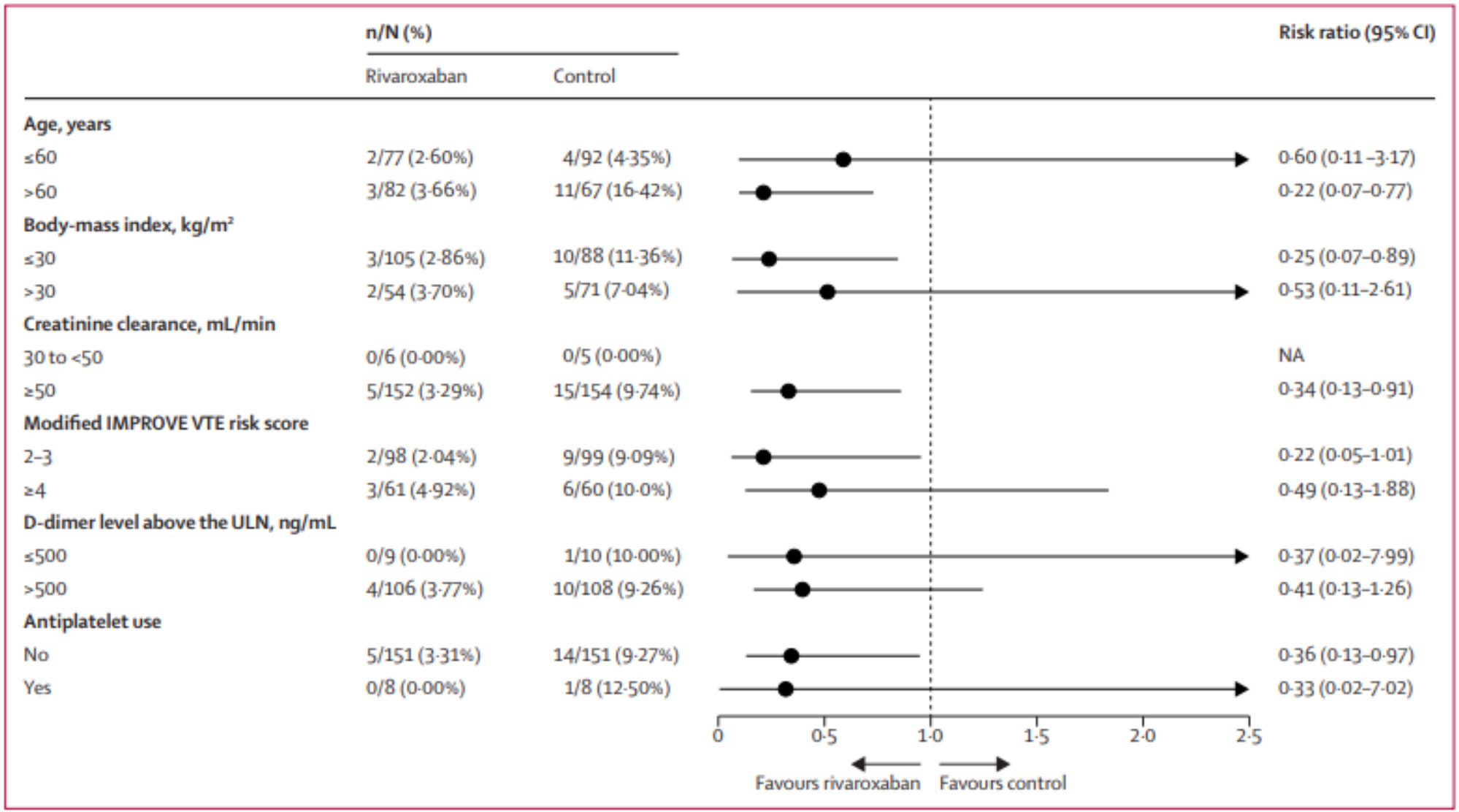

Figure 3: **Subgroup analysis**

IMPROVE VTE=International Medical Prevention Registry on Venous Thromboembolism venous thromboembolism. ULN=upper limit of normal.

Conclusions

- In conclusion, in patients at high risk discharged after hospitalization due to COVID-19, evidence suggests that thromboprophylaxis with rivaroxaban 10 mg/day through 35 days improved clinical outcomes, reducing thrombotic events, compared with no post-discharge anticoagulation.
- This is the first randomized study in the field of extended post-discharge thromboprophylaxis for patients with COVID-19 that has shown clinical benefit.
- Other clinical studies are actively assessing extended thromboprophylaxis in patients with COVID-19 and we are waiting for the results.