MEDICALLY ILL HOSPITALIZED PATIENTS FOR COVID –19 THROMBOSIS EXTENDED PROPHYLAXIS WITH RIVAROXABAN THERAPY: **THE MICHELLE TRIAL**

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On Behalf of The Michelle Trial Investigators

ESC CONGRESS 2021
THE DIGITAL EXPERIENCE

DECLARATION OF INTEREST

FOR EDUARDO RAMACCIOTTI

RESEARCH SUPPORT/P.I.	BMS/PFE, BAYER, MCTI
EMPLOYEE	No relevant conflicts of interest to declare
CONSULTANT	No relevant conflicts of interest to declare
MAJOR STOCKHOLDER	No relevant conflicts of interest to declare
SPEAKERS BUREAU	BMS/PFE, ASPEN, BAYER, Daiichi-Sankyo, BIOMM
HONORARIA	No relevant conflicts of interest to declare
SCIENTIFIC ADVISORY BOARD	BMS/PFE, BAYER, Daiichi-Sankyo

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Bayer (*)

(*) *Unrestricted research grant from Bayer S.A., which was not involved in design, conduct or interpretation of the study*

BACKGROUND

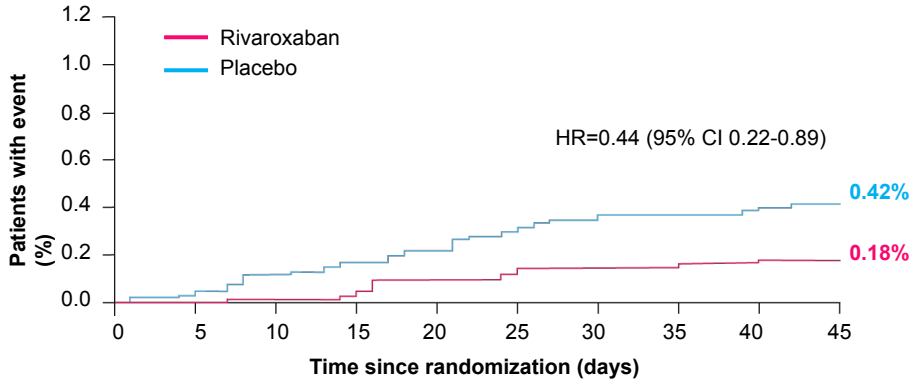
1. The devastating Coronavirus disease (COVID-19) pandemic is associated with a high prothrombotic state [1]
2. It is unclear if the coagulation abnormalities occur because of the direct effect of SARS-CoV-2 or indirectly by the cytokine storm and endothelial damage or by a combination of mechanisms [2]
3. There is a clear indication of in-hospital pharmacological thromboprophylaxis for every patient with COVID-19 after bleeding risk assessment [3]
4. There is no consensus on the role of extended thromboprophylaxis [4]
5. Current antithrombotic statements are conflicting for the need (or not) for post-hospital discharge thromboprophylaxis in hospitalized COVID-19 patients [5]

1. Klok et al. Thromb Res 2020;191:145-147; 2. Ackermann et al. N Engl J Med 2020;383(2):120-128; 3. Spyropoulos et al. J Thromb Haemost 2020;18(8):1859-1865; 4. Moores et al. Chest 2020;158(3):1143-1163; 5. Gerotziafas et al. Thromb Haemost 2020;120(12):1597-1628.

↓56% symptomatic VTE

No ↑Bleeds

Significant Reduction of Symptomatic VTE with Rivaroxaban After Discharge in Acutely Medically Ill Patients



Spyropoulos A *et al*, *N Engl J Med* 2018

IMPROVE DD VTE

RISK SCORE

VTE RISK FACTOR	POINTS
Previous VTE	3
Known thrombophilia	2
Lower-limb paralysis	2
History of cancer (*)	2
Immobilization ≥1 day (*)	1
ICU/CCU stay	1
Age >60 years	1
D dimer≥ 2X UNL	2

(*) Modified for the MARINER clinical trial | ICU = intensive care unit; CCU = critical care unit.

Spyropoulos AC et al Chest 2011; 140:706-14

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Power:

Rivaroxaban is not approved for patients admitted or discharged for an acute medical illness by EMEA

KEY INCLUSION AND EXCLUSION CRITERIA

KEY INCLUSION CRITERIA

- Patients ≥ 18 years hospitalized for minimum of 3 days with standard dose thromboprophylaxis (LMWH, fondaparinux or UFH) prior to randomization for SARS-CoV-2 infection (COVID-19)
- Total modified IMPROVE VTE Risk Score ≥ 4 OR total modified IMPROVE VTE Risk Score 2 or 3 and D dimer > 500 ng/ml during index hospitalization

KEY EXCLUSION CRITERIA

- Bleeding Risks
  - Any bleeding within 3 months
  - Surgery, biopsy or trauma 4 weeks prior or planned
  - Active gastroduodenal ulcer
  - Active cancer
- Required anticoagulation after discharge
- Use of dual antiplatelet therapy during the index hospitalization
- Creatinine clearance < 30 ml/min
- Concomitant Medications
  - Combined P-gp and strong CYP3A4 inhibitors
  - Combined P-gp and strong CYP3A4 inducers

CLINICAL OUTCOMES

PRIMARY OUTCOME

Composite of symptomatic VTE, VTE-related death, and VTE detected at bilateral lower limbs venous duplex scan and computed tomography pulmonary angiogram and symptomatic arterial thromboembolism, myocardial infarction (MI), non-hemorrhagic stroke, major adverse limb event (MALE), and cardiovascular (CV) death at day 35

KEY SAFETY OUTCOME

Incidence of major bleeding according to ISTH criteria

SECONDARY OUTCOMES

Symptomatic and fatal VTE
Symptomatic VTE + all cause mortality
Symptomatic VTE, MI, stroke and cardiovascular death

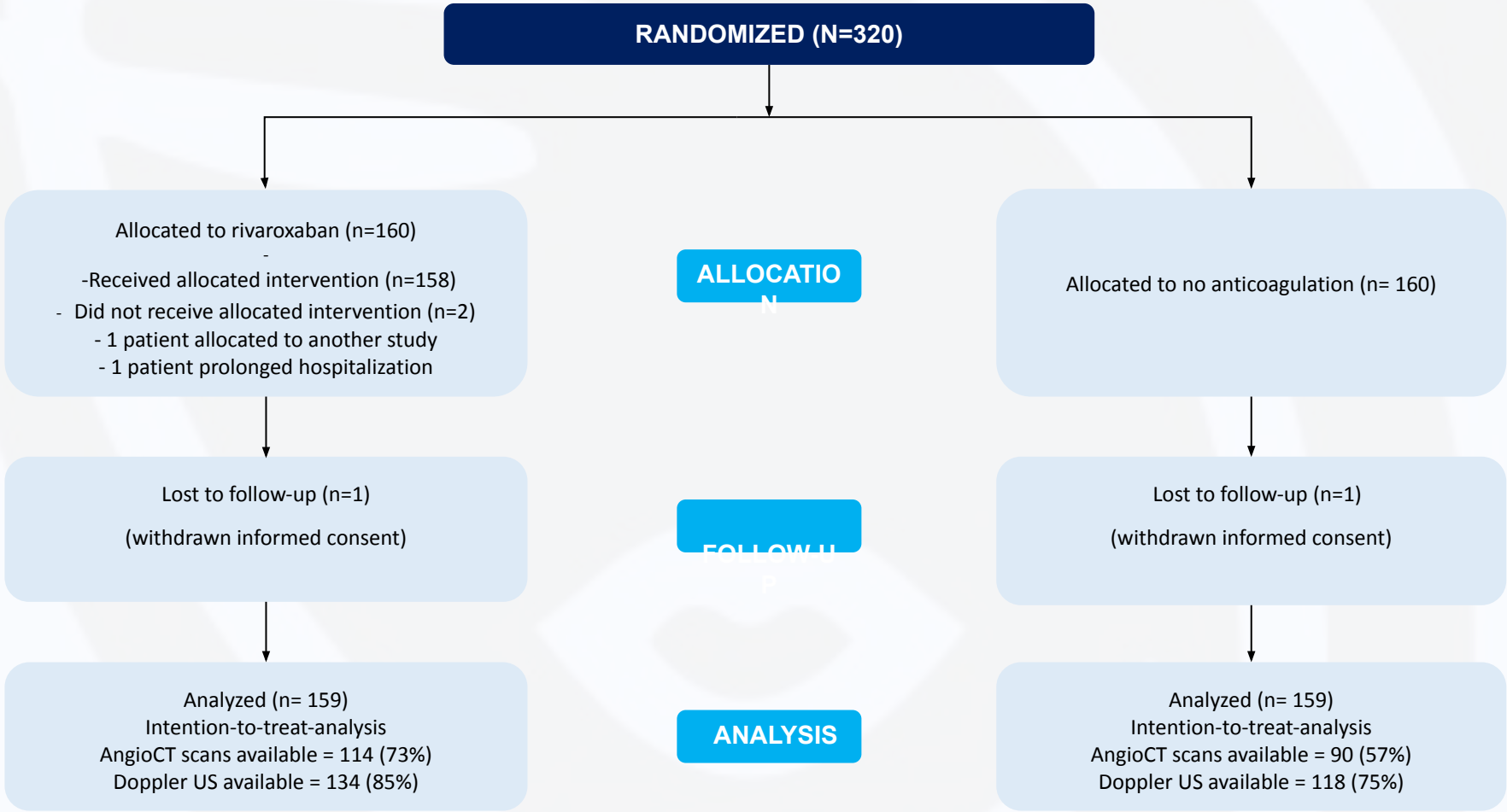
Clinical outcomes were adjudicated by an independent committee in a blinded fashion

STATISTICAL ANALYSIS

SAMPLE SIZE CALCULATIONS

1. Power of 80% and α =0.05
2. Anticipated occurrence of the primary efficacy endpoint of 15% of patients in the control group and 5% of patients in the treatment group (RRR = 67%)
3. If there is a true difference in favor of the proposed treatment of an absolute risk reduction of 10%
(15% *vs*. 5%), then 282 patients were required
4. With a drop-out rate of 10%, a total of **320** patients was necessary (160 per arm)
5. The primary analysis was performed using the intention-to-treat principle

STUDY FLOW-DIAGRAM

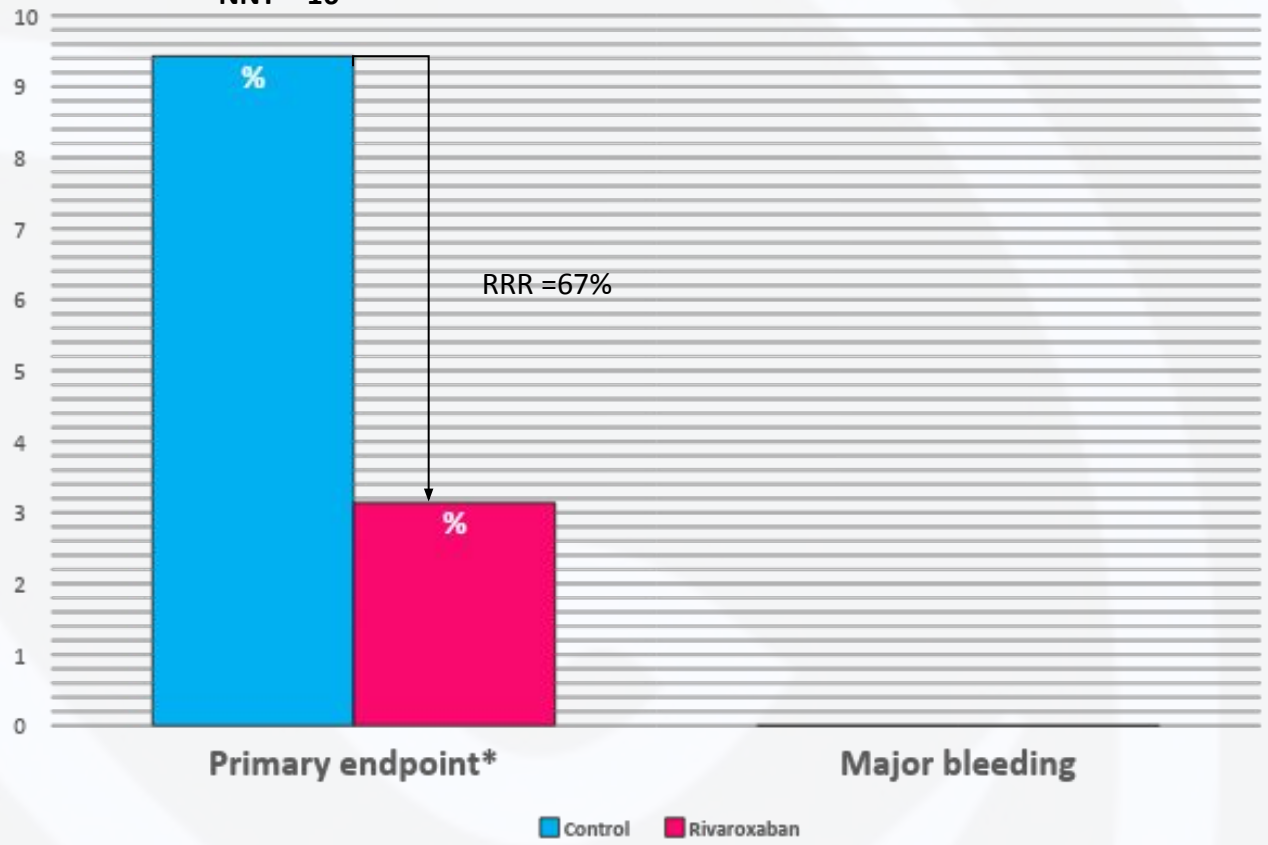


BASELINE CHARACTERISTICS

CHARACTERISTICS	RIVAROXABAN (N=159)	CONTROL (N=159)
Mean age(yr) – mean(SD)	57.8 (14.8)	56.4 (15.6)
Age ≥75 yr — n° (%)	18 (11.3%)	15 (9.4%)
Female sex — n° (%)	62 (39.0%)	65 (40.9%)
BMI – mean(SD)	29.6 (5.6)	29.9 (6.0)
Clearance n./total(%)		
30 to <50 ml/min	6/158 (3.8%)	5/157 (3 .2%)
≥50 ml/min	152/158 (96.2%)	152/157 (96.8%)
Mean duration of index hospitalization — days -mean(SD)	16.4 (46.7)	12.6 (28.5)
ICU or CCU stay — n° (%)	86 (54.1%)	79 (49.7%)
In-hospital enoxaparin 40 mg use — n° (%)	136 (85.5%)	137 (86.2%)
In-hospital unfractionated heparin use — n° (%)	23 (14.5%)	22 (13.8%)
IMPROVE score n.(%)		
2-3	98 (61.6%)	99 (62.3%)
≥4	61 (38.4%)	60 (37.7%)
D-Dimer level above the UNL during index hospitalization — n°/total (%)	106/115 (92.2%)	108/118 (91.5%)
Antiplatelets use — n° (%)	8 (5.0%)	8 (5.0%)

PRIMARY EFFICACY/SAFETY OUTCOMES

RR = 0.33 (0.13—0.90)
p=0.03 (superiority)
NNT = 16

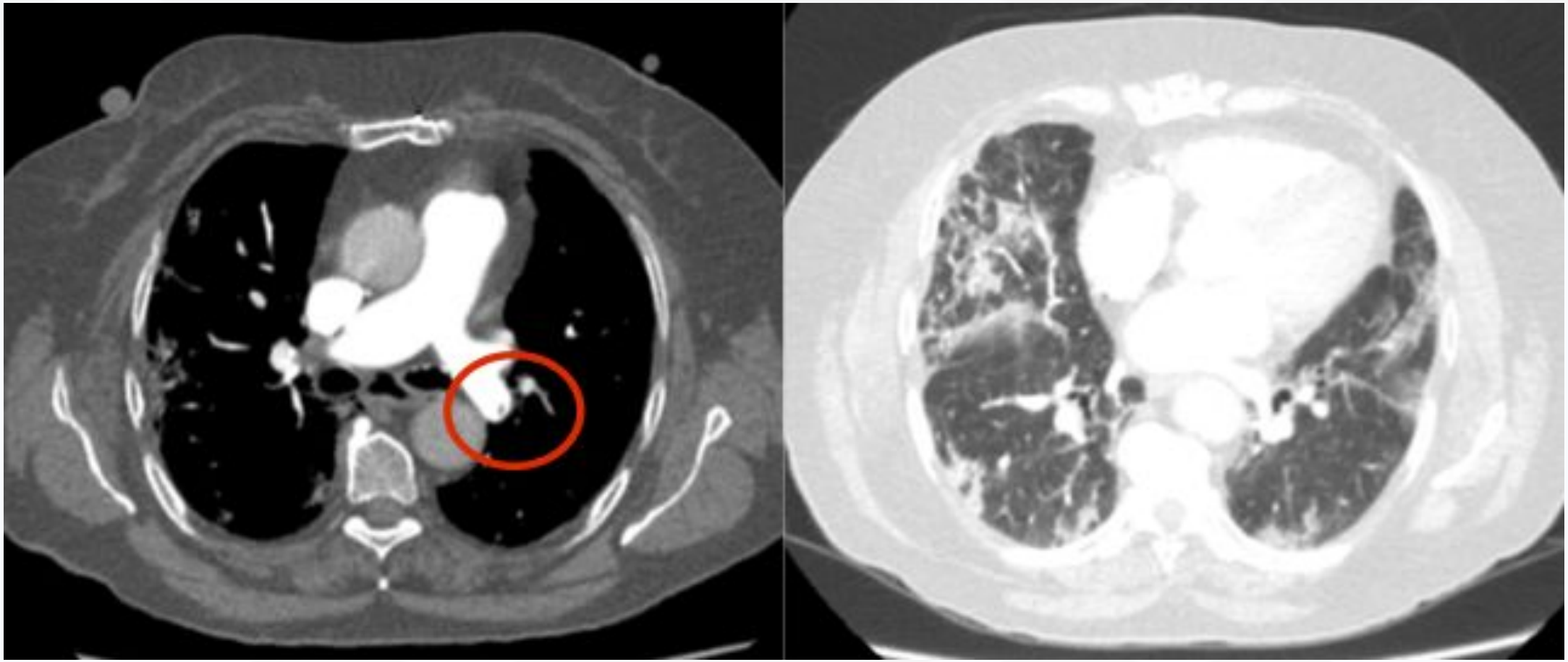


*Composite of composite of symptomatic VTE, VTE-related death, asymptomatic VTE (Doppler and AngioCT scan) and symptomatic ATE, MI, non-hemorrhagic stroke, (MALE), and cardiovascular death at day 35.

SECONDARY EFFICACY OUTCOMES

Secondary efficacy outcomes	RIVAROXABAN (N = 159)	CONTROL (N = 159)	RELATIVE RISK (95% CI)
Symptomatic + fatal VTE	1/159 (0.63%)	8/159 (5.03%)	0.13 (0.02 – 0.99)
Symptomatic VTE + all cause mortality	4/159 (2.52%)	9/159 (5.66%)	0.44 (0.14 – 1.41)
A composite of Symptomatic VTE, MI, stroke and cardiovascular deaths	1/159 (0.63%)	9/159 (5.66%)	0.11 (0.01 – 0.87)
Components of the primary outcome			
Symptomatic DVT	0	3 (1.89%)	0.14 (0.01 – 2.74)
Symptomatic PE	1 (0.63%)	2 (1.26%)	0.50 (0.05 – 5.46)
Fatal PE	0	3 (1.89%)	0.14 (0.01 – 2.74)
Asymptomatic DVT detected at duplex scan	3 (1.89%)	1 (0.63%)	3.00 (0.32 – 28.53)
Asymptomatic PE detected at CT pulmonary angiogram	1 (0.63%)	4 (2.52%)	0.25 (0.03– 2.21)
Symptomatic arterial thrombosis	0	1 (0.63%)	0.33 (0.01 – 8.12)
Myocardial infarction	0	0	-
Non-hemorrhagic stroke	0	0	-
Major adverse limb event (MALE)	0	0	-
Cardiovascular deaths	0	1 (0.63%)	0.33 (0.01 – 8.12)

SECONDARY EFFICACY OUTCOMES

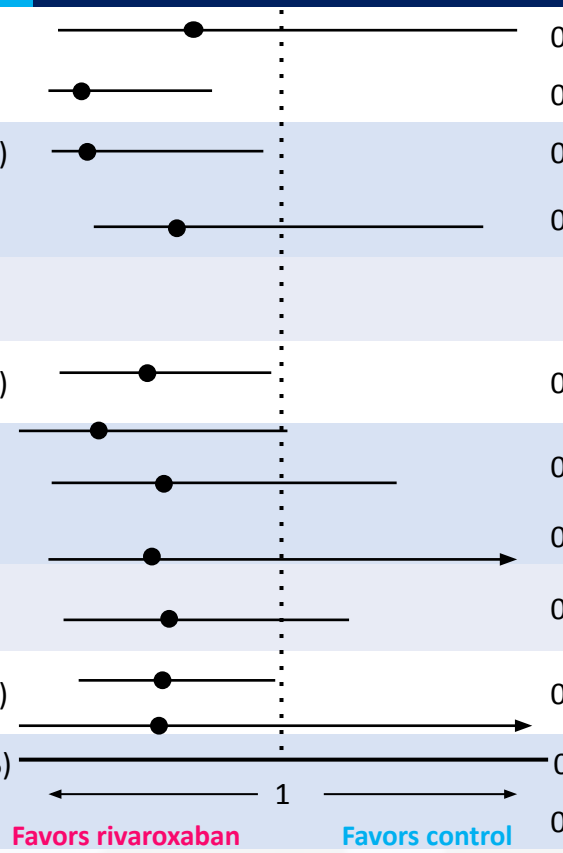


SAFETY OUTCOMES

	Rivaroxaban (n=159)	Control (n=159)
Principal safety outcome: major bleeding	**0**	**0**
Clinically relevant nonmajor bleeding	**2 (1.26%)**	**2 (1.26%)**
Another bleeding	**2 (1.26%)**	**1 (0.63%)**
A combination of major and clinically relevant non-major bleeding and other bleeding	**4 (2.51%)**	**3 (1.89%)**

SUBGROUP ANALYSIS

SUBGROUP		RIVAROXABAN n./total(%)	CONTROL n./total(%)	RR (IC 95%)
Age (yrs)	≤60	2/77 (2.60%)	4/92 (4.35%)	0.60 (0.11 – 3.17)
	>60	3/82 (3.66%)	11/67 (16.42%)	0.22 (0.07 – 0.77)
BMI	≤30	3/105 (2.86%)	10/88 (11.36%)	0.25 (0.07 – 0.89)
	>30	2/54 (3.70%)	5/71 (7.04%)	0.53 (0.11 – 2.61)
Creatinine Clearance ml/min	30 to <50 ml/min	0/6	0/5	---
	≥50 ml/min	5/152 (3.29%)	15/154 (9.74%)	0.34 (0.13 – 0.91)
Modified IMPROVE VTE risk score	2-3	2/98 (2.04%)	9/99 (9.09%)	0.22 (0.05 – 1.01)
	≥4	3/61(4.92%)	6/60 (10.0%)	0.49 (0.13 – 1.88)
D-Dimer level above the UNL	≤500 ng/ml	0/9 (0.00%)	1/10 (10.00%)	0.37 (0.02 – 7.99)
	>500 ng/ml	4/106 (3.77%)	10/108 (9.26%)	0.41 (0.13 – 1.26)
Antiplatelets use — no. (%)	no	5/151 (3.31%)	14/151 (9.27%)	0.36 (0.13 - 0.97)
	yes	0/8 (.00%)	1/8(12.5%	0.33 (0.02 – 7.02)



CONCLUSION

In patients discharged after hospitalization due to COVID-19 with increased IMPROVE score, thromboprophylaxis with rivaroxaban 10 mg once-daily for 35 days **improved clinical outcomes**, **without increasing bleeding** compared with no out-of-hospital anticoagulation

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