THE MICHELLE TRIAL

ESC CONGRESS 2021
THE DIGITAL EXPERIENCE

THE MICHELLE TRIAL

MEDICALLY ILL HOSPITALIZED PATIENTS FOR COVID – THROMBOSIS EXTENDED PROPHYLAXIS WITH RIVAROXABAN THERAPY

Eduardo Ramacciotti, MD, Ph.D, **Leandro Barile Agati**, Ph.D, **Daniela Calderaro**, MD, PhD, Valéria Cristina Resende Aguiar, MD, Giuliano Giova Volpiani, MD, Caroline Candida Carvalho de Oliveira, MD, Elizabeth Rodrigues. Ph. D, Marcone Lima Sobreira, MD, Ph. D , Edwaldo Edner Joviliano, MD, Ph. D, Cesar Dusilek, MD, Kengi Itinose, MD, Rogério Aparecido Dedivitis, MD, Ph.D, André Sementilli Cortina, MD, Suzanna Maria Viana Sanches, MD, Nara Franzin de Moraes, MD, Paulo Fernando Guimarães Morando Marzocchi Tierno MD, André Luiz Malavasi Longo de Oliveira, MD, Adriano Tachibana, MD, Ph.D, Rodrigo Caruso Chate, MD, Ph.D, Marcus Vinícius Barbosa Santos, MD, Bruno Bezerra de Menezes Cavalcante, MD, Ricardo Cesar Rocha Moreira, MD, Chang Chiann, Ph.D, **Alfonso Tafur**, MD, **Alex C. Spyropoulos**, MD, **Renato D. Lopes**, MD, Ph.D.

On Behalf of The Michelle Trial Investigators

Funded by

SCIENCE VALLEY Research Institute
Tech Science® for life

Collaboration

BAYER

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

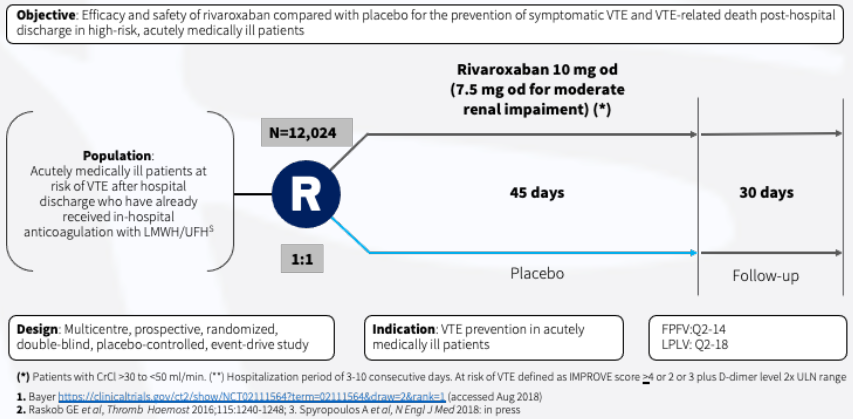
The **MICHELLE** trial was funded by an unrestricted research grant from **Bayer S.A.**

BACKGROUND

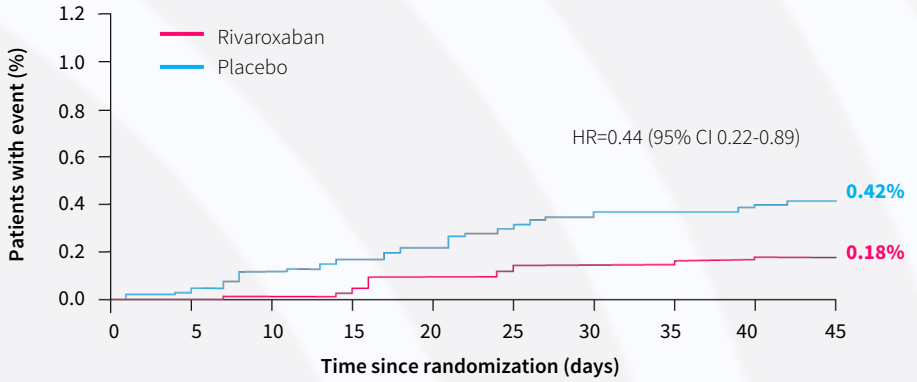
1. The devastating Coronavirus disease (COVID-19) pandemic is associated with a high prothrombotic state.[1]
2. It is unclear if the coagulation abnormalities occur because of the direct effect of SARS-CoV-2 or indirectly by the cytokine storm and endothelial damage or by a combination of mechanisms.[2]
3. There is a clear indication of in-hospital pharmacological thromboprophylaxis for every patient with COVID-19 after bleed risk assessment.[3]
4. However, there is much debate regarding the best dosage regimen, and 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.

MARINER Evaluated Rivaroxaban Versus Placebo for Prophlaxis of VTE After Hospital Discharge in Acutely Medically Ill Patients

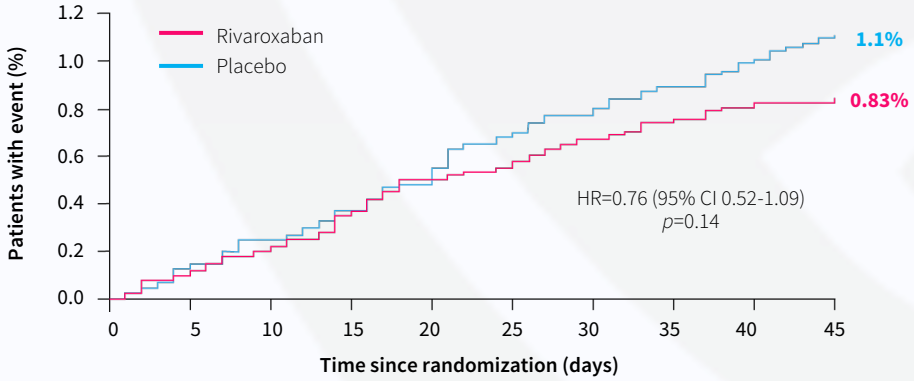


Significant Reduction of Symptomatic VTE with Rivaroxaban After Discharge in Acutely Medically Ill Patients



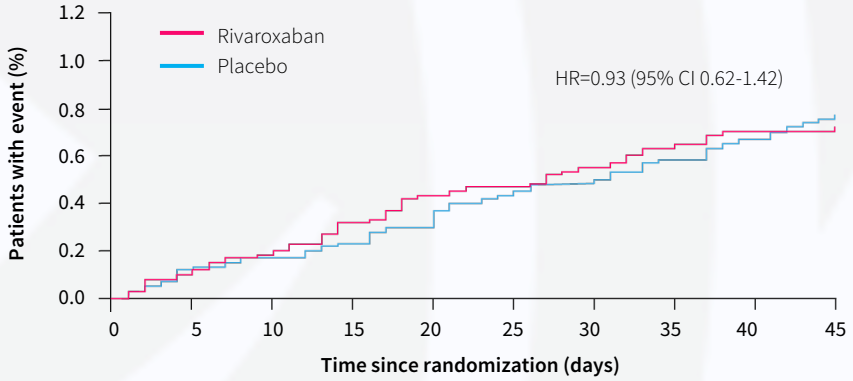
VTE-Related Death Rates with Rivaroxaban Were Not Significantly Different vs Placebo

Cumulative event rates for composite of symptomatic VTE or VTE-related death (*)



VTE-Related Death Rates with Rivaroxaban Were Not Significantly Different vs Placebo

Cumulative event rates for VTE-related death (*)



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

THE MICHELLE TRIAL

↓56% symptomatic VTE

NoBleeds

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

TRIAL ORGANIZATION

EXECUTIVE/STEERING COMMITTEE

Eduardo Ramacciotti | Science Valley Research Institute
Leandro Barile Agati | Science Valley Research Institute
Daniela Calderaro|, Heart Institute (InCor) and Clinics Hospital
Alfonso Tafur | Northshore University Health System
Alex C. Spyropoulos | Northwell Institutes for Medical Research
Renato D. Lopes | Brazilian Clinical Research Institute (BCRI)
Duke Clinical Research Institute (DCRI)

DATA SAFETY MONITORING BOARD

Rogério Krakauer (Santa Casa de São Paulo School of Medical Sciences)
Carlos Augusto de Aguiar Quadros (Infectious diseases, Leforte Hospital)

STATISTICAL ANALYSIS

Chang Chiann (University of São Paulo)

CLINICAL EVENTS CLASSIFICATION (CEC) COMMITTEE

Science Valley Research Institute

ACADEMIC COORDINATING CENTER

Science Valley Research Institute

SPONSOR/ FUNDING

Science Valley Research Institute

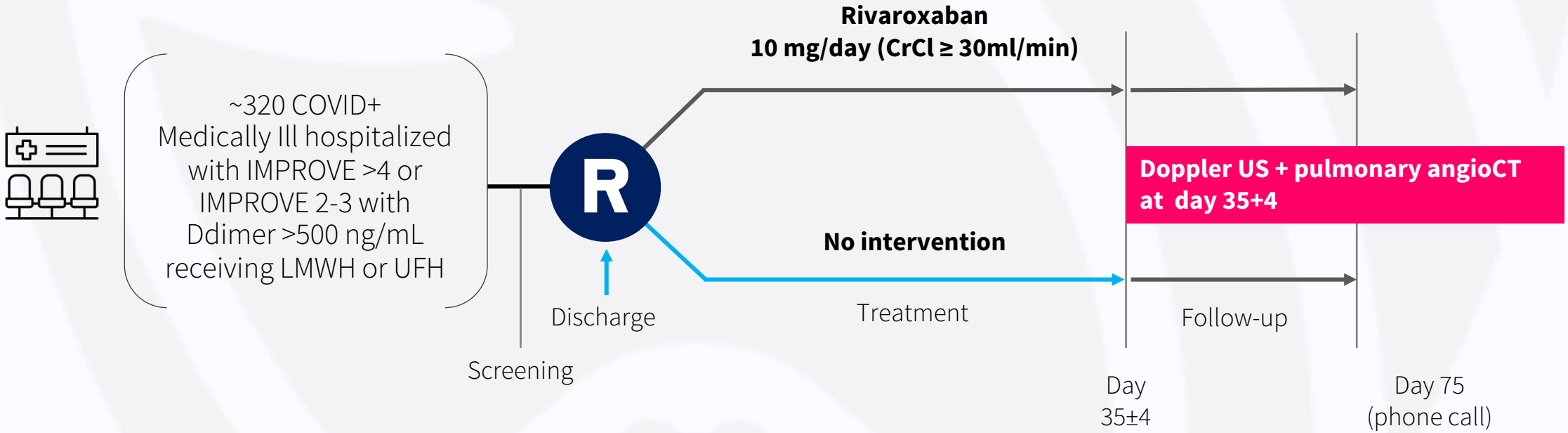
COLLABORATION

Bayer [*]

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

MICHELLE STUDY DESIGN

Design: Prospective, randomized, open-label, controlled, multi-center trial



Primary endp: symptomatic VTE, VTE-related death, VTE detected by mandatory bilateral lower limbs venous duplex scan and pulmonary angioCT on day 35±4 post-hospital discharge and (myocardial infarction [MI], non-hemorrhagic stroke, major adverse limb events [MALE] and cardiovascular [CV] death + all cause death up to day 35±4 post-hospital discharge.

Power: 80%, Two sided alpha 0.05 (Control 15%, Treatment 5% 60% RRR)

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

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

MICHELLE
TRIAL ENDPOINTS

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 OUTCOME

A composite of MI, stroke, arrhythmias, heart failure, VTE, and all-cause death.

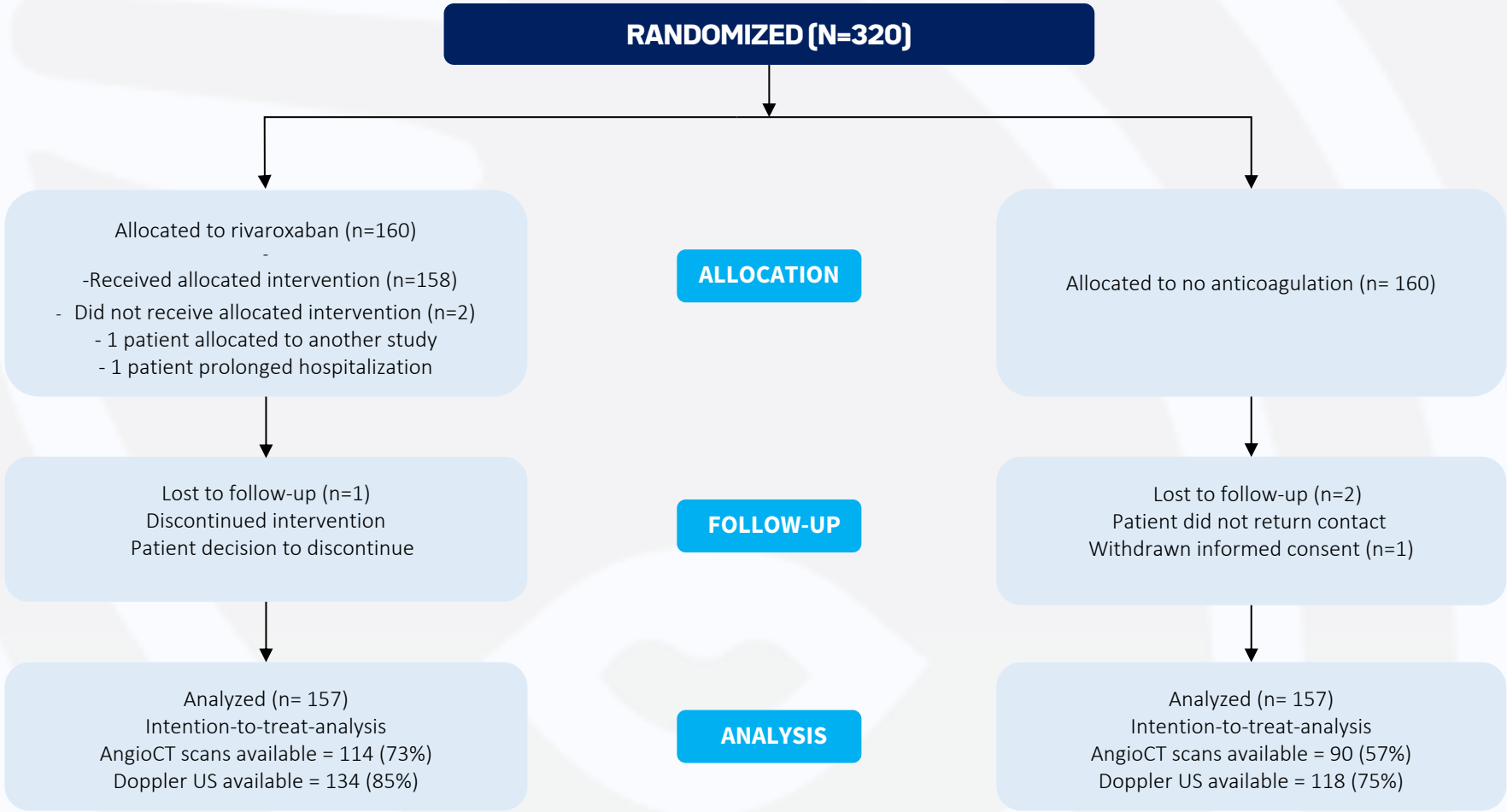
Endpoints were adjudicated by a blinded independent committee

STATISTICAL ANALYSIS

SAMPLE SIZE CALCULATIONS

1. Power of 80% and α =0.05
2. Anticipated occurrence of the primary efficacy endpoint of 15% in the control group and 5% of the treatment group (RRR = 67%).
3. If there is a true difference in favor of the proposed treatment 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

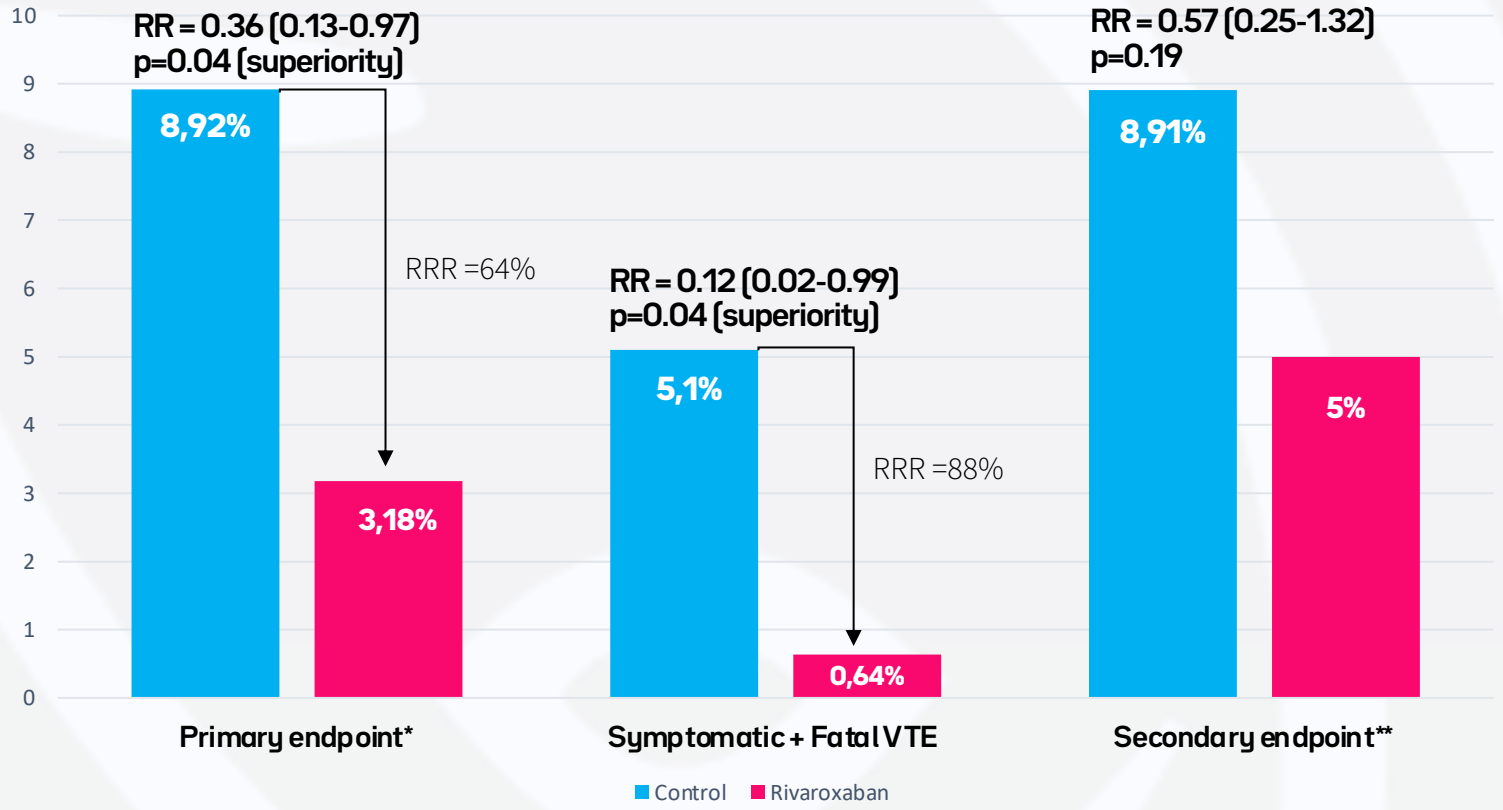
STUDY FLOW-DIAGRAM



BASELINE CHARACTERISTICS

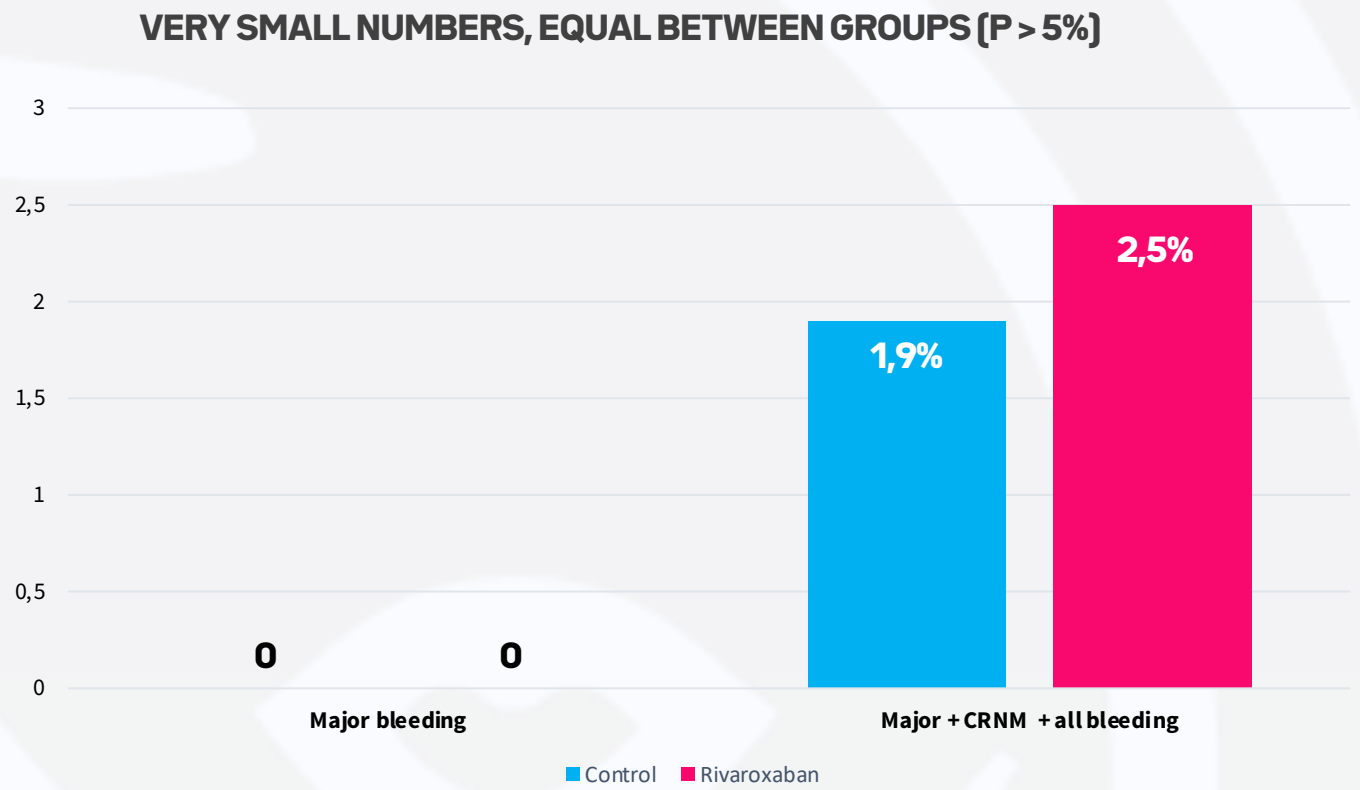
CHARACTERISTICS	RIVAROXABAN (N=157)	CONTROL (N=157)
Mean age(yr) – mean(SD)	57.73 (14.64)	56.21 (15.57)
Age ≥75 yr — nº (%)	17 (10.8%)	15 (9.6%)
Female sex — nº (%)	62 (39.5%)	64 (40.8%)
BMI – mean(SD)	29.55 (5.60)	29.94 (6.08)
Creatinine Clearance ml/min – nº/total (%)		
30 to <50 ml/min	4/157 (2.5%)	3/155 (1.9%)
≥50 ml/min	153/157 (97.5%)	152/155 (98.1%)
Mean duration of index hospitalization — days -mean(SD)	16.48 (46.97)	12.54 (28.69)
ICU or CCU stay — nº (%)	84 (53.5%)	78 (49.7%)
Enoxaparin 40 mg use — nº (%)	134 (85.4%)	137 (87.3%)
Modified IMPROVE VTE risk score — nº (%)		
2-3	132 (85.4%)	137 (87.3%)
≥4	23 (14.6%)	20 (12.7%)
D-Dimer level above the UNL during index hospitalization — nº/total (%)	105/114 (92.1%)	107/116 (92.2%)
Antiplatelets use — nº (%)	8 (5.1%)	8 (5.1%)

EFFICACY OUTCOMES



*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; ** MI, stroke, arrhythmias, heart failure, VTE, and all-cause death

SAFETY OUTCOMES



RISK & BENEFITS

RISKS & BENEFITS	
NNT for primary outcome	18
NNT for symptomatic + fatal VTE	23
NNT for PE+cardiovascular death	20
NNH	N/A

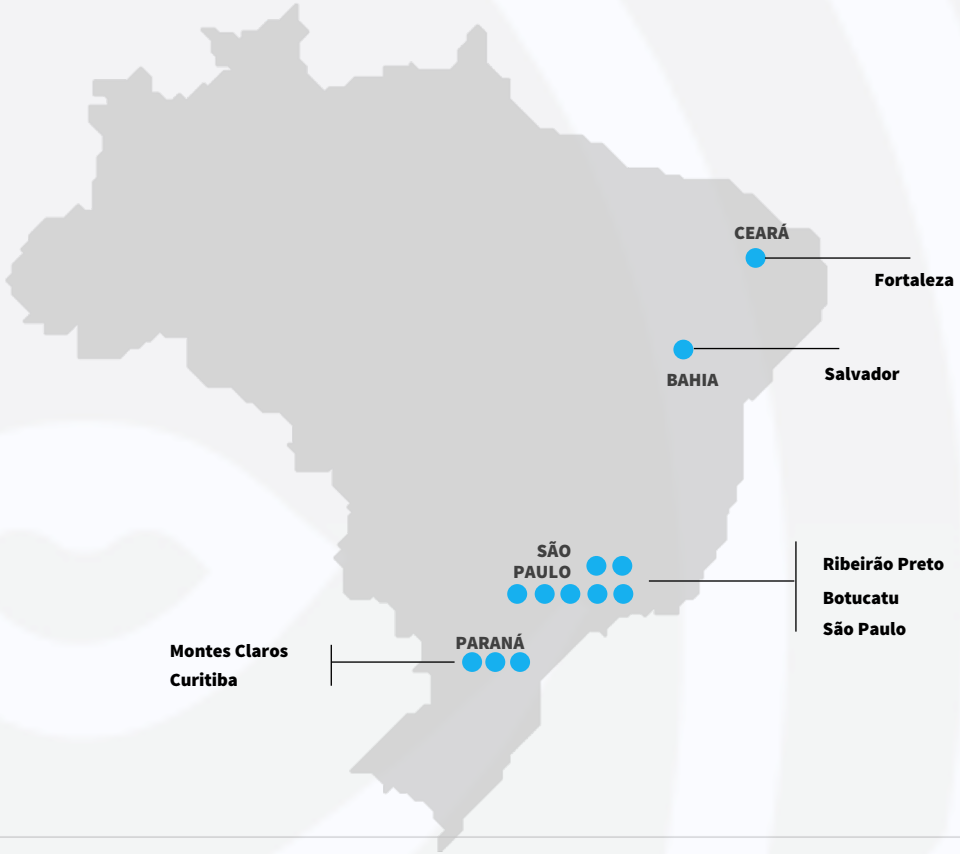
CONCLUSION

Thromboprophylaxis with rivaroxaban 10 mg once-daily for 35 days after hospitalization for COVID-19 in patients with high IMPROVE score (2-3 with elevated D-dimer levels or ≥4) **improved clinical outcomes**, including VTE and VTE-related death, without increasing bleeding compared with no out-of-hospital anticoagulation.

ACKNOWLEDGMENTS

Thank you to Science Valley Research Institute, Bayer Brazil team, investigators, hospitals, study coordinators, DSMB, CEC, core-lab, and study participants who made the MICHELLE trial possible.

SITE	RECRUITED	CITY
HMCG	63	São Paulo
Rocio	45	Montes Claros
Barueri	45	Barueri
FMRP-USP	43	Ribeirão Preto
Couto Maia	39	Salvador
HNSG	29	Curitiba
Liberdade	22	São Paulo
Morumbi	15	São Paulo
HAPVIDA	7	Fortaleza
Incor	6	São Paulo
Pérola	5	São Paulo
Botucatu	1	Botucatu
Erasto Gaertner	0	Curitiba
Santa Casa de Santos	0	Santos



SCIENCE VALLEY
Research Institute
Tech Science® for life

THANKYOU

www.svriglobal.com

agati@svriglobal.com . ramacciotti@svriglobal.com . contato@svriglobal.com

SÃO PAULO
SCIENCE VALE CONSULTORIA, PESQUISA E DESENVOLVIMENTO NA ÁREA MÉDICA LTDA.
Santo André – SP, Brazil

MIAMI
SCIENCE VALLEY RESEARCH INSTITUTE LLC
BISCAYNE BLVD
NORTH Miami Beach, FL. US 33181