Anticoagulation in Patients Hospitalized with COVID-19

The AntiCoagulaTIon cOroNavirus (ACTION) Trial

ACTION COALIZÃO

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on behalf of the ACTION COALITION COVID-19 Brazil Investigators

AMERICAN COLLEGE of CARDIOLOGY

Disclosures

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- Details at: https://dcri.org/about-us/conflict-of-interest
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Background

- Venous and arterial thromboembolic events have been reported in patients with COVID-19.[1,2]
- Elevated biomarkers of thrombosis, such as D-dimer, are associated with disease progression and higher mortality.[3]
- Recent data suggest that anticoagulation might improve clinical outcomes in COVID-19, but the optimal strategy, including for which patients, type of anticoagulant, dose, and duration remains unknown.[4]
- To assess whether a strategy of therapeutic anticoagulation primarily with rivaroxaban is effective in preventing complications in patients hospitalized with COVID-19 and elevated D-dimer levels, we conducted a randomized clinical trial comparing the efficacy and safety of therapeutic versus prophylactic anticoagulation.

1. Tang N et al. J Thomb Haemost. 2020;18:844-7
2. Klok FA et al. Thromb Res. 2020;191:145-7
3. Gungor B et al. Am J Emerg Med. 2021;39:173-9
4. Nadkarni GN et al. J Am Coll Cardiol. 2020;76:1815-26

Trial Organization

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ACADEMIC COORDINATING CENTER

Brazilian Clinical Research Institute

SPONSOR

COALITION COVID-19 Brazil

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Trial Design

Lopes RD, et al. AHJ, 2021

INCLUSION CRITERIA

- Patients aged ≥18 years
- Hospitalized with a confirmed diagnosis of COVID-19 and duration of symptoms related to hospitalization ≤14 days.
- Elevated D-dimer (>ULN) at admission

Randomize
N: 615 patients

MAIN EXCLUSION CRITERIA

- Indication for therapeutic anticoagulation at screening
- eCrCl <30 ml/min
- Platelets <50,000 /mm^3
- Use of P2Y12 inhibitor or ASA >100 mg daily
- Very high risk of bleeding

Therapeutic anticoagulation

Stable Patients ↓ In-hospital rivaroxaban 20 mg daily

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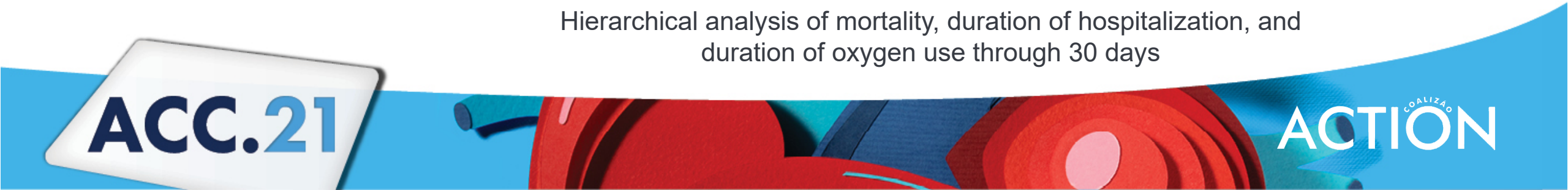
Unstable Patients ↓ In-hospital enoxaparin 1mg/kg twice daily

Followed by rivaroxaban through 30 days, irrespective of duration of hospitalization

Standard of care with in-hospital prophylactic dose anticoagulation

PRIMARY OUTCOME

Hierarchical analysis of mortality, duration of hospitalization, and duration of oxygen use through 30 days



Outcomes

Primary Outcome: hierarchical analysis of mortality, duration of hospitalization, and duration of oxygen use through 30 days

Primary Safety Outcome: major or clinically relevant non-major bleeding according to ISTH criteria

Key Secondary Outcomes: death, myocardial infarction, venous thromboembolism, stroke, or major adverse limb event

Statistical Analysis

Main analysis followed the intention-to-treat principle, including all randomized participants

Primary Analysis

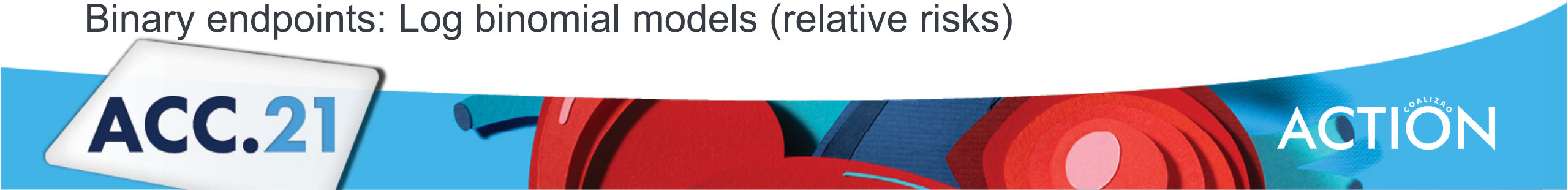
Unmatched Win Ratio method stratified by clinical condition (stable/unstable at screening)

For the primary outcome, it is calculated by the total number of wins divided by the total number of losses between the two study groups within each strata

Ratio >1 reflects a better outcome

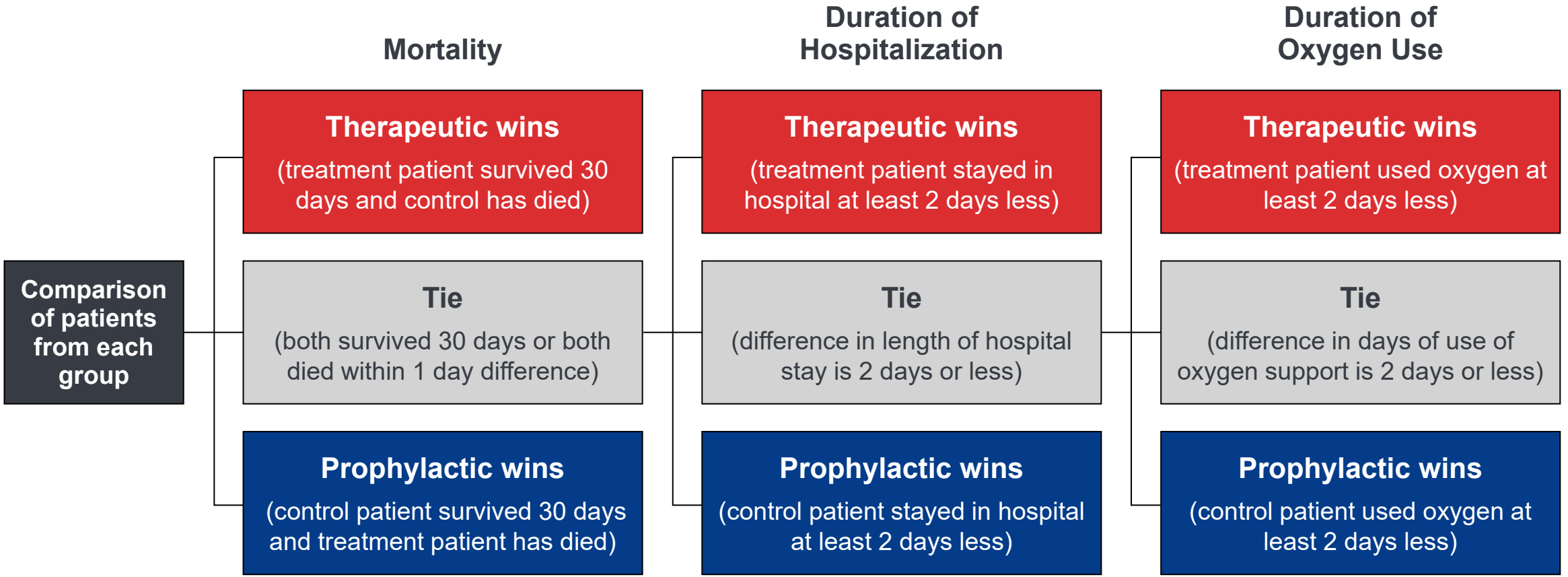
Secondary Analyses

Binary endpoints: Log binomial models (relative risks)

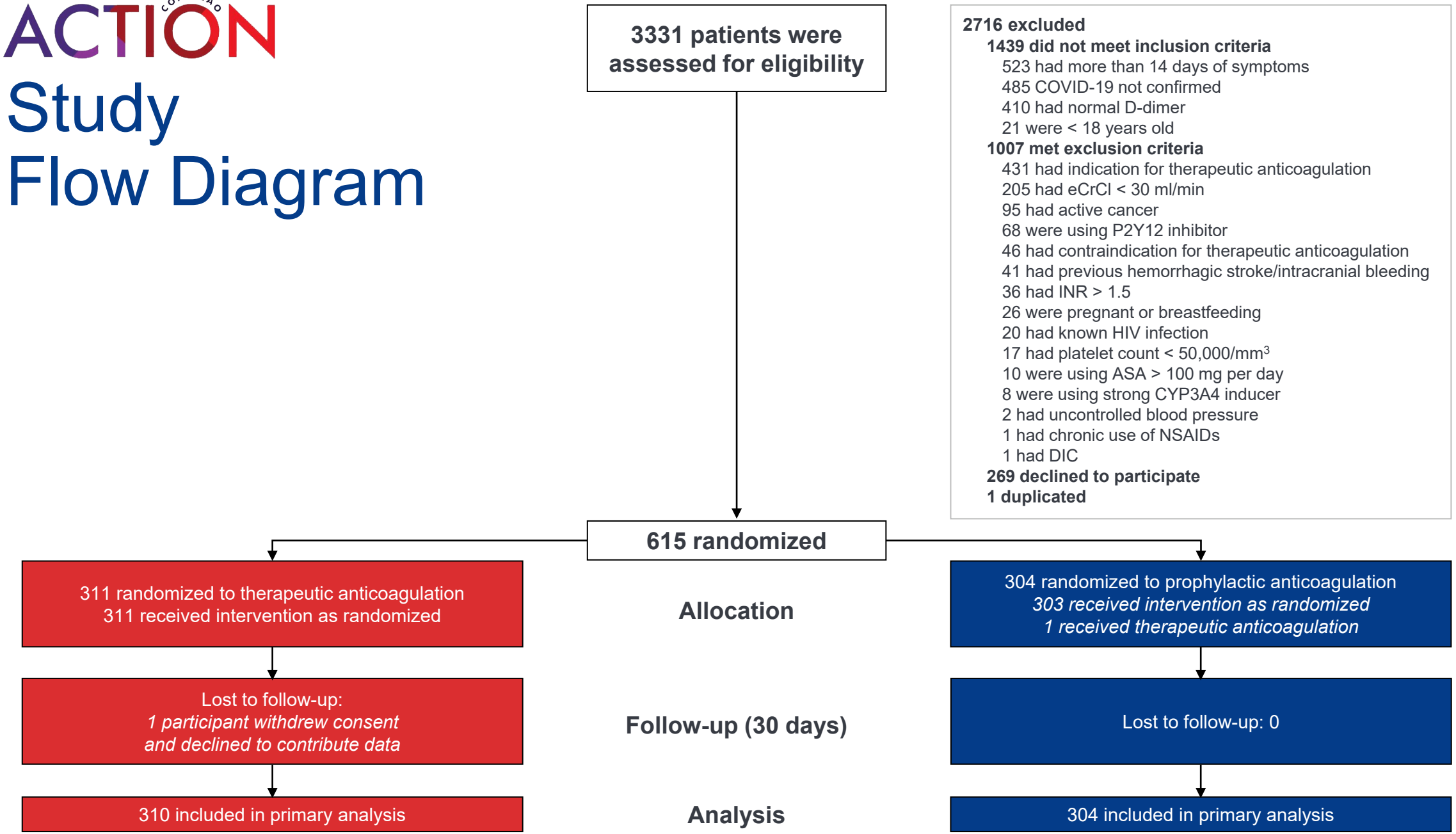


Statistical Analysis

Primary outcome—unmatched stratified win ratio



ACTION Study Flow Diagram



Baseline Characteristics

Characteristic	Therapeutic (N=311)	Prophylactic (N=304)
Age, mean ± SD, yrs	56.7 ± 14.1	56.5 ± 14.5
Male sex, no. (%)	192 (61.7%)	176 (57.9%)
BMI, mean ± SD, kg/m²	30.3 ± 6.0	30.3 ± 6.1
Chronic lung disease, no. (%)	7 (2.3%)	12 (3.9%)
Diabetes, no. (%)	83 (26.7%)	67 (22.0%)
Current smoker / Former smoker	56 (18.0%)	63 (20.7%)
Hypertension, no. (%)	151 (48.6%)	151 (49.7%)
Heart failure, no. (%)	8 (2.6%)	5 (1.6%)
Coronary disease, no. (%)	12 (3.9%)	16 (5.3%)

BMI denotes body mass index;
SD, standard deviation.

Baseline Characteristics

Characteristic	Therapeutic (N=311)	Prophylactic (N=304)
Clinical condition, no. (%)*		
Unstable	23 (7.4%)	16 (5.3%)
Stable	288 (92.6%)	288 (94.7%)
Time from symptom onset to hospital admission, median (25th, 75th), days	8.0 (6.0, 10.0)	7.0 (6.0, 9.0)
Patient needed oxygen administration, no. (%)	236 (75.9%)	224 (73.7%)
Catheter or oxygen mask	185 (59.5%)	184 (60.5%)
High-flow nasal cannula	26 (8.4%)	22 (7.2%)
Tracheal intubation	23 (7.4%)	15 (4.9%)
Non-invasive ventilation	2 (0.6%)	3 (1.0%)
Disease state at baseline, no. (%)†		
Mild	30 (9.6%)	39 (12.8%)
Moderate	257 (82.6%)	249 (81.9%)
Severe	24 (7.7%)	16 (5.3%)

*Unstable patients were defined as those with COVID-19–related critical illness, suffered from a life-threatening condition, required mechanical ventilation or vasopressors, and/or were unable to take oral medication.

†Mild disease includes cases without criteria to be classified within the “moderate” or “severe” groups. Moderate disease is characterized by oxygen saturation <94% or pulmonary infiltrates >50% or ratio of partial pressure of arterial oxygen to fraction of inspired oxygen <300. Severe disease is defined as respiratory failure or hemodynamic instability or multiple organ dysfunction.

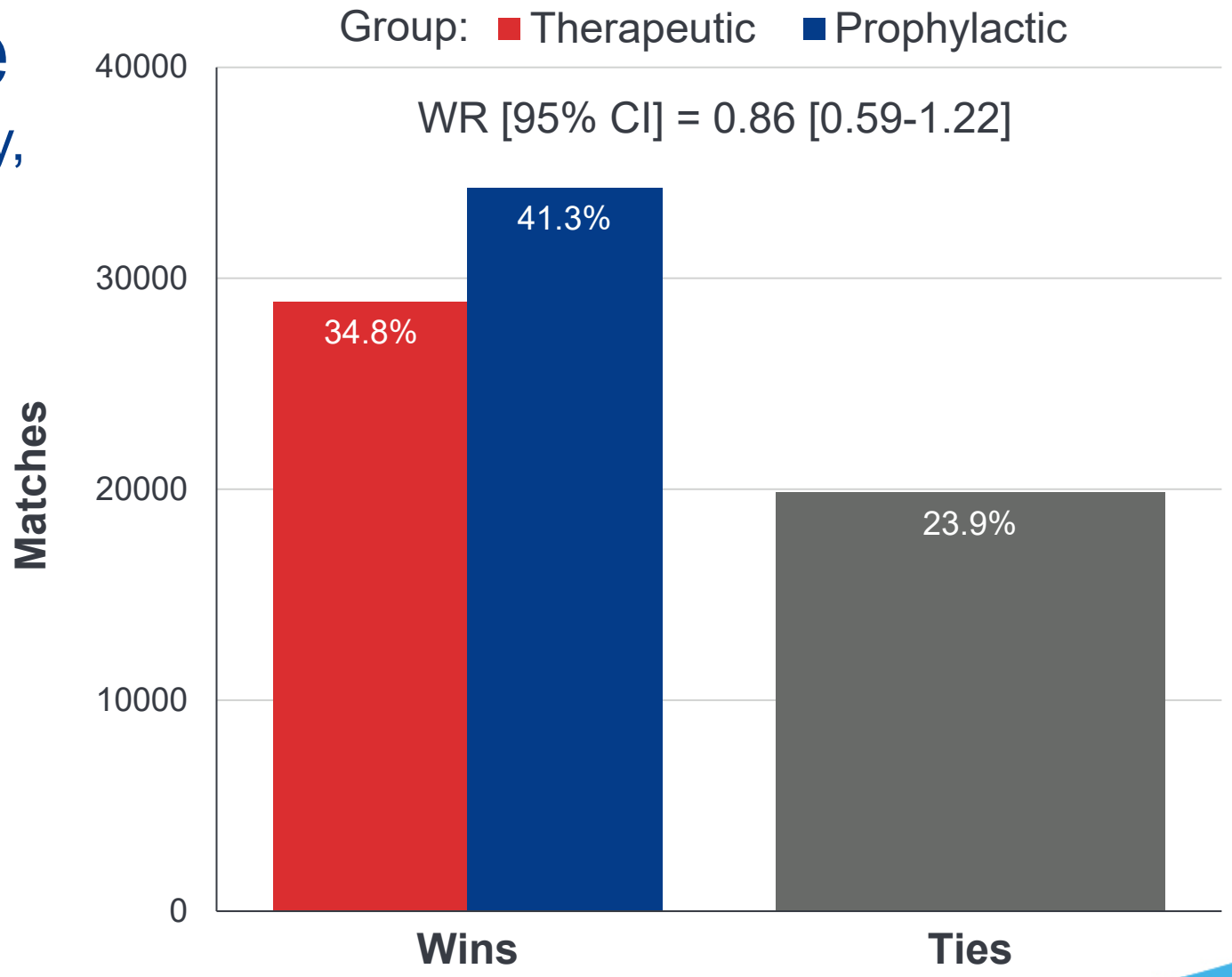
Baseline Characteristics

Characteristic	Therapeutic (N=311)	Prophylactic (N=304)
Anticoagulation before randomization	285 (91.7%)	275 (90.5%)
Standard prophylactic dose	175 (56.3%)	187 (61.6%)
Dose >standard prophylactic*	110 (35.4%)	88 (28.9%)
Baseline medication		
Antiplatelet	22 (7.1%)	26 (8.6%)
Vasopressor	16 (5.1%)	8 (2.6%)
Systemic corticosteroids	257 (82.6%)	253 (83.2%)
D-dimer ≥3 x ULN, no. (%)	84 (27.0%)	83 (27.3%)

*Dose > standard prophylactic is considered any dose greater than the recommended doses for hospitalized patients.
ULN denotes upper limit of normal

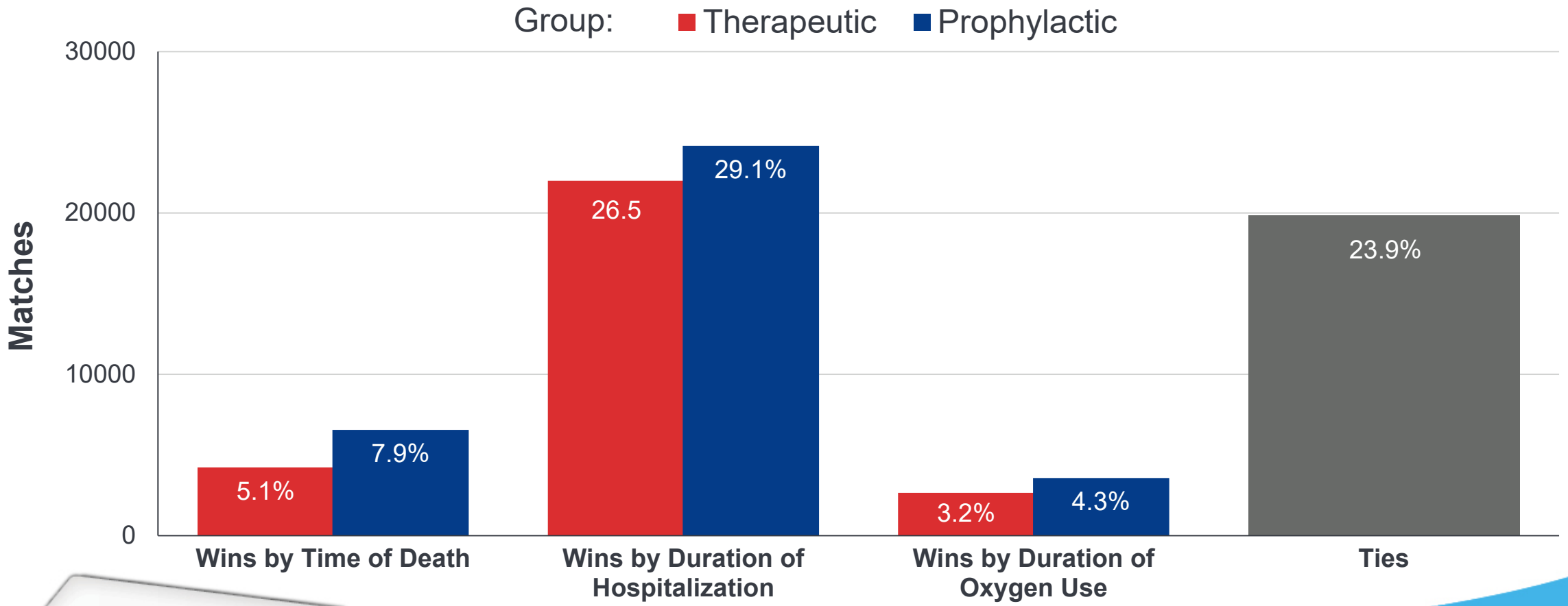
Primary Outcome

Hierarchical analysis of mortality, duration of hospitalization, and duration of oxygen use through 30 days



Components of the Primary Outcome

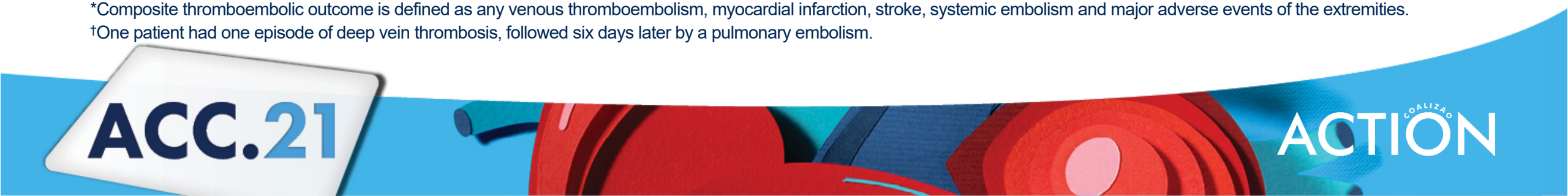
Hierarchical analysis of mortality, duration of hospitalization, and duration of oxygen use through 30 days



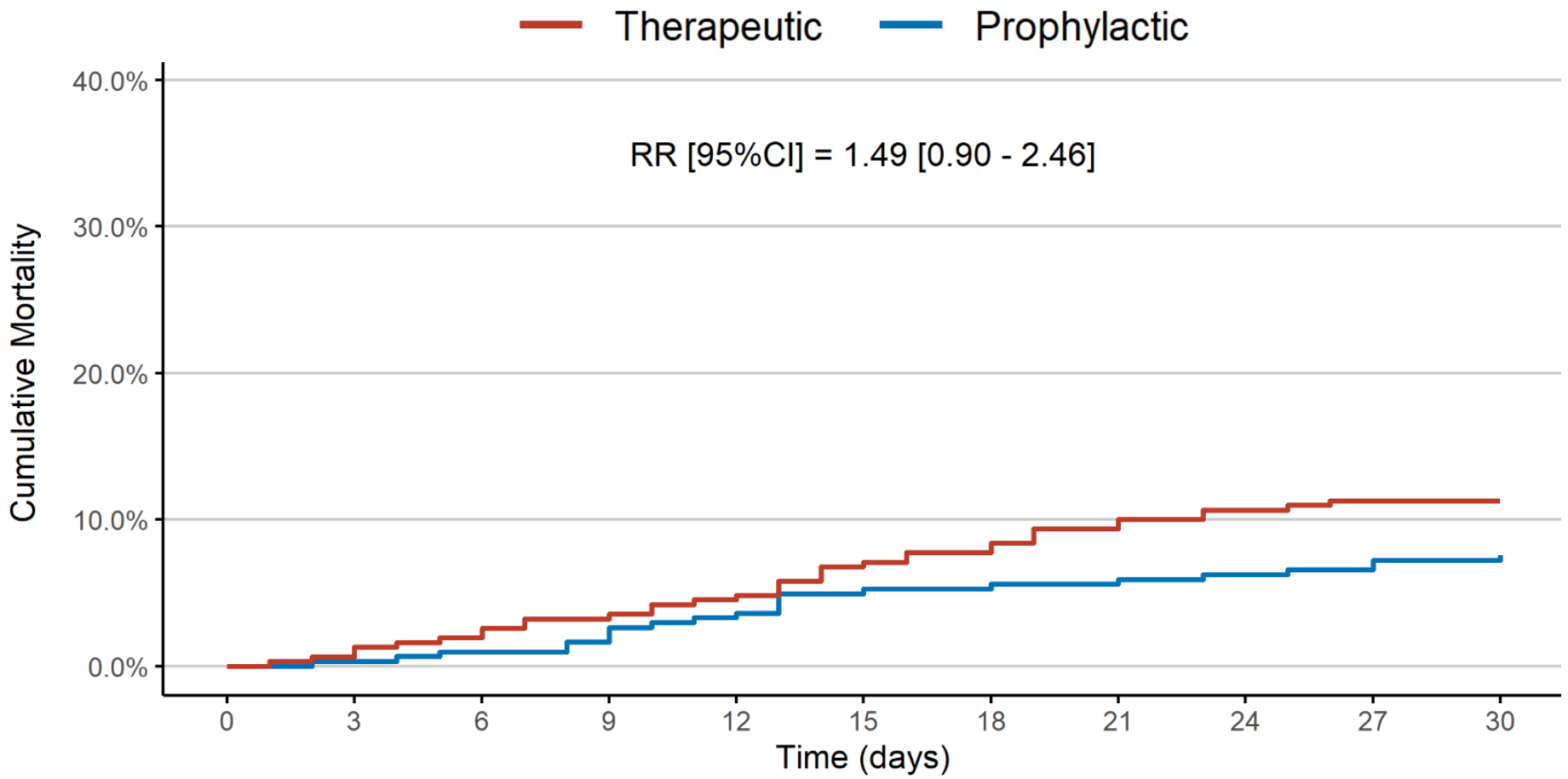
Efficacy Outcomes

Efficacy Outcome	Therapeutic (N=310)	Prophylactic (N=304)	Effect Measure	Effect (95% CI)
Composite thromboembolic outcome*	23/310 (7.4%)	30/304 (9.9%)	Relative Risk	0.75 (0.45–1.26)
Myocardial infarction	13/310 (4.2%)	14/304 (4.6%)	Relative Risk	0.91 (0.44–1.91)
Venous thromboembolism†	11/310 (3.5%)	18/304 (5.9%)	Relative Risk	0.60 (0.29–1.25)
Deep vein thrombosis	5/310 (1.6%)	5/304 (1.6%)	Relative Risk	0.98 (0.29–3.35)
Pulmonary embolism	7/310 (2.3%)	13/304 (4.3%)	Relative Risk	0.53 (0.21–1.31)
Stroke	1/310 (0.3%)	0/304 (0.0%)	---	---
Major adverse limb event	0/310 (0.0%)	1/304 (0.3%)	---	---
Composite thrombotic outcome and all-cause mortality	46/310 (14.8%)	44/304 (14.5%)	Relative Risk	1.03 (0.70–1.50)
All-cause mortality	35/310 (11.3%)	23/304 (7.6%)	Relative Risk	1.49 (0.90–2.46)

*Composite thromboembolic outcome is defined as any venous thromboembolism, myocardial infarction, stroke, systemic embolism and major adverse events of the extremities.
†One patient had one episode of deep vein thrombosis, followed six days later by a pulmonary embolism.



30-Day Mortality



Patients at risk

Prophylactic	304	303	301	299	294	289	288	287	285	284	282
Therapeutic	310	308	304	300	296	289	286	281	277	275	275

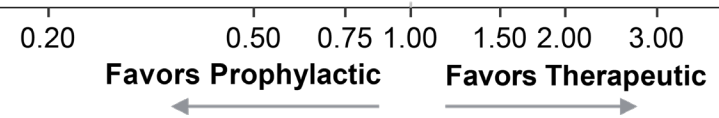
Safety Outcomes

Safety Outcome	Therapeutic (N=310)	Prophylactic (N=304)	Effect Measure	Effect (95% CI)
ISTH major bleeding or clinically relevant non-major bleeding	26/310 (8.4%)	7/304 (2.3%)	Relative Risk	3.64 (1.61–8.27)
Major bleeding	10/310 (3.2%)	4/304 (1.3%)	Relative Risk	2.45 (0.78–7.73)
Clinically relevant non-major bleeding	16/310 (5.2%)	3/304 (1.0%)	Relative Risk	5.23 (1.54–17.77)
Any bleeding	36/310 (11.6%)	9/304 (3.0%)	Relative Risk	3.92 (1.92–8.00)
Net clinical benefit*	56/310 (18.1%)	47/304 (15.5%)	Relative Risk	1.17 (0.82–1.66)

*Net clinical benefit is defined as composite outcome including any composite thromboembolic outcome, all-cause mortality, and ISTH definitions of major or clinically relevant non-major bleeding.

Subgroup Analysis

Subgroup		Patients	Therapeutic Wins	Prophylactic Wins	Win Ratio [IC 95%]
Strata	Unstable	*39*	183	164	1.12 [0.44 - 2.82]
	Stable	*575*	28716	34124	0.84 [0.64 - 1.11]
Age	≤ 60 years	*350*	10579	11574	0.91 [0.64 - 1.31]
	> 60 years	*264*	6104	8731	0.70 [0.48 - 1.02]
D-dimer tertiles (x ULN)	1.00-1.54	*205*	3321	3669	0.88 [0.56 - 1.40]
	1.54-2.57	*204*	3566	4875	0.73 [0.47 - 1.14]
	2.57-726.00	*205*	3869	4386	0.88 [0.56 - 1.38]
Symptom onset to randomization	1 to 9 days	*258*	6029	7440	0.81 [0.55 - 1.20]
	10 or 11 days	*174*	2497	2870	0.87 [0.52 - 1.46]
	12 to 15 days	*182*	3043	3607	0.84 [0.53 - 1.35]
Oxygen use at randomization	None	*155*	1880	1613	1.17 [0.63 - 2.16]
	Non-invasive oxygen support	*420*	15113	19220	0.79 [0.57 - 1.08]
	Mechanical ventilation	*39*	199	154	1.29 [0.52 - 3.23]
Disease severity at admission	Mild	*69*	349	326	1.07 [0.42 - 2.74]
	Moderate	*505*	22565	26519	0.85 [0.64 - 1.14]
	Severe	*40*	222	145	1.53 [0.61 - 3.84]
BMI	≥ 30 kg/m²	*264*	5807	7650	0.76 [0.51 - 1.13]
	< 30 kg/m²	*350*	11310	12973	0.87 [0.62 - 1.23]
Corticosteroids use at randomization	No	*105*	795	1308	0.61 [0.32 - 1.17]
	Yes	*509*	23840	27078	0.88 [0.66 - 1.17]



Conclusion

In patients hospitalized with COVID-19 with elevated D-dimer levels, initial in-hospital therapeutic anticoagulation with rivaroxaban 20 mg once daily for stable patients or enoxaparin for unstable patients followed by rivaroxaban through 30 days **did not** improve clinical outcomes and **increased** bleeding compared with in-hospital prophylactic anticoagulation.

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