Effectiveness and Safety of Rivaroxaban Versus Warfarin in Patients with Pulmonary Embolism and Right Ventricular Dysfunction

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Background

- Right ventricular dysfunction (RVD) occurs as a consequence of pulmonary embolism (PE) and is associated with significantly higher risk of PE-related mortality and venous thromboembolism (VTE) recurrence[1–3]
- Direct oral anticoagulants (DOACs), including rivaroxaban, are generally preferred over vitamin K antagonists (VKAs), such as warfarin, for the prevention of VTE events among patients with PE as they are associated with a lower risk of major bleeding while maintaining similar efficacy[4–6]
- However, there is limited evidence available for patients with both PE and RVD
  - Phase III trials of DOACs in PE excluded patients with hemodynamic compromise or did not have sufficient sample size to evaluate this specific condition[7,8]
  - Limited real-world evidence in this population due to the lack of International Classification of Diseases (ICD) codes for RVD[9]

The goal of this study was to compare the effectiveness and safety of rivaroxaban versus warfarin among patients with PE and RVD using real-world data

1. Harjola et al. *Eur J Heart Fail.* 2016; 18:226-41; **2.** ten Wolde et al. *Arch Intern Med*. 2004; 164(15):1685-9; **3.** Grifoni et al. Arch Intern Med. 2006; 166(19):2151-6; **4.** Ortel et al. *Blood Adv.* 2020; 4(19):4693-738; **5.** Stevens et al. *Chest.* 2021; 160(6):e545-e608; **6.** Konstantinides et al. *Eur Respir J.* 2019; 54(3):1901647; **7.** Büller et al. *N Engl J Med*. 2012; 366(14):1287-97; **8.** Agnelli et al. *Eur Respir J.* 2015; 45(5):1142-9; **9.** Dini et al. *Heart Fail Rev.* 2023; 28:757-77.

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Study Design – Data Source

Real-world observational study using electronic health record (EHR) data from Mass General Brigham's Research Patient Data Registry (MGB RPDR) PE Data Mart, with data ranging from January 2013 – May 2023

De-identified clinical information for >7 million patients and >3 billion records available, including demographics, prescriptions, providers, visits, diagnoses, procedures, laboratories, and microbiology

Hospital inpatient and outpatient clinical data from EHR from 8 major hospitals affiliated with the Harvard Medical School*

The MGB RPDR PE Data Mart also includes clinical notes which can be analyzed using natural language processing (NLP) to extract clinical information such as evidence of RVD

* Massachusetts General Hospital, Brigham and Women's Hospital, Brigham and Women's Faulkner Hospital, Massachusetts Eye and Ear Hospital, McLean Hospital, Newton-Wellesley Hospital, Salem Hospital (formerly North Shore Medical Center), Spaulding Rehabilitation Hospital

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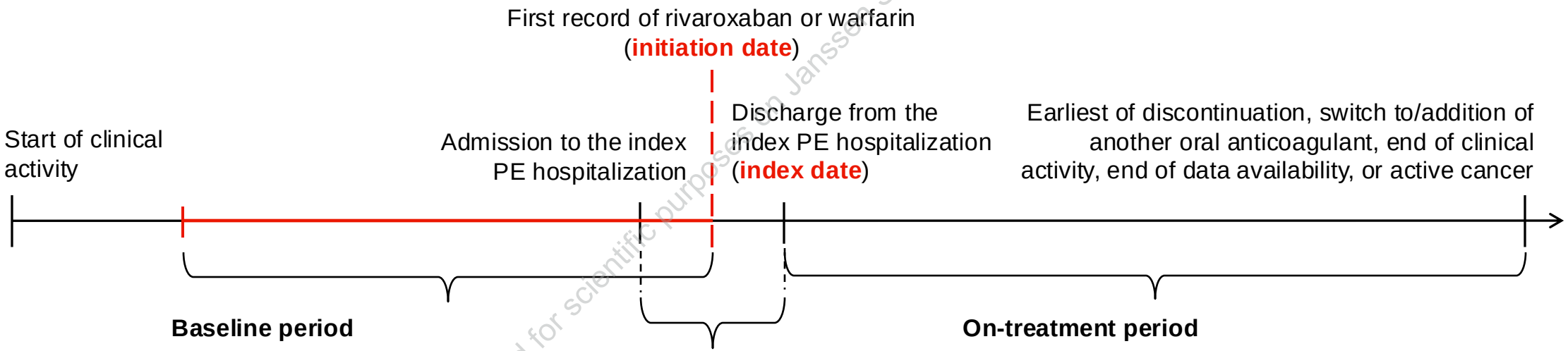
Study Design Scheme

Patients with PE were classified into mutually exclusive **rivaroxaban** and **warfarin** cohorts based on the first anticoagulant prescribed during their first observed hospitalization for PE



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Study Design – RVD Identification

Evidence of RVD was assessed via **natural language processing** (NLP) of clinical notes using the following terms:

- Acute cor pulmonale
- Increased RV to LV ratio
- McConnell's sign
- Right heart strain
- Right ventricular dilatation
- Right ventricular dilation
- Right ventricular dysfunction
- Right ventricular enlargement
- Right ventricular failure
- Right ventricular hypokinesis/pressure/strain

- RVD terms with a negation word (e.g., "none", "without") within the same sentence were not considered

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Study Design – Patient Eligibility Criteria

Inclusion Criteria

- Initiation of rivaroxaban (15 mg or 20 mg) or warfarin during a hospitalization with ≥1 diagnosis of PE in any position (index PE hospitalization)
- Prescription of the index agent (rivaroxaban or warfarin, depending on which was prescribed first) as the first oral anticoagulant prescribed after discharge from the index PE hospitalization
- Evidence of RVD during the index PE hospitalization
- ≥6 months of clinical activity prior to the initiation date

Exclusion Criteria

- VTE in the 3 months prior, prescription of an OAC within ≤6 months before, or prescription of rivaroxaban 2.5 mg during the index PE hospitalization
- Antiphospholipid syndrome, mechanical heart valve procedure, or active cancer within ≤6 months before or during the index PE hospitalization
- Severe renal dysfunction (estimated glomerular filtration rate [eGFR]<30) or pregnancy within ≤6 months before initiation
- Hip or knee replacement surgery within ≤35 days before initiation

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Study Outcomes and Statistical Analysis

Effectiveness was evaluated using time-to-first VTE recurrence, defined as a hospitalization with a primary diagnosis of VTE

Safety was evaluated using time-to-first major bleeding event, defined using the Cunningham algorithm which identifies non-traumatic bleeding related hospitalizations

The proportion of international normalized ratio (INR) measurements within therapeutic range (INR within 2–3) for warfarin users on-treatment was described

To account for right censoring, effectiveness and safety were assessed using Kaplan-Meier analysis, and event rates were compared at 6-month intervals up to 36 months on-treatment using hazard ratios (HR), 95% confidence intervals (CI), and p-values from Cox proportional hazards models

Propensity score overlap weighting (PS-OW) was used to adjust for confounding between cohorts, with balance in baseline characteristics* evaluated using standardized differences

* The following demographics and baseline characteristics were included in the PS model: age; sex; race; year of index agent initiation date; RVD terms identified during the index PE hospitalization; unprovoked index PE; baseline healthcare resource utilization; Quan-Charlson comorbidity index; modified Registro Informatizado de Enfermedad TromboEmbólica bleeding score; major bleeding; comorbidities, medications, and procedures with prevalence ≥10% in either cohort; eGFR; hemoglobin level; and red blood cell, white blood cell, and platelet counts

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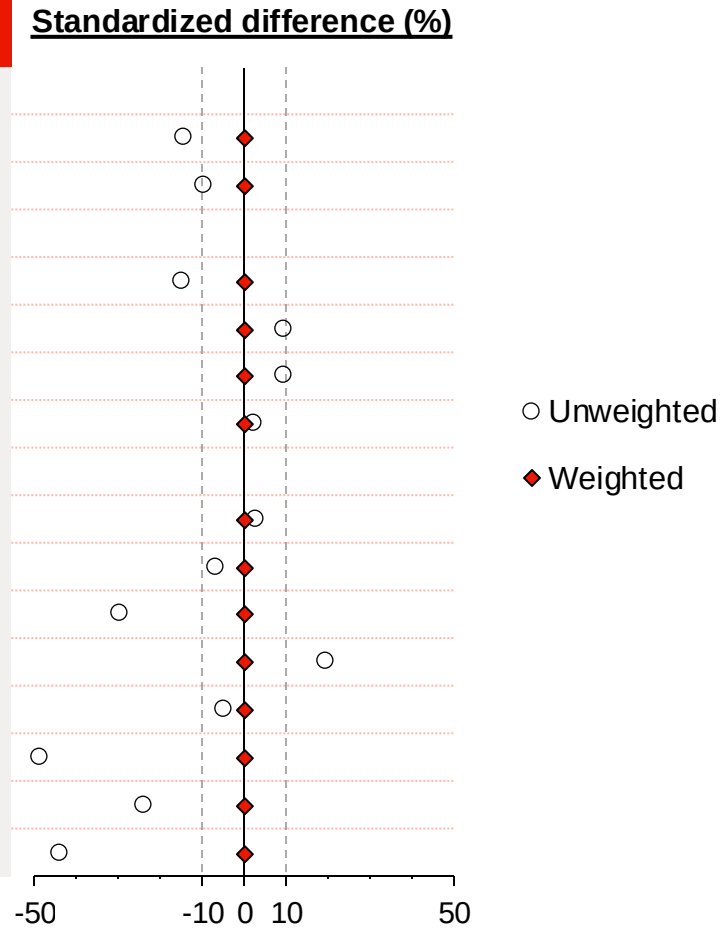
Demographics and Clinical Characteristics (1/2)

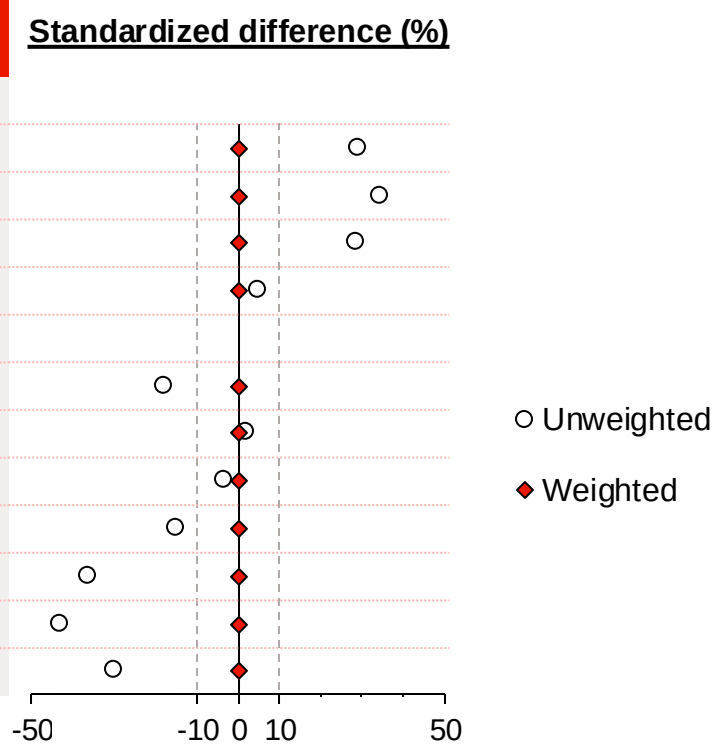
All characteristics were well-balanced after weighting

Characteristics after weighting	Rivaroxaban (N = 246)	Warfarin (N = 315)
On-treatment period, days, mean ± SD	699 ± 857	599 ± 764
Age, years, mean ± SD	63 ± 15	63 ± 17
Female, n (%)	130 (52.6)	166 (52.6)
Race, n (%)		
White	188 (76.5)	241 (76.5)
Black	38 (15.3)	48 (15.3)
Other	14 (5.7)	18 (5.7)
Unknown	6 (2.5)	8 (2.5)
RVD terms during the index PE hospitalization, n (%)		
Right ventricular strain	177 (71.8)	226 (71.8)
Right ventricular dilation	98 (40.0)	126 (40.0)
Right ventricular dysfunction	83 (33.7)	106 (33.7)
Acute cor pulmonale	34 (13.8)	44 (13.8)
McConnell's sign	22 (9.1)	29 (9.1)
Quan-CCI score, mean ± SD	1.8 ± 1.9	1.8 ± 1.8
Modified RIETE bleeding score, mean ± SD	2.7 ± 1.7	2.7 ± 1.6
Major bleeding, n (%)	15 (6.3)	20 (6.3)



Demographics and Clinical Characteristics (2/2)

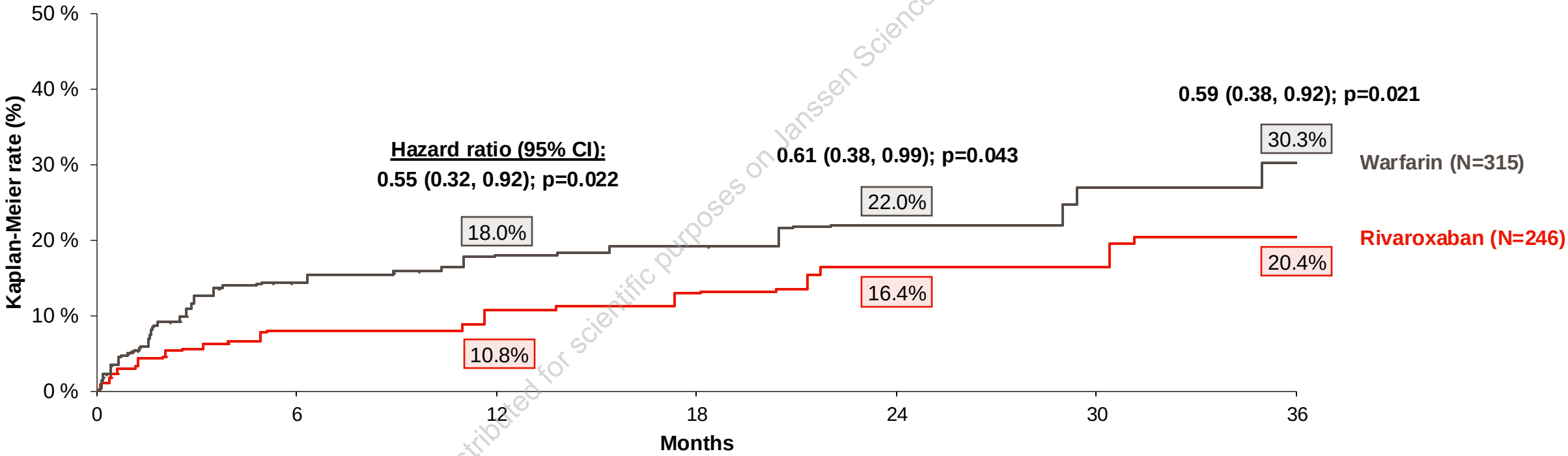
Characteristics after weighting	Rivaroxaban (N = 246)	Warfarin (N = 315)
Lab value of interest within normal range, n (%)		
Hemoglobin level (g/dL; females 12–16; males: 14–18)	82 (33.3)	105 (33.3)
Red blood cell count (4–6 x 10^6 cells/uL)	144 (58.7)	185 (58.7)
White blood cell count (4.5–11 x 10^3 cells/uL)	199 (80.7)	254 (80.7)
Platelet count (150–450 x 10^3 cells/uL)	199 (81.0)	255 (81.0)
Comorbidities of interest, n (%)		
Obesity (BMI ≥30 or diagnosis)	108 (43.9)	138 (43.9)
Coronary artery disease	68 (27.6)	87 (27.6)
Sleep apnea	49 (19.9)	63 (19.9)
Pulmonary hypertension	32 (12.9)	41 (12.9)
Hypotension	37 (15.2)	48 (15.2)
Atrial fibrillation	27 (10.9)	34 (10.9)
Stroke/embolism	15 (6.2)	19 (6.2)



While on-treatment, 86.3% warfarin users had one or more INR measurements, with an average of 50.9% of measurement per patient being within therapeutic range (INR in 2–3)

Kaplan-Meier Rates of Recurrent VTE

Rivaroxaban was associated with a 45% and 41% lower risk of experiencing VTE recurrence at 12 months and 36 on-treatment, respectively, compared to warfarin



Warfarin patients							
At-risk	315	173	107	87	76	69	54
Rivaroxaban patients							
At-risk	246	142	107	84	72	65	54

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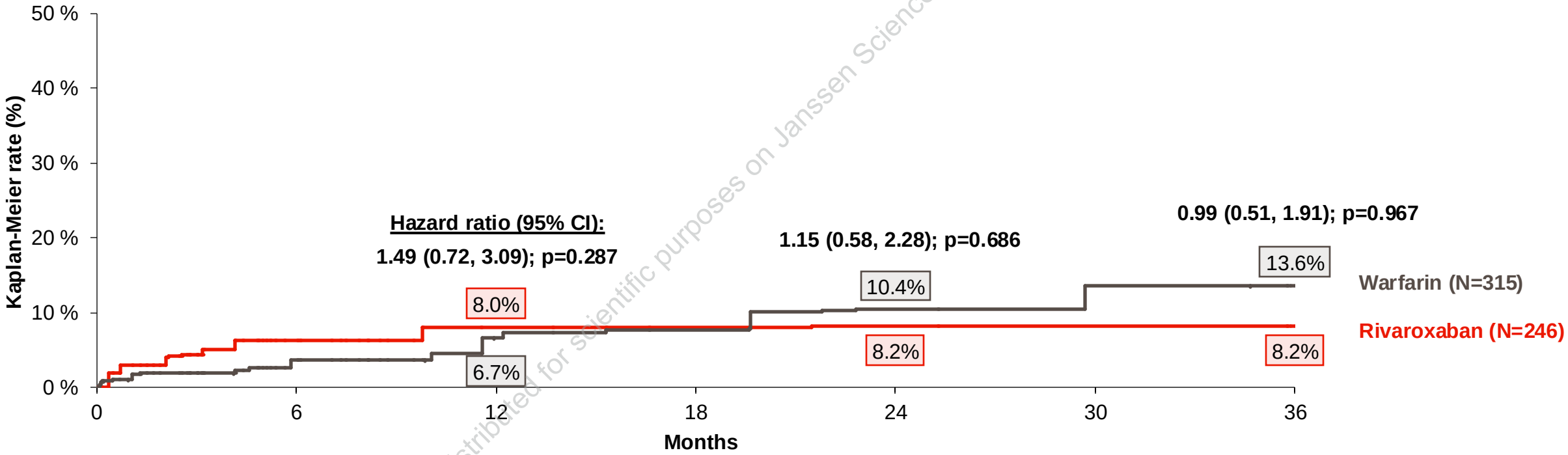
Kaplan-Meier Rates of Major Bleeding

No statistically significant difference was observed in the risk of major bleeding between rivaroxaban and warfarin



Warfarin patients							
At-risk	315	181	114	93	78	73	56
Rivaroxaban patients							
At-risk	246	140	110	86	75	67	59

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Limitations

The analysis of EHR data depends on the correct entry of diagnosis, procedure, and drug codes, and coding inaccuracies may lead to misidentification

Despite the use of PS-OW to balance demographic and clinical characteristics, there is a potential for residual confounding

All patients included in the study were treated in Massachusetts which may affect the generalizability of our findings

Limitations related to prescription data:

- Given limited information on days' supply, the date of discontinuation of rivaroxaban or warfarin was defined as the date of last prescription of the index agent plus the median time between consecutive prescriptions
- A prescription does not necessarily indicate that the prescription was filled or that the medication was taken as prescribed

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Conclusions

- Rivaroxaban was associated with significantly lower risk of VTE recurrence than warfarin at all time points
- There was no significant difference in the risk of major bleeding among those treated with rivaroxaban versus warfarin
- Rivaroxaban may offer an effective and safe alternative to warfarin for the treatment of PE among patients with RVD

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