Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

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on behalf of the EINSTEIN CHOICE Steering Committee and Investigators

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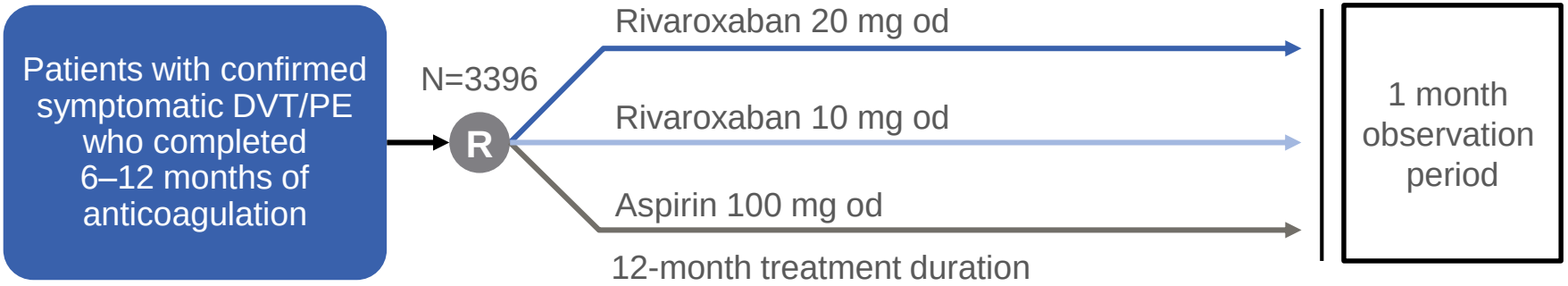
* last 3 years

Background

- In patients without reversible risk factors, the risk of recurrent venous thromboembolism is up to 10% in the first year if anticoagulation therapy is stopped
- Although extended anticoagulation therapy prevents recurrent venous thromboembolism, concerns about bleeding often lead to reluctance to continue treatment beyond 6 to 12 months
- Lower dose anticoagulant therapy, or aspirin instead of an anticoagulant may reduce this bleeding risk
- Head-to-head comparison is necessary to determine the relative efficacy and safety of these approaches

Study Design

- Aim: Compare the efficacy and safety of once daily rivaroxaban (20 or 10 mg) with aspirin (100 mg) in VTE patients who completed 6 to 12 months of treatment and with equipoise regarding the need for extended anticoagulation
- Randomized, double-blind, active-comparator, event-driven, superiority study



Weitz JI *et al*. *Thromb Haemost* 2015;114:645–50

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Outcomes

- Efficacy outcomes:
  - Primary: Symptomatic recurrent VTE (Non-fatal DVT or PE, fatal PE, or unexplained death where PE cannot be excluded)
  - Symptomatic recurrent VTE or MI, ischemic stroke or systemic embolism
  - Symptomatic recurrent VTE or venous thrombosis in other locations
  - Symptomatic recurrent VTE or all-cause mortality
- Safety outcomes
  - Principal: Major bleeding (ISTH)
  - Clinically relevant nonmajor bleeding (ISTH)
  - Nonmajor bleeding associated with study drug interruption for >14 days

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Sample Size Considerations and Analyses

- Assumptions
  - Rivaroxaban 20 mg vs aspirin HR=0.3 (RRR=70%)
  - Rivaroxaban 10 mg vs aspirin HR=0.4 (RRR=60%)
- With 80 primary efficacy outcomes
  - 90% power with a two-sided alpha of 0.05 to demonstrate that both doses of rivaroxaban are superior to aspirin
  - Not powered to detect differences between 20 and 10 mg rivaroxaban regimens
- Analyses based on stratified Cox proportional hazard model
  - Primary efficacy analysis was performed on all randomized patients who received at least one dose of study medication (intention-to-treat population)

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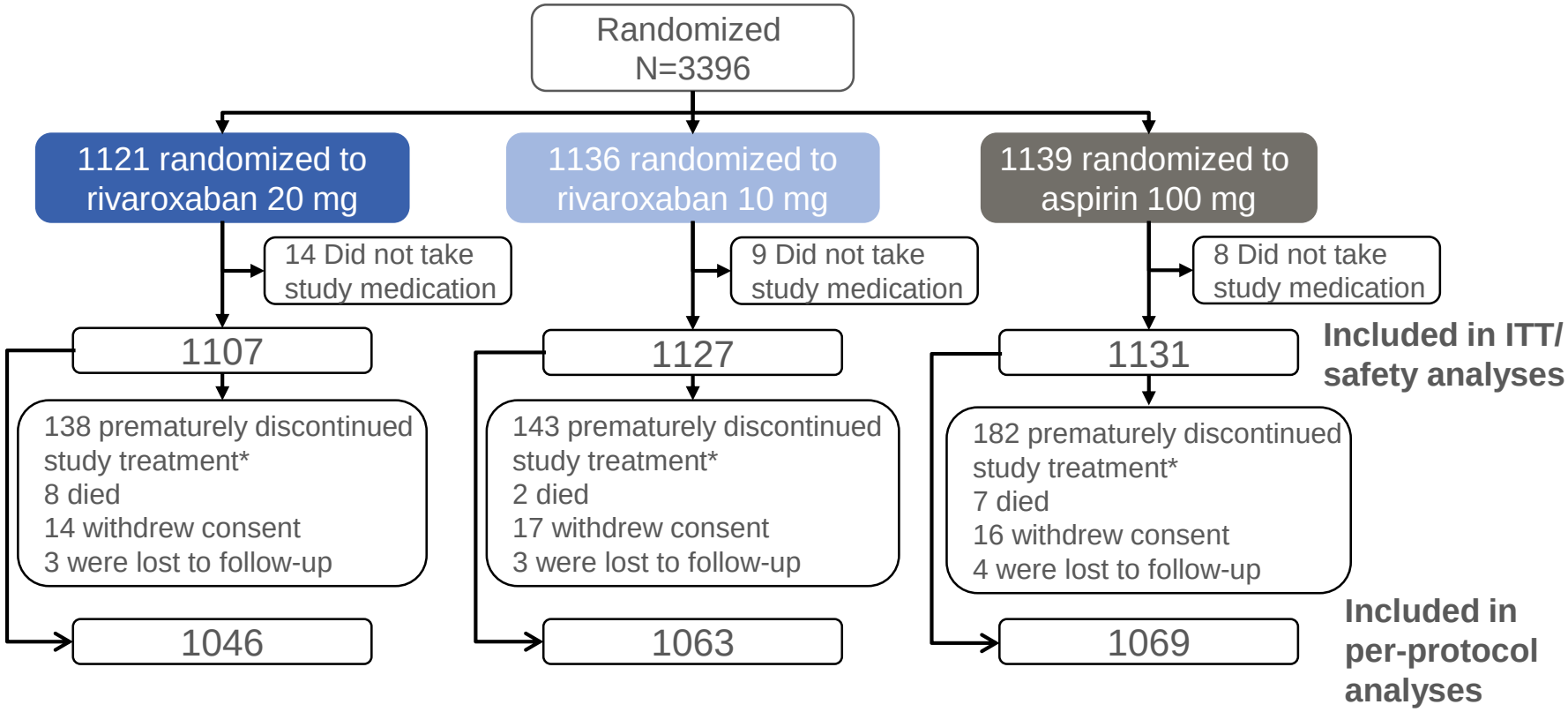
Patient Flow



*The other main reasons for premature discontinuation of study medication were adverse events, noncompliance with study drug, protocol violations, and efficacy or safety outcomes.
ITT (Intention to treat): all randomized patients who received at least one dose of study medication

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Clinical Characteristics*

Outcome		Rivaroxaban 20 mg (n=1107)	Rivaroxaban 10 mg (n=1127)	Aspirin 100 mg (n=1131)
Male, n (%)		602 (54.4)	620 (55.0)	643 (56.9)
Age, (mean years±SD)		57.9±14.7	58.8±14.7	58.8±14.7
Body mass index, n (%)	<30 kg/m^2	712 (64.3)	751 (66.6)	756 (66.8)
	≥30 kg/m^2	394 (35.6)	376 (33.4)	375 (33.2)
Creatinine clearance, n (%)	<30 ml/min	1 (0.1)	2 (0.2)	1 (0.1)
	30–<50 ml/min	40 (3.6)	49 (4.3)	63 (5.6)
	50–<80 ml/min	279 (25.2)	302 (26.8)	277 (24.5)
	≥80 ml/min	787 (71.1)	774 (68.7)	790 (69.8)

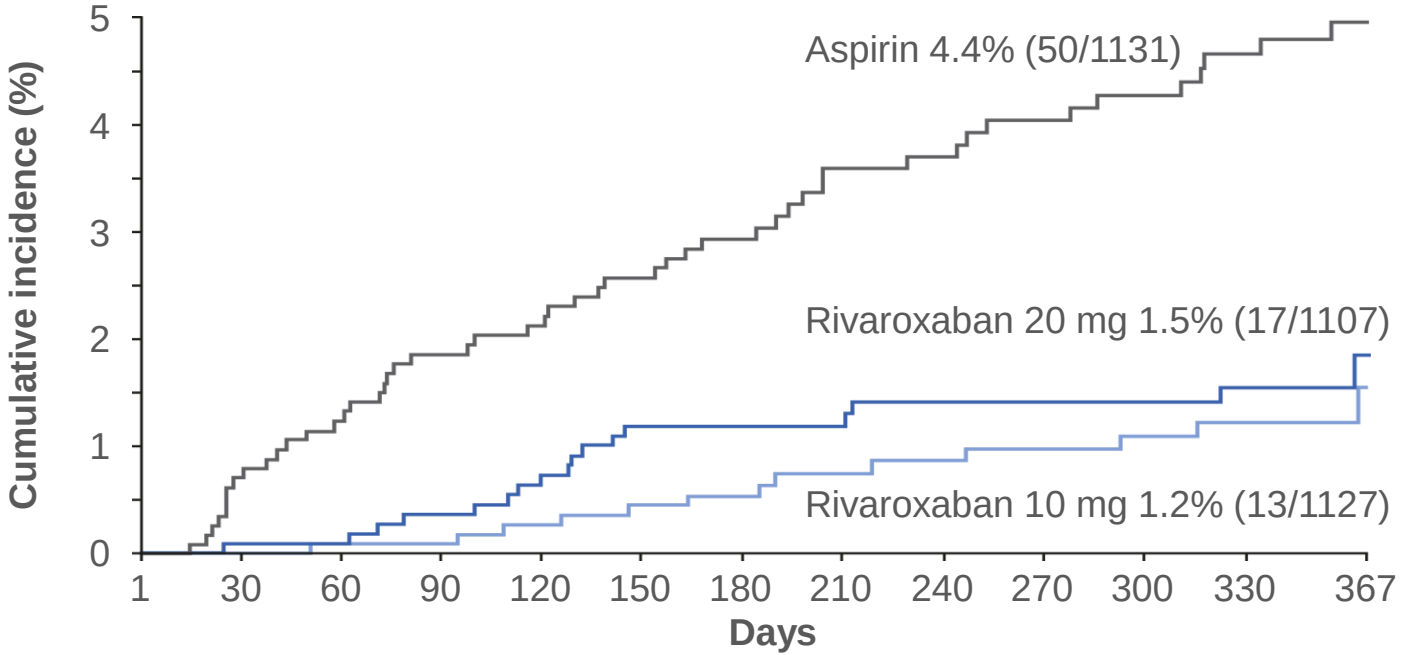
*Differences in baseline characteristics were not significant; SD, standard deviation

Clinical Characteristics*

Outcome		Rivaroxaban 20 mg (n=1107)	Rivaroxaban 10 mg (n=1127)	Aspirin 100 mg (n=1131)
Index event, n (%)	DVT	565 (51.0)	565 (50.1)	577 (51.0)
	PE	381 (34.4)	381 (33.8)	366 (32.4)
	Both	155 (14.0)	179 (15.9)	181 (16.0)
	Asymptomatic or unconfirmed	6 (0.5)	2 (0.2)	7 (0.6)
Classification of index VTE, n (%)	Unprovoked	441 (39.8)	480 (42.6)	468 (41.4)
	Provoked	666 (60.2)	647 (57.4)	663 (58.6)
History of prior VTE, n (%)		198 (17.9)	197 (17.5)	194 (17.2)
Known thrombophilia, n (%)		79 (7.1)	74 (6.6)	70 (6.2)
Active cancer, n (%)		25 (2.3)	27 (2.4)	37 (3.3)
Study drug duration (median days, IQR)		349 (189-362)	353 (190-362)	350 (186-362)

*Differences in baseline characteristics were not significant; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism, IQR, Interquartile range

Recurrent VTE – Cumulative Incidence



Number of patients at risk													
Rivaroxaban 20 mg	1107	1102	1095	1090	1084	1079	997	876	872	860	794	718	0
Rivaroxaban 10 mg	1126	1124	1119	1118	1111	1109	1029	890	886	867	812	723	0
Aspirin	1131	1121	1111	1103	1094	1088	1010	859	857	839	776	707	0

VTE, Venous thromboembolism; HR, hazard ratio

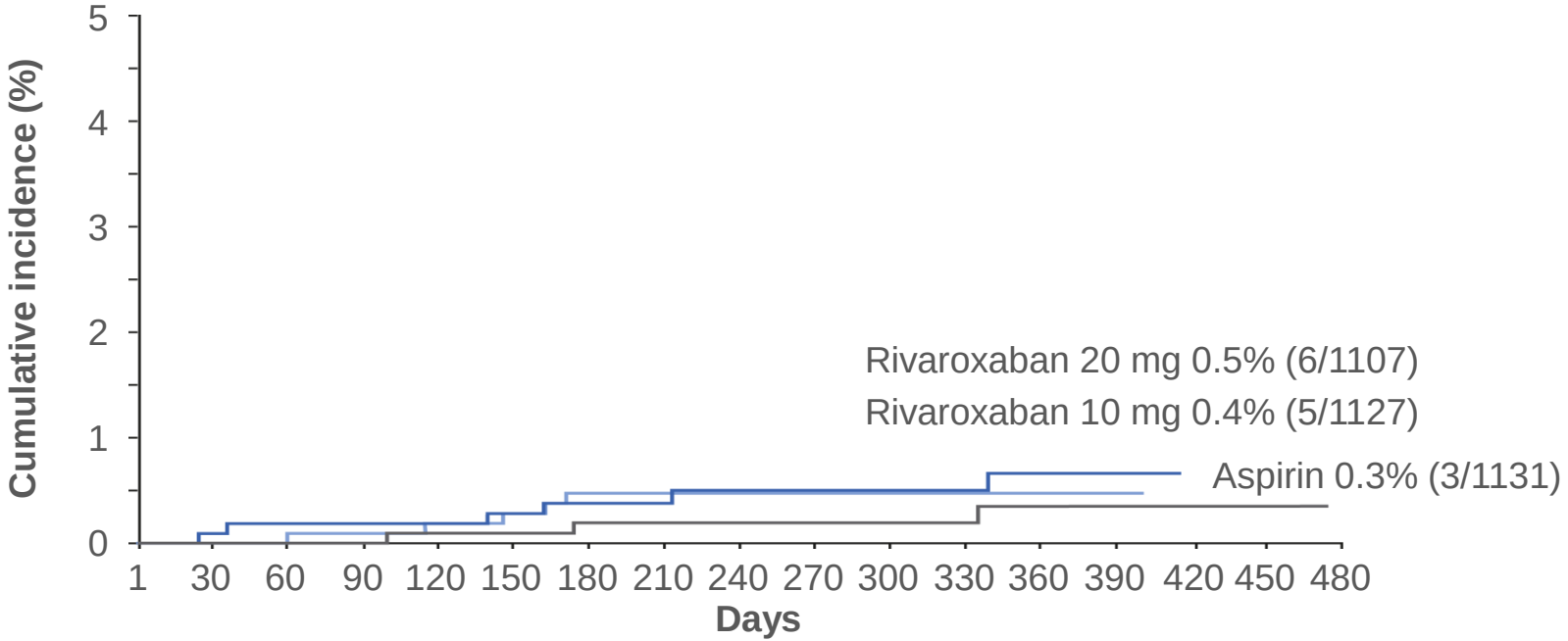
Efficacy Outcome Analyses

	Rivaroxaban 20 mg (n=1107)	Rivaroxaban 10 mg (n=1127)	Aspirin 100 mg (n=1131)	Hazard Ratio (95% CI)		
				Rivaroxaban 20 mg vs aspirin*	Rivaroxaban 10 mg vs aspirin*	Rivaroxaban 20 mg vs 10 mg#
Recurrent VTE	**17 (1.5)**	**13 (1.2)**	**50 (4.4)**	**0.34 (0.20–0.59)**	**0.26 (0.14–0.47)**	**1.34 (0.65–2.75)**
DVT	9 (0.8)	7 (0.6)	29 (2.6)			
PE	6 (0.5)	5 (0.4)	19 (1.7)			
PE+DVT	0	1 (0.1)	0			
Fatal VTE	2 (0.2)	0	2 (0.2)			
Recurrent VTE, MI, ischemic stroke or SE	19 (1.7)	18 (1.6)	56 (5.0)	0.34 (0.20–0.57)	0.32 (0.19–0.54)	1.08 (0.57–2.06)
Recurrent VTE, all-cause mortality	23 (2.1)	15 (1.3)	55 (4.9)	0.42 (0.26–0.68)	0.27 (0.15–0.47)	1.57 (0.82–3.00)
Recurrent VTE, venous thrombosis in other locations	20 (1.8)	16 (1.4)	57 (5.0)	0.35 (0.21–0.58)	0.28 (0.16–0.48)	1.28 (0.66–2.46)
Recurrent VTE, MI, ischemic stroke, SE, venous thrombosis in other locations	22 (2.0)	21 (1.9)	63 (5.6)	0.35 (0.22–0.57)	0.33 (0.20–0.54)	1.07 (0.59–1.95)

*all p- values<0.001; # all p- values not significant

CI, confidence interval; MI, myocardial infarction; SE, systemic embolism; VTE venous thromboembolism

Major Bleeding – Cumulative Incidence



Number of patients at risk																	
Rivaroxaban 20 mg	1107	1081	1063	1048	1036	1024	963	818	801	780	712	642	449	10	0	0	0
Rivaroxaban 10 mg	1126	1103	1080	1070	1058	1046	988	823	812	790	733	653	469	8	0	0	0
Aspirin	1131	1096	1075	1058	1040	1023	970	800	791	768	709	645	445	5	2	2	0

Treatment-emergent major bleeding: onset during study treatment up to 2 days after stop of study treatment

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Bleeding Outcomes

	Rivaroxaban 20 mg (n=1107)	Rivaroxaban 10 mg (n=1127)	Aspirin 100 mg (n=1131)	Hazard Ratio (95% CI)		
				Rivaroxaban 20 mg vs aspirin	Rivaroxaban 10 mg vs aspirin	Rivaroxaban 20 mg vs 10 mg
Major bleeding	**6 (0.5)**	**5 (0.4)**	**3 (0.3)**	**2.01 (0.50–8.04)**	**1.64 (0.39–6.84)**	**1.23 (0.37–4.03)**
Fatal, n (%)	1 (<0.1)	0	1 (0.1)			
Non-fatal bleeding in a critical site, n (%)	4 (0.4)	2 (0.2)	1 (0.1)			
Other,* n (%)	1 (0.1)	3 (0.3)	1 (0.1)			
Major or clinically relevant nonmajor bleeding	36 (3.3)	27 (2.4)	23 (2.0)	1.59 (0.94–2.69)	1.16 (0.67–2.03)	1.37 (0.83–2.26)
Clinically relevant nonmajor bleeding	30 (2.7)	22 (2.0)	20 (1.8)	1.53 (0.87–2.69)	1.09 (0.59–2.00)	1.40 (0.81–2.43)
Nonmajor bleeding with study drug interruption ≥14 days	17 (1.5)	12 (1.1)	12 (1.1)	1.44 (0.69–3.02)	0.99 (0.44–2.20)	1.46 (0.70–3.06)

All p- values not significant

*Other: Non-fatal, non-critical bleeding, but fall in hemoglobin ≥2 g/dl and/or transfusions ≥2 units; CI, confidence interval;

Recurrent VTE– According to Risk Profile and Duration of Anticoagulation Prior to Randomization

Outcome	Rivaroxaban 20 mg	Rivaroxaban 10 mg	Aspirin 100 mg
Recurrent VTE, all patients, n/N (%)	17/1107 (1.5)	13/1127 (1.2)	50/1131 (4.4)
Risk profile index event, n/N (%)			
Unprovoked	8/441 (1.8)	7/480 (1.5)	26/468 (5.6)
Provoked	9/666 (1.4)	6/647 (0.9)	24/663 (3.6)
History of prior VTE, n/N (%)			
Yes	3/198 (1.5)	2/197 (1.0)	17/194 (8.8)
No	14/909 (1.5)	11/930 (1.2)	33/937 (3.5)
Duration of anticoagulation prior to randomization, n/N (%)			
<9 months	12/774 (1.6)	7/782 (0.9)	35/793 (4.4)
≥9 months	5/333 (1.5)	6/345 (1.7)	15/338 (4.4)

Summary and Conclusions

- In patients with symptomatic VTE who completed 6 to 12 months of treatment and with equipoise regarding the need for extended anticoagulation
  - Both rivaroxaban regimens (20 or 10 mg once daily) are superior to aspirin for the primary and other efficacy outcomes and are associated with similar rates of bleeding
  - Compared with aspirin, numbers needed to treat with rivaroxaban 20 or 10 mg for one year to prevent one VTE without an increase in bleeding are 33 and 30, respectively
  - Consistent results in subgroups of patients

- Rivaroxaban 10 mg once daily provides an additional option for extended VTE treatment
  - Patients requiring full-dose anticoagulant therapy were excluded and may need extended treatment with the 20 mg once daily rivaroxaban regimen

*Number needed to treat (NNT) compared with aspirin for primary efficacy outcome up to 1 year

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