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Rivaroxaban for Thromboprophylaxis after Hospitalization for Medical Illness

Alex C. Spyropoulos, M.D., Walter Ageno, M.D., Gregory W. Albers, M.D., C. Gregory Elliott, M.D., Jonathan L. Halperin, M.D., William R. Hiatt, M.D., Gregory A. Maynard, M.D., P. Gabriel Steg, M.D., Jeffrey I. Weitz, M.D., Eunyoung Suh, Ph.D., Theodore E. Spiro, M.D., Elliot S. Barnathan, M.D., and Gary E. Raskob, Ph.D., for the MARINER Investigators*

Group G

Instructor:
Alex C. Spyropoulos, M.D.
Members:
Nefeli Eleni Kounatidou , Theodora Koutsouri, Evangelia Vlachou

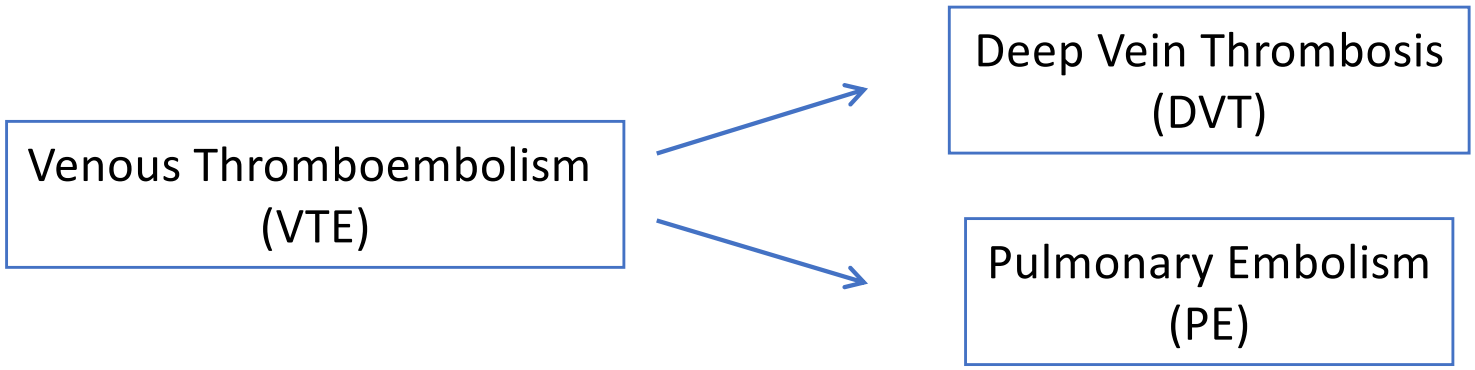
1.Introduction

2.Methods & Results

3.Discussion

VTE

= severe cause of morbidity and mortality in medically ill patients



- 10 million annual cases reported worldwide
- individual lifetime risk of >8%
- VTE represents the third leading cause of vascular disease

Secemsky EA, J Am Heart Assoc, 2018

Risk of developing VTE in the medically ill

⇒ Development of VTE **Risk Assessment Models (RAMs)**

Table 2: Risk score points assigned to each independent VTE risk factor in hospitalised acutely ill medical patients – the IMPROVE VTE associative RAM * [adapted from ref (4)].

VTE risk factor	Points for the risk score
Previous VTE	3
Thrombophilia**	2
Lower limb paralysis	2
Cancer***	2
Immobilisation****	1
ICU/CCU stay	1
Age > 60 years	1

0-1: low risk VTE < 1.0%
2-3: moderate risk ~ 1.0-1.5%
4≥: high risk ≥ 4%

Table 4: The IMPROVEDD VTE risk score* [adapted from ref (61)].

Factor	Points
Previous VTE	3
Known thrombophilia	2
Current lower-limb paralysis	2
Current cancer	2
Immobilised ≥ 7 days	1
ICU or CCU stay	1
Age > 60 years	1
D-dimer ≥ 2 × ULN	2

* A score of 2 or more constitutes at-VTE risk.

⇒**Identify patient sub group that will benefit**

Alex C. Spyropoulos, Gary E. Raskob,Thromb Haemost, 2017

When is a VTE most likely to occur?

Acute hospitalization period: (~ 6–14 days) patient immobility and disease severity

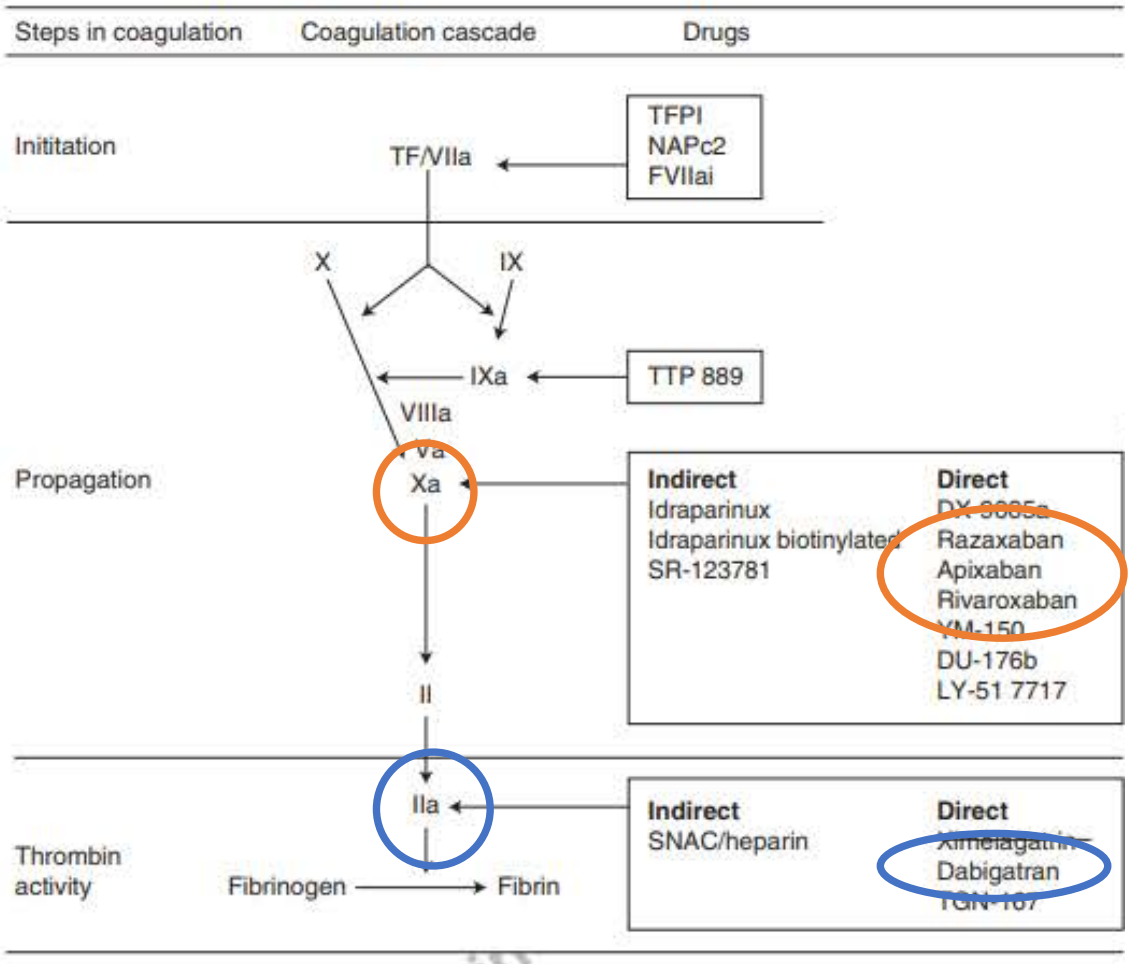
Post-hospital discharge period: (up to 90 days) disease-specific exacerbation of a patient's underlying illness

The majority (~80 %) of VTE events occur in the **first 45 days** after hospital discharge

Chronic medical illness phase:
a chronic medical condition.

Noel C. Chan, Circulation Research, 2019
Alex C. Spyropoulos, Gary E. Raskob,Thromb Haemost, 2017

The Coagulation Cascade
Targets of DOACs



Spyropoulos A., Cardiovascular and Renal, 2007

Pharmacokinetic profile of DOACs

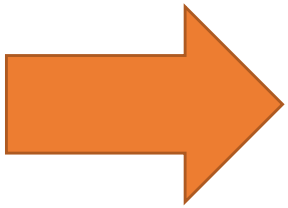
Agent	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of Action	Inhibition factor II	Inhibition of factor X	Inhibition of factor X	Inhibition of factor X
Half-life	7-9 h after first dose, 12-14 h after multiple doses	9 h in young & adults, 12 h in elderly over 75 years	12 h	8-10 h
Time to reach plasma peak	0.5-2 h	2-4 h	3 h	1-2 h
Bioavailability	6.5 %	> 80%	> 50%	> 45%
Excretion	Kidney 80%	Kidney 66%, of which 33% unmodified biliary-fecal system 35%	Kidney 25%, biliary-fecal system 75%	Kidney 35%, biliary-fecal system 65%
Plasma protein binding	35%	90%	85%	55%
Substrate of cytochrome P3A4	No	Yes	Yes	Yes
Substrate of P-glycoprotein	Yes	Yes	Yes	Yes

Almarshad F, Am J Blood Res, 2018

Evaluating DOACs for extended VTE treatment

RCTs
LMWH ***vs*** DOACs

APEX
MAGELLAN
ADOPT
EXCLAIM



relative risk reduction (RRR) in **ultrasonographic DVT** was modest (~25 %) in the extended therapy groups at ~35 to 42 days

decrease in symptomatic DVT
Relative Risk (RR) = 0.52, 95 % CI 0.35–0.77

& **symptomatic non-fatal PE** [RR = 0.61, 95 % CI 0.38–0.99]

Alex C. Spyropoulos, Gary E. Raskob,Thromb Haemost, 2017
Liew, A.Y.L., Piran, S., Eikelboom, J.W. et al. J Thromb Thrombolysis, 2017

x2 increase in major bleeding

RR = 2.08, 95 % CI 1.50–2.90

net-clinical benefit of extended thromboprophylaxis ????

Trial	APEX [4]	MAGELLAN [3]	ADOPT [2]	EXCLAIM [9]
Study design	Randomized double blind, double dummy, multicenter	Randomized double blind, double dummy, multicenter	Randomized double blind, double dummy, multicenter	Randomized double blind, multicenter
Treatment arm	Betrixaban 80 mg once daily	Rivaroxaban 10 mg once daily	Apixaban 2.5 mg twice daily	Enoxaparin 40 mg once daily
Comparison	EDT (betrixaban)	EDT (rivaroxaban)	EDT (apixaban)	EDT (enoxaparin)
	SDT (enoxaparin)	SDT (enoxaparin)	SDT (enoxaparin)	SDT (enoxaparin)
Route of administration	Oral	Oral	Oral	Subcutaneous
Control arm	Enoxaparin for 10 ± 4 days followed by placebo	Enoxaparin for 10 ± 4 days followed by placebo	Enoxaparin for duration of hospital stay for a minimum of 6 days followed by placebo	Enoxaparin during hospitalization followed by placebo
Duration of anticoagulation (days)	35–42	35 ± 4	30	28 ± 4
Primary efficacy outcome	Asymptomatic proximal DVT between days 32–47, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death related to VTE	Asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death related to VTE up to day 35	Asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death related to VTE	Symptomatic or asymptomatic proximal DVT, symptomatic PE, or fatal PE
Primary safety outcome	Major bleeding at any point until 7 days after discontinuation of all study medications	Major bleeding or clinically relevant nonmajor bleeding observed no later than 2 days after discontinuation of all study medications	Major bleeding or clinically relevant nonmajor bleeding	Major bleeding during and up to 2 days after discontinuation of all study medications
Number of patients randomized	7,513	8,101	6,528	6,085
Mean age, years	76.6	71.0*	66.8	67.9
Women, n (%)	4,088 (54.4)	3,712 (45.8)	3,325 (50.9)	3,019 (49.6)
	ılization			
HF, n (%)	3,349 (44.6)	2,620 (32.3)	2,516 (38.5)	1,110 (18.2)
Acute ischemic stroke, n (%)	843 (11.2)	1,399 (17.3)	NR	389 (6.4)
Acute respiratory failure, n (%)	922 (12.3)	2,268 (27.8)	2,421 (37.1)	1,805 (29.7)
Acute inflammatory rheumatic diseases, n (%)	226 (3.0)	303 (3.7)	124 (1.9)	173 (2.8)
Active cancer, n (%)	NR	592 (7.3)	211 (3.2)	96 (1.6)
Infection without septic shock, n (%)	NR	3,682 (45.5)	1,447 (22.2)	1,982 (32.6)
Other (plus not reported), n (%)	NR	58 (0.7)	20 (0.3)	408 (6.7)
	ctors			
Age ≥75 years, n (%)	5,092 (67.8)	3,116 (38.5)	NR	1,781 (29.3)
Previous VTE, n (%)	608 (8.1)	381 (4.7)	265 (4.1)	402 (6.6)
History of HF (NYHA class III/IV), n (%)	1,718 (22.9)	2,790 (34.4)	2,478 (38.0)	1,110 (18.2)
Acute infectious disease, n (%)	1,222 (16.3)	1,167 (14.4)	NR	NR
History of cancer, n (%)	909 (12.1)	1,378 (17.0)	632 (9.7)	817 (13.4)

MARINER trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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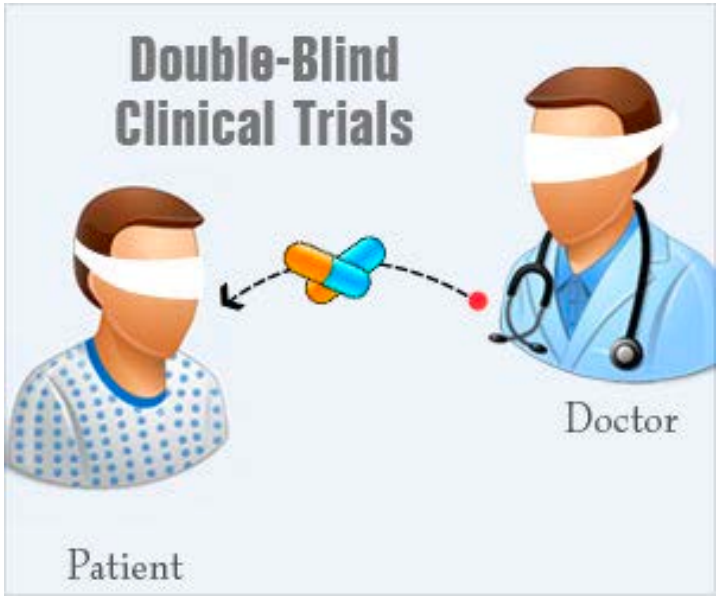
METHODS

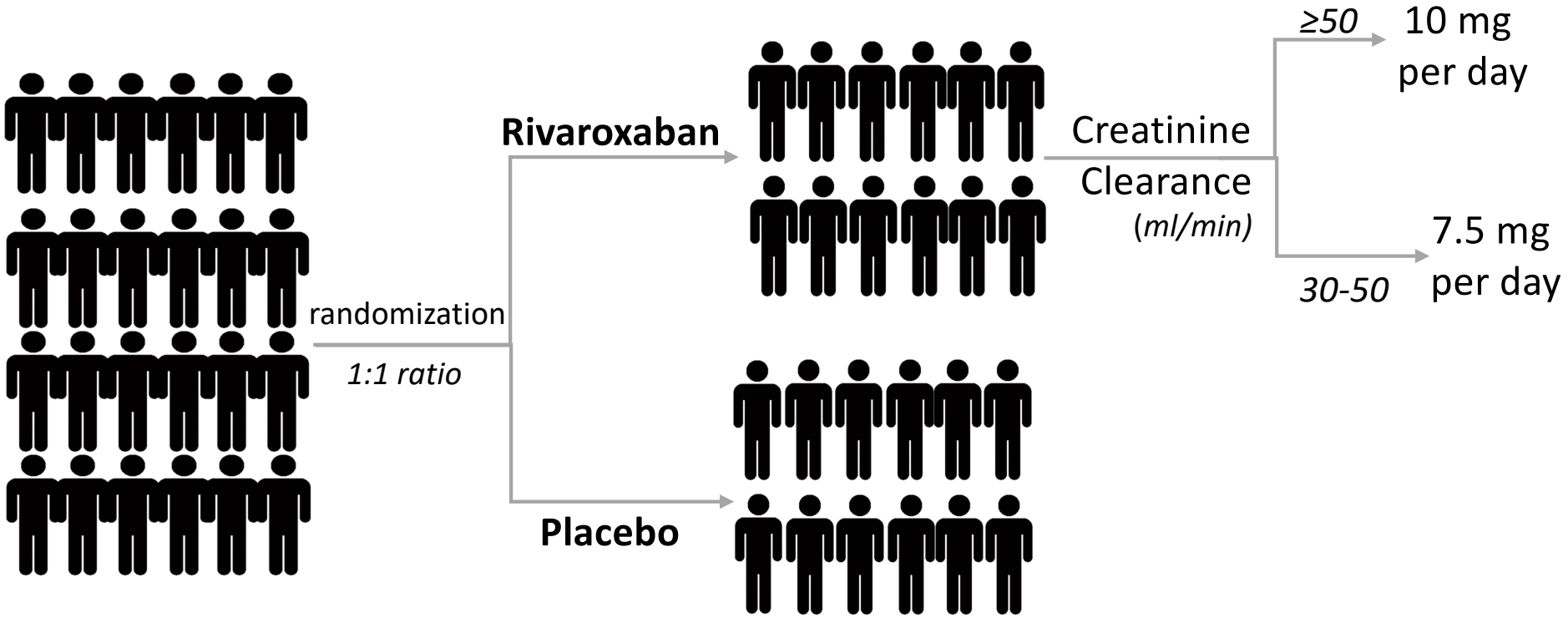
Randomized, double-blind, placebo-controlled, multinational (36 countries) clinical trial with intention to treat analysis

Randomization was performed with the use of an **interactive Web-based system**, with stratification according to:

- **country**
- **creatinine clearance**



Trial Regimen and Follow-up



- Duration: **45 days**

- Patients were instructed to **report symptoms or signs** associated with
  - deep vein thrombosis,
  - pulmonary embolism,
  - bleeding

- Follow up of **all** the patients: at approximately **7 days, 21 days**, and **45 days**, after randomization, regardless of whether they continued to take rivaroxaban or placebo.

Outcome Measures

Primary Efficacy Outcome

composite of any symptomatic VTE

or

death related to VTE

(i.e., death due to pulmonary embolism,)

Secondary Efficacy Outcomes (prespecified)

1)symptomatic nonfatal VTE
2)death related to VTE
} analyzed separately

3)composite of nonfatal VTE or death from any cause

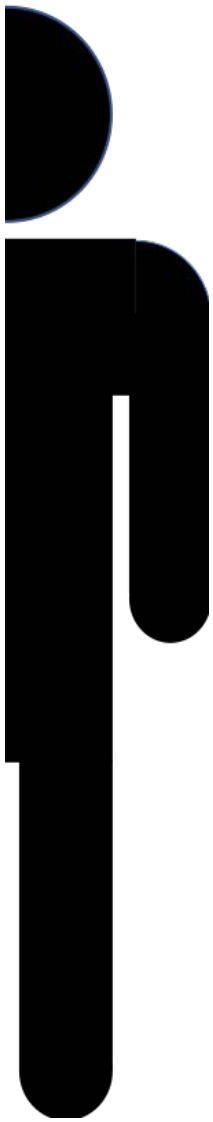
4)composite of non fatal symptomatic VTE, myocardial infarction nonhemorrhagic stroke, or cardiovascular death

5)death from any cause.

Principal Safety Outcome → major bleeding

Other Safety Outcomes → were nonmajor clinically relevant bleeding, other bleeding, and adverse events

Patients



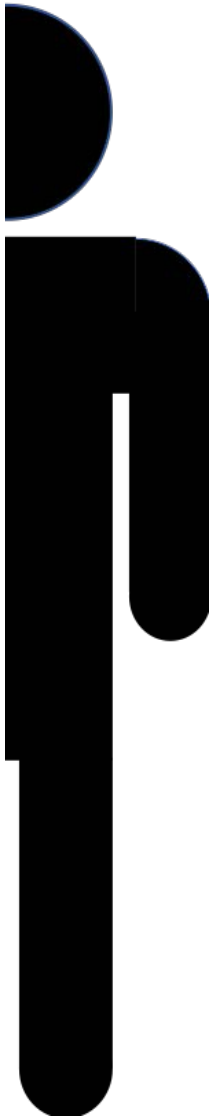
- ✓ **≥ 40** years old
- ✓ **hospitalized** for 3 -10 consecutive days
- ✓ with one of the following conditions:
  - i. **heart failure** with a left ventricular ejection fraction of 45% or less
  - ii. **acute respiratory insufficiency**
  - iii. **exacerbation of chronic obstructive pulmonary disease**
  - iv. **acute ischemic stroke**
  - v. **acute infectious or inflammatory disease**, including rheumatic diseases
- ✓ **additional risk factors for venous thromboembolism**:

  Modified IMPROVE VTE risk score *≥4*

  or

  2-3 risk score + plasma d-dimer level of more than twice the upper limit of the normal range
- ✓ **thromboprophylaxis** with low-molecular-weight heparin or unfractionated heparin during the index hospitalization

Excluded Patients



- conditions treated with **anticoagulant** or **dual antiplatelet therapy**
- **active cancer**
- a history of **recent bleeding** (within 3 months) or **high risk of bleeding!**
- other **contraindications to rivaroxaban**

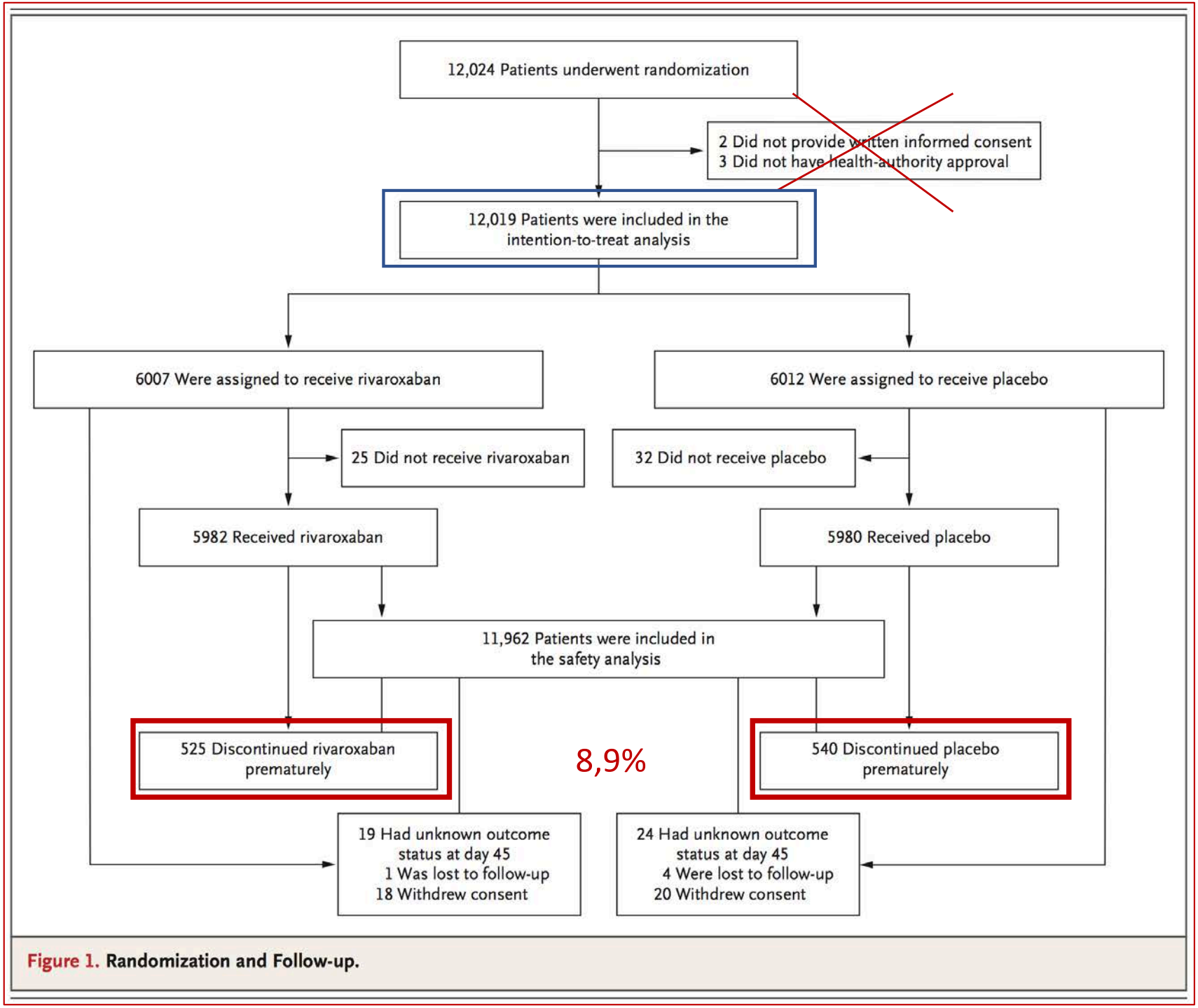


Figure 1. Randomization and Follow-up.

The base line characteristics of the patients were **similar** in the two trial groups

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Rivaroxaban (N=6007)	Placebo (N=6012)
Mean age — yr	69.7	69.7
Age ≥75 yr — no. (%)	2154 (35.9)	2140 (35.6)
Male sex — no. (%)	3130 (52.1)	3154 (52.5)
White race — %†	5782 (96.3)	5808 (96.6)
Mean weight — kg	80.8	80.6
BMI‡	29.0	28.8
Creatinine clearance — no. (%)		
30 to <50 ml/min	1098 (18.3)	1099 (18.3)
≥50 ml/min	4909 (81.7)	4913 (81.7)
Reason for index hospitalization — no./total no. (%)		
Heart failure	2435/6003 (40.6)	2399/6011 (39.9)
Respiratory insufficiency or exacerbation of COPD	1575/6003 (26.2)	1611/6011 (26.8)
Ischemic stroke	860/6003 (14.3)	866/6011 (14.4)
Infectious disease	1048/6003 (17.5)	1045/6011 (17.4)
Inflammatory disease	85/6003 (1.4)	90/6011 (1.5)
Mean duration of index hospitalization — days	6.7	6.7
Mean duration of in-hospital thromboprophylaxis — days	6.2	6.2
History of VTE — no. (%)	765 (12.7)	748 (12.4)
History of cancer — no. (%)	488 (8.1)	533 (8.9)
ICU or CCU stay — no. (%)	3260 (54.3)	3240 (53.9)
Current lower-limb paralysis or paresis — no. (%)	1115 (18.6)	1122 (18.7)
Modified IMPROVE VTE risk score — no. (%)§		
2	2098 (34.9)	2151 (35.8)
3	1886 (31.4)	1779 (29.6)
≥4	2019 (33.6)	2075 (34.5)
D-Dimer level more than twice the upper limit of the normal range during index hospitalization — no. (%)¶	4226 (70.4)	4239 (70.5)
Aspirin use — no. (%)	3159 (52.6)	3046 (50.7)
Thienopyridine use — no. (%)	360 (6.0)	388 (6.5)

* CCU denotes cardiac care unit, COPD chronic obstructive pulmonary disease, ICU intensive care unit, and VTE venous thromboembolism.
† Race was reported by the patient.
‡ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
§ Modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) risk scores range from 0 to 10, with higher scores indicating a higher risk of venous thromboembolism (minimal clinically important difference, 2). Eleven patients had protocol violations: three patients in the rivaroxaban group and seven patients in the placebo group had a score of 1, and one patient in the rivaroxaban group had a score of 0.
¶ The normal range for D-dimer level was defined according to the local laboratory criteria.

RESULTS

Table 2. Clinical Outcomes during the 45-Day Treatment Phase.*

Outcome	Rivaroxaban	Placebo	Hazard Ratio (95% CI)†
	no. of patients/total no. (%)		
Primary efficacy outcome			
Symptomatic VTE or VTE-related death	50/6007 (0.83)	66/6012 (1.10)	0.76 (0.52–1.09)‡
Creatinine clearance ≥50 ml/min, 10-mg dose	32/4909 (0.65)	48/4913 (0.98)	0.67 (0.43–1.04)
Creatinine clearance 30 to <50 ml/min, 7.5-mg dose	18/1098 (1.64)	18/1099 (1.64)	1.00 (0.52–1.92)
Secondary efficacy outcomes			
VTE-related death	43/6007 (0.72)	46/6012 (0.77)	0.93 (0.62–1.42)
Symptomatic VTE	11/6007 (0.18)	25/6012 (0.42)	0.44 (0.22–0.89)
Symptomatic VTE or death from any cause	78/6007 (1.30)	107/6012 (1.78)	0.73 (0.54–0.97)
Symptomatic VTE, myocardial infarction, nonhemorrhagic stroke, or cardiovascular death	94/6007 (1.56)	120/6012 (2.00)	0.78 (0.60–1.02)
Death from any cause	71/6007 (1.18)	89/6012 (1.48)	0.80 (0.58–1.09)
Safety outcomes			
Principal safety outcome: major bleeding	17/5982 (0.28)	9/5980 (0.15)	1.88 (0.84–4.23)
Creatinine clearance ≥50 ml/min, 10-mg dose	13/4890 (0.27)	9/4890 (0.18)	1.44 (0.62–3.37)
Creatinine clearance 30 to <50 ml/min, 7.5-mg dose	4/1092 (0.37)	0/1090	—
Criteria for major bleeding§			
Hemoglobin decrease ≥2 g/dl	14/5982 (0.23)	6/5980 (0.10)	2.33 (0.89–6.05)
Transfusion of ≥2 units of packed red cells	11/5982 (0.18)	3/5980 (0.05)	3.66 (1.02–13.10)
Critical site	3/5982 (0.05)	2/5980 (0.03)	1.50 (0.25–8.97)
Fatal	2/5982 (0.03)	0/5980	—
Nonmajor clinically relevant bleeding	85/5982 (1.42)	51/5980 (0.85)	1.66 (1.17–2.35)
Other bleeding	54/5982 (0.90)	34/5980 (0.57)	1.59 (1.03–2.44)

* Symptomatic VTE included deep-vein thrombosis in the legs and nonfatal pulmonary embolism. VTE-related death included death due to pulmonary embolism and death in which pulmonary embolism could not be ruled out as the cause. Cardiovascular death included death due to a known cardiovascular cause and death in which a cardiovascular cause, including pulmonary embolism, could not be ruled out.
† The confidence intervals have not been adjusted, and inferences drawn from the intervals may not be reproducible.
‡ P=0.14.
§ Some patients may have had more than one criterion.

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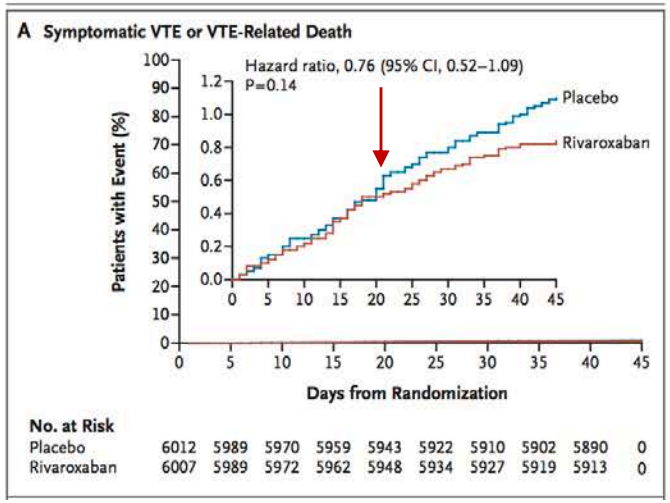

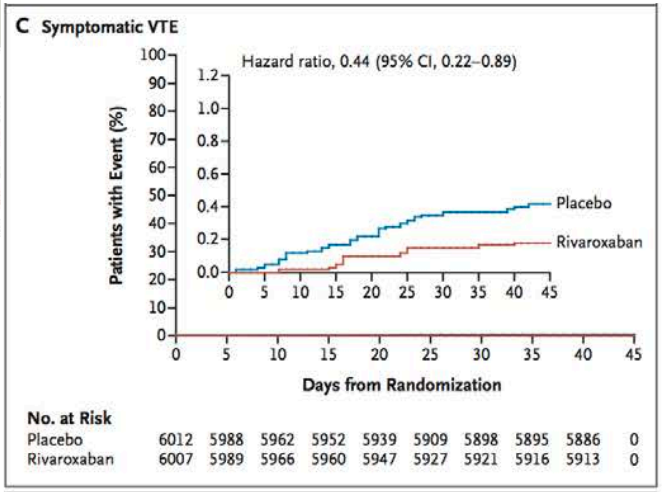

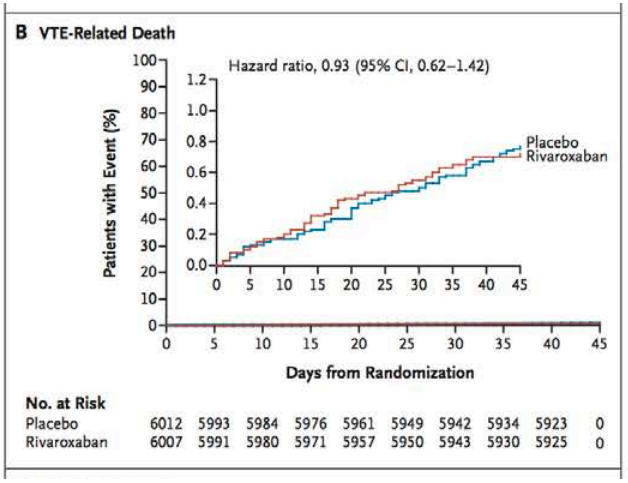

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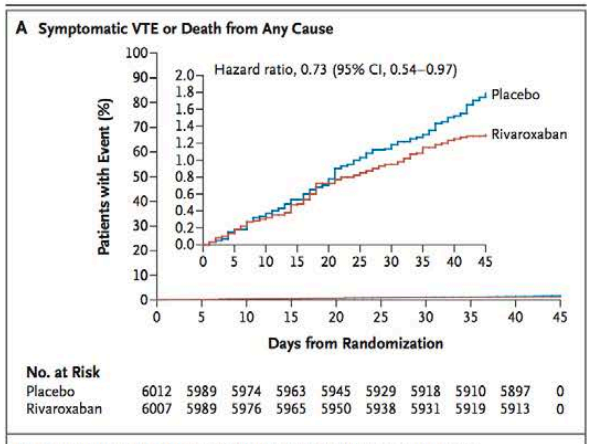

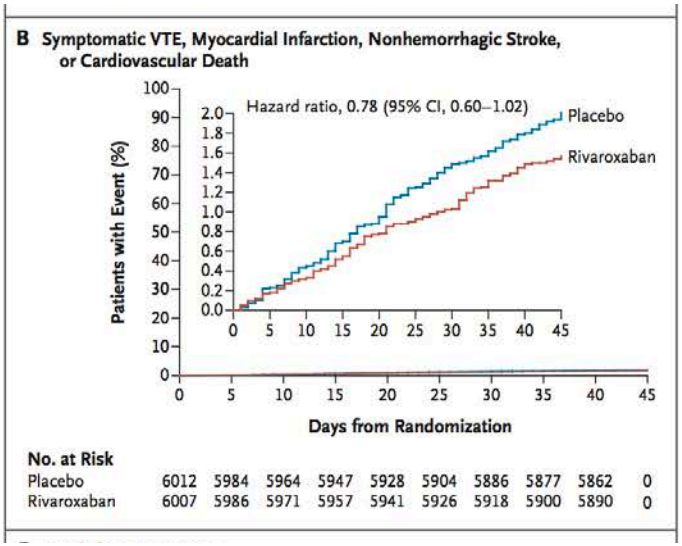

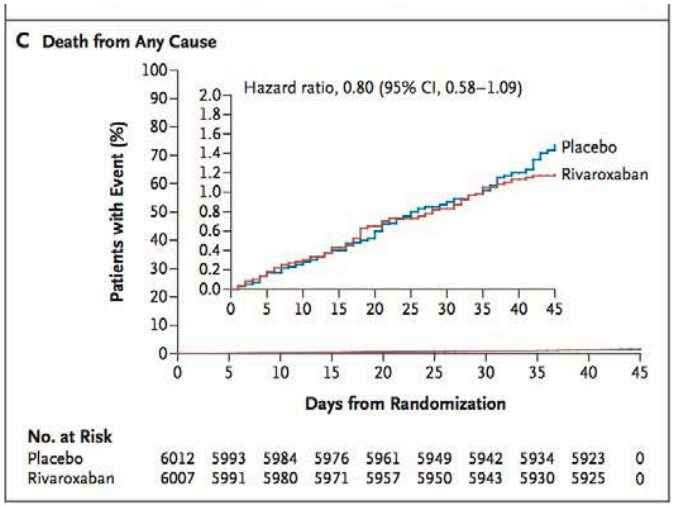

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Safety was enhanced by:

1. initiating rivaroxaban **at discharge**
2. **excluding patients in high risk of bleeding**
3. **reducing the dose** to 7.5 mg daily in patients with moderate renal impairment

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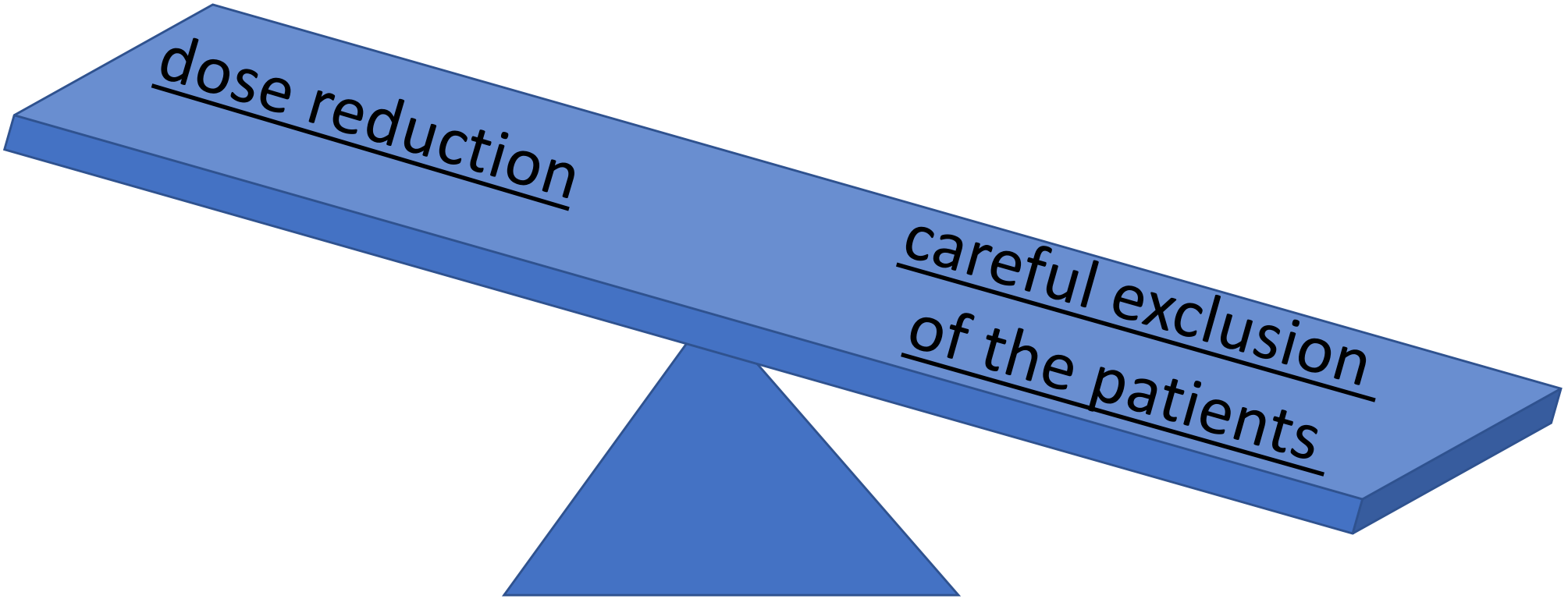
Safety outcomes			
Principal safety outcome: major bleeding	17/5982 (0.28)	9/5980 (0.15)	1.88 (0.84–4.23)
Creatinine clearance ≥50 ml/min, 10-mg dose	13/4890 (0.27)	9/4890 (0.18)	1.44 (0.62–3.37)
Creatinine clearance 30 to <50 ml/min, 7.5-mg dose	4/1092 (0.37)	0/1090	—
Criteria for major bleeding§			
Hemoglobin decrease ≥2 g/dl	14/5982 (0.23)	6/5980 (0.10)	2.33 (0.89–6.05)
Transfusion of ≥2 units of packed red cells	11/5982 (0.18)	3/5980 (0.05)	3.66 (1.02–13.10)
Critical site	3/5982 (0.05)	2/5980 (0.03)	1.50 (0.25–8.97)
Fatal	2/5982 (0.03)	0/5980	—
Nonmajor clinically relevant bleeding	85/5982 (1.42)	51/5980 (0.85)	1.66 (1.17–2.35)
Other bleeding	54/5982 (0.90)	34/5980 (0.57)	1.59 (1.03–2.44)

* Symptomatic VTE included deep-vein thrombosis in the legs and nonfatal pulmonary embolism. VTE-related death included death due to pulmonary embolism and death in which pulmonary embolism could not be ruled out as the cause. Cardiovascular death included death due to a known cardiovascular cause and death in which a cardiovascular cause, including pulmonary embolism, could not be ruled out.
† The confidence intervals have not been adjusted, and inferences drawn from the intervals may not be reproducible.
‡ P=0.14.
§ Some patients may have had more than one criterion.


dose reduction
careful exclusion
of the patients

1.Introduction

2.Methods & Results

3.Discussion

DISCUSSION

Table 1. Study designs, treatment protocols, and baseline patient profiles across the EDT trials.

Trial	MARINER [5]	APEX [4]	MAGELLAN [3]	ADOPT [2]	EXCLAIM [9]
Study design	Randomized, double blind, placebo-controlled, multicenter	Randomized double blind, double dummy, multicenter	Randomized double blind, double dummy, multicenter	Randomized double blind, double dummy, multicenter	Randomized double blind, multicenter
Treatment arm	Rivaroxaban 10 mg once daily†	Betrixaban 80 mg once daily	Rivaroxaban 10 mg once daily	Apixaban 2.5 mg twice daily	Enoxaparin 40 mg once daily
Comparison	EDT (rivaroxaban)	EDT (betrixaban)	EDT (rivaroxaban)	EDT (apixaban)	EDT (enoxaparin)
	SDT (placebo)	SDT (enoxaparin)	SDT (enoxaparin)	SDT (enoxaparin)	SDT (enoxaparin)
Route of administration	Oral	Oral	Oral	Oral	Subcutaneous
Control arm	Placebo	Enoxaparin for 10 ± 4 days followed by placebo	Enoxaparin for 10 ± 4 days followed by placebo	Enoxaparin for duration of hospital stay for a minimum of 6 days followed by placebo	Enoxaparin during hospitalization followed by placebo
Duration of anticoagulation (days)	45	35–42	35 ± 4	30	28 ± 4
Primary efficacy outcome	Symptomatic VTE or death related to VTE through day 45	Asymptomatic proximal DVT between days 32–47, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death related to VTE	Asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death related to VTE up to day 35	Asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death related to VTE	Symptomatic or asymptomatic proximal DVT, symptomatic PE, or fatal PE
Primary safety outcome	Major bleeding	Major bleeding at any point until 7 days after discontinuation of all study medications	Major bleeding or clinically relevant nonmajor bleeding observed no later than 2 days after discontinuation of all study medications	Major bleeding or clinically relevant nonmajor bleeding	Major bleeding during and up to 2 days after discontinuation of all study medications
Number of patients randomized	12,024	7,513	8,101	6,528	6,085
Mean age, years	69.7	76.6	71.0*	66.8	67.9
Women, n (%)	5,733 (47.7)	4,088 (54.4)	3,712 (45.8)	3,325 (50.9)	3,019 (49.6)
	Reason for Hospitalization				
HF, n (%)	4,835 (40.2)	3,349 (44.6)	2,620 (32.3)	2,516 (38.5)	1,110 (18.2)
Acute ischemic stroke, n (%)	1,726 (14.4)	843 (11.2)	1,399 (17.3)	NR	389 (6.4)
Acute respiratory failure, n (%)	3,186 (26.5)	922 (12.3)	2,268 (27.8)	2,421 (37.1)	1,805 (29.7)
Acute inflammatory rheumatic diseases, n (%)	175 (1.5)	226 (3.0)	303 (3.7)	124 (1.9)	173 (2.8)
Active cancer, n (%)	NR	NR	592 (7.3)	211 (3.2)	96 (1.6)
Infection without septic shock, n (%)	2,093 (17.4)	NR	3,682 (45.5)	1,447 (22.2)	1,982 (32.6)
Other (plus not reported), n (%)	NR	NR	58 (0.7)	20 (0.3)	408 (6.7)
	Additional Risk Factors				
Age ≥75 years, n (%)	4,294 (35.7)	5,092 (67.8)	3,116 (38.5)	NR	1,781 (29.3)
Previous VTE, n (%)	1,513 (12.6)	608 (8.1)	381 (4.7)	265 (4.1)	402 (6.6)
History of HF (NYHA class III/IV), n (%)	NR	1,718 (22.9)	2,790 (34.4)	2,478 (38.0)	1,110 (18.2)
Acute infectious disease, n (%)	NR	1,222 (16.3)	1,167 (14.4)	NR	NR
History of cancer, n (%)	1,021 (8.5)	909 (12.1)	1,378 (17.0)	632 (9.7)	817 (13.4)

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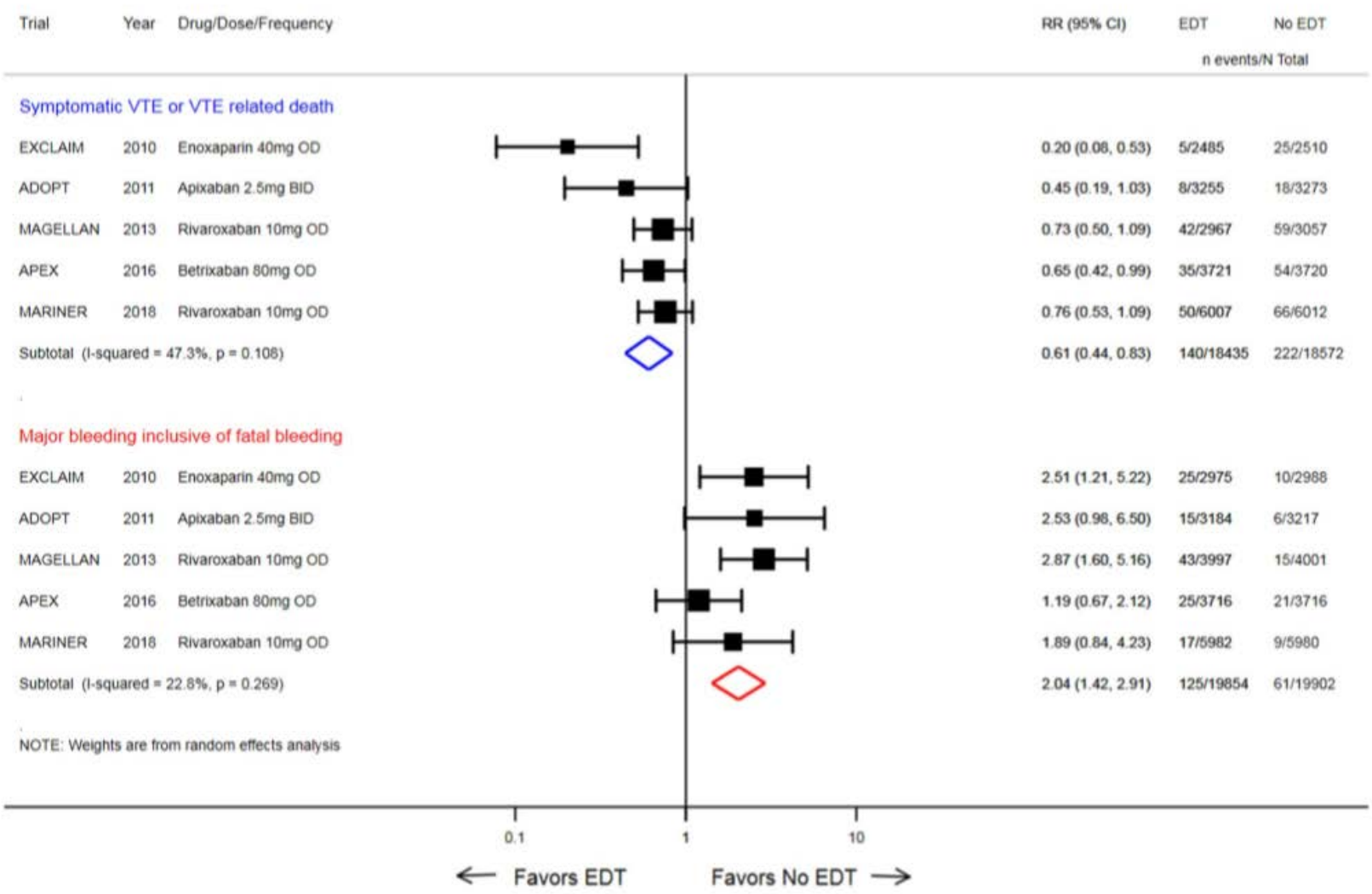

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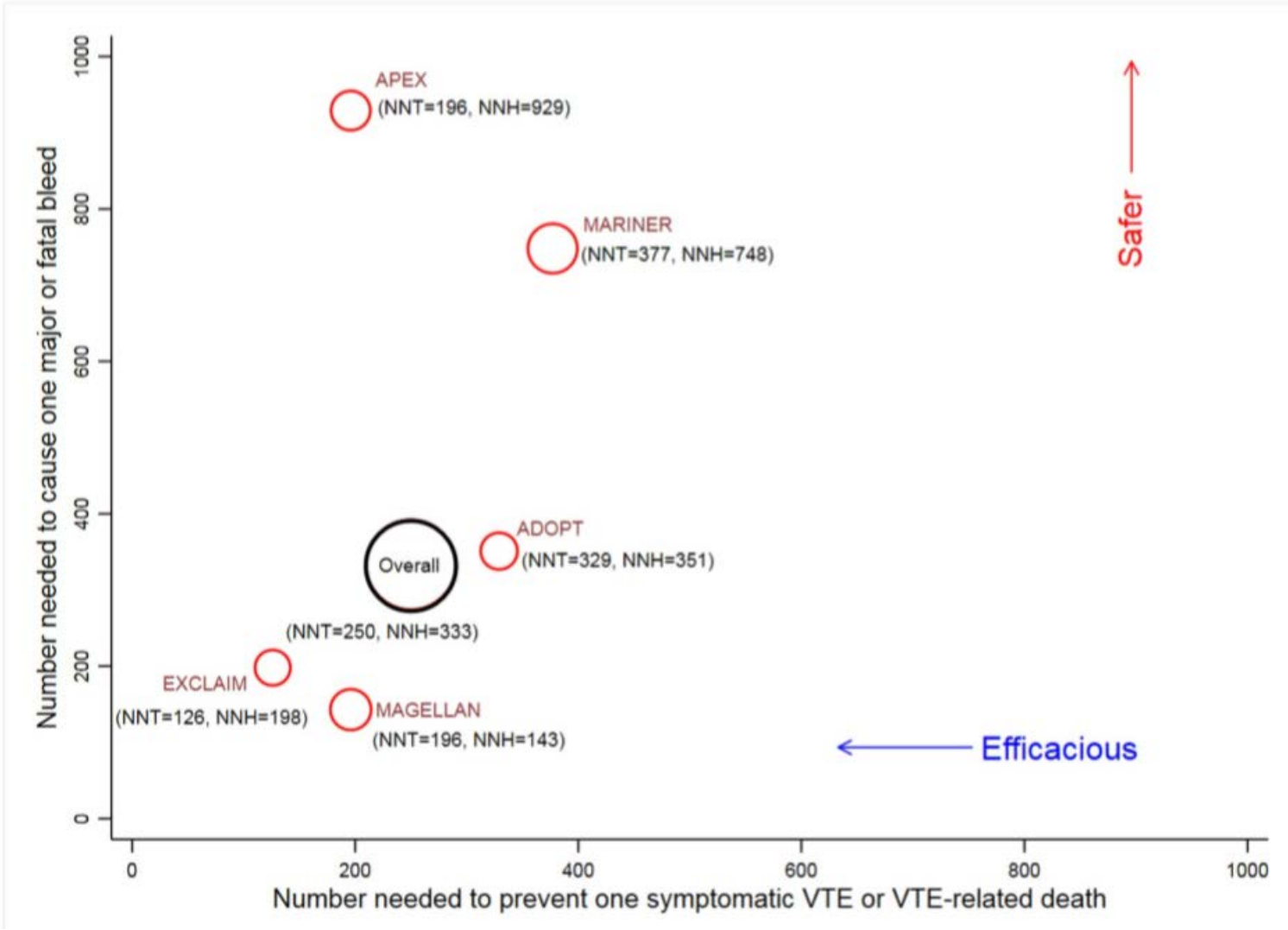

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COMPERING WITH PREVIOUS CLINICAL TRIALS

- VTE-related death in the placebo group (0.77%) was higher than in trials of other direct oral anticoagulants.

A. In MAGELLAN trial involving medically ill patients, treatment with rivaroxaban (10 mg/daily for 35 days) ↓ VTE but ↑ major bleeding.

Goal of the MARINER trial was to improve the safety of rivaroxaban in this population.

GOAL ACHIEVED

➢ <u>Safety was enhanced by:</u>

1. initiating rivaroxaban at discharge,
2. excluding patients identified as **high risk** for bleeding in the previous trial.

active cancer
gastrointestinal ulcer
bronchiectasis
bleeding in the previous 3 months
receiving dual antiplatelet therapy

COMPERING WITH PREVIOUS CLINICAL TRIALS

B. In MAGELLAN trial involving patients with renal insufficiency (have higher thrombotic and bleeding events), treatment with rivaroxaban (10 mg/daily for 35 days)

1. effective in patients with moderate renal insufficiency
2. but associated with ↑ bleeding.

GOAL ACHIEVED

- **In MARINER trial**, treatment with rivaroxaban (7.5 mg/daily for 45 days)
  1. low incidence of bleeding in patients with moderate renal insufficiency
  2. but not with a lower risk of the primary efficacy outcome than placebo.

STRATEGY OF DOSE REDUNCTION TO IMPRONE SAFETY HAS AN ABSOLUTE LIMIT, AFTER THAT LIMIT REACH THERE IS NO ABSOLUTE EFFECT

Strengths

-validated risk score

-elevated d-dimer levels

-inclusion criteria represent 25-30% of all hospitalized medical patients.

Limitations

-incidence in the placebo group was 1.1% rather than the expected 2.5%.

-difficulty in defining VTE–related death, ONLY 14 AUTOPSES

-possible underdosing of patients with moderate renal impairment.

-not record all the patients who were assessed for inclusion

MARINE TRIAL

Rivaroxaban trea
1)was not associated or symptomatic VTE t
2)had
3)it was assc
4)The i s low (0.28%;
5)the imp propriate on of medically i VTE in this population.
6)Although we obs matic VTE with rivaroxaban than with placebo, no significant differenc E–related mortality was observed.

In conclusion

A) NO significant benefit of this rivaroxaban regimen

B) Usefulness of extended thromboprophylaxis remains uncertain (low incidence of events and lack of effect on VTE–related death)

FUTURE STUDIES

A. USE ALL CAUSE MORTALITY

B. STRATEGY MINOR BLEEDING TO PREVENT HEART ATTACK EQUASITION

C. FOCUS ON HIGH RISK PATIENTS INSTEAD OF REDUCTION THE DRUG DOSE

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Thank you for your attention !