¿Qué hay de nuevo en antitrombosis?

- **Fibrilación auricular**
- **Clopidogrel y omeprazol**
- **Enfermedad tromboembólica venosa**

REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Improving Stroke Risk Stratification in Atrial Fibrillation

Gregory Y. H. Lip, MD,[a] Jonathan L. Halperin, MD[b]

[a]*University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, England;* [b]*The Cardiovascular Institute, Mount Sinai Medical Center, New York, New York.*

Am J Med; 2010: 123, 484-488

CLINICAL SIGNIFICANCE

- Current stroke risk stratification schema for atrial fibrillation have many limitations.
- Rather than focusing on identifying "high-risk" patients, we should focus on the optimal identification of "low-risk" patients with atrial fibrillation.
- A simple, novel risk factor-based approach involving a simple scoring system (CHA_2DS_2-VASc) demonstrates improvement over previous schemes in identifying high-risk subjects, whereas those designated "low risk" rarely developed thromboembolism and only a small proportion are classified as "intermediate risk."

Table 9. Stroke Risk in Patients With Nonvalvular AF Not Treated With Anticoagulation According to the $CHADS_2$ Index

$CHADS_2$ Risk Criteria	Score
Prior stroke or TIA	2
Age >75 years	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1

TABLE 13. Antithrombotic Therapy for Patients With Atrial Fibrillation

Risk Category	Recommended Therapy
No risk factors	Aspirin, 81 to 325 mg daily
One moderate-risk factor	Aspirin, 81 to 325 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5)
Any high-risk factor or more than 1 moderate-risk factor	Warfarin (INR 2.0 to 3.0, target 2.5)*

$CHADS_2$ score	Patients (n = 1733)	Adjusted stroke rate (%/year)[a] (95% confidence interval)
0	120	1.9 (1.2–3.0)
1	463	2.8 (2.0–3.8)
2	523	4.0 (3.1–5.1)
3	337	5.9 (4.6–7.3)
4	220	8.5 (6.3–11.1)
5	65	12.5 (8.2–17.5)
6	5	18.2 (10.5–27.4)

Table 8 CHA_2DS_2VASc score and stroke rate

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

Table 9 Approach to thromboprophylaxis in patients with AF

Risk category	CHA_2DS_2-VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥2 'clinically relevant non-major' risk factors	≥ 2	OAC[a]
One 'clinically relevant non-major' risk factor	1	Either OAC[a] or aspirin 75–325 mg daily. Preferred: OAC rather than aspirin.
No risk factors	0	Either aspirin 75–325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.

What do the RE-LY, AVERROES and ROCKET-AF trials tell us for stroke prevention in atrial fibrillation?

Ingo Ahrens[1]; Gregory Y. H. Lip[2]; Karlheinz Peter[3]

[1]Innere Medizin III, Kardiologie und Angiologie, Universitätsklinik Freiburg, Germany; [2]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; [3]Atherothrombosis & Vascular Biology, Baker IDI Heart and Diabetes Institute, Melbourne,Victoria, Australia

Thromb Haemost 2011; 105: 574-578

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Table 1: The RE-LY, AVERROES and ROCKET-AF trials compared. The table is based on preliminary data presented for AVERROES and ROCKET-AF (8, 9).

Trial	RE-LY	AVERROES	ROCKET-AF
Drug and doses	Dabigatran etexilate 150 mg BID or 110 mg BID	Apixaban 5 mg BID	Rivaroxaban 20 mg QD (15 mg QD in patients with creatinine clearance 30–49 ml/min)
Number of patients	18,113	5,600	14,000
Design	Randomised, open label	Randomised, double-blind	Randomised double-blind, double dummy
Condition	AF within 6 months prior randomisation + 1 risk factor	AF within 6 months prior randomisation + 1 risk factor	AF within 6 months prior randomisation + 2 risk factors
Previous stroke / TIA (i.e. secondary prevention subgroup)	20%	13.5%	55%
Mean $CHADS_2$ score	2.1	2.1	3.5
Warfarin naive	50.4%	60.5%	37.5%
Comparator	Dose adjusted warfarin (INR 2.0–3.0, 67% of time in range)	Aspirin (81–324 mg QD)	Dose adjusted warfarin (INR 2.0–3.0, 57.8% of time in range)

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Primary endpoint: Stroke and systemic embolism (in % per year)	1.71% warfarin 1.54% dabigatran 110 mg (p=0.34) 1.11% dabigatran 150 mg (p<0.001)	3.9% aspirin 1.7% apixaban (p<0.001)	2.42% warfarin 2.12% rivaroxaban (p=0.117)
Major bleeding events	3.57% warfarin 2.87% dabigatran 110 mg (p=0.003) 3.32% dabigatran 150 mg (p=0.31)	1.2% aspirin 1.4% apixaban (p=0.33)	3.45% warfarin 3.6% rivaroxaban (p=0.576)
ICH (in % per year)	0.74% warfarin 0.23% dabigatran 110 mg (p<0.001) 0.3% dabigatran 150 mg (p<0.001)	0.3% aspirin 0.4% apixaban (p=0.83)	0.74% warfarin 0.49% rivaroxaban (p=0.019)
Comment	Dabigatran 110 mg non-inferior to warfarin with 20% less major bleeding events and significantly less ICH Dabigatran 150 mg superior to warfarin with similar rate of major bleeding and significantly less ICH	Apixaban superior to aspirin, with similar rate of major bleeding (and ICH) and better tolerated (with less discontinuations)	Rivaroxaban non-inferior to warfarin, with non-significant superiority on intention to treat analysis, but superiority achieved with on-treatment analysis

ICH = intracranial haemorrhage, INR = international normalised ratio, TIA = temporary ischaemic attack.

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- Anticoagulación en ETV

Interaction of Clopidogrel and Omeprazole

TO THE EDITOR: The label for clopidogrel warns physicians to "avoid concomitant use of . . . strong or moderate CYP2C19 inhibitors." Such inhibitors (e.g., omeprazole) decrease the formation of the active metabolite of clopidogrel, the source of its antiplatelet effects.

Mary Ross Southworth, Pharm.D.
Robert Temple, M.D.
Food and Drug Administration
Silver Spring, MD

No potential conflict of interest relevant to this letter was reported.

1. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or

ORIGINAL ARTICLE

Concomitant Use of Proton Pump Inhibitors and Clopidogrel in Patients With Coronary, Cerebrovascular, or Peripheral Artery Disease in the Factores de Riesgo y ENfermedad Arterial (FRENA) Registry

Juan Francisco Sánchez Muñoz-Torrero, MD, PhD, Domingo Escudero, MD, PhD,† Carmen Suárez, MD, PhD,‡ Carmen Sanclemente, MD,§ Ma Teresa Pascual, MD,‖ José Zamorano, MD, PhD,¶ Javier Trujillo-Santos, MD, PhD,** and Manuel Monreal, MD, PhD‖ the Factores de Riesgo y ENfermedad Arterial (FRENA) Investigators*

Annals of Internal Medicine

ARTICLE

Outcomes With Concurrent Use of Clopidogrel and Proton-Pump Inhibitors

A Cohort Study

Wayne A. Ray, PhD; Katherine T. Murray, MD; Marie R. Griffin, MD, MPH; Cecilia P. Chung, MD, MPH; Walter E. Smalley, MD, MPH; Kathi Hall, BS; James R. Daugherty, MS; Lisa A. Kaltenbach, MS; and C. Michael Stein, MB, ChB

Figure 1. **HRs for gastroduodenal and other bleeding, according to PPI use.**

Bleeding Hospitalization: Site of Bleeding

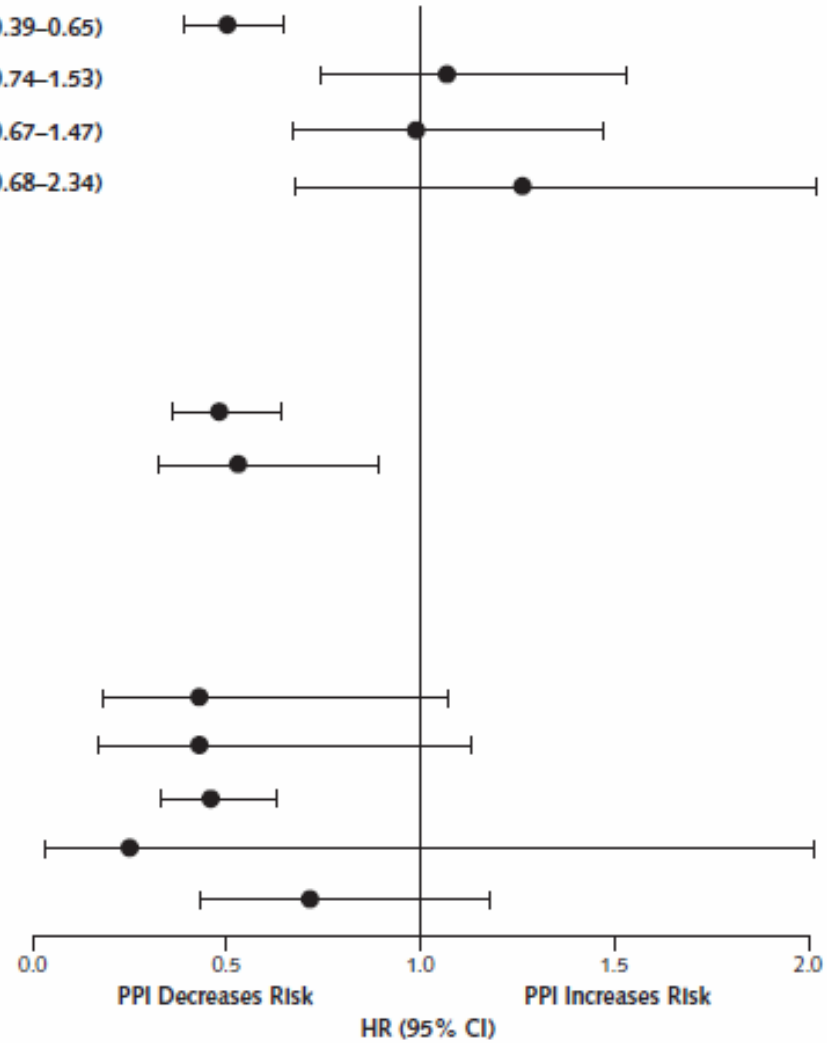
	No PPI (9621 Person-Years) Events (Rate*)	PPI (7688 Person-Years) Events (Rate*)	HR (95% CI)
Gastroduodenal	117 (12.2)	63 (8.2)	0.50 (0.39–0.65)
Other	108 (11.2)	117 (15.2)	1.07 (0.74–1.53)
Other GI	76 (7.9)	81 (10.5)	0.99 (0.67–1.47)
Other non-GI	32 (3.3)	36 (4.7)	1.26 (0.68–2.34)

Gastroduodenal Bleeding: PPI Dose

	Person-Years (Events)	HR (95% CI)
Low	5974 (45)	0.48 (0.36–0.64)
High	1490 (14)	0.53 (0.32–0.89)

Gastroduodenal Bleeding: Individual PPIs

	Person-Years (Events)	HR (95% CI)
Esomeprazole	747 (5)	0.43 (0.18–1.07)
Omeprazole	704 (5)	0.43 (0.16–1.13)
Pantoprazole	4629 (34)	0.46 (0.33–0.63)
Rabeprazole	288 (1)	0.25 (0.03–2.01)
Lansoprazole	1096 (14)	0.71 (0.43–1.18)



GI = gastrointestinal; HR = hazard ratio; PPI = proton-pump inhibitor.
* Rate is per 1000 person-years. Analysis by PPI dose and individual drug excludes person-time with concurrent use of multiple PPIs.

Figure 2. **HRs for serious CVD, according to PPI use.**

Serious CVD: Type

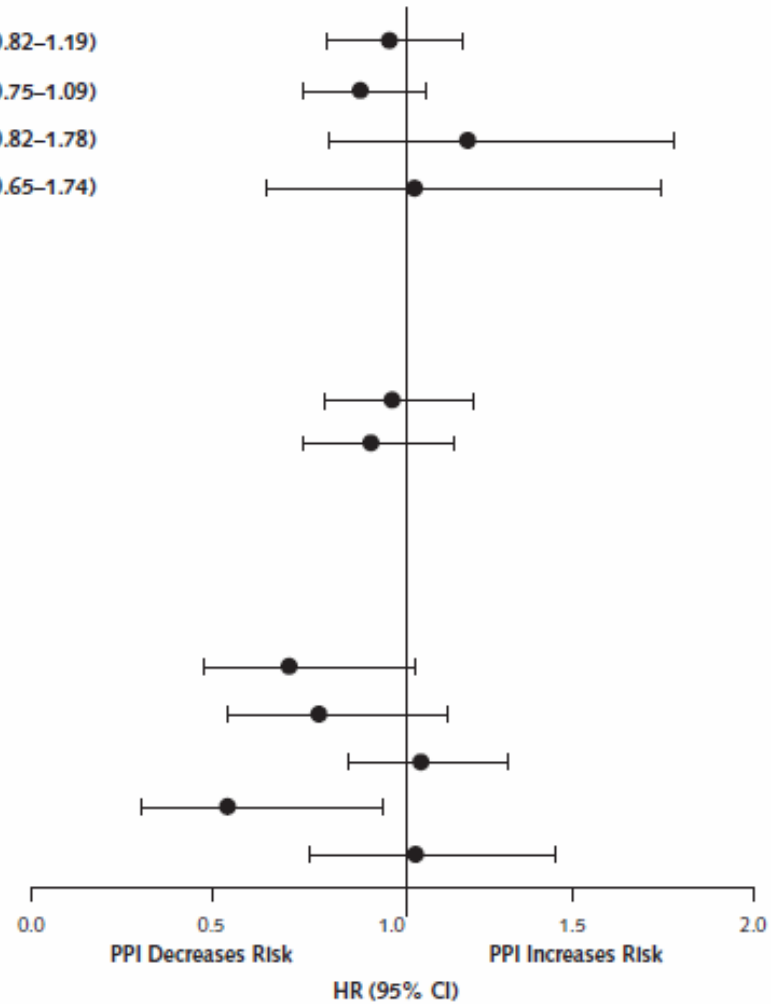
	No PPI (8995 Person-Years) Events (Rate*)	PPI (7226 Person-Years) Events (Rate*)	HR (95% CI)
All	580 (64.5)	461 (63.8)	0.99 (0.82–1.19)
AMI/SCD	403 (44.8)	292 (40.4)	0.91 (0.75–1.09)
Stroke	97 (10.8)	105 (14.5)	1.21 (0.82–1.78)
Other CV death	80 (8.9)	64 (8.9)	1.06 (0.65–1.74)

Serious CVD: PPI Dose

	Person-Years (Events)	HR (95% CI)
Low	5603 (359)	1.00 (0.81–1.22)
High	1413 (84)	0.94 (0.75–1.17)

Serious CVD: Individual PPIs

	Person-Years (Events)	HR (95% CI)
Esomeprazole	690 (30)	0.71 (0.48–1.06)
Omeprazole	660 (41)	0.79 (0.54–1.15)
Pantoprazole	4349 (272)	1.08 (0.88–1.32)
Rabeprazole	275 (9)	0.54 (0.30–0.97)
Lansoprazole	1042 (91)	1.06 (0.77–1.45)



AMI = acute myocardial infarction; CV = cardiovascular; CVD = cardiovascular disease; HR = hazard ratio; PPI = proton-pump inhibitor; SCD = sudden cardiac death.

* Rate is per 1000 person-years. Analysis by PPI dose and individual drug excludes person-time with concurrent use of multiple PPIs.

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- Clopidogrel y omeprazol
- **Anticoagulación en ETV**

Extended-Duration Venous Thromboembolism Prophylaxis in Acutely Ill Medical Patients With Recently Reduced Mobility

A Randomized Trial

Russell D. Hull, MBBS; Sebastian M. Schellong, MD; Victor F. Tapson, MD; Manuel Monreal, MD; Meyer-Michel Samama, MD, PharmD; Philippe Nicol, PhD; Eric Vicaut, MD, PhD; Alexander G.G. Turpie, MD; and Roger D. Yusen, MD, MPH, for the EXCLAIM (Extended Prophylaxis for Venous ThromboEmbolism in Acutely Ill Medical Patients With Prolonged Immobilization) study*

Context

Four weeks of enoxaparin therapy reduces VTE incidence more than 1 week of treatment in surgical patients at high risk for VTE. The same has not yet been shown for medical patients.

Contribution

Adding 28 days of enoxaparin treatment to an initial 10-day course reduced VTE incidence more than it increased major bleeding events in female, older, or sedentary patients with acute medical illness.

Caution

Trial eligibility criteria had to be modified after interim analyses suggested that extended-duration enoxaparin did more harm than good.

Implication

Extended-duration enoxaparin seems to have a favorable benefit–risk ratio in high-risk subgroups of patients with acute medical illness.

—The Editors

ORIGINAL ARTICLE

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

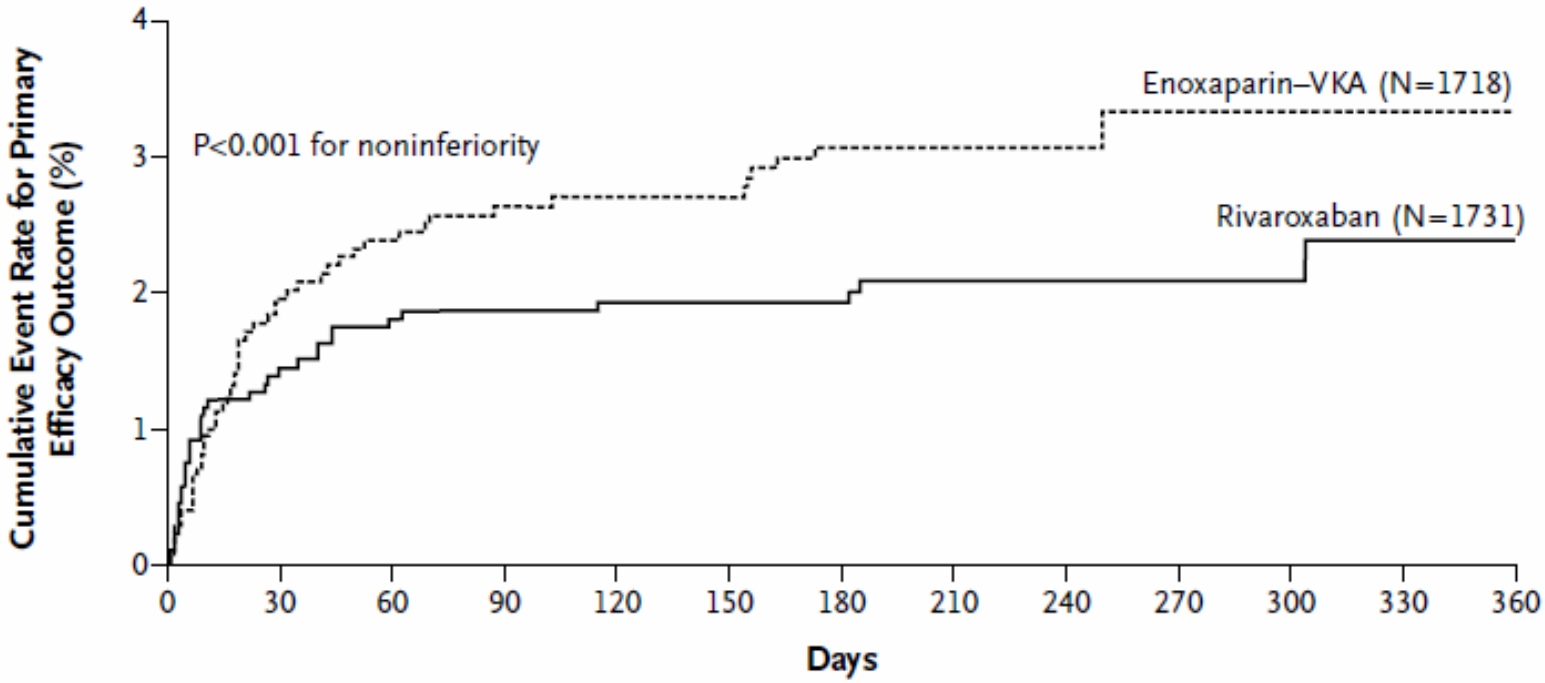
The EINSTEIN Investigators*

METHODS

We conducted an open-label, randomized, event-driven, noninferiority study that compared oral rivaroxaban alone (15 mg twice daily for 3 weeks, followed by 20 mg once daily) with subcutaneous enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for 3, 6, or 12 months in patients with acute, symptomatic DVT. In parallel, we carried out a double-blind, randomized, event-driven

N Engl J Med 2010;363:2499-510.

A **Acute DVT Study**



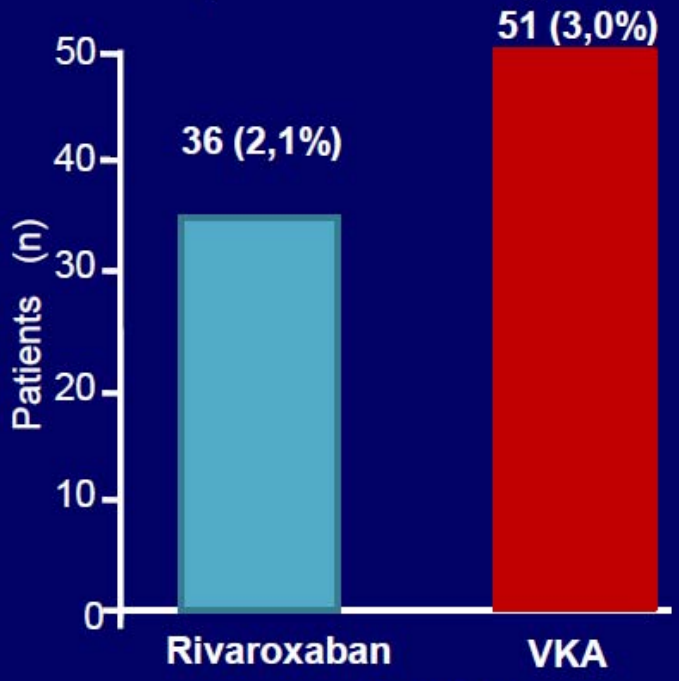
No. at Risk													
Rivaroxaban	1731	1668	1648	1621	1424	1412	1220	400	369	363	345	309	266
Enoxaparin–VKA	1718	1616	1581	1553	1368	1358	1186	380	362	337	325	297	264

EINSTEIN DVT

Rivaroxaban 15 mg bid / 3wks
20 mg od for 3, 6, 12 mo
Max. 2 days pretreatment LMWH/Fonda

I°EP: Sympt. rec. VTE =
rec. DVT + non-fatal PE + fatal PE

HR 0.68; 95% CI: 0.44 – 1.04
p < 0.0001 for non-inferiority



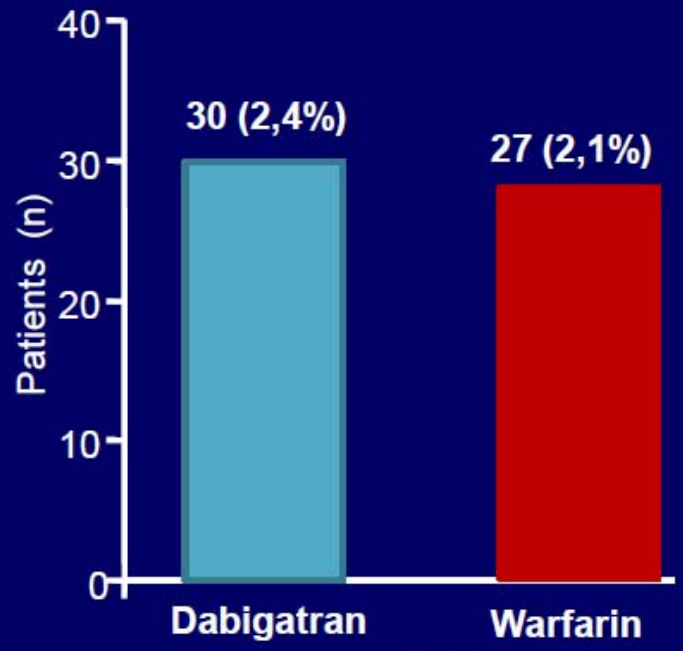
N=3449 Pat.

RECOVER™
Study of treatment of venous thromboembolism

Dabigatran 150 mg bid / 6mo
5-10 days pretreatment LMWH/Fonda

I°EP: Rec. sympt. VTE + VTE assoc. death

HR 1.10; 95% CI: 0.65 – 1.84
p < 0.001 for non-inferiority



N=2539 Pat.

Data from Schulman (2009) N Engl J Med 361: 2342-2352

Therapeutic Potential of Oral Factor Xa Inhibitors

Elaine M. Hylek, M.D., M.P.H.

thrombin. The potential impact of these oral, highly specific, fixed-dose drugs that do not require routine monitoring will no doubt be substantial. Currently, millions of people worldwide are relegated to receiving no therapy or therapy that has been proven to be ineffective, because they lack access to the monitoring expertise needed to safely and effectively administer warfarin. It is conceivable that the oral factor Xa inhibitors, as compared with warfarin, will prove to be safer in clinical practice because they are administered in fixed doses, do not interfere with diet, and have fewer interactions with other drugs. Given the nine different tablet strengths of warfarin, transitions in care settings and fluctuations in health status invariably create opportunities for unintended harm. A growing

Translating the efficacy and safety that have been shown in clinical trials to real-world practice is often a challenge because, as compared with patients in real-world practices, participants in trials are usually younger, have less medically complex illnesses, are more likely to be adherent, and have been specifically selected on the basis of having a lower risk of bleeding. Concomitant antiplatelet therapy is either discouraged or considered to be an exclusion criterion. The