DABİGATRAN

DR. ERDEM DİKER

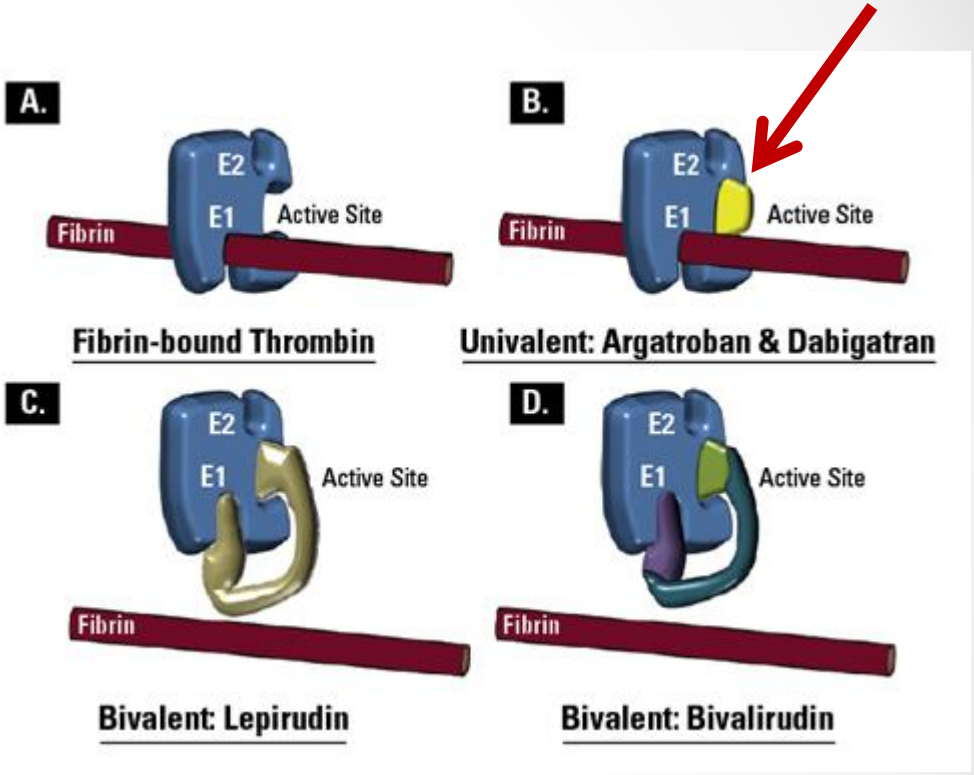
DİREK TROMBİN İNHİBİTÖRLERİ

'BİVALENT' TROMBİN İNHİBİTÖRLERİ:

- Hirudin
- Bivaluridin
- Lepirudin

'UNİVALENT' TROMBİN İNHİBİTÖRLERİ

- Argatroban
- Ximelagatran
- Melagatran
- **DABİGATRAN**



The NEW ENGLAND JOURNAL of MEDICINE

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Dabigatran versus Warfarin in Patients with Atrial Fibrillation

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Table 2. Efficacy Outcomes, According to Treatment Group.

Event	Dabigatran, 110 mg (N=6015)		Dabigatran, 150 mg (N=6076)		Warfarin (N=6022)		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*						
Stroke or systemic embolism*	182	1.53	134	1.11	199	1.69	0.91 (0.74–1.11)	<0.001 for noninferiority, 0.34	0.66 (0.53–0.82)	<0.001 for noninferiority, <0.001	0.73 (0.58–0.91)	0.005
Stroke	171	1.44	122	1.01	185	1.57	0.92 (0.74–1.13)	0.41	0.64 (0.51–0.81)	<0.001	0.70 (0.56–0.89)	0.003
Hemorrhagic	14	0.12	12	0.10	45	0.38	0.31 (0.17–0.56)	<0.001	0.26 (0.14–0.49)	<0.001	0.85 (0.39–1.83)	0.67
Ischemic or unspecified	159	1.34	111	0.92	142	1.20	1.11 (0.89–1.40)	0.35	0.76 (0.60–0.98)	0.03	0.69 (0.54–0.88)	0.002
Nondisabling stroke	60	0.50	44	0.37	69	0.58	0.86 (0.61–1.22)	0.40	0.62 (0.43–0.91)	0.01	0.72 (0.49–1.07)	0.10
Disabling or fatal stroke	112	0.94	80	0.66	118	1.00	0.94 (0.73–1.22)	0.65	0.66 (0.50–0.88)	0.005	0.70 (0.53–0.94)	0.02
Myocardial infarction	86	0.72	89	0.74	63	0.53	1.35 (0.98–1.87)	0.07	1.38 (1.00–1.91)	0.048	1.02 (0.76–1.38)	0.88
Pulmonary embolism	14	0.12	18	0.15	11	0.09	1.26 (0.57–2.78)	0.56	1.61 (0.76–3.42)	0.21	1.27 (0.63–2.56)	0.50
Hospitalization	2311	19.4	2430	20.2	2458	20.8	0.92 (0.87–0.97)	0.003	0.97 (0.92–1.03)	0.34	1.06 (1.00–1.12)	0.04
Death from vascular causes	289	2.43	274	2.28	317	2.69	0.90 (0.77–1.06)	0.21	0.85 (0.72–0.99)	0.04	0.94 (0.79–1.11)	0.44
Death from any cause	446	3.75	438	3.64	487	4.13	0.91 (0.80–1.03)	0.13	0.88 (0.77–1.00)	0.051	0.97 (0.85–1.11)	0.66

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. P values are for superiority, unless otherwise indicated. The modified Rankin scale (on which scores can range from 0 [no neurologic disability] to 5 [severe disability], with 6 indicating a fatal stroke) was used to categorize stroke: nondisabling stroke was defined by a score of 0 to 2, and disabling or fatal stroke, a score of 3 to 6.

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Table 3. Safety Outcomes, According to Treatment Group.*

Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*						
Major bleeding	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31	1.16 (1.00–1.34)	0.052
Life threatening	145	1.22	175	1.45	212	1.80	0.68 (0.55–0.83)	<0.001	0.81 (0.66–0.99)	0.04	1.19 (0.96–1.49)	0.11
Non–life threatening	198	1.66	226	1.88	208	1.76	0.94 (0.78–1.15)	0.56	1.07 (0.89–1.29)	0.47	1.14 (0.95–1.39)	0.17
Gastrointestinal†	133	1.12	182	1.51	120	1.02	1.10 (0.86–1.41)	0.43	1.50 (1.19–1.89)	<0.001	1.36 (1.09–1.70)	0.007
Minor bleeding	1566	13.16	1787	14.84	1931	16.37	0.79 (0.74–0.84)	<0.001	0.91 (0.85–0.97)	0.005	1.16 (1.08–1.24)	<0.001
Major or minor bleeding	1740	14.62	1977	16.42	2142	18.15	0.78 (0.74–0.83)	<0.001	0.91 (0.86–0.97)	0.002	1.16 (1.09–1.23)	<0.001
Intracranial bleeding	27	0.23	36	0.30	87	0.74	0.31 (0.20–0.47)	<0.001	0.40 (0.27–0.60)	<0.001	1.32 (0.80–2.17)	0.28
Extracranial bleeding	299	2.51	342	2.84	315	2.67	0.94 (0.80–1.10)	0.45	1.07 (0.92–1.25)	0.38	1.14 (0.97–1.33)	0.11
Net clinical benefit outcome‡	844	7.09	832	6.91	901	7.64	0.92 (0.84–1.02)	0.10	0.91 (0.82–1.00)	0.04	0.98 (0.89–1.08)	0.66

Newly Identified Events in the RE-LY Trial

TO THE EDITOR: We wish to update our article about the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial (Sept. 17, 2009, issue).[1] After the database was locked on August 15, 2009, we identified several additional primary efficacy and safety outcome events during routine clinical site closure visits. These events included two systemic embolic events and nine major hemorrhages. Subsequently, after discussions with the Food and Drug Administration, the primary and secondary efficacy and safety data were checked for consistency, and the study database was reevaluated for possible underreporting of events. To achieve this, all free text, outcomes, and adverse events in the database were searched with the use of multiple algorithms to identify any symptom that might suggest the possibility of any primary or secondary event or bleeding. This included an examination of all decreases in the hemoglobin level by more than 2 g per deciliter between visits, other markers of potential bleeding, new pathologic Q waves on routine electrocardiography (ECG), and any report of weakness or other symptoms that might be potentially related to a stroke. This process resulted in the identification of 81 new events in 80 patients. These included 1 stroke, 1 systemic embolic event, 4 clinical myocardial infarctions, 1 pulmonary embolism, 5 transient ischemic attacks, and 69 major hemorrhages.

Although silent myocardial infarction, defined as the new appearance of pathologic Q waves on ECG, was part of the RE-LY definition of myocardial infarction, no cases of silent myocardial infarction were reported by investigators during the course of the study. However, review of the routine ECG reports revealed 28 cases fulfilling the criteria for silent myocardial infarction.

All these newly identified events were adjudicated in a blinded fashion and in accordance with the study protocol. Two rounds of data entry were performed for all data on the international normalized ratio (INR), for purposes of validation. This resulted in a change in the mean percentage

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Table 1. Published and Revised Data for Primary Efficacy and Safety Outcomes and Myocardial Infarction, According to Treatment Group.*

Event	Dabigatran, 110 mg (N=6015)		Dabigatran, 150 mg (N=6076)		Warfarin (N=6022)		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*				
Stroke or systemic embolism										
Published	182	1.53	134	1.11	199	1.69	0.91 (0.74–1.11)	0.34	0.66 (0.53–0.82)	<0.001
Revised	183	1.54	134	1.11	202	1.71	0.90 (0.74–1.10)	0.30	0.65 (0.52–0.81)	<0.001
Major bleeding										
Published	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31
Revised	342	2.87	399	3.32	421	3.57	0.80 (0.70–0.93)	0.003	0.93 (0.81–1.07)	0.32
Myocardial infarction										
Published	86	0.72	89	0.74	63	0.53	1.35 (0.98–1.87)	0.07	1.38 (1.00–1.91)	0.048
Revised	98	0.82	97	0.81	75	0.64	1.29 (0.96–1.75)	0.09	1.27 (0.94–1.71)	0.12

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. P values are for superiority. CI denotes confidence interval.

ONLINE FIRST

Dabigatran Association With Higher Risk of Acute Coronary Events

Meta-analysis of Noninferiority Randomized Controlled Trials

Ken Uchino, MD; Adrian V. Hernandez, MD, PhD

Background: The original RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) trial suggested a small increased risk of myocardial infarction (MI) with the use of dabigatran etexilate vs warfarin in patients with atrial fibrillation. We systematically evaluated the risk of MI or acute coronary syndrome (ACS) with the use of dabigatran.

Methods: We searched PubMed, Scopus, and the Web of Science for randomized controlled trials of dabigatran that reported on MI or ACS as secondary outcomes. The fixed-effects Mantel-Haenszel (M-H) test was used to evaluate the effect of dabigatran on MI or ACS. We expressed the associations as odds ratios (ORs) and their 95% CIs.

Results: Seven trials were selected (N=30 514), including 2 studies of stroke prophylaxis in atrial fibrillation, 1 in acute venous thromboembolism, 1 in ACS, and 3 of short-term prophylaxis of deep venous thrombosis. Control arms included warfarin, enoxaparin, or placebo administration. Dabigatran was significantly associated with a higher risk of MI or ACS than that seen with agents used in the control group (dabigatran, 237 of 20 000 [1.19%] vs control, 83 of 10 514 [0.79%]; OR_{M-H}, 1.33; 95% CI, 1.03-1.71; $P=.03$). The risk of MI or ACS was similar when using revised RE-LY trial results (OR_{M-H}, 1.27; 95% CI, 1.00-1.61; $P=.05$) or after exclusion of short-term trials (OR_{M-H}, 1.33; 95% CI, 1.03-1.72; $P=.03$). Risks were not heterogeneous for all analyses ($I^2=0\%$; $P \geq .30$) and were consistent using different methods and measures of association.

Conclusions: Dabigatran is associated with an increased risk of MI or ACS in a broad spectrum of patients when tested against different controls. Clinicians should consider the potential of these serious harmful cardiovascular effects with use of dabigatran.

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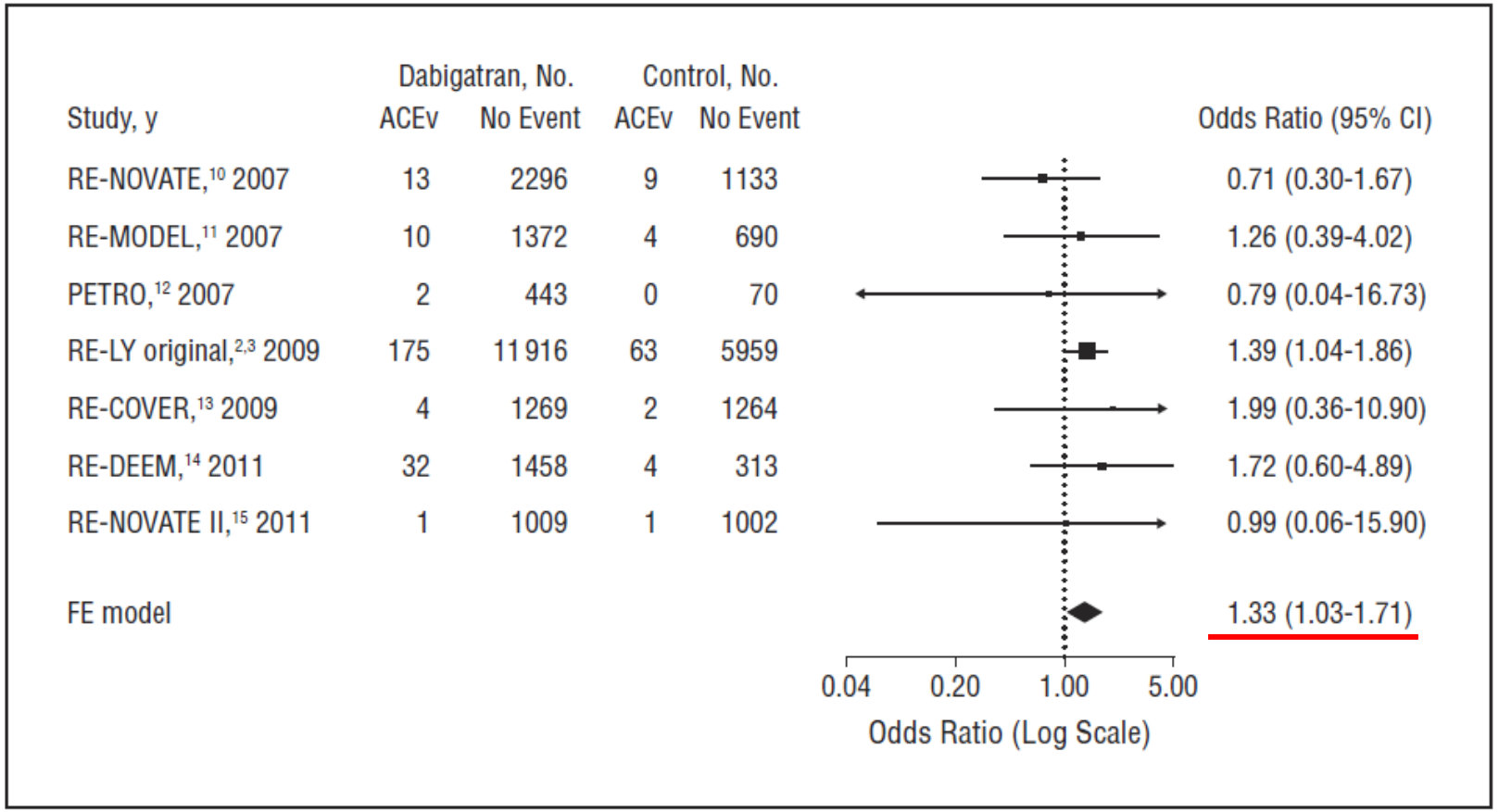

Figure 2. Risk of myocardial infarction and acute coronary syndrome across 7 studies, including original Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) results. ACEv indicates acute coronary events; FE, fixed effects; PETRO, Prevention of Embolic and Thrombotic Events in Patients With Persistent AF Study; rectangles, odds ratios; limit lines, 95% CIs; diamond, overall odds ratio and 95% CI; and arrows, 95% CIs that exceed the limits of the graph (0.04-5.00).

Myocardial Ischemic Events in Patients With Atrial Fibrillation Treated With Dabigatran or Warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) Trial

Stefan H. Hohnloser, MD; Jonas Oldgren, MD; Sean Yang, PhD; Lars Wallentin, MD; Michael Ezekowitz, MD; Paul Reilly, MD; John Eikelboom, MD; Martina Brueckmann, MD; Salim Yusuf, MD; Stuart J. Connolly, MD

Background—There is a modest risk of myocardial infarction (MI) and myocardial ischemic events in patients with atrial fibrillation.

Methods and Results—Data from the RE-LY study (Randomized Evaluation of Long-Term Anticoagulation Therapy) were used to report rates of MI, unstable angina, cardiac arrest, and cardiac death and the prespecified net clinical benefit and treatment effects of dabigatran versus warfarin. MI occurred at annual rates of 0.82% and 0.81% with dabigatran 110 or 150 mg BID compared with 0.64% with warfarin (hazard ratio [HR] 1.29, 95% confidence interval [CI] 0.96–1.75, P=0.09 for dabigatran 110 mg; HR 1.27, 95% CI 0.94–1.71, P=0.12 for dabigatran 150 mg). Annual rates of a composite of MI, unstable angina, cardiac arrest, and cardiac death were 3.16% per year with dabigatran 110 mg, 3.33% per year with dabigatran 150 mg, and 3.41% per year with warfarin (HR versus warfarin 0.93, 95% CI 0.80–1.06, P=0.28 for dabigatran 110 mg and HR 0.98, 95% CI 0.85–1.12, P=0.77 for dabigatran 150 mg). Events prespecified as "net clinical benefit" (all strokes, systemic embolism, MI, pulmonary embolism, major bleeding, and all-cause death) occurred at a rate of 7.34% per year with dabigatran 110 mg, 7.11% per year with dabigatran 150 mg, and 7.91% per year with warfarin (HR 0.92, 95% CI 0.84–1.01, P=0.09 for dabigatran 110 mg and HR 0.90, 95% CI 0.82–0.99, P=0.02 for dabigatran 150 mg). The relative effects of dabigatran versus warfarin on myocardial ischemic events were consistent in patients with or without a baseline history of MI or coronary artery disease.

Conclusions—There was a nonsignificant increase in MI with dabigatran compared with warfarin, but other myocardial ischemic events were not increased. Treatment effects of dabigatran were consistent in patients at higher and lower risk of myocardial ischemic events.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT 00262600.

(*Circulation*. 2012;125:669-676.)

Table 1. Cardiac Events During RE-LY

	Dabigatran 110 mg BID (n=6015)		Dabigatran 150 mg BID (n=6076)		Warfarin (n=6022)		Dabigatran 110 mg BID vs Warfarin			Dabigatran 150 mg BID vs Warfarin			Dabigatran vs Warfarin		
	n	Rate per 100 Person-Years	n	Rate per 100 Person-Years	n	Rate per 100 Person-Years	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Total MI	98	0.82	97	0.81	75	0.64	1.29	0.96–1.75	0.09	1.27	0.94–1.71	0.12	1.28	0.98–1.67	0.07
Clinical MI	87	0.73	89	0.74	66	0.56	1.30	0.95–1.80	0.10	1.32	0.96–1.81	0.09	1.31	0.99–1.74	0.06
Silent MI	11	0.09	8	0.07	9	0.08	1.22	0.50–2.93	0.66	0.87	0.34–2.27	0.72	1.04	0.47–2.31	0.92
Fatal MI (death within 30 d)	16	0.13	13	0.11	12	0.10	1.32	0.63–2.80	0.46	1.06	0.49–2.33	0.88	1.19	0.61–2.34	0.61
Other myocardial events															
UA	133	1.12	163	1.35	166	1.41	0.79	0.63–1.00	0.047	0.96	0.78–1.20	0.74	0.88	0.73–1.06	0.19
Cardiac death	177	1.49	161	1.34	174	1.48	1.01	0.82–1.24	0.94	0.91	0.73–1.12	0.37	0.96	0.80–1.15	0.64
Cardiac arrest	23	0.19	25	0.21	25	0.21	0.91	0.52–1.60	0.74	0.98	0.56–1.70	0.94	0.94	0.58–1.53	0.81
MI, UA, cardiac arrest, or cardiac death	376	3.16	401	3.33	402	3.41	0.93	0.80–1.06	0.28	0.98	0.85–1.12	0.77	0.95	0.84–1.07	0.42
PCI or CABG surgery	48	0.40	44	0.37	46	0.39	1.04	0.69–1.55	0.87	0.94	0.62–1.42	0.76	0.99	0.69–1.40	0.93
MI, UA, CABG, PCI, cardiac arrest, or cardiac death	402	3.38	425	3.53	424	3.60	0.94	0.82–1.07	0.36	0.98	0.86–1.13	0.82	0.96	0.85–1.08	0.50
Stroke, SEE, MI, UA, CABG, PCI, cardiac arrest, cardiac death	567	4.76	538	4.47	601	5.10	0.93	0.83–1.05	0.24	0.88	0.78–0.98	0.03	0.90	0.82–1.00	0.05
Net clinical benefit	873	7.34	855	7.11	933	7.91	0.92	0.84–1.01	0.09	0.90	0.82–0.99	0.02	0.91	0.84–0.99	0.02

Efficacy and Safety of Dabigatran Etexilate and Warfarin in "Real-World" Patients With Atrial Fibrillation

A Prospective Nationwide Cohort Study

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Flemming Skjøth, MSC, PHD,* Karen Margrete Due, MSC,* Torbjörn Callréus, MD, PHD,‡
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Aalborg and Copenhagen, Denmark; and Birmingham, United Kingdom

Objectives The aim of this study was to assess the efficacy and safety in an "everyday clinical practice" population of anticoagulant-naïve patients with atrial fibrillation (AF) treated with dabigatran etexilate after its post-approval availability in Denmark, compared with warfarin.

Background Concerns have been raised about an excess of bleeding events or myocardial infarction (MI) among patients treated with the new oral direct thrombin inhibitor, dabigatran etexilate.

Methods From the Danish Registry of Medicinal Product Statistics, we identified a dabigatran-treated group and a 1:2 propensity-matched warfarin-treated group of 4,978 and 8,936, respectively. Comparisons on efficacy and safety outcomes were made on the basis of Cox-proportional hazards models stratified on propensity-matched groups.

Results Stroke and systemic embolism were not significantly different between warfarin- and dabigatran-treated patients. Adjusted mortality was significantly lower with both dabigatran doses (110 mg b.i.d., propensity-match group stratified hazard ratio [aHR]: 0.79, 95% confidence interval [CI]: 0.65 to 0.95; 150 mg b.i.d., aHR: 0.57, 95% CI: 0.40 to 0.80), when compared with warfarin. Pulmonary embolism was lower compared with warfarin for both doses of dabigatran. Less intracranial bleeding was seen with both dabigatran doses (110 mg b.i.d., aHR: 0.24, 95% CI: 0.08 to 0.56; 150 mg b.i.d., aHR: 0.08, 95% CI: 0.01 to 0.40). The incidence of MI was lower with both dabigatran doses (110 mg b.i.d., aHR: 0.30, 95% CI: 0.18 to 0.49; 150 mg b.i.d., aHR: 0.40, 95% CI: 0.21 to 0.70). Gastrointestinal bleeding was lower with dabigatran 110 mg b.i.d. (aHR: 0.60, 95% CI: 0.37 to 0.93) compared with warfarin but not dabigatran 150 mg b.i.d. The main findings were broadly consistent in a subgroup analysis of dabigatran users with ≥1-year follow-up (median follow-up 13.9 months [interquartile range: 12.6 to 15.3 months]).

Conclusions In this "everyday clinical practice" post-approval nationwide clinical cohort, there were similar stroke/systemic embolism and major bleeding rates with dabigatran (both doses) compared with warfarin. Mortality, intracranial bleeding, pulmonary embolism, and MI were lower with dabigatran, compared with warfarin. We found no evidence of an excess of bleeding events or MI among dabigatran-treated patients in this propensity-matched comparison against warfarin, even in the subgroup with ≥1-year follow-up. (J Am Coll Cardiol 2013;61:2264–73)

Table 3 Subgroup Analysis on Dabigatran Users With More Than 1-Year Follow-Up

Outcome	Warfarin vs. Dabigatran 110 mg b.i.d. HR	95% CI	Warfarin vs. Dabigatran 150 mg b.i.d. HR	95% CI	p Value*
Stroke					
Crude	0.95	(0.62–1.41)	1.58	(1.06–2.30)	0.05
Adjusted	0.84	(0.53–1.31)	1.53	(0.96–2.43)	0.15
Death					
Crude	0.93	(0.72–1.18)	0.39	(0.25–0.59)	<0.0001
Adjusted	0.82	(0.62–1.06)	0.58	(0.35–0.92)	0.03
Myocardial infarction					
Crude	0.60	(0.33–1.02)	0.62	(0.30–1.14)	0.10
Adjusted	0.50	(0.26–0.89)	0.74	(0.34–1.48)	0.06
Major bleeding					
Crude	0.77	(0.51–1.14)	0.63	(0.36–1.02)	0.12
Adjusted	0.74	(0.47–1.14)	0.66	(0.36–1.14)	0.15
Gastrointestinal bleeding					
Crude	0.58	(0.30–1.02)	0.70	(0.34–1.29)	0.15
Adjusted	0.61	(0.30–1.13)	0.78	(0.35–1.59)	0.26

Dabigatran's 'Real-World' Data About Risk of Myocardial Infarction and Gastrointestinal Bleeding Contradicts With Randomized Trials

We read with great interest the article by Larsen et al. (1) examinir the safety of dabigatran, especially with regard to myocardi infarction (MI) and gastrointestinal bleeding using Danish nation databases. They report a remarkable, highly significant 60% to 70 risk reduction in MIs with dabigatran as compared with warfar ($p < 0.0001$). Similarly, they report a 40% reduction in incide... gastrointestinal bleeding with 110 mg dabigatran twice daily compared with warfarin, which was again statistically significant.

While examination of observational administrative datasets may sometimes be helpful to answer certain questions, the gold standard for determining drug safety and efficacy is careful analysis of all

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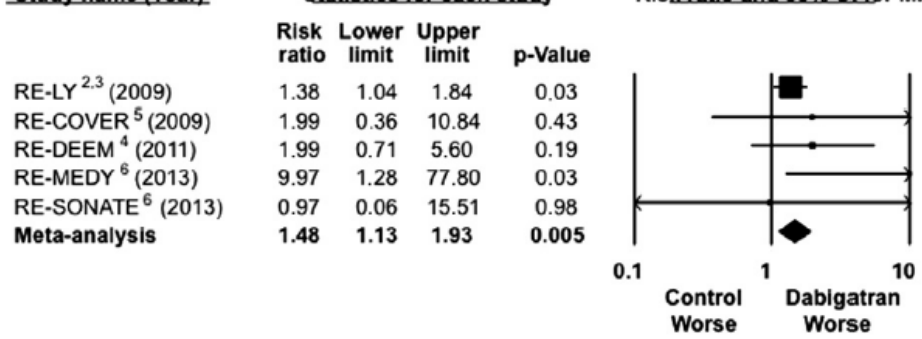

Figure 1 **Forest Plot for the Effect of Dabigatran Versus Control on Incident MI**

CI = confidence interval; MI = myocardial infarction; RE-COVER = Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism; RE-DEEM = RandomizEd Dabigatran Etexilate Dose Finding Study in Patients With Acute Coronary Syndromes Post Index Event With Additional Risk Factors for Cardiovascular Complications Also Receiving Aspirin and Clopidogrel: Multi-centre, Prospective, Placebo Controlled, Cohort Dose Escalation Study; RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy; RE-MEDY = A Phase III, Randomised, Multicenter, Double-blind, Parallel-group, Active Controlled Study to Evaluate the Efficacy and Safety of Oral Dabigatran Etexilate (150 mg bid) Compared to Warfarin (INR 2.0-3.0) for the Secondary Prevention of Venous Thromboembolism; RE-SONATE = Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etexilate in the Long-term Prevention of Recurrent Symptomatic Proximal Venous Thromboembolism in Patients With Symptomatic Deep-vein Thrombosis or Pulmonary Embolism.

Reply

Dabigatran's 'Real-World' Data About Risk of Myocardial Infarction and Gastrointestinal Bleeding Contradicts With Randomized Trials

Dr. Sipahi and colleagues express concern about the discrepancy of our observational study with randomized controlled studies, and point to residual confounding as a possible explanation. We have already discussed these issues in the paper (1), but will expand on our discussion in the following paragraph.

In observational studies of intended drug effects or safety, substantial confounding (by indication) is to be expected because the perceived risk is often closely related to the physician's choice of treatment (2). Where there is confounding, there is also the possibility of residual confounding. Taken to the extreme, heterogeneity in risk factors (measured or unmeasured) between treatment groups in key risk factors is a *possible* explanation for the observed associations. However, "possible" need not mean "plausible." Indeed, a careful choice of methods and principles can mitigate confounding concerns in observational studies (3).

In our study, we adopted a new-user design to ensure that meaningful comparisons were made (4). We explored both propensity

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http://dx.doi.org/10.1016/j.jacc.2013.05.067

Please note: Dr. Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, and Boehringer Ingelheim; and has been on the Speaker's Bureaus for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi. Drs. Larsen and Rasmussen have been on the Speaker's Bureaus for Bayer, BMS/Pfizer, and Boehringer Ingelheim. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Larsen TB, Rasmussen LH, Skjoth F, et al. Efficacy and safety of dabigatran etexilate and warfarin in 'real world' patients with atrial fibrillation: a prospective nationwide cohort study. J Am Coll Cardiol


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Welcome to Mini-Sentinel
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Dabigatran and Postmarketing Reports of Bleeding

Mary Ross Southworth, Pharm.D., Marsha E. Reichman, Ph.D., and Ellis F. Unger, M.D.

In the months following the approval of the oral anticoagulant dabigatran (Pradaxa, Boehringer Ingelheim) in October 2010, the Food and Drug Administration (FDA) received through the FDA Adverse Event Reporting System (FAERS) many reports of serious and fatal bleeding events associated with use of the drug. Because dabigatran is an anticoagulant, reports of bleeding were anticipated, but the rate of reported incidents

The RE-LY trial enrolled patients with nonvalvular atrial fibrillation and at least one risk factor for stroke. Dabigatran at a dose of 150 mg twice daily was shown to be superior to warfarin for reducing the combined rate of stroke and systemic embolism (1.1 vs. 1.7 per 100 patient-years) among these patients. Dabigatran resulted in a lower rate of both thrombotic and hemorrhagic strokes than warfarin, and the mortality rate was

would be reported after the product was approved, but the number of reports was sufficiently high to prompt the FDA to initiate a review of the spontaneous reports received by FAERS. We were concerned that postmarketing use of dabigatran might be different from its use in the RE-LY trial (e.g., different patient populations, dosing, concomitant medications, and degree of renal impairment) or that adjustments for renal func-

N Engl J Med 2013

Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.*

Analysis	Dabigatran			Warfarin		
	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)
Gastrointestinal hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,599	16	1.6	43,541	160	3.5
Sensitivity analysis without required diagnosis of atrial fibrillation	12,195	19	1.6	119,940	338	3.1
Intracranial hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,587	8	0.8	43,594	109	2.4
Sensitivity analysis without required diagnosis of atrial fibrillation	12,182	10	0.9	120,020	204	1.9

* Patients were included in the cohorts if, in the 183 days before the index dispensing of dabigatran or warfarin, they were enrolled in plans for drug and medical coverage and had been given a diagnosis of atrial fibrillation in any care setting. Patients were excluded from the cohorts if, in the 183 days before the index dispensing, they had a claim for an event of interest in an inpatient or emergency department setting or a claim for dispensing of dabigatran or warfarin. Events were assessed during drug exposure, from inpatient or emergency department settings only.

N Engl J Med 2013

Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation

David J. Graham, MD, MPH; Marsha E. Reichman, PhD; Michael Wernecke, BA; Rongmei Zhang, PhD; Mary Ross Southworth, PharmD; Mark Levenson, PhD; Ting-Chang Sheu, MPH; Katrina Mott, MHS; Margie R. Goulding, PhD; Monika Houstoun, PharmD, MPH; Thomas E. MaCurdy, PhD; Chris Worrall, BS; Jeffrey A. Kelman, MD, MMSc

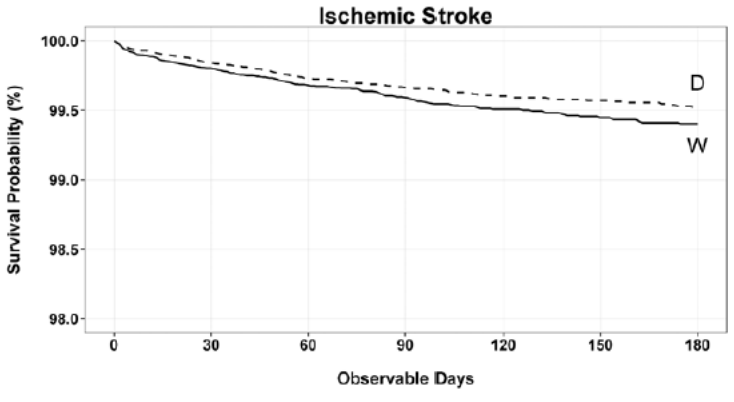
Background—The comparative safety of dabigatran versus warfarin for treatment of nonvalvular atrial fibrillation in general practice settings has not been established.

Methods and Results—We formed new-user cohorts of propensity score–matched elderly patients enrolled in Medicare who initiated dabigatran or warfarin for treatment of nonvalvular atrial fibrillation between October 2010 and December 2012. Among 134414 patients with 37587 person-years of follow-up, there were 2715 primary outcome events. The hazard ratios (95% confidence intervals) comparing dabigatran with warfarin (reference) were as follows: ischemic stroke, 0.80 (0.67–0.96); intracranial hemorrhage, 0.34 (0.26–0.46); major gastrointestinal bleeding, 1.28 (1.14–1.44); acute myocardial infarction, 0.92 (0.78–1.08); and death, 0.86 (0.77–0.96). In the subgroup treated with dabigatran 75 mg twice daily, there was no difference in risk compared with warfarin for any outcome except intracranial hemorrhage, in which case dabigatran risk was reduced. Most patients treated with dabigatran 75 mg twice daily appeared not to have severe renal impairment, the intended population for this dose. In the dabigatran 150-mg twice daily subgroup, the magnitude of effect for each outcome was greater than in the combined-dose analysis.

Conclusions—In general practice settings, dabigatran was associated with reduced risk of ischemic stroke, intracranial hemorrhage, and death and increased risk of major gastrointestinal hemorrhage compared with warfarin in elderly patients with nonvalvular atrial fibrillation. These associations were most pronounced in patients treated with dabigatran 150 mg twice daily, whereas the association of 75 mg twice daily with study outcomes was indistinguishable from warfarin except for a lower risk of intracranial hemorrhage with dabigatran. (***Circulation***. **2015;131:157-164. DOI: 10.1161/CIRCULATIONAHA.114.012061.**)

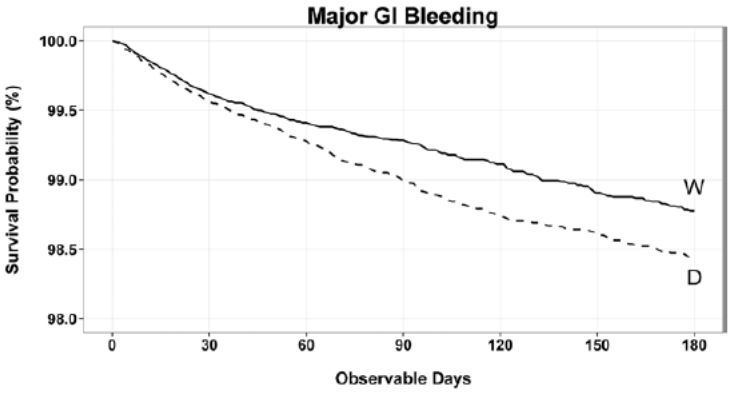
Key Words: anticoagulant ■ pharmacoepidemiology ■ safety ■ thrombin inhibitor ■ warfarin

Graham et al, Circulation. 2015;131:157-164.



Number at Risk

Warfarin (W)	67,207	60,238	40,757	31,740	17,550	13,812	11,389
Dabigatran (D)	67,207	61,498	34,258	25,686	17,365	13,715	11,208



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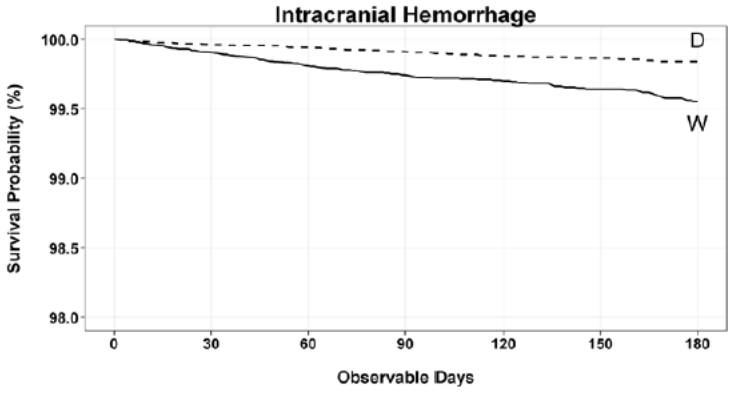

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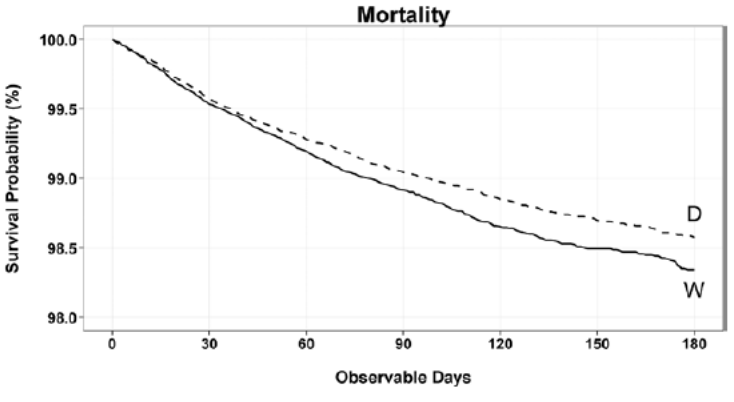

Number at Risk

Warfarin (W)	67,207	60,921	41,062	31,907	17,659	13,875	11,440

Graham et al, Circulation. 2015;131:157-164.

Table 2. Outcome Event Counts, Incidence Rates, and Adjusted Hazard Ratios With 95% CIs Comparing Propensity Score–Matched New-User Cohorts of Dabigatran and Warfarin Treated for Nonvalvular Atrial Fibrillation, With Warfarin as the Reference Group

	No. of Events		Incidence Rate per 1000 Person-Years		Adjusted Hazard Ratio (95% CI)	*P* Value
	Dabigatran	Warfarin	Dabigatran	Warfarin		
Primary outcomes						
Ischemic stroke	205	270	11.3	13.9	0.80 (0.67–0.96)	0.02
Major hemorrhage	777	851	42.7	43.9	0.97 (0.88–1.07)	0.50
Gastrointestinal	623	513	34.2	26.5	1.28 (1.14–1.44)	<0.001
Intracranial	60	186	3.3	9.6	0.34 (0.26–0.46)	<0.001
Intracerebral	44	142	2.4	7.3	0.33 (0.24–0.47)	<0.001
Acute myocardial infarction	285	327	15.7	16.9	0.92 (0.78–1.08)	0.29
Secondary outcomes						
All hospitalized bleeds	1079	1139	59.3	58.8	1.00 (0.92–1.09)	0.97
Mortality*	603	744	32.6	37.8	0.86 (0.77–0.96)	0.006

*For 1064 deaths not preceded by a primary study outcome, the adjusted hazard ratio (95% confidence interval [CI]) was 0.89 (0.79–1.00; *P*=0.051), whereas for 283 deaths occurring within 30 days after a primary outcome, the adjusted hazard ratio (95% CI) was 0.77 (0.61–0.98; *P*=0.03).

Graham et al, Circulation. 2015;131:157-164.

Research

Original Investigation

Risk of Bleeding With Dabigatran in Atrial Fibrillation

Inmaculada Hernandez, PharmD; Seo Hyon Baik, PhD; Antonio Piñera, MD; Yuting Zhang, PhD

IMPORTANCE It remains unclear whether dabigatran etexilate mesylate is associated with higher risk of bleeding than warfarin sodium in real-world clinical practice.

OBJECTIVE To compare the risk of bleeding associated with dabigatran and warfarin using Medicare data.

DESIGN, SETTING, AND PARTICIPANTS In this retrospective cohort study, we used pharmacy and medical claims in 2010 to 2011 from a 5% random sample of Medicare beneficiaries. We identified participants as those newly diagnosed as having atrial fibrillation from October 1, 2010, through October 31, 2011, and who initiated dabigatran or warfarin treatment within 60 days of initial diagnosis. We followed up patients until discontinued use or switch of anticoagulants, death, or December 31, 2011.

EXPOSURES Dabigatran users (n = 1302) and warfarin users (n = 8102).

MAIN OUTCOMES AND MEASURES We identified any bleeding events and categorized them as major and minor bleeding by anatomical site. Major bleeding events included intracranial hemorrhage, hemoperitoneum, and inpatient or emergency department stays for hematuria, gastrointestinal, or other hemorrhage. We used a propensity score weighting mechanism to balance patient characteristics between 2 groups and Cox proportional hazards regression models to evaluate the risk of bleeding. We further examined the risk of bleeding for 4 subgroups of high-risk patients: those 75 years or older, African Americans, those with chronic kidney disease, and those with more than 7 concomitant comorbidities.

RESULTS Dabigatran was associated with a higher risk of bleeding relative to warfarin, with hazard ratios of 1.30 (95% CI, 1.20-1.41) for any bleeding event, 1.58 (95% CI, 1.36-1.83) for major bleeding, and 1.85 (95% CI, 1.64-2.07) for gastrointestinal bleeding. The risk of intracranial hemorrhage was higher among warfarin users, with a hazard ratio of 0.32 (95% CI, 0.20-0.50) for dabigatran compared with warfarin. Dabigatran was consistently associated with an increased risk of major bleeding and gastrointestinal hemorrhage for all subgroups analyzed. The risk of major bleeding among dabigatran users was especially high for African Americans and patients with chronic kidney disease.

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JAMA Intern Med. 2015;175(1):18-24

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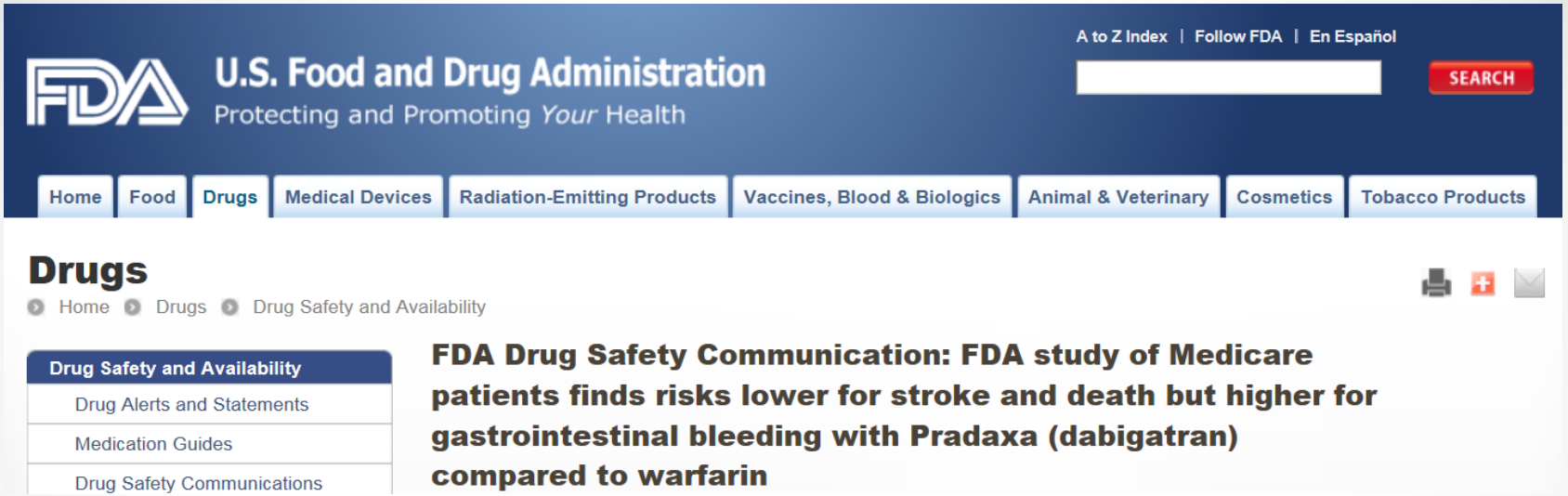
Table 2. Adjusted Incidence Rates of Bleeding Events by Treatment Group

Outcome	Incidence Rates, % (95% CI)[a] Warfarin (n = 8102)	Dabigatran (n = 1302)	*P* Value
By severity			
Any	26.5 (24.3-28.6)	32.7 (29.9-35.4)	<.001
Major	5.9 (5.1-6.6)	9.0 (7.8-10.2)	<.001
Minor	23.6 (21.4-25.8)	28.6 (25.8-31.3)	<.001
By anatomical site			
Intracranial bleeding	1.8 (1.4-2.2)	0.6 (0.3-0.8)	<.001
Gastrointestinal bleeding	10.0 (9.0-11.0)	17.4 (15.7-19.2)	<.001
Hematuria	8.8 (6.9-10.7)	12.0 (9.3-14.7)	<.001
Vaginal bleeding	0.3 (0.2-0.4)	0.7 (0.4-0.9)	.003
Hemarthrosis	0.2 (0.1-0.3)	0.5 (0.3-0.7)	.007
Hemoptysis	1.4 (0.9-1.8)	2.0 (1.3-2.7)	.03
Epistaxis	3.1 (2.5-3.6)	2.0 (1.5 -2.5)	.002
NOS hemorrhage	5.9 (4.9-6.9)	4.4 (3.5-5.4)	.003

JAMA Intern Med. 2015;175(1):18-24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FDA Drug Safety Communication: FDA study of Medicare patients finds risks lower for stroke and death but higher for gastrointestinal bleeding with Pradaxa (dabigatran) compared to warfarin

Safety Announcement

[05-13-2014] In its ongoing review of the blood thinner Pradaxa (dabigatran), the U.S. Food and Drug Administration (FDA) recently completed a new study in Medicare patients comparing Pradaxa to the blood thinner warfarin (Coumadin, Jantoven, and generics), for risk of ischemic or clot-related stroke, bleeding in the brain, major gastrointestinal (GI) bleeding, myocardial infarction (MI), and death. Pradaxa and warfarin are used to reduce the risk of stroke and blood clots in patients with a common type of abnormal heart rhythm called non-valvular atrial fibrillation (AF).

The new study included information from more than 134,000 Medicare patients, 65 years or older, and found that among new users of blood-thinning drugs, Pradaxa was associated with a lower risk of clot-related strokes, bleeding in the brain, and death, than warfarin. The study also found an increased risk of major gastrointestinal bleeding with use of Pradaxa as compared to warfarin. The MI risk was similar for the two drugs.

Importantly, the new study is based on a much larger and older patient population than those used in FDA's earlier review of post-market data, and employed a more sophisticated analytical method to capture and analyze the events of concern. This study's findings, except with regard to MI, are consistent with the clinical trial results that provided the basis for Pradaxa's approval.

As a result of our latest findings, we still consider Pradaxa to have a favorable benefit to risk profile and have made no changes to the current label or recommendations for use. Patients should not stop taking Pradaxa (or warfarin) without first talking with their health care professionals. Stopping the use of blood-thinning medications such as Pradaxa and warfarin can increase the risk of stroke and lead to permanent disability and death. Health care professionals who prescribe Pradaxa should continue to follow the dosing recommendations in the drug label.

We urge both health care professionals and patients to report side effects involving Pradaxa or warfarin to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.