DABİGATRAN

Dr. Erdem Diker

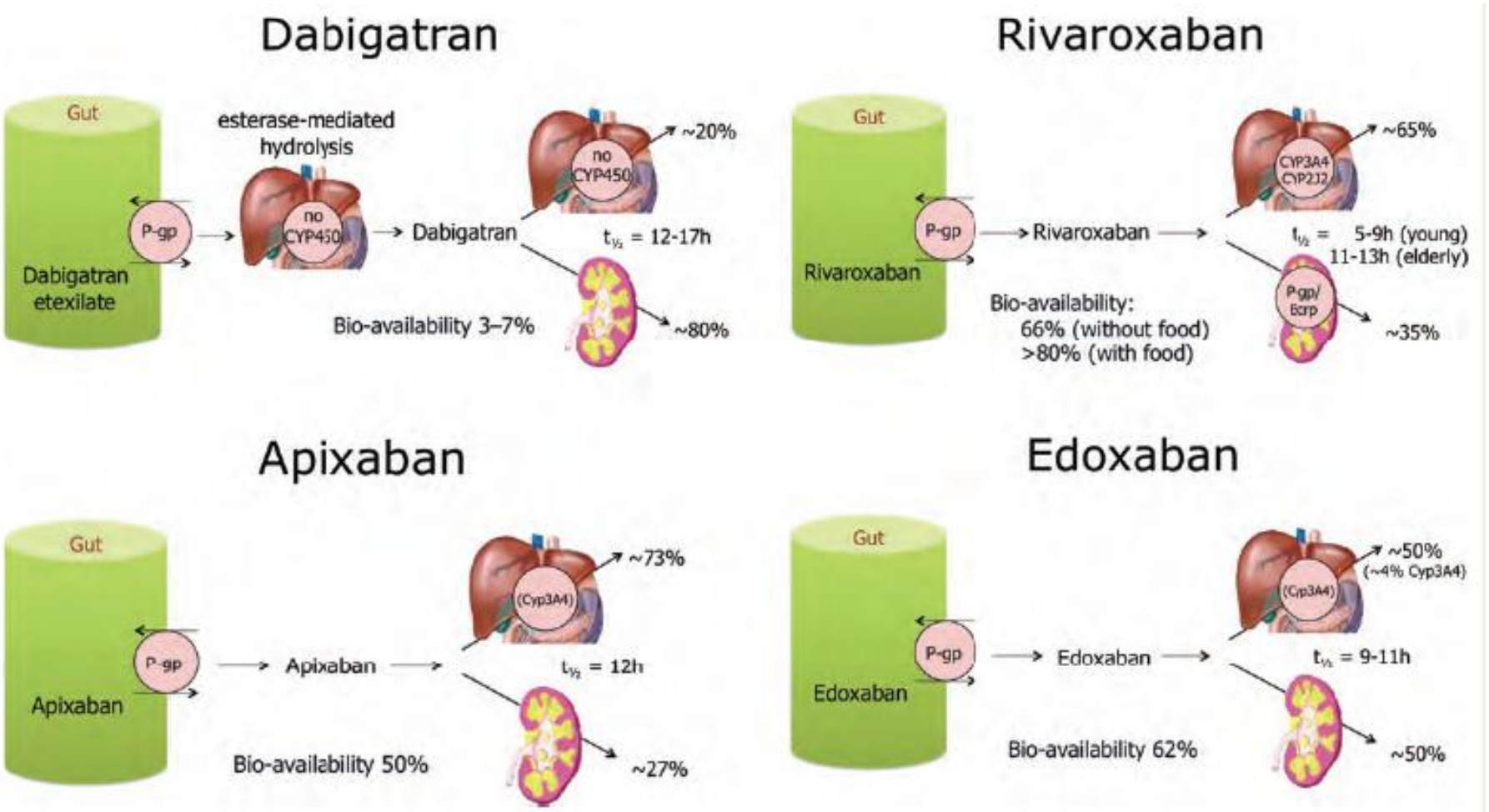

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Table 4 Absorption and metabolism of the different NOACs

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Bio-availability	3–7%	50%	62%[17]	66% without food Almost 100% with food
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose (if normal renal function; see also Section 8)	20%/80%	73%/27%[18]	50%/50%[9]	65%/35%
Liver metabolism: CYP3A4 involved	No	Yes (elimination; minor CYP3A4 contribution)[19]	Minimal (<4% of elimination)	Yes (elimination)
Absorption with food	No effect	No effect	6–22% more[20]	+39% more[21]
Intake with food recommended?	No	No	No official recommendation yet	Mandatory
Absorption with H2B/PPI	−12–30%[22–24]	No effect	No effect	No effect[21,25]
Asian ethnicity	+25%[24]	No effect	No effect[20]	No effect
GI tolerability	Dyspepsia 5–10%	No problem	No problem	No problem
Elimination half-life	12–17 h[23]	12 h	9–11 h[9]	5–9 h (young) 11–13 h (elderly)

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	Via	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%[29]	No data yet	No effect[30]	No effect[27,31]
Digoxin	P-gp competition	No effect[32]	No data yet	No effect[30]	No effect[27,33]
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12–180%[24] (reduce dose and take simultaneously)	No data yet	+53% (SR)[30] (reduce dose by 50%)[a]	Minor effect (use with caution if CrCl 15–50 ml/min)
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[24]	+40%[SmPC]	No data yet	Minor effect (use with caution if CrCl 15–50 ml/min)
Quinidine	P-gp competition	+50%	No data yet	+80%[30] (reduce dose by 50%)[b]	+50%
Amiodarone	P-gp competition	+12–60%[24]	No data yet	No effect[30]	Minor effect (use with caution if CrCl 15–50 ml/min)
Dronedarone	P-gp and CYP3A4 inhibitor	+70–100% (US: 2 × 75 mg)	No data yet	+85% (reduce dose by 50%)[a]	No data yet
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP competition; CYP3A4 inhibition	+140–150% (US: 2 × 75 mg)	+100%[SmPC]	No data yet	Up to +160%[27]
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[27]
Cyclosporin; tacrolimus	P-gp competition	No data yet	No data yet	No data yet	+50%
Clarithromycin; erythromycin	P-gp competition and CYP3A4 inhibition	+15–20%	No data yet	No data yet	+30–54%[26,27]
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase[SmPC]	No data yet	Up to +153%[27]
Rifampicin; St John's wort; carbamazepine; phenytoin;	P-gp/ BCRP and CYP3A4/CYP2J2	−66%[34]	−54%[SmPC]	−35%	Up to −50%

Table 6 Estimated drug half-lives and effect on area under the curve NOAC plasma concentrations in different stages of chronic kidney disease compared to healthy controls

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
CrCl ≥60 ml/min CKD Stage I and II	~14 h[48]	No data	~8.6 h[49]	~8.5 h[50] (+44%)
CrCl 30–60 ml/min CKD Stage III	~18 h[48]	No data	~9.4 h[49]	~9 h (+52%)
CrCl 15–30 ml/min CKD Stage IV	~28 h[48]	No data	~16.9 h[49]	~9.5 h (+64%)
CrCl ≤15 ml/min CKD Stage V	No data	No data	No data	No data

[a]No EMA approval yet. Needs update after finalisation of SmPC.
CKD, chronic kidney disease; CrCl, creatinine clearance.
Hatching, no available data yet.

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Table 7 NOACs in renal dysfunction: Approved European labels and dosing in chronic kidney disease

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Fraction renally excreted of absorbed dose	80%	27%	50%[9]	35%
Bio-availability	3–7%	50%	62%[17]	66% without food Almost 100% with food
Fraction renally excreted of administered dose	4%	14%	37%[9]	33%
Approved for CrCl ≥ ...	≥30 ml/min	≥15 ml/min	Not available	≥15 ml/min
Dosing recommendation	CrCl ≥50 ml/min: no adjustment (i.e. 150 mg bid)	Serum creatinine ≥1.5 mg/dl: no adjustment (i.e. 5 mg bid)	Not available	CrCl ≥50 ml/min: no adjustment (i.e. 20 mg qd)
Dosing if CKD	When CrCl 30–49 ml/min, 150 mg bid is possible (SmPC) but 110 mg bid if 'high risk of bleeding' (SmPC) or 'recommended' (GL update)[2] Note: 75 mg bid approved in US only:[b] • if CrCl 15–30 ml/min • if CrCl 30–49 ml/min and other orange factor Table 5 (e.g. verapamil)	CrCl 15–29 ml/min: 2.5 mg bid Serum creatinine ≥1.5 mg/dl in combination with age ≥80 years or weight ≤60 kg,[SmPC] or with other 'yellow' factor (Table 5): 2.5 mg bid	Not available	15 mg qd when CrCl 15–49 ml/min
Not recommended if	CrCl <30 ml/min	CrCl <15 ml/min	Not available	CrCl <15 ml/min

Table 3 Interpretation of coagulation assays in patients treated with different NOACs

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Plasma peak level	2 h after ingestion	1–4 h after ingestion	1–2 h after ingestion	2–4 h after ingestion
Plasma trough level	12–24 h after ingestion	12–24 h after ingestion	12–24 h after ingestion[9]	16–24 h after ingestion
PT	Cannot be used	Cannot be used	Prolonged but no known relation with bleeding risk[5,9]	Prolonged: may indicate excess bleeding risk but local calibration required
INR	Cannot be used	Cannot be used	Cannot be used	Cannot be used
aPTT	At trough: >2x ULN suggests excess bleeding risk	Cannot be used	Prolonged but no known relation with bleeding risk[9]	Cannot be used
dTT	At trough: >200 ng/ml or >65 s: excess bleeding risk	Cannot be used	Cannot be used[10]	Cannot be used
Anti-FXa chromogenic assays	Not applicable	No data yet	Quantitative;[10] no data on threshold values for bleeding or thrombosis	Quantitative; no data on threshold values for bleeding or thrombosis
ECT	At trough: ≥3× ULN: excess bleeding risk	Not affected	Not affected	Not affected

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Table 1 New anticoagulant drugs, approved or under evaluation for prevention of systemic embolism or stroke in patients with non-valvular atrial fibrillation

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Action	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Dose	150 mg bid 110 mg bid	5 mg bid 2.5 mg bid	60 mg qd 30 mg qd 15 mg qd	20 mg qd 15 mg qd
Phase 3 clinical trial	RE-LY[3]	ARISTOTLE[4] AVERROES[4]	ENGAGE-AF[5]	ROCKET-AF[6]

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2009. 심장학회

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Dabigatran versus Warfarin in Patients with Atrial Fibrillation

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Table I. RE-LY inclusion criteria

1.) AF documented as follows:
There is ECG documented AF on the day of screening or randomization
The patient has had a symptomatic episode of paroxysmal or persistent AF documented by 12-lead ECG within 6 m before randomization
There is documentation of symptomatic or asymptomatic paroxysmal or persistent AF on 2 separate occasions, at least 1 day apart, one of which is within 6 m before randomization. In this case, AF may be documented by 12 lead ECG, rhythm strip, pacemaker/ICD electrogram, or Holter ECG. The duration of AF should be at least 30 s. Electrograms (not marker channels or mode switch episodes) from pacemakers and defibrillators can be used to document only 1 episode of paroxysmal or persistent AF
2.) In addition to documented AF, patients must have one of the following:
a. History of previous stroke, TIA, or systemic embolism
b. Ejection fraction <40% documented by echocardiogram, radionuclide or contrast angiogram in the last 6 m
c. Symptomatic heart failure, New York Heart Association class 2 or higher in the last 6 m
d. Age ≥75 y
e. Age ≥65 y and one of the following:
i) Diabetes mellitus on treatment
ii) Documented coronary artery disease (any of: prior myocardial infarction, positive stress test, positive nuclear perfusion study, prior CABG surgery or PCI, angiogram showing ≥75% stenosis in a major coronary artery
iii) Hypertension requiring medical treatment
3.) Age >18 y at entry
4.) Written, informed consent

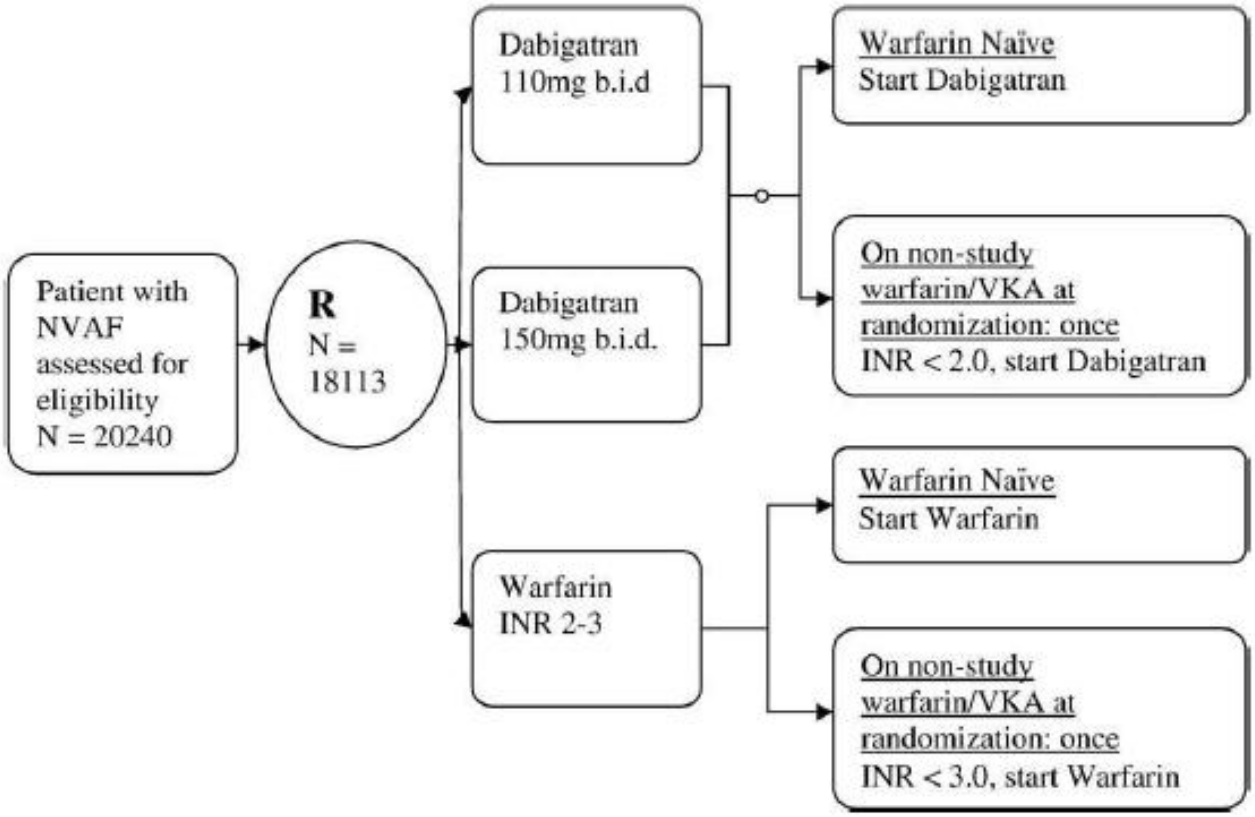
Rationale and design of RE-LY: Randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran Am Heart Journal 2009

Table II. RE-LY exclusion criteria

1. History of heart valve disorders (ie, prosthetic valve or hemodynamically relevant valve disease)
2. Severe, disabling stroke within the previous 6 m, or any stroke within the previous 14 d
3. Conditions associated with an increased risk of bleeding:
   a. Major surgery in the previous month
   b. Planned surgery or intervention in the next 3 m
   c. History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding
   d. Gastrointestinal hemorrhage within the past year
   e. Symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 d
   f. Hemorrhagic disorder or bleeding diathesis
   g. Need for anticoagulant treatment of disorders other than AF
   h. Fibrinolytic agents within 48 h of study entry
   i. Uncontrolled hypertension (systolic blood pressure >180 mm Hg and/or diastolic blood pressure >100 mm Hg)
   j. Recent malignancy or radiation therapy (≤6 m) and not expected to survive 3 y
4. Contraindication to warfarin treatment
5. Reversible causes of atrial fibrillation (eg, cardiac surgery, pulmonary embolism, untreated hyperthyroidism).
6. Plan to perform a pulmonary vein ablation or surgery for cure of the AF
7. Severe renal impairment (estimated creatinine clearance ≤30 mL/min)
8. Active infective endocarditis

Rationale and design of RE-LY: Randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran Am Heart Journal 2009

Figure 1



Design of the RE-LY trial. *R*, Randomization.

Rationale and design of RE-LY: Randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran Am Heart Journal 2009

or autopsy. Major bleeding was defined as a reduction in the hemoglobin level of at least 20 g per liter, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. Life-threatening bleeding was a subcategory of major bleeding that consisted of fatal bleeding, symptomatic intracranial bleeding, bleeding with a decrease in the hemoglobin level of at least 50 g per liter, or bleeding requiring transfusion of at least 4 units of blood or inotropic agents or necessitating surgery. All other bleeding was considered minor.

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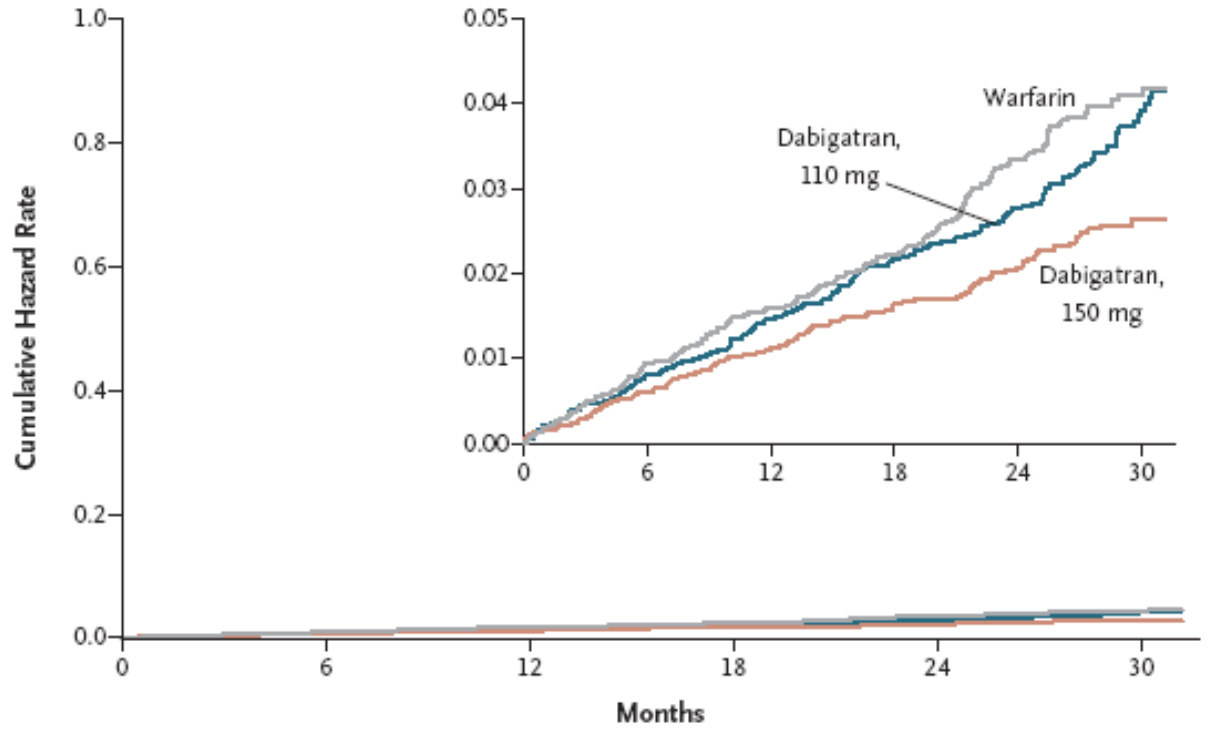

No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

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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

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

Table 4. Discontinuation of the Study Drug, Adverse Events, and Liver Function According to Treatment Group.*

Variable	Dabigatran, 110 mg (N=6015)	Dabigatran, 150 mg (N=6076)	Warfarin (N=6022)
	number of patients (percent)		
Study-drug discontinuation			
Discontinued at 1 yr†	862 (15)	935 (16)	608 (10)
Discontinued at 2 yr†	1161 (21)	1211 (21)	902 (17)
Reason for discontinuation			
Patient's decision	440 (7.3)	474 (7.8)	375 (6.2)
Outcome event	192 (3.2)	164 (2.7)	130 (2.2)
Serious adverse event‡	163 (2.7)	166 (2.7)	105 (1.7)
Gastrointestinal symptoms§	134 (2.2)	130 (2.1)	38 (0.6)
Gastrointestinal bleeding	58 (1.0)	80 (1.3)	54 (0.9)
Adverse events¶			
Dyspepsia‖	707 (11.8)	688 (11.3)	348 (5.8)
Dizziness	486 (8.1)	506 (8.3)	568 (9.4)
Dyspnea	557 (9.3)	580 (9.5)	586 (9.7)
Peripheral edema	473 (7.9)	478 (7.9)	468 (7.8)
Fatigue	399 (6.6)	401 (6.6)	372 (6.2)
Cough	344 (5.7)	348 (5.7)	364 (6.0)
Chest pain	312 (5.2)	377 (6.2)	357 (5.9)
Back pain	316 (5.3)	314 (5.2)	337 (5.6)
Arthralgia	270 (4.5)	335 (5.5)	346 (5.7)
Nasopharyngitis	337 (5.6)	330 (5.4)	336 (5.6)
Diarrhea	377 (6.3)	397 (6.5)	346 (5.7)
Atrial fibrillation	330 (5.5)	357 (5.9)	349 (5.8)
Urinary tract infection	273 (4.5)	289 (4.8)	335 (5.6)
Upper respiratory tract infection	288 (4.8)	285 (4.7)	313 (5.2)
Liver function			
ALT or AST >3× ULN	124 (2.1)	117 (1.9)	132 (2.2)
ALT or AST >3× ULN with concurrent bilirubin >2× ULN	13 (0.2)	13 (0.2)	21 (0.3)
Hepatobiliary disorder**			
Serious adverse event	33 (0.5)	34 (0.6)	33 (0.5)
Non–serious adverse event	101 (1.7)	109 (1.8)	112 (1.9)

* ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.

RELYABLE: Outcomes for the two dabigatran doses in the 2.3-year extension study

Event	Dabigatran 150 mg (%/y)	Dabigatran 110 mg (%/y)	HR (95%CI)
Stroke/systemic embolism	1.46	1.60	0.91 (0.69-1.20)
Major bleed	3.74	2.99	1.26 (1.04-1.53)
Intracranial bleed	0.33	0.25	1.31 (0.68-2.51)
Death	3.02	3.10	0.97(0.80-1.19)
Stroke, systemic embolism, MI, pulmonary embolism, major bleed, or death	7.36	6.89	1.07 (0.94-1.22)