

Dabigatran versus Warfarin in Patients with Atrial Fibrillation¹

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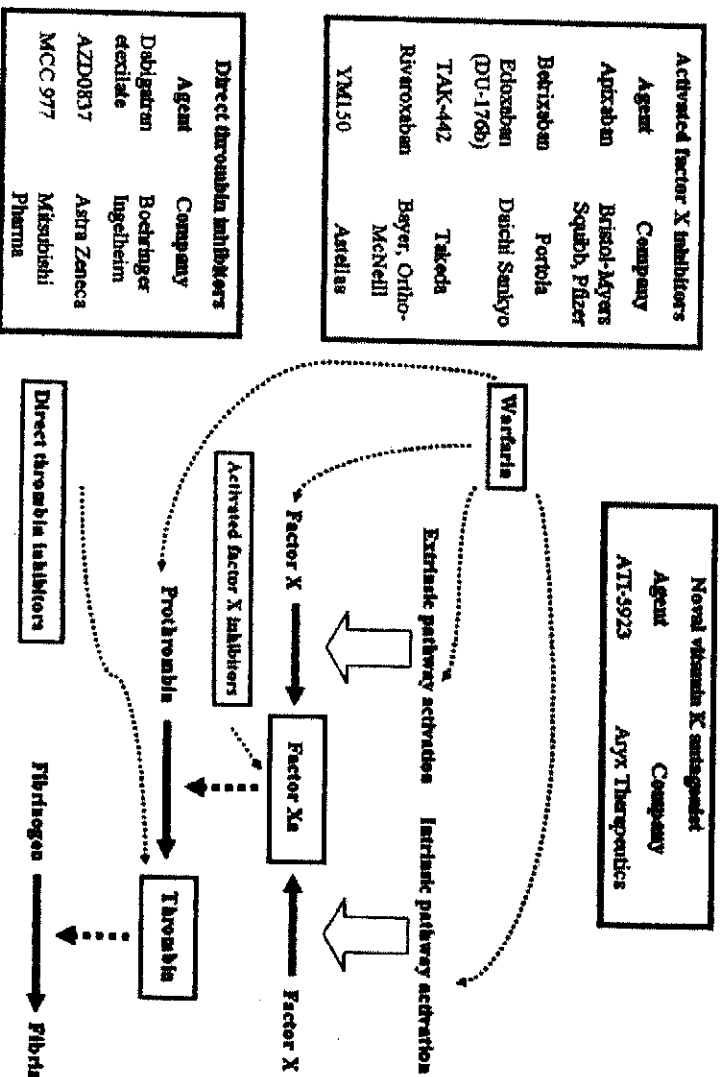
BACKGROUND

Atrial fibrillation (AF)¹

- Definition
 - Supraventricular tachyarrhythmia characterized by uncoordinated atrial activation resulting in atrial mechanical function deterioration
- Risks
 - Cardiomyopathy
 - Stroke
- Pharmacologic Treatment
 - Rate control
 - Rhythm control
 - Antithrombotic therapy^{III,IV}

Dabigatran (Pradaxa[®])^V

- Indications and Usage
 - Direct thrombin inhibitor for use in patients with non-valvular atrial fibrillation to reduce the risk of stroke and systemic embolism
- Mechanism of Action
 - Active dabigatran and its active moieties are competitive, direct thrombin inhibitors inhibiting both free and fibrin-bound thrombin and so preventing the development of a thrombus by stopping the conversion of fibrinogen to fibrin. Thrombin-induced platelet aggregation is also inhibited



Note: Development of AZD0837 has been halted and the status of MCC977 is unclear.

Fig. 1. Schematic diagram showing therapeutic targets and examples of different anticoagulants.

- Pharmacokinetics
 - Absorption
 - Bioavailability: 3-7%; increases by 75% without the capsule shell (do not open, break, or chew)
 - C_{max} : 1 h in fasting state, increased to 2 h with high-fat meal without effect on bioavailability
 - Steady state: 3 d^{viii}
 - Distribution
 - Protein binding: 35%
 - Vd: 50-70 L
 - Metabolism
 - Hepatic: prodrug hydrolyzed by carboxylesterases to form dabigatran, the active moiety, further metabolized through conjugation forming four active acyl glucuronide isomers
 - No CYP450 metabolism and no effect on CYP activity
 - Excretion^{viii}
 - Urine 7% (primarily unchanged), feces 86%
 - Renal, 80% of clearance
 - Dialyzable (hemodialysis), 60% over 2-3 h
 - $t_{1/2}$ 12-17 h; renal impairment 15-34 h

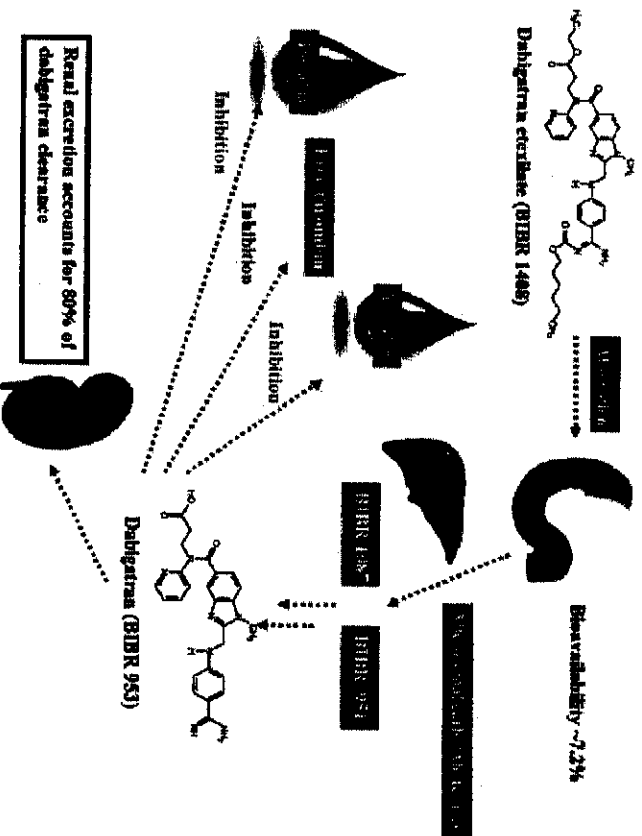


Fig. 2. Pharmacology of dabigatran esterase.

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- Dosage Forms and Strengths
 - 75 mg and 150 mg capsules
- Dosage and Administration
 - CrCl >30 mL/min: 150 mg by mouth twice daily
 - CrCl 15-30 mL/min: 75 mg by mouth twice daily
 - CrCl <15 mL/min or dialysis: no recommendation available
 - Hepatic impairment: moderate; large variability between subjects but no evidence of consistent pharmacodynamic or exposure changes
 - Converting to Warfarin
 - CrCl >50 mL/min: start warfarin 3 d before discontinuing dabigatran
 - CrCl 31-50 mL/min: start warfarin 2 d before discontinuing dabigatran
 - CrCl 15-30 mL/min: start warfarin 1 d before discontinuing dabigatran
 - CrCl <15 mL/min: no recommendations can be made

- Converting *from Warfarin*
 - Discontinue warfarin and initiate dabigatran when INR is <2.0
 - INR may reflect dabigatran's potential elevating effect for at least 2 d after discontinued
- Converting *to parenteral anticoagulants*
 - Wait 12 h (CrCl ≥30 mL/min) or 24 h (CrCl <30 mL/min) after the last dose of dabigatran before starting parenteral anticoagulant treatment
- Converting *from parenteral anticoagulants*
 - Start dabigatran 0-2 h before next dose of intermittent anticoagulation was to be administered
 - Start dabigatran when continuously infused anticoagulant is discontinued
- Surgery and Interventions
 - CrCl ≥50 mL/min: discontinue dabigatran 1-2 d before procedure
 - CrCl <50 mL/min: discontinue dabigatran 3-5 d before procedure
 - Longer times should be considered for patients in whom complete hemostasis may be required (e.g., patients undergoing major surgery; placement of a spinal or epidural catheter or port, or spinal puncture)
 - Bleeding risk assessment
 - Ecarin clotting time (ECT), if ECT is not available then use PTT (PTT values >2.5 x control may indicate overanticoagulation)
- Overdosage
 - Discontinue dabigatran
 - No antidote
 - Supportive measures
 - Surgical hemostasis
 - Dialysis
 - FFP, PRBC
 - Platelets
 - PCC, rFVIIa, FII, IX, X concentrates
- Contraindications
 - History of serious hypersensitivity reaction to dabigatran
 - Active pathological bleeding
- Warnings and Precautions
 - Serious and, sometimes, fatal bleeding
 - Increased risk of stroke when temporarily discontinued
 - Avoid concomitant use with P-gp inducers (e.g., rifampin) due to decreased dabigatran exposure
- Adverse Reactions
 - GI: dyspepsia (11%); includes abdominal discomfort/pain, epigastric discomfort)
 - Hematologic: bleeding (8% to 33%; major: ≤6%)
- Drug Interactions
 - No dose adjustment for P-gp inhibitors (e.g., verapamil, ketoconazole, amiodarone, clarithromycin)
 - Avoid use with rifampin (P-gp inducer, see above in Warnings and Precautions)
- Pregnancy and Lactation
 - Pregnancy category C
 - Use caution, excretion in breast milk unknown

PREVIOUS TRIALS (atrial fibrillation)

Study Design	Patient Population	Intervention	Results	Conclusion
Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO study)	502 patients, with non-valvular AF at high risk for thromboembolism	Dabigatran (50 to 300 mg twice daily) ± ASA (81 mg or 325 mg daily) in a 3×3 factorial fashion v. dose-adjusted warfarin to aim INR 2.0 to 3.0	Primary objective: major bleeding events limited to dabigatran 300 mg daily + ASA (6%) compared to same dose without ASA (0%), p <0.02; total bleeding events 300 mg (23%) and 150 mg (18%) groups, compared with 7% in the 50 mg group, p=0.0002 and p=0.01, respectively	Dabigatran 150 mg twice daily was well tolerated with effective anticoagulant activity Serious liver toxicity not seen with dabigatran treatment
Ezekowicz et al, 2007 ^{ix} Phase II, multi-center randomized trial			Secondary objective: D-dimer suppression for dabigatran activity evaluation (baseline to 12 wk): dabigatran 50 mg twice daily 13% increase, p=0.0008; 150 mg twice daily 3% increase, p=0.027	

Dabigatran versus Warfarin in Patients with Atrial Fibrillation ^{ix,xi} RE-LY trial

STUDY OBJECTIVE

- Safety and efficacy of dabigatran for prevention of systemic embolism and stroke in non-valvular atrial fibrillation patients

METHODS

Study design

- Phase 3, prospective, randomized, multinational trial of patients with nonvalvular atrial fibrillation at increased stroke risk
- Dabigatran doses: blinded
- Warfarin: open-label
- Funded by Boehringer Ingelheim (Pradaxa[®]-dabigatran manufacturer)

Study population

- Inclusion criteria
 - Documented atrial fibrillation
 - One of characteristics
 - h/o CVA or TIA
 - NYHA Class II or higher
 - LVEF <40%
 - ≥75 y old or 65-74 y old with diabetes, HTN, CAD
- Exclusion criteria
 - Stroke within 14 d or severe stroke within 6 months
 - Severe valvular disorder
 - Increased hemorrhage risk
 - CrCl <30 mL/min
 - Active hepatic disease
 - Pregnancy

Treatment groups

- Dabigatran 110 mg twice daily
- Dabigatran 150 mg twice daily
- Warfarin adjusted with goal INR 2.0-3.0

Outcomes

- Primary study outcome
 - Stroke or systemic embolism
- Secondary study outcomes
 - Stroke
 - Systemic embolism
 - Death
- Primary safety outcome
 - Major bleeding
- Primary net clinical benefit
 - Major bleeding, major vascular events, death

Statistical Analysis

- Non-inferiority
 - Upper bound of one-sided 97.5% confidence interval for RR fall below 1.46
 - $P < 0.025$ (higher of two doses)
 - $P \geq 0.025$ (higher of two), $P < 0.0125$ (lower of two)
- If non-inferiority established
 - Two-tailed tests of superiority P values
- Power
 - Non-inferiority: 84% power (15,000 patients)
 - Protocol change to 18,000 patients to maintain power if low event rate

RESULTS

Characteristics

- 18,113 patients
 - Dabigatran 110 mg group – 6015 patients
 - Dabigatran 150 mg group – 6076 patients
 - Warfarin group – 6022 patients
- Table 1 - p values are not provided and no comment on statistically significant differences, if any

Follow-up

- Median 2.0 years
- 20 patients lost
- 99.9% complete follow-up
- Therapeutic INR: Mean 64%
- Rates of discontinuation
 - 1 year: dabigatran 110 mg (15%), dabigatran 150 mg (16%), warfarin (10%), $P < 0.001$
 - 2 years: dabigatran 110 mg (21%), dabigatran 150 mg (21%), warfarin (17%), $P < 0.001$

Outcomes

- Primary outcome: systemic embolism or stroke
 - Both dabigatran doses were non-inferior to warfarin, $P < 0.001$
 - Dabigatran 110 mg dose was not superior to warfarin
 - Dabigatran 150 mg dose was superior to warfarin and dabigatran 110 mg
- Secondary outcomes
 - Stroke
 - Stroke (any): dabigatran 150 mg group statistically fewer than others
 - Hemorrhagic stroke: both dabigatran groups statistically fewer
 - Ischemic or unspecified strokes: dabigatran 150 mg group statistically fewer than others
 - Disabling or fatal stroke: dabigatran 150 mg statistically fewer than other groups
 - Non-disabling stroke: dabigatran 150 mg significantly fewer than warfarin
 - Systemic embolism
 - Pulmonary embolism: no statistically significant differences
 - MI: When data were originally published reported higher rate in both dabigatran doses compared to warfarin, $P=0.048$ for 150 mg dose. Last month's NEJM updated data after the study database reevaluation (see table 1). Twenty-eight cases of silent MI were revealed changing the $P=0.12$
 - Death
 - Any cause: no statistically significant difference between groups, trend towards fewer in dabigatran 150 mg group compared to warfarin group
 - Vascular causes: Dabigatran 150 mg statistically fewer compared to warfarin
 - Other outcomes
 - Hospitalization: dabigatran 110 mg group significantly lower than others

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 (95% CI)		Dabigatran, 150 mg vs. Warfarin (95% CI)		Dabigatran, 150 mg vs. 110 mg (95% CI)	
	no. of patients	%/yr	no. of patients	%/yr	no. of patients	%/yr	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Stroke or systemic embolism*	182	1.53	134	1.11	199	1.69	0.91 (0.74-1.11)	<0.001 for noninferiority, 0.14	0.66 (0.53-0.82)	<0.001 for noninferiority, <0.001	0.73 (0.58-0.93)	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
Non-disabling 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 (0.51-0.94)	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 (0.61-2.56)	0.50
Hospitalization	2313	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

Event	Dabigatran, 110 mg (N=6015)		Dabigatran, 150 mg (N=6076)		Warfarin (N=6022)		Dabigatran, 110 mg vs. Warfarin (95% CI)		Dabigatran, 150 mg vs. Warfarin (95% CI)	
	no. of patients	%/yr	no. of patients	%/yr	no. of patients	%/yr	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
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.

- Primary safety outcome
 - Major bleeding
 - Dabigatran 110 mg statistically less compared to warfarin
 - Dabigatran 150 mg and warfarin not statistically significant
 - GI bleeding
 - Dabigatran 150 mg significantly higher rate compared to warfarin group
 - Other bleeding
 - Life threatening, intracranial bleeding, and minor bleeding: dabigatran groups significantly lower rates
- Primary net clinical benefit (Major bleeding, major vascular events, death)
 - Dabigatran 150 mg group statistically fewer patients than warfarin group

Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin		Dabigatran, 110 mg vs. Warfarin (95% CI)		Dabigatran, 150 mg vs. Warfarin (95% CI)		Dabigatran, 150 mg vs. 110 mg (95% CI)	
	no. of patients	%/yr	no. of patients	%/yr	no. of patients	%/yr	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
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)	0.37
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‡ correct	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

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. Hemorrhagic stroke was a subcategory of stroke in the efficacy analysis and in the safety analysis is also counted as major, life-threatening bleeding and as part of intracranial bleeding.
 † Gastrointestinal bleeding could be life threatening or non-life threatening.
 ‡ The net clinical benefit outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding.

Adverse events

- Dyspepsia
 - Warfarin group (5.8%), dabigatran 110 mg (11.8%), dabigatran 150 mg (11.3%), P<0.001 both groups
- Liver function
 - No difference in frequency of AST or ALT elevations >3x ULN between groups

AUTHOR'S DISCUSSION

- Both dabigatran doses were non-inferior to warfarin
- Dabigatran 150 mg dose superior to warfarin
- No evidence of hepatotoxicity
- Important dabigatran advantage
 - Statistically lower rate of hemorrhagic stroke in both dabigatran doses compared to warfarin without reduction in ischemic stroke efficacy for 150 mg dose
- Warfarin major bleeding rates higher than in other trials
- Dabigatran 150 mg rate of GI bleeding significantly higher, formulation that lowers pH may explain GI bleeding and dyspepsia associated with dabigatran

LIMITATIONS

- Potential bias in event reporting due to open-label warfarin use
 - Blinded outcome evaluation to reduce bias potential
 - Absence of bias supported by difference in GI bleed rates

APPLICATION TO CLINICAL PRACTICE

- Drug company that makes dabigatran, Boehringer Ingelheim, funded research
- Many investigators affiliated with Boehringer Ingelheim
- Lack of dabigatran antidote
- Large number of patients, multinational, large number of centers
- Dabigatran GI bleed rate
 - Cost^{xiii}
- Would recommend considering dabigatran treatment
 - Difficulty maintaining therapeutic INR
 - Inability to adhere to frequent monitoring
 - Concomitant medications with warfarin drug interactions

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