Blood Thinners part 1:
New Anticoagulants

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July 24, 2012

Handout available at www.drstultz.com

Southwest Cardiology

Disclosures

- Unfortunately, no conflicts of interest
- Brand names will be used
- On label and Off label use will be discussed
- Unapproved investigational products will be discussed

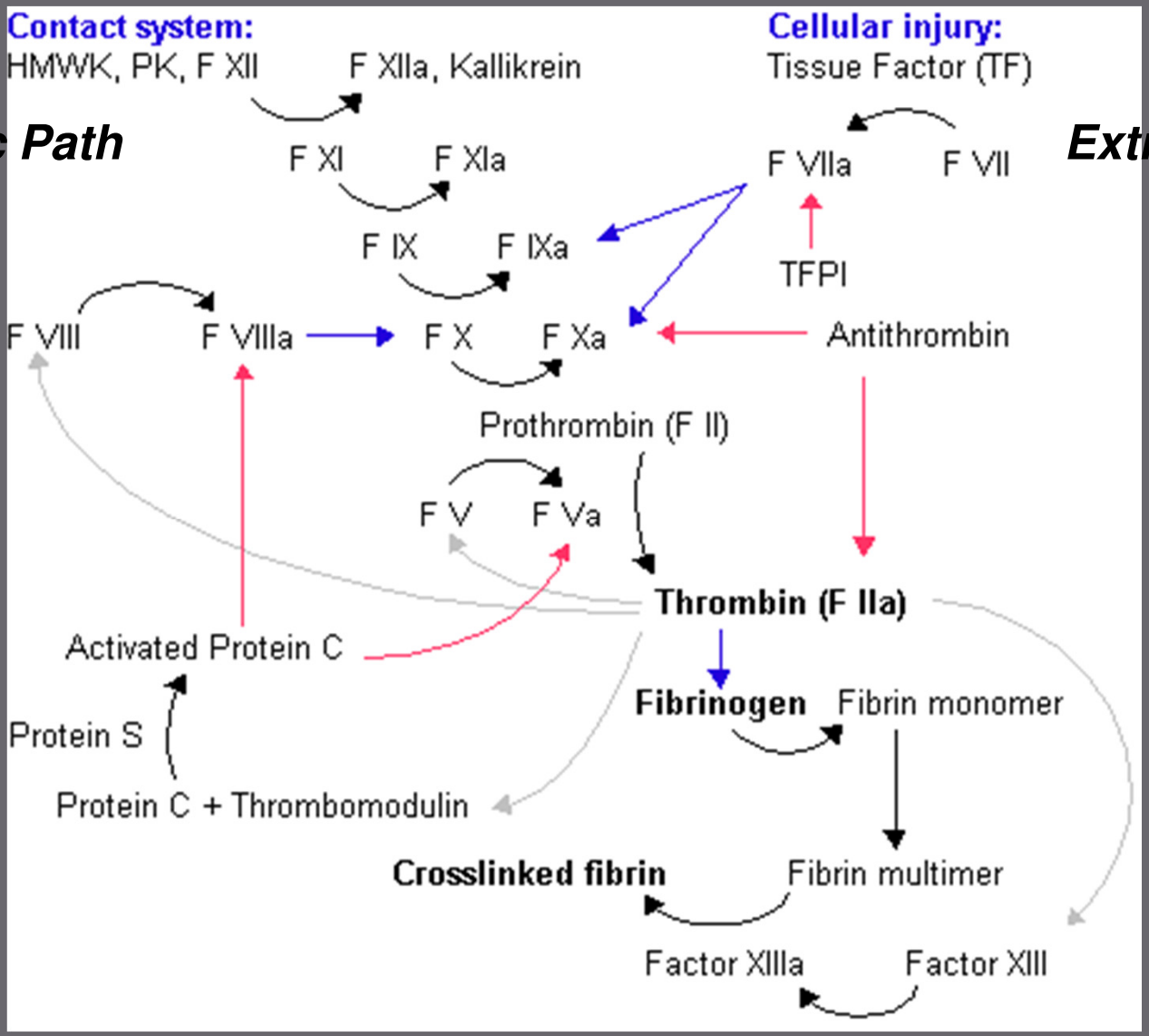
Objectives of Conference

- Understand the use of anticoagulant therapy in the context of atrial fibrillation
- Identify 2 new anticoagulant medications
- Discuss advantages and disadvantages of new anticoagulant medications

Coagulation Cascade

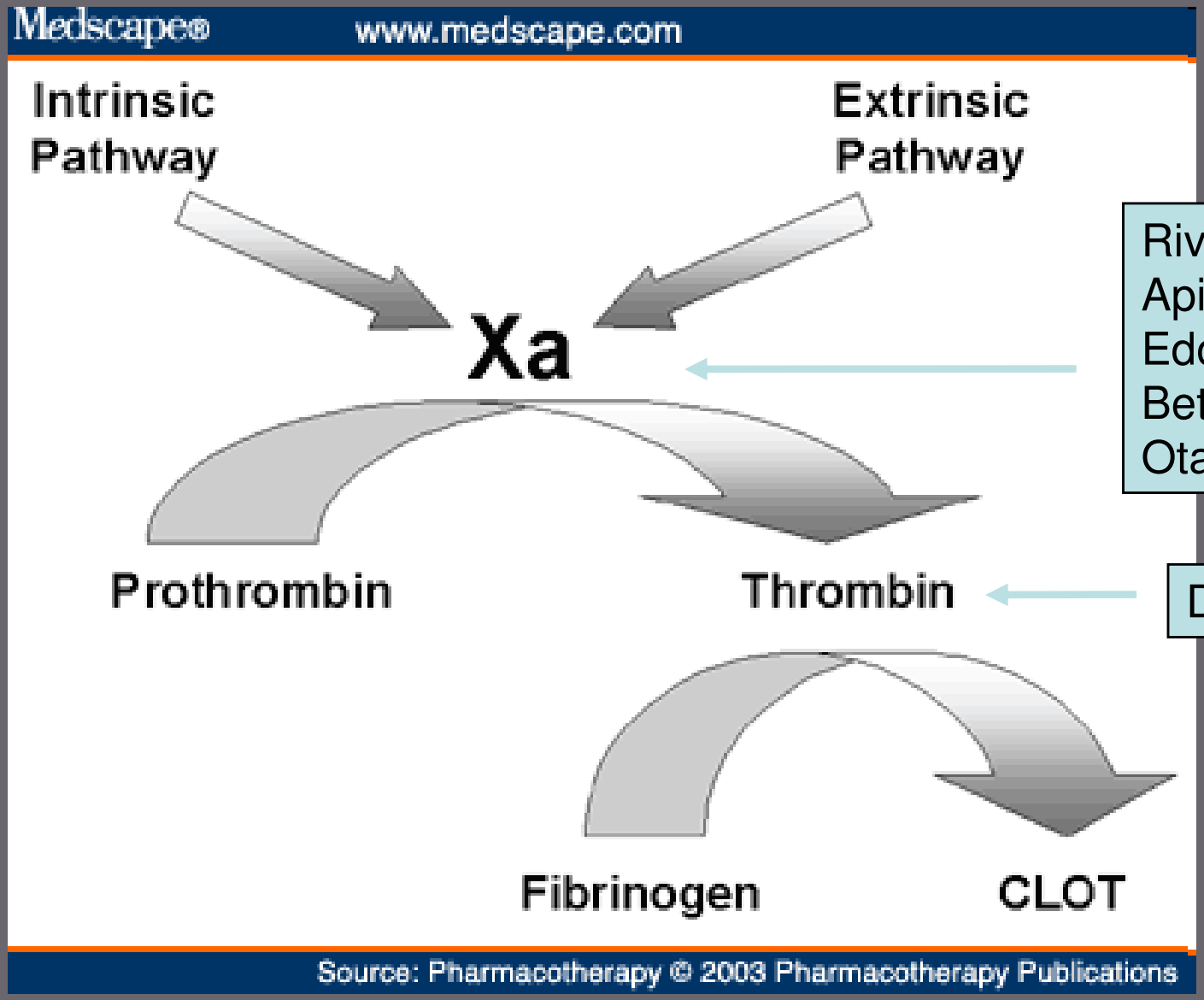
Intrinsic Path

Extrinsic Path



http://usmlewiki.org/index.php?title=USMLE_Wiki:Hemodynamic_Disorders

Simplified Coagulation Cascade



Rivaroxaban
Apixaban
Edoxaban
Betrixaban
Otamixaban

Dabigatran

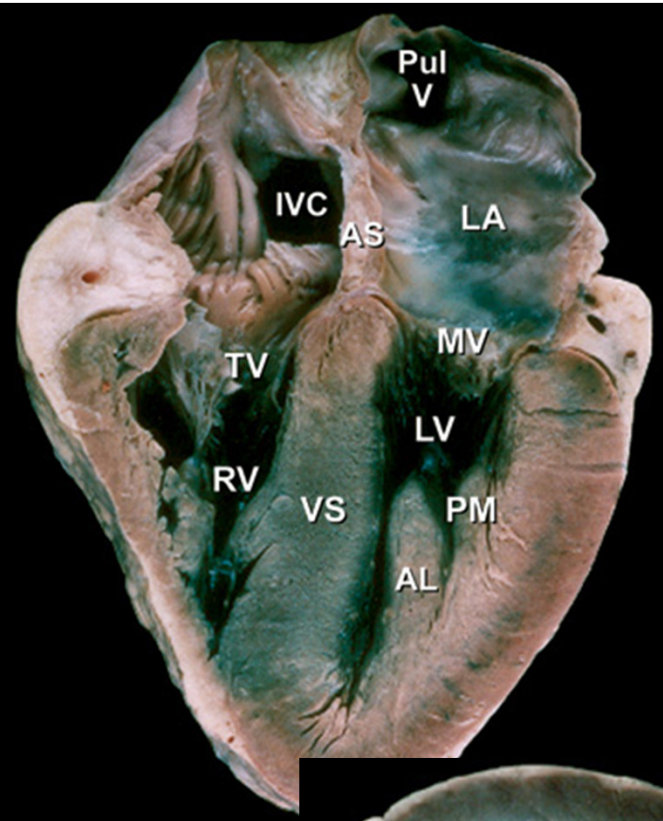
http://www.medscape.com/viewarticle/456874_2

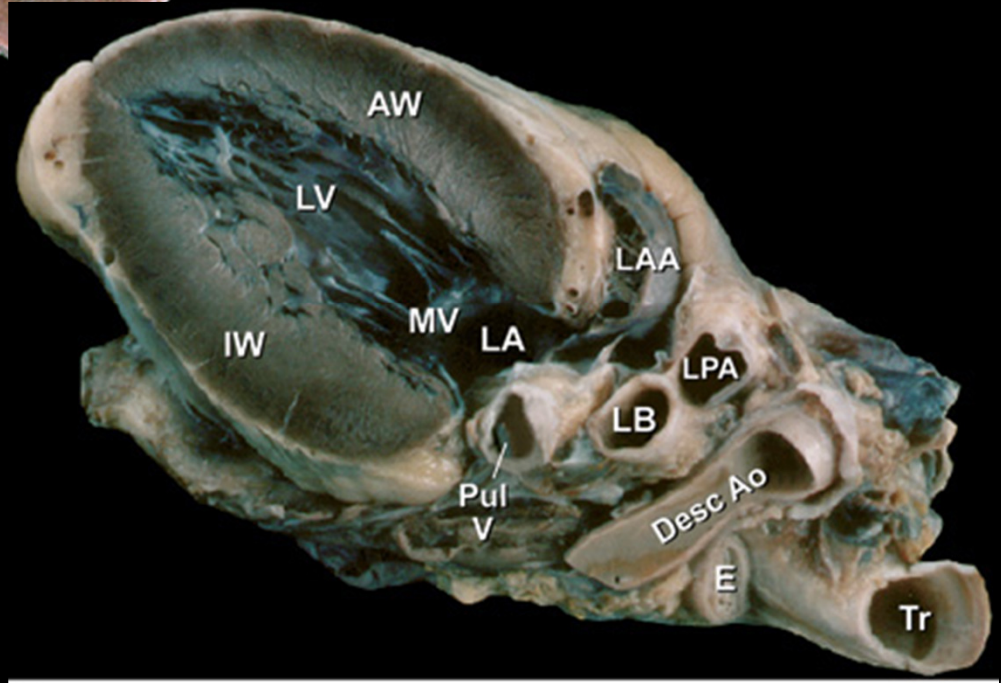
Why use anticoagulation for atrial fibrillation?

- Prevention of stroke and systemic embolization
- Stratify patients for risk of stroke
  - $CHADS_2$ schema
  - CHA_2DS_2-VASC schema
    - CHF/LV dysfunction, Hypertension, Age ≥75 (2), Diabetes, Stroke or TIA (2), Vascular disease, Age 65-74, Female gender.

Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010 Feb;137(2):263-72. Epub 2009 Sep 17.

Left Atrial Appendage





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Source: Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson
P: *Hurst's The Heart*, 12th Edition: http://www.accessmedicine.com

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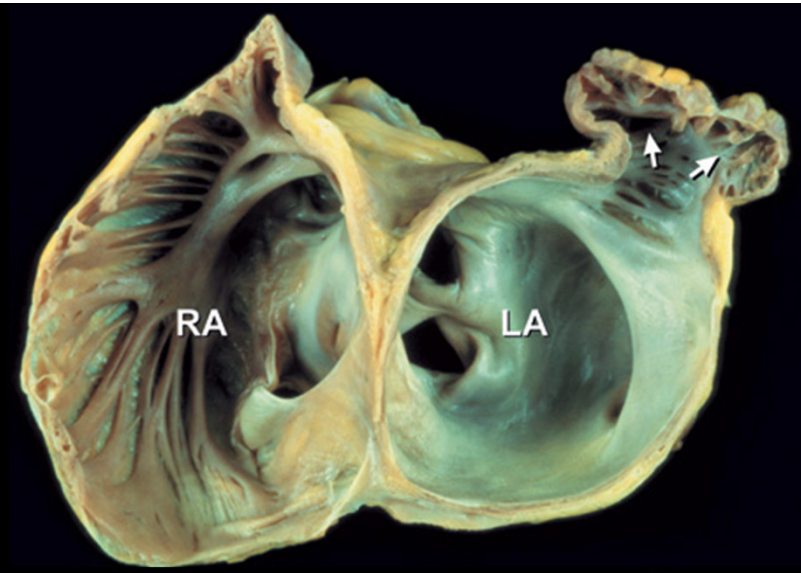

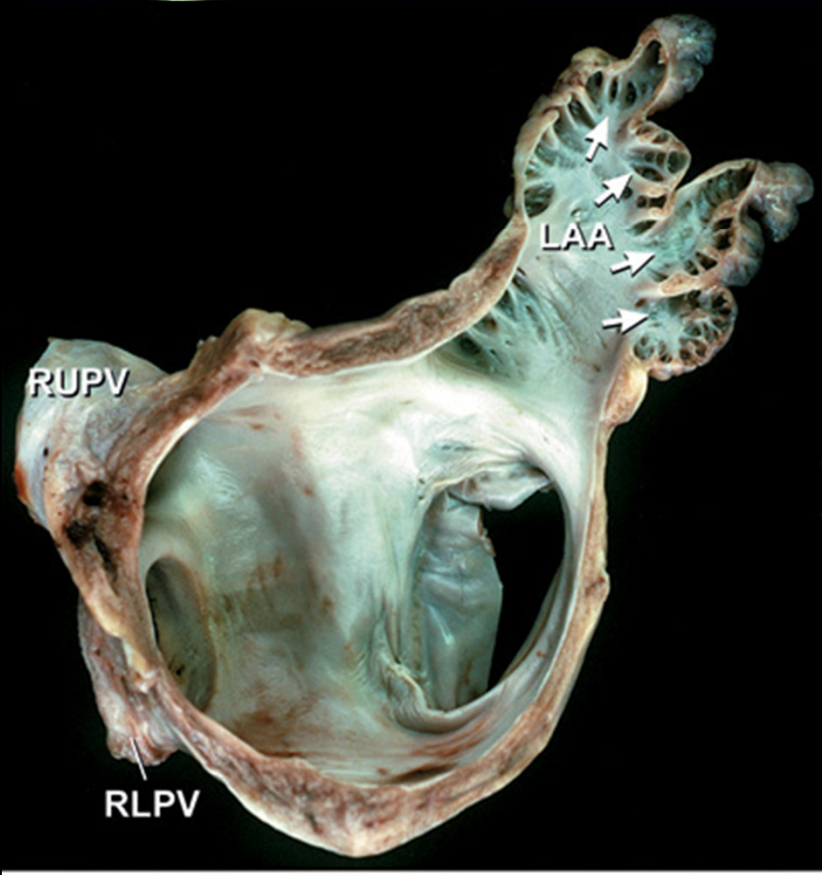

A

Source: Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson
P: *Hurst's The Heart*, 12th Edition: http://www.accessmedicine.com

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SPAF Trials

Trial	Time Interval	Main Findings
SPAF I		
Warfarin vs. placebo	1987–1989	Warfarin substantially reduces stroke
Aspirin vs. placebo	1987–1990	Aspirin reduces stroke
SPAF II		
Warfarin vs. aspirin, age ≤ 75 y	1987–1992	Small absolute reduction in stroke by warfarin over aspirin in unselected patients
Warfarin vs. aspirin, age > 75 y	1989–1992	High rate of intracranial bleeding with warfarin (INR, 2–4.5) in patients >75 years of age offset reduction in ischemic stroke
SPAF III		
Warfarin INR 2–3 vs. aspirin plus low-intensity, fixed-dose warfarin in selected high-risk patients	1993–1995	Warfarin INR 2–3 offers large benefits over aspirin plus low-intensity, fixed-dose warfarin for high-risk patients
Aspirin-treated low-risk cohort	1993–1997	Patients whose stroke risk is low when given aspirin can be identified (validation of the SPAF risk stratification scheme)

* All were randomized trials, except the nonrandomized aspirin-treated low-risk cohort clinical trial in SPAF III, in which all participants were prescribed aspirin and followed to validate the stroke risk stratification scheme. INR = international normalized ratio; SPAF = Stroke Prevention in Atrial Fibrillation.

Hart RG, Halperin JL, Pearce LA, Anderson DC, Kronmal RA, McBride R, Nasco E, Sherman DG, Talbert RL, Marler JR; Stroke Prevention in Atrial Fibrillation Investigators. Lessons from the Stroke Prevention in Atrial Fibrillation trials. Ann Intern Med. 2003 May 20;138(10):831-8.

REVIEW ARTICLE

Current Trial-Associated Outcomes With Warfarin in Prevention of Stroke in Patients With Nonvalvular Atrial Fibrillation

- How good is Modern Warfarin Therapy?
- Meta-Analysis of warfarin arms of 8 novel anticoagulation trials, 2006-2011
  - 32,053 patients, 55,789 patient-years
- Proportion of time spent in therapeutic window 55-68%
- **Annual** risk of stroke or non-CNS embolism
  - 0.9% for $CHADS_2 \leq 1$
  - 1.4% for $CHADS_2 = 2$
  - 2.5% for $CHADS_2 \geq 3$
- 0.6% risk of intracranial bleed
- 3%-7.6% risk of death or major bleed

Agarwal S, Hachamovitch R, Menon V. Current Trial-Associated Outcomes With Warfarin in Prevention of Stroke in Patients With Nonvalvular Atrial Fibrillation: A Meta-analysis. Arch Intern Med. 2012 Apr 23;172(8):623-31. Epub 2012 Mar 26.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

- RE-LY Trial: Dabigatran
  - Direct thrombin inhibitor (DTI)
  - Serum half life 12-17 hours
  - No need to monitor anticoagulation
  - Renal excretion
  - Rapid onset – 2 hours to peak serum concentration
- Compared 2 doses of dabigatran (110mg bid and 150mg bid – randomized and blinded) vs. open label warfarin

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. Epub 2009 Aug 30. Erratum in: N Engl J Med. 2010 Nov 4;363(19):1877.
Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. Clin Pharmacokinet. 2008;47(5):285-95.

RE-LY
Inclusion Criteria

- Atrial fibrillation documented in past 6 months
- At least 1 risk factor
  - Prior stroke or TIA
    - Excluded if within 14 days, or severe stroke in past 6 months
  - LVEF < 40%
  - CHF with NYHA class 2 symptoms in past 6 months
  - Age ≥ 75
  - Age 65-74 + 1 more risk factor:
    - DM, HTN, or CAD

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. Epub 2009 Aug 30. Erratum in: N Engl J Med. 2010 Nov 4;363(19):1877.

RE-LY
Summary of Enrollment

- 18,113 patients enrolled
- Mean age 71 years
- Mean $CHADS_2$ score was 2.1
- Half had prior treatment with warfarin

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. Epub 2009 Aug 30. Erratum in: N Engl J Med. 2010 Nov 4;363(19):1877.

Outcomes of RE-LY

- Median followup 2.0 years
- Primary outcome
  - Stroke **or** systemic embolism
- Secondary outcome
  - Stroke
  - Systemic embolism
  - Death
- Safety
  - Major hemorrhage

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. Epub 2009 Aug 30. Erratum in: N Engl J Med. 2010 Nov 4;363(19):1877.

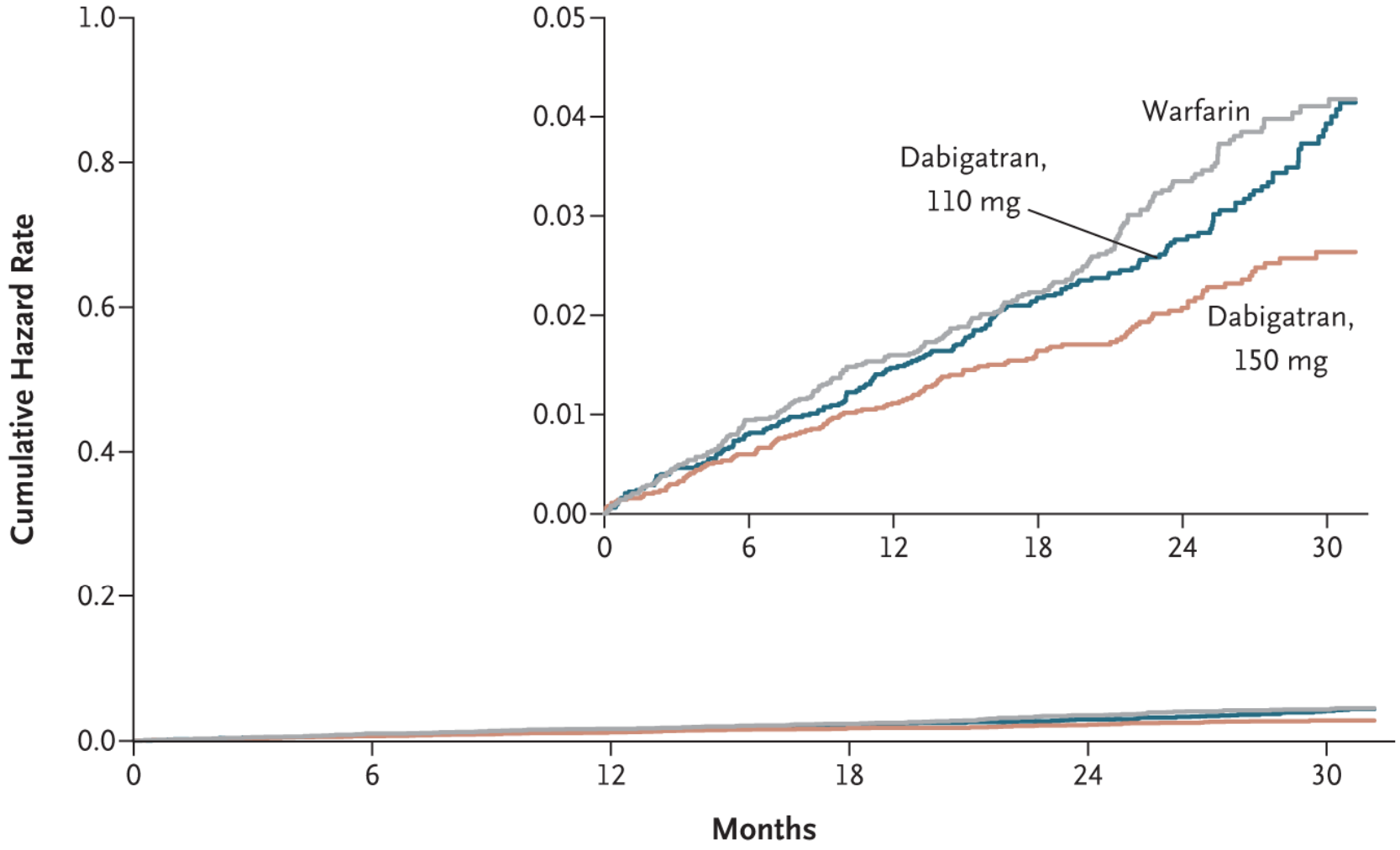
Dabigatran Outcomes

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	
	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, 0.34	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.

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. Epub 2009 Aug 30. Erratum in: N Engl J Med. 2010 Nov 4;363(19):1877.



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.

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. Epub 2009 Aug 30. Erratum in: N Engl J Med. 2010 Nov 4;363(19):1877.

Safety of Dabigatran

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

* 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.

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. Epub 2009 Aug 30. Erratum in: N Engl J Med. 2010 Nov 4;363(19):1877.

Side Effects of Dabigatran

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)

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. Epub 2009 Aug 30. Erratum in: N Engl J Med. 2010 Nov 4;363(19):1877.

Conclusions of RE-LY

- Warfarin group time in therapeutic range = 65%
- Dabigatran **150mg** bid vs warfarin (%/yr)
  - Reduced stroke or embolism (1.1% vs. 1.7%)
  - Reduced Ischemic stroke (0.9% vs. 1.2%)
  - Reduced hemorrhagic CVA (0.1% vs. 0.4%)
  - Mortality benefit?
    - Vascular death (2.3% vs. 2.7%, *p=0.04*)
    - All cause death (3.6% vs. 4.1%, *p=0.051*)
  - *Trended* increased MI (0.7% vs. 0.5%, *p=0.07*)

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. Epub 2009 Aug 30. Erratum in: N Engl J Med. 2010 Nov 4;363(19):1877.
Jeffrey, Susan. "RE-LY: Post hoc analysis confirms benefit of dabigatran relative to warfarin at all INR levels." theheart.org by WebMD. 22 Feb. 2012 <http://www.theheart.org/article/1024935.do>.

Conclusions of RE-LY

- Dabigatran 150mg bid vs warfarin (%/yr)
  - Reduced Life threatening bleed (1.5% vs. 1.8%)
  - Reduced minor bleeding (14.8% vs. 16.4%)
  - Increased Major GI bleeding (1.5% vs. 1.0%)
  - Increased dyspepsia (11.3% vs. 5.8% total)
  - Increased discontinuation rate
    - 16% vs. 10% at 1 year
    - 21% vs. 17% at 2 years

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. Epub 2009 Aug 30. Erratum in: N Engl J Med. 2010 Nov 4;363(19):1877.

FDA Approval of Dabigatran (Pradaxa)
October 2010

- Indicated to reduce risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
- 150mg po bid recommended dose
- 75mg po bid recommended for patients with significant renal failure (Creatinine clearance 15-30mL/min)
- No recommendation for dosing on dialysis

Pradaxa [Package Insert]. Ridgefield, CT: Boehringer Ingelheim, November 2011.

Why not 110mg po bid?

- No advantage over warfarin to prevent ischemic stroke (1.3% vs. 1.1%, p=0.35)
- But did decrease bleeding
  - Major bleed 2.7% vs. 3.4%
  - Minor bleed 13.2% vs. 16.4%
  - Intracranial bleed 0.2% vs. 0.7%

Wood, Shelley. "Dabigatran Q+A: The who, when, and how for switching, starting, and stopping the new oral anticoagulant." theheart.org by WebMD. 7 Feb. 2012 <http://www.theheart.org/article/1142899.do>.

Why 75mg po bid?

- Dose not studied in the RE-LY trial
- Based on pharmacokinetic data of excretion

Wood, Shelley. "Dabigatran Q+A: The who, when, and how for switching, starting, and stopping the new oral anticoagulant." theheart.org by WebMD. 7 Feb. 2012 <http://www.theheart.org/article/1142899.do>.

What does "Non-Valvular" Mean?

- Not clearly defined
- Valvular atrial fibrillation
  - Severe mitral stenosis
  - Mechanical or prosthetic heart valves
  - Any valvular lesion requiring surgery

Pearls for Dabigatran

- For surgery
  - Hold 1-2 days if normal renal function
  - Hold 3-5 days for impaired renal function (CrCl <50mL/min)
- Interaction with Dronederone (Multaq) [and ketoconazole]
  - Consider reducing dose to 75mg b.i.d. for CrCl 30-50mL/min
- Rifampin is contraindicated due to increased gut excretion of dabigatran
- No specific antidote for bleeding
  - Stop dabigatran immediately
  - Dabigatran is dialyzable

Wood, Shelley. "Dabigatran Q+A: The who, when, and how for switching, starting, and stopping the new oral anticoagulant." theheart.org by WebMD. 7 Feb. 2012 <http://www.theheart.org/article/1142899.do>.
Pradaxa [Package Insert]. Ridgefield, CT: Boehringer Ingelheim, November 2011.

Converting warfarin/Dabigatran

- From warfarin to dabigatran
  - Stop warfarin, start dabigatran when INR <2.0
- From dabigatran to warfarin
  - start warfarin x days before stopping dabigatran
    - Normal renal function: 3 days
    - CrCl 30-50mL/min: 2 days
    - CrCl 15-30mL/min: 1 day
    - CrCl <15 mL/min: no recommendation

Pradaxa [Package Insert]. Ridgefield, CT: Boehringer Ingelheim, November 2011.

Risk of Myocardial Infarction with Dabigatran

- RE-LY
  - 0.74% vs. 0.53%/year (p 0.07)
- Meta-analysis of 30,514 patients
  - RE-LY =
    - 59% of patients &
    - 74% of events!
  - Duration of other trials ≅ 6 months or less
- # Needed to harm = 476

Study, y	Dabigatran, No. ACEv	Dabigatran, No. No Event	Control, No. ACEv	Control, No. No Event	Odds Ratio (95% CI)
RE-NOVATE,[10] 2007	13	2296	9	1133	0.71 (0.30-1.67)
RE-MODEL,[11] 2007	10	1372	4	690	1.26 (0.39-4.02)
PETRO,[12] 2007	2	443	0	70	0.79 (0.04-16.73)
RE-LY original,[2,3] 2009	175	11916	63	5959	1.39 (1.04-1.86)
RE-COVER,[13] 2009	4	1269	2	1264	1.99 (0.36-10.90)
RE-DEEM,[14] 2011	32	1458	4	313	1.72 (0.60-4.89)
RE-NOVATE II,[15] 2011	1	1009	1	1002	0.99 (0.06-15.90)
FE model					1.33 (1.03-1.71)

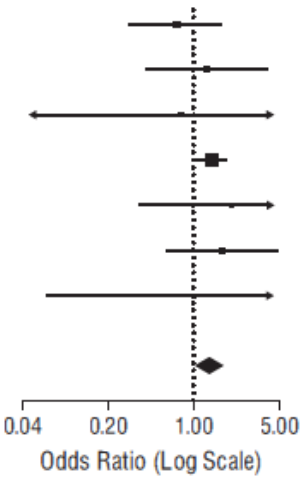
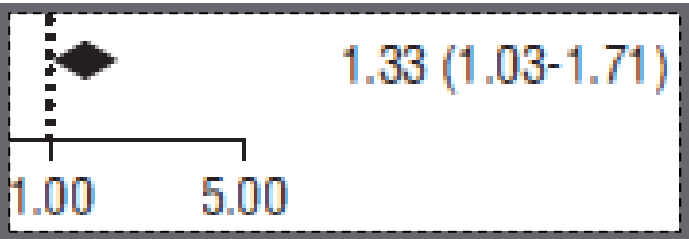


Figure 2. Risk of myocardial infarction and acute coronary syndrome across 7 studies, including original Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) results. ACEv indicates acute coronary events; FE, fixed effects; PETRO, Prevention of Embolic and Thrombotic Events in Patients With 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).



Uchino K, Hernandez AV. Dabigatran Association With Higher Risk of Acute Coronary Events: Meta-analysis of Noninferiority Randomized Controlled Trials. Arch Intern Med. 2012 Jan 9.

Dabigatran Shelf Life

- Initial concern for hygroscopic effects on capsules
  - Initial guidance was to use within 30 days of opening bottle/exposing to air
- Current PI states that capsules should be used within 4 months of opening bottle

Pradaxa [Package Insert]. Ridgefield, CT: Boehringer Ingelheim, November 2011.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

- ROCKET-AF Trial: Rivaroxaban
  - Direct Factor Xa Inhibitor
  - Serum half life 5-9 hours
  - No need to monitor anticoagulation
  - Combined renal and gut elimination
  - Rapid onset – 1 to 4 hours
- Randomized trial of rivaroxaban 20mg daily vs. warfarin

Abdulsattar Y, Bhambri R, Nogid A. Rivaroxaban (Xarelto) for the Prevention of Thromboembolic Disease: An Inside Look at the Oral Direct Factor Xa Inhibitor. P T. 2009 May;34(5):238-244.

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91.

ROCKET-AF Inclusion Criteria

- Non-valvular atrial fibrillation with at least moderate stroke risk (ie $CHADS_2 \geq 2$)
  - History of stroke, TIA, or systemic embolism OR
  - At least 2 of the following risk factors:
    - CHF or LVEF ≤35%
    - Hypertension
    - Age ≥75 years
    - Diabetes

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91.

ROCKET-AF
Summary of Enrollment

- 14,264 patient enrolled
- Median age 73 years
- Mean $CHADS_2$ score = 3.5
- 62% had prior treatment with warfarin

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91.

Outcomes of ROCKET-AF

- Median followup 1.9 years
- Designed as noninferiority trial
  - Allowed for superiority testing of secondary and safety endpoints
- Primary outcome
  - Stroke or systemic embolism
- Secondary outcome
  - Composite of stroke, systemic embolism, or death from cardiovascular causes
  - Composite of stroke, systemic embolism, death from cardiovascular causes, or myocardial infarction
  - Individual components of the composite end points
- Safety
  - Composite of major and nonmajor clinically relevant bleeding events

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91.

Outcomes

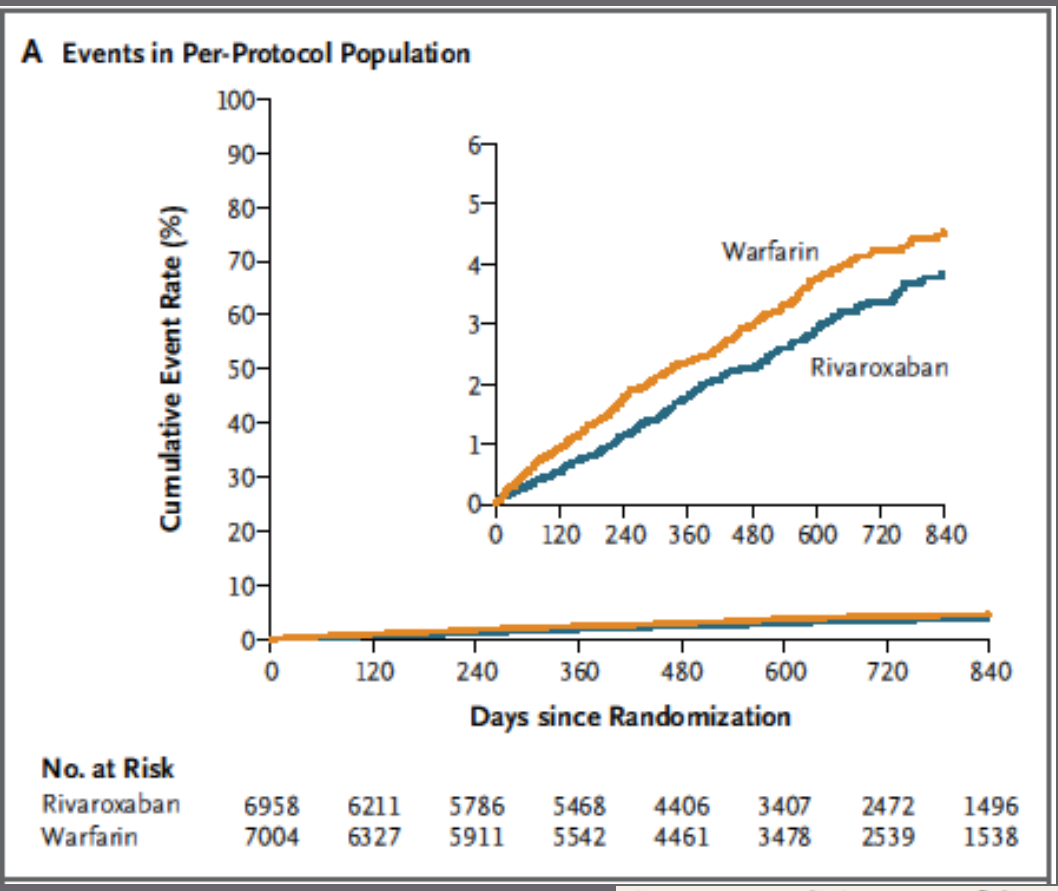
Table 2. Primary End Point of Stroke or Systemic Embolism.*

Study Population	Rivaroxaban			Warfarin			Hazard Ratio (95% CI)†	P Value	
	No. of Patients	No. of Events	Event Rate	No. of Patients	No. of Events	Event Rate		Noninferiority	Superiority
			no./100 patient-yr			*no./100 patient-yr*			
Per-protocol, as-treated population‡	6958	188	1.7	7004	241	2.2	0.79 (0.66–0.96)	<0.001	
Safety, as-treated population	7061	189	1.7	7082	243	2.2	0.79 (0.65–0.95)		0.02
Intention-to-treat population§	7081	269	2.1	7090	306	2.4	0.88 (0.75–1.03)	<0.001	0.12
During treatment		188	1.7		240	2.2	0.79 (0.66–0.96)		0.02
After discontinuation		81	4.7		66	4.3	1.10 (0.79–1.52)		0.58

* The median follow-up period was 590 days for the per-protocol, as-treated population during treatment; 590 days for the safety, as-treated population during treatment; and 707 days for the intention-to-treat population.
† Hazard ratios are for the rivaroxaban group as compared with the warfarin group.
‡ The primary analysis was performed in the as-treated, per-protocol population during treatment.
§ Follow-up in the intention-to-treat population continued until notification of study termination.

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91.

Primary Outcome



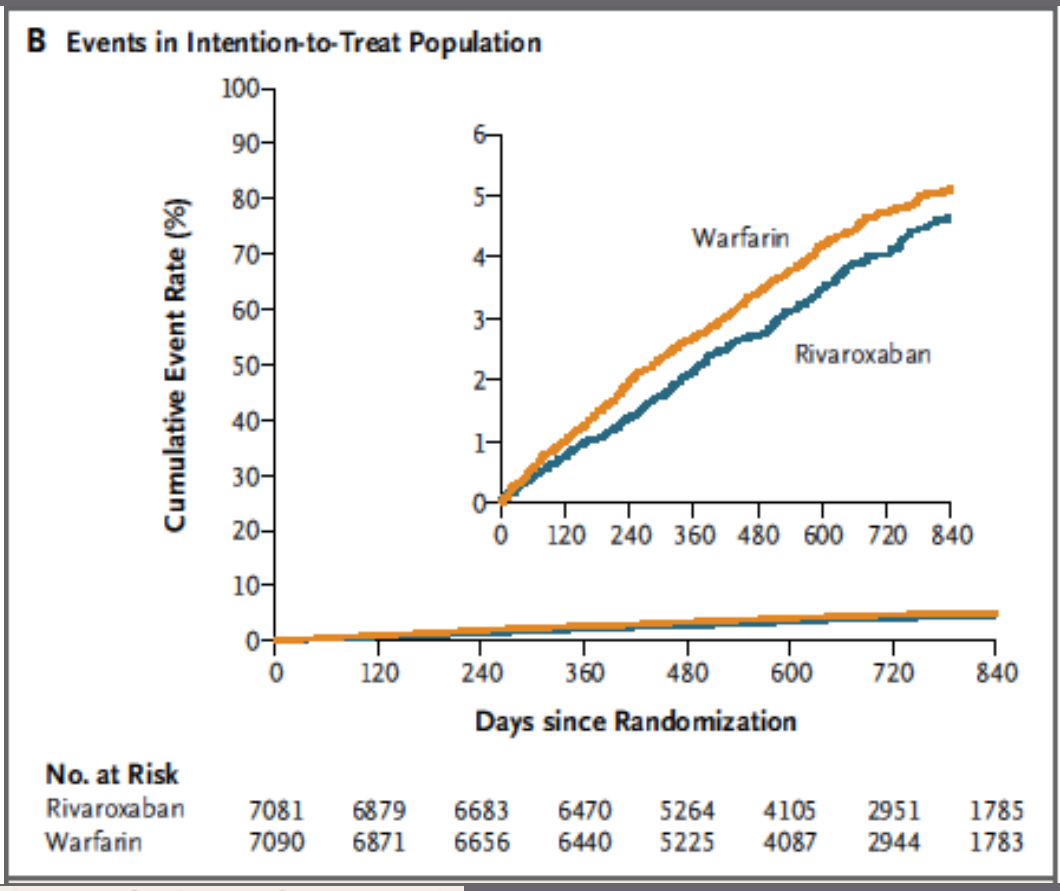


Figure 1. Cumulative Rates of the Primary End Point (Stroke or Systemic Embolism) in the Per-Protocol Population and in the Intention-to-Treat Population.

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91.

Secondary Outcomes

Online Table 4. Secondary Efficacy Outcomes* by Treatment Group†

	Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin	
	Total	Event Rate (100 Pt-Yr)‡	Total	Event Rate (100 Pt-Yr)‡	Hazard Ratio (95% CI)§	P Value‖
Secondary efficacy endpoints, no. (%)¶						
Stroke	184 (2.61)	1.65	221 (3.12)	1.96	0.85 (0.70, 1.03)	0.092
Hemorrhagic	29 (0.41)	0.26	50 (0.71)	0.44	0.59 (0.37, 0.93)	0.024
Ischemic	149 (2.11)	1.34	161 (2.27)	1.42	0.94 (0.75, 1.17)	0.581
Non-CNS systemic embolism, no. (%)	5 (0.07)	0.04	22 (0.31)	0.19	0.23 (0.09, 0.61)	0.003
Myocardial infarction, no. (%)	101 (1.43)	0.91	126 (1.78)	1.12	0.81 (0.63, 1.06)	0.121
All-cause mortality, no. (%)**	208 (2.95)	1.87	250 (3.53)	2.21	0.85 (0.70, 1.02)	0.073

Supplement to: Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91

Bleeding Events

Table 3. Rates of Bleeding Events.*

Variable	Rivaroxaban (N=7111)		Warfarin (N=7125)		Hazard Ratio (95% CI)†	P Value‡
	Events	Event Rate	Events	Event Rate		
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*		
Principal safety end point: major and nonmajor clinically relevant bleeding§	1475 (20.7)	14.9	1449 (20.3)	14.5	1.03 (0.96–1.11)	0.44
Major bleeding						
Any	395 (5.6)	3.6	386 (5.4)	3.4	1.04 (0.90–1.20)	0.58
Decrease in hemoglobin ≥2 g/dl	305 (4.3)	2.8	254 (3.6)	2.3	1.22 (1.03–1.44)	0.02
Transfusion	183 (2.6)	1.6	149 (2.1)	1.3	1.25 (1.01–1.55)	0.04
Critical bleeding¶	91 (1.3)	0.8	133 (1.9)	1.2	0.69 (0.53–0.91)	0.007
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5	0.50 (0.31–0.79)	0.003
Intracranial hemorrhage	55 (0.8)	0.5	84 (1.2)	0.7	0.67 (0.47–0.93)	0.02
Nonmajor clinically relevant bleeding	1185 (16.7)	11.8	1151 (16.2)	11.4	1.04 (0.96–1.13)	0.35

* All analyses of rates of bleeding are based on the first event in the safety population during treatment.
† Hazard ratios are for the rivaroxaban group as compared with the warfarin group and were calculated with the use of Cox proportional-hazards models with the study group as a covariate.
‡ Two-sided P values are for superiority in the rivaroxaban group as compared with the warfarin group.
§ Minimal bleeding events were not included in the principal safety end point.
¶ Bleeding events were considered to be critical if they occurred in intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular (with compartment syndrome), or retroperitoneal sites.

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91.

Conclusions of ROCKET-AF

- Warfarin group time in therapeutic range = 58%
- Rivaroxaban 20mg daily vs warfarin (%/yr)
  - Per-Protocol noninferior stroke or embolism (1.7% vs. 2.2%)
  - As treated composite of major and nonmajor clinically relevant bleeding events reduced (1.7% vs. 2.2%)
  - Intention to treat noninferior stroke or embolism (2.1% vs. 2.4%)
  - Increased major GI bleeding (total 3.2% vs. 2.2%)
  - Decreased rate of critical, fatal, and intracranial bleed

O'Riordan, Michael. "FDA approves rivaroxaban for stroke prevention in AF patients." theheart.org by WebMD. 22 Feb. 2012 <http://www.theheart.org/article/1304213.do>.
Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91.

Increased risk of Stroke when stopping rivaroxaban

- At the end of study, warfarin patients were generally maintained, and rivaroxaban patients were transitioned to warfarin
- During the 28 days following the end of the study, there were 22 strokes in the 4637 (0.5%) patients taking XARELTO vs. 6 in the 4691 (0.1%) patients taking warfarin
- # Needed to Harm = 250

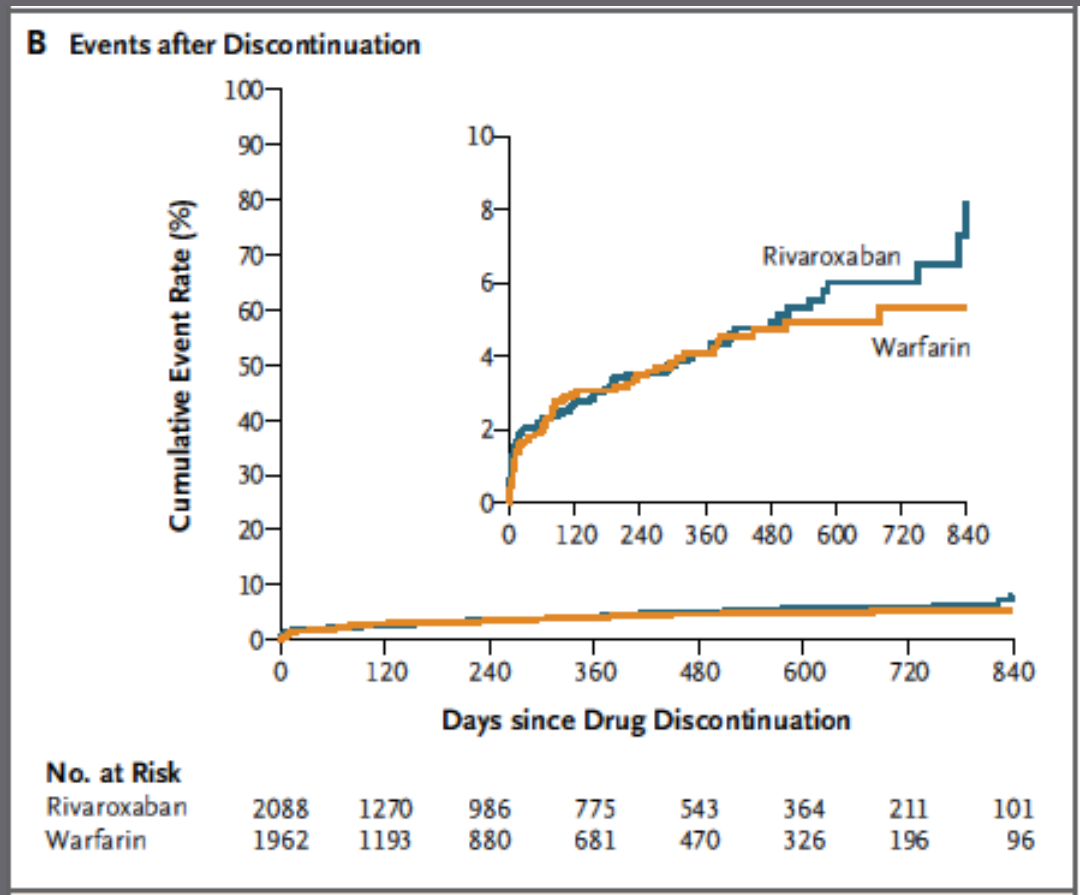


Figure 2. Cumulative Rates of the Primary End Point during Treatment and after Discontinuation in the Intention-to-Treat Population.

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91.
Xarelto [Package Insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc., December 2011.

FDA Approval of Rivaroxaban (Xarelto) November 2011

- Indicated to reduce risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
- Also has indication for DVT prophylaxis for knee & hip replacement
- 20mg po daily with evening meal
- 15mg po daily recommended for patients with renal failure (Creatinine clearance 15-50mL/min)

O'Riordan, Michael. "FDA approves rivaroxaban for stroke prevention in AF patients." theheart.org by WebMD. 22 Feb. 2012 <http://www.theheart.org/article/1304213.do>.
Xarelto [Package Insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc., December 2011.

FDA Approval of Rivaroxaban
November 2011

- Black Box Warning!
  - Discontinuing Xarelto places patients at an increased risk of thrombotic events. if anticoagulation with Xarelto must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant

Xarelto [Package Insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc., December 2011.

Converting warfarin/Rivaroxaban

- From warfarin to rivaroxaban
  - Stop warfarin, and start rivaroxaban when INR ≤3.
- From rivaroxaban to warfarin
  - No clear guidance!
  - "One approach is to discontinue XARELTO and begin both a parenteral anticoagulant and warfarin at the time the next dose of XARELTO would have been taken."

Xarelto [Package Insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc., December 2011.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 5, 2012 VOL. 366 NO. 1

Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

Jessica L. Mega, M.D., M.P.H., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., Jean-Pierre Bassand, M.D., Deepak L. Bhatt, M.D., M.P.H., Christoph Bode, M.D., Paul Burton, M.D., Ph.D., Marc Cohen, M.D., Nancy Cook-Bruns, M.D., Keith A.A. Fox, M.B., Ch.B., Shinya Goto, M.D., Sabina A. Murphy, M.P.H., Alexei N. Plotnikov, M.D., David Schneider, M.D., Xiang Sun, Ph.D., Freek W.A. Verheugt, M.D and C. Michael Gibson, M.D., for the ATLAS ACS 2–TIMI 51 Investigators*

- ATLAS ACS 2 – TIMI 51 Trial
- Double blind, placebo controlled trial
- Added rivaroxaban 2.5mg or 5mg po b.i.d. to standard therapy in patients post acute coronary syndrome

http://www.kaccents.com/For_Home/Garden/Romans/15666.htm

Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FW, Gibson CM; ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012 Jan 5;366(1):9-19

ATLAS ACS2 – TIMI 51 Inclusion Criteria

- Acute coronary syndrome hospitalization in past 7 days
  - Unstable angina, NSTEMI, STEMI
- Patients ≤55 years old must have either
  - Prior myocardial infarction OR
  - Diabetes Mellitus
- Exclusion criteria
  - Platelets <90,000/mm3
  - Hemoglobin < 10 g/dL
  - included a platelet count
  - Creatinine clearance < 30 mL/min
  - Clinically significant GI bleed in past 12 months
  - Prior intracranial hemorrhage
  - Previous ischemic stroke or transient ischemic attack in patients taking both aspirin and a thienopyridine

ATLAS ACS2 – TIMI 51
Summary of Enrollment

- 15,526 patients enrolled
- Mean age ≅ 62 years

Table 1. Baseline Characteristics of the Patients.*

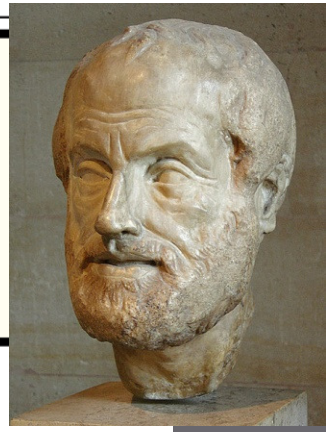
Characteristic	Rivaroxaban		Placebo (N = 5176)
	2.5 mg Twice Daily (N = 5174)	5 mg Twice Daily (N = 5176)	
Medical history — no. (%)			
Previous myocardial infarction	1363 (26.3)	1403 (27.1)	1415 (27.3)
Hypertension	3470 (67.1)	3499 (67.6)	3494 (67.5)
Diabetes	1669 (32.3)	1648 (31.8)	1647 (31.8)
Hypercholesterolemia	2498 (48.3)	2544 (49.1)	2496 (48.2)
Index diagnosis — no. (%)			
STEMI	2601 (50.3)	2584 (49.9)	2632 (50.9)
NSTEMI	1321 (25.5)	1335 (25.8)	1323 (25.6)
Unstable angina	1252 (24.2)	1257 (24.3)	1221 (23.6)
PCI or CABG for index event — no. (%)	3138 (60.6)	3123 (60.3)	3126 (60.4)
Medications — no. (%)			
Aspirin	5105 (98.7)	5099 (98.5)	5108 (98.7)
Thienopyridine	4790 (92.6)	4812 (93.0)	4811 (92.9)
Beta-blocker	3426 (66.2)	3394 (65.6)	3444 (66.5)
ACE inhibitor or ARB	2022 (39.1)	1977 (38.2)	2050 (39.6)
Statin	4304 (83.2)	4342 (83.9)	4321 (83.5)
Calcium-channel blocker	820 (15.8)	742 (14.3)	764 (14.8)

ATLAS ACS2 – TIMI 51
Outcomes – Estimated 2 year event rates

	2.5mg bid	5mg bid	Placebo	NNT	P
Death from cardiovascular causes, myocardial infarction, or stroke	9.1	8.8	10.7	63/53	0.02/0.03
Myocardial infarction	6.1	4.9	6.6	200/59	0.3/0.02
Death from any cause	2.9	4.4	4.5	63/1000	0.002/0.66
TIMI Major Bleeding	1.8	2.4	0.6	(-83)/(-56)	<0.001/ <0.001

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 15, 2011 VOL. 365 NO. 11



Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

- Aristotle Trial: Apixaban
  - Direct selective Factor Xa Inhibitor
  - Rapid onset – 3 hours
  - Half life approximately 12 hours
  - Non-renal elimination
  - Randomized, double blind trial of apixaban 5 mg (or 2.5mg) po b.i.d. vs. warfarin (target INR 2-3)

http://www.stpeterslist.com/738/st-thomas-introduction-to-the-politics-8-comments-on-aristotles-text/aristoteles_louvre/
ARISTOTLE trial
APPRAISE trial

ARISTOSTLE Inclusion Criteria

- Atrial fibrillation
  - At enrollment OR
  - At least 2 episodes separated by 2 weeks documented in past 1 year
- At least 1 risk factor
  - Age ≥ 75
  - Prior stroke, TIA or systemic embolism
  - CHF in prior 3 months OR LVEF ≤40%
  - Diabetes Mellitus
  - Hypertension requiring medication treatment
- 2.5mg b.i.d. dose used in patients with 2 of the following:
  - Age ≥ 80 years,
  - Weight ≤ 60kg
  - Creatinine ≥ 1.5 mg per deciliter

Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011 Sep 15;365(11):981-92

ARISTOSTLE
Summary of Enrollment

- 18,201 patients enrolled
- Median age 71 years
- Mean $CHADS_2$ score was 2.1
- 43% had prior treatment with warfarin
- 4.7% of apixaban patients on 2.5mg dose

Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011 Sep 15;365(11):981-92

ARISTOTLE Outcomes

- Median followup 1.8 years
- Designed as noninferiority trial, but also tested for superiority
- Primary Outcome
  - stroke or systemic embolism
- Secondary Outcome
  - All cause death
  - Also myocardial infarction
- Safety
  - Major bleeding

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ARISTOTLE Outcomes

Table 2. Efficacy Outcomes.*

Outcome	Apixaban Group (N=9120)		Warfarin Group (N=9081)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	*%/yr*	*no.*	*%/yr*		
Primary outcome: stroke or systemic embolism	212	1.27	265	1.60	0.79 (0.66–0.95)	0.01
Stroke	199	1.19	250	1.51	0.79 (0.65–0.95)	0.01
Ischemic or uncertain type of stroke	162	0.97	175	1.05	0.92 (0.74–1.13)	0.42
Hemorrhagic stroke	40	0.24	78	0.47	0.51 (0.35–0.75)	<0.001
Systemic embolism	15	0.09	17	0.10	0.87 (0.44–1.75)	0.70
Key secondary efficacy outcome: death from any cause	603	3.52	669	3.94	0.89 (0.80–0.998)	0.047
Other secondary outcomes						
Stroke, systemic embolism, or death from any cause	752	4.49	837	5.04	0.89 (0.81–0.98)	0.02
Myocardial infarction	90	0.53	102	0.61	0.88 (0.66–1.17)	0.37
Stroke, systemic embolism, myocardial infarction, or death from any cause	810	4.85	906	5.49	0.88 (0.80–0.97)	0.01
Pulmonary embolism or deep-vein thrombosis	7	0.04	9	0.05	0.78 (0.29–2.10)	0.63

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ARISTOTLE Safety Outcomes

Table 3. Bleeding Outcomes and Net Clinical Outcomes.*

Outcome	Apixaban Group (N=9088)		Warfarin Group (N=9052)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	*%/yr*	*no.*	*%/yr*		
Primary safety outcome: ISTH major bleeding†	327	2.13	462	3.09	0.69 (0.60–0.80)	<0.001
Intracranial	52	0.33	122	0.80	0.42 (0.30–0.58)	<0.001
Other location	275	1.79	340	2.27	0.79 (0.68–0.93)	0.004
Gastrointestinal	105	0.76	119	0.86	0.89 (0.70–1.15)	0.37
Major or clinically relevant nonmajor bleeding	613	4.07	877	6.01	0.68 (0.61–0.75)	<0.001
GUSTO severe bleeding	80	0.52	172	1.13	0.46 (0.35–0.60)	<0.001
GUSTO moderate or severe bleeding	199	1.29	328	2.18	0.60 (0.50–0.71)	<0.001
TIMI major bleeding	148	0.96	256	1.69	0.57 (0.46–0.70)	<0.001
TIMI major or minor bleeding	239	1.55	370	2.46	0.63 (0.54–0.75)	<0.001
Any bleeding	2356	18.1	3060	25.8	0.71 (0.68–0.75)	<0.001
Net clinical outcomes						
Stroke, systemic embolism, or major bleeding	521	3.17	666	4.11	0.77 (0.69–0.86)	<0.001
Stroke, systemic embolism, major bleeding, or death from any cause	1009	6.13	1168	7.20	0.85 (0.78–0.92)	<0.001

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Conclusions of ARISTOTLE

- Apixaban 5mg bid vs warfarin (%/yr)
  - Reduced stroke or embolism (1.3% vs. 1.6%)
  - Reduced all cause death (3.5% vs. 3.9%)
  - Reduced major bleeding (2.1% vs. 3.1%)
  - Reduced intracranial bleed (0.3% vs. 0.8%)
  - No difference in
    - Ischemic stroke (1.0% vs. 1.1%)
    - MI (0.5% vs. 0.6%)

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FDA Approval of apixaban (Eliquis)?

- Approved in Europe for DVT prophylaxis for knee and hip surgery (2.5mg po daily)

Comparing the Trials
Outcomes

Patient Population	Dabigatran	Rivaroxaban	Apixaban
Age	71 ± 8	73	70
$CHADS_2$ Score	2.1 ± 1.1	3.5 ± 1	2.1 ± 1.1
Drug/Coumadin (incidence per year)			
Any Stroke or Embolism	1.1%/1.7%	2.1%/2.4%	1.3%/1.6%
Ischemic stroke	0.9%/1.2%	2.1%/2.3%	1.0%/1.1%
Hemorrhagic stroke	0.1%/0.4%	0.4%/0.7%	0.2%/0.5%
All cause death	3.6%/4.1%	3.0%/3.5%	3.4%/3.9%
Major Bleed	3.1%/3.4%	5.6%/5.4%	4.1%/6.0%
GI Bleed	1.5%/1.0%	3.2%/2.2%	0.8%/0.9%

Comparing the Trials
Number Needed to Treat/Harm

Patient Population	Dabigatran	Rivaroxaban	Apixaban
Age	71 ± 8	73	70
$CHADS_2$ Score	2.1 ± 1.1	3.5 ± 1	2.1 ± 1.1
# Needed to Treat (v warfarin for 1 year)			
Any Stroke or Embolism	167	333 (ITT)	303
Ischemic stroke	333	1250 (NS)	1250 (NS)
Hemorrhagic stroke	357	333	434
All cause death	200 (p=0.051)	172 (p=0.073)	238 (p=0.047)
(Prevent) Major Bleed	400 (p=0.052)	-769 (NS)	51
GI Bleed	-204	-101	1000 (NS)

Conclusions

- Novel anticoagulants offer benefit of fixed doses without need for monitoring
- All 3 show reduced hemmorhagic stroke rates
- All 3 at least trend toward mortality reduction
- Dabigatran has shown reduced ischemic stroke rates
- Rivaroxaban has advantage of once a day dosing
- Apixaban shows overall less bleeding risk
- Pradaxa (Dabigatran) has concerns
  - Dyspepsia
  - Risk of Myocardial infarction?
- Xarelto (Rivaroxaban) has concerns
  - Increase risk of stroke following cessation?
- Eliquis (Apixaban) concerns?
  - Not yet approved!

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