

Prevention of Thromboembolism in Patients with Atrial Fibrillation

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Jonathan L. Halperin, M.D.

The Cardiovascular Institute
Mount Sinai Medical Center



Disclosure

Relationships with Industry

Consulting fees from the following companies involved in development of investigational drugs or devices:

- Astellas Pharma
- Bayer HealthCare
- Biotronik
- Boehringer Ingelheim
- Daiichi Sanyo Pharma
- Johnson & Johnson
- Portola Pharmaceuticals
- Sanofi-Aventis

Atrial Fibrillation

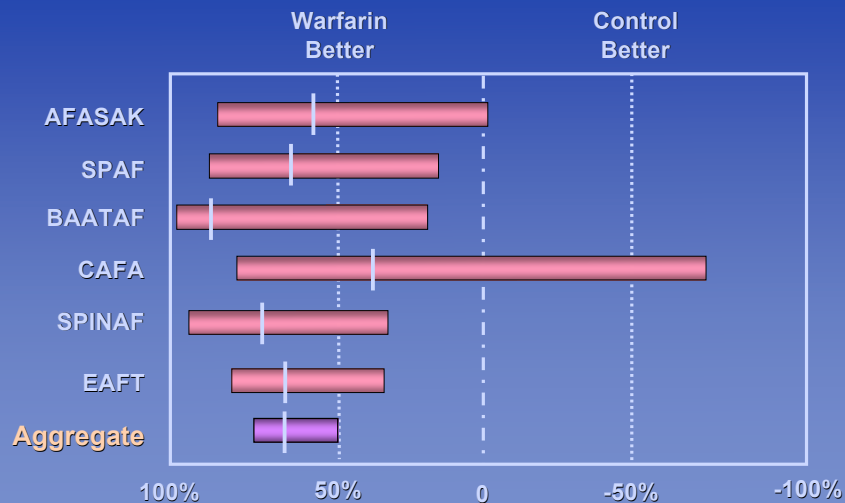
A Substantial Threat to the Brain

- Affects ~4% of people aged ≥ 60 years
~9% of those aged ≥ 80 years
- 5%/year stroke rate
- 12%/year for those with prior stroke
- \$ billions annual cost for stroke care
- Cardioembolic strokes are often disabling

AF identifies millions of people with a five-fold increased risk of stroke

Anticoagulation in Atrial Fibrillation

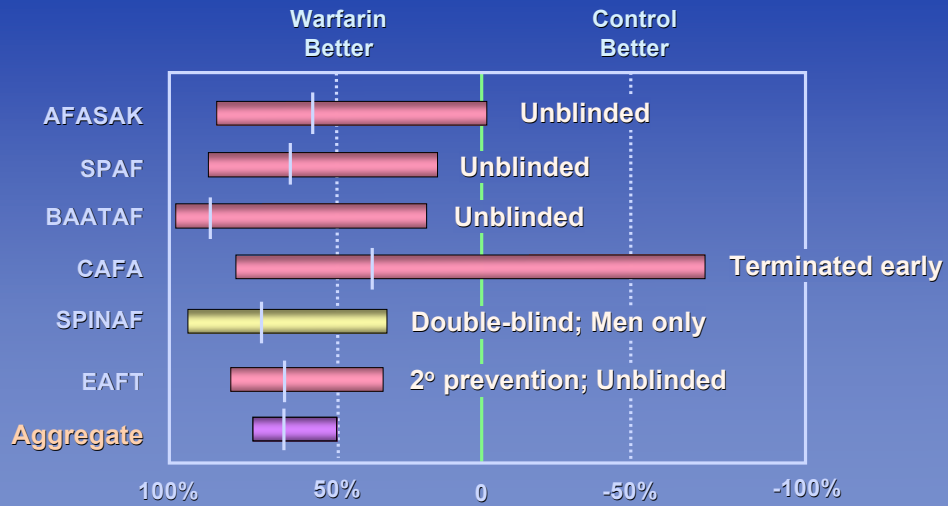
Stroke Risk Reductions



Hart R, et al. *Ann Intern Med* 2007;146:857.

Anticoagulation in Atrial Fibrillation

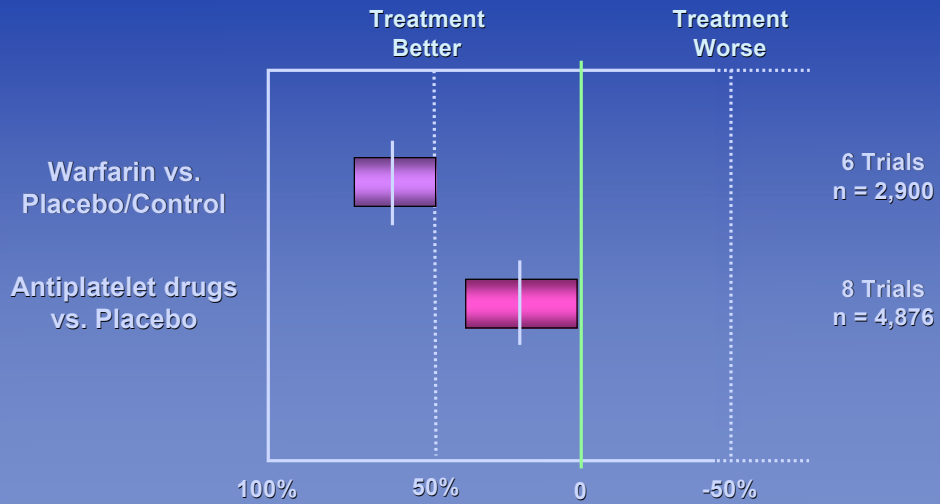
The Standard of Care for Stroke Prevention



Hart R, et al. *Ann Intern Med* 2007;146:857.

Antithrombotic Therapy for Atrial Fibrillation

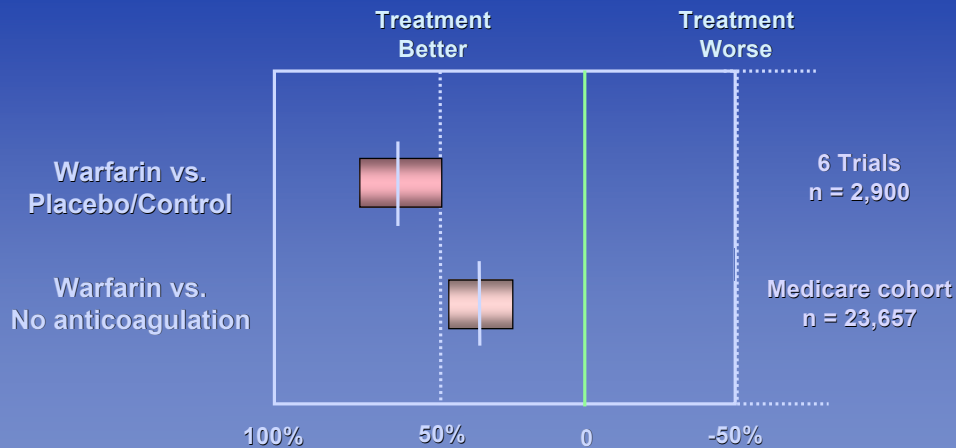
Stroke Risk Reduction



Hart R, et al. *Ann Intern Med* 2007;146:857.

Efficacy of Warfarin in Trials vs. Practice

Stroke Risk Reductions



Hart R, et al. *Ann Intern Med* 2007;146:857.
Birman-Deych E. *Stroke* 2006; 37: 1070-1074.

Intracerebral Hemorrhage

The Most Feared Complication of Antithrombotic Therapy

- >10% of intracerebral hemorrhages (ICH) occur in patients on antithrombotic therapy
- Aspirin increases the risk of ICH by ~40%
- Warfarin (INR 2-3) doubles the risk of ICH to 0.3-0.6%/year
- ICH during anticoagulation is catastrophic

Hart RG, et al. *Stroke* 2005;36:1588.

Risk Stratification in AF

Stroke Risk Factors

High-Risk Factors

- Mitral stenosis
- Prosthetic heart valve
- History of stroke or TIA

Moderate-Risk Factors

- Age >75 years
- Hypertension
- Diabetes mellitus
- Heart failure or ↓ LV function

Less Validated Risk Factors

- Age 65–75 years
- Coronary artery disease
- Female gender
- Thyrotoxicosis

Dubious Factors

- Duration of AF
- Pattern of AF
(persistent vs. paroxysmal)
- Left atrial diameter

Singer DE, et al. *Chest* 2004;126:429S.

Fang MC, et al. *Circulation* 2005; 112: 1687.

The CHADS₂ Index

Stroke Risk Score for Atrial Fibrillation

	<u>Score (points)</u>	<u>Prevalence (%)*</u>
Cardiac failure	1	32
Hypertension	1	65
Age >75 years	1	28
Diabetes mellitus	1	18
Stroke or TIA	2 (<i>should be 3</i>)	10
High risk	≥3	22
Moderate risk	1-2	33-50
Low risk	0-1	18-51

VanWalraven C, et al. *Arch Intern Med* 2003; 163:936.

* Nieuwlaet R, et al. (EuroHeart survey) *Eur Heart J* 2006 (E-published).

The CHADS₂ Index

Stroke Risk Score for Atrial Fibrillation

	Score (points)	Risk of Stroke (%/year)
	0	1.9
Approximate Risk threshold for Anticoagulation	1	2.8
	2	4.0
	3	5.9
	4	8.5
	5	12.5
	6	18.2

Van Walraven C, et al. *Arch Intern Med* 2003; 163:936.

Go A, et al. *JAMA* 2003; 290: 2685.

Gage BF, et al. *Circulation* 2004; 110: 2287.

Antithrombotic Therapy for Atrial Fibrillation

Risk Category	Recommended Therapy
No risk factors CHADS₂ = 0	Aspirin, 81-325 mg qd
One moderate risk factor CHADS₂ = 1	Aspirin, 81-325 mg/d or Warfarin (INR 2.0-3.0, target 2.5)
Any high risk factor or >1 moderate risk factor CHADS₂ ≥ 2 or Mitral stenosis	Warfarin (INR 2.0-3.0, target 2.5)
Prosthetic valve	Warfarin (INR 2.5-3.5, target 3.0)

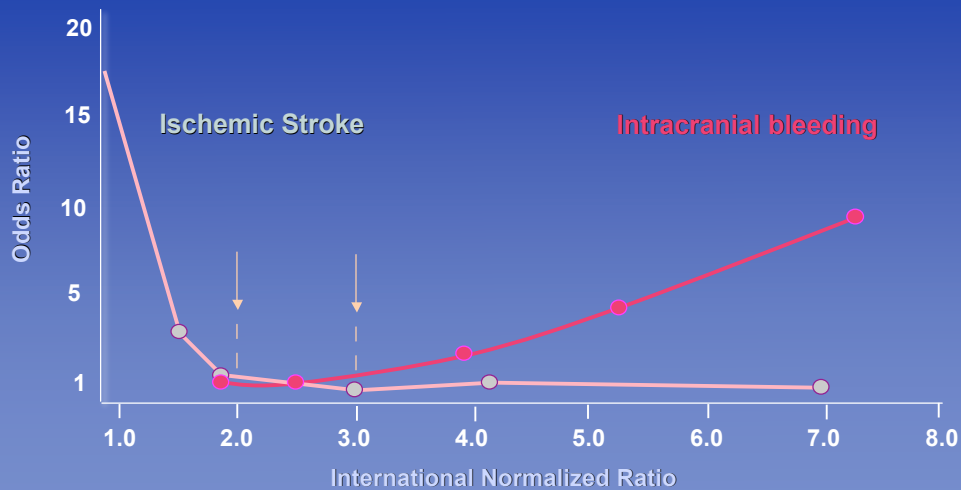
Fuster V, et al. *Eur Heart J* 2006;27:1979.



"Actually, it's more of a guideline than a rule."

- Bill Murray in Ghostbusters[©] (1984),
relaxing his rule "never to get involved with possessed people" in response to Sigourney Weaver's seductive advances.

INR at the Time of Stroke or Bleeding *Efficacy and Safety of Warfarin*



Fang MC, et al. *Ann Intern Med* 2004; 141:745.
Hylek EM, et al. *N Engl J Med* 1996; 335:540.

The ACTIVE Trials

Stroke Rates and Risk Reductions

Treatment	VKA	C+A	Aspirin
ACTIVE W (Annual Rate)	1.4	2.4	~
ACTIVE A (Annual Rate)	~	2.4	3.3
RRR versus Aspirin	-58%	-28%	~
RRR versus C+A	-42%	~	~

VKA = oral anticoagulant
C+A = clopidogrel + aspirin

Connolly SJ, et al. *Lancet* 2006; 367:1903.
Connolly SJ, et al. *N Engl J Med* 2009; 360:2066.

The Ideal Anticoagulant

Essential Properties

- Wide therapeutic margin
- Convenient dosing
- Lack food or drug interactions
- No need for laboratory monitoring
- Readily reversible effect
- Affordable

Investigational Anticoagulant Targets

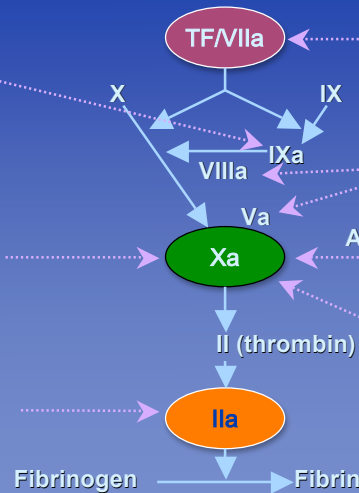
ORAL

PARENTERAL

TTP889

Rivaroxaban
Apixaban
Edoxaban
Betrixaban
YM150
LY517717
TAK 42

Dabigatran



TFPI (tifacogin)

APC (drotrecogin alfa)
STM (ART-123)

AT
Idraparinux

DX-9065a
Otamixaban

APC activated protein C
AT antithrombin
STM soluble thrombomodulin
TF tissue factor
FPI tissue factor pathway inhibitor

Adapted from Weitz JI. *Thromb Haemost* 2007; 5 Suppl 1:65-7.

Emerging Anticoagulants

Potential Alternatives to Warfarin

Thrombin inhibitors

Direct, oral

Ximelagatran

Dabigatran

Factor Xa inhibitors

Indirect, parenteral

Idraparinux

Direct, oral

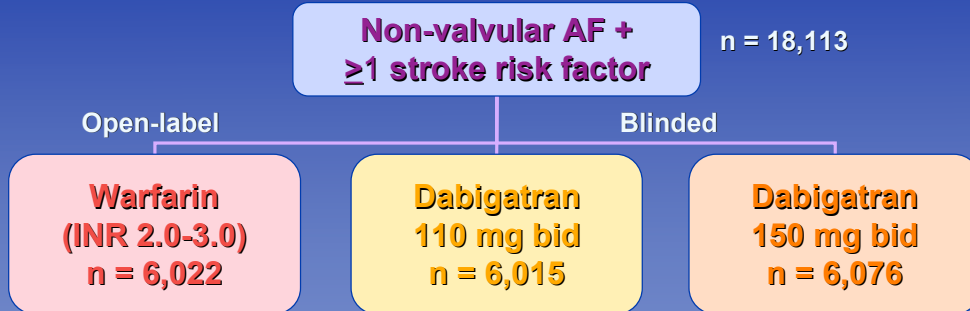
Rivaroxaban

Apixaban

others

RE-LY[®] Trial

Randomized Evaluation of Long-term Anticoagulant Therapy with Dabigatran Etexilate

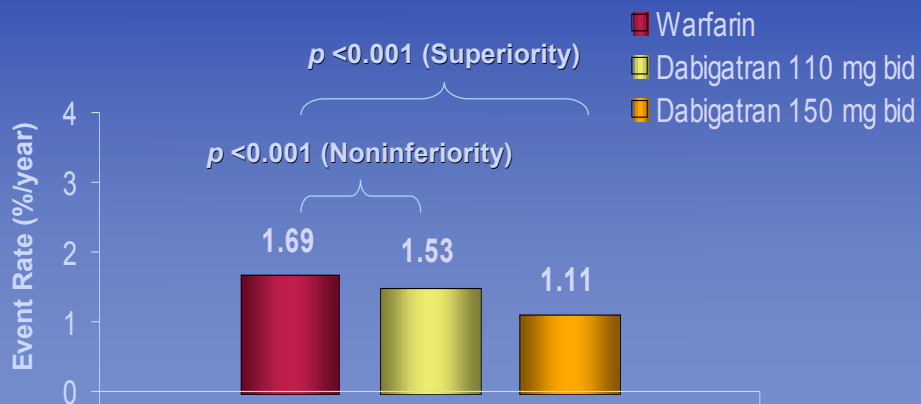


Primary objective: noninferiority vs. warfarin
Observation period: minimum 1, mean 2, maximum 3 years
Primary endpoint: all stroke + systemic embolism
Safety measure: bleeding during treatment

Connolly SJ et al. *N Engl J Med* 2009; 361, 1139.

RE-LY Trial Primary Events

All Strokes and Systemic Embolic Events

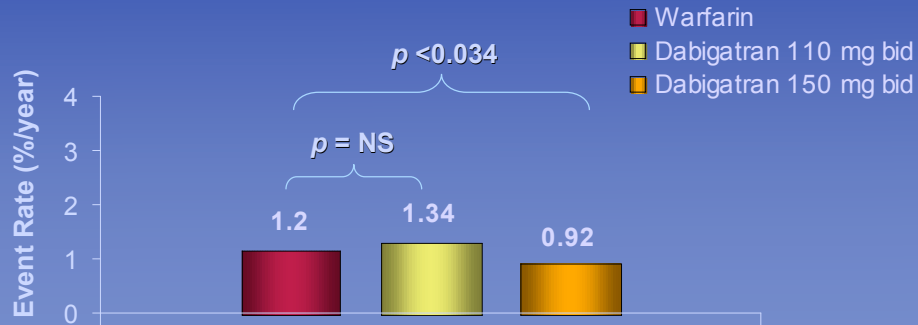


Connolly SJ et al. *N Engl J Med* 2009; 361, 1139.

RE-LY Trial

Nonhemorrhagic Stroke Events

Ischemic Strokes and Strokes of Unspecified Mechanism

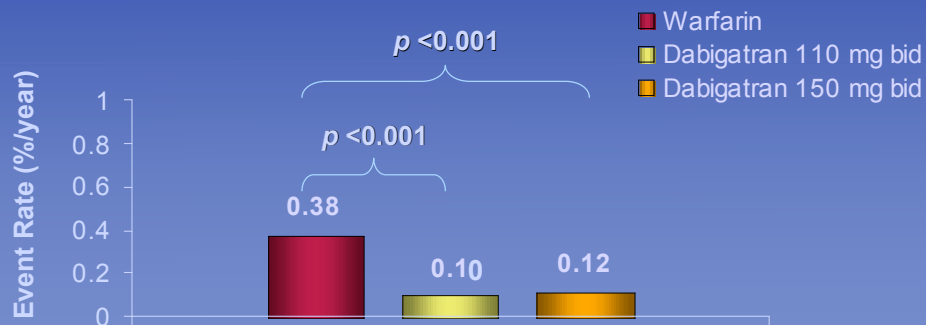


Connolly SJ et al. *N Engl J Med* 2009; 361, 1139.

RE-LY Trial

Hemorrhagic Stroke Events

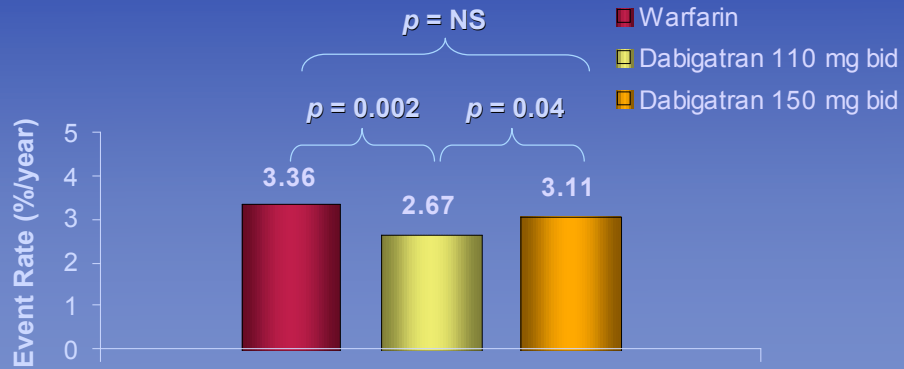
Intracerebral hemorrhages



Connolly SJ et al. *N Engl J Med* 2009; 361, 1139.

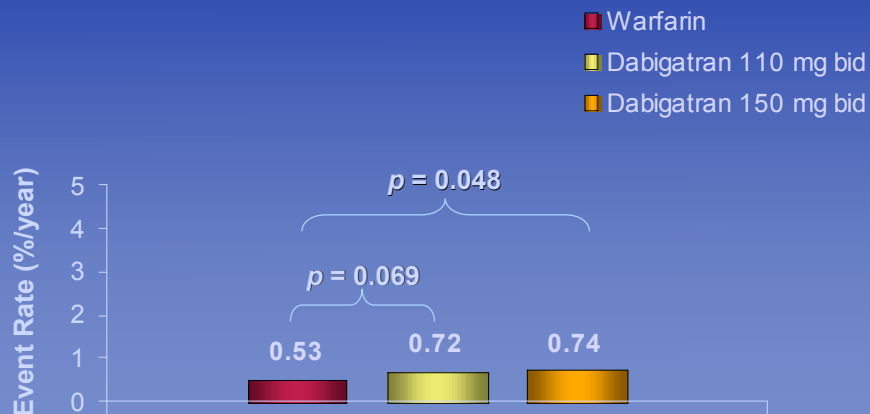
RE-LY Trial All Major Bleeding

Hgb ↓ ≥ 2 g/dl or Transfusion ≥ 2 units or Critical Site



Connolly SJ et al. *N Engl J Med* 2009; 361, 1139.

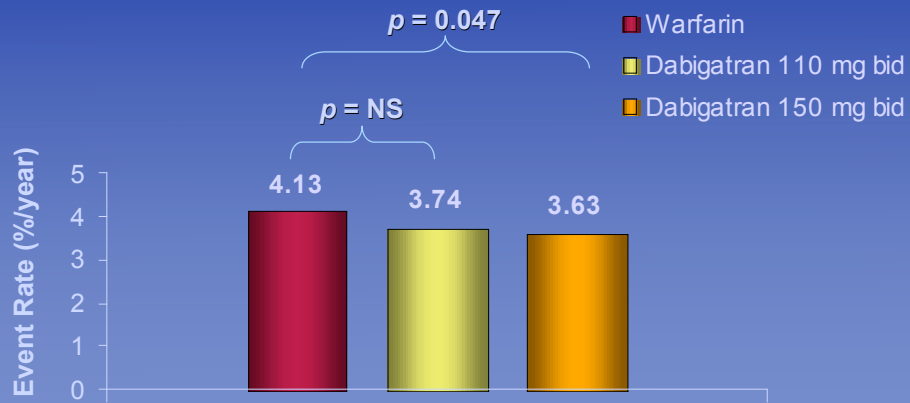
RE-LY Trial Acute Myocardial Infarction



Connolly SJ et al. *N Engl J Med* 2009; 361, 1139.

RE-LY Trial

All-Cause Mortality

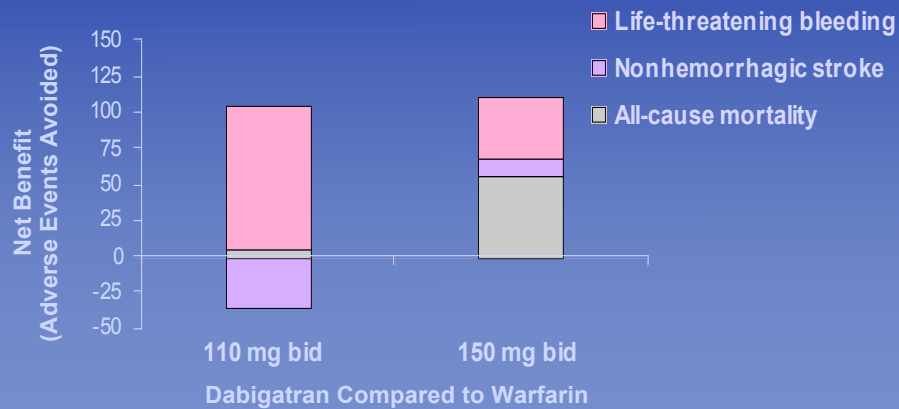


Connolly SJ et al. *N Engl J Med* 2009; 361, 1139.

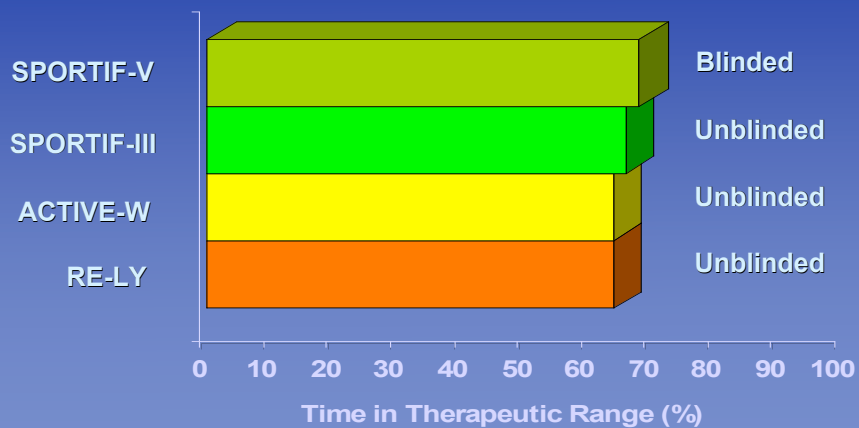
RE-LY Trial

Net Clinical Benefit

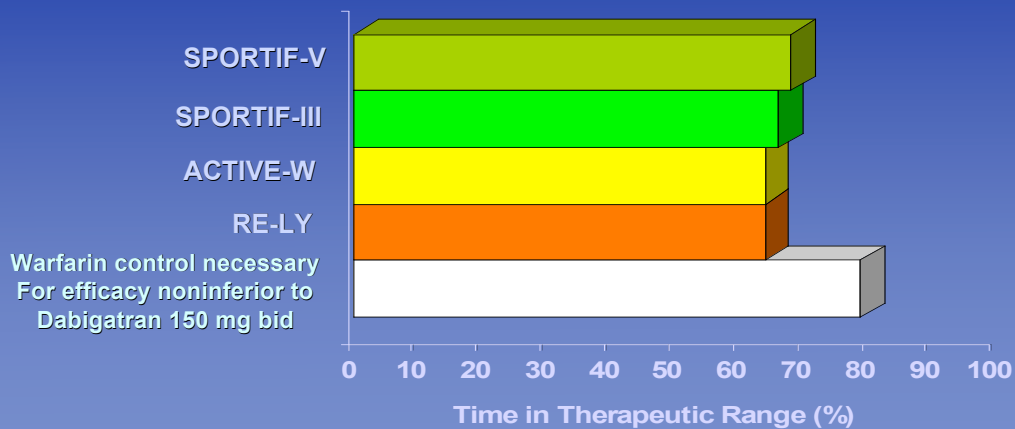
Nonhemorrhagic strokes + Life-threatening bleeds + Deaths



Quality of Warfarin Control *International Normalized Ratio*



Quality of Warfarin Control *International Normalized Ratio*



Gage BF. *N Engl J Med* 2009; 361, 1200.

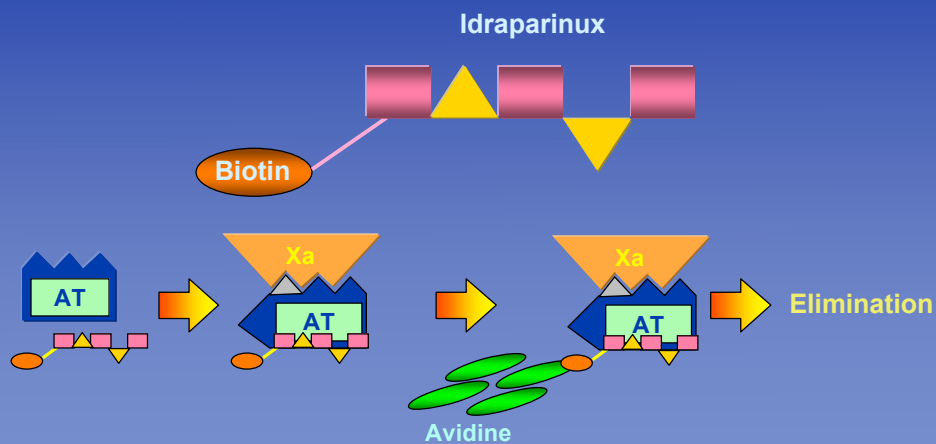
Oral Factor Xa Inhibitors

Ongoing Phase III Trials for Prevention of Stroke and Systemic Embolism in Patients with AF

Trial Acronym	Drug	Dose	Comparator	N	Risk factors
ROCKET-AF	Rivaroxaban	20 mg* qd	Warfarin (INR 2-3)	14,000	≥2
ARISTOTLE	Apixaban	5 mg b.i.d.	Warfarin (INR 2-3)	15,000	≥1
ENGAGE-AF	Edoxaban	30 mg qd 60 mg* qd	Warfarin (INR 2-3)	16,500	≥2

* Adjusted based on renal function

Biotinylated Idraparinux A Reversible Anticoagulant



Sanofi-Aventis

Emerging Anticoagulants

Regulatory Issues

- Open-label vs. blinded trial design
- Issues related to active-control trial design
- How many trials are needed?
- Avoiding “market creep” to unapproved indications
- Assessing patient-oriented outcomes

Alternatives to Anticoagulation

Atrial Fibrillation

Current approaches

Restoration and maintenance of sinus rhythm

- Antiarrhythmic drug therapy
- Catheter ablation
- Maze operation

Emerging (investigational) approaches

Isolation of the left atrial appendage

- Trans-catheter occluding devices
- Thoracoscopic epicardial plication
- Amputation

***Is atrial fibrillation the cause of stroke
or a marker of a population at risk?***

Patient Selection for Anticoagulation

Additional Considerations

- Risk of bleeding
- Newly anticoagulated vs. established therapy
- Availability of high-quality anticoagulation management program
- Patient preferences

From Fermented Sweet Clover to Molecular Targeting of Coagulation

The Promise of New Anticoagulants



The Goal:

To bring effective therapy to many more patients and prevent thousands of strokes.