

What's New in Atrial Fibrillation

Rate Control, Anticoagulation and Procedures

Society for Hospital Medicine

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Disclosure

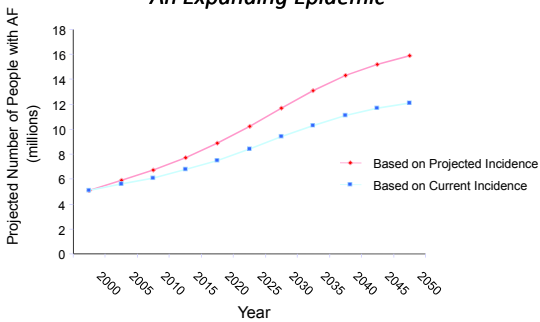
Relationships with Industry

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

- Astellas Pharma, U.S.
- Atritech, Inc.
- Bayer HealthCare
- Biotronik, Inc.
- Boehringer Ingelheim
- Daiichi Sankyo Pharma
- Johnson & Johnson
- Portola Pharmaceuticals
- Sanofi-Aventis

Projected U.S. Prevalence of AF

An Expanding Epidemic



Miyakasa Y, et al. *Circulation* 2006; 114: 119.

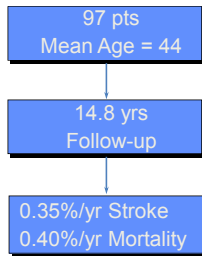
Atrial Fibrillation

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
- AF-related strokes have worse outcomes

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

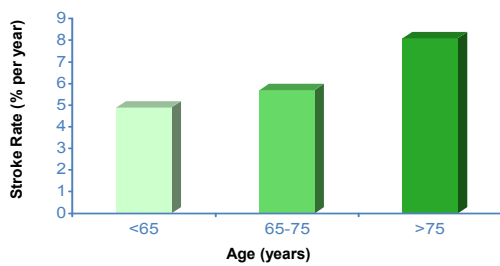
Natural History of "Lone" Atrial Fibrillation No Cardiopulmonary Disease; <60 Years Old



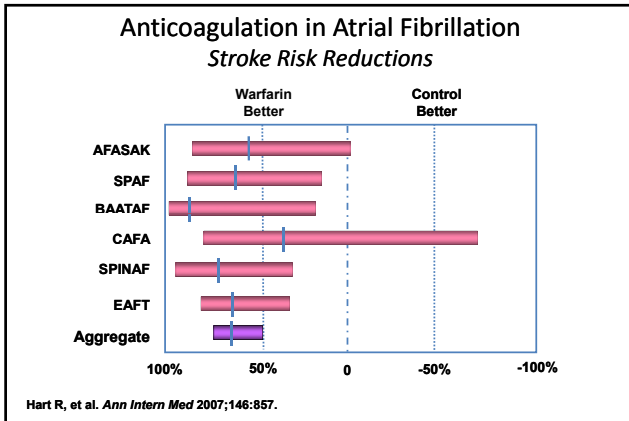
Kopecky S, et al. *N Engl J Med* 1987; 317:689.

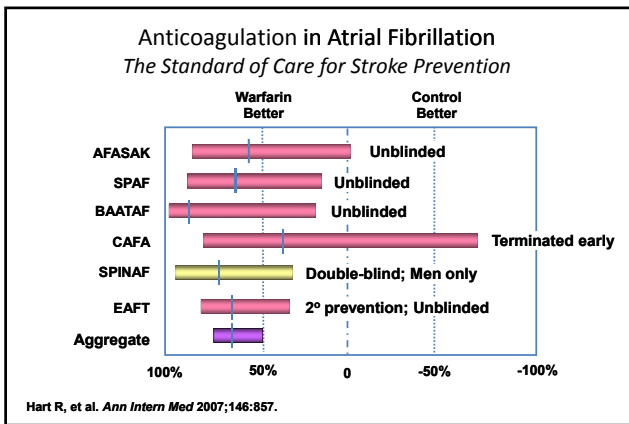
Stroke Risk in Atrial Fibrillation

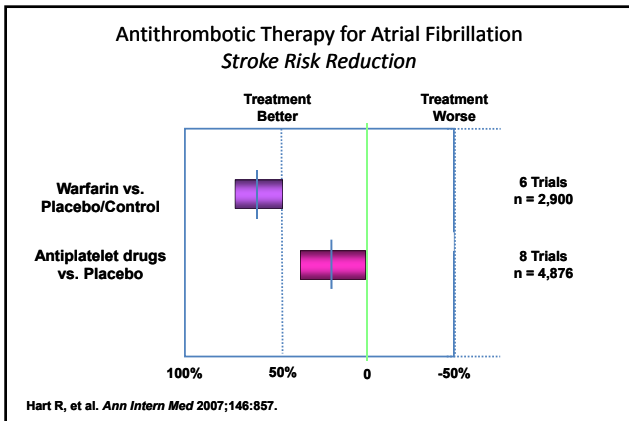
Untreated Control Groups of Randomized Trials

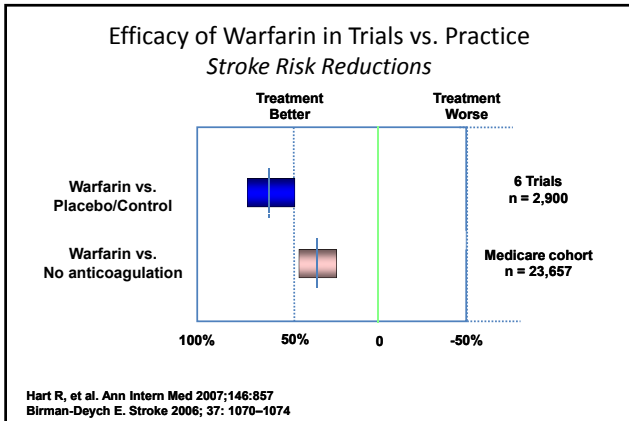


Atrial Fibrillation Investigators. *Arch Intern Med* 1994;154:1449.









Intracerebral Hemorrhage

The Most Feared Complication of Antithrombotic Therapy

- >10% of intracerebral hemorrhages (ICH) occur in patients on antithrombotic therapy
- Aspirin increases the by ~ 40%
- Warfarin (INR 2–3) doubles the risk 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

Singer DE, et al. *Chest* 2004;126:429S.
 Fang MC, et al. *Circulation* 2005; 112: 1687.

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

Singer DE, et al. *Chest* 2008;133:546S.
Fang MC, et al. *Circulation* 2005; 112: 1687.

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Less Validated Risk Factors

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

Singer DE, et al. *Chest* 2004;126:429S.
Fang MC, et al. *Circulation* 2005; 112: 1687.

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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

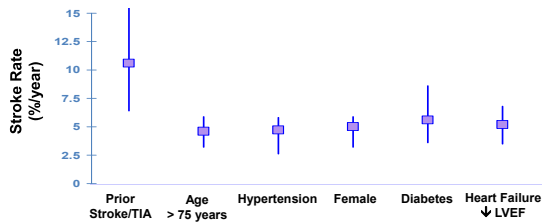
Stroke Risk Score for Atrial Fibrillation

	Score (points)	Prevalence (%)*
Congestive Heart failure	1	32
Hypertension	1	65
Age >75 years	1	28
Diabetes mellitus	1	18
Stroke or TIA	2	10
Moderate-High risk	≥2	50-60
Low risk	0-1	40-50

Van Walraven C, et al. *Arch Intern Med* 2003; 163:936.
 * Nieuwlaat R, et al. (EuroHeart survey) *Eur Heart J* 2006 (E-published).

Nonvalvular Atrial Fibrillation

Stroke Rates Without Anticoagulation According to Isolated Risk Factors



Hart RG et al. *Neurology* 2007; 69: 546.

The CHADS₂ Index

Stroke Risk in Patients with Atrial Fibrillation

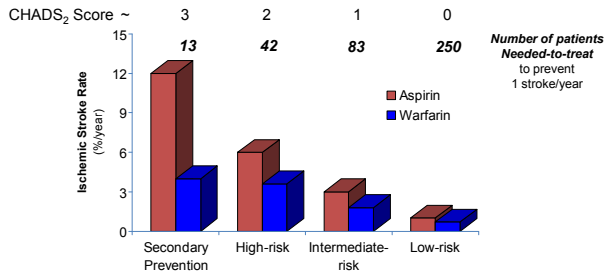
	Score (points)	Risk of Stroke (%/year)
	0	1.9
	1	2.8
Approximate Risk threshold for Anticoagulation	2	4.0
	3	5.9
	4	8.5
	5	12.5
	6	18.2

3%/year

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.

Risk Stratification and Anticoagulation

Stroke Reduction with Warfarin Instead of Aspirin



EAFT Study Group. *Lancet* 1993; 324:1255.
Zabalgaitia M, et al. *J Am Coll Cardiol* 1998; 31:1622.

Antithrombotic Therapy for Atrial Fibrillation ACC/AHA/ESC Guidelines 2006

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.



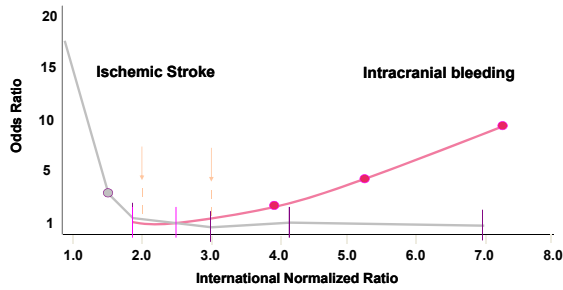
"Actually, it's more of a guideline than a rule."

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

Patient Selection for Anticoagulation
Additional Considerations

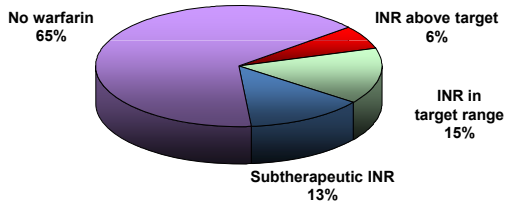
- Risk of bleeding
- Newly anticoagulated vs. established therapy
- Availability of high-quality anticoagulation management program
- Patient preferences

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

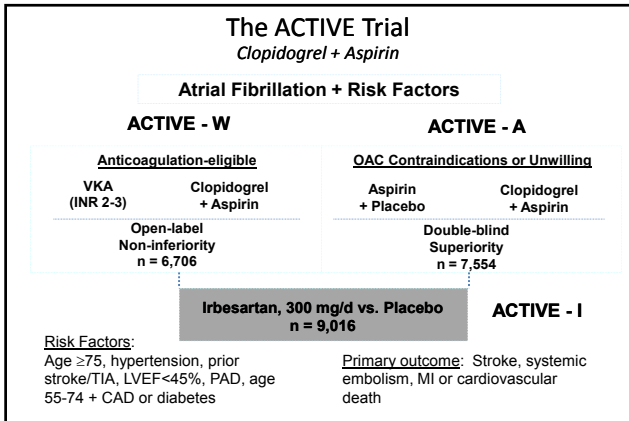


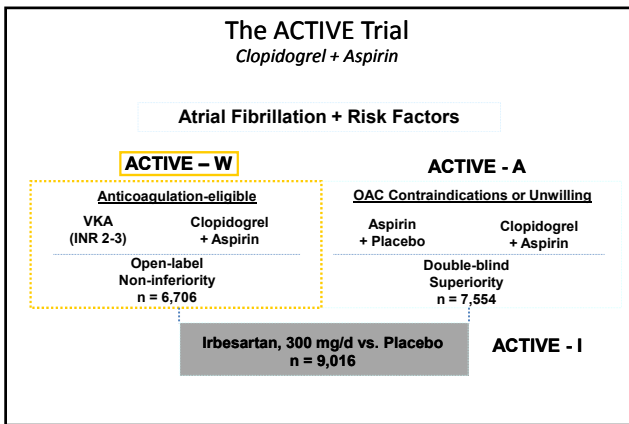
Fang MC, et al. *Ann Intern Med* 2004; 141:745.
Hylek EM, et al. *N Engl J Med* 1996; 335:540.

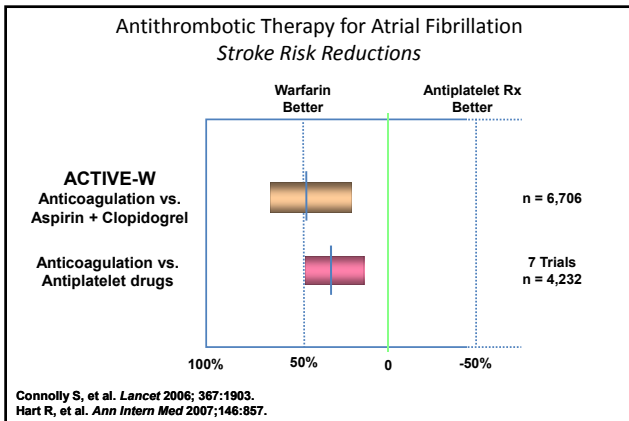
Warfarin for Atrial Fibrillation
Limitations Lead to Inadequate Treatment
Adequacy of Anticoagulation in Patients with AF in Primary Care Practice

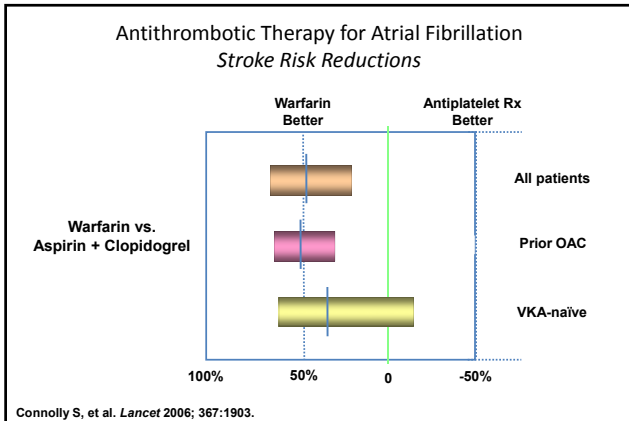


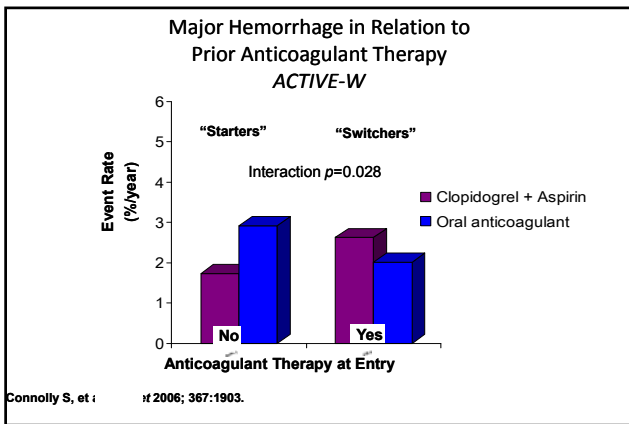
Samsa GP, et al. *Arch Intern Med* 2000;160:967.

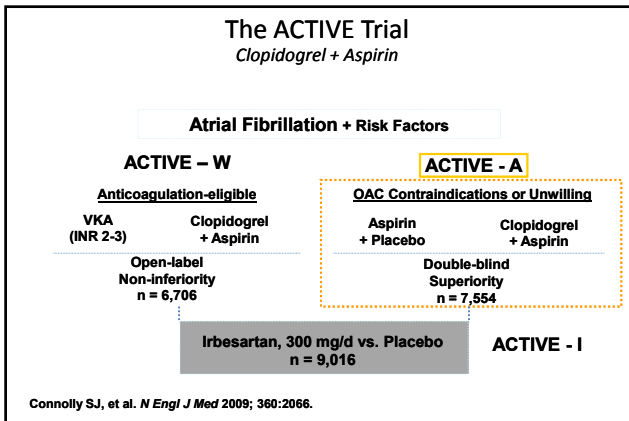












ACTIVE-A

Reasons for Exclusion from Anticoagulation

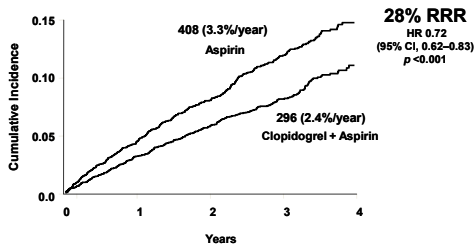
Risk factor for bleeding*	23%
Physician judgment against anticoagulation for patient	50%
Patient preference only	26%

- * Inability to comply with INR monitoring
- * Predisposition to falling or head trauma
- * Persistent hypertension >160/100 mmHg
- * Previous serious bleeding on VKA
- * Severe alcohol abuse within 2 years
- * Peptic ulcer disease
- * Thrombocytopenia
- * Chronic need for NSAID

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

ACTIVE-A

Total Stroke Rates



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

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.

Warfarin Dosing and Genomics

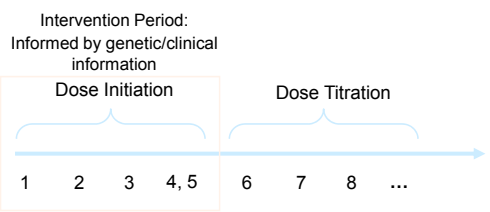
CYP2C9 – Gene encoding cytochrome P450 hepatic enzyme responsible for primary clearance of S-warfarin, the active enantiomer; variant alleles are associated with sensitivity to warfarin.

VKORC1 – Gene encoding vitamin K epoxide reductase complex 1; variant alleles are associated with warfarin resistance.

Warfarin Dosing and Genomics Keeping Ahead of the Data

The screenshot shows the FDA News page for the article "FDA Approves Updated Warfarin (Coumadin) Prescribing Information". The article is dated August 16, 2007. It discusses the approval of updated labeling for Coumadin, explaining that people's genetic makeup may influence how they respond to the drug. The article highlights the opportunity for healthcare providers to use genetic tests to improve their initial estimate of a reasonable warfarin dose for individual patients. The text is enclosed in a purple border.

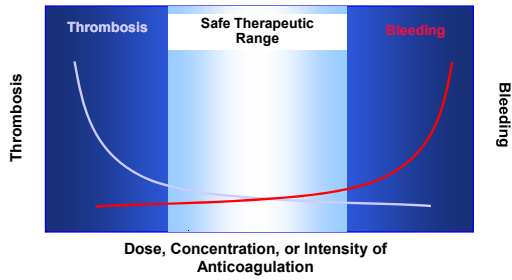
COAG Clarification of Optimal Anticoagulation Through Genetics



Objective: To compare the effect of pharmacogenetic & clinical warfarin dosing algorithms on initial proportion of time in therapeutic range of anticoagulation intensity

The Ideal Anticoagulant

Wide Therapeutic Margin



Investigational Anticoagulant Targets

ORAL

TTP889

Rivaroxaban
Apixaban
LY517717
YM150
DU-176b
Betrixaban
TAK 42

Dabigatran

PARENTERAL

TFPI (tifactin)

APC (drotrecogin alfa)
sTM (ART-123)

Idraparinux

DX-9065a
Otamixaban

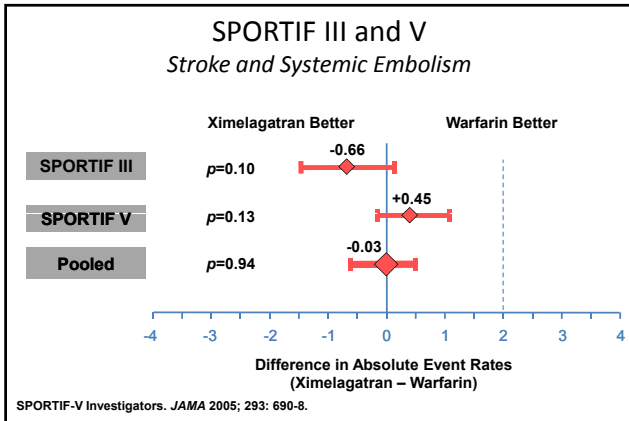
APC activated protein C
AT antithrombin
sTM soluble thrombomodulin
TF tissue factor
FPI tissue factor pathway inhibitor

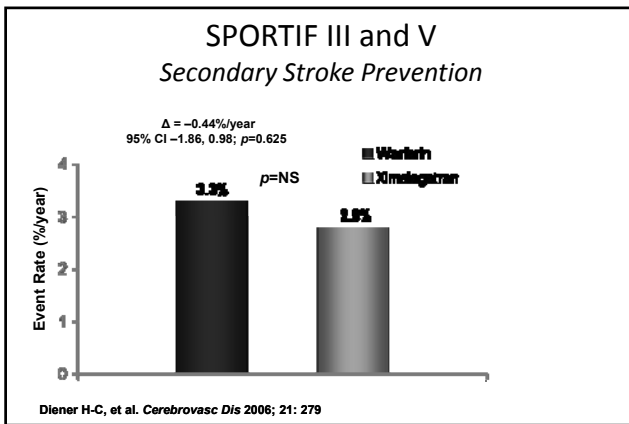
Adapted from Weitz JI. *Thromb Haemost* 2007; 5 Suppl 1:65-7.

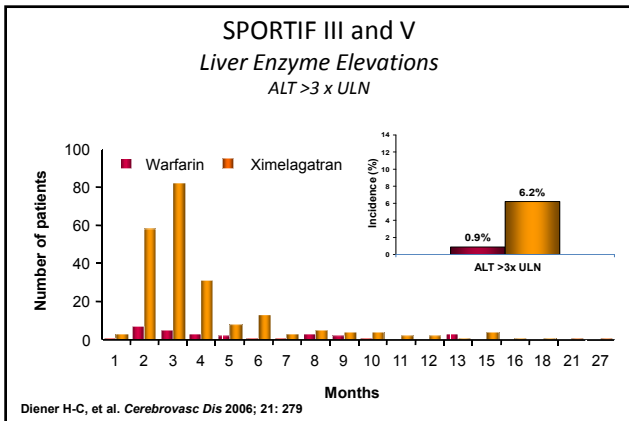
New Anticoagulant Development

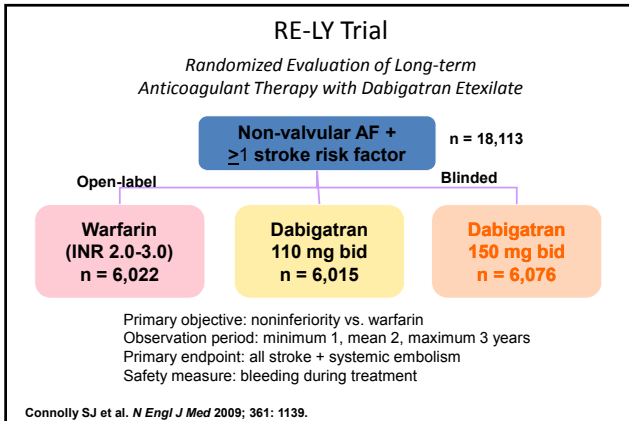
The Clinical Trial Pathway

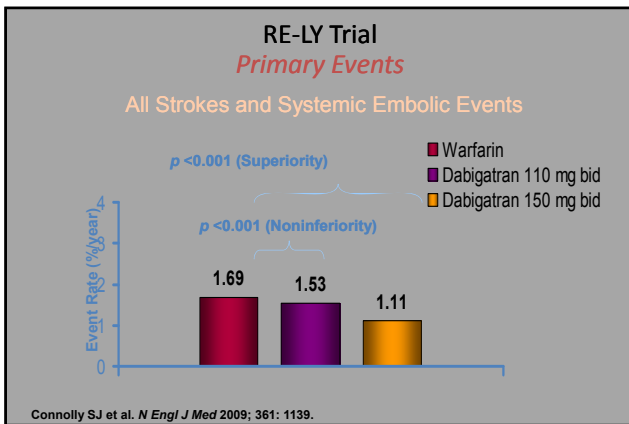


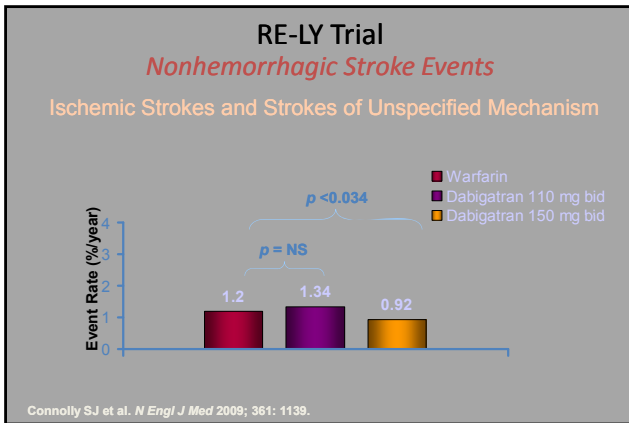


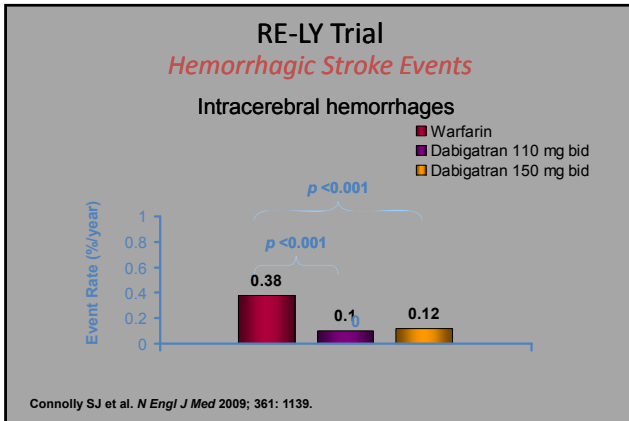


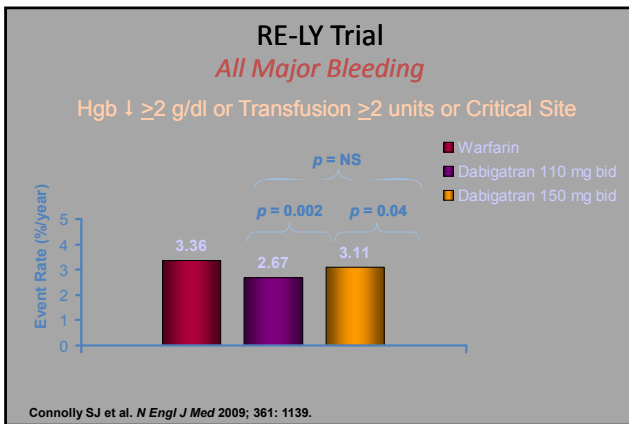


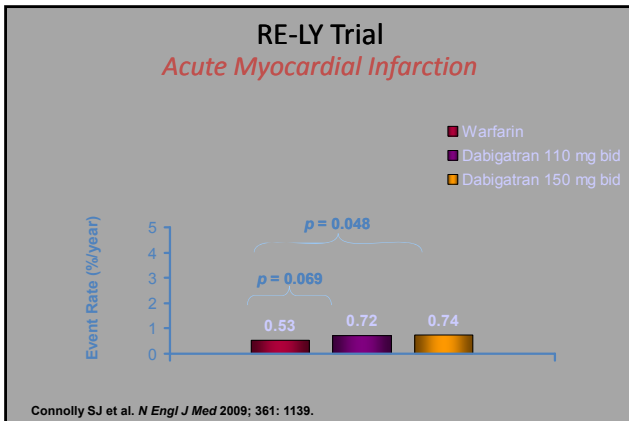


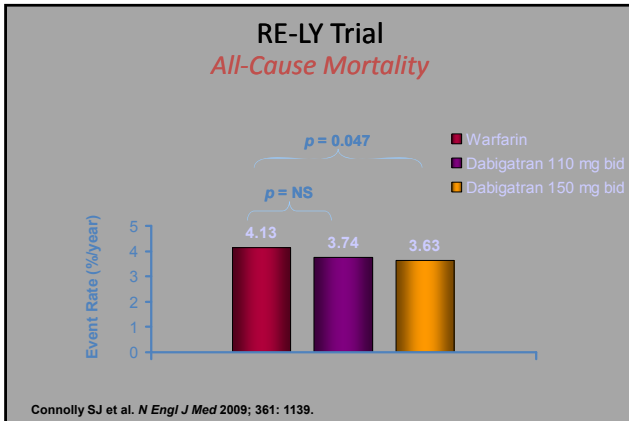


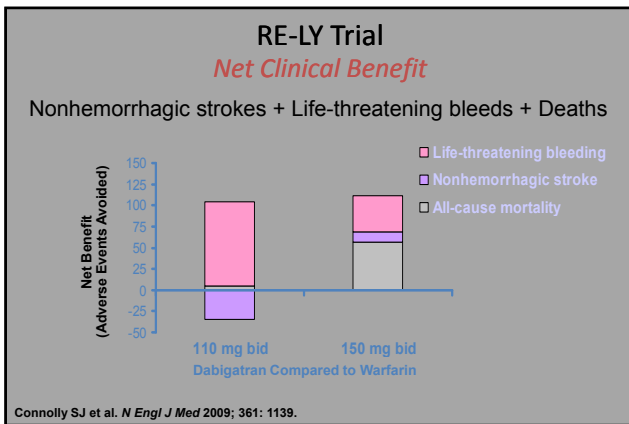






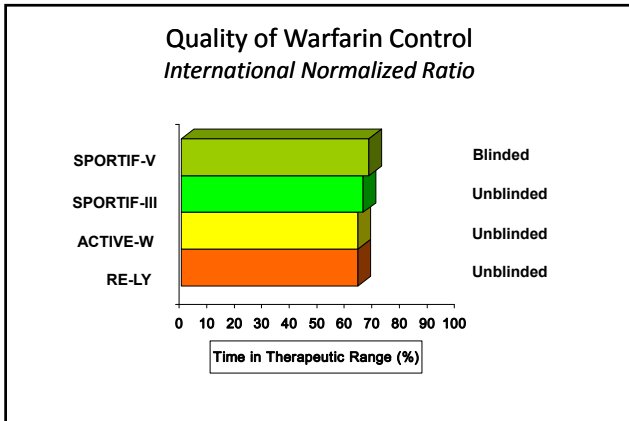


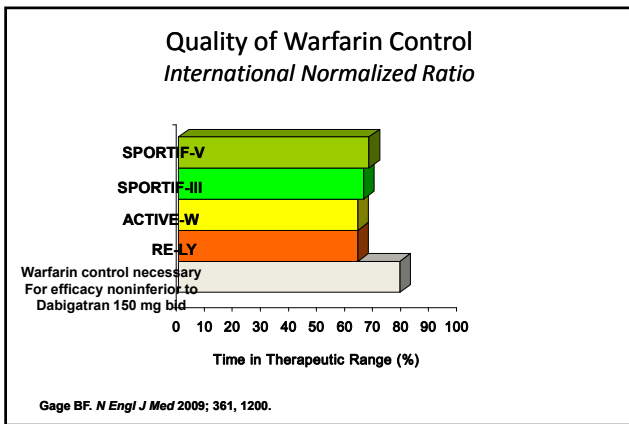


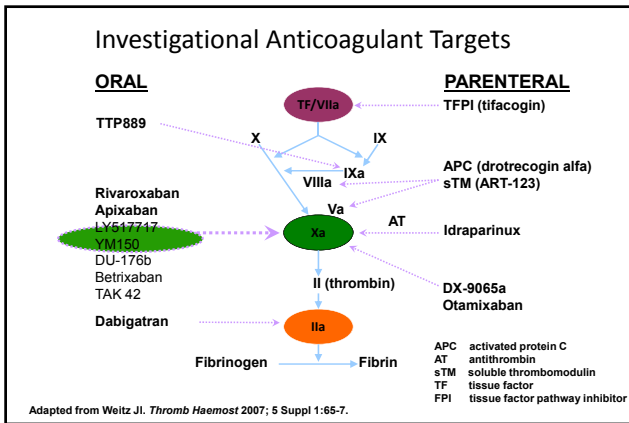


Dabigatran for Atrial Fibrillation *Dose Selection*

- **Potential advantage of two dose formulations**
 - **Dabigatran 110 mg bid**
 - Patients at low risk of thromboembolism or high risk of bleeding
 - **Dabigatran 150 mg bid**
 - Patients at high risk of thromboembolism or low risk of bleeding







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 bid	Warfarin (INR 2-3)	15,000	≥ 1
ENGAGE-AF	Edoxaban	30 mg bid 60 mg* qd	Warfarin (INR 2-3)	16,500	≥ 2

* Adjusted based on renal function

Emerging Anticoagulants

Regulatory Issues

- Open-label vs. blinded trial design
- Issues related to active-control trial design
- How many trials are needed?
- Preventing use for 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

Obliteration of the left atrial appendage

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

Strokes after Conversion to NSR
Rate vs. Rhythm Control Trials

	n	Rate control	Rhythm control	RR (95% CI)	p
AFFIRM	4,917	5.7%	7.3%	1.28 (0.95-1.72)	0.12
RACE	522	5.5%	7.9%	1.44 (0.75-2.78)	0.44
STAF	266	1.0%	3.0%	3.01 (0.35-25.3)	0.52
PIAF	252	0.8%	0.8%	1.02 (0.73-2.16)	0.49
Total	5,957	5.0%	6.5%	1.28 (0.98-1.66)	0.08

Verheugt F, et al. *J Am Coll Cardiol* 2003;41(suppl):130A.

AFFIRM Trial
Stroke Rates

- 74% of all strokes were proven ischemic
 - 44% occurred after stopping warfarin
 - 28% in patients taking warfarin with INR <2.0
 - 42% occurred during documented AF

Wyse AG, et al. *N Engl J Med* 2002; 347: 1825.

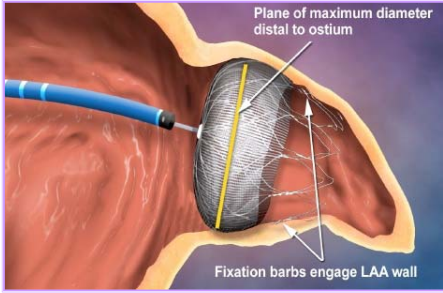
ATHENA Trial
Dronedarone vs. Placebo in Patients with AF
Stroke Rates (Secondary Analysis)

Event	Placebo (%/y)	Dronedarone (%/y)	HR (95% CI)	p
Stroke	1.79	1.19	0.66	0.027
Stroke or TIA	2.05	1.37	0.67	0.020
Fatal stroke	0.54	0.36	0.67	0.247

Hohnloser SH, et al. *N Engl J Med* 2009; 360: 668-78.

Percutaneous LAA Occlusion

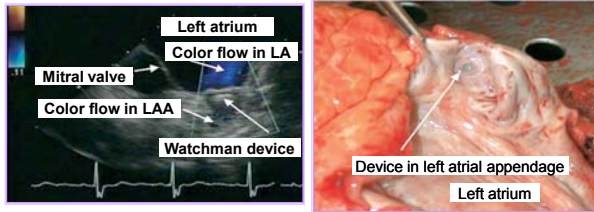
The WATCHMAN® Device



Syed T, Halperin JL. *Nature Clin Pract Cardiovasc Med* 2007; 4:428
 Holmes DR, et al. *Lancet* 2009; 374: 534

Percutaneous LAA Occlusion

The WATCHMAN Device

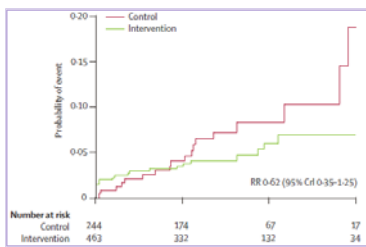


Sick PB, et al. *J Am Coll Cardiol* 2007; 49: 1490.

PROTECT-AF Trial

Primary Efficacy Endpoint

Stroke, Systemic Embolism + CV Death

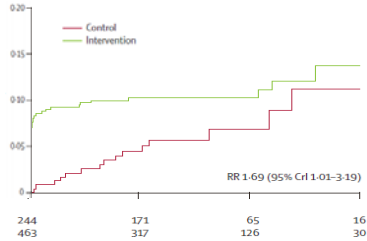


Holmes D, et al. *Lancet* 2009; 374: 534.

PROTECT-AF Trial

Primary Safety Endpoint

Major Bleeding, Pericardial Effusion + Device Embolization

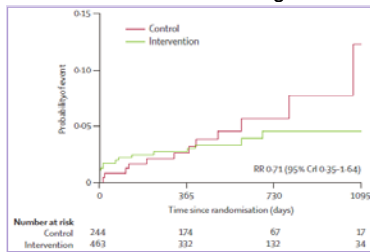


Holmes D, et al. *Lancet* 2009; 374: 534.

PROTECT-AF Trial

Cumulative Rates of All Strokes

Ischemic + Hemorrhagic



Holmes D, et al. *Lancet* 2009; 374: 534.

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- Amputation

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

Issues in AF Patient Management
Unanswered Questions

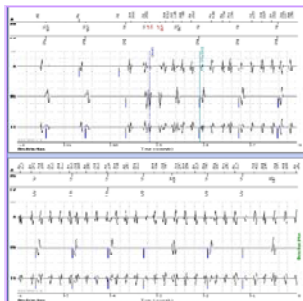
- Does successful rhythm control eliminate the need for anticoagulation?
- How to exclude recurrent AF when pursuing a rhythm-control strategy?

IMPACT Trial
*Rhythm-Guided Anticoagulation
In Patients with Implanted Devices*

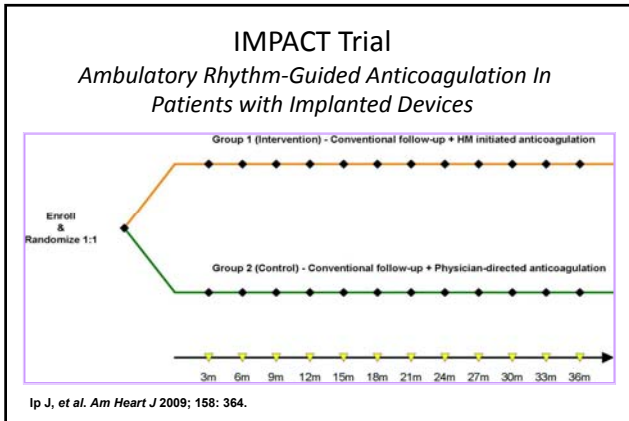


Ip J, et al. *Am Heart J* 2009; 158: 364.

IMPACT Trial
*Rhythm-Guided Anticoagulation
In Patients with Implanted Devices*



Ip J, et al. *Am Heart J* 2009; 158: 364.



IMPACT Trial

Rhythm-Guided Initiation of Anticoagulation

CHADS ₂ score	AF/AFI duration (during 48 h) warranting initiation of anticoagulation
1 - 2	48 h
3 - 4	24 h
5 - 6 or prior thromboembolism	≤12 h

Ip J, et al. Am Heart J 2009; 158: 364.

IMPACT Trial

Rhythm-Guided Interruption of Anticoagulation

CHADS ₂ score	Period free from AF/AFI warranting cessation of anticoagulation
1 - 2	30
3 - 4	60
5 - 6 or prior thromboembolism	Maintain anticoagulation

Ip J, et al. Am Heart J 2009; 158: 364.

Atrial Fibrillation and Thromboembolism
The Next Challenges

- Better tools to stratify bleeding risk
- Noninvasive imaging and biomarkers of inflammation and thrombosis to predict clinical events and guide therapy
- Confirming successful rhythm control over time
- Targeted therapy to prevent AF in patients at risk

From Fermented Sweet Clover
to Molecular Targeting of Coagulation
The Promise of New Approaches



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

Thank you!
