MMS/Mass Coalition Program, Nov. 4, 2008

Patients with AF: Who Should be on Warfarin?

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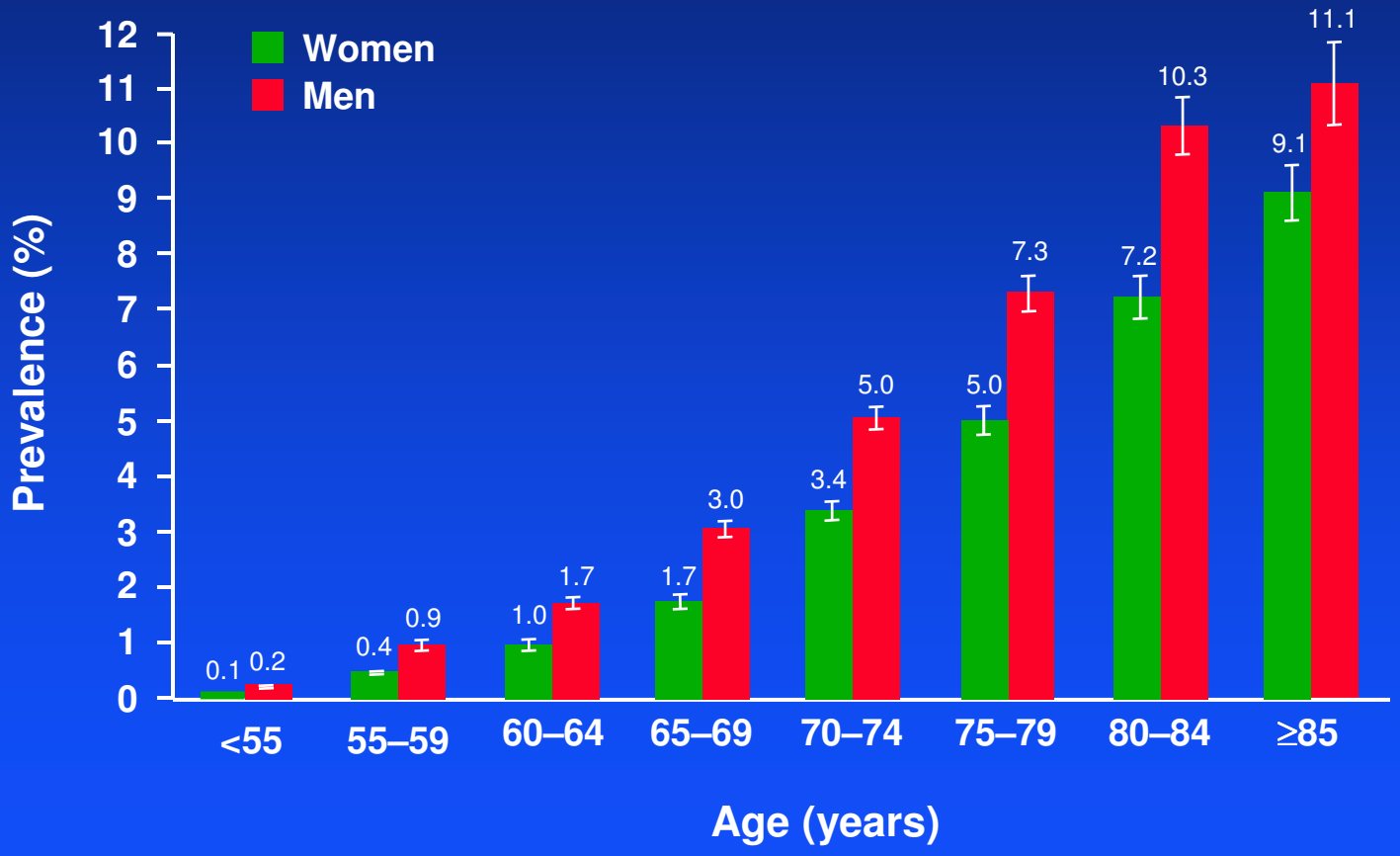
Speaker Disclosure Information

DISCLOSURE INFORMATION:
The following relationships exist related to this presentation:

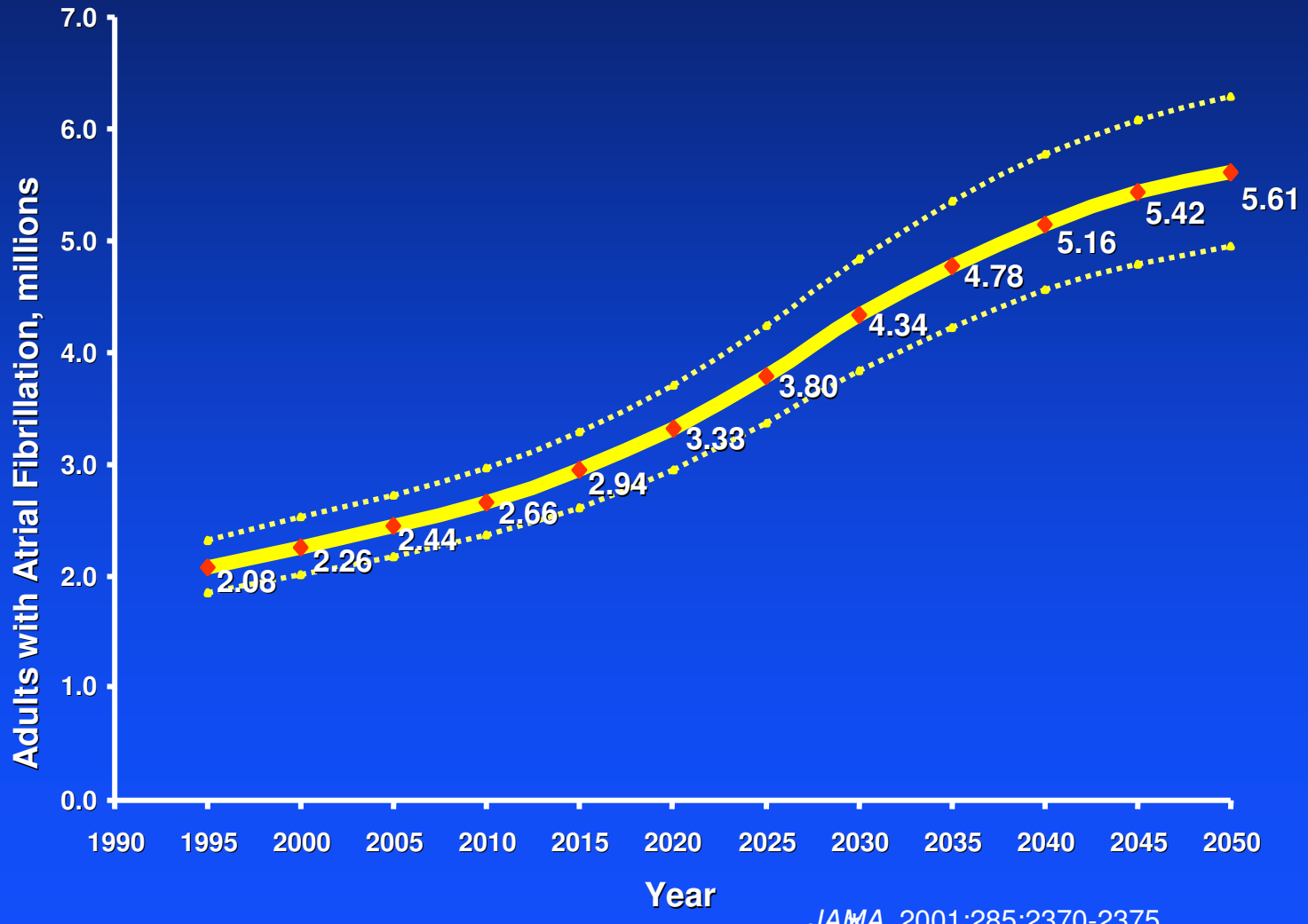
Daniel E. Singer, M.D.:
Consultant: AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, GSK, Medtronic, and Johnson and Johnson.
Research Support: Daiichi Sankyo
Symposium Presentation: Bristol Myers Squibb, Pfizer

Prevalence of Diagnosed AF by Age and Sex



Go AS *et al. JAMA* 2001;285:2370–2375

Projected Number of Adults with AF in the US, 1995-2050



JAMA. 2001;285:2370-2375

AF and Stroke: Framingham Study, 30-Year Follow-up*

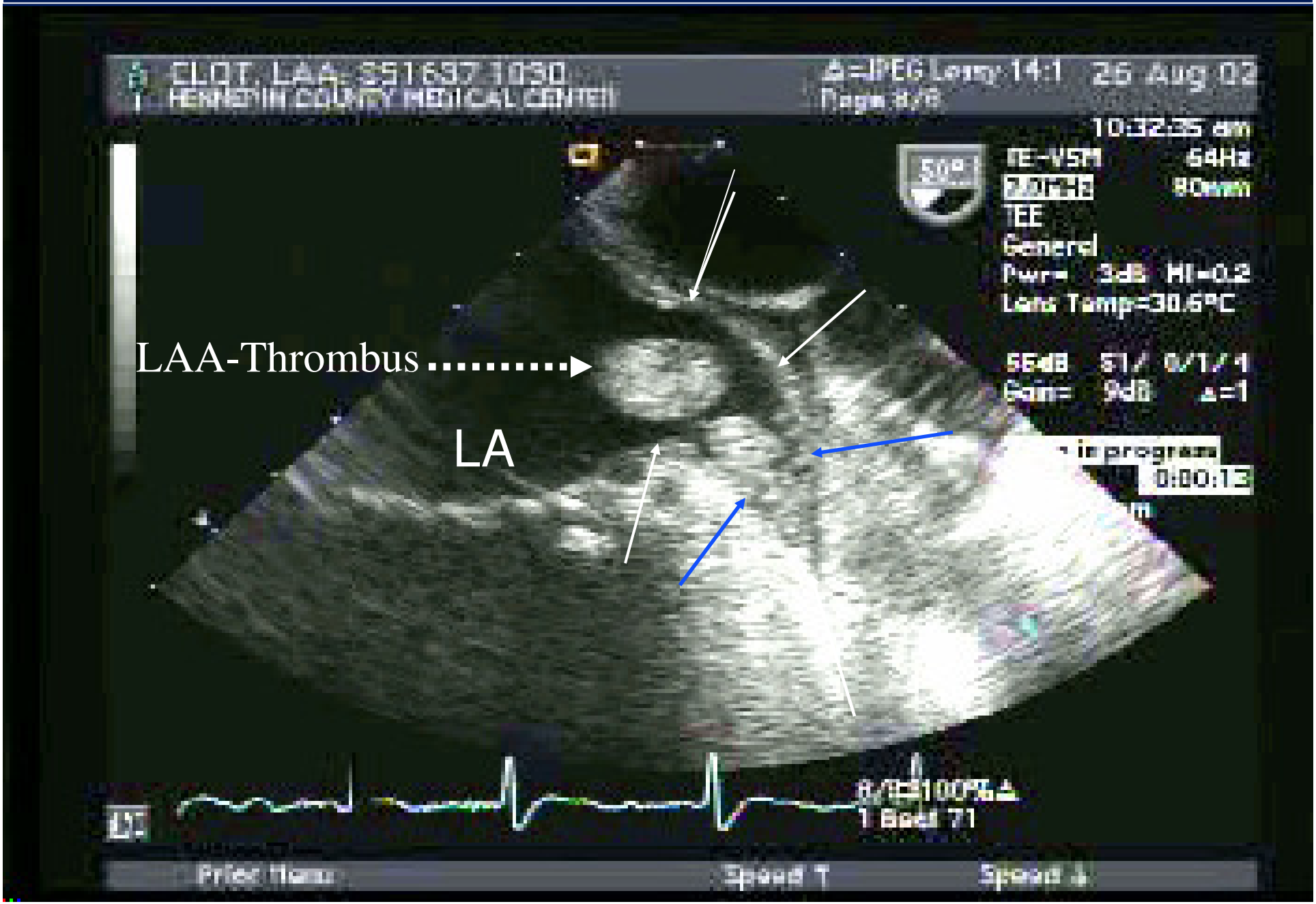
Age	Relative risk for stroke: AF vs NSR
60-69	4.7
70-79	5.4
80-89	5.0

** Wolf PA, Abbott RD, Kannel WB, Arch Intern Med 1987;147: 1561-1564; adjusted for BP*

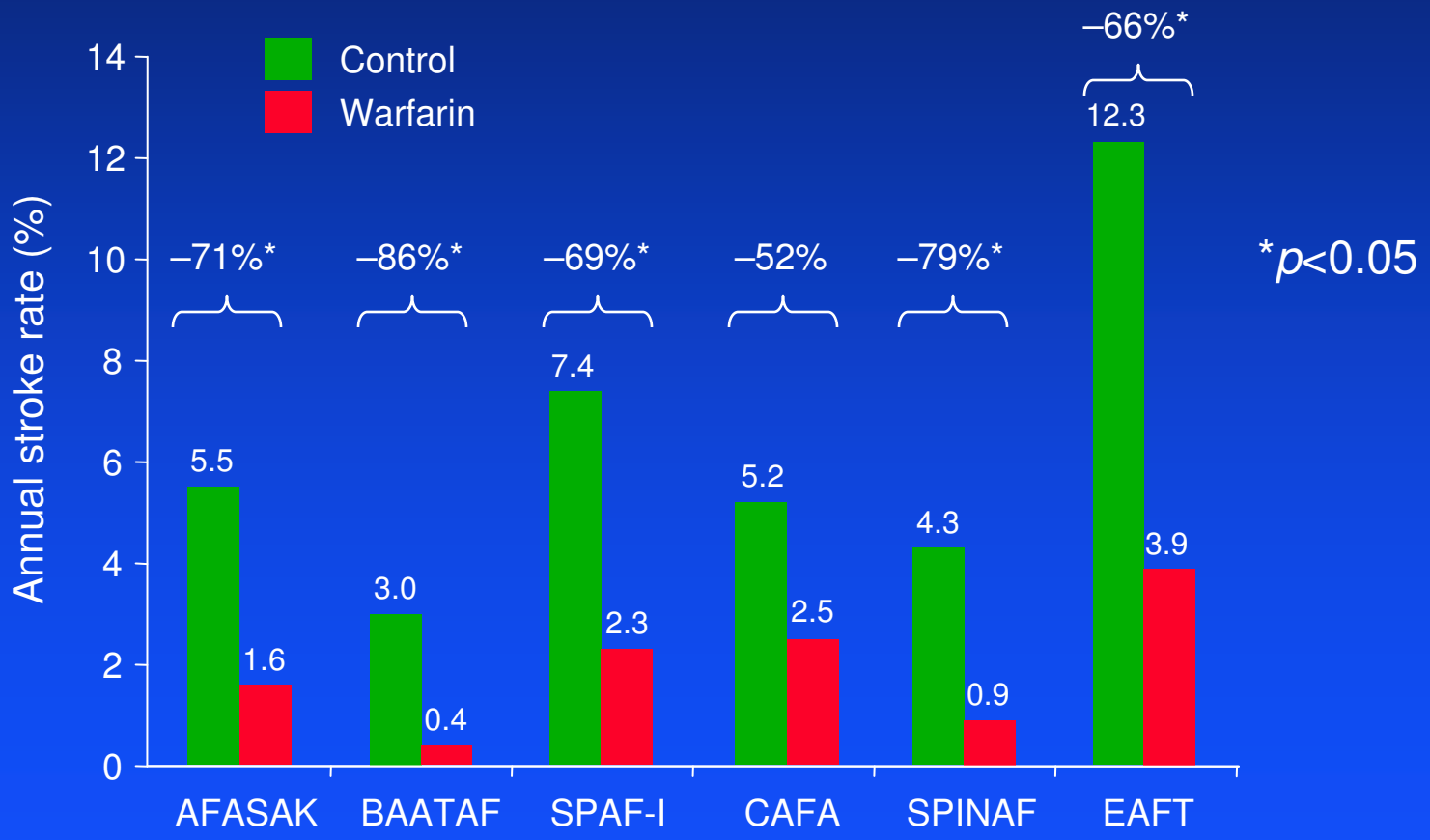
AF: Putative Mechanism for Stroke

AF → loss of atrial contraction → LA thrombus → embolism

Left atrial appendage thrombus



RCTs of VKA vs Control to Prevent Stroke in AF



Go AS *et al. Progr Cardiovasc Dis* 2005;48:108–124

Efficacy of Anticoagulation for AF

Trial Target Ranges: INR ~ 1.8-4.2

	Relative Risk Reduction	Absolute Risk Reduction
Pooled 1° RCTs	68% (50-79%)	3.1% per year
EAFT	66% (43-80%)	8.4% per year

Safety of Anticoagulation for AF

	Absolute Rates of Intracranial Hemorrhage:	
	Anticoagulation	Control
Pooled 1° RCTs	0.3% per yr	0.1% per yr

Efficacy of Aspirin for AF

Pooled 3 trials versus placebo:

AFASAK	75 mg daily
SPAF I	325 mg daily
EAFT	300 mg daily

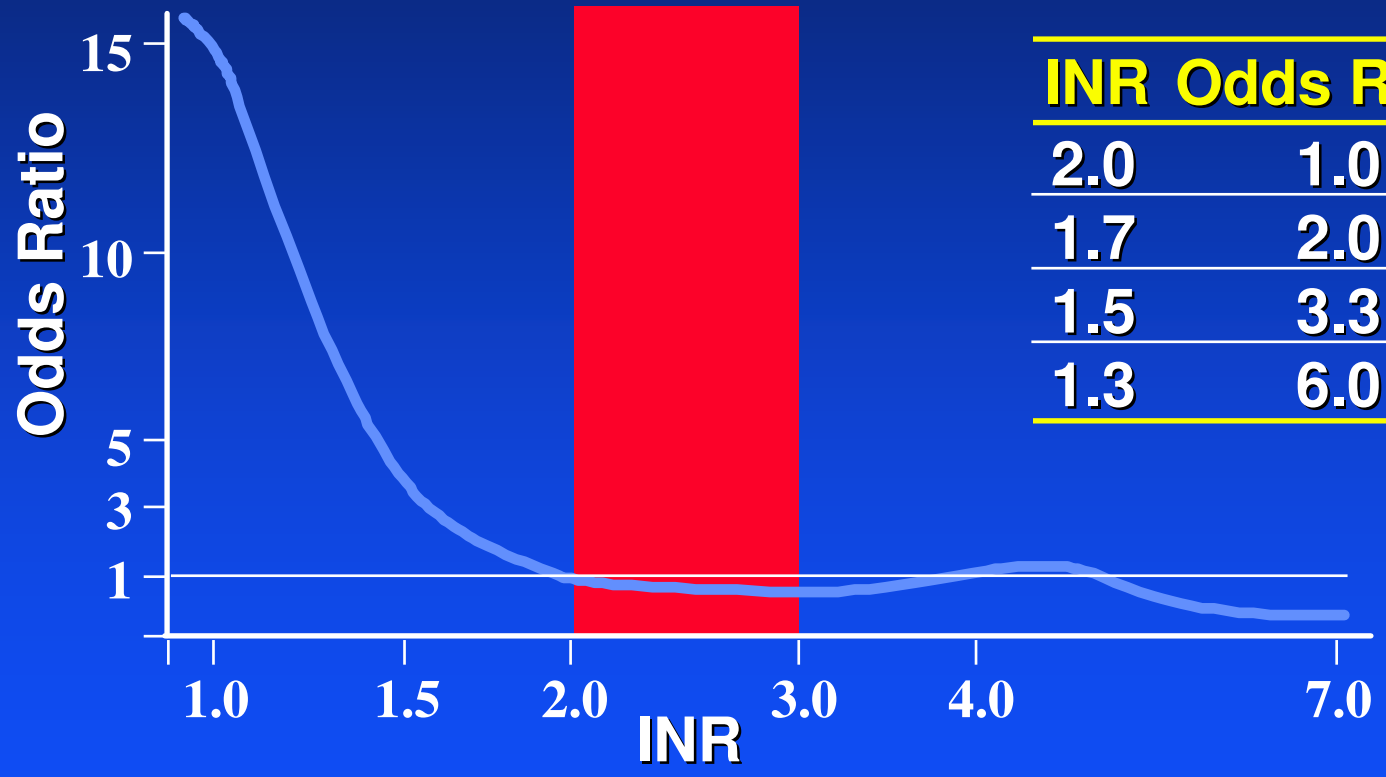
Relative Risk Reduction: 21% (0-38%)
No signif impact on severe/fatal stroke

**JAMA 2002;288:2441-2448 (AFASAK I &II, EAFT, PATAF, SPAF I-III)*

The Optimal INR

For an anticoagulant where toxicity results from an exaggeration of the beneficial effect, choosing the right “dose,” here INR, is crucial.

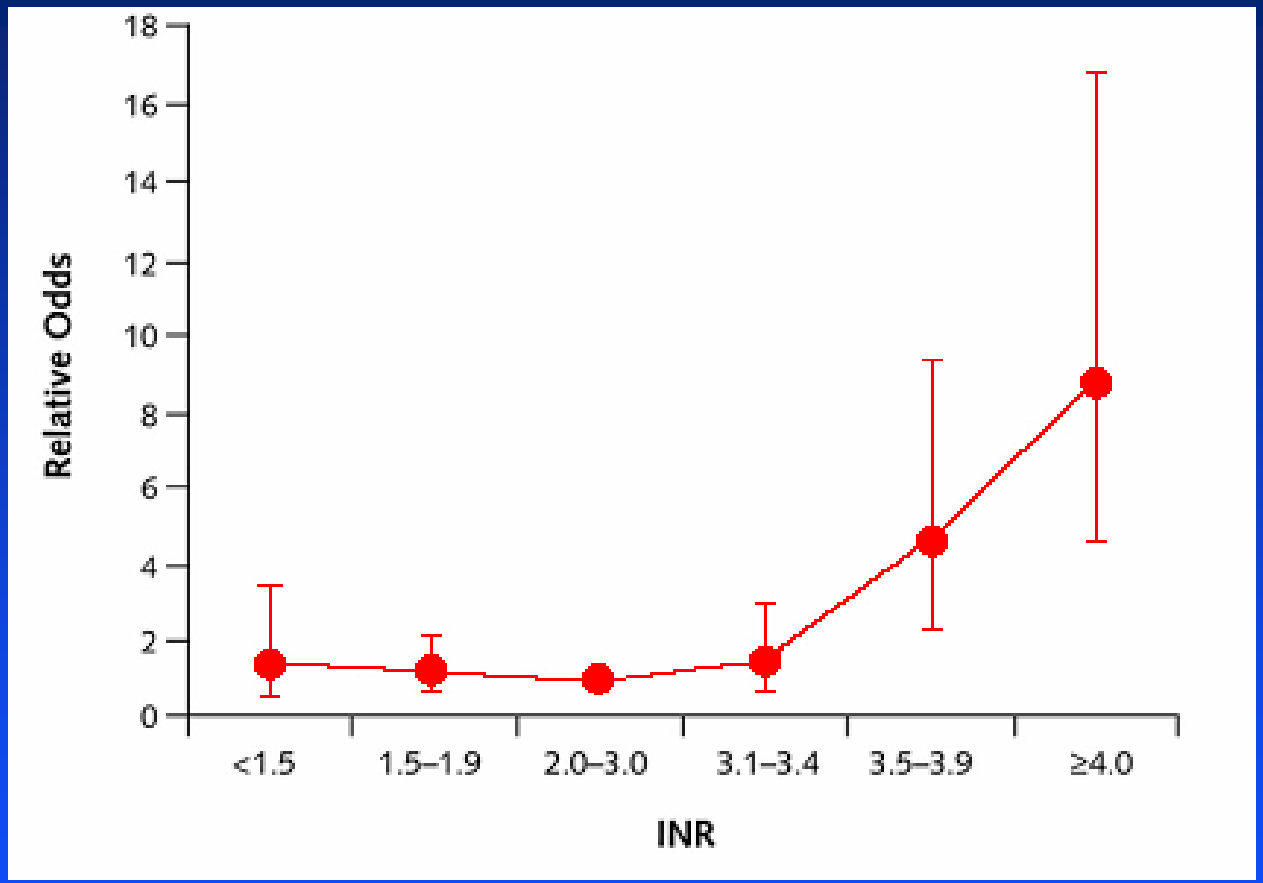
Lowest Effective Anticoagulation Intensity for Warfarin Therapy



INR	Odds Ratio
2.0	1.0
1.7	2.0
1.5	3.3
1.3	6.0

Hylek EM, et al. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with non-rheumatic atrial fibrillation. N Engl J Med 1996;335:540-546.

Relative Odds of ICH by INR Intervals



Fang et al. Ann Intern Med 2004;141:745-52

Antithrombotic Trials in AF: Core Findings

Anticoag. at INR 2.0-3.0 very effective

- *Generally safe*
- *Moderately burdensome*

Aspirin is much less effective

Anticoagulation for AF: For Whom?

Guideline perspective:

- Anticoagulate AF patients whose risk of stroke is high enough to “merit” the burden and hemorrhage risk of warfarin therapy
- ASA for others

Pooled Analysis of AF Trials: Risk Factors for Stroke*

Variable	Relative Risk (RR) Multivariate
Prior stroke/TIA	2.5
Hx HBP	1.6
Age**	1.4
Hx Diabetes	1.7

***RR per decade*

**Arch Intern Med 1994;154:1449-1457*

Echo Risk Factors for Stroke With AF: Pooled Analysis of Control Arms of 3 RCTs*

Feature	RR	p value
LV dysfunction		
mild	1.4	0.002
severe	2.9	<0.001

**Arch Intern Med 1998;158:1316-1320, univariate*

Risk of Stroke in AF: Impact of Paroxysmal AF

From pooled trials (~25% had PAF)

RR (PAF/Sust AF) = ~1.0

$CHADS_2$ AF Stroke Risk Score*

C = CHF	1 point
H = Hypertension	1 point
A = Age >75 years	1 point
D = Diabetes	1 point
S = Prior Stroke/TIA	2 points

NB: Applies to persistent or paroxysmal AF

*Gage, et al. JAMA 2001; 285(22): 2864-70

$CHADS_2$ AF Stroke Risk Score

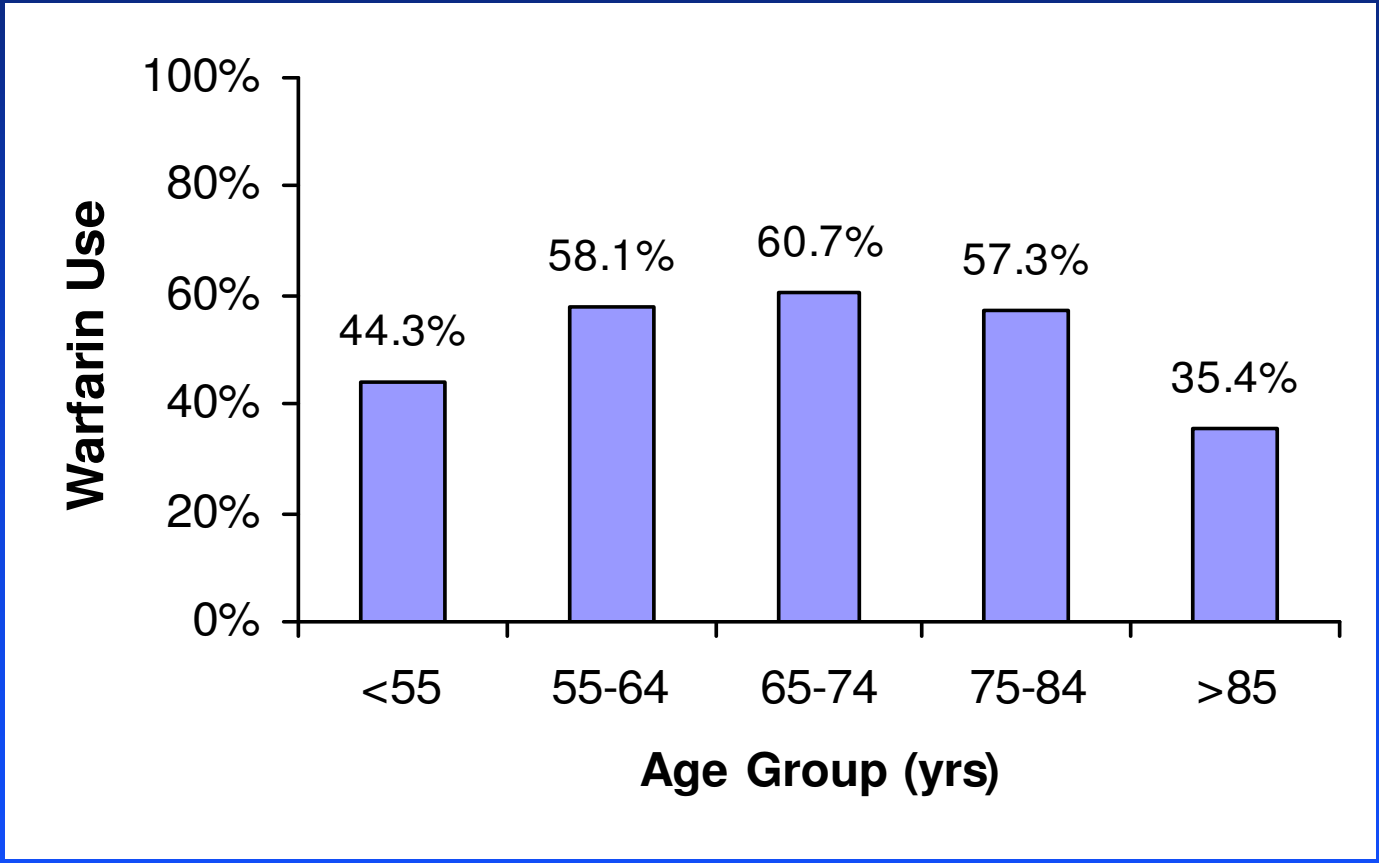
Risk of Stroke in National Registry of Atrial Fibrillation (NRAF) Participants, Stratified by $CHADS_2$ Score*

$CHADS_2$ Score	No. of Patients (n = 1733)	No. of Strokes (n = 94)	Adjusted Stroke Rate, (95% CI)
0	120	2	1.9 (1.2-3.0)
1	463	17	2.8 (2.0-3.8)
2	523	23	4.0 (3.1-5.1)
3	337	25	5.9 (4.6-7.3)
4	220	19	8.5 (6.3-11.1)
5	65	6	12.5 (8.2-17.5)
6	5	2	18.2 (10.5-27.4)

**C=CHF, H=HBP, A=age >75, D=diabetes, S=prior stroke/TIA. Gage, et al. JAMA 2001; 285(22): 2864-70*

What is the case's $CHADS_2$ score?

Prevalent warfarin use by age among ambulatory patients with no contraindications to warfarin: ATRIA Study*



*Ann Intern Med 1999;131:927

BAFTA Study: Warfarin, INR 2-3 vs ASA, 75mg/d, in the Elderly with AF*

N=973, age >=75: mean age = 81.5 yrs

Outcome: Disabling stroke, SE, ICH

Relative risk=0.48, (95% CI 0.28-0.80)**

- Annual risk on warfarin = 1.8%
- Annual risk on aspirin = 3.8%
- Bleeding rates ~same on warfarin and aspirin in this elderly cohort.

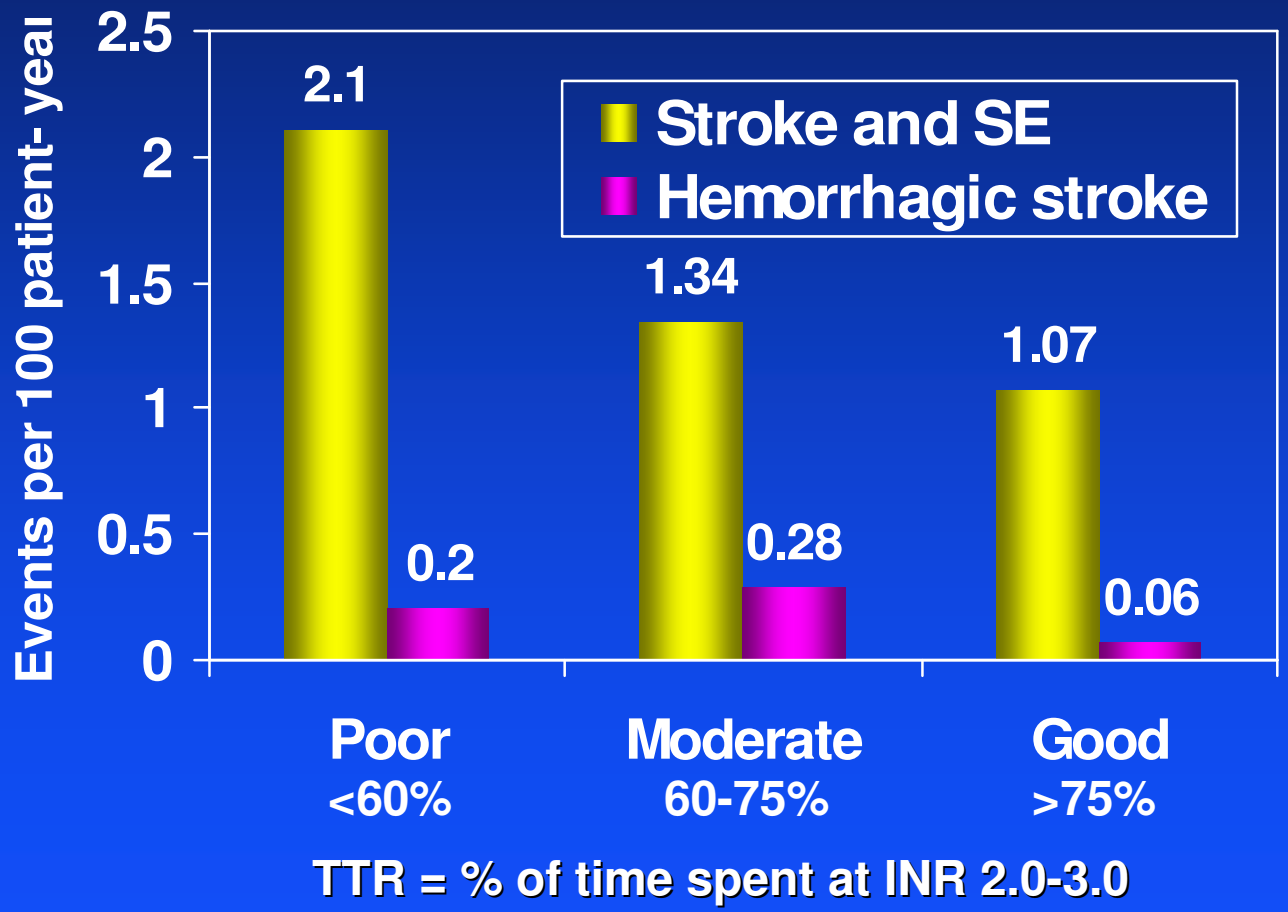
**Mant JM, et al. Lancet 2007; 370: 493-503; **Analysis by intention to treat*

The Importance of "TTR" in Achieving the Net Benefit of Warfarin in AF

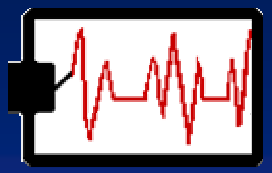
Doing the right thing

Doing the right thing *right*

Stroke and Systemic Emboli (SE) Outcomes by INR Control Category: Results from SPORTIF III and V*



*White, HD et al. Comparison of Outcomes Among Patients Randomized to Warfarin Therapy According to Anticoagulant Control. Arch Intern Med. 2007; 167:239-245.



ACCP 2008* Antithrombotic Therapy in AF:

The 2008 Guidelines

*Chest 2008;133:546S-592S

Applying a Risk-based Philosophy to Anticoagulation in AF

- Assume oral VKA has great efficacy: RRR of 67% vs no Rx; RRR of 50% vs ASA
- Absolute benefit proportional to absolute risk, untreated or treated with ASA. Evidence that untreated strokes rates are decreasing.
- At some low expected benefit, 0.5-1.0%/yr, the risk and burden of VKA are not warranted

Underlying Values and Assumptions

- Incorporate patient preferences particularly for lower risk patients
- Assume that the patient is not at high risk for bleeding and that good control of anticoagulation will occur

Recommendations for Long-Term Anticoagulant Therapy in AF

- *1.1.1* For patients with AF (including PAF) with any of the following:
  - Prior stroke, TIA or systemic embolism
- Recommend anticoagulation with an oral VKA target INR 2.5 (target range 2.0-3.0), *(Grade 1A)*

continued

Recommendations for Long-Term Anticoagulant Therapy in AF

- *1.1.2* Patients with AF (including PAF) with two or more of the following:
  - Age >75 years
  - History of hypertension
  - Diabetes mellitus
  - Moderately or severely impaired LV systolic function and/or clinical heart failure
- Recommend anticoagulation with an oral VKA target INR 2.5 (target range 2.0-3.0), *(Grade 1A)*

continued

Recommendations for Long-Term Anticoagulant Therapy in AF

- *1.1.3* Patients with AF with only one of the following ($CHADS_2$=1):
  - Age >75 years
  - History of hypertension
  - Diabetes mellitus
  - Moderately or severely impaired systolic function and/or clinical heart failure

- Recommend anticoagulation with an oral VKA, target INR 2.5 (target range 2.0-3.0) *(Grade 1A)*, or with aspirin 75-325 mg/day *(Grade 1B)*, although VKA is suggested *(Grade 2A)*.
  - Emphasize role of informed patient.

continued

Recommendations for Long-Term Anticoagulant Therapy in AF

- *1.1.4* Patients with sustained or paroxysmal AF with none of the following ($CHADS_2$=0):
  - Prior stroke, TIA or systemic embolism
  - Age >75 years
  - History of hypertension
  - Diabetes mellitus
  - Moderately or severely impaired systolic function and/or clinical heart failure

- Recommend long-term aspirin therapy at a dose of 75-325 mg/day, *(Grade 1B)*

Recommendations for AF with mitral stenosis *(1.3.1)* and AF with a prosthetic heart valve *(1.3.2)*

- *1.3.1* For patients with AF and mitral stenosis, we recommend long-term anticoagulation with an oral VKA, such as warfarin, target INR 2.5 (range 2.0-3.0) *(Grade 1B)*

- *1.3.2* For patients with AF and a prosthetic heart valve, we recommend long-term anticoagulation at an intensity appropriate for the specific type of prosthesis *(Grade 1B)*

Anticoagulation for elective cardioversion of AF ≥ 48 hours or unknown duration

- ***2.1.1*** For patients with AF of ≥48 hours or of unknown duration for whom pharmacologic or electrical cardioversion is planned, we recommend:
  - Anticoagulation with an oral vitamin K antagonist, target INR of 2.5 (range, 2.0-3.0)
    - For 3 weeks before elective cardioversion
    - And for at least 4 weeks after sinus rhythm has been maintained *(Grade 1C)*

continued

ACCP 8: Key Points for Long-term Antithrombotic Therapy

- Age 65-75 yrs is no longer considered a risk factor
- Either VKA or aspirin is acceptable for AF patients with one stroke risk factor, other than prior ischemic stroke, although VKA is favored
- We again stress INR 2-3 as the appropriate target and do not endorse lower INR targets in elderly (e.g., ACC/AHA/ESC INR 1.6-2.5)
- We recommend broader acceptable dosing range for ASA 75-325 mg, not just 325 mg as in ACCP 7 (2004)

Stroke Prevention in AF: What's needed now?

1. Optimizing warfarin therapy:
   - Quality improvement for anticoagulation
   - Dedicated anticoagulation units
   - Self-testing/self-management
   - Better initiation and maintenance dosing
     - ?clinical+genotype-guided
2. With high quality anticoagulation assured, more patients can be safely and effectively treated.

THE END