Stroke and Bleeding Risk for AF

Thoranis Chantrarat MD.

Phramongkutklao College of Medicine

Atrial fibrillation--Clot

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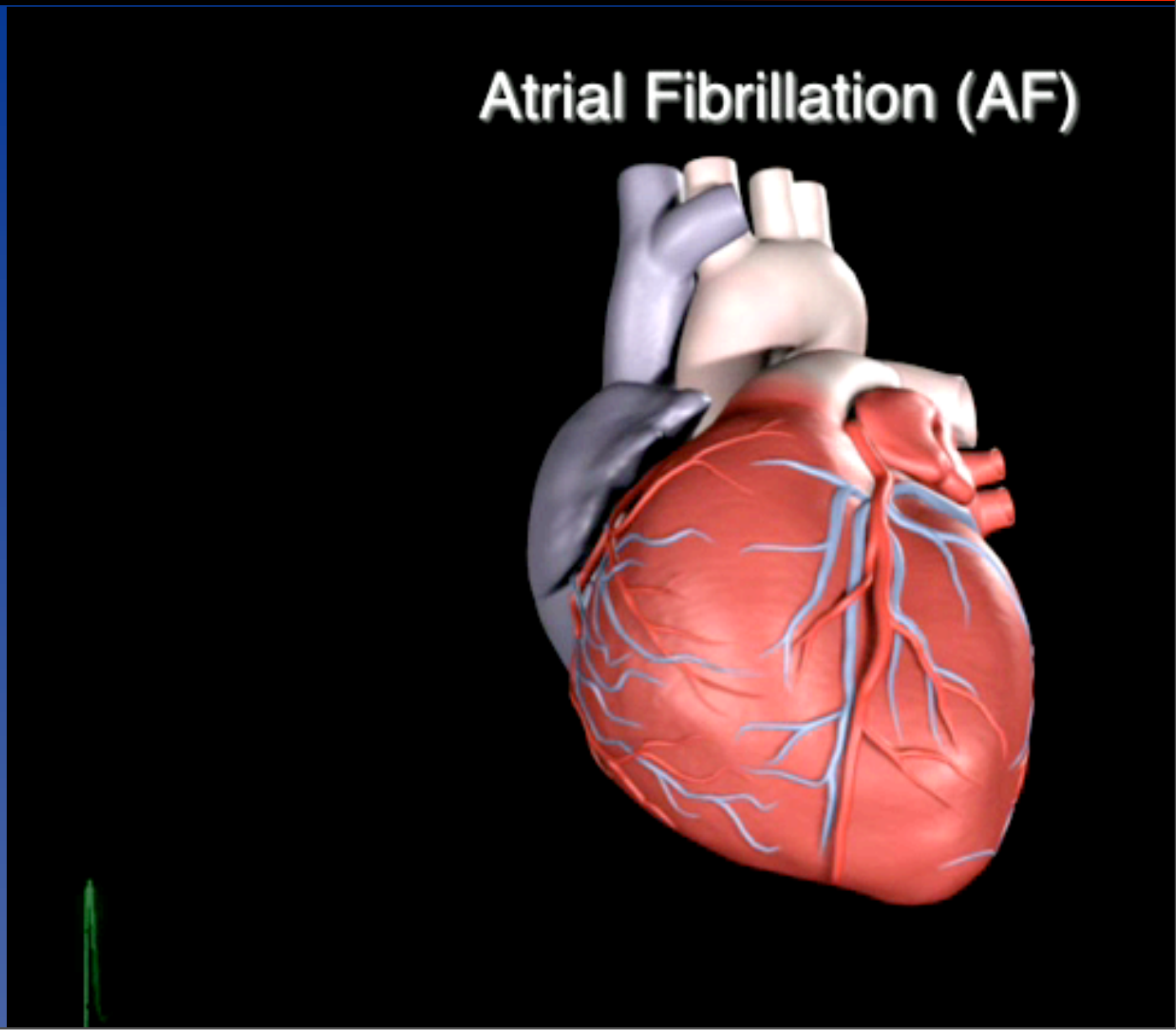

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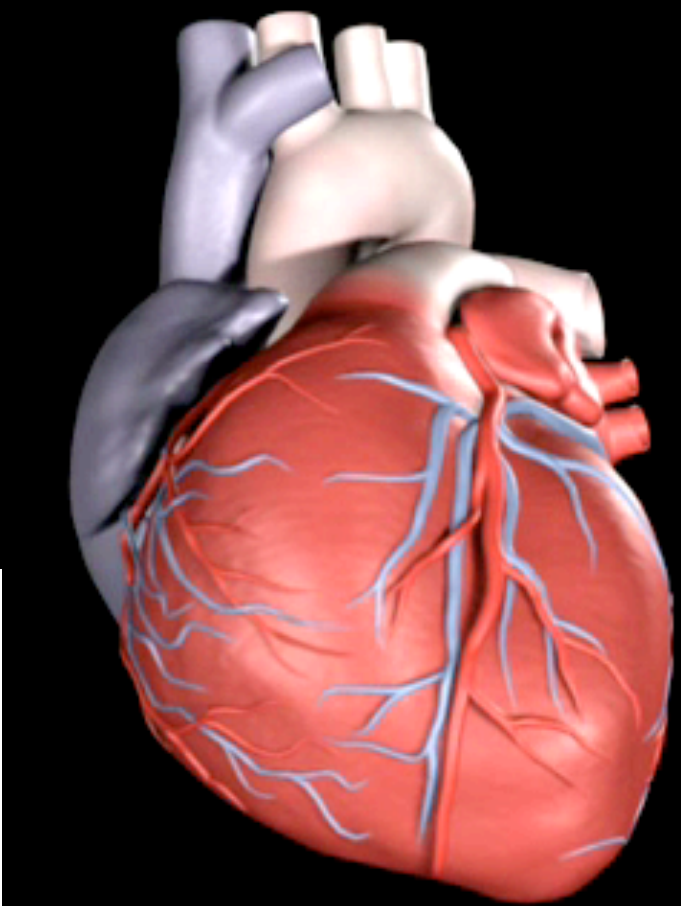

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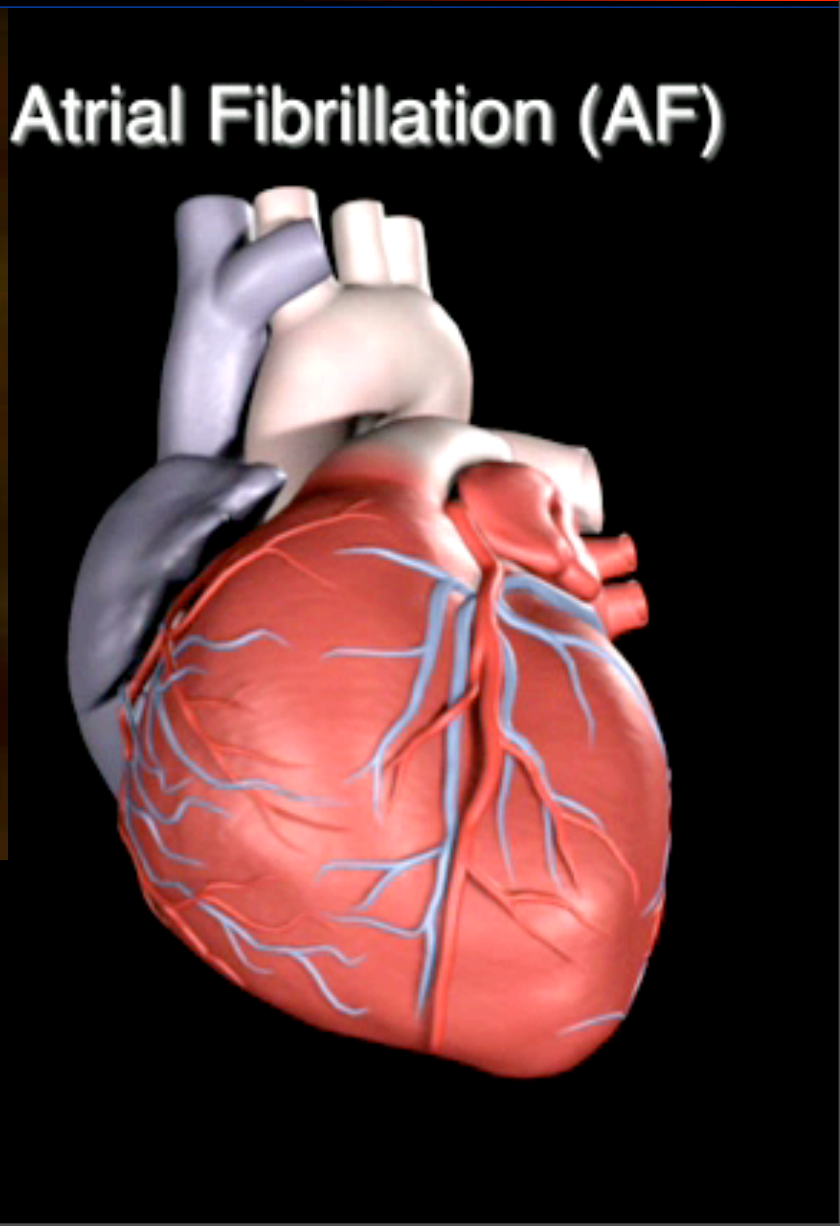

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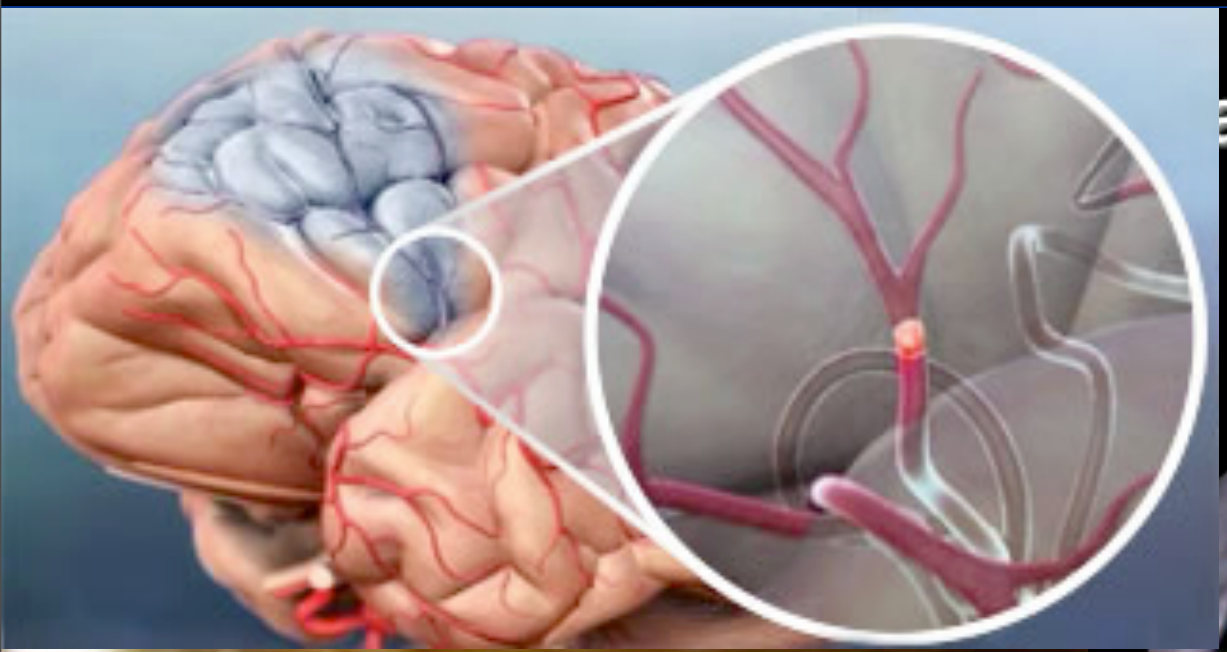

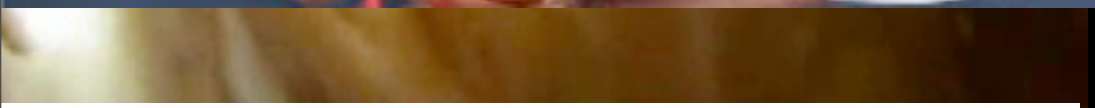

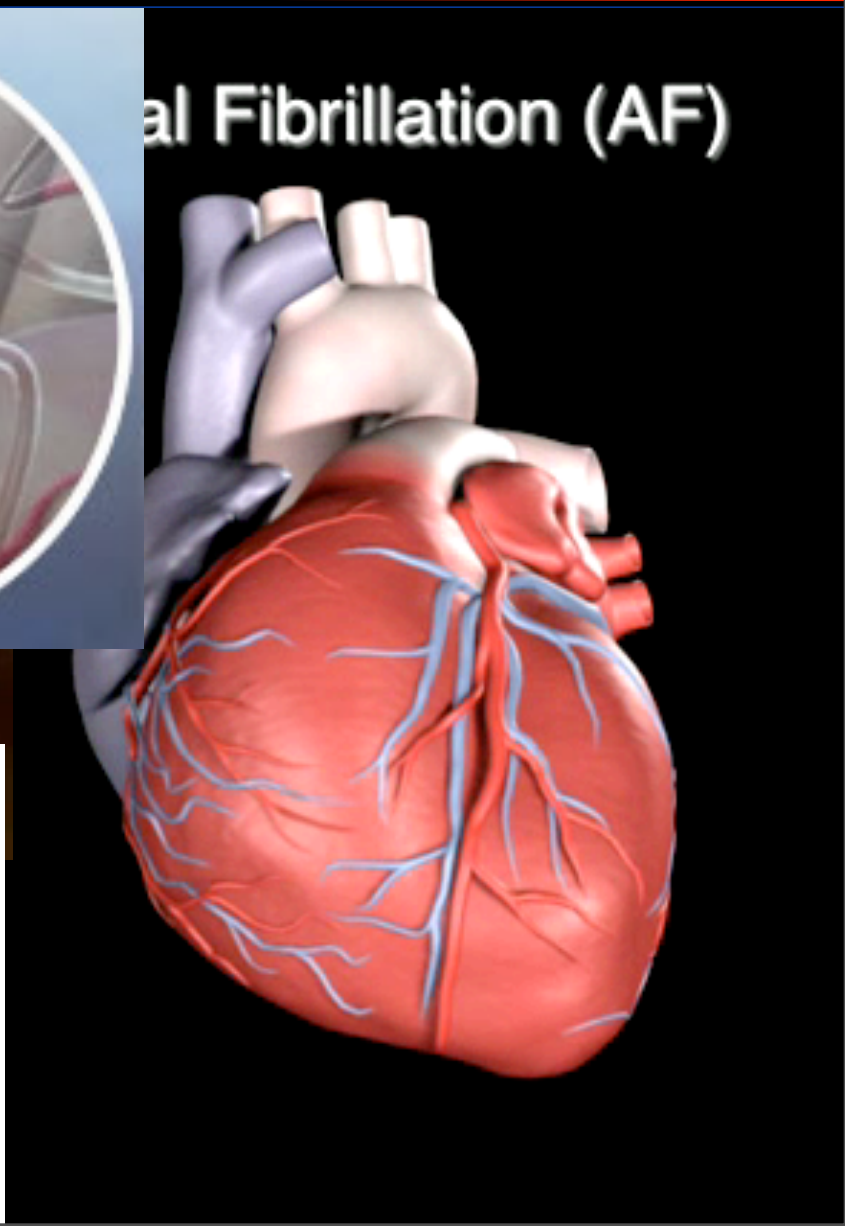

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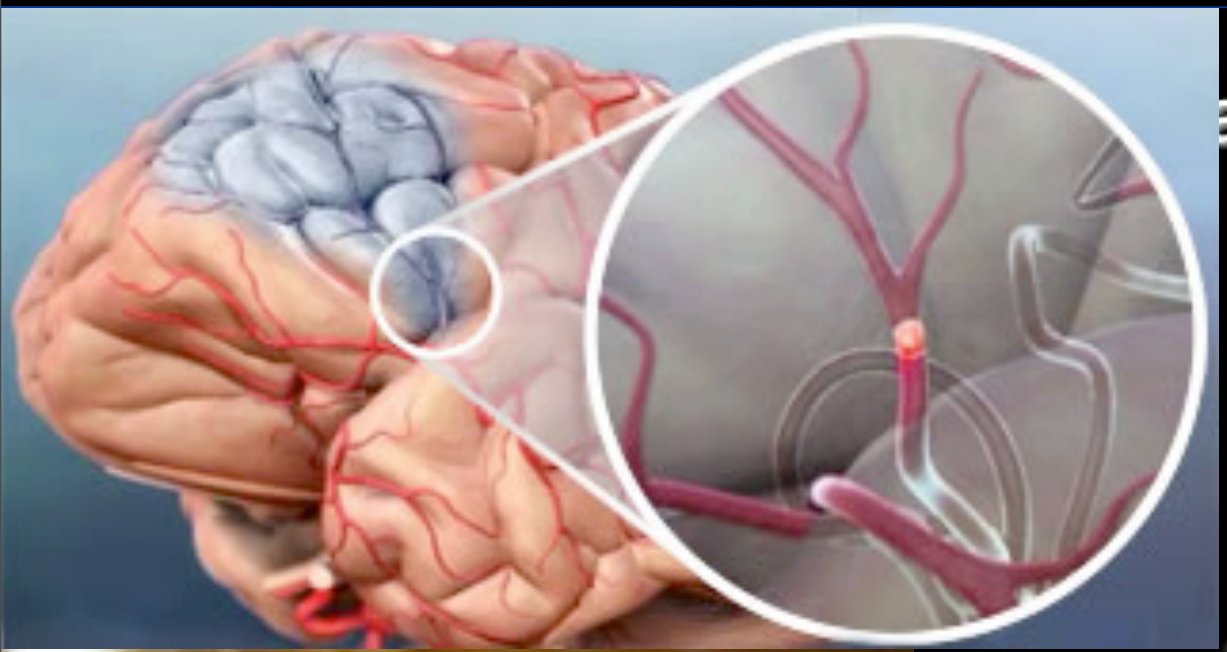
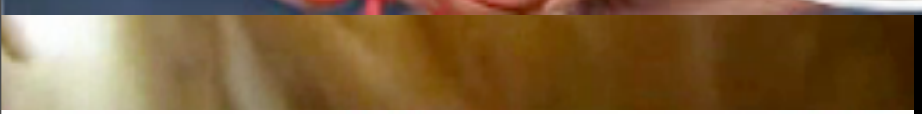
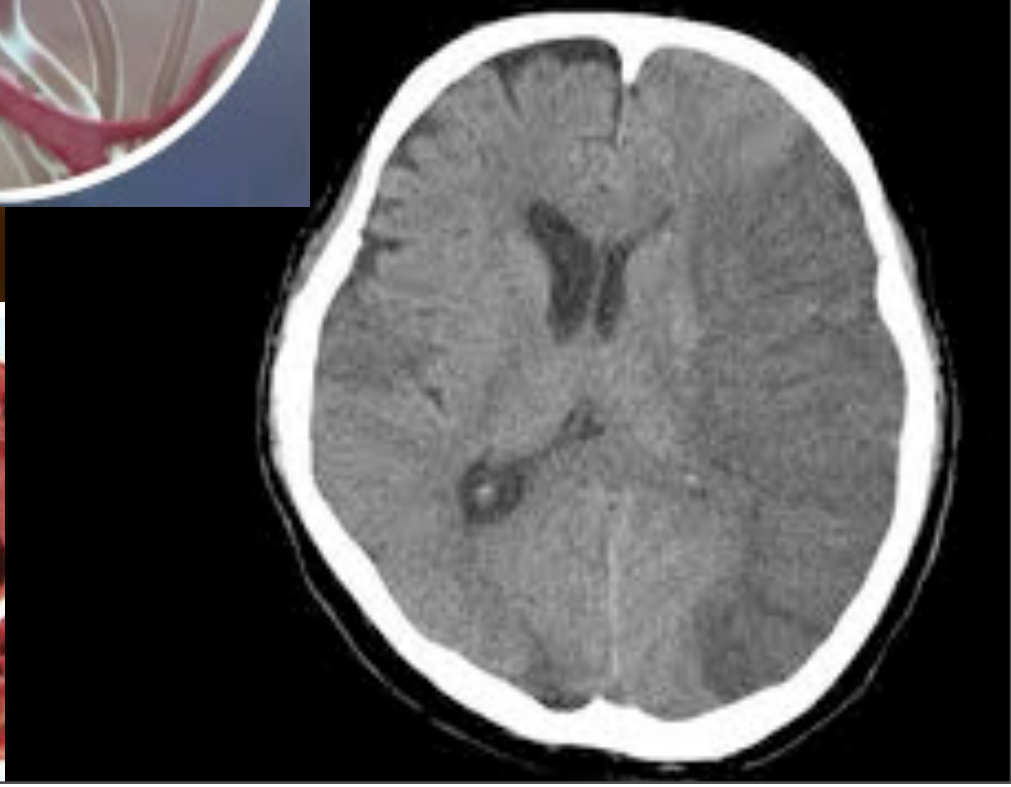






AF and Risk for Stroke

- The annual rate of ischemic stroke is **approximately 5%** among people with nonvalvular AF, 2 to 7 times that of people without AF
- The rate of brain ischemia (TIAs and "silent" strokes) exceeds 7%
- Long-term follow-up studies:
  - In the Framingham study, people with rheumatic heart disease and AF had a 17-fold increase in stroke risk compared with age-matched controls and a 5-fold increase compared with those who had nonrheumatic AF
  - Risk increases with age: in the Framingham cohort, annual attributable stroke risk was 1.5% for participants aged 50 to 59 years, 23.5% for those aged 80 to 89 years

Fuster V, et al. *Circulation*. 2006;114:257-354.

AF-RELATED STROKES ARE ASSOCIATED WITH GREATER DISABILITY AND A HIGHER MORTALITY RATE

Disability at clinical presentation[1]

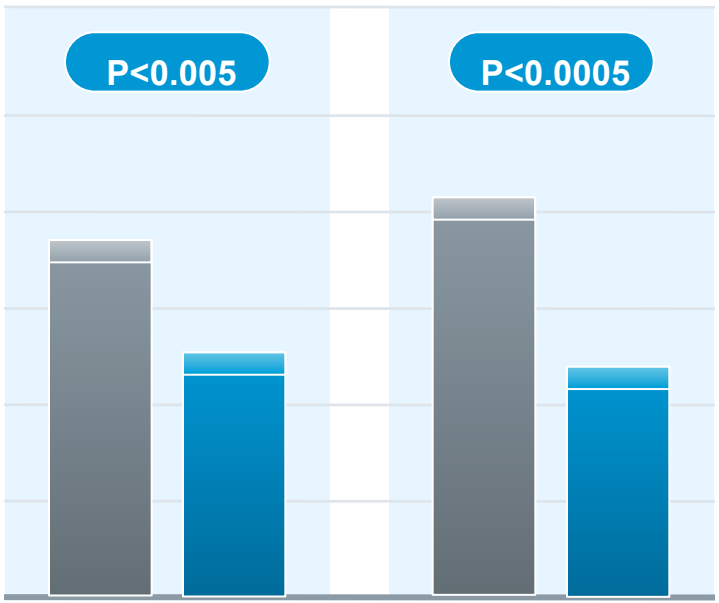
30-day post-stroke mortality[2]

1. Dulli DA, et al. *Neuroepidemiology* 2003;22:118-123. 2. Lin HJ, et al. *Stroke* 1996;27:1760-1764.

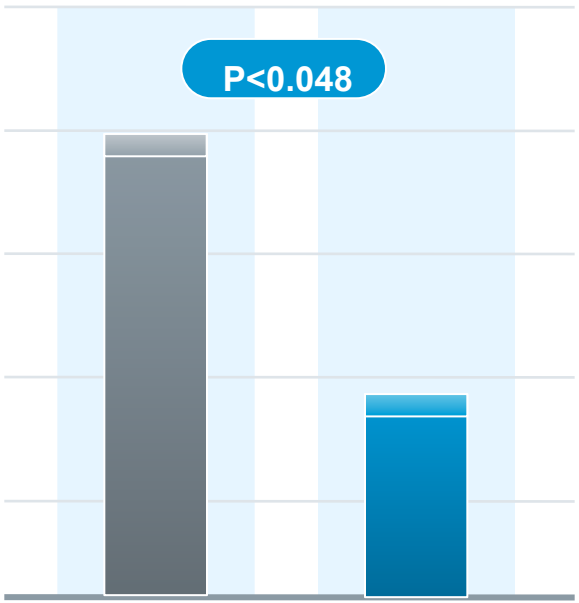
AF-RELATED STROKES ARE ASSOCIATED WITH GREATER DISABILITY AND A HIGHER MORTALITY RATE

Strokes with AF (N=216) **Strokes without AF** (N=845)

Disability at clinical presentation[1]



30-day post-stroke mortality[2]



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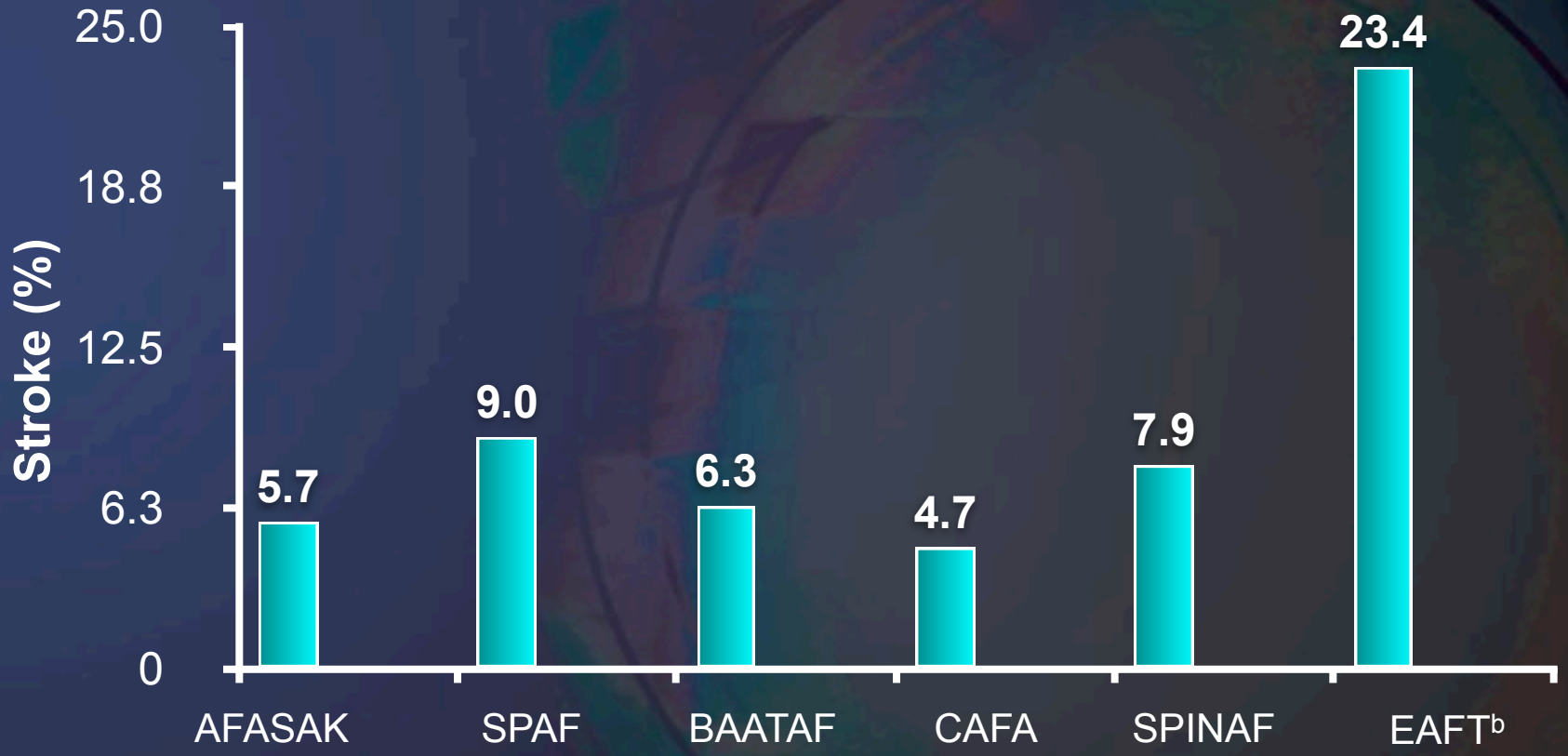
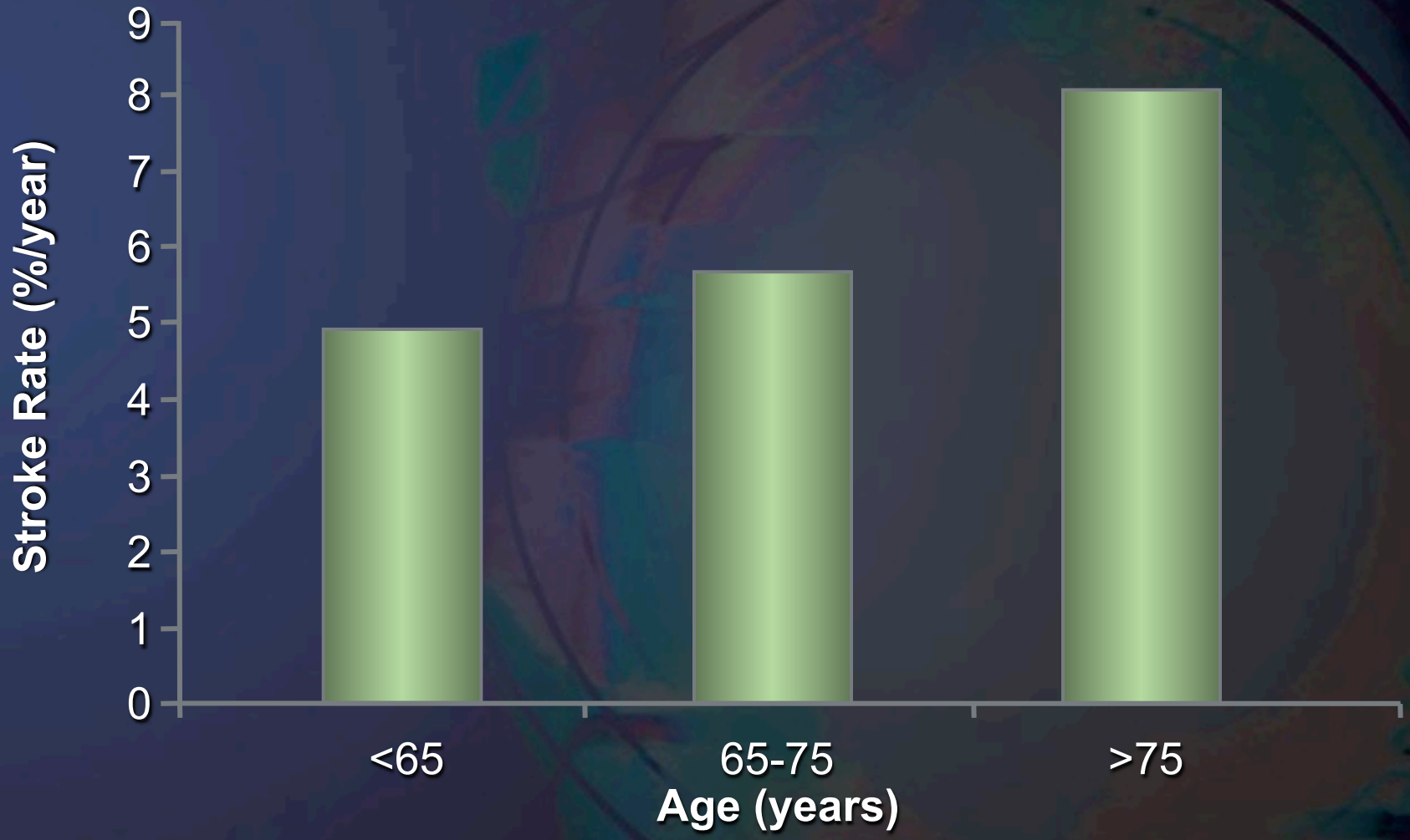
Stroke Rates in Placebo-Treated Patients With AF[a]



[a]Patients not anticoagulated; [b]Secondary prevention.

Hart et al. *Ann Intern Med. Ann Intern Med*. 2007;146:857-867.

Stroke Rates by Age in Patients With AF in Untreated Control Groups



Fuster et al. *J Am Coll Cardiol*. 2006;48:854-906.

The CHADS2 Index Stroke Risk Score for AF

	Score (points)	Prevalence (%)
Prior stroke or TIA	2	10
Age >75 years	1	28
Hypertension	1	65
Diabetes mellitus	1	18
Heart failure	1	32
High risk	≥3	22
Moderate risk	1-2	33-50
Low risk	0-1	18-51

van Walraven et al. *Arch Intern Med.* 2003;163:936-943; Nieuwlaat et al. Euro Heart Survey. *Eur Heart J.* 2006 (Epub).

Risk Factors for Stroke and Systemic Embolism in Patients With Nonvalvular AF

Risk Factors	Relative Risk*
Previous stroke or TIA	2.5
History of hypertension	1.6
CHF	1.4
Advanced age (continuous, per decade)	1.4
Diabetes mellitus	1.7
Coronary artery disease	1.5

- Age <75 yr and no risk factors, stroke risk = 1% annually
- Age <75 yr with hypertension or diabetes, risk 2.5% annually
- Age >75 yr with hypertension, risk 7.5% annually
- Age >75 yr with history of TIA or stroke, risk 13% annually

*Relative risk in comparison with patients with AF without these risk factors.

Ziv O, Choudhary G. *Prim Care.* 2005; 32:1083-1107.

Antithrombotic Therapy for Patients With AF

Risk Category	Recommended Therapy
No risk factors	Aspirin, 81 to 325 mg/d
One moderate-risk factor	Aspirin, 81-325 mg/d, or warfarin (INR 2.0-3.0, target 2.5)
Any high-risk factor or more than 1 moderate-risk factor	Warfarin (INR 2.0-3.0, target 2.5)*

Less Validated or Weaker Risk Factors	Moderate-Risk Factors	High-Risk Factors
Female sex	Age ≥75 y	Previous stroke, TIA, or embolism
Age 65-74 y	Hypertension	Mitral stenosis
Coronary artery disease	Heart failure	Prosthetic heart valve
Thyrotoxicosis	LV ejection fraction ≤35%	
	Diabetes mellitus	

*If patient has a mechanical valve, target INR is >2.5.
INR = international normalized ratio; LV = left ventricular; TIA = transient ischemic attack.

Fuster V, et al. *Circulation.* 2006;114:e257-354.

Stroke Risk Stratification

$CHAD_2$ criteria and score: 2 points for prior stroke or TIA; 1 point each for age >75 years, hypertension, diabetes mellitus, and heart failure.

Stroke Risk of Patients With Nonvalvular AF According to $CHADS_2$ Score*

$CHADS_2$ Score	Patients (N = 1733)	Adjusted Stroke Rate (%/y) (95% CI)
0	120	1.9 (1.2 to 3.0)
1	463	2.8 (2.0 to 3.8)
2	523	4.0 (3.1 to 5.1)
3	337	5.9 (4.6 to 7.3)
4	220	8.5 (6.3 to 11.1)
5	65	12.5 (8.2 to 17.5)
6	5	18.2 (10.5 to 27.4)

*Patients not treated with anticoagulation. Adjusted stroke rate derived from multivariate analysis assuming no aspirin use. Data are from van Walraven WC, et al. *Arch Intern Med.* 2003;163:936-943; and Gage BF, et al. *JAMA*. 2001;285:2864-2870.

$CHADS_2$ = cardiac failure, hypertension, age, diabetes, and stroke (doubled).
Adapted from Fuster V, et al. *Circulation*. 2006;114:257-354. [10]

Risk factors included in various stroke risk stratification schemes and published guidelines

Risk stratification schemes		Risk factor						
		Age	Female	Prior stroke or TE event	Hypertension	Heart failure	Diabetes	Vascular disease
SPAF[116]	1999	>75[a]	√[a]	√	√	–	√	–
AF Investigators[117]	1994	65–75; >75	–	√	√	–	√	–
$CHADS_2$[42]	2001	≥75	–	√	√	√	√	–
Framingham[63]	2003	√	√	√	√	–	√	–
van Walraven[118]	2003	–	–	√	√	–	√	√
Rietbrock[45]	2008	√	√	√	–	–	√	–
CHA_2DS_2-VASc[71]	2009	65–74; ≥75	√	√	√	√	√	√
Guidelines and consensus statements								
ACCP[6]	2012	65–74; >75	√	√	√	√	√	√
Canadian Guidelines[119]	2010	≥75	–	√	√	√	√	–
ESC[1,78]	2010, 2012	65–74; ≥75	√	√	√	√	√	√
RCPE consensus statement[120]	2012	65–74; ≥75	√	√	√	√	√	√
Canadian Guidelines focused update[27]	2012	65–74; ≥75	√	√	√	√	√	√

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Comparison of Risk Stratification Schemes to Predict Thromboembolism in People With Nonvalvular Atrial Fibrillation

Margaret C. Fang, MD, MPH,* Alan S. Go, MD,*† Yuchiao Chang, PHD,‡ Leila Borowsky, MPH,‡ Niela K. Pomernacki, RD,† Daniel E. Singer, MD,‡ for the ATRIA Study Group

San Francisco and Oakland, California; and Boston, Massachusetts

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FOCUS ISSUE: ATRIAL FIBRILLATION **Clinical Research**

Atrial Fibrillation and Embolism

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San Francisco and Oakland, California; and Boston, Massachusetts

assessed the predictive ability of these 5 risk stratification schemes when applied to a large, independent, community cohort of patients with AF.

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FOCUS ISSUE: ATRIAL FIBRILLATION **Clinical Research**

Atrial Fibrillation and Embolism

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The ATRIA (AnTicoagulation and Risk Factors In Atrial Fibrillation) study is a cohort of 13,559 adults with diagnosed nonvalvular AF who received care within Kaiser Permanente of Northern California

Margare MPH,‡
Niela K.

San Francisco and Oakland, California; and Boston, Massachusetts

assessed the predictive ability of these 5 risk stratification schemes when applied to a large, independent, community cohort of patients with AF.

Risk Stratification Schemes

Risk Scheme	Low Risk	Intermediate Risk	High Risk
AFI	Age <65 yrs and no risk factors	Age >65 yrs and no other risk factors	Prior ischemic stroke or transient ischemic attack, history of hypertension, history of diabetes mellitus
SPAF	No risk factors	History of hypertension	Prior stroke, women older than 75 yrs, recent clinical heart failure, left ventricular fractional shortening ≤25% on echocardiography
$CHADS_2$†	Score 0	Score 1 to 2	Score 3 to 6
Framingham‡	Score 0 to 7	Score 8 to 15	Score 16 to 31
7th ACCP	Age <65 yrs and no other risk factors	Age 65 to 75 yrs and no other risk factors	Prior ischemic stroke, age >75 yrs, moderate to severe left ventricular dysfunction, history of hypertension, diabetes mellitus

Risk Stratification Schemes

The 7th ACCP guideline's categories of low-risk, intermediate-risk, and high-risk categories, corresponded to absolute thromboembolism rates of 0.13%, 0.89%, and 2.5% per year

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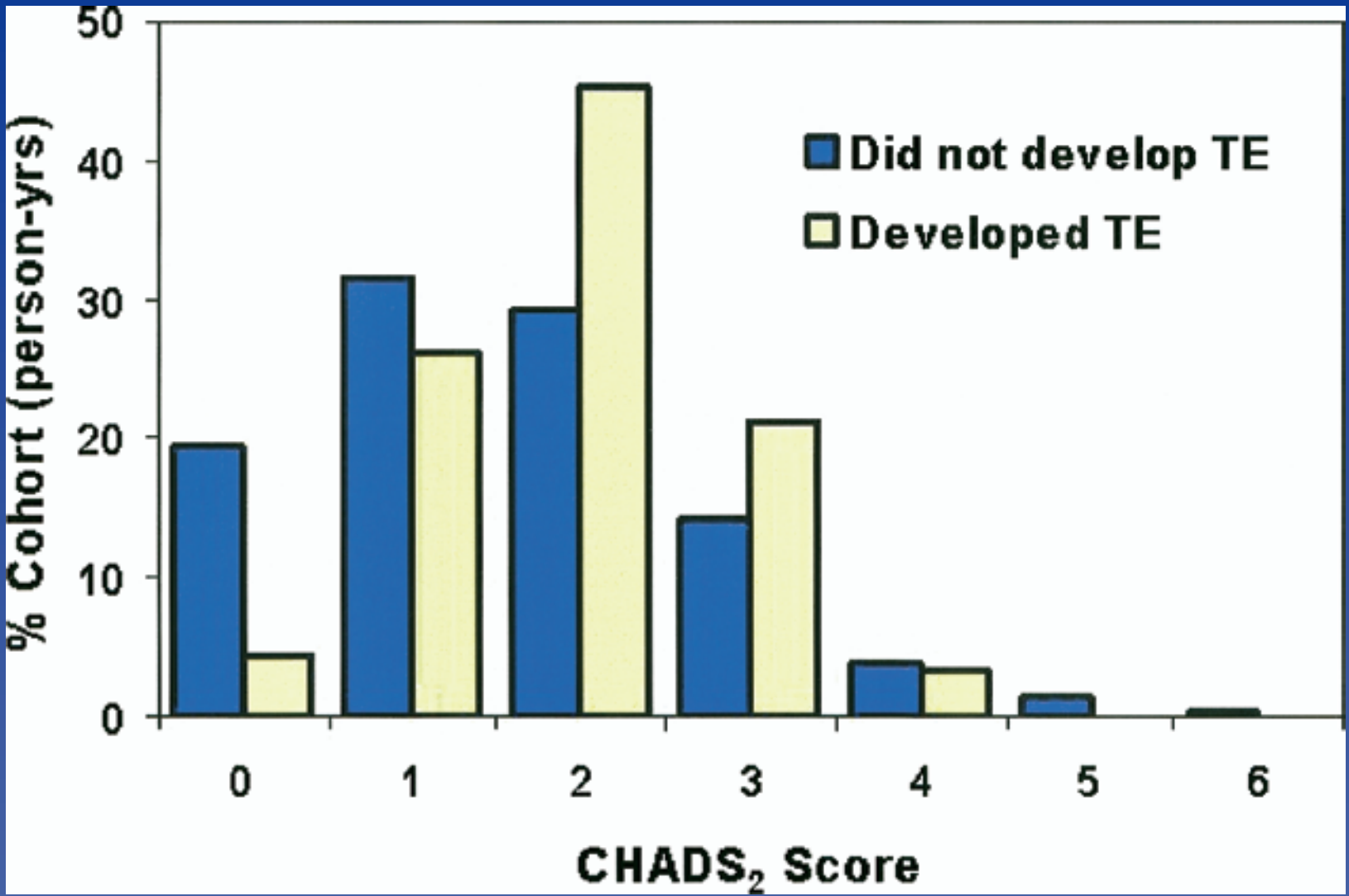
SP/			
CH/			
Fra			
7th			

A c-statistic of 1 indicates perfect discrimination, whereas a value of 0.5 indicates no discrimination

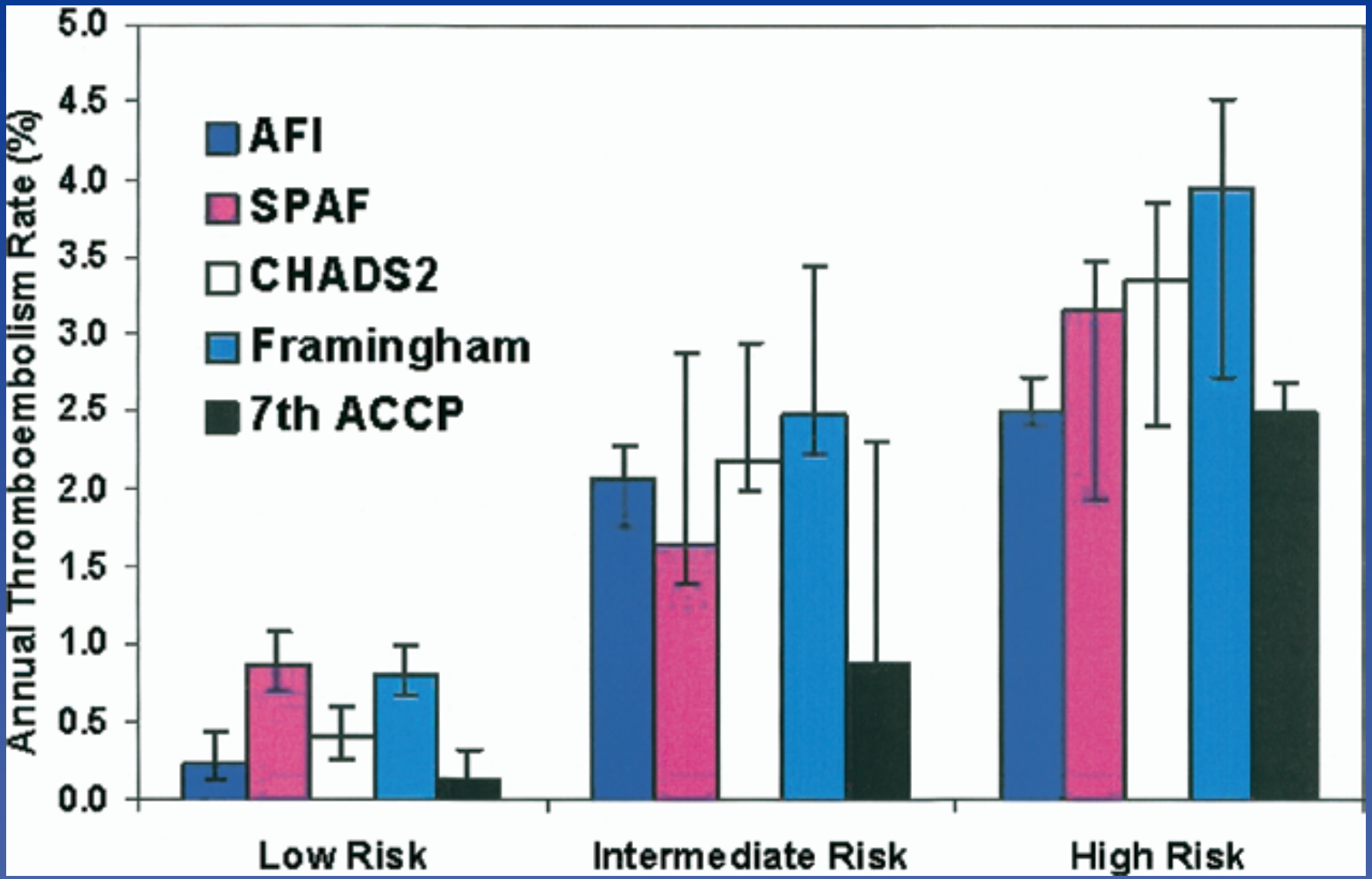
Proportion of ATRIA Cohort Categorized by 5 Risk Stratification Schemes Used to Predict Atrial Fibrillation–Related Thromboembolism and Discriminatory Ability of Risk Schemes (c-Statistics)

	Risk for Thromboembolism (%)			c-Statistic	
	Low	Intermediate	High	All Patients	Subgroup*
AFI	13.1	24.7	62.3	0.56	0.61
SPAF	27.7	28.5	43.8	0.60	0.65
$CHADS_2$	18.8	61.2	20.1	0.58	0.67
Framingham	37.1	46.6	16.4	0.62	0.69
7th ACCP	11.7	7.9	80.4	0.56	0.60

Proportion of ATRIA Cohort Off Warfarin and Categorized by CHADS2 Scores, Stratified by Development of TE



Annual TE Rates Across Risk Groups Using 5 Risk Stratification Schemes Used to Predict AF-Related TE



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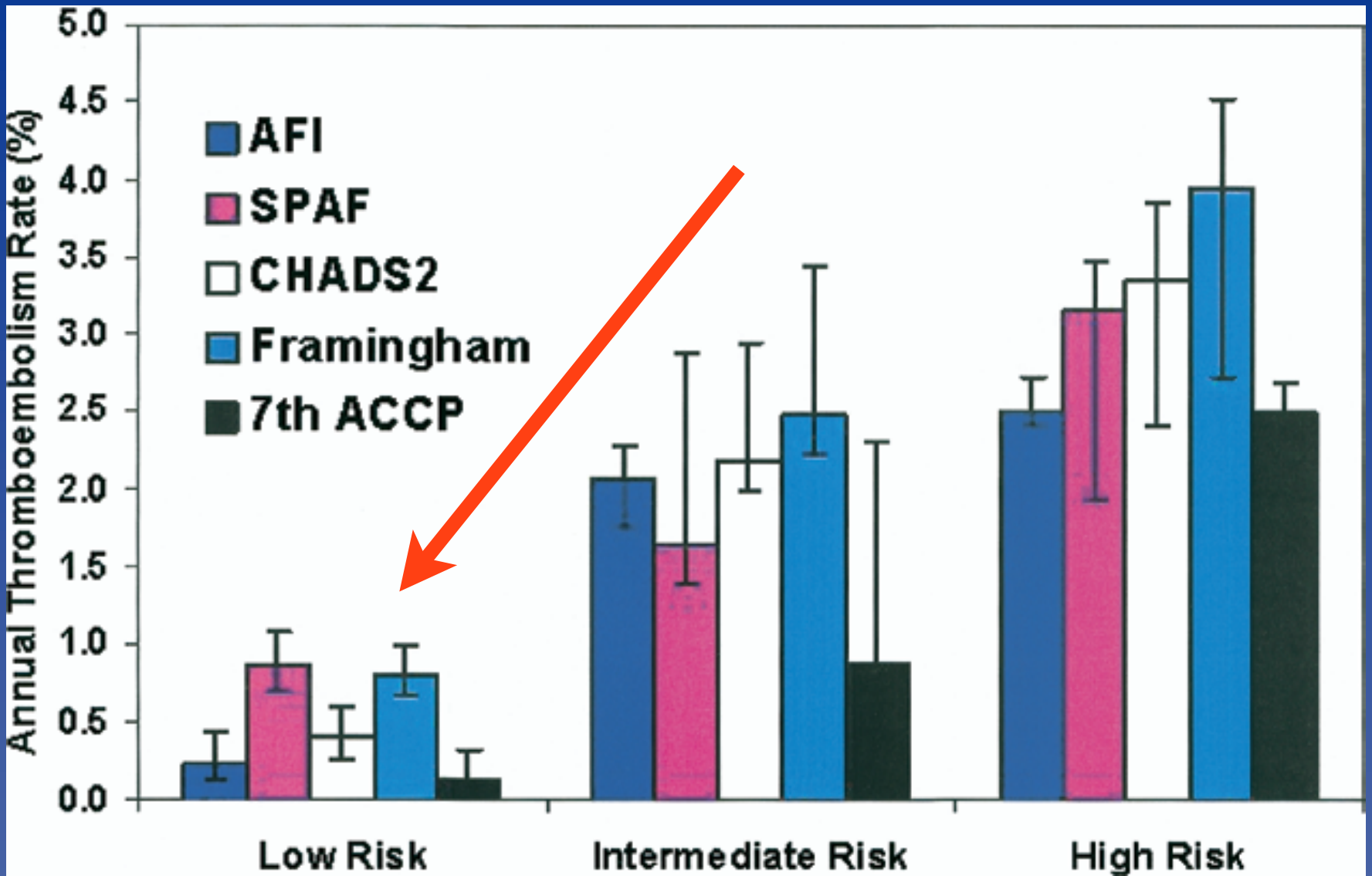

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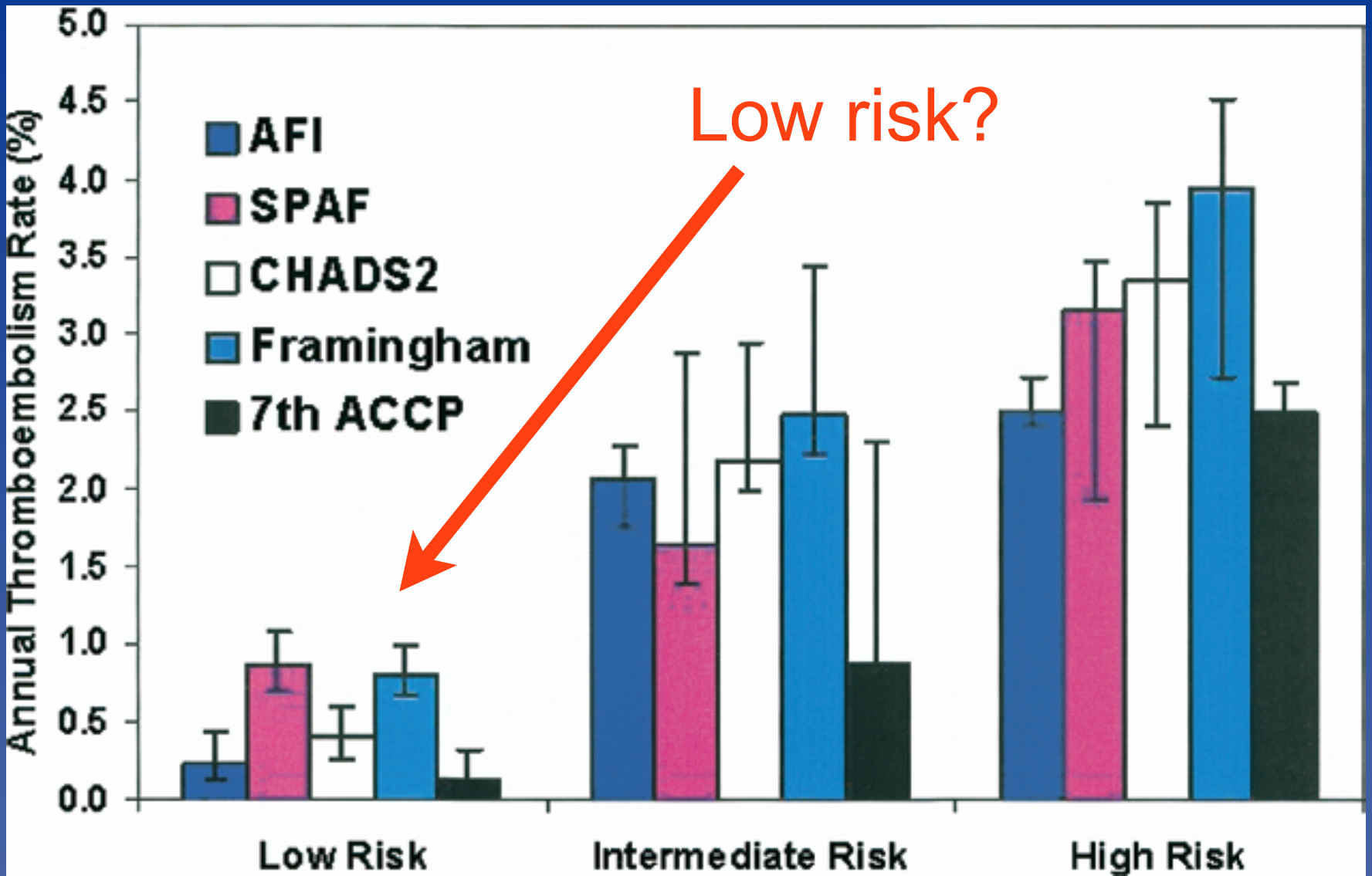
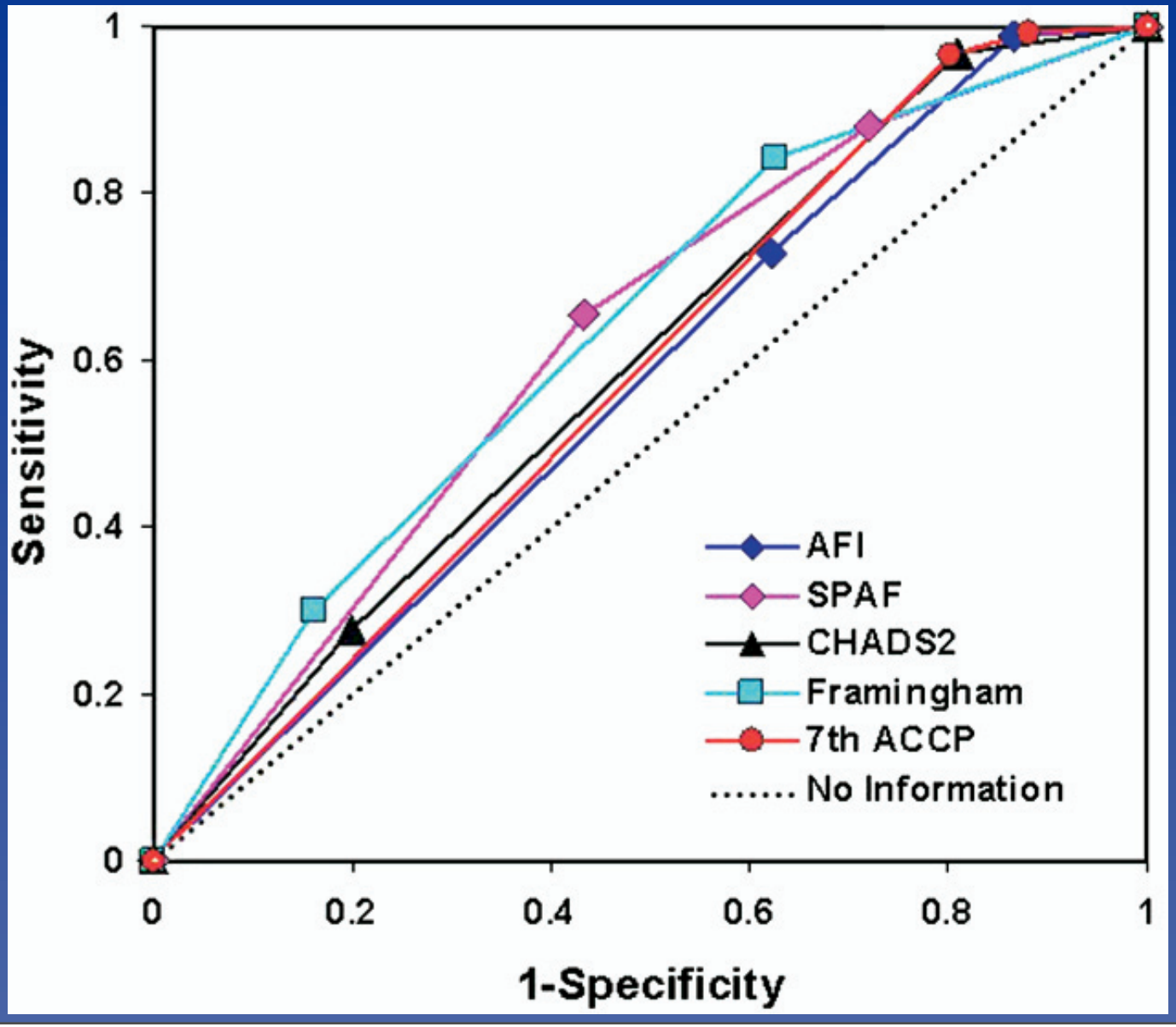


ROC Curves for 5 Risk Stratification Schemes Used to Predict AF-Related Thromboembolism



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REVIEW

Stroke and Thromboembolism in Atrial Fibrillation

– Systematic Review of Stroke Risk Factors and Risk Stratification Schema –

Ron Pisters, MD, PhD; Deirdre A. Lane, PhD; Francisco Marin, MD, PhD;
A. John Camm, MD; Gregory Y. H. Lip, MD

The present analysis aimed to systematically review
(a) the independent risk factors for stroke in AF patients,
(b) the published RSMs and
(c) the published cost-effectiveness data of (new) oral anticoagulant and antiplatelet agents for stroke prevention in AF patients

Age as a risk factor

Study	n	Age risk factor	Stroke rate test	Stroke rate ref.	RR/OR/HR (95% CI)	P value
Cabin HS, 1990[18]	272	Age >70 vs. ≤70 years	13%	7%	NA (bivariate analysis)	NS
Petersen P, 1990[32]	336	Correlation with increasing age	NA	NA	LR Enter 0.01	NS
Moulton AW, 1991[22]	265	Age >75 vs. ≤75 years	NA	NA	OR 1.72 (1.04–2.84)	<0.05
SPAF Investigators, 1992[40]	568	Incremental risk per decade	NA	NA	RR 1.2 (0.9–1.6)	NS
Laupacis A, 1994[4] (AF Invest. 1994)	1,593	Incremental risk per decade	NA	NA	RR 1.4	<0.05
Van Latum JC, 1995[24]	375	≥60–69 vs. <60 years	NA	NA	HR 0.8 (0.3–1.9)	NS
		≥70–79 vs. <60 years	NA	NA	HR 0.9 (0.4–2.1)	NS
		≥80 vs. <60 years	NA	NA	HR 0.6 (0.2–1.6)	NS
Ezekowitz M, 1998[34] (using clinical factors alone)	1,066	Incremental risk per decade	NA	NA	RR 1.5 (1.1–1.9)	0.008
Ezekowitz M, 1998[34] (using clinical and echo- cardio-graphic features)	1,010	Incremental risk per decade	NA	NA	RR 1.5 (1.1–2.0)	0.006
Nakagami H, 1998[31]	290	Incremental risk per decade	NA	NA	OR 1.33 (1.04–1.71)	NS
SPAF III, 1998[27]	892	Incremental risk per decade	NA	NA	RR 1.7 (1.1–2.6)	0.01
Stollberger C, 1998[35]	409	Correlation with increasing age	NA	NA	RR 1.1 (1.0–1.11)	<0.001
Hart RG, 1999[28]	2,012	Incremental risk per decade	NA	NA	RR 1.8	<0.001
Hart RG, 2000[29] (paroxysmal AF)	460	Incremental risk per decade	NA	NA	RR 2.1	<0.001
Hart RG, 2000[29] (persistent AF)	1,552	Incremental risk per decade	NA	NA	RR 1.7	<0.001
Inoue H, 2000[20]	740	Age >65 years	NA	NA	RR 3.33 (1.92–5.81)	0.0001
Wang TJ, 2003[36]	705	Incremental risk per decade	NA	NA	HR 1.32 (1.02–1.76) (for stroke)	<0.05
		Incremental risk per decade	NA	NA	HR 2.13 (1.86–2.44) (for stroke or death)	<0.05
Stollberger C, 2004[33]	409	Correlation with increasing age	NA	NA	RR 1.05 (1.02–1.09)	0.0006
Frost L, 2007[19]	141,493	Age 70–74 vs. 40–44 years (for men)	NA	NA	HR 6.31 (4.78–8.33)	<0.05
Ruigómez A, 2009[23]	831	Age >80 vs. 40–59 years	NA	NA	RR 5.8 (1.9–17.6)	<0.05
Lip GYH, 2010[15]	1,577	Age >75 vs. ≤75 years	3.6%	1.8%	OR 1.46 (0.63–3.65)	NS
Hobbs FD, 2011[30]	665	Incremental risk per 5 years	NA	NA	HR 1.26 (0.93–1.72)	NS
Lin LY, 2011[21]	7,920	Age ≥75 vs. 20–64 years	NA	NA	OR 1.652 (1.313–2.080)	<0.001
Van Staa TP, 2011[25]	79,844	Age 50–59 vs. 60–69 years	NA	NA	RR 0.44 (0.28–0.69)	<0.05
		Age <50 vs. 60–69 years	NA	NA	RR 0.14 (0.06–0.34)	<0.05
		Age ≥80 vs. 60–69 years	NA	NA	RR 2.22 (1.78–2.76)	<0.05
		Age 70–79 vs. 60–69	NA	NA	RR 1.42 (1.12–1.78)	<0.05

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Stollberger C, 2004[33]	409	Correlation with increasing age	NA	NA	RR 1.05 (1.02–1.09)	0.0006
Frost L, 2007[19]	141,493	Age 70–74 vs. 40–44 years (for men)	NA	NA	HR 6.31 (4.78–8.33)	<0.05
Ruigómez A, 2009[23]	831	Age >80 vs. 40–59 years	NA	NA	RR 5.8 (1.9–17.6)	<0.05
Lip GYH, 2010[15]	1,577	Age >75 vs. ≤75 years	3.6%	1.8%	OR 1.46 (0.63–3.65)	NS
Hobbs FD, 2011[30]	665	Incremental risk per 5 years	NA	NA	HR 1.26 (0.93–1.72)	NS
Lin LY, 2011[21]	7,920	Age ≥75 vs. 20–64 years	NA	NA	OR 1.652 (1.313–2.080)	<0.001
Van Staa TP, 2011[25]	79,844	Age 50–59 vs. 60–69 years	NA	NA	RR 0.44 (0.28–0.69)	<0.05
		Age <50 vs. 60–69 years	NA	NA	RR 0.14 (0.06–0.34)	<0.05
		Age ≥80 vs. 60–69 years	NA	NA	RR 2.22 (1.78–2.76)	<0.05
		Age 70–79 vs. 60–69	NA	NA	RR 1.42 (1.12–1.78)	<0.05

Age as a risk factor

Study	n	Age risk factor	Stroke rate test	Stroke rate ref.	RR/OR/HR (95% CI)	P value
Cabin HS, 1990[18]	272	Age >70 vs. ≤70 years	13%	7%	NA (bivariate analysis)	NS
Petersen P, 1990[32]	336	Correlation with increasing age	NA	NA	LR Enter 0.01	NS
Moulton AW, 1991[22]	265	Age >75 vs. ≤75	NA	NA	OR 1.72 (1.04–2.84)	<0.05
Age >65 years	NA		NA		RR 3.33 (1.92–5.81)	0.0001
Van Latum JC, 1995[24]	375	≥60–69 vs. <60 years	NA	NA	HR 0.8 (0.3–1.9)	NS
		≥70–79 vs. <60 years	NA	NA	HR 0.9 (0.4–2.1)	NS
		≥80 vs. <60 years	NA	NA	HR 0.6 (0.2–1.6)	NS
Ezekowitz M, 1998[34] (using	1,066	Incremental risk per	NA	NA	RR 1.5 (1.1–1.9)	0.008
Age 50–59 vs. 60–69 years	NA		NA		RR 0.44 (0.28–0.69)	<0.05
Age <50 vs. 60–69 years	NA		NA		RR 0.14 (0.06–0.34)	<0.05
Age ≥80 vs. 60–69 years	NA		NA		RR 2.22 (1.78–2.76)	<0.05
Age 70–79 vs. 60–69 years	NA		NA		RR 1.42 (1.12–1.78)	<0.05
Frost L, 2007[19]	141,493	Age 70–74 vs. 40–44 years (for men)	NA	NA	HR 6.31 (4.78–8.33)	<0.05
Ruigómez A, 2009[23]	831	Age >80 vs. 40–59 years	NA	NA	RR 5.8 (1.9–17.6)	<0.05
Lip GYH, 2010[15]	1,577	Age >75 vs. ≤75 years	3.6%	1.8%	OR 1.46 (0.63–3.65)	NS
Hobbs FD, 2011[30]	665	Incremental risk per 5 years	NA	NA	HR 1.26 (0.93–1.72)	NS
Lin LY, 2011[21]	7,920	Age ≥75 vs. 20–64 years	NA	NA	OR 1.652 (1.313–2.080)	<0.001
Van Staa TP, 2011[25]	79,844	Age 50–59 vs. 60–69 years	NA	NA	RR 0.44 (0.28–0.69)	<0.05
		Age <50 vs. 60–69 years	NA	NA	RR 0.14 (0.06–0.34)	<0.05
		Age ≥80 vs. 60–69 years	NA	NA	RR 2.22 (1.78–2.76)	<0.05
		Age 70–79 vs. 60–69	NA	NA	RR 1.42 (1.12–1.78)	<0.05

Sex as a risk factor

Study	n	Sex comparison	Stroke rate test	Stroke rate ref.	RR/OR/HR (95% CI)	P value
Aronow WS, 1989[37]	110	F vs. M	NA	NA	OR 0.85	NS
Cabin HS, 1990[18]	272	F vs. M	14%	6%	NA (bivariate analysis)	0.023
					CRC 1.0	0.014
Petersen P, 1990[32]	336	F vs. M	NA	NA	LR Enter 0.48	NS
Laupacis A, 1994 (AF Investig. 1994)[4]	1,593	F vs. M	NA	NA	NA	NS
Van Latum JC, 1995[24]	375	F vs. M	NA	NA	HR 1.5 (1.0–2.4)	NR
Ezekowitz M, 1998[34] (using clinical factors alone)	1,066	F vs. M	NA	NA	NA	NS
Aronow WS, 1998[38]	312	M vs. F	NA	NA	RR 0.98 (0.67–1.43)	NS
Nakagami H, 1998[31]	290	F vs. M	NA	NA	OR 0.98 (0.55–1.72)	NS
SPAF III, 1998[27]	892	F vs. M	NA	NA	NA	NS
Stollberger CM, 1998[35]	409	F vs. M	NA	NA	NS	NS
Hart RG, 1999[28]	2,012	F vs. M	NA	NA	RR 1.6	0.01
Hart RG, 2000[29] (paroxysmal AF)	460	F vs. M	NA	NA	NA	NS
Hart RG, 2000[29] (persistent AF)	1,552	F vs. M	NA	NA	RR 1.8	0.004
Inoue H, 2000[20]	740	M vs. F	NA	NA	OR 2.00 (1.07–3.72)	0.0291
Wang TJ, 2003[36]	705	F vs. M	NA	NA	1.92 (1.20–3.07)	<0.05
Fang M, 2005[39]	13,559	F vs. M	3.5%	1.8%	RR 1.6 (1.3–1.9)	<0.05
Ruigomez A, 2009[23]	831	M vs. F	NA	NA	RR 1.0 (0.6–1.7)	NS
Lip GYH, 2010[15]	1,084	F vs. M	3.6%	1.4%	OR 2.53 (1.08–5.92)	0.03
Hobbs FD, 2011[30]	665	F vs. M	NA	NA	HR 0.99 (0.57–1.70)	NS
Lin LY, 2011[21]	7,920	F vs. M	NA	NA	OR 0.942 (0.787–1.127)	NS
Van Staa TP, 2011[25]	79,844	M vs. F	NA	NA	RR 0.95 (0.84–1.06)	NS

HT > 160 as a risk factor

Study	n	Stroke rate test	Stroke rate ref.	RR/OR/HR (95% CI)	P value
(A) SBP >160 mmHg as a risk factor for stroke in terms of whether or not the study reported SBP >160 mmHg as a significant risk factors					
SPAF study, 1995[41]	854	NA	NA	RR 2.2 (1.3–3.6)	0.004
Van Latum JC, 1995[24]	375	NA	NA	HR 1.7 (1.0–2.9)	NR
Hart RG, 1999[28]	2,012	NA	NA	RR 2.3	<0.001
Hart RG, 2000[29] (paroxysmal AF)	460	NA	NA	NA	NS
Hart RG, 2000[29] (persistent AF)	1,552	NA	NA	RR 2.8	<0.001
Wang TJ, 2003[36] (per 10 mmHg increase)	705	NA	NA	HR 1.06 (0.97–1.17) (for stroke)	NS
		NA	NA	HR 1.06 (1.02–1.11) (for stroke or death)	<0.05
van Staa TP, 2011[25] (140–159 vs. <120 mmHg)	79,844	NA	NA	RR 2.74 (1.21–6.19)	<0.05
van Staa TP, 2011[25] (160–179 vs. <120 mmHg)	79,844	NA	NA	RR 1.49 (0.55–4.00)	NS
van Staa TP, 2011[25] (≥180 vs. <120 mmHg)	79,844	NA	NA	RR 4.28 (1.25–14.64)	<0.05

Presence of HT as a risk factor

(B) Presence of Htn (including a history of Htn) as a risk factor for stroke in terms of whether or not the study reported Htn as a significant risk factor

Aronow WS, 1989[37]	110	NA	NA	OR 12.51	<0.01
Cabin HS, 1990[18]	272	12%	8%	NA (bivariate analysis)	NS
Petersen P, 1990[32]	336	NA	NA	LR Enter 0.8	NS
Moulton AW, 1991[22]	265	NA	NA	OR 1.89 (1.15–3.10)	<0.05
SPAF Investigators, 1992[40]	568	NA	NA	RR 2.2 (1.1–4.3)	0.02
Laupacis A, 1994[4] (AF Investig. 1994)	1,593	NA	NA	RR 1.6	<0.05
Ezekowitz M, 1998[27] (using clinical factors alone)	1,066	NA	NA	RR 1.5 (0.9–2.5)	0.11
Ezekowitz M, 1998[34] (using clinical and echocardiographic features)	1,010	NA	NA	RR 1.5 (0.9–2.5)	0.13
Aronow WS, 1998[38]	312	NA	NA	RR 1.254 (0.847–1.855)	NS
Seidl K, 1998[42]	191	NA	NA	OR 6.5 (1.5–45)	<0.05
SPAF III, 1998[27]	892	3.6% per year	1.1% per year	RR 3.3 (1.7–6.9)	0.001
Stollberger C, 1998[35]	409	NA	NA	RR 3.6 (1.8–8.4)	0.001
Hart RG, 1999[28]	2,012	NA	NA	RR 2.0	<0.001
Hart RG, 2000[29] (paroxysmal AF)	460	NA	NA	RR 3.4	0.003
Hart RG, 2000[29] (persistent AF)	1,552	NA	NA	RR 1.8	0.008
Stollberger C, 2004[33]	409	NA	NA	NA	NS
Ruigomez A, 2009[23]	831	NA	NA	RR 0.6 (0.3–1.1)	NS
Lip GYH, 2010[15]	1,084	2.6%	1.7%	OR 1.01 (0.38–2.66)	NS
Hobbs FD, 2011[30]	665	NA	NA	HR 1.10 (0.62–1.95)	NS
Lin LY, 2011[21]	7,920	NA	NA	OR 2.656 (2.140–3.296)	<0.001

CAD as a risk factor

Study	n	SHD definition	Stroke rate test	Stroke rate ref.	RR/OR/HR (95% CI)	P value
SPAF III, 1998[27]	892	Ischemic heart disease	NA	NA	NA	NS
Stollberger CM, 1998[35]	409	Ischemic heart disease	NA	NA	NA	NS
Aronow WS, 1989[37]	110	MI	NA	NA	OR 4.84	<0.01
Petersen P, 1990[32]	336	MI	28%/2 y	11%/2 y	LR 4.33	0.0375
Laupacis A, 1994[4] (AF Investig. 1994)	1,593	MI	NA	NA	RR 1.2	NS
Aronow WS, 1998[38]	312	MI	NA	NA	RR 0.87 (0.60–1.26)	NS
Hobbs FDR, 2011[30]	665	MI	NA	NA	HR 0.52 (0.18–1.50)	NS
Lin LY, 2011[21]	7,920	Coronary artery disease	NA	NA	OR 1.07 (0.83–1.36)	NS
Lin LY, 2011[21]	7,920	MI	NA	NA	OR 1.42 (0.91–2.23)	NS
Cabin HS, 1990[18]	272	Structural heart disease	14%	5%	NA	0.02
		Structural heart disease	NA	NA	CRC 0.9	0.037
Ruigomez A, 2009[23]	831	Structural heart disease (other cardiac disease)	NA	NA	RR 0.8 (0.2–3.2)	NS
Laupacis A, 1994[4] (AF Investig. 1994)	1,593	Angina	NA	NA	NA	NS
Hobbs FD, 2011[30]	665	Angina	NA	NA	HR 1.12 (0.30–2.44)	NS

Heart failure as a risk factor

SPAF Investig., 1992[26]	568	CHF	NA	NA	RR 2.0 (0.8–4.7)	NS
Laupacis A, 1994[4] (AF Investigators 1994	1,593	CHF	NA	NA	RR 1.4	NS
Ezekowitz M, 1998[34] (using clinical factors alone)	1,066	CHF	NA	NA	RR 1.7 (1.1–2.7)	0.03
Ezekowitz M, 1998[34] (AF Investig. 1998) (using clinical and echocardiographic features)	1,010	CHF	NA	NA	RR 1.4 (0.8–2.3)	0.16
SPAF III, 1998[27]	892	CHF	NA	NA	NA	NS
Hart RG, 1999[28]	2,012	CHF	NA	NA	NA	NS
Lip GYH, 2010[15]	1,577	CHF	2.4%	2.3%	OR 0.72 (0.27–1.88)	NS
Hobbs FD, 2011[30]	665	CHF	NA	NA	HR 0.78 (0.36–1.68)	NS
Lin LY, 2011[21]	7,920	CHF	NA	NA	OR 1.611 (1.299–1.999)	<0.001
Van Staa TP, 2011[25]	79,844	CHF	NA	NA	RR 1.26 (1.11–1.42)	<0.05
SPAF Investig., 1992[26]	568	LV dysfunction	NA	NA	RR 2.0 (1.0–4.0)	0.05
SPAF Study, 1995[41]	854	LV dysfunction	NA	NA	1.8 (1.2–3.0)	0.02
AFI Echo, 1998[34] (AF Investig. 1998) (Using clinical and echocardiographic features)	1,010	LV dysfunction (moderate to severe vs. none to mild)	NA	NA	RR 2.5 (1.5–4.4)	<0.001
Aronow WS, 1998[38]	312	LV ejection fraction	NA	NA	RR 1.795 (1.214–2.653)	0.003
Stollberger CM, 1998[35]	409	LV dysfunction	NA	NA	NA	NS
Stollberger CM, 2004[33]	409	LV dysfunction	NA	NA	NA	NS
Stollberger CM, 1998[35]	409	NYHA >II	NA	NA	NA	NS
Stollberger CM, 2004[33]	409	NYHA >II (vs. no heart failure)	NA	NA	NA	NS
Hart RG, 1999[28]	2,012	LV dysfunction	NA	NA	NA	NS
Lip GYH, 2010[15]	1,577	LV ejection fraction <40%	0.8%	2.1%	0.34 (0.04–2.73)	NS

Heart failure as a risk factor

SPAF Investig., 1992[26]	568	CHF	NA	NA	RR 2.0 (0.8–4.7)	NS
Laupacis A, 1994[4] (AF Investigators 1994	1,593	CHF	NA	NA	RR 1.4	NS
Ezekowitz M, 1998[34] (using clinical factors alone)	1,066	CHF	NA	NA	RR 1.7 (1.1–2.7)	0.03
Ezekowitz M, 1998[34] (AF Investig. 1998) (using clinical and echocardiographic features)	1,010	CHF	NA	NA	RR 1.4 (0.8–2.3)	0.16
SPAF III, 1998[27]	892	CHF	NA	NA	NA	NS
Hart RG, 1999[28]	2,012	CHF	NA	NA	NA	NS
Lip GYH, 2010[15]	1,577	CHF	2.4%	2.3%	OR 0.72 (0.27–1.88)	NS
Hobbs FD, 2011[30]	665	CHF	NA	NA	HR 0.78 (0.36–1.68)	NS
Lin LY, 2011[21]	7,920	CHF	NA	NA	OR 1.611 (1.299–1.999)	<0.001
Van Staa TP, 2011[25]	79,844	CHF	NA	NA	RR 1.26 (1.11–1.42)	<0.05
SPAF Investig., 1992[26]	568	LV dysfunction	NA	NA	RR 2.0 (1.0–4.0)	0.05
SPAF Study, 1995[41]	854	LV dysfunction	NA	NA	1.8 (1.2–3.0)	0.02
AFI Echo, 1998[34] (AF Investig. 1998) (Using clinical and echocardiographic features)	1,010	LV dysfunction (moderate to severe vs. none to mild)	NA	NA	RR 2.5 (1.5–4.4)	<0.001
Aronow WS, 1998[38]	312	LV ejection fraction	NA	NA	RR 1.795 (1.214–2.653)	0.003
Stollberger CM, 1998[35]	409	LV dysfunction	NA	NA	NA	NS
Stollberger CM, 2004[33]	409	LV dysfunction	NA	NA	NA	NS
Stollberger CM, 1998[35]	409	NYHA >II	NA	NA	NA	NS
Stollberger CM, 2004[33]	409	NYHA >II (vs. no heart failure)	NA	NA	NA	NS
Hart RG, 1999[28]	2,012	LV dysfunction	NA	NA	NA	NS
Lip GYH, 2010[15]	1,577	LV ejection fraction <40%	0.8%	2.1%	0.34 (0.04–2.73)	NS

Heart failure as a risk factor

SPAF Investig., 1992[26]	568	CHF	NA	NA	RR 2.0 (0.8–4.7)	NS
Laupacis A, 1994[4] (AF Investigators 1994	1,593	CHF	NA	NA	RR 1.4	NS
Ezekowitz M, 1998[34] (using clinical factors alone)	1,066	CHF	NA	NA	RR 1.7 (1.1–2.7)	0.03
Ezekowitz M, 1998[34] (AF Investig. 1998) (using clinical and echocardiographic features)	1,010	CHF	NA	NA	RR 1.4 (0.8–2.3)	0.16
SPAF II						NS
Hart RG						NS
Lip GYH						NS
Hobbs I						NS
Lin LY,						.001
Van Sta						.05
SPAF In						.05
SPAF S						.02
AFI Ech (Using features						.001
Aronow						.003
Stollber						NS
Stollberger CM, 2004	409	LV dysfunction	NA	NA	NA	NS
Stollberger CM, 1998[35]	409	NYHA >II	NA	NA	NA	NS
Stollberger CM, 2004[33]	409	NYHA >II (vs. no heart failure)	NA	NA	NA	NS
Hart RG, 1999[28]	2,012	LV dysfunction	NA	NA	NA	NS
Lip GYH, 2010[15]	1,577	LV ejection fraction <40%	0.8%	2.1%	0.34 (0.04–2.73)	NS

Heart failure as a risk factor

SPAF Investig., 1992[26]	568	CHF	NA	NA	RR 2.0 (0.8–4.7)	NS
Laupacis A, 1994[4] (AF Investigators 1994	1,593	CHF	NA	NA	RR 1.4	NS
Ezekowitz M, 1998[34] (using clinical factors alone)	1,066	CHF	NA	NA	RR 1.7 (1.1–2.7)	0.03
Ezekowitz M, 1998[34] (AF Investig. 1998) (using clinical and echocardiographic features)	1,010	CHF	NA	NA	RR 1.4 (0.8–2.3)	0.16
SPAF II						NS
Hart RG						NS
Lip GYH						NS
Hobbs I						NS
Lin LY,						.001
Van Sta						.05
SPAF I						.05
SPAF S						.02
AFI Ech (Using features						.001
Aronow						.003
Stollber						NS
Stollberger CM, 2004	409	LV dysfunction	NA	NA	NA	NS
Stollberger CM, 1998[35]	409	NYHA >II	NA	NA	NA	NS
Stollberger CM, 2004[33]	409	NYHA >II (vs. no heart failure)	NA	NA	NA	NS
Hart RG, 1999[28]	2,012	LV dysfunction	NA	NA	NA	NS
Lip GYH, 2010[15]	1,577	LV ejection fraction <40%	0.8%	2.1%	0.34 (0.04–2.73)	NS

LV dysfunction	NA	NA	RR 2.0 (1.0–4.0)	0.05
LV dysfunction	NA	NA	1.8 (1.2–3.0)	0.02
LV dysfunction (moderate to severe vs. none to mild)	NA	NA	RR 2.5 (1.5–4.4)	<0.001
LV ejection fraction	NA	NA	RR 1.795 (1.214–2.653)	0.003
LV dysfunction	NA	NA	NA	NS
LV dysfunction	NA	NA	NA	NS

Structural as a risk factor

Aronow WS, 1989[37]	110	LV hypertrophy	NA	NA	OR 6.56	<0.01
Aronow WS, 1998[38]	312	LV hypertrophy	NA	NA	RR 2.792 (1.784–4.370)	0.0001
AFI Echo, 1998[34] (AF Investig. 1998) (using clinical and echocardiographic features)	1,010	Mitral valve prolapse	NA	NA	NA	NS
AFI Echo, 1998 (AF Investig. 1998) (using clinical and echocardiographic features)	1,010	Mitral valve regurgitation	NA	NA	NA	NS
Aronow WS, 1998[38]	312	Mitral stenosis	NA	NA	RR 1.98 (1.09–3.58)	0.025
Aronow WS, 1998[38]	312	Mitral annular calcification	NA	NA	RR 1.210 (0.774–1.892)	NS
Nakagami, 1998[31]	290	Mitral valve regurgitation (≤mild vs. ≥moderate)	25%	9%	OR 0.45 (0.2–0.97)	<0.05

PAD as a risk factor

					(0.884–1.301)	
Ruigomez A, 2009[23]	831	Peripheral vascular disease	NA	NA	RR 2.6 (1.3–5.1)	<0.05
Lip, 2010[15]	1,577	Vascular disease	3.6%	1.5%	OR 2.27 (0.94–5.46)	0.063
Lin LY, 2011[21]	7,920	Peripheral artery disease	NA	NA	OR 1.81 (1.19–2.77)	0.006
Rasmussen LH, 2011[44]	57,053	Vascular disease	20.8%	8.0%	HR 1.91 (1.44–2.54) (Stroke or death)	<0.05
		Vascular disease	8.6%	4.6%	HR 0.80 (0.53–1.20) (Stroke)	NS

DM as a risk factor

Ruigomez A, 2009[23]	831	Hyperlipidemia	NA	NA	RR 1.2 (0.4–3.4)	NS
Petersen P, 1990[32]	336	DM	NA	NA	LR Enter 0.16	NS
Laupacis A, 1994[4] (AF Investig. 1994)	1,593	DM	NA	NA	RR 1.7	<0.05
Ezekowitz M, 1998[34] (using clinical factors alone)	1,066	DM	NA	NA	RR 1.7 (1.0–2.8)	0.05
Ezekowitz M, 1998[34] (using clinical and echocardiographic features)	1,010	DM	NA	NA	RR 1.7 (1.0–2.9)	0.05
Aronow WS, 1998[38]	312	DM	NA	NA	RR 0.83 (0.56–1.22)	NS
Seidl K, 1998[42]	191	DM	NA	NA	NA	NS
SPAF III, 1998[27]	892	DM	NA	NA	NA	NS
Stollberger CM, 1998[35]	490	DM	NA	NA	NA	NS
Hart RG, 1999[28]	2,012	DM	NA	NA	RR 1.9 (for disabling/ fatal stroke)	0.02
Wang TJ, 2003[36]	705	DM	NA	NA	HR 1.80 (1.43–3.13) (for stroke)	<0.05
			NA	NA	HR 1.40 (1.07–1.83) (for stroke or death)	<0.05
Lip GYH, 2010[15]	1,577	DM	4.3%	1.9%	OR 1.79 (0.73–4.40)	NS
Hobbs FD, 2011[30]	665	DM	NA	NA	HR 2.06 (1.07–3.98)	0.03
Lin LY, 2011[21]	7,920	DM	NA	NA	OR 1.341 (1.092–1.648)	0.005
Van Staa TP, 2011[25]	79,844	DM	NA	NA	RR 1.33 (1.14–1.55)	<0.05

Risk stratification model

(B) Stroke risk factors included in each RSM

RSM (year)	AF duration	Age	DM	Female	Htn	Vasc	SHD	Stroke/TE	Thyrotox
ACCP (1998)	–	+	+	–	+	–	+	–	+
ACCP (2004)[87]	–	+	+	–	+	–	+	+	–
AFI (1994)[4]	–	–	+	–	+	–	–	+	–
AFI (1999)	–	+	+	–	+	–	–	+	–
AFI (2003)[51]	–	–	+	–	+	–	+	+	–
AHA/ACC/ESC (2001)[47]	–	+	+	–	+	–	+	–	+
CHADS2 (2001)[49]	–	+	+	–	+	–	+	+	–
EAFT (1995)[24]	+	+	–	–	+	–	+	+	–
Framingham (2003)[36]	–	+	+	+	+	–	–	–	–
SPAF (1992)[40]	–	–	–	–	+	–	+	+	–
SPAF (1995)[41]	–	+	–	+	+	–	+	+	–
SPAF (1998)[27]	–	+	–	+	+	–	+	+	–
SPAF (1999)[29]	–	+	+	+	+	–	–	–	–
SPAF (1999)[28]	–	+	+	+	+	–	–	–	–
Rietbrock-$CHADS_2$ (2008)[90]	–	+	+	+	+	–	–	+	–
CHA_2DS_2-VASc (2010)[15]	–	+	+	+	+	+	+	+	–

Risk stratification model

(B) Stroke risk factors included in each RSM

RSM (year)	AF duration	Age	DM	Female	Htn	Vasc	SHD	Stroke/TE	Thyrotox
ACCP (1998)	–	+	+	–	+	–	+	–	+
ACCP (2004)[87]	–	+	+	–	+	–	+	+	–
AFI (1994)[4]	–	–	+	–	+	–	–	+	–
AFI (1999)	–	+	+	–	+	–	–	+	–
AFI (2003)[51]	–	–	+	–	+	–	+	+	–
AHA/ACC/ESC (2001)[47]	–	+	+	–	+	–	+	–	+
CHADS2 (2001)[49]	–	+	+	–	+	–	+	+	–
EAFT (1995)[24]	–	+	–	–	+	–	+	+	–
Framingham (2003)[36]	–	+	+	+	+	–	–	–	–
SPAF (1992)[40]	–	–	–	–	+	–	+	+	–
SPAF (1995)[41]	–	+	–	+	+	–	+	+	–
SPAF (1998)[27]	–	+	–	+	+	–	+	+	–
SPAF (1999)[29]	–	+	+	+	+	–	–	–	–
SPAF (1999)[28]	–	+	+	+	+	–	–	–	–
Rietbrock-$CHADS_2$ (2008)[90]	–	+	+	+	+	–	–	+	–
CHA_2DS_2-VASc (2010)[15]		+	+	+	+	+	+	+	–

Risk stratification model

(B) Stroke risk factors included in each RSM

RSM (year)	AF duration	Age	DM	Female	Htn	Vasc	SHD	Stroke/TE	Thyrotox
ACCP (1998)	–	+	+	–	+	–	+	–	–
ACCP (2004)[87]	–	+	+	–	+	–	+	+	–
AFI (1994)[4]	–	–	+	–	+	–	–	+	–
AFI (1999)	–	+	+	–	+	–	–	+	–
AFI (2003)[51]	–	–	+	–	+	–	+	+	–
AHA/ACC/ESC (2001)[47]	–	+	+	–	+	–	+	–	–
CHADS2 (2001)[49]	–	+	+	–	+	–	+	+	–
EAFT (1995)[24]	–	+	–	–	+	–	+	+	–
Framingham (2003)[36]	–	+	+	+	+	–	–	–	–
SPAF (1992)[40]	–	–	–	–	+	–	+	+	–
SPAF (1995)[41]	–	+	–	+	+	–	+	+	–
SPAF (1998)[27]	–	+	–	+	+	–	+	+	–
SPAF (1999)[29]	–	+	+	+	+	–	–	–	–
SPAF (1999)[28]	–	+	+	+	+	–	–	–	–
Rietbrock-CHADS$_2$ (2008)[90]	–	+	+	+	+	–	–	+	–
CHA$_2$DS$_2$-VASc (2010)[15]		+	+	+	+	+	+	+	–

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AHA/ACC/ESC (2001)[47]	–	+	+	–	+	–	+	–	–
CHADS2 (2001)[49]	–	+	+	–	+	–	+	+	–
EAFT (1995)[24]	–	+	–	–	+	–	+	+	–
Framingham (2003)[36]	–	+	+	+	+	–	–	–	–
SPAF (1992)[40]	–	–	–	–	+	–	+	+	–
SPAF (1995)[41]	–	+	–	+	+	–	+	+	–
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SPAF (1999)[29]	–	+	+	+	+	–	–	–	–
SPAF (1999)[28]	–	+	+	+	+	–	–	–	–
Rietbrock-CHADS$_2$ (2008)[90]	–	+	+	+	+	–	–	+	–
CHA$_2$DS$_2$-VASc (2010)[15]	+	+	+	+	+	+	+	+	–

C statistic Prediction model

RSM	Gage BF, 2001[49]	Gage BF, 2004[52]	Lip, GYH, 2010[15]	Olesen JB, 2011[16]	Hobbs FD, 2011[30]
ACCP (1998)	NR	0.58	NR	NR	NR
ACCP (2008)	NA	NA	0.57	NR	0.60
AFI (1994)[4]	0.68	0.63	0.57	NR	NR
$CHADS_2$ (2001)[49]	0.82	0.70	0.56	0.72	0.55
Framingham (2003)[36]	NR	0.69	0.64	NR	0.59
SPAF (1998)[27]	NR	0.64	NR	NR	NR
SPAF (1999)[29]	0.74	NR	0.55	NR	NR
AHA/ACC/ESC (2006)[89]	NA	NA	0.57	NR	0.61
Rietbrock-$CHADS_2$ (2008)[90]	NA	NA	0.59	NR	0.62
CHA_2DS_2-VASc (2010)[15]	NA	NA	0.61	0.85	0.60

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SPAF (1998)[27]	NR	0.64	NR	NR	NR
SPAF (1999)[29]	0.74	NR	0.55	NR	NR
AHA/ACC/ESC (2006)[89]	NA	NA	0.57	NR	0.61
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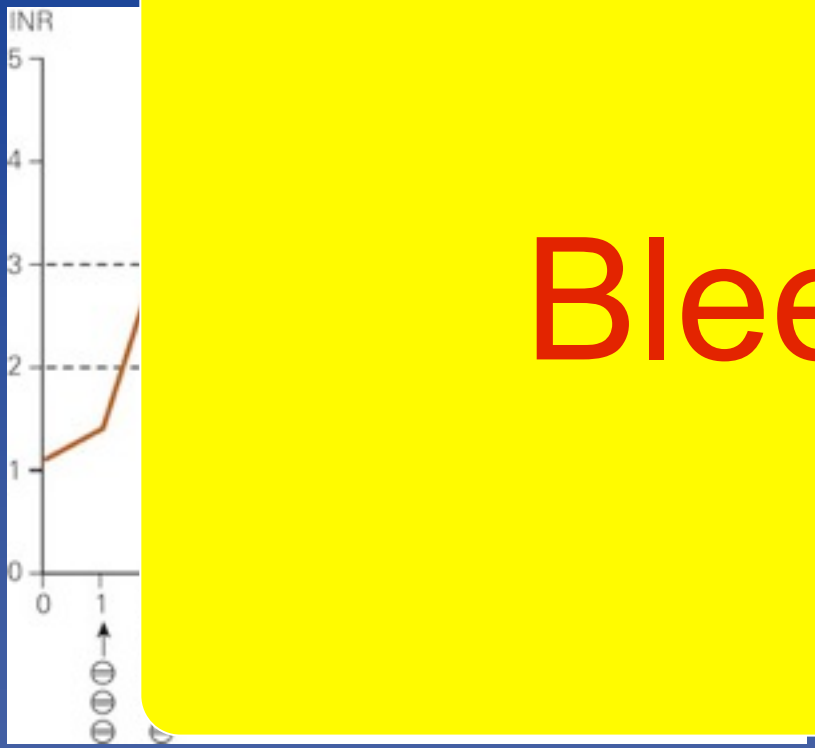
- the strongest, independent predictors of stroke are
- 1.a prior stroke or TIA,
- 2.age >75 years,
- 3.hypertension,
- 4.diabetes mellitus and
- 5.structural heart disease.

- Sex, heart failure and vascular disease cause more discussion because the available evidence favoring thier use as risk factors in AF per se is not as convincing

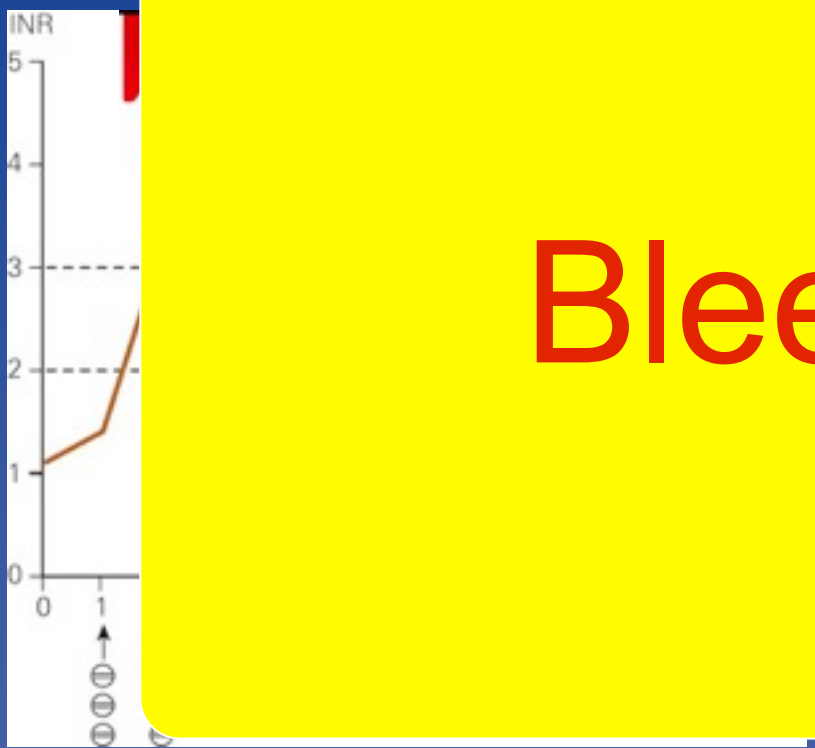
CHA_2DS_2-VASc	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Aged 65–74 years	1
Sex category (i.e. female gender)	1
Maximum score	9

Warfarin



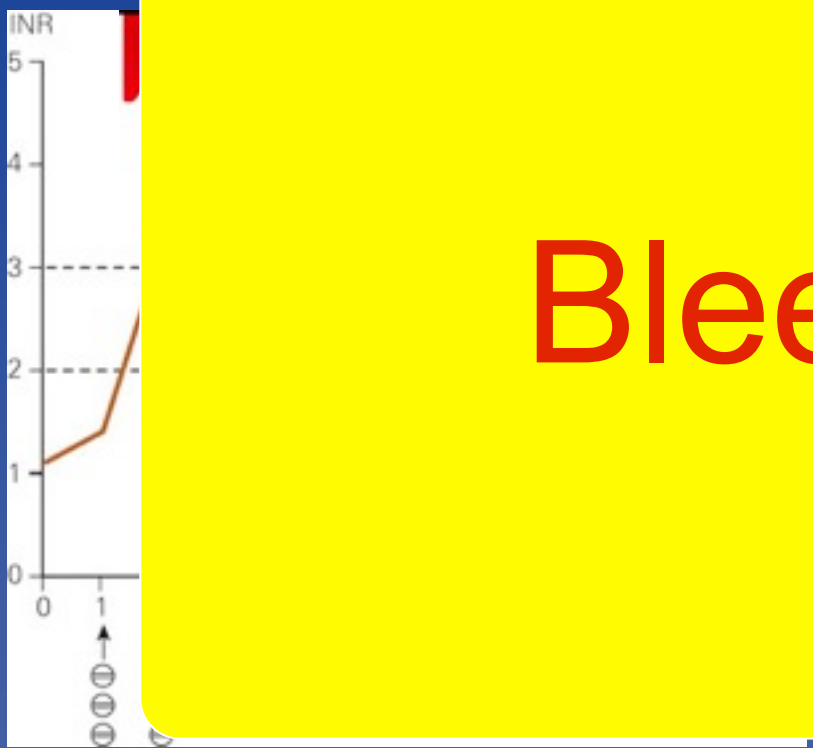
Bleeding

Warfarin



Bleeding

Warfarin



Bleeding

Table 5. Incidence Rates of Ischemic Stroke and Intracranial Hemorrhage among Patients with Nonvalvular Atrial Fibrillation Who Were Taking Warfarin, According to the International Normalized Ratio (INR) at the Time of the Stroke.*

INR	Person-yr†	Stroke (95% CI) (N=152)	Person-yr†	Intracranial Hemorrhage (95% CI) (N=58)
		rate/100 person-yr		*rate/100 person-yr*
<1.5	556	7.7 (5.7–10.4)	561	0.5 (0.2–1.7)
1.5–1.9	2847	1.9 (1.4–2.4)	2867	0.3 (0.1–0.6)
2.0–2.5	5357	0.4 (0.3–0.7)	5400	0.3 (0.2–0.4)
2.6–3.0	2388	0.9 (0.6–1.4)	2409	0.5 (0.3–0.9)
3.1–3.5	834	0.7 (0.3–1.6)	843	0.6 (0.3–1.4)
3.6–3.9	243	0.4 (0.1–2.9)	247	0.4 (0.1–2.9)
4.0–4.5	144	1.4 (0.4–5.5)	147	2.7 (1.0–7.3)
>4.5	115	2.6 (0.8–8.1)	118	9.4 (5.2–16.9)

Hylek, EM *et al. N Engl J Med*. 2003;349:1019-2614

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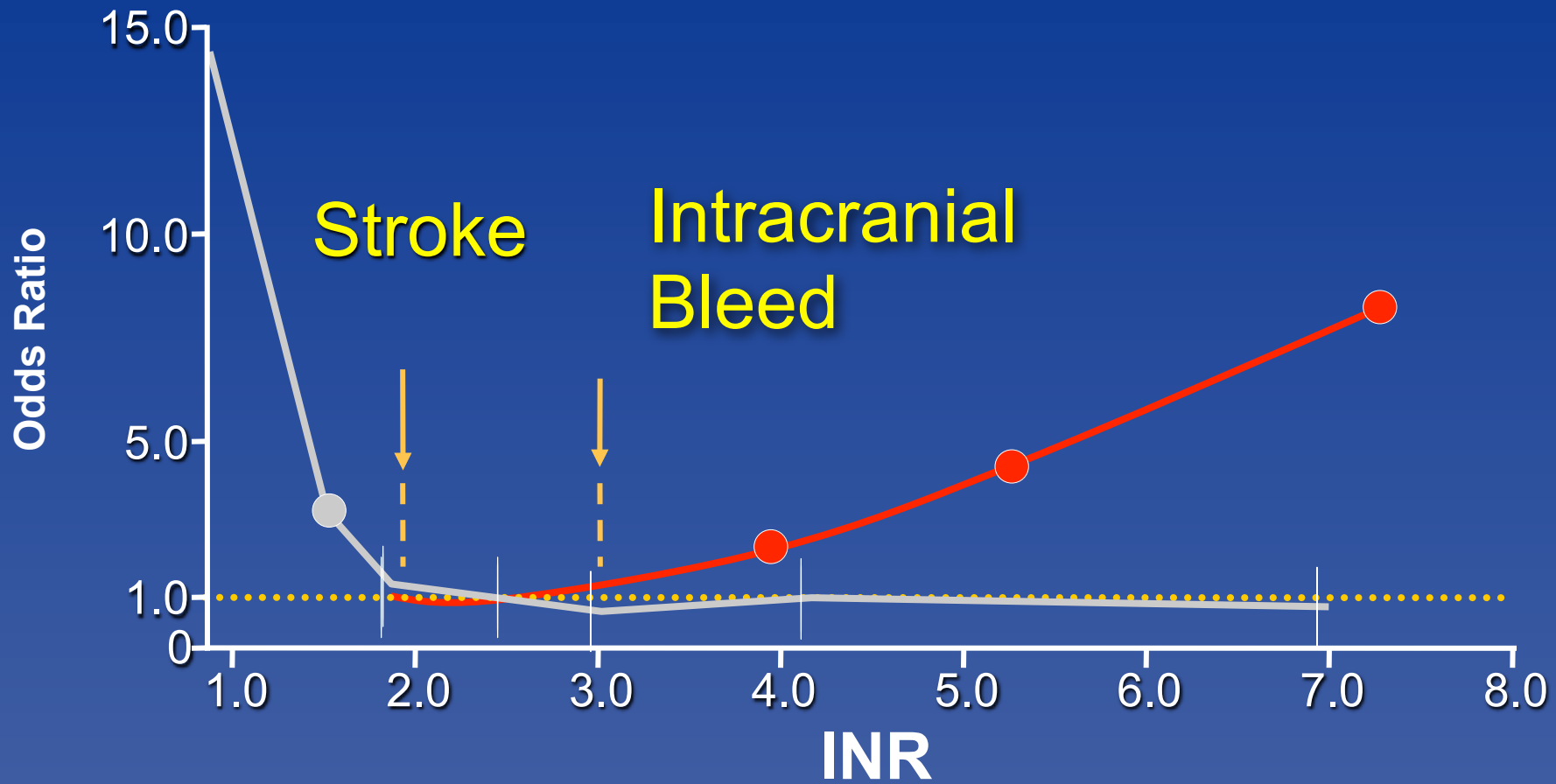
Adjusted Odds Ratios for Ischemic Stroke and Intracranial Bleeding in Relation to Intensity of Anticoagulation



Fuster et al. *J Am Coll Cardiol*. 2001;38:1231-1266.

CMAJ RESEARCH

Rates of hemorrhage during warfarin therapy for atrial fibrillation

Tara Gomes MHSc, Muhammad M. Mamdani PharmD MPH, Anne M. Holbrook MD PharmD, J. Michael Paterson MSc, Chelsea Hellings MSc, David N. Juurlink MD PhD

Table 1 (part 2 of 2): Baseline characteristics of people starting warfarin therapy after atrial fibrillation was diagnosed

Characteristic	Patients, no. (%)* *n* = 125 195
Medication use (past 120 d)	
Acetylsalicylic acid and clopidogrel	557 (0.4)
Acetylsalicylic acid and dipyridamole	817 (0.7)
Other nonsteroidal anti-inflammatory drugs	20 671 (16.5)
Clopidogrel	4 151 (3.3)
Ticlopidine	1 092 (0.9)
Time to starting warfarin therapy, d, median (IQR)	7 (2–22)
0	21 573 (17.2)
1–7	41 278 (33.0)
8–14	21 090 (16.8)
15–30	16 976 (13.6)
31–100	24 278 (19.4)
$CHADS_2$ score (components)	
Congestive heart failure	44 011 (35.2)
Hypertension	94 063 (75.1)
Age > 75 yr	78 408 (62.6)
Diabetes	30 437 (24.3)
Previous stroke	26 661 (21.3)
$CHADS_2$ score	
0	8 655 (6.9)
1	30 108 (24.0)
2	44 716 (35.7)
3	29 713 (23.7)
4	9 599 (7.7)
5	1 860 (1.5)
6	544 (0.4)

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Majority had CHADS 2-3

Rate of Hemorrhage

Table 2: Rates of hemorrhage by length of time since starting warfarin therapy

Characteristic	Hemorrhages during 5-yr follow-up, no. (%)*	Rate of hemorrhage, % per person-year (95% CI)		
		First 30 d	Remainder of 5-yr follow-up	Overall
Overall, no.	10 840	11.8 (11.1–12.4)	3.4 (3.4–3.5)	3.8 (3.8–3.9)
$CHADS_2$ score				
0	382 (3.5)	7.2 (5.5–9.5)	1.6 (1.4–1.7)	1.8 (1.6–2.0)
1	1 845 (17.0)	7.3 (6.3–8.4)	2.3 (2.2–2.4)	2.5 (2.4–2.6)
2–3	7 053 (65.1)	13.3 (12.5–14.3)	3.8 (3.7–3.9)	4.3 (4.2–4.4)
4–6	1 560 (14.4)	16.7 (14.3–19.4)	6.0 (5.7–6.3)	6.7 (6.3–7.0)
Type of hemorrhage				
Intracranial	549 (5.1)	0.4 (0.4–0.5)	0.2 (0.2–0.2)	0.2 (0.2–0.2)
Upper gastrointestinal	2 829 (26.1)	4.0 (3.8–4.2)	0.9 (0.8–0.9)	1.0 (1.0–1.0)
Lower gastrointestinal	3 956 (36.5)	4.6 (4.4–4.9)	1.2 (1.2–1.3)	1.4 (1.4–1.4)
Other	4 190 (38.7)	4.7 (4.5–5.0)	1.3 (1.3–1.3)	1.5 (1.5–1.5)

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Hemorrhage
4.3%

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Hemorrhage
4.3%

Age <75 Years

Age ≤ 75 yr, no.	3684	9.2 (8.4–10.2)	2.6 (2.5–2.7)	2.9 (2.8–3.0)
$CHADS_2$ score				
0	382 (10.4)	7.2 (5.5–9.5)	1.6 (1.4–1.7)	1.8 (1.6–2.0)
1	1 204 (32.7)	6.8 (5.7–8.1)	2.0 (1.9–2.2)	2.3 (2.1–2.4)
2–3	1 881 (51.1)	12.1 (10.6–13.9)	3.4 (3.3–3.6)	3.9 (3.7–4.0)
4–6	217 (5.9)	13.1 (8.2–20.7)	5.5 (4.8–6.4)	6.0 (5.3–6.9)
Type of hemorrhage				
Intracranial	194 (5.3)	0.4 (0.3–0.4)	0.1 (0.1–0.1)	0.2 (0.1–0.2)
Upper gastrointestinal	1 055 (28.6)	3.9 (3.5–4.3)	0.7 (0.7–0.7)	0.8 (0.8–0.9)
Lower gastrointestinal	1 268 (34.4)	3.5 (3.2–3.9)	0.9 (0.9–0.9)	1.0 (1.0–1.0)
Other	1 406 (38.2)	3.3 (3.0–3.7)	1.0 (1.0–1.0)	1.1 (1.1–1.1)

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Upper gastrointestinal	1 055 (28.6)	3.9 (3.5–4.3)	0.7 (0.7–0.7)	0.8 (0.8–0.9)
Lower gastrointestinal	1 268 (34.4)	3.5 (3.2–3.9)	0.9 (0.9–0.9)	1.0 (1.0–1.0)
Other	1 406 (38.2)	3.3 (3.0–3.7)	1.0 (1.0–1.0)	1.1 (1.1–1.1)

Intracranial Hemorrhage 5%

Age <75 Years

Age ≤ 75 yr, no.	3684	9.2 (8.4–10.2)	2.6 (2.5–2.7)	2.9 (2.8–3.0)
$CHADS_2$ score				
0	382 (10.4)			1.8 (1.6–2.0)
1	1 204 (32.7)			(2.1–2.4)
2–3	1 881 (51.1)			.7–4.0)
4–6	217 (5.9)			5.3–6.9)
Type of hemorrhage				
Intracranial	194 (5.3)			0.2 (0.1–0.2)
Upper gastrointestinal	1 055 (28.6)	3.9 (3.5–4.3)	0.7 (0.7–0.7)	0.8 (0.8–0.9)
Lower gastrointestinal	1 268 (34.4)	3.5 (3.2–3.9)	0.9 (0.9–0.9)	1.0 (1.0–1.0)
Other	1 406 (38.2)	3.3 (3.0–3.7)	1.0 (1.0–1.0)	1.1 (1.1–1.1)

0.2% ICH

Age> 75 years

Age > 75 yr, no.	7 156	13.7 (12.7–14.6)	4.1 (4.0–4.2)	4.6 (4.5–4.7)
$CHADS_2$ score				
0	0 (0.0)	—	—	—
1	641 (9.0)	8.5 (6.6–10.9)	2.8 (2.6–3.1)	3.1 (2.9–3.4)
2–3	5 172 (72.3)	13.8 (12.8–15.0)	4.0 (3.9–4.1)	4.5 (4.4–4.6)
4–6	1 343 (18.8)	17.3 (14.6–20.3)	6.1 (5.7–6.4)	6.8 (6.4–7.1)
Type of hemorrhage				
Intracranial	355 (5.0)	0.5 (0.4–0.5)	0.2 (0.2–0.2)	0.2 (0.2–0.2)
Upper gastrointestinal	1 774 (24.8)	4.1 (3.8–4.3)	1.0 (1.0–1.0)	1.1 (1.1–1.2)
Lower gastrointestinal	2 688 (37.6)	5.5 (5.1–5.9)	1.5 (1.5–1.6)	1.7 (1.7–1.8)
Other	2 784 (38.9)	5.7 (5.3–6.1)	1.6 (1.5–1.6)	1.8 (1.8–1.8)

Age> 75 years

Age > 75 yr, no.	7 156	13.7 (12.7–14.6)	4.1 (4.0–4.2)	4.6 (4.5–4.7)
$CHADS_2$ score				
0	0 (0.0)			—
1	641 (9.0)			(2.9–3.4)
2–3	5 172 (72.3)			4–4.6)
4–6	1 343 (18.8)			.4–7.1)
Type of hemorrhage				
Intracranial	355 (5.0)			0.2 (0.2–0.2)
Upper gastrointestinal	1 774 (24.8)	4.1 (3.8–4.3)	1.0 (1.0–1.0)	1.1 (1.1–1.2)
Lower gastrointestinal	2 688 (37.6)	5.5 (5.1–5.9)	1.5 (1.5–1.6)	1.7 (1.7–1.8)
Other	2 784 (38.9)	5.7 (5.3–6.1)	1.6 (1.5–1.6)	1.8 (1.8–1.8)

Intracranial Hemorrhage 5%

Age> 75 years

Age > 75 yr, no.	7 156	13.7 (12.7–14.6)	4.1 (4.0–4.2)	4.6 (4.5–4.7)
$CHADS_2$ score				
0	0 (0.0)			—
1	641 (9.0)			(2.9–3.4)
2–3	5 172 (72.3)			4–4.6)
4–6	1 343 (18.8)			.4–7.1)
Type of hemorrhage				
Intracranial	355 (5.0)			0.2 (0.2–0.2)
Upper gastrointestinal	1 774 (24.8)	4.1 (3.8–4.5)	(1.0–1.0)	1.1 (1.1–1.2)
Lower gastrointestinal	2 688 (37.6)	5.5 (5.1–5.9)	1.5 (1.5–1.6)	1.7 (1.7–1.8)
Other	2 784 (38.9)	5.7 (5.3–6.1)	1.6 (1.5–1.6)	1.8 (1.8–1.8)

0.2% ICH

Bleeding score

- HEMORR$_2$HAGES
- ATRIA
- HAS-BLED

HAS-BLED

HAS-BLED	Score
Hypertension, i.e. uncontrolled BP	1
Abnormal renal/liver function	1 or 2
Stroke	1
Bleeding tendency or predisposition	1
Labile INRs (if on warfarin)	1
Age (e.g. >65, frail condition)	1
Drugs (e.g. concomitant aspirin or NSAIDs) or alcohol excess/abuse	1
	9

HAS-BLED

HAS-BL	Score
Hyperter	1
Abnorma	1 or 2
Stroke	1
Bleeding	1
Labile IN	1
Age (e.g. >65, frail condition)	1
Drugs (e.g. concomitant aspirin or NSAIDs) or alcohol excess/abuse	1
	9

should not on its own be used to exclude patients from OAC therapy

Assess risk of stroke
(CHA_2DS_2-VASc score)

0

I

≥2

Oral anticoagulant therapy

Assess bleeding risk
(HAS-BLED score)
Consider patient values
and preferences

No antithrombotic
therapy

NOAC

VKA

- Thank You