'The burden of stroke and thromboembolism in atrial fibrillation - is there hope for the future?

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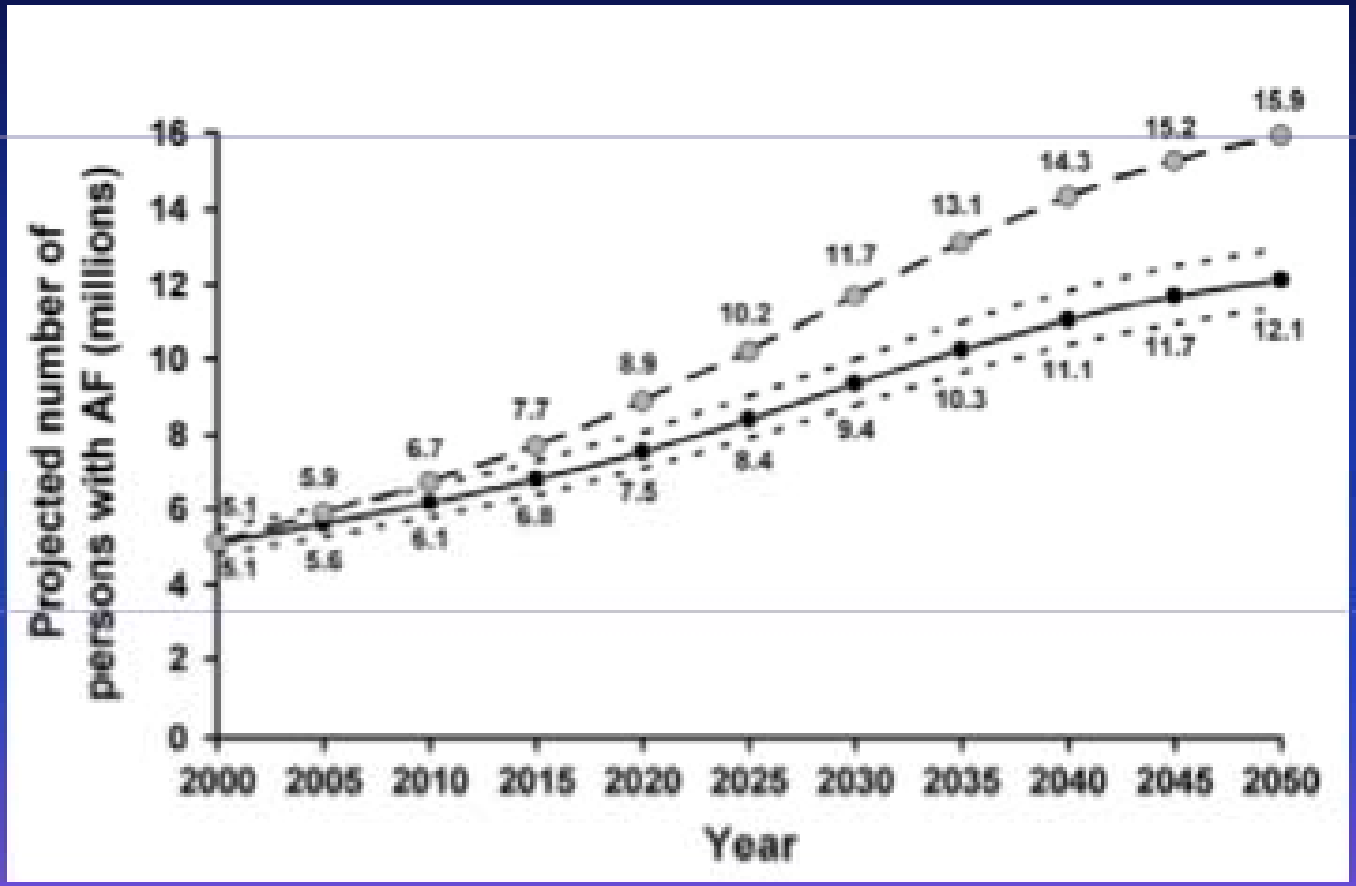
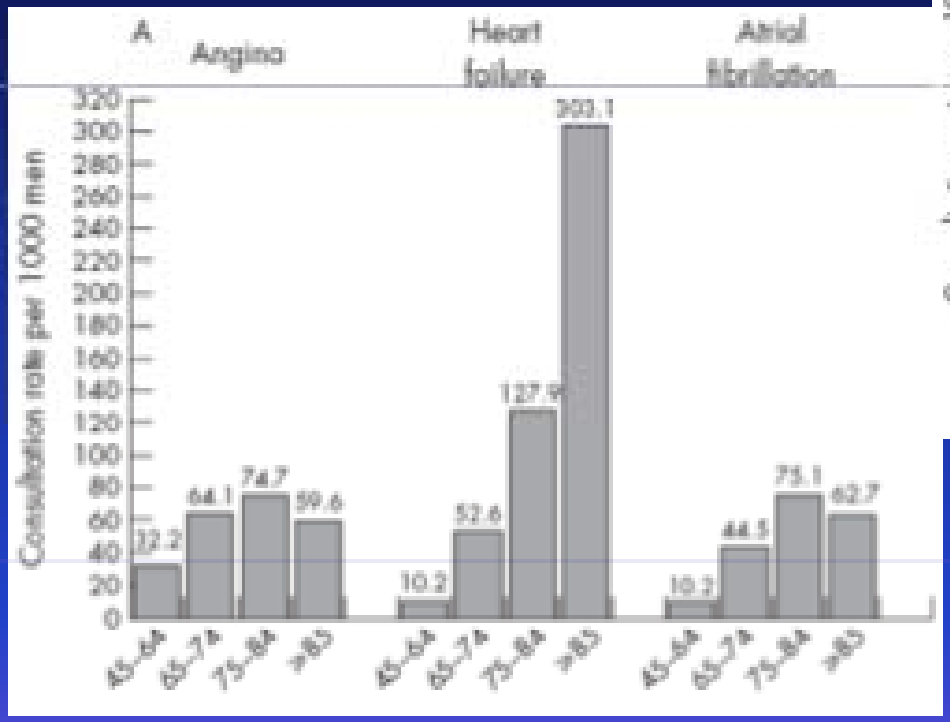
Projected numbers with AF in the USA, assuming no further increase in age-adjusted AF incidence *(solid curve)* and a continued increase in incidence rate as evident in 1980-2000 *(dotted curve)*

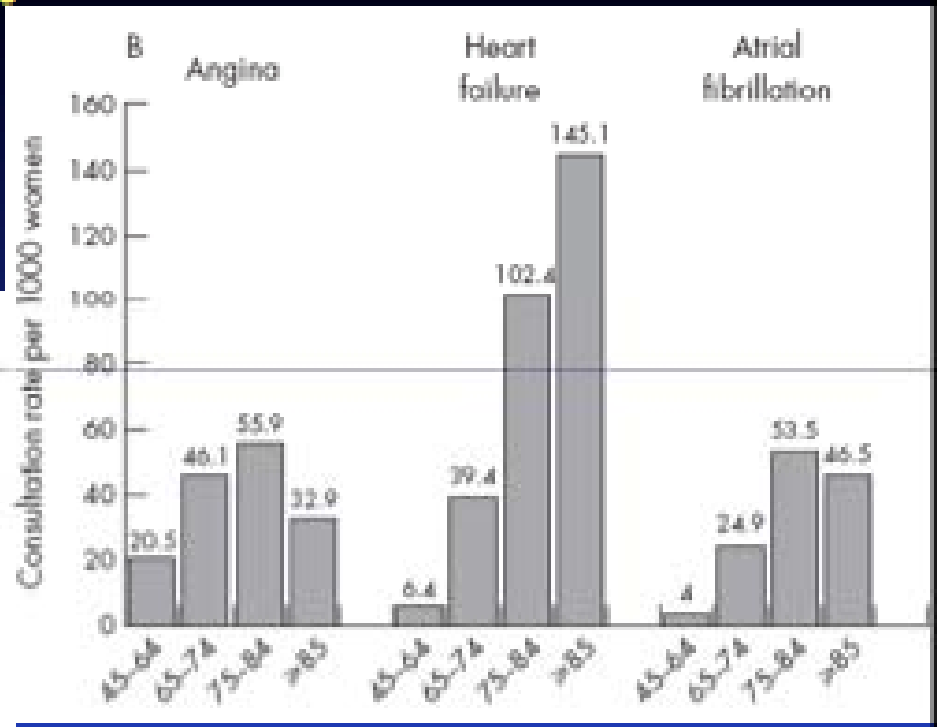
Miyasaka et al Circulation 2006;114:119-125



Prevalence, incidence, primary care burden and treatment of AF in Scotland

Murphy et al Heart 2007;93:606–612.



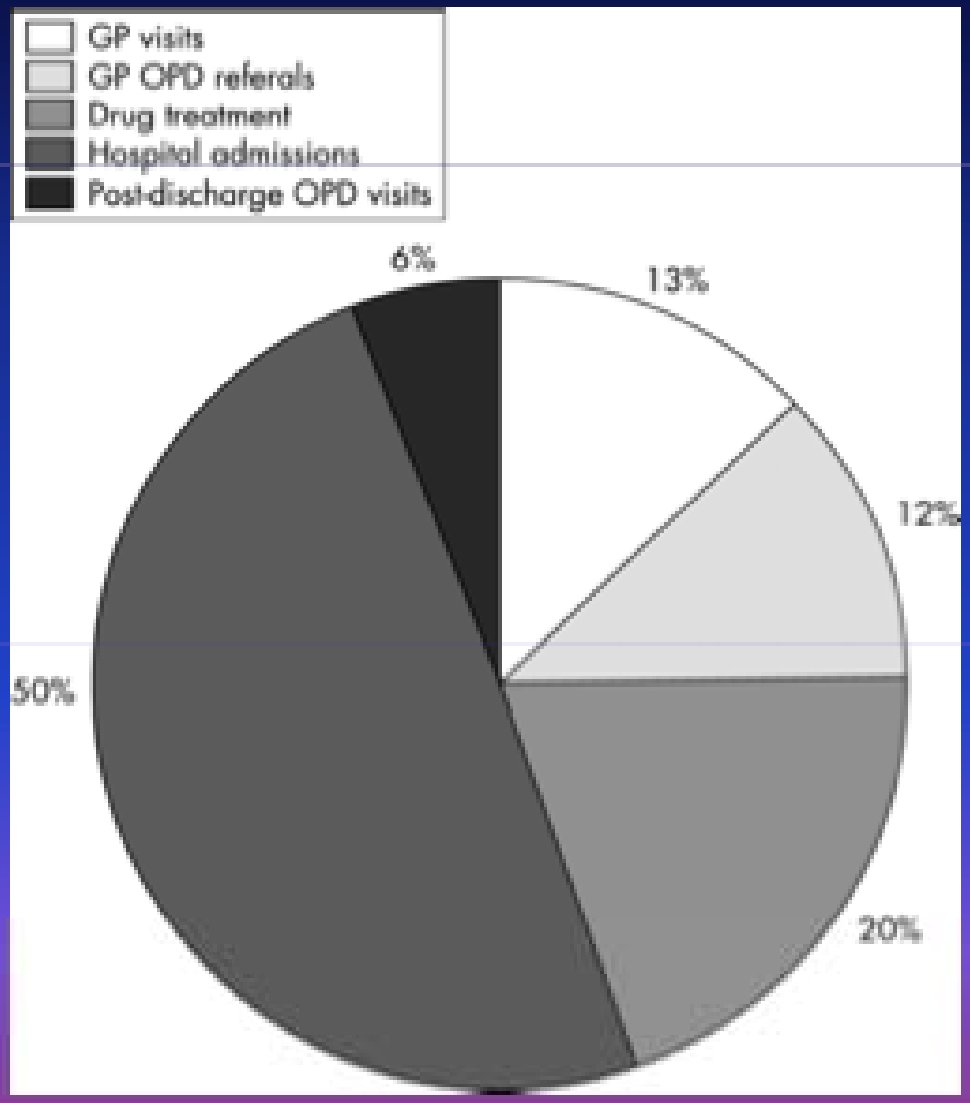


Age-stratified general practitioner consultation rates per 1000 population for heart failure, angina and atrial fibrillation in men (A) and women (B).

Prevalence of AF was 8.7/1000: higher in men (9.4/1000) vs women (7.9/1000).
Incidence of AF was 0.9/1000–1.0/1000 in men and 0.8/1000 in women.

Components of health care expenditure related to AF in the UK in 1995 (excluding secondary admissions and long term nursing home care) *Stewart et al Heart 2004;90:286-292*

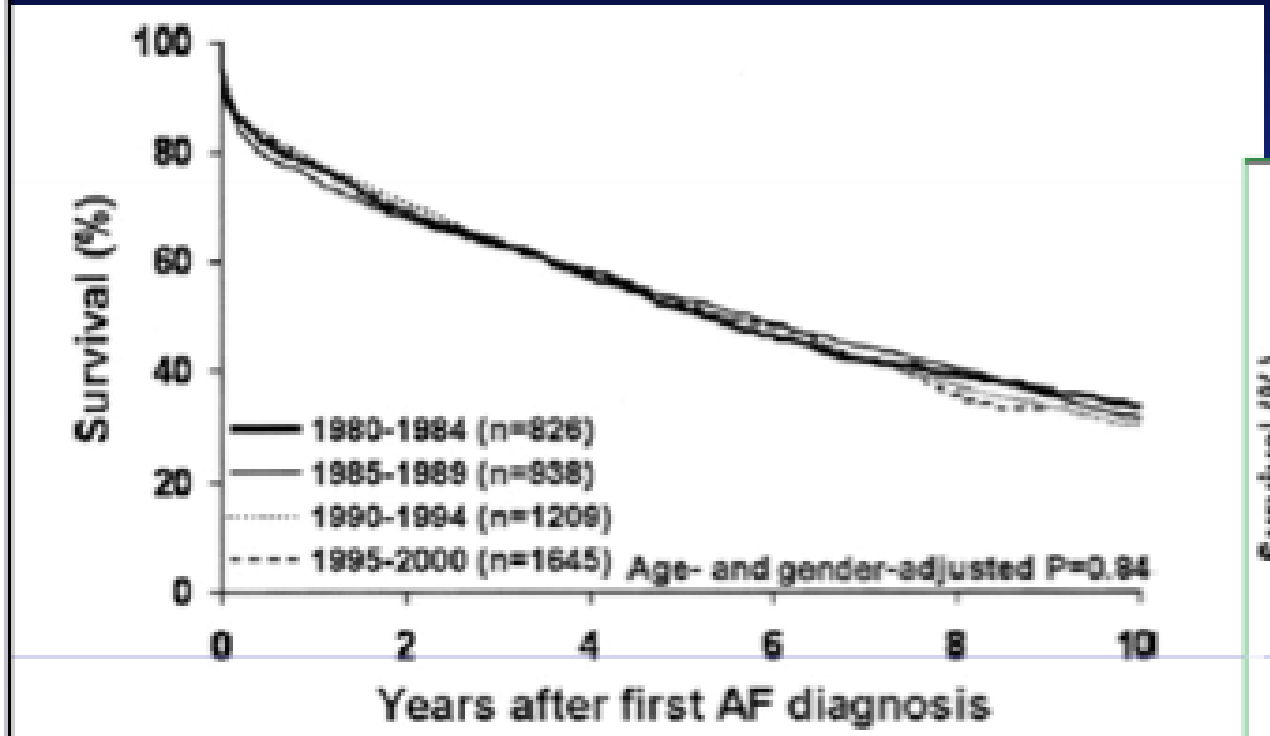
GP, general practitioner;
OPD, outpatient department.

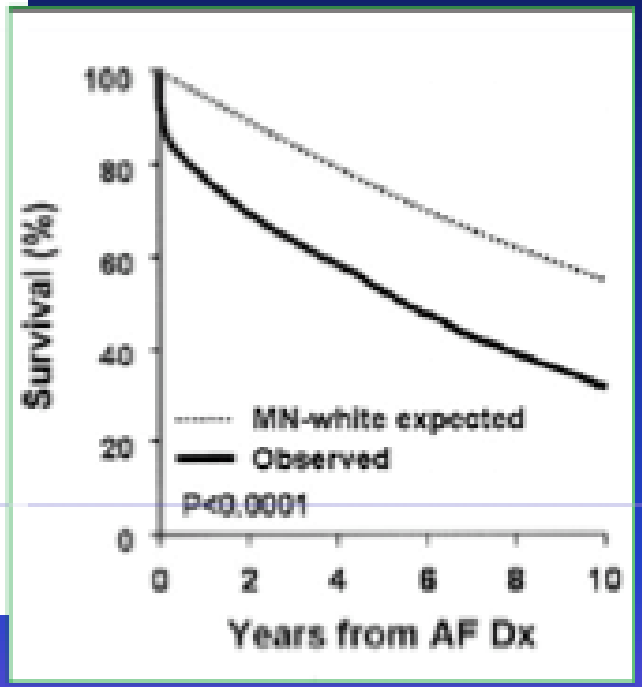


The direct cost of AF rose to £459 million pounds (approx Euro 65m) in 2000, equivalent to **0.97% of total NHS expenditure** based on 1995 figures.

Mortality Trends in Patients Diagnosed With First AF: A 21-Year Community-Based Study

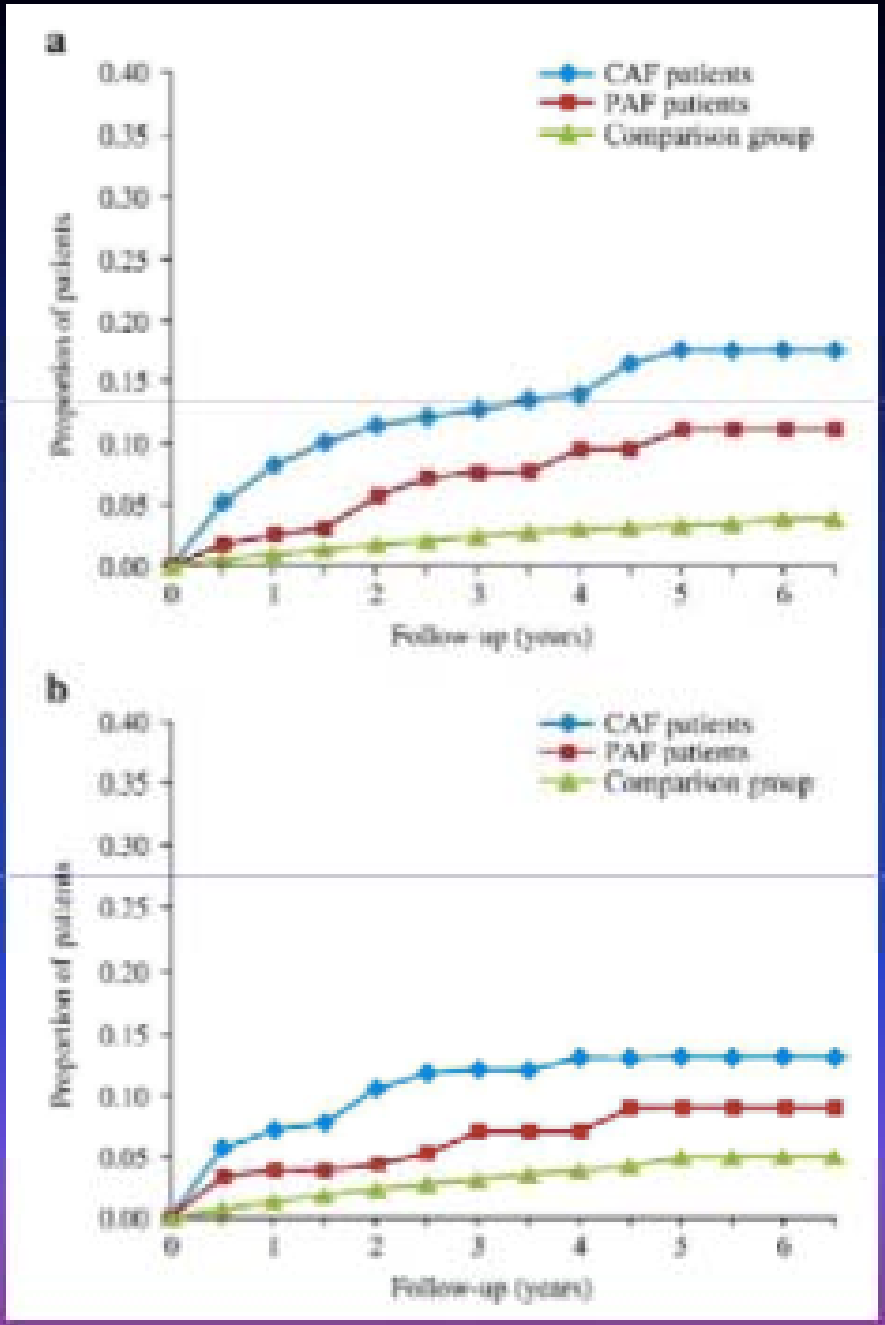
Miyasaka et al J Am Coll Cardiol 2007;49:986–92

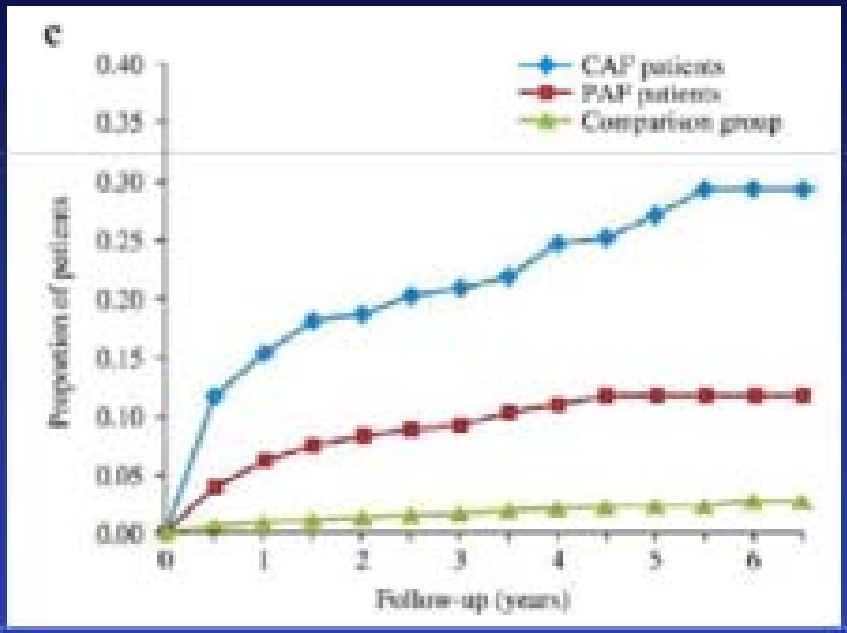




Survival for the entire study population of patients diagnosed with first AF vs the age- and gender-matched general Minnesota (MN) population.

Risk of cardiovascular and cerebrovascular events after AF diagnosis *Ruigómez et al IJC 08*



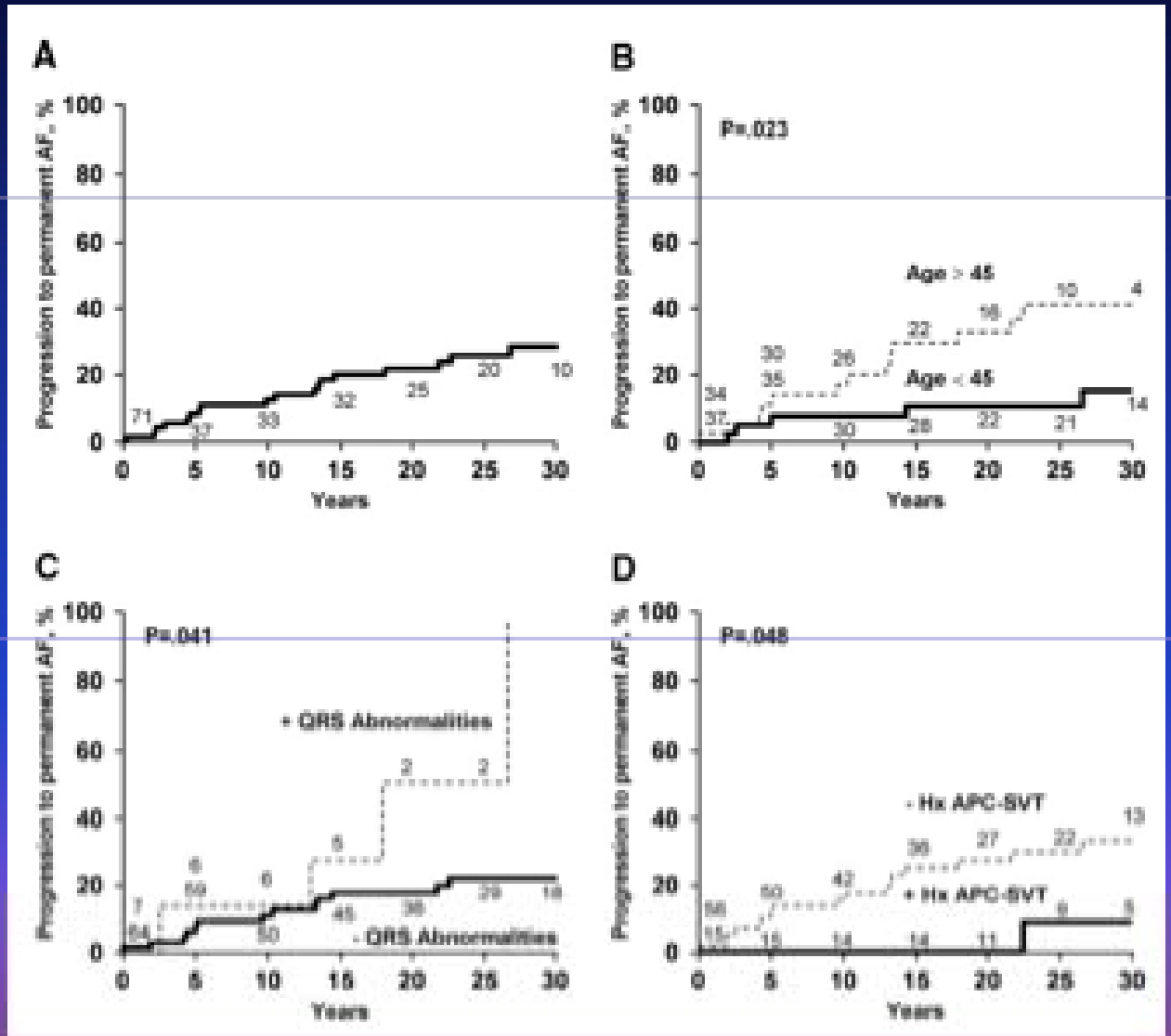


Proportion of each study group developing
(a) ischemic cerebrovascular events
(b) coronary events; and (c) heart failure
…. throughout the follow-up period.

GPRD - first diagnosis of AF (n=831) vs control group without AF (n=8226).

Long-Term Progression and Outcomes With Aging in Patients With Lone AF: A 30-Year FU Study

Jahangir et al Circulation. 2007;115:3050-3056



Long-term progression of paroxysmal or persistent *lone AF* to permanent AF(A) *.. a 30-yr cumulative probability of 29% (95%CI 16-42)*

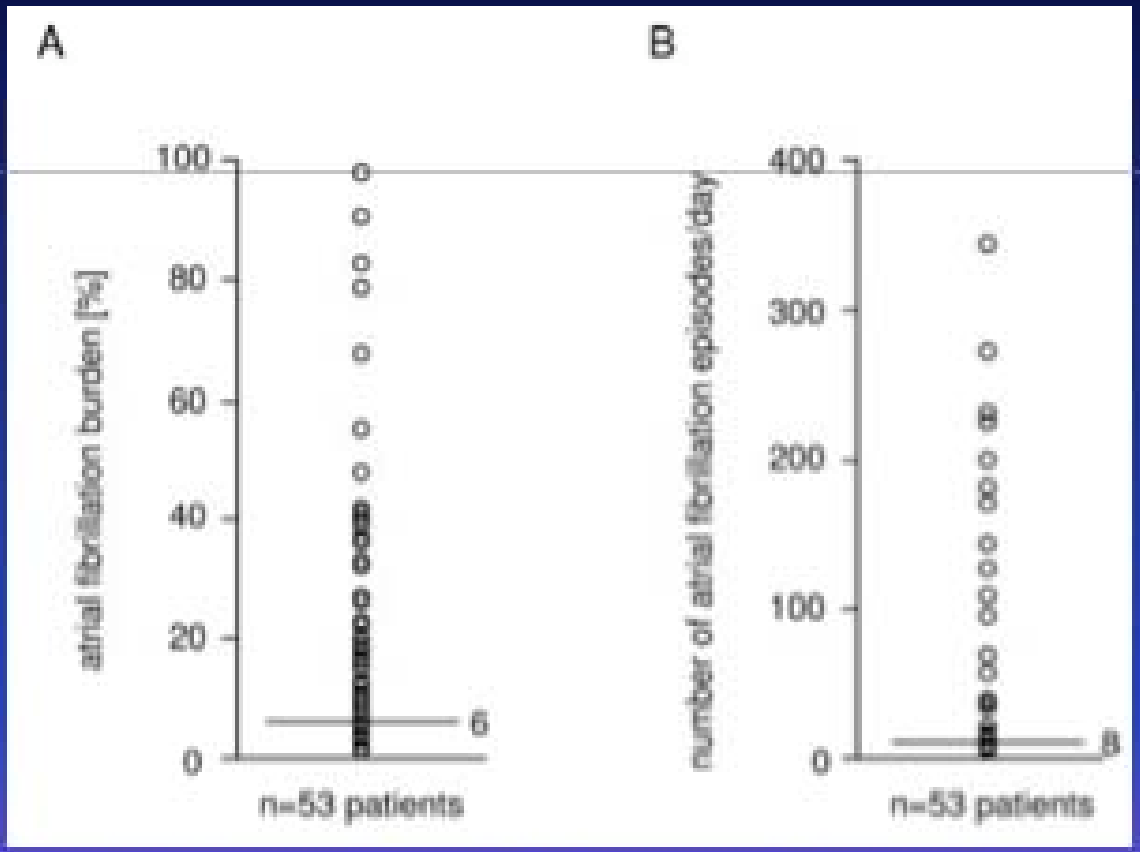
.... according to:

- Age at diagnosis (B),
- Presence of QRS abnormalities (C), or
- History (Hx) of premature complexes (APC) or supraventricular tachycardia (SVT; D).

Do we look hard enough for AF in stroke ... and its burden

Atrial Fibrillation Therapy (AFT) study: Individual AF burden (%) (A) and number of AF episodes per day (B)

Hoffmann et al Circulation. 2006;113:1933-1941

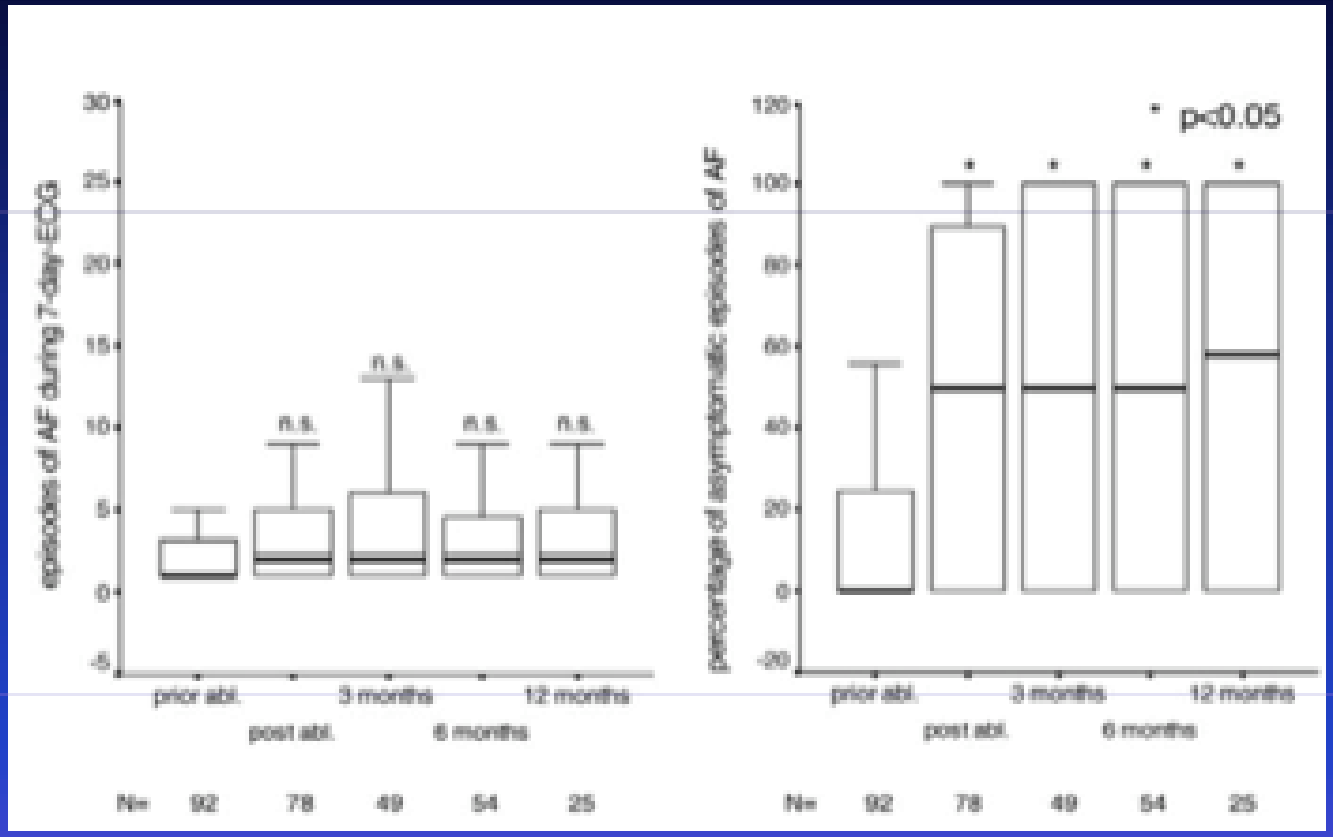


The horizontal bar indicates median values.

Vitatron Selection DDDR pacemaker

Perception of AF Before and After Radiofrequency Catheter Ablation

Hindricks et al Circulation. 2005;112:307-313



In 52 patients (57%), both symptomatic and asymptomatic AF episodes recorded…

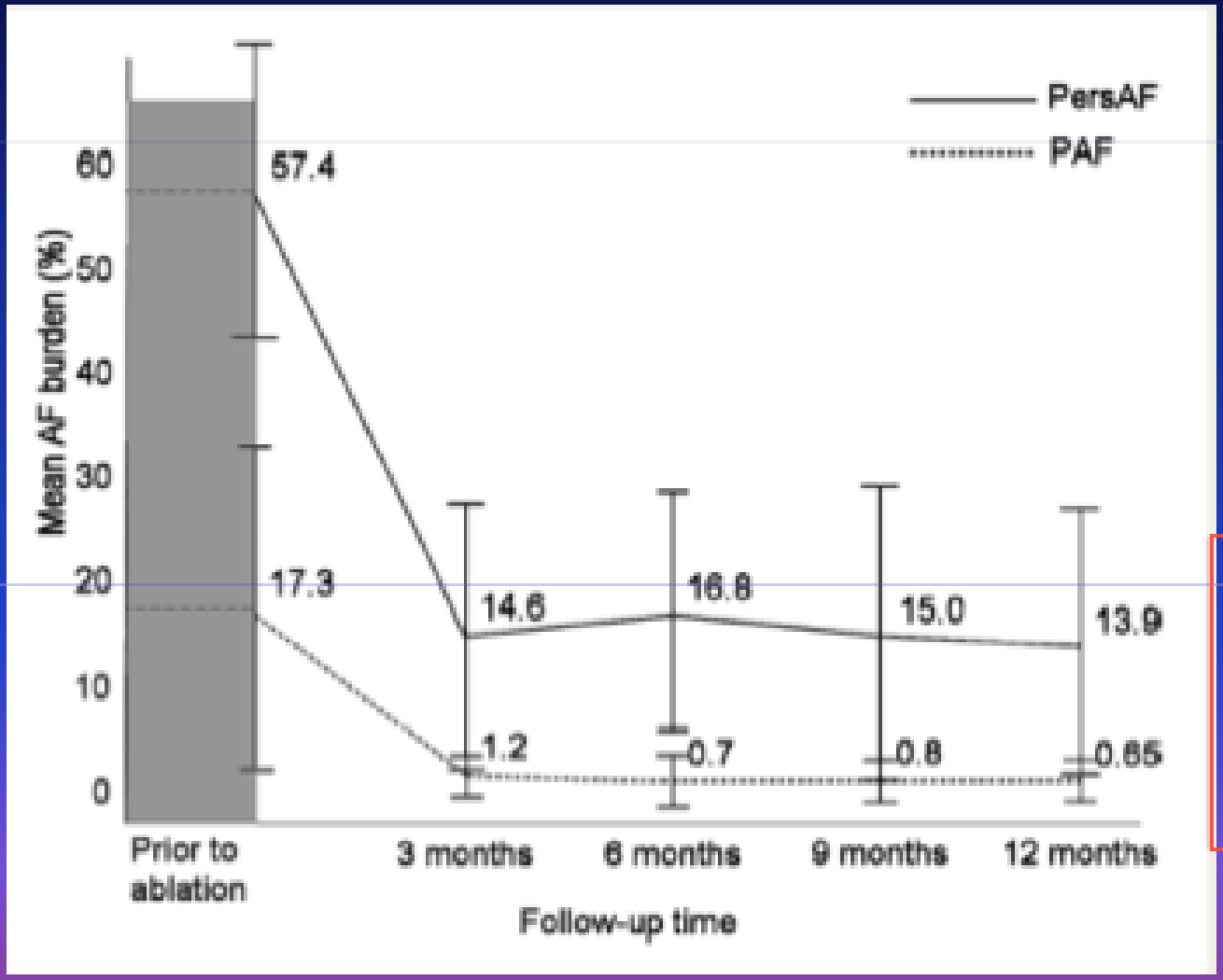
…in 5%, all documented AF episodes were asymptomatic.

After ablation, the % with only asymptomatic AF recurrences increased to 37% ($P<0.05$) at 6-mth FU.

Even in patients presenting with highly symptomatic AF, asymptomatic episodes may occur and significantly increase after catheter ablation.

A symptom-only–based follow-up would overestimate the success rate.

AF burden after catheter ablation: A prospective rhythm analysis in pacemaker patients with continuous atrial monitoring *Steven et al EHJ 2008;29(8):1037-42.*



Time course of AF recurrence during follow-up (after 3, 6, 9 and 12 months) showing the AF burden in mean percentage

37 patients (mean age 64.6±10 years)

Complete AF freedom was observed in 85% (17 patients) of PAF patients and 59% (10 patients) in patients with PersAF.

Usefulness of Ambulatory 7-Day ECG Monitoring for the Detection of AF and Flutter After Acute Stroke/TIA

Jabaudon et al Stroke. 2004;33:1647-1651

	Standard ECG	24-hr Holter*	7d-ELR†
% AF positive (95% CI)	6.7 (3.6–12.1)	5.0 (2.3–10.2)	5.7 (2.1–12.9)
NNS (95% CI)	15 (9–28)	20 (10–44)	18 (8–48)
% total AF cases	45.5	31.8	22.7
Cumulative AF risk, % (95% CI)	6.7 (3.6–12.1)	10.6 (5.6–14.6)	16.4 (8.7–20.1)
Monitoring time needed to detect 1 event‡	6.9 minutes	18 days	117 days

*With normal standard ECG.

†With normal standard ECG and 24-hr Holter.

‡(Monitoring time per patient×n monitored patients)/(n recordings with AF). ELR indicates event-loop recording; NNS, number needed to screen.

Noninvasive Cardiac Monitoring for Detecting Paroxysmal Atrial Fibrillation or Flutter After Acute Ischemic Stroke *Liao et al Stroke 2007;38;2935-2940*

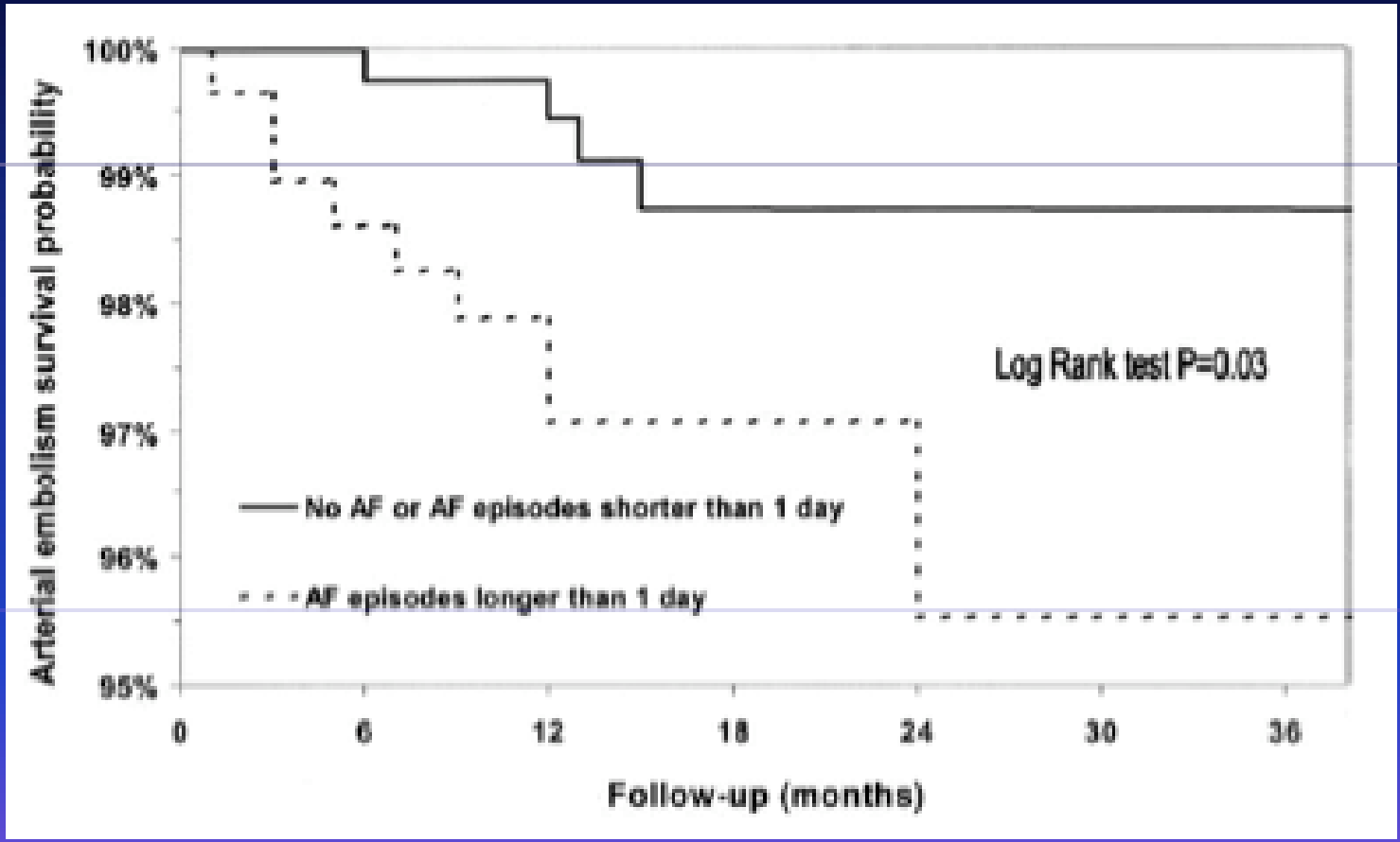
Study, Year	N	Intervention	Duration of Monitoring	Definition of Atrial Fibrillation	New Atrial Fibrillation/Flutter	Initiation of Monitoring
Barthelemy et al, 2003	60	Cardiac event recorder (n*=52)	4 days (70.1 hours)	≥30 seconds	7.7%	10 days from stroke event
		Holter monitor (n=55)	24 hours		5.5%	Admission to neurology ward
Jabaudon et al, 2004	149	Holter monitor (n=139)	21 hours	Not stated	5.0%	8 days after admission
		Event loop recorder (n=88)	159 hours	AF detected by manual review	5.7%	55 days after admission
Hornig et al, 1996	261	Holter monitor (n=261)	24 hours	Not stated; evaluated by cardiologist	3.8%	ND
Rem et al, 1985	184	Continuous cardiac monitoring (n=159)	48 hours	Not stated; evaluated by neurology resident	2.5%	ND
		Holter monitor (n=51)	24–48 hours		3.9%	ND
Schuchert et al, 1999	82	Holter monitor (n=82)	72 hours	At least 1 minute	6.1%	2–3 weeks after acute stroke

*n values indicate subjects without atrial fibrillation/flutter on history or previously.
ND indicates no data.

Screening consecutive patients with ischemic stroke with routine Holter monitoring will identify new atrial fibrillation/flutter in approximately one in 20 patients

Monitored AF Duration Predicts Arterial Embolic Events in Patients with Antitachycardia Pacemakers

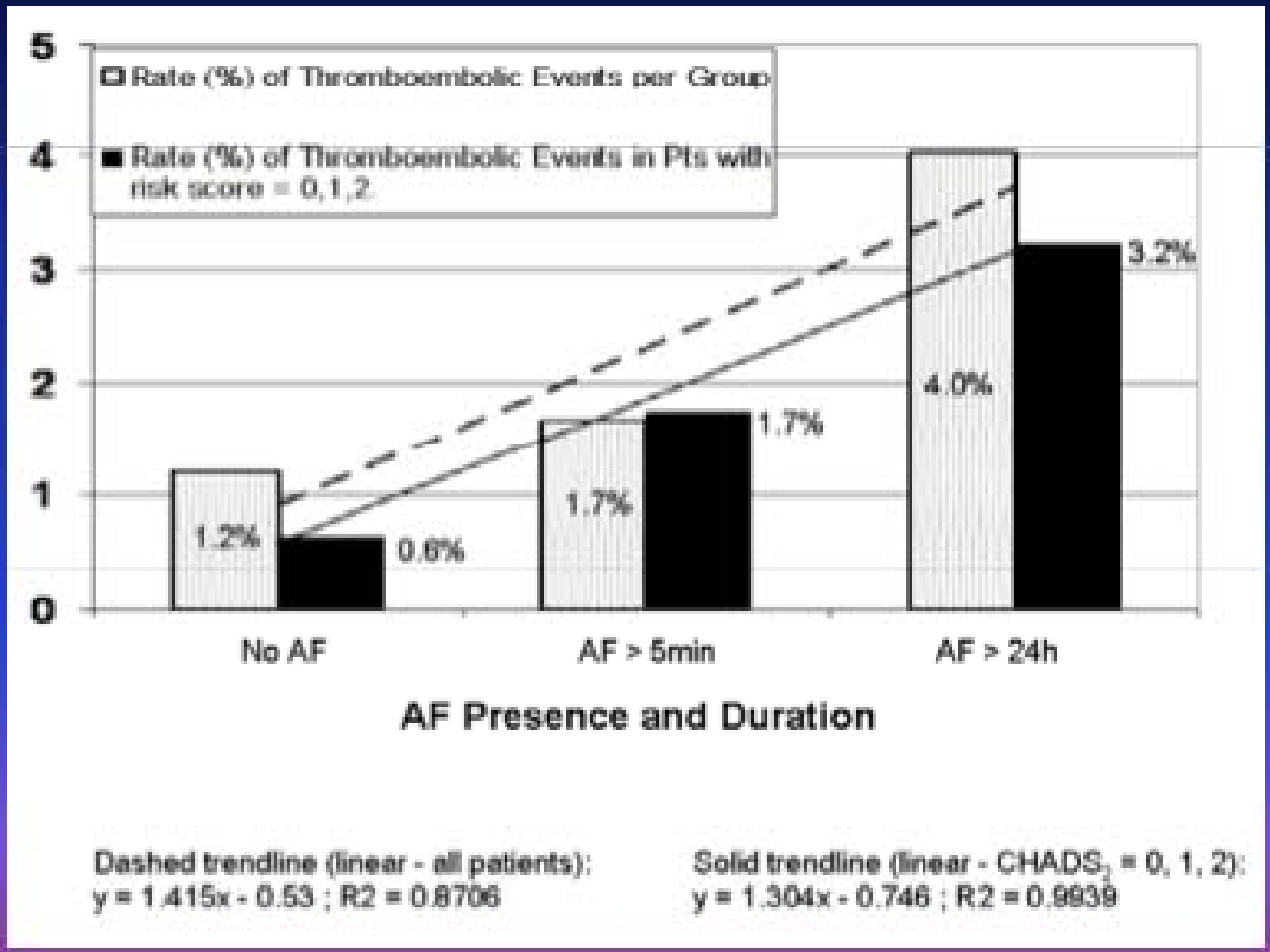
Capucci et al J Am Coll Cardiol 2005;46:1913–20



Kaplan-Meier cumulative survival from embolic events for patients with AF episodes longer than one day and for patients without AF recurrences or with AF episodes shorter than one day.

Presence and duration of AF detected by continuous monitoring: crucial implications for the risk of TE events

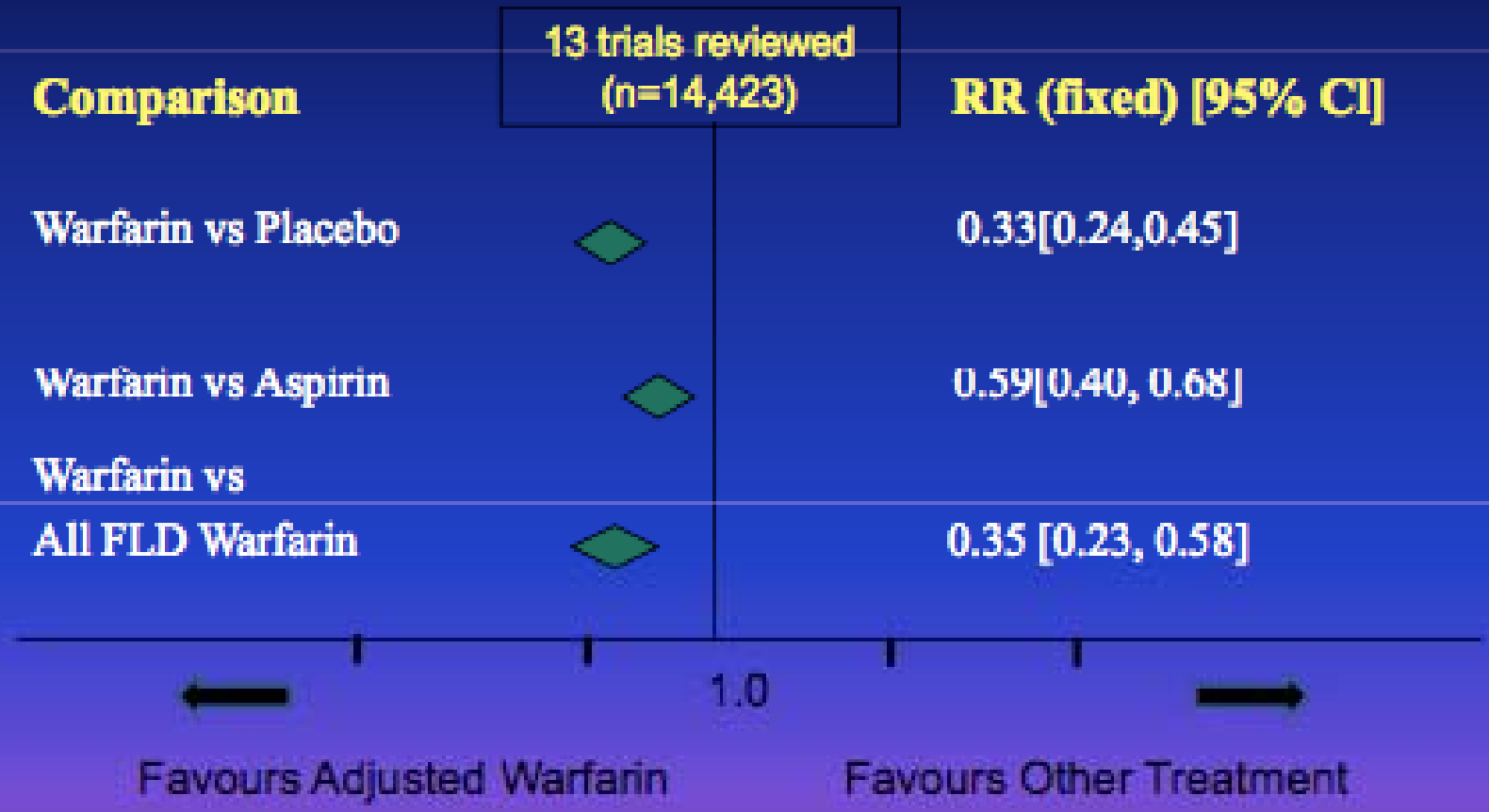
Botto et al J Cardiovasc Electrophysiol 2008



How can we approach the management of stroke and thromboembolism in atrial fibrillation?

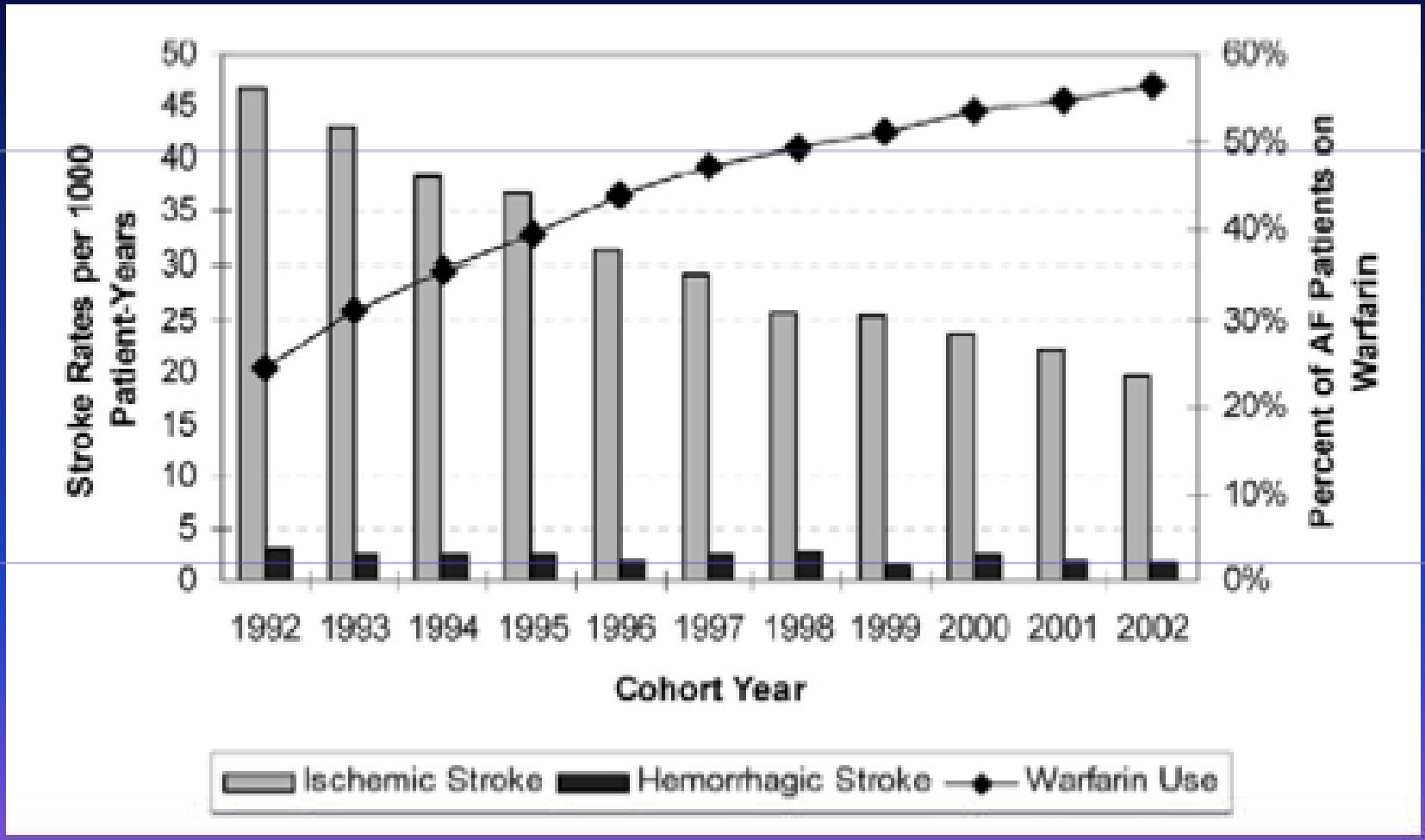
Meta-analysis of ischaemic stroke/systemic embolism with adjusted-dose OAC in AF

Lip and Edwards. Thromb Res 2006;118(3):321-33.



Trends in warfarin use and overall ischemic and hemorrhagic strokes among prevalent patients with AF

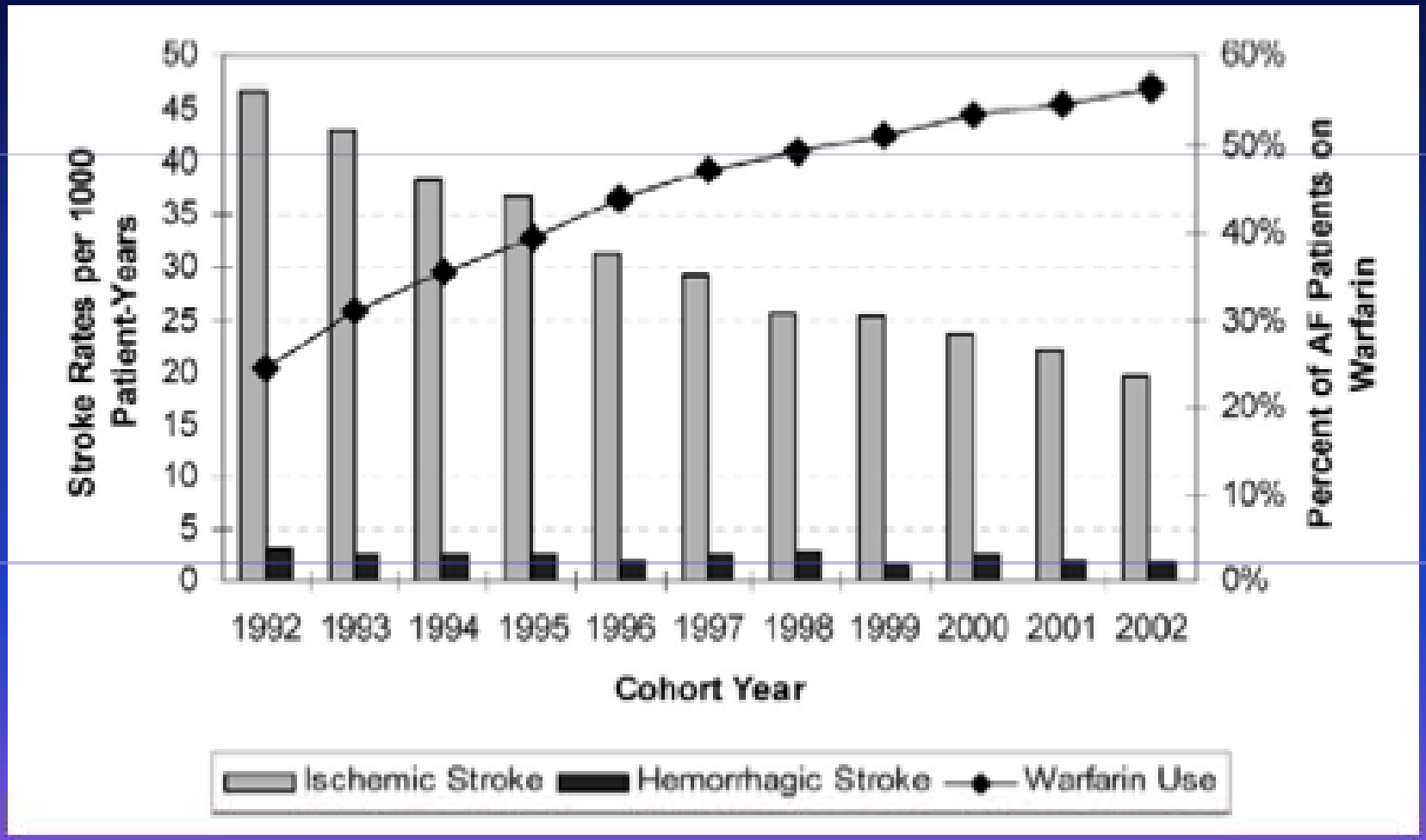
Lakshminarayan et al Stroke.2006;37:1969-1974.



Medicare patients aged ≥65 years,

Trends in warfarin use and overall ischemic and hemorrhagic strokes among prevalent patients with AF

Lakshminarayan et al Stroke.2006;37:1969-1974.



Medicare patients aged ≥65 years,

Potentially Preventable Strokes in High-Risk Patients With AF Who Are Not Adequately Anticoagulated *Gladstone et al Stroke 2008*

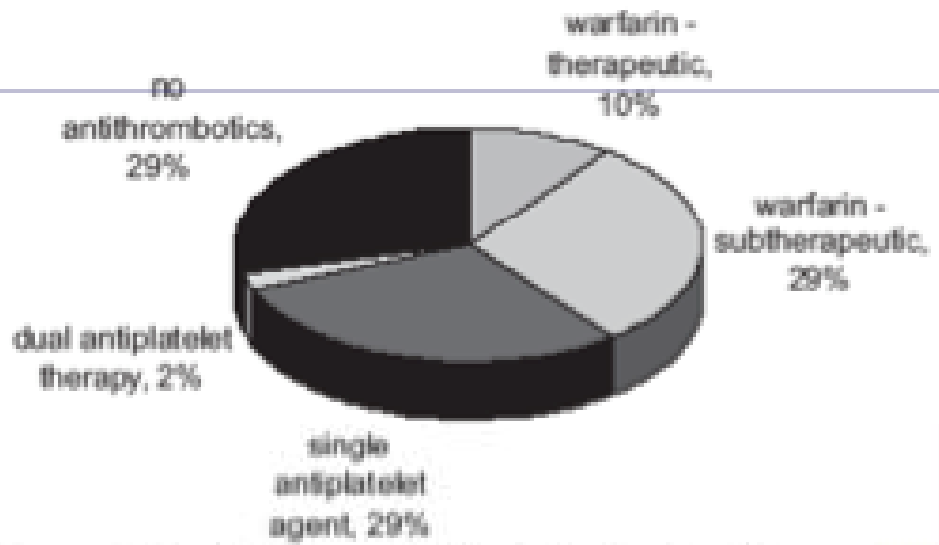


Figure 1. Preadmission medications in patients with known atrial fibrillation who were admitted with acute ischemic stroke (high-risk cohort, n=597).

'In high-risk patients with AF admitted with a stroke …. most were either not taking warfarin or were subtherapeutic at the time of ischemic stroke. …..'

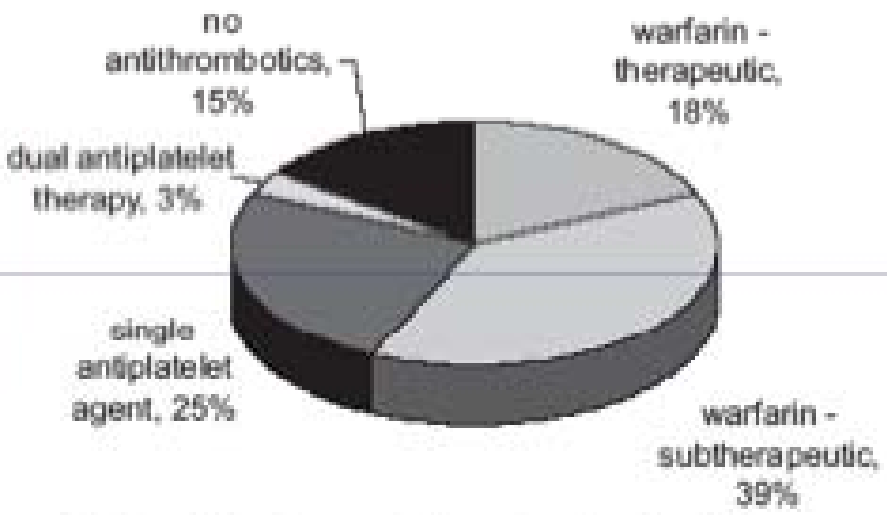


Figure 2. Preadmission medications in patients with known atrial fibrillation and a previous ischemic stroke/TIA who were admitted with acute ischemic stroke (very high-risk cohort, n=323).

Stroke risk stratification in AF … which is best?

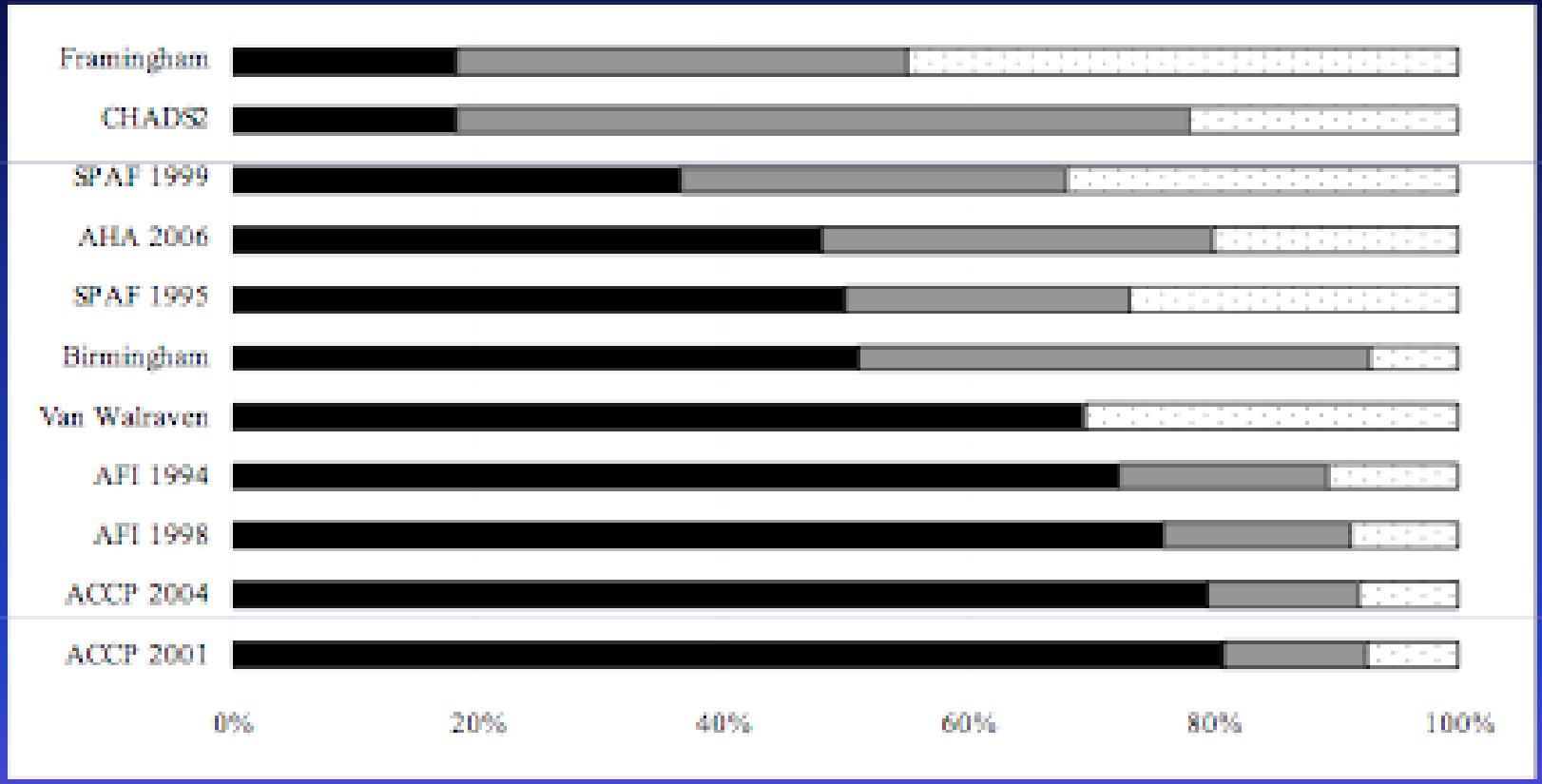
Lip and Tse. Lancet 2007 August 18;370(9587):604-18

Trial	Risk strata		
	High	Intermediate	Low
AFI1[73]	Age >65 years History of hypertension, CAD, or diabetes mellitus		Age <65 years No high-risk features
SPAF[88]	Women aged >75 years SBP >160 mm Hg LV dysfunction (echo or clinical)	History of hypertension No high-risk features	No history of hypertension No high-risk features
CHADS2[76,*]	Score 3–6	Score 1–2	Score 0
Framingham[71]	Weighted point scoring system. Points are given for the following risk factors: being older (max score <10); sex (female=6, males=0); raised blood pressure (<4); and diabetes (6). Total score (max 31 points) corresponds to a predicted 5 year stroke risk: 0–7=low risk; 8–13=intermediate risk; 14–31=high risk		
ACCP[89]	Prior stroke, TIA, or systemic embolic event; age >75 years; moderate or severely impaired LV function with or without congestive cardiac failure; hypertension or diabetes	Age 65–75 years with no other risk factors	<65 years with no risk factors
NICE/Birmingham[90]	Previous ischaemic stroke or TIA or thromboembolic event; age ≥75 years with hypertension, diabetes, or vascular disease; clinical evidence of valve disease or heart failure; impaired LV function on echocardiography	Age ≥65 years with no high risk factors; age <75 with hypertension, diabetes, or vascular disease	Age <65 years, with no history of embolism, hypertension, diabetes, or other clinical risk factors
ACC/AHA/ESC guidelines[91]	Prior thromboembolism (stroke, TIA, systemic embolism); valve disease; more than one of: age ≥75 years, hypertension, heart failure, impaired LV systolic function; or diabetes mellitus	Age ≥75 years; hypertension; heart failure; impaired LV systolic function; or diabetes mellitus	AF (no other risk factors)

Summary of the main stroke risk stratification schemes for patients with AF. *Secondary prevention study. AFI=Atrial Fibrillation Investigators. CAD=coronary artery disease. SPAF=Stroke Prevention in Atrial Fibrillation. SBP=systolic blood pressure. LV=left ventricular. ACCP=American College of Chest Physicians. TIA=transient ischaemic attack. AF=atrial fibrillation. Adapted with permission from Elsevier.[74]

Comparison of 12 Risk Stratification Schemes to Predict Stroke in Patients with Nonvalvular AF

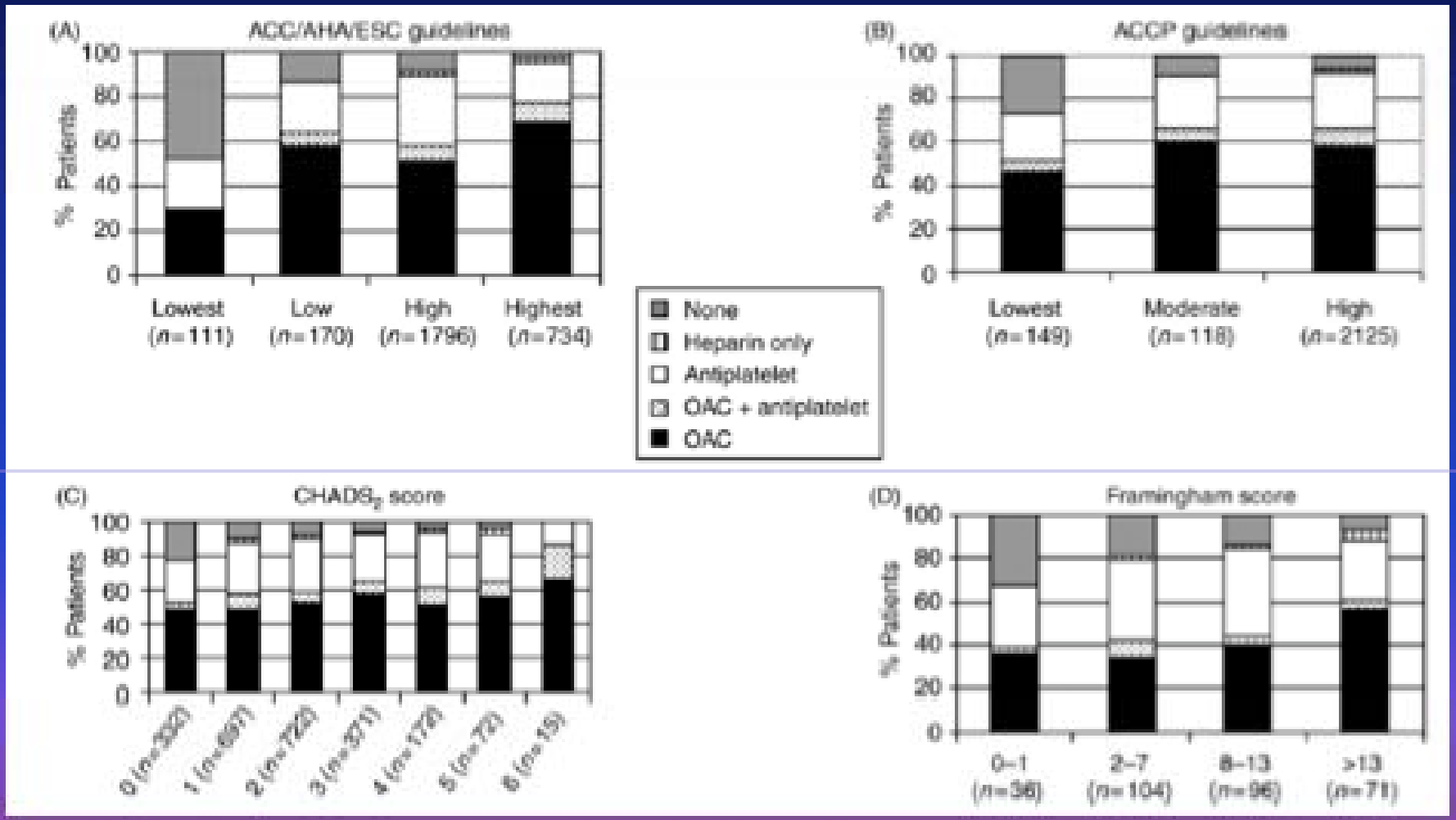
Stroke Risk in Atrial Fibrillation Working Group. Stroke 2008



Relative distribution of patients predicted to have high (black), moderate (gray) and low (white) stroke risk by applying different risk stratification schemes to a representative cohort of AF patients

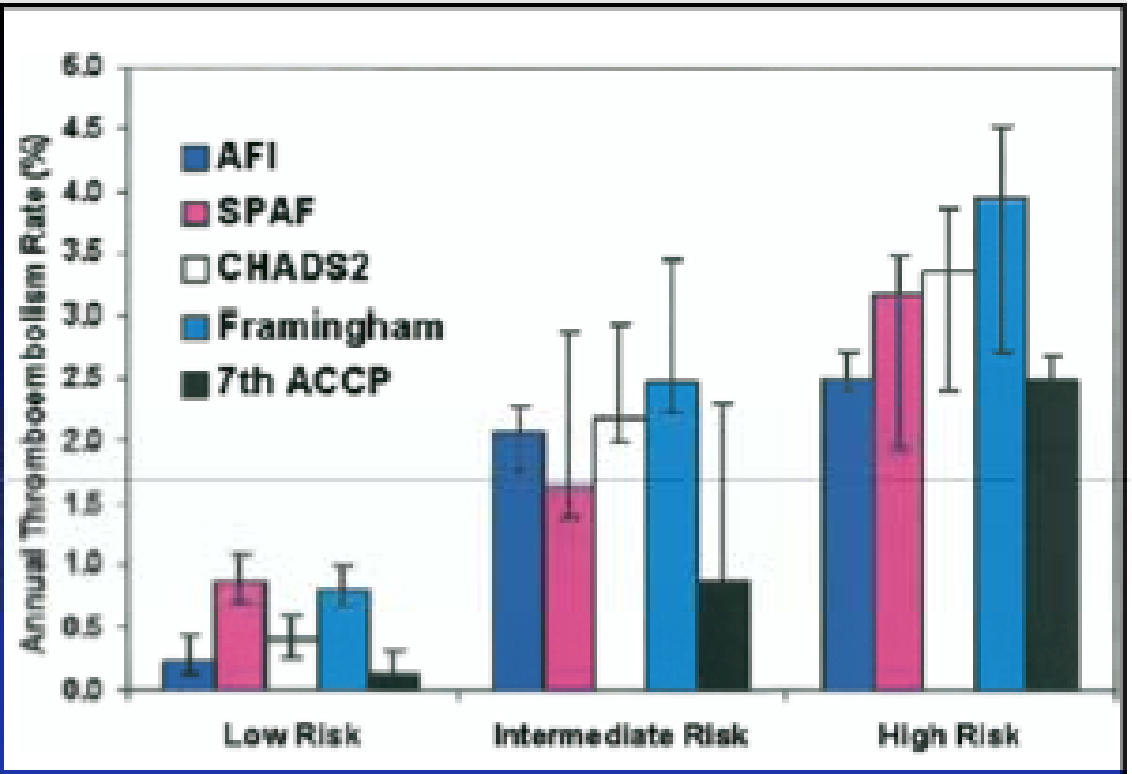
EHS: Antithrombotic drug prescription per risk category according to the ACC/AHA/ESC guidelines (A), ACCP (B), CHADS2 score (C), and Framingham score (D).

Eur Heart J 2006 27, 3018–3026



Comparison of Risk Stratification Schemes to Predict Thromboembolism in Nonvalvular AF

Fang et al
J Am Coll Cardiol 2008;51:810–5

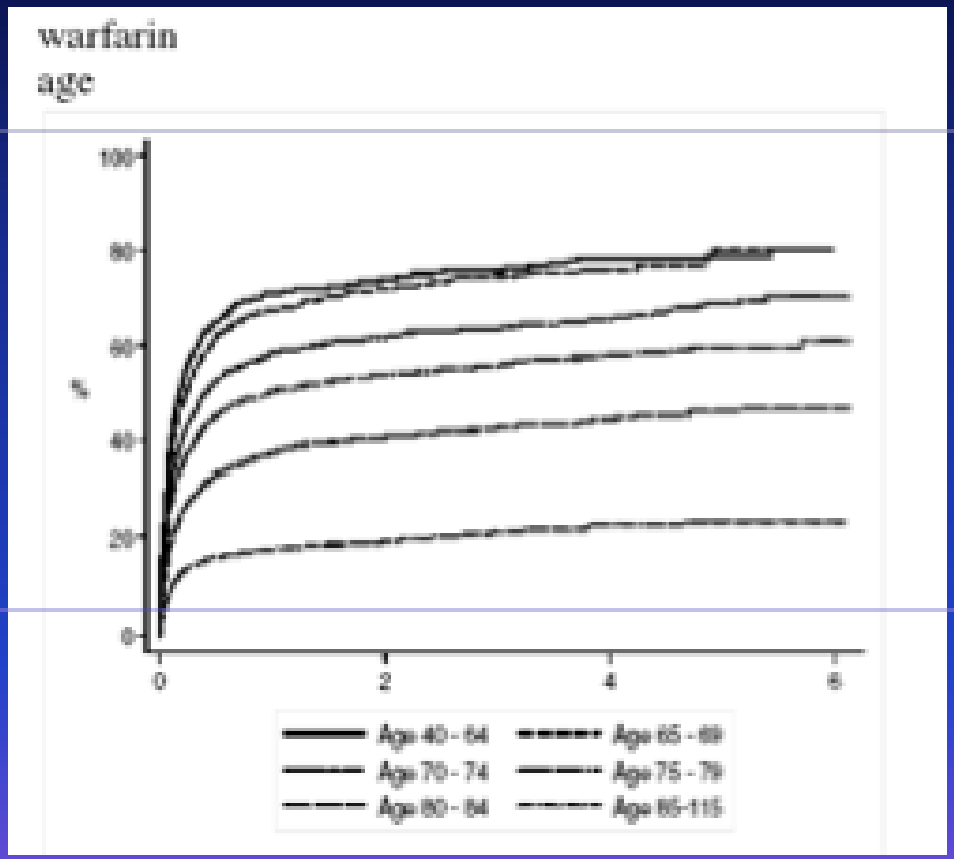


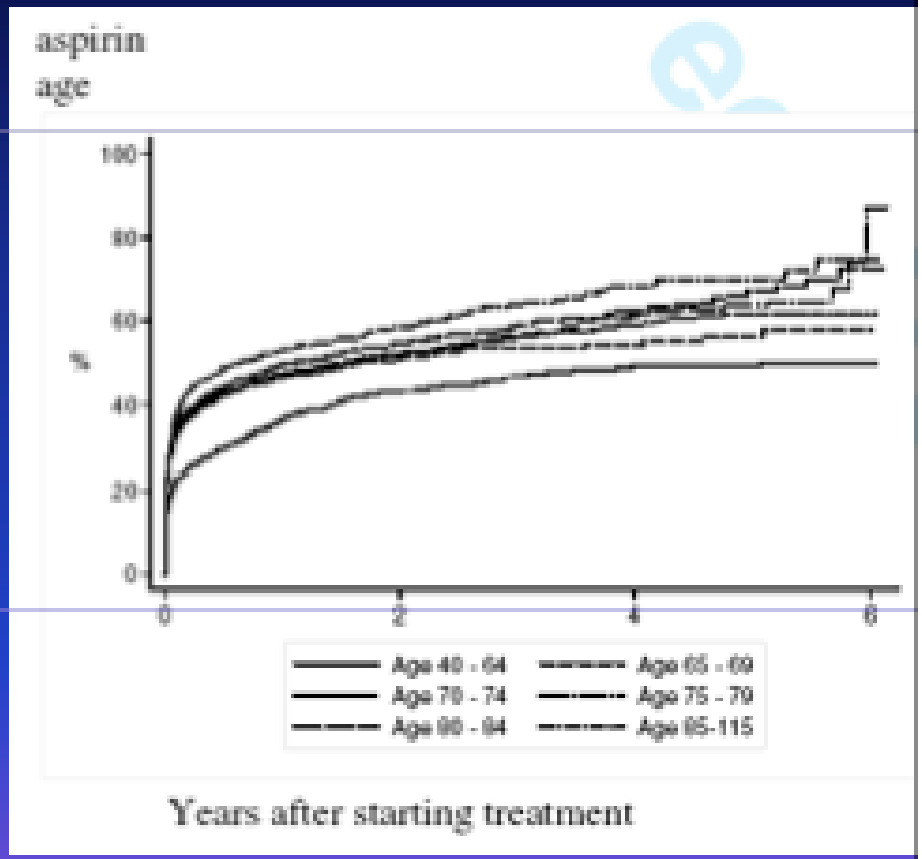
	Risk for Thromboembolism (%)			c-Statistic	
	Low	Intermediate	High	All Patients	Subgroup*
AFI	13.1	24.7	62.3	0.56	0.61
SPAF	27.7	28.5	43.8	0.60	0.65
$CHADS_2$	18.8	61.2	20.1	0.58	0.67
Framingham	37.1	46.6	16.4	0.62	0.69
7th ACCP	11.7	7.9	80.4	0.56	0.60

*Subgroup of 5,588 patients not on warfarin at baseline and with continuous follow-up off of warfarin for at least 12 months.

Proportion of AF patients initiated with warfarin and aspirin over time stratified by age score

Gallagher et al J Thromb Haemost 2008

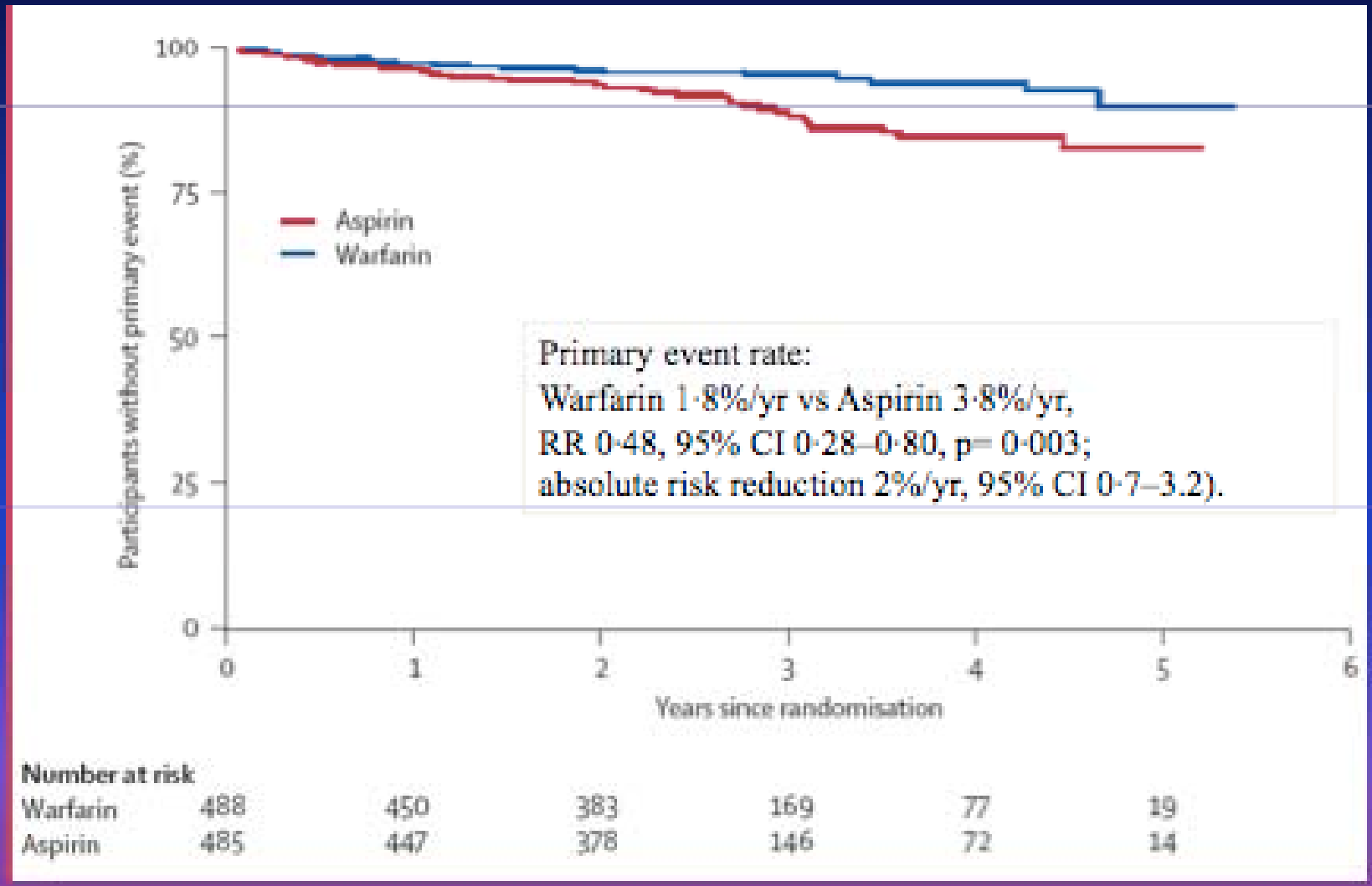




GPRD; N=41,910 Chronic AF patients.

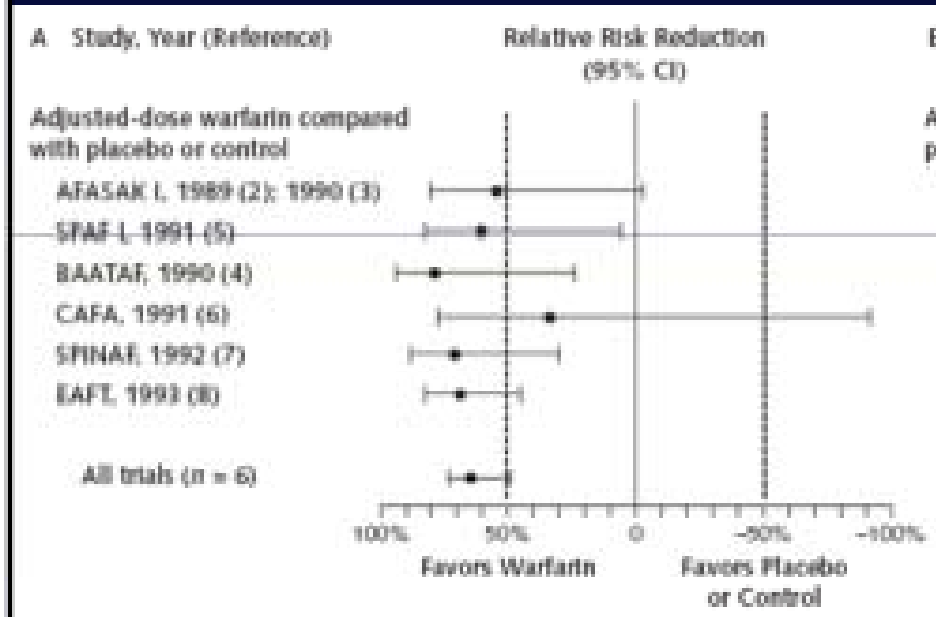
Warfarin vs aspirin for stroke prevention in an elderly community population with AF: the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA

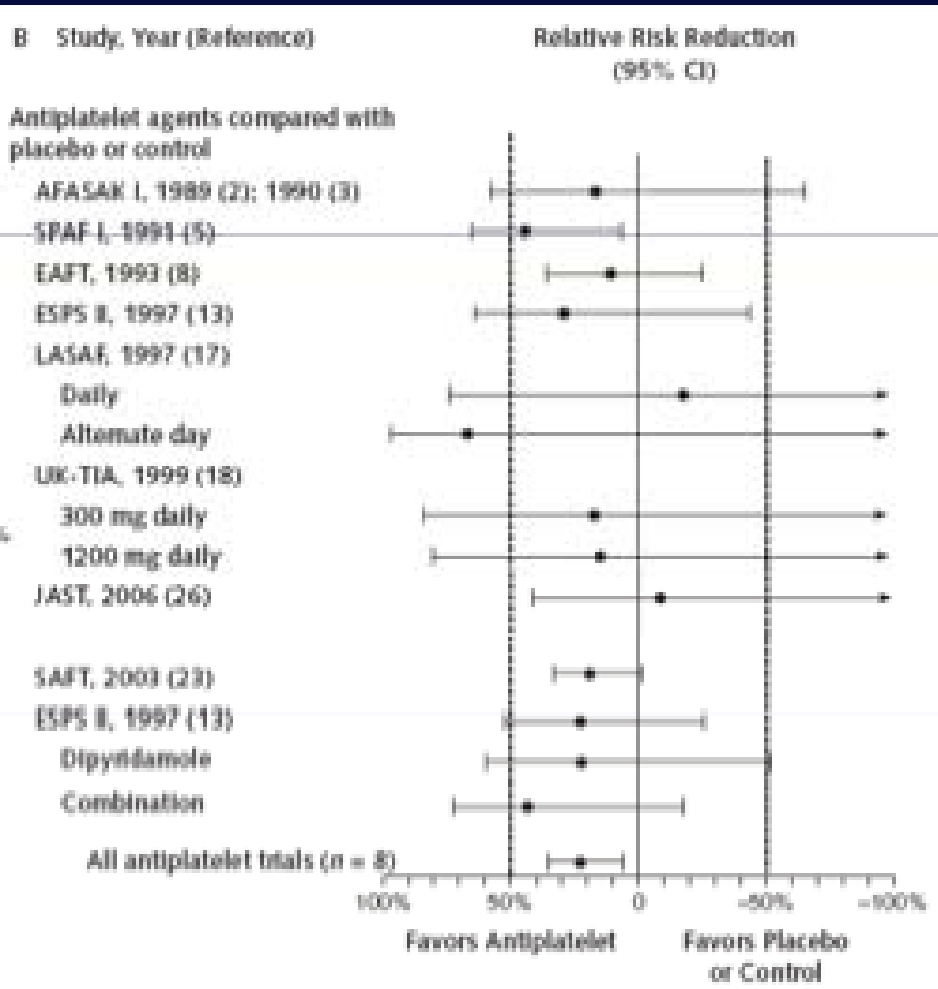
Mant et al Lancet 2007; 370: 493–503



Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular AF

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

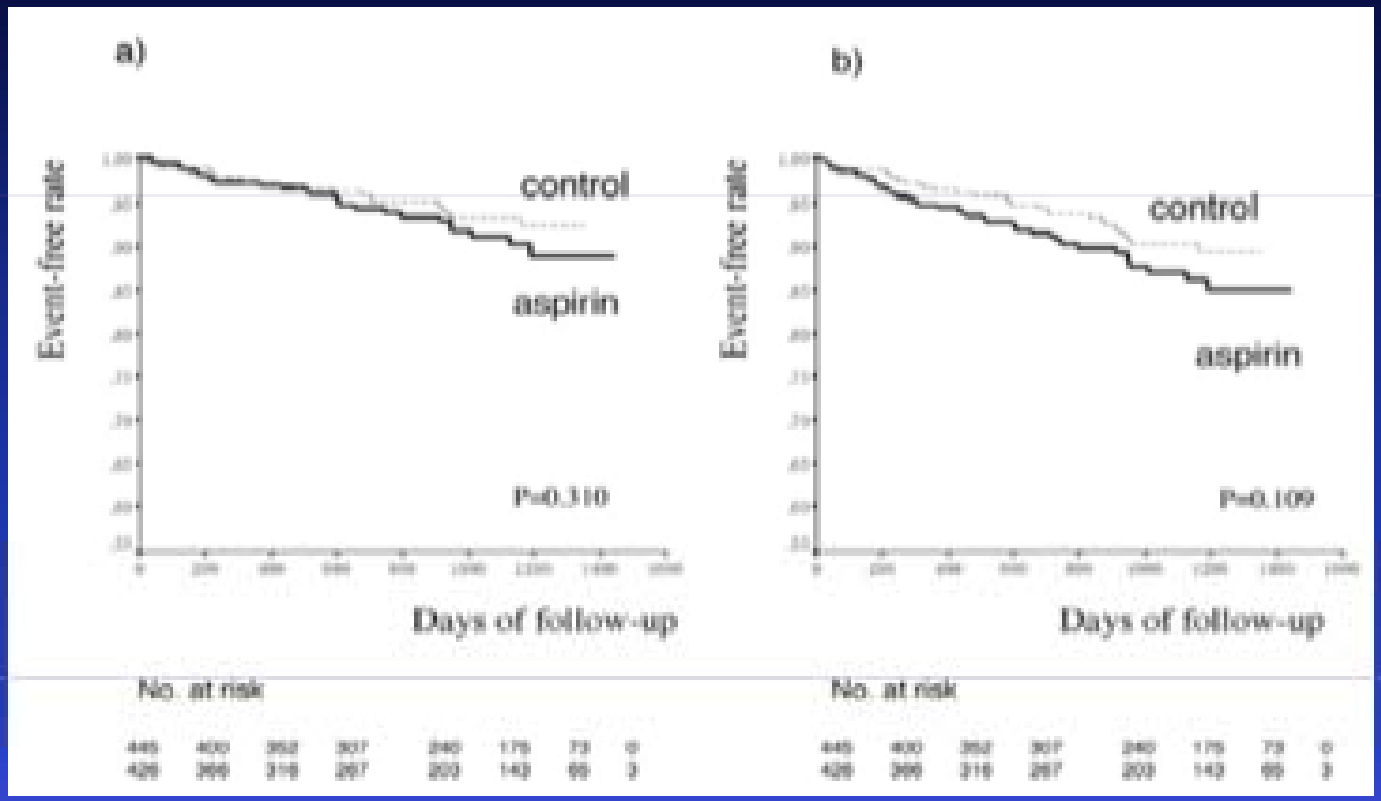




Comparison	RRR
OAC vs control	64%
APT vs control	22%

Low-Dose Aspirin for Prevention of Stroke in Low-Risk Patients With AF:Japan AF Stroke Trial

Sato et al Stroke. 2006;37:447-451



Primary end points included cardiovascular death, symptomatic brain infarction, or TIA, whereas the secondary end points included noncardiovascular death, intracranial hemorrhage, major bleeding, and peripheral embolization.

Kaplan–Meier survival curves for primary end points(a) and for primary plus secondary end points (b). **Treatment with aspirin 150-200mg/day was not superior to treatment without aspirin for primary end points (log-rank; *P*=0.310) and secondary end points (log-rank; *P*=0.109)**

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Don't add aspirin for associated stable vascular disease in a patient with atrial fibrillation receiving anticoagulation

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BMJ 2008;336:654-5
doi:10.1136/bmj.39511.704586.AD

The clinical problem

Atrial fibrillation is the commonest cardiac arrhythmia, with increasing prevalence and incidence.[1] Adjusted dose oral anticoagulation (such as with warfarin) is the most effective treatment for stroke prevention in high risk patients with atrial fibrillation.[2]

However, common practice is to add aspirin (or other antiplatelet treatment) to warfarin in atrial

clinical trials[4] of warfarin versus ximelagatran (an oral direct thrombin inhibitor) in moderate to high risk patients with atrial fibrillation compared aspirin users with non-users. This analysis found no additive effect of taking aspirin (with either of the anticoagulation treatments) in preventing stroke or reducing vascular events (including death or myocardial infarction).[4] Specifically, the rate of myocardial infarction with

BMJ

KEY POINTS

Adding aspirin to warfarin does not seem to prevent stroke and vascular events in patients with atrial fibrillation and stable vascular disease

Bleeding risks are much higher in patients prescribed both warfarin and aspirin

We should stop prescribing aspirin plus warfarin to prevent stroke and vascular events in stable patients with atrial fibrillation who are receiving anticoagulation treatment

Annals of Medicine.
2008, 1–9, iFirst article

informa
healthcare

REVIEW ARTICLE

Antithrombotic therapy in patients treated with oral anticoagulation undergoing coronary artery stenting. An expert consensus document with focus on atrial fibrillation

ANDREA RUBBOLI[1], JONATHAN L. HALPERIN[2], K. E. JUHANI AIRAKSINEN[3], MICHAEL BUERKE[4], ERIC BECKHOUT[5], SAUL B. FREEDMAN[6], ANTHONY H. GERSHLICK[7], AXEL SCHLITT[4], HUNG FAT TSE[8], FREEK W. A. VERHEUGT[9] & GREGORY Y. H. LIP[10]

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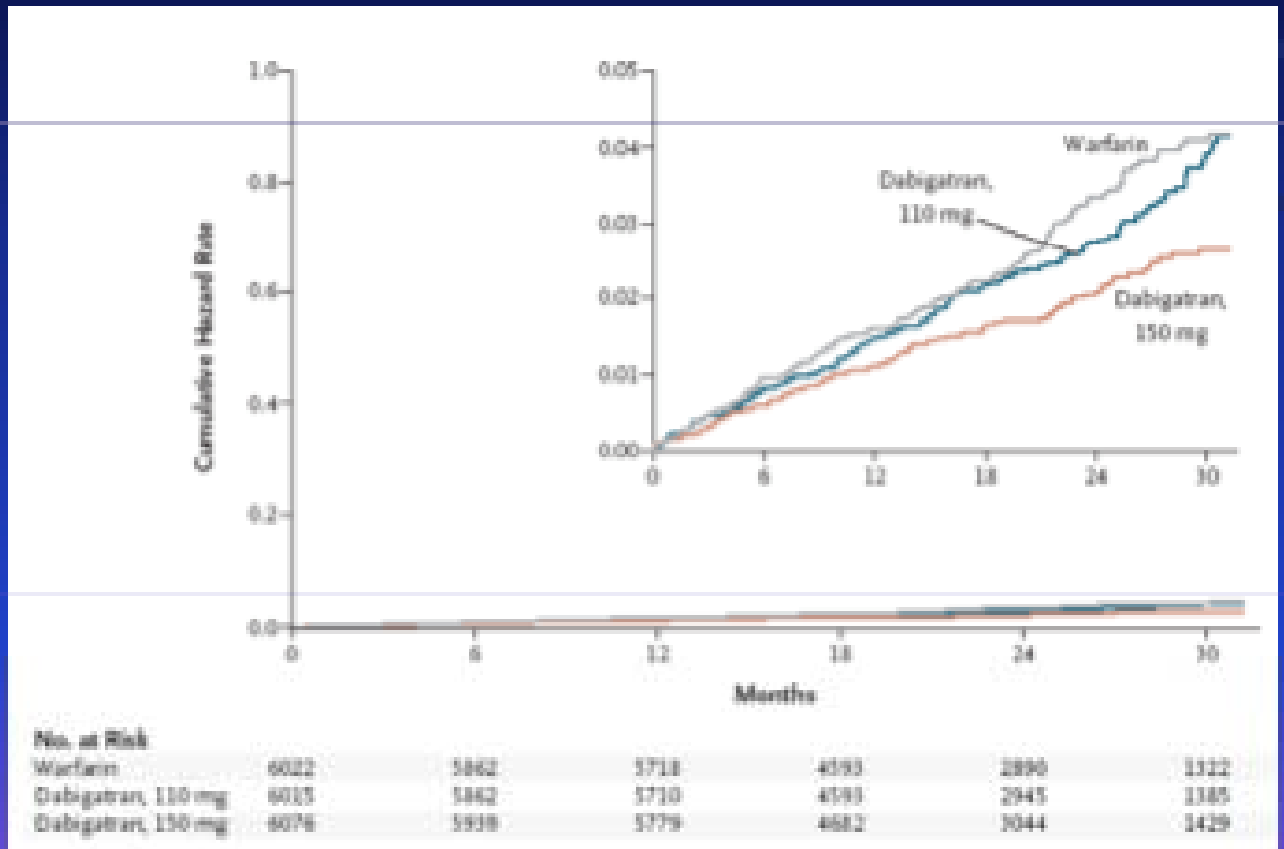
Is there hope for the future?

RE-LY® – Randomized Evaluation of Long-term Anticoagulant Therapy with Dabigatran Etexilate

Connolly et al N Engl J Med 2009 doi 10.1056/NEJMoa090556



Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group

N=18113

RR with dabigatran 110mg, 0.91; 95%CI 0.74 -1.11; P<0.001 for noninferiority) and with dabigatran 150mg, RR 0.66; 95% CI, 0.53 to 0.82; P<0.001 for superiority).

Phase III antithrombotic therapy trials in AF [in 2009] … *www.clinicaltrials.gov*

	RE-LY	ROCKET AF	ARISTOTLE	AVERROES
Drug	Dabigatran	Rivaroxaban	Apixaban	Apixaban
Blinding	Single	Double	Double	Double
Dosing regimen	bid	od	bid	bid
Doses	110 or 150 mg	20 mg [15mg for moderate renal impairment]	5 mg	5 mg 2.5 mg
Control	Open-label warfarin	Double-blind warfarin	Double-blind warfarin	Double-blind ASA
INR	Range 2–3	Target 2.5	Range 2–3	–
No. of patients	18,000	14,000	15,000	5,600
Duration	25 months	33 months	–	–

Phase III antithrombotic therapy trials in AF [in 2009] … *www.clinicaltrials.gov*

	BOREALIS-AF	ENGAGE-AF TIMI48	Others
Drug	SSR126517E 'biotinylated idraparinux'	Edoxaban [DU176b]	Lots!
Blinding	Double	Double	…
Dosing regimen	once-weekly subcutaneous injection	od	…
Doses	….	Low dose vs High dose [vs VKA]	…
Control	Double-blind warfarin	Double-blind warfarin	…
INR	Target 2.5	Range 2–3	–
No. of patients	9,600	16,500	…
Duration	Dec 07 – Mar 11	Nov 08 – Mar 11	–

The burden of stroke and thromboembolism in atrial fibrillation - is there hope for the future?

- The prevalence of AF is increasing, resulting in a major public health burden.
- What is less clear is the required 'burden' of the arrhythmia (that is, AF episodes and duration) necessary for precipitating stroke and thromboembolism.
- The number of AF episodes per day – as well as AF burden – can vary greatly. Also, paroxysms of AF are frequently asymptomatic.
- Antithrombotic therapy helps prevent the burden of stroke and thromboembolism in AF
  - Aspirin may have limited benefit on AF mortality/moribidity
  - New oral anticoagulant drugs may hold much promise