Optimal antithrombotic therapy for atrial fibrillation in the elderly patients

Rossella Marcucci

21 ottobre 2011

Advances in cardiovascular arrhytmies and great innovations in cardiology
XXIV Giornate Cardiologiche Torinesi

ELDERLY PATIENTS AND AF

Epidemiology

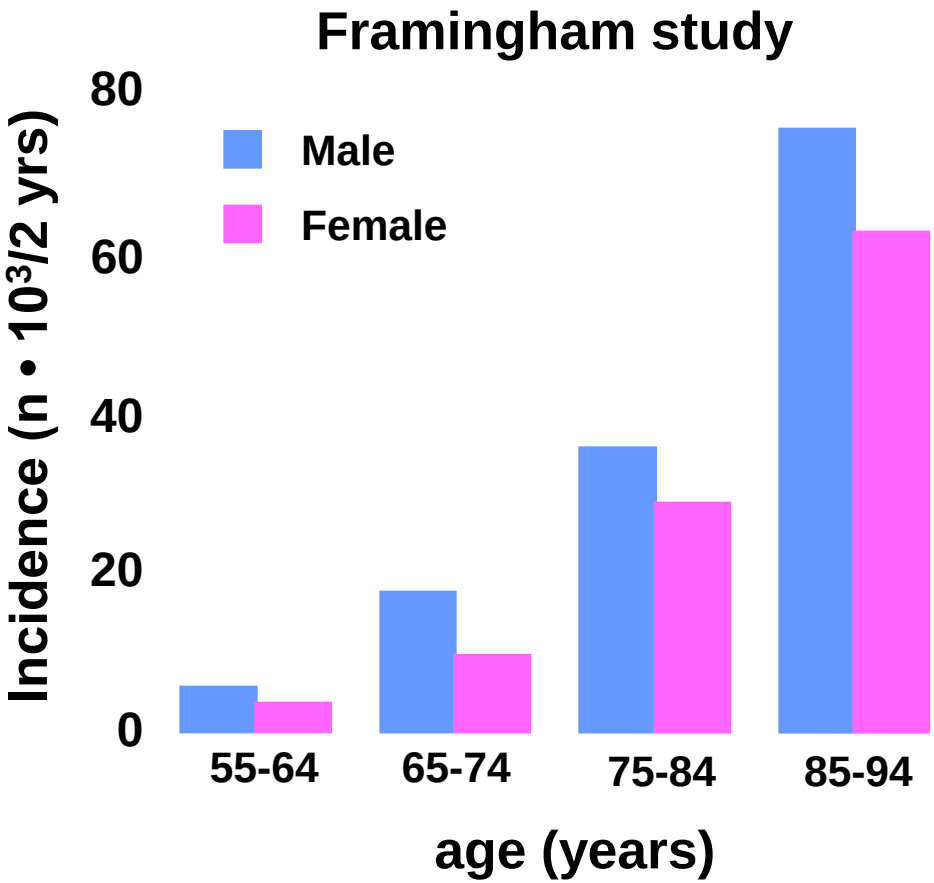
ATRIAL FIBRILLATION: the entity of the problem

- 1 % PREVALENCE IN THE GENERAL POPULATION
- **10% PREVALENCE AFTER 80 YEARS**
- 4,5%/anno RISK OF STROKE (MEDIUM)
- 12%/anno RISK OF STROKE RECURRENCE
- 15% % OF STROKE SECONDARY TO AF
- **23% % OF STROKE SECONDARY TO AF AFTER 80 YEARS**
- **40% DEATH OR MAJOR INABILITY AFTER STROKE**

Antithrombotic and thrombolytic therapy 8th ed: ACCP Guidelines, CHEST 2008

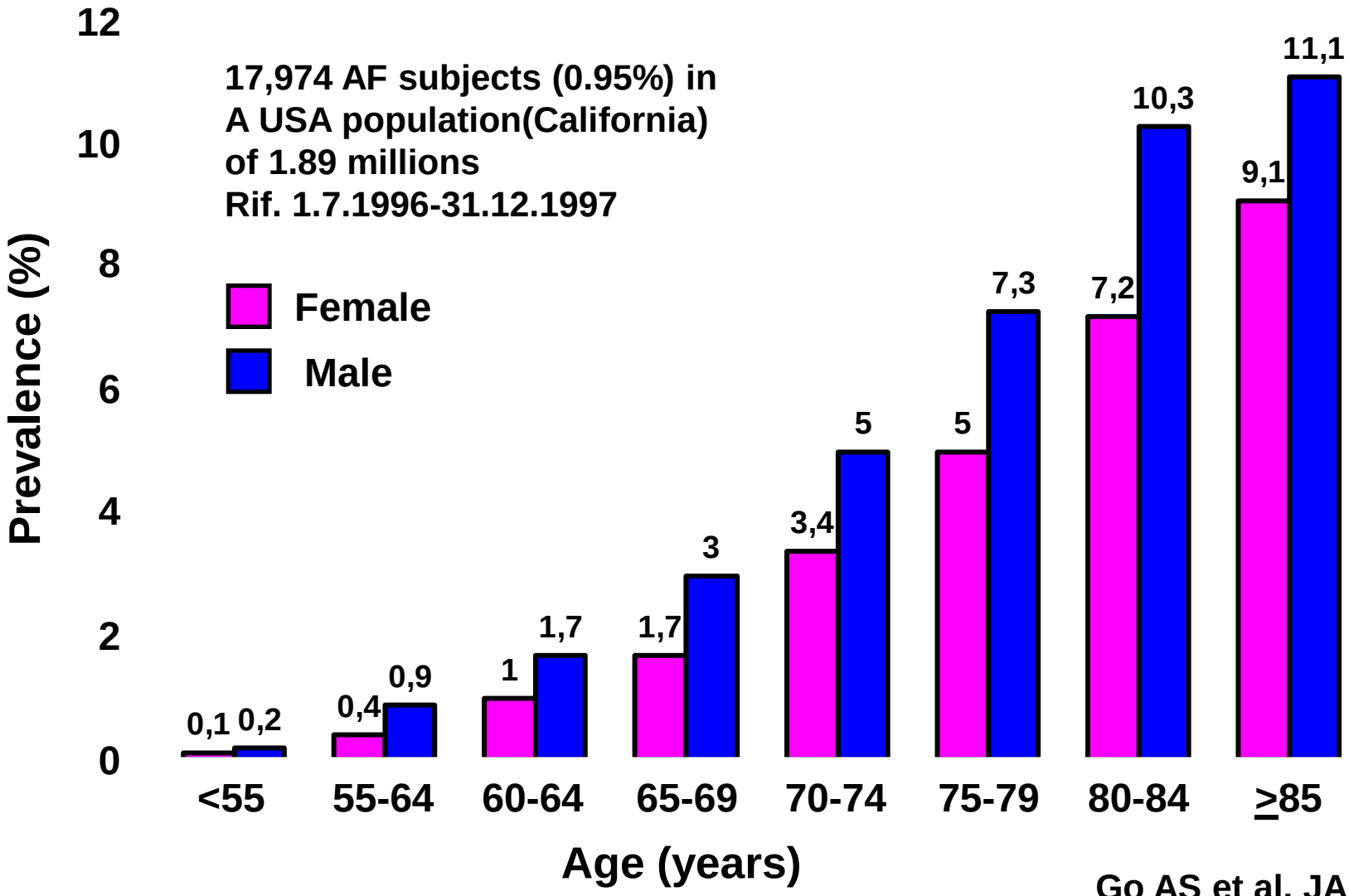
Epidemiology

Incidence and prevalence of AF increase with increasing age



Benjamin EJ, et al. JAMA 1994

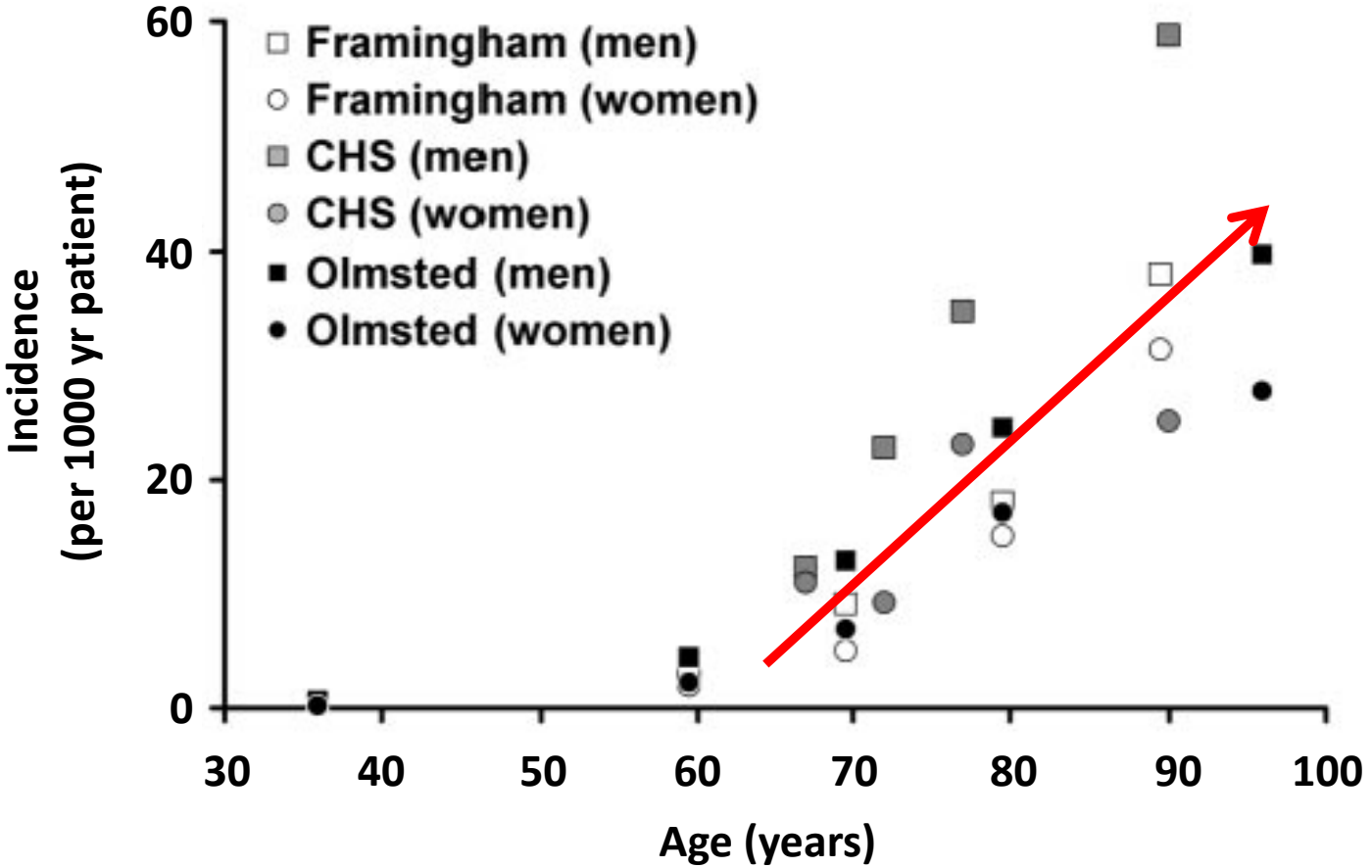
Prevalence of AF according to age ad sex in ATRIA study



Go AS et al, JAMA 2001

Secular Trends in Incidence of Atrial Fibrillation in Olmsted County, Minnesota, 1980 to 2000, and Implications on the Projections for Future Prevalence

Incidence of AF according to age



Miyasaka Y. Circulation, 2006

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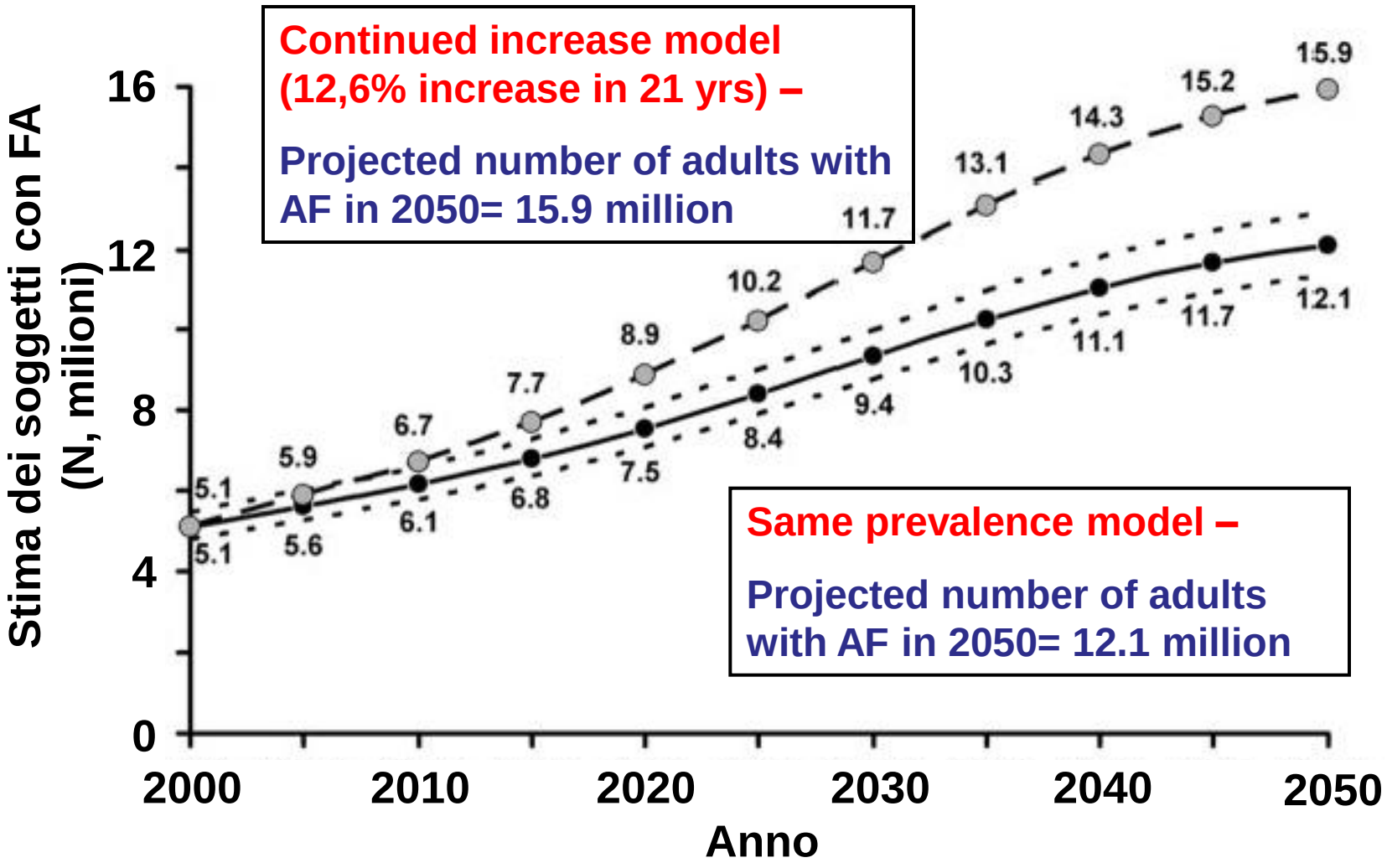


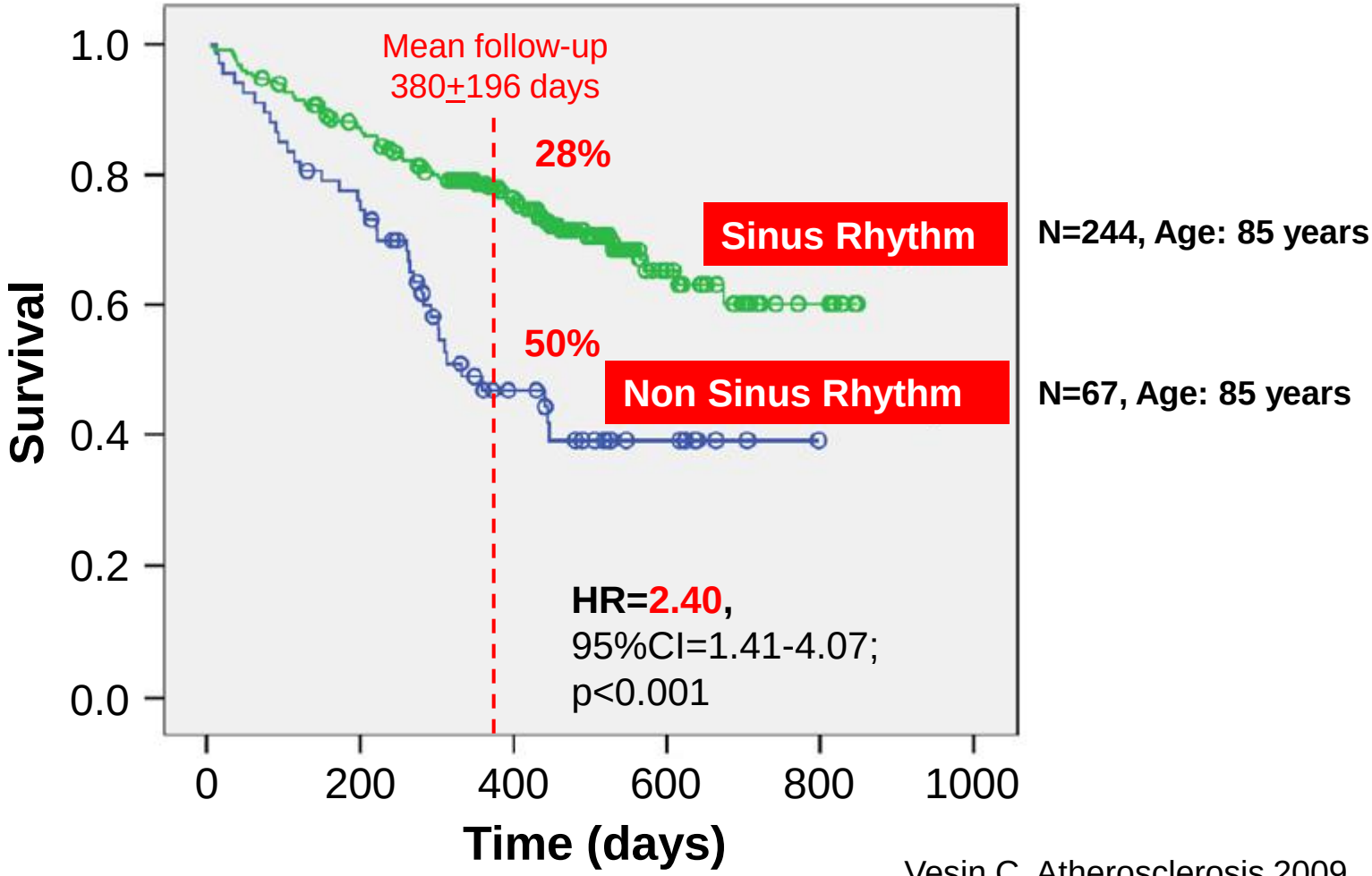
Miyasaka Y. Circulation, 2006

ELDERLY PATIENTS, AF and STROKE

Epidemiology

Predictive factors for all-cause mortality in the hospitalized elderly subject: The importance of arrhythmia

The "**PR**onostic cardiovasculaire et **O**ptimisation **T**herapeutique **E**n **GER**iatrie" (**PROTEGER**) study - N=331; *age >70 years & history of CVD; 2 geriatric dep.t (Paris, France)*



Vesin C, Atherosclerosis 2009

Increasing age as a risk factor for stroke in AF

Study	N	Age risk factor	P-value
Hart RG, 1999[11]	2,012	Incremental risk per decade	<0.001
Hart RG, 2000[13]	460	Incremental risk per decade	<0.001
Laupacis A, 1994[10]	1,593	Incremental risk per decade	<0.05
Nakagami H, 1998[19]	290	Incremental risk per decade	NS
SPAF Investigators., 1992[18]	568	Incremental risk per decade	NS
The SPAF III Writing Committee, 1998[12]	892	Incremental risk per decade	0.01
van Latum JC, 1995[16]	375	Incremental risk per decade	NS
Wang TJ, 2003[14]	705	Incremental risk per decade	<0.05
Petersen P, 1990[17]	336	Correlation with increasing age	NS
Stollberger C, 2004[15]	409	Correlation with increasing age	0.0006
Moulton AW, 1991[22]	265	Age > 75	<0.05
Cabin HS, 1990[20]	272	Age > 70	NS
Inoue H, 2000[21]	740	Age > 65	0.0001

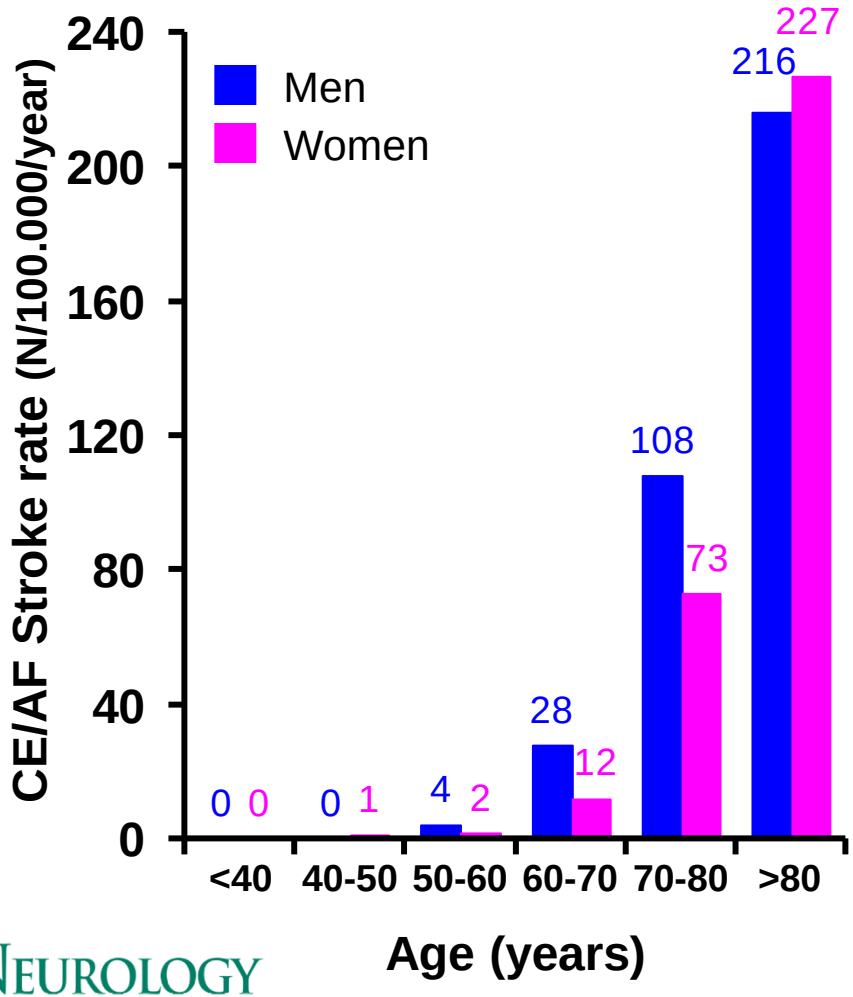
N = sample size; NS = not significant ($p>0.05$).

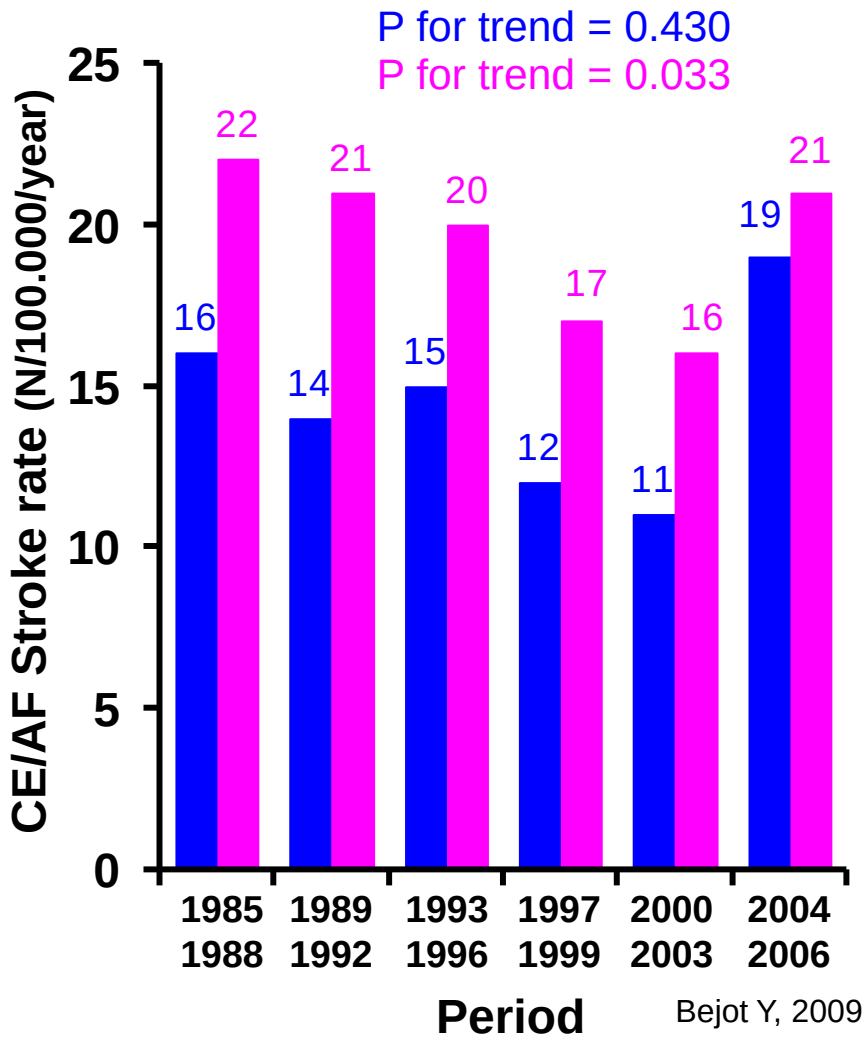
Hughes M and Lip G, TH 2008

Epidemiology of ischemic stroke from atrial fibrillation in Dijon, France, from 1985 to 2006

At risk = 148.810 / Men = 69.025 (46.4%)

CE/AF stroke = 572/3064 (18.7%)
CE/AF 80.6 vs Other strokes 73.6 years





NEUROLOGY

Bejot Y, 2009

Characteristics, Outcome, and Care of Stroke Associated With Atrial Fibrillation in Europe

Data From a Multicenter Multinational Hospital–Based Registry (The European Community Stroke Project)

Clinical state at time of maximum impairment among patients with and without AF in a European Concerted Action
(7 Countries, first stroke, age: 72 years, N=4462)

18.0%

(%)	Atrial Fibrillation		P
	Yes (N=803)	No (N=3659)	
Confusion	39.0	27.6	<0.001
Coma	12.3	7.6	<0.001
Paralysis	51.4	36.6	<0.001
Aphasia	41.8	30.3	<0.001
Disarthria	35.0	33.2	NS
Swallowing problems	40.3	23.6	<0.001
Urinary incontinence	54.6	38.7	<0.001

Stroke
Journal of the American Heart Association

Lamassa M, 2001

Characteristics, Outcome, and Care of Stroke Associated With Atrial Fibrillation in Europe

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Stroke
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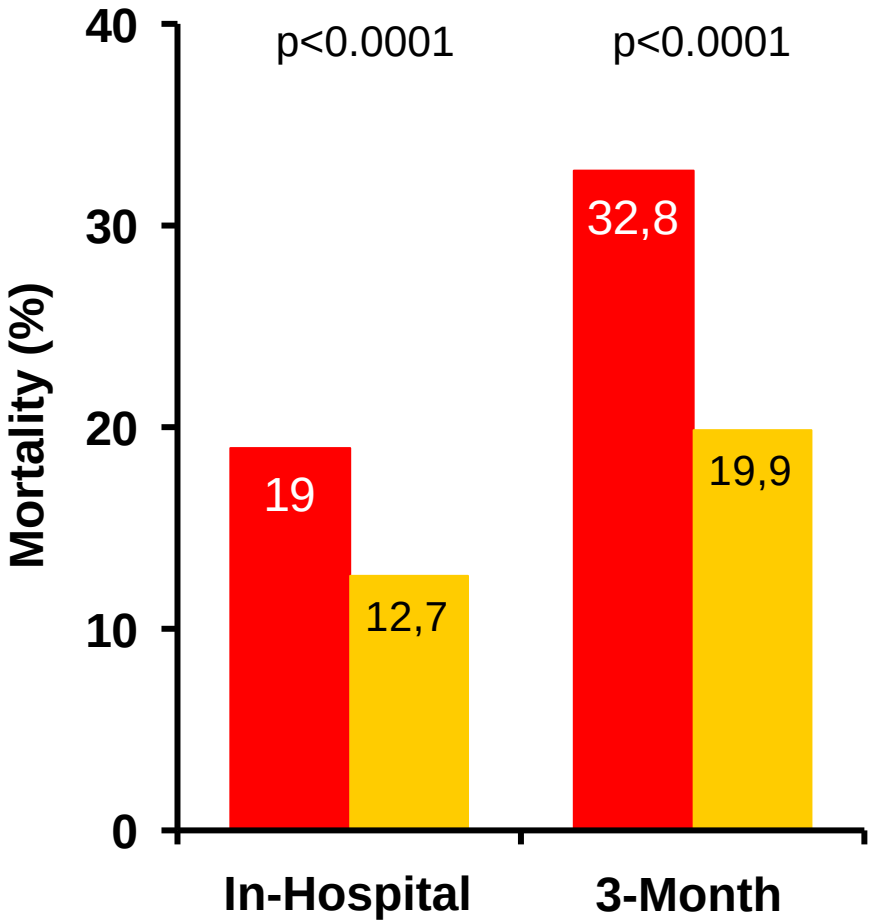
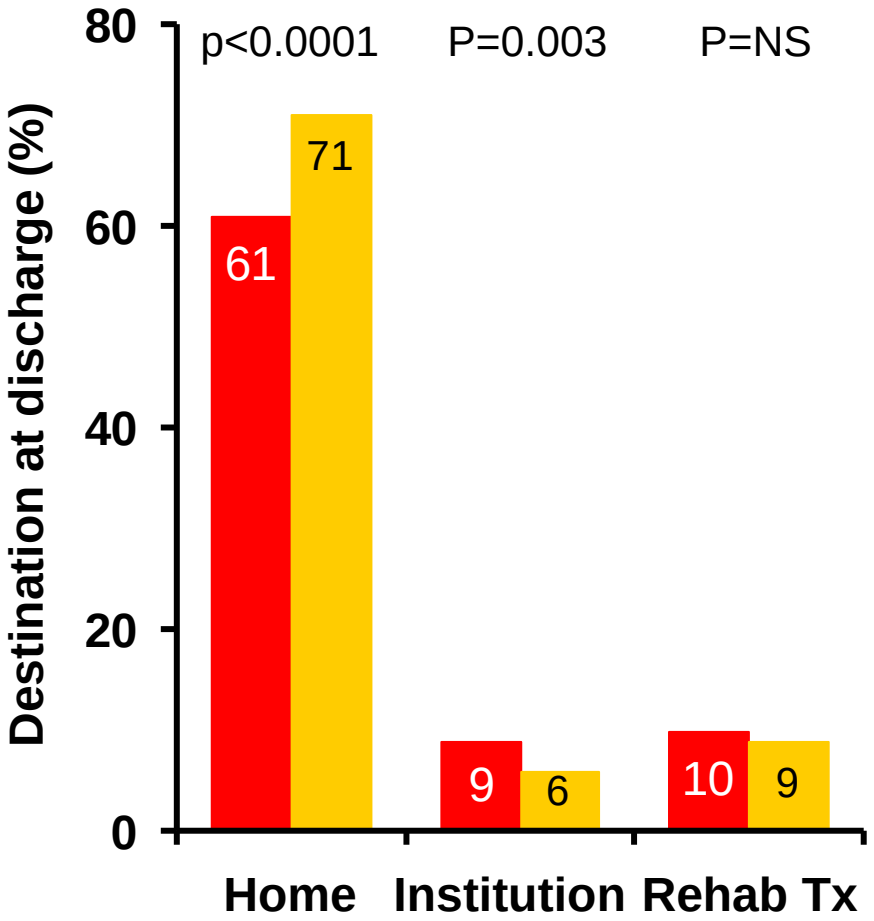
Lamassa M, 2001

AF – Age: **77**** yrs, Women: **58%****

No AF – Age: **71** yrs, Women: **48%**





: **p<0.001 vs the same category of No AF pts

Risk factors and outcome of subtypes of ischemic stroke. Data from a multicenter multinational hospital-based registry. The European Community Stroke Project

Predictors of 3-month disability (Barthel Index 0-14) and handicap (Rankin Scale Score 2-5) (A European Concerted Action – 12 Centers, 7 Countries, N=2472, Age: 71 yrs, Men: 52.1%, AFib: 19.1%)

	OR (95% CI)	
	Disability	**Handicap**
Atrial Fibrillation	1.41 (1.03-1.93)	1.43 (1.02-2.01)
Pre-stroke Rankin Scale Score (2-5)	2.80 (2.05-3.82)	2.98 (2.05-4.33)
OCSP Subtypes		
Lacunar	1	1
Total Anterior	3.27 (2.30-4.66)	2.71 (1.91-3.85)
Partial Anterior	1.73 (1.25-2.38)	1.52 (1.25-2.38)
Posterior	0.88 (0.57-1.35)	1.06 (0.76-1.49)

OCSP: Oxfordshire Community Stroke Project

Di Carlo A
J Neurol Sci 2006

ELDERLY PATIENTS, AF and STROKE:

Which antithrombotic therapy?

Stroke risk stratification schema

Risk scheme	Low risk	Intermediate risk	High risk
AFI Investigators (1994)	Age <65y and no risk factors	Age >65y and no other risk factors	Prior stroke/TIA, hypertension, diabetes
$CHADS_2$ (2001) - classical	Score 0	Score 1-2	Score 3-6
$CHADS_2$ (2001) - revised	Score 0	Score 1	Score ≥2
NICE guidelines (2006)	Age <65y with no moderate/high risk factors	Age ≥65y with no high risk factors Age <75y with hypertension, diabetes or vascular disease*	Previous stroke/TIA or thromboembolic event Age ≥75y with hypertension, diabetes or vascular disease Clinical evidence of valve disease or heart failure, or impaired left ventricular function
ACC/AHA/ESC guidelines (2006)	No risk factors	Age ≥75y, or hypertension, or heart failure, or LVEF ≤35%, or diabetes	Previous stroke, TIA or embolism, or ≥2 moderate risk factors of (age ≥75y, hypertension, heart failure, LVEF ≤35%, diabetes)
8th ACCP guidelines (2008)	No risk factors	Age >75y, or hypertension, or moderately or severely impaired LVEF and/or heart failure, or diabetes	Previous stroke, TIA or embolism, or ≥2 moderate risk factors of (age ≥75y, hypertension, moderately or severely impaired LVEF and/or heart failure, diabetes)
CHA_2DS_2-VASc (2010)	No risk factors	One 'combination' risk factor: (heart failure / LVEF ≤40, hypertension, diabetes, vascular disease*, female gender, age 65-74)	Previous stroke, TIA or embolism, or age ≥75y, or ≥2 'combination' risk factors (heart failure / LVEF ≤40, hypertension, diabetes, vascular disease*, female gender, age 65-74)

$CHADS_2$ SCORE

Congestive heart failure	1 punto
Hypertension	1 punto
Age >75 years	1 punto
Diabetes Mellitus	1 punto
Stroke/TIA	2 punti

Punteggio 0-6 punti

Basso rischio=0

Rischio moderato=1-2

Alto rischio 3-6

Gage BF, JAMA 2001

The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)

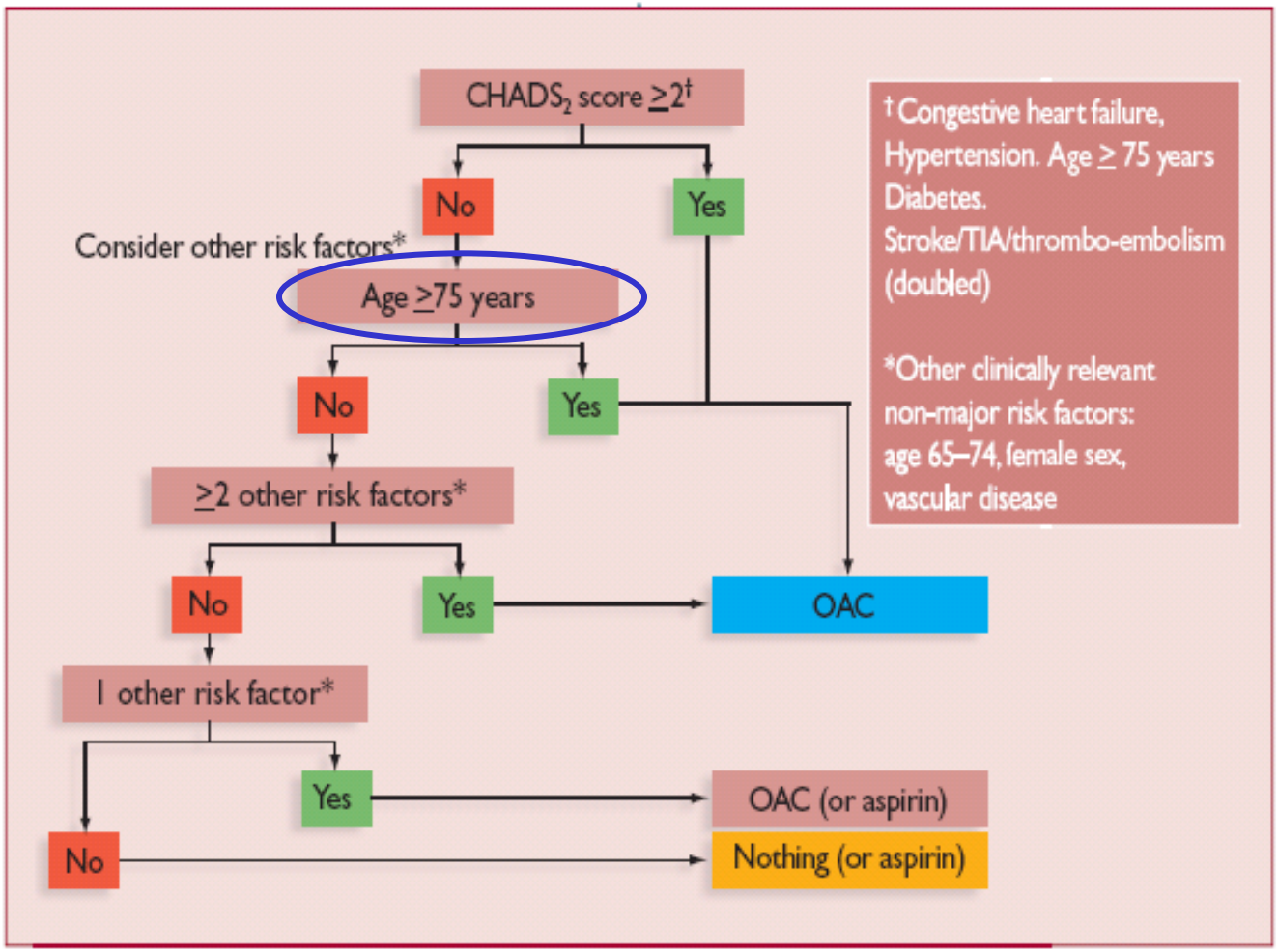


Figure 4 Clinical flowchart for the use of oral anticoagulation for stroke prevention in AF. AF = atrial fibrillation; OAC = oral anticoagulant; TIA = transient ischaemic attack. A full description of the CHADS$_2$ can be found on page 13.

Europace 2010

CHA_2DS_2Vasc SCORE

Congestive heart failure	1 punto
Hypertension	1 punto
Age 65-75 years	1 punto
Age >75 years	2 punti
Diabetes Mellitus	1 punto
Stroke/TIA	2 punti
CAD/AOP	1 punto
Female sex	1 punto

Punteggio 0-9 punti

Lip G, CHEST 2009

European Heart Journal
doi:10.1093/eurheartj/ehq278

Guidelines for the management of atrial fibrillation

The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)

Risk category	CHA_2DS_2-VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥2 'clinically relevant non-major' risk factors	≥ 2	OAC[a]
One 'clinically relevant non-major' risk factor	1	Either OAC[a] or aspirin 75–325 mg daily. Preferred: OAC rather than aspirin.
No risk factors	0	Either aspirin 75–325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.

EHJ, August 2010

Relative effects of antithrombotic therapies on all stroke from randomised trials in AF

Warfarin

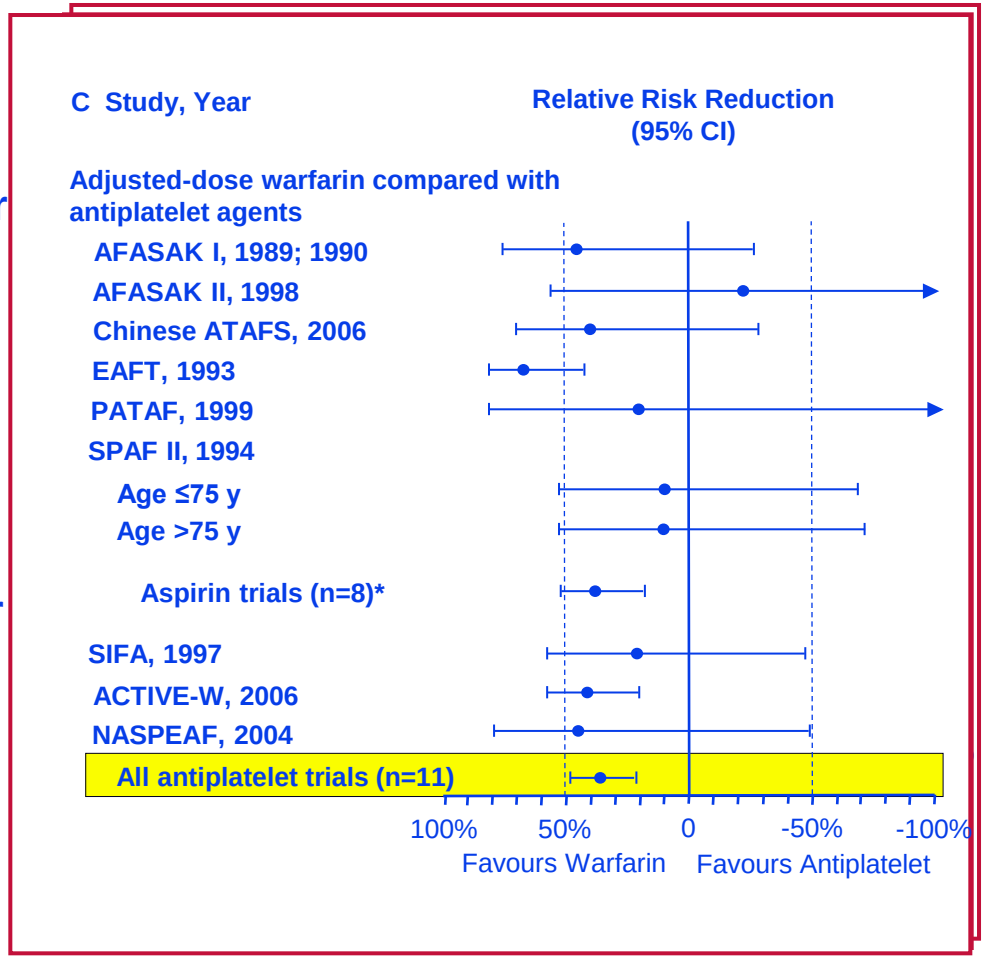
Relative RR vs. placebo 64% (CI 49–74)
Absolute risk reduction primary 2.7%/yr
Absolute risk reduction secondary 8.4%/yr
NNT primary prevention 37
NNT secondary prevention 12

ASA

Relative RR vs. placebo 22% (CI -1–35)
Absolute risk reduction primary 0.8%/yr
Absolute risk reduction secondary 2.5%/yr
NNT primary prevention 125
NNT secondary prevention 40

Warfarin vs ASA

Relative RR 38% (CI 23–48)



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

Relative effects of antithrombotic therapies on all stroke from randomised trials in AF

BLEEDING
Warfarin vs ASA

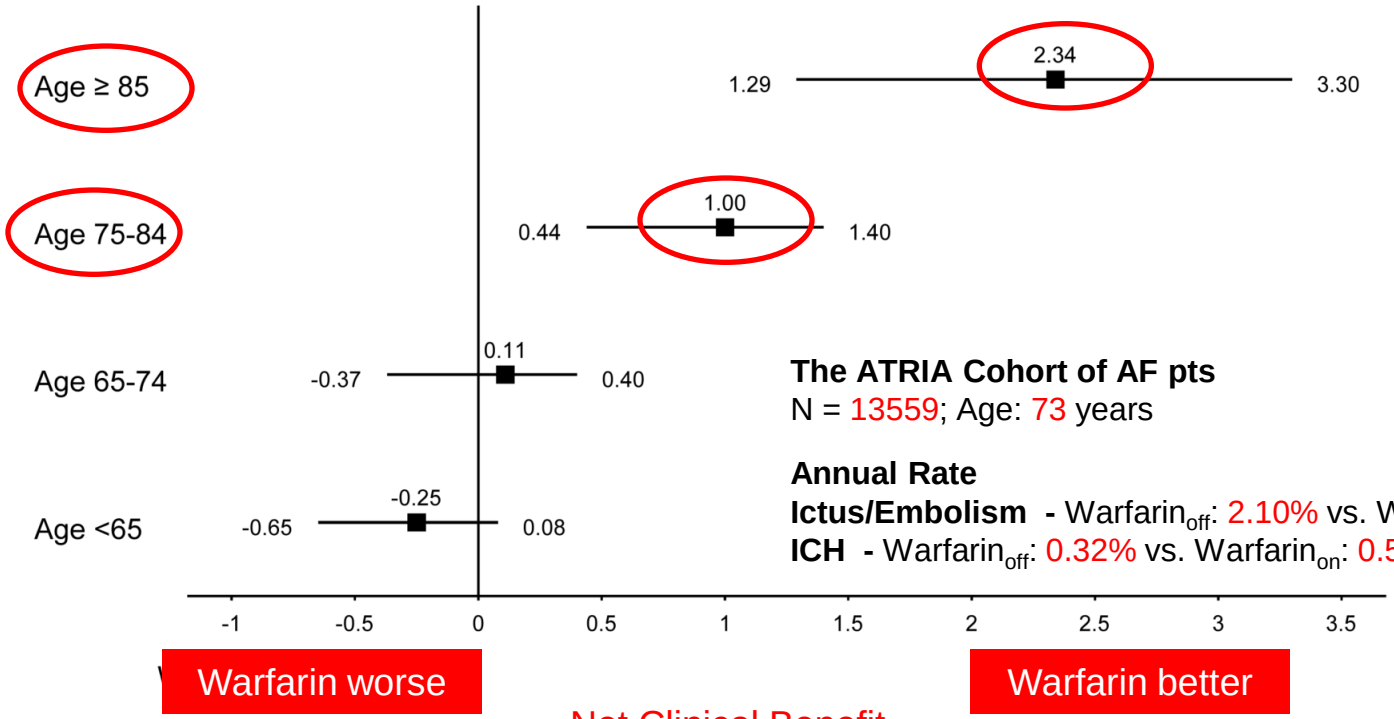
>50% RISK OF INTRACRANIAL HEMORRHAGE
70% RISK OF MAJOR EXTRACRANIAL HEMORRHAGE

Warfarin do NOT reduce mortality from any cause or from vascular causes

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

The Net Clinical Benefit of Warfarin Anticoagulation in Atrial Fibrillation

Daniel E. Singer, MD, Yuchiao Chang, PhD, Margaret C. Fang, MD, MPH, Leila H. Borowsky, MPH, Niela K. Pomernacki, RD, Natalia Udaltsova, PhD, and Alan S. Go, MD
Massachusetts General Hospital, Boston, Massachussetts, and University of California, San Francisco, San Francisco, and Kaiser Permanente of Northern California, Oakland, California.



The ATRIA Cohort of AF pts
N = 13559; Age: 73 years

Annual Rate
Ictus/Embolism - $Warfarin_{off}$: 2.10% vs. $Warfarin_{on}$: 1.27%
ICH - $Warfarin_{off}$: 0.32% vs. $Warfarin_{on}$: 0.58%

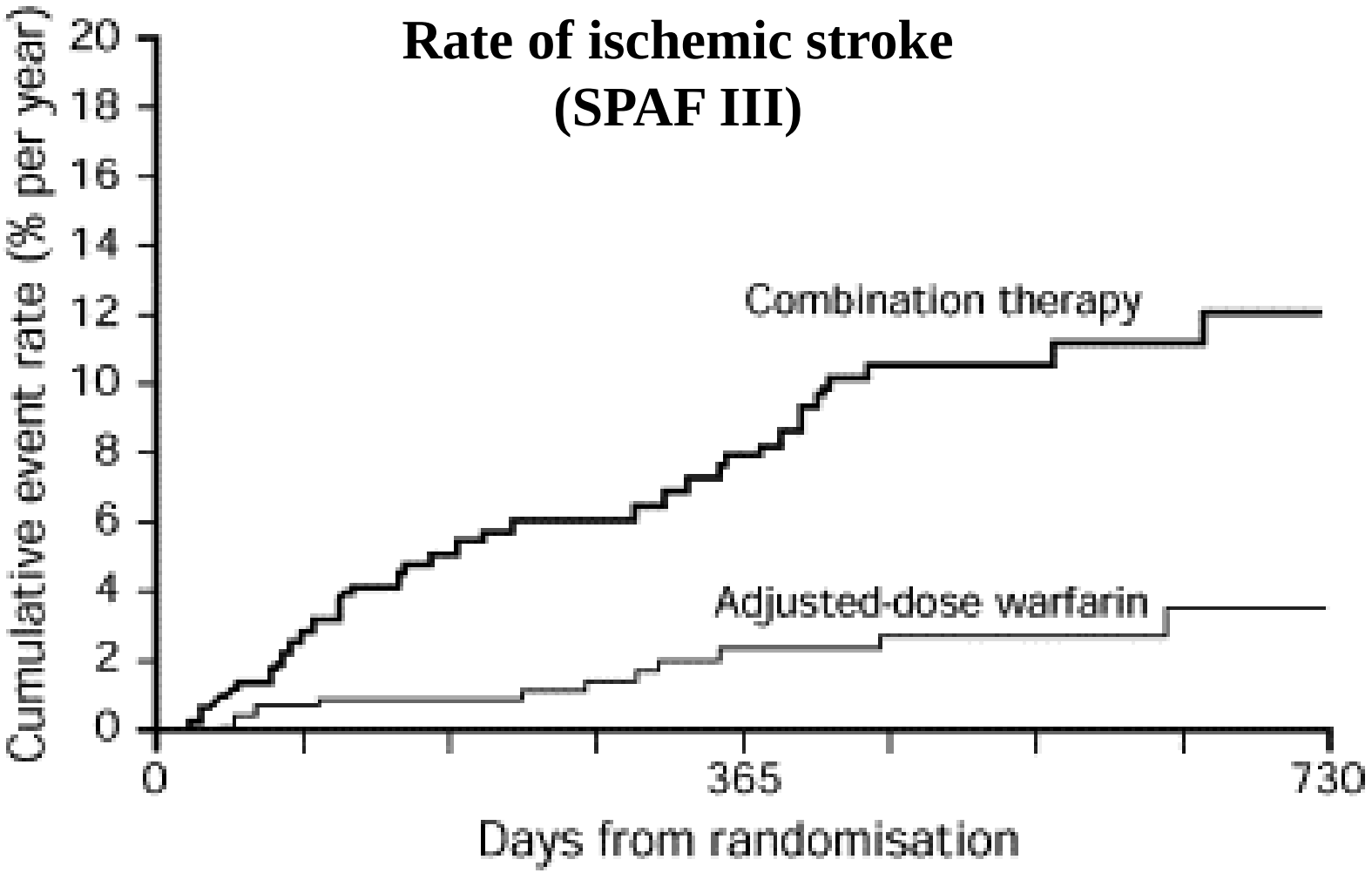
Net Clinical Benefit :
(annual rate of ischemic strokes / systemic emboli prevented by warfarin)
minus (intracranial hemorrhages due to warfarin) * impact weight
The impact weight was 1.5, reflecting the greater clinical impact of intracranial hemorrhage versus thromboembolism

Ann Intern Med, 2009

ELDERLY PATIENTS, AF and STROKE:

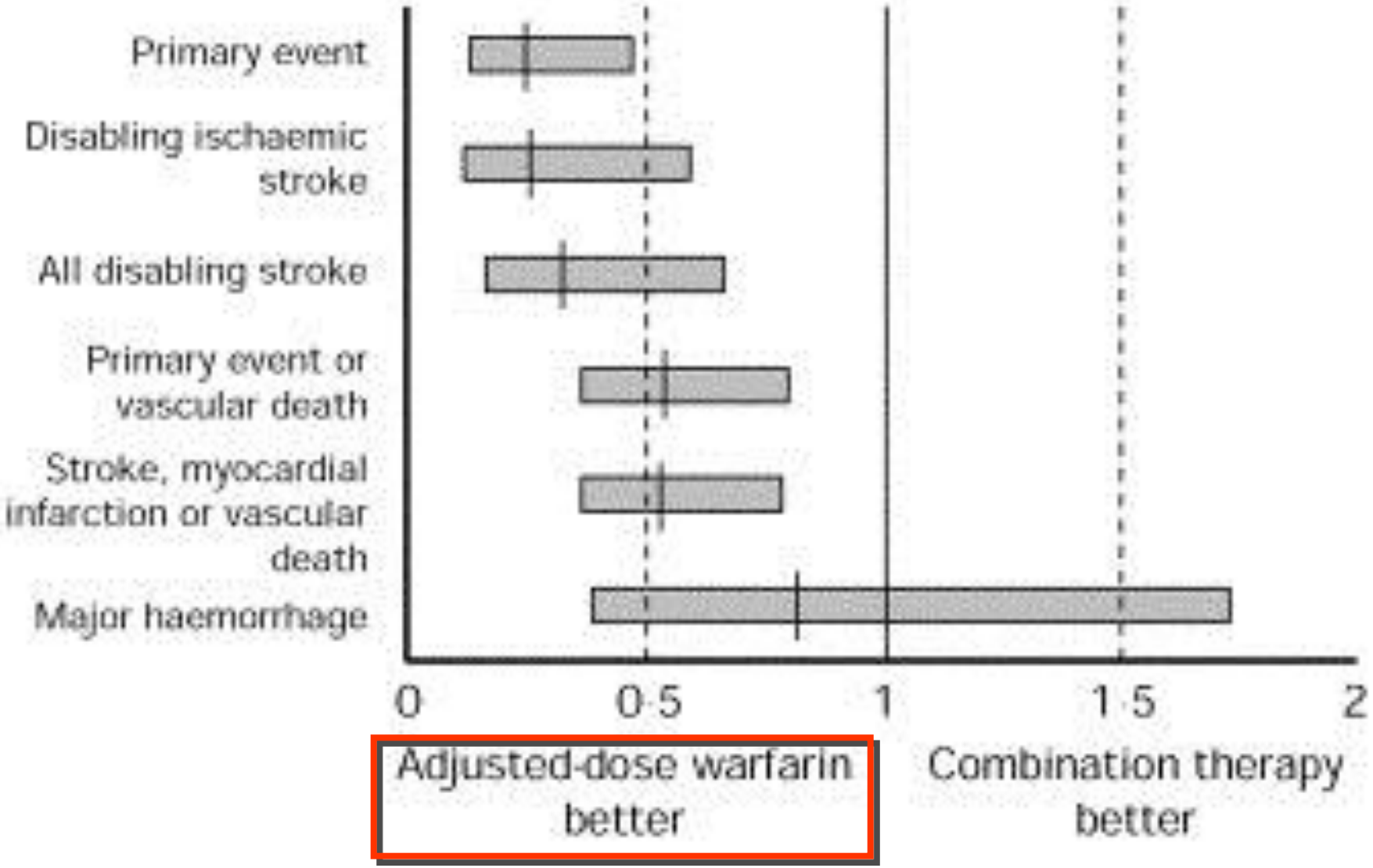
OAT:
are there alternative therapies?

Rate of ischemic stroke (SPAF III)



Number at risk

Combination therapy				
521	378	265	166	61
Warfarin therapy				
523	397	273	173	65


Primary event
Disabling ischaemic stroke
All disabling stroke
Primary event or vascular death
Stroke, myocardial infarction or vascular death
Major haemorrhage
0
0·5
1
1·5
2
Adjusted-dose warfarin better
Combination therapy better

SPAF III

ACTIVE-A

Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation

The ACTIVE Investigators*

Outcome	Clopidogrel plus Aspirin (N=3772)		Aspirin (N=3782)		Relative Risk (95% CI)	P Value
	no. of events	*%/yr*	*no. of events*	*%/yr*		
Primary outcome	832	6.8	924	7.6	0.89 (0.81–0.98)	0.01
Stroke						
Any	296	2.4	408	3.3	0.72 (0.62–0.83)	<0.001
Ischemic	235	1.9	343	2.8	0.68 (0.57–0.80)	
Hemorrhagic	30	0.2	22	0.2	1.37 (0.79–2.37)	
Of uncertain type	41	0.3	51	0.4	0.81 (0.54–1.22)	
Fatal	70	0.5	93	0.7	0.75 (0.55–1.03)	
Stroke, according to severity						
Nondisabling	107	0.9	153	1.2	0.70 (0.54–0.89)	0.004
Disabling or fatal	198	1.6	267	2.1	0.74 (0.62–0.89)	0.001
Myocardial infarction	90	0.7	115	0.9	0.78 (0.59–1.03)	[illegible]
Non–central nervous system systemic embolism	54	0.4	56	0.4	0.96 (0.66–1.40)	0.84
Death from vascular causes	600	4.7	599	4.7	1.00 (0.89–1.12)	0.97
Death from any cause	825	6.4	841	6.6	0.98 (0.89–1.08)	0.69

N Engl J Med 2009

ACTIVE-A

Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation

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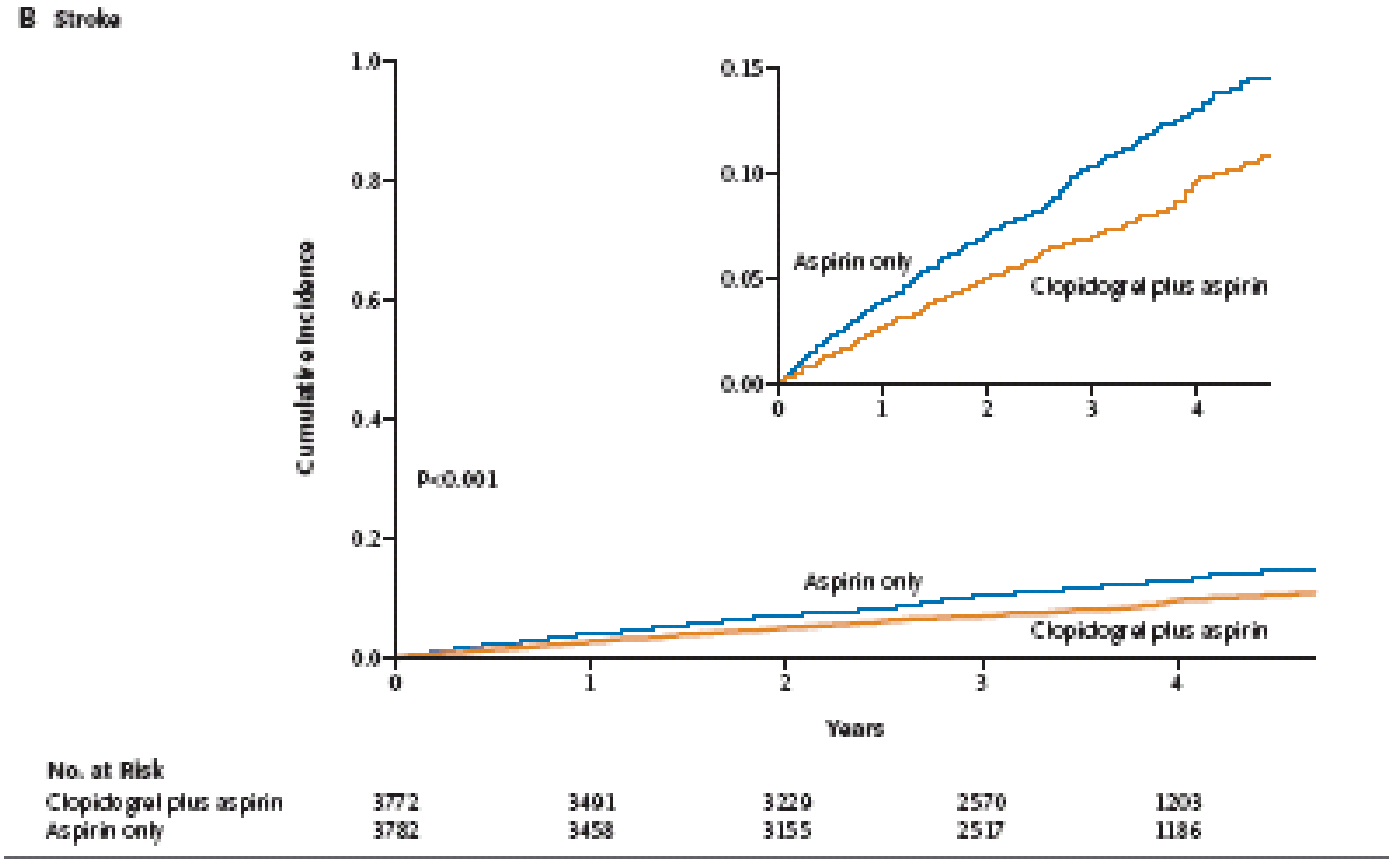

N Engl J Med 2009

Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation

The ACTIVE Investigators*

Bleeding	Clopidogrel plus Aspirin		Aspirin		Relative Risk (95% CI)	P Value
	no. of events	*%/yr*	*no. of events*	*%/yr*		
Major bleeding	251	2.0	162	1.3	1.57 (1.29–1.92)	<0.001
Severe	190	1.5	122	1.0	1.57 (1.25–1.98)	<0.001
Fatal	42	0.3	27	0.2	1.56 (0.96–2.53)	0.07
Minor bleeding	408	3.5	175	1.4	2.42 (2.03–2.89)	<0.001
Any bleeding	1014	9.7	651	5.7	1.68 (1.52–1.85)	<0.001
Site of major bleeding*						
Gastrointestinal	132	1.1	68	0.5	1.96 (1.46–2.63)	<0.001
Gastrointestinal, with transfusion	117	0.9	61	0.5	1.93 (1.42–2.63)	<0.001
Intracranial	54	0.4	29	0.2	1.87 (1.19–2.94)	0.006
Extracranial	200	1.6	134	1.1	1.51 (1.21–1.88)	<0.001

N Engl J Med 2009

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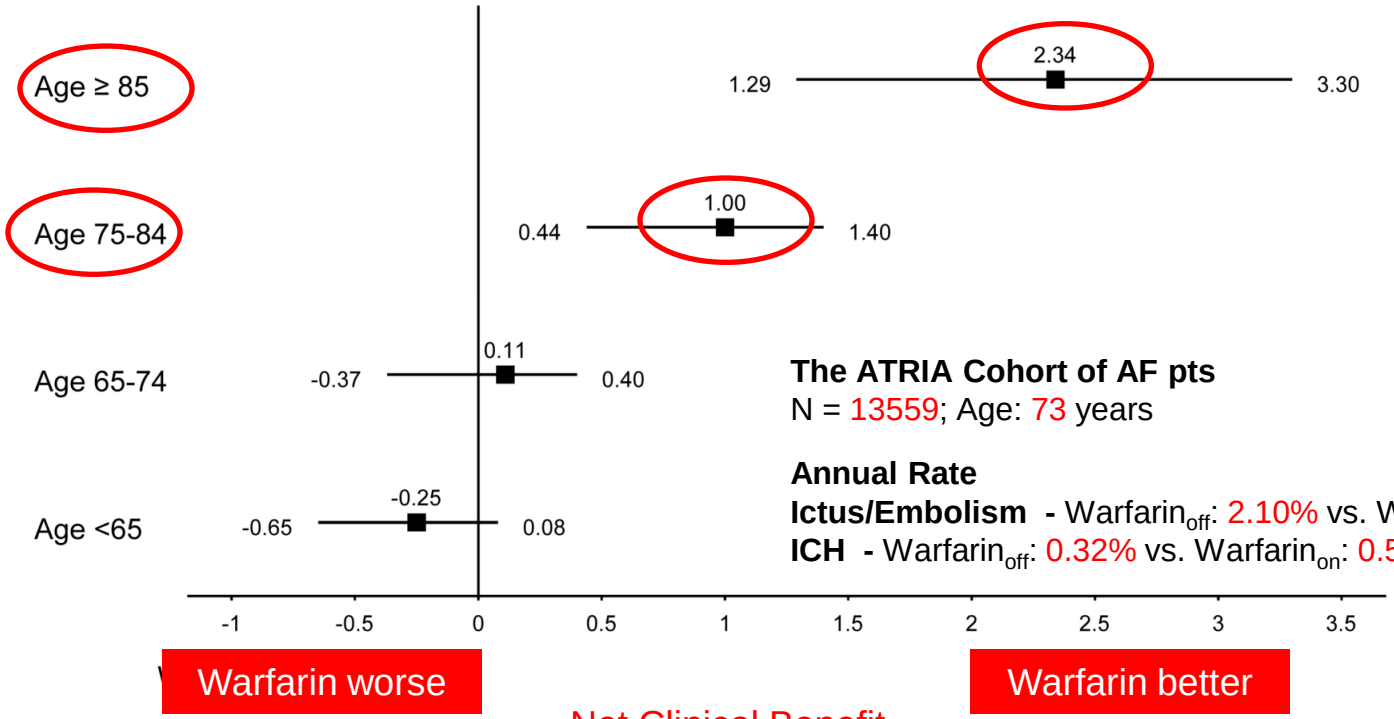

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Ann Intern Med, 2009

AF, Risk of Stroke, Anticoagulation

clinical practice

- Only **56.5%** of patients at very high risk of stroke were taking anticoagulants in 2003, whereas **38.2%** of patients at low risk of stroke received anticoagulants.

- Many patients who may benefit from anticoagulation still do not receive it, whereas others at lower risk of stroke do.

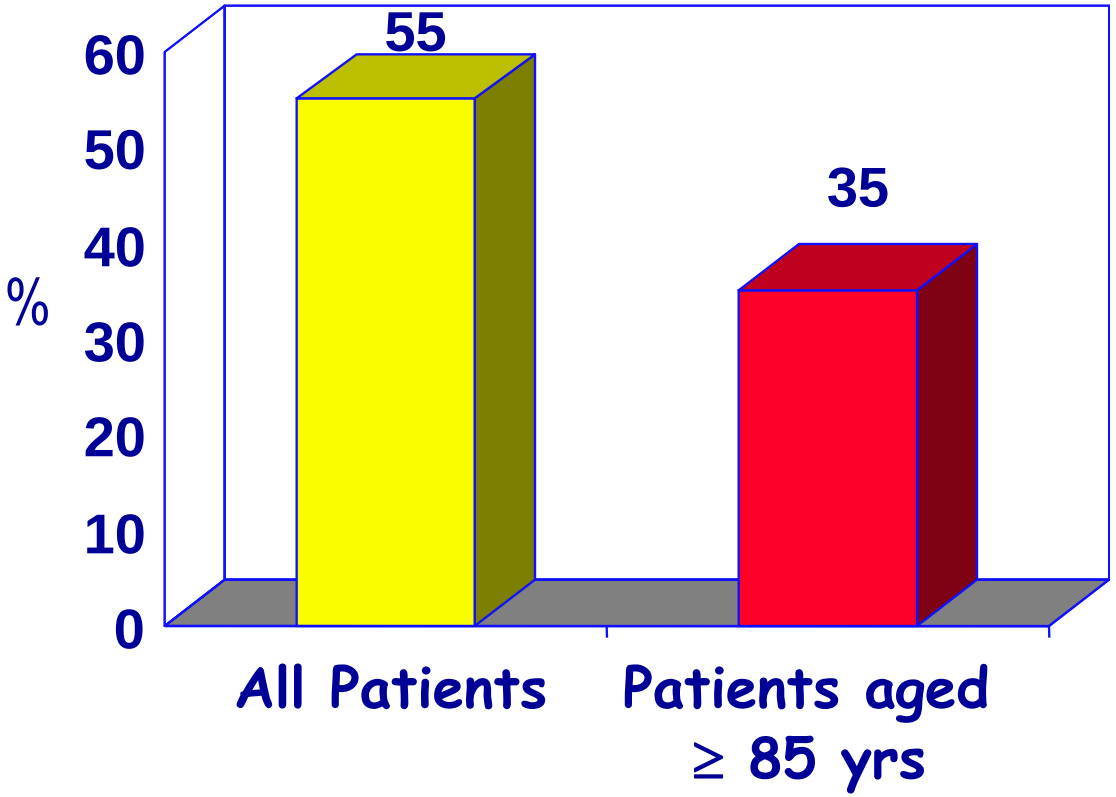
•Trends in the prevalence of diagnosed atrial fibrillation, its treatment with anticoagulation and predictors of such treatment in UK primary care. Heart 2006;92:1064–1070.

•Atrial Fibrillation and Stroke in the General Medicare Population. A 10-Year Perspective (1992 to 2002). Stroke 2006;37:1969-1974.

Underutilization of Warfarin in Clinical Practice

HMO- based study of > 11,000 pts with AF and without contraindications to warfarin

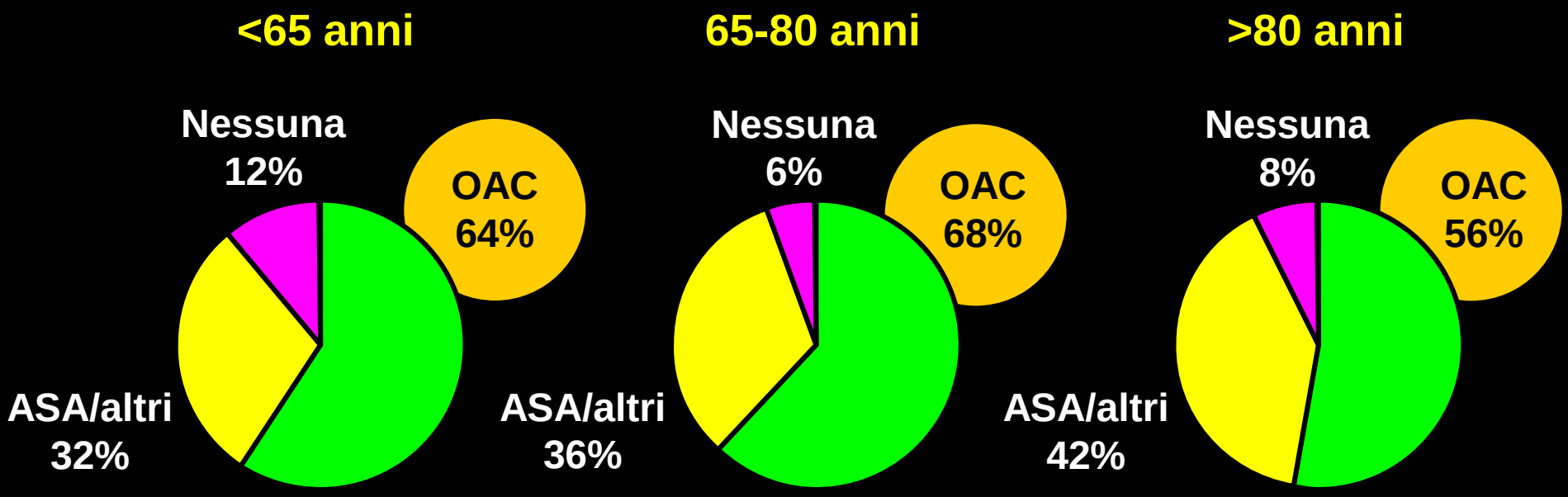
Pts receiving warfarin



ATRIA Study

Go AS et al, Ann Intern Med 1999; 131: 927-934

Uso di anticoagulanti orali e di antiaggreganti nell' EHS-AF, per gruppi di età



OAC: anticoagulanti orali

ASA/altri: aspirina, ticlopidina, clopidogrel

Nessuna: nessuna terapia

EUROPEAN SOCIETY OF CARDIOLOGY®

Europace (2011) **13**, 723–746
doi:10.1093/europace/eur126

EHRA POSITION PAPER

Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis

Gregory Y.H. Lip (Chair)[1*†], Felicita Andreotti[2†‡], Laurent Fauchier[3†], Kurt Huber[4*†], Elaine Hylek[5†], Eve Knight[6†], Deirdre A. Lane[1†], Marcel Levi[7†], Francisco Marin[8†], Gualtiero Palareti[9†], and Paulus Kirchhof (Co-chair)[10†]

HAS-BLED bleeding risk score

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

› 3 high risk: attention both with *ASA* and *OAT*

Pisters The Euro Heart Survey. Chest 2010

Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial

Jonathan Mant, FD Richard Hobbs, Kate Fletcher, Andrea Roalfe, David Fitzmaurice, Gregory YH Lip, Ellen Murray, on behalf of the BAFTA investigators and the Midland Research Practices Network (MidReC)**

975 patients aged > 75 years (mean age 81.5)

Randomised to warfarin (INR 2.0-3.0) or aspirin 75 mg

Mant et al; Lancet 2007

	Warfarin (n=488)		Aspirin (n=485)		Warfarin vs aspirin	
	n	Risk per year	n	Risk per year	RR (95% CI)	p
Stroke	21	1·6%	44	3·4%	0·46 (0·26–0·79)	0·003
By severity						
Fatal	13	1·0%	21	1·6%	0·59 (0·27–1·24)	0·14
Disabling non-fatal	8	0·6%	23	1·8%	0·33 (0·13–0·77)	0·005
Type of stroke*						
Ischaemic	10	0·8%	32	2·5%	0·30 (0·13–0·63)	0·0004
Haemorrhagic	6	0·5%	5	0·4%	1·15 (0·29–4·77)	0·83
Unknown	5	0·4%	7	0·5%	0·69 (0·17–2·51)	0·53
Other intracranial haemorrhage†	2	0·2%	1	0·1%	1·92 (0·10–113·3)	0·65
Systemic embolism‡	1	0·1%	3	0·2%	0·32 (0·01–3·99)	0·36
Total number of events	24	1·8%	48	3·8%	0·48 (0·28–0·80)	0·0027

RR=relative risk. *Type of stroke was determined by the endpoint committee on the basis of brain imaging or post-mortem findings. If neither of these was available, the stroke was classified as unknown. †The three other intracranial haemorrhages were subdural; two of these were fatal (one in each treatment group). ‡Two of the systemic emboli were fatal (one in each treatment group).

Table 3: **Nature of primary events**

Mant et al; Lancet 2007

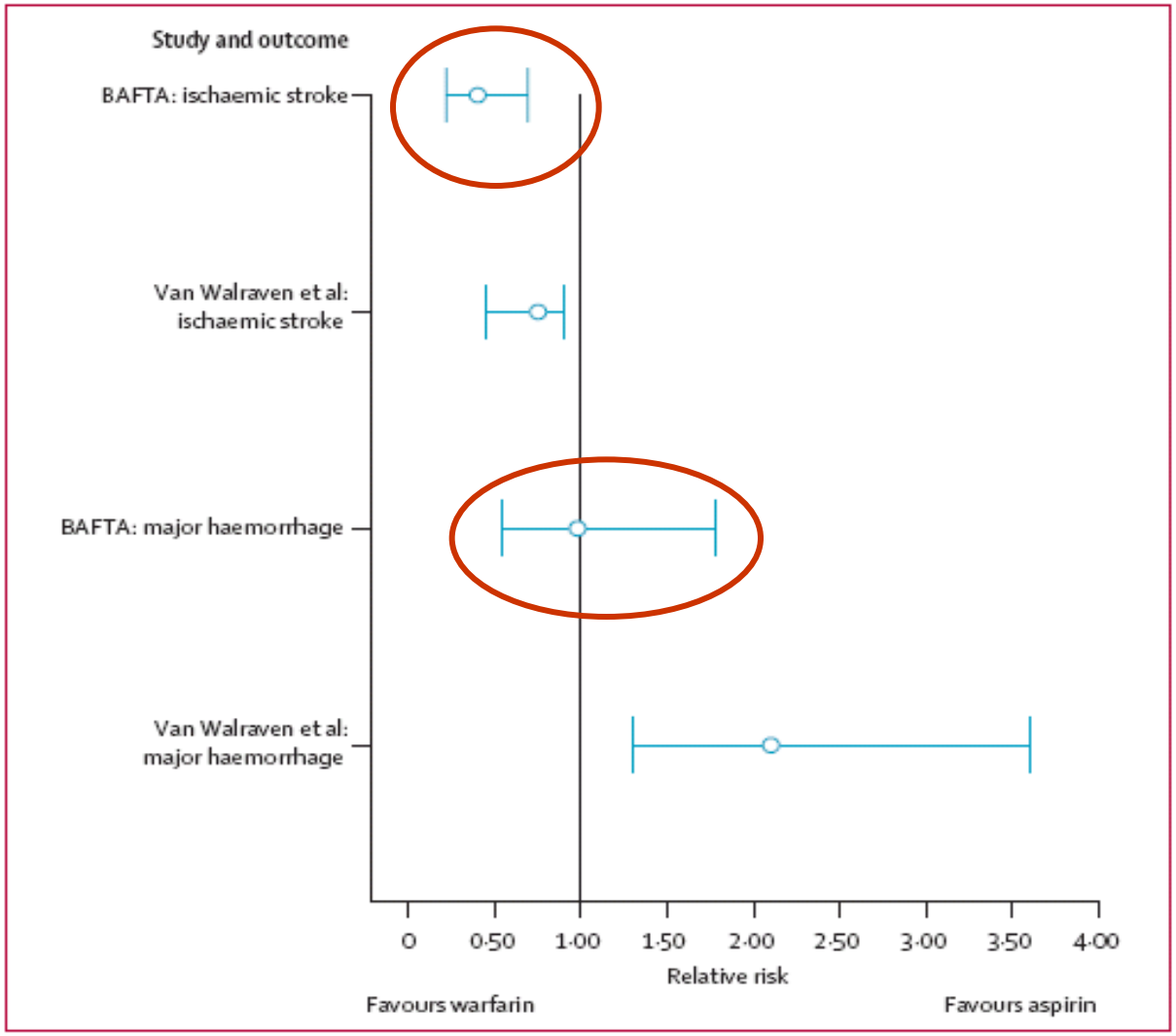


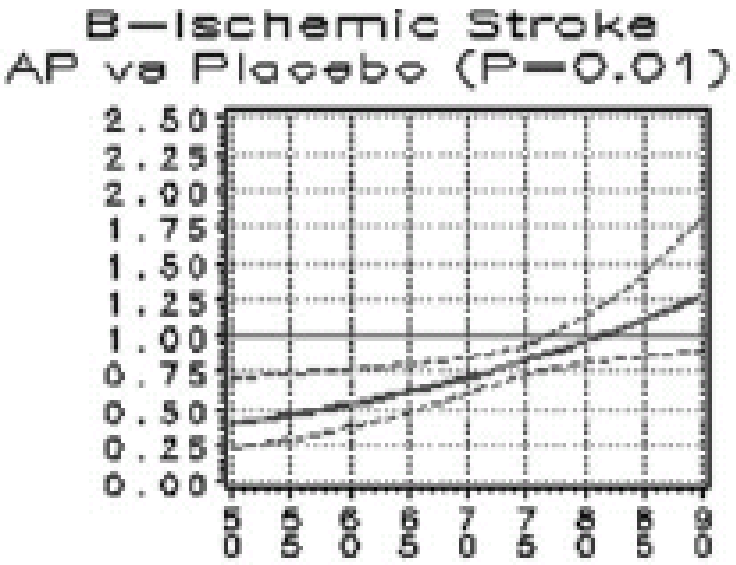
Figure 5: **Indirect comparison of results from BAFTA for ischaemic stroke and major haemorrhage with results from six other randomised trials of aspirin versus anticoagulation**
BAFTA results are compared with those from a meta-analysis by Van Walraven and colleagues[3] that used data from individual patients aged ≥75 years from six previous studies.

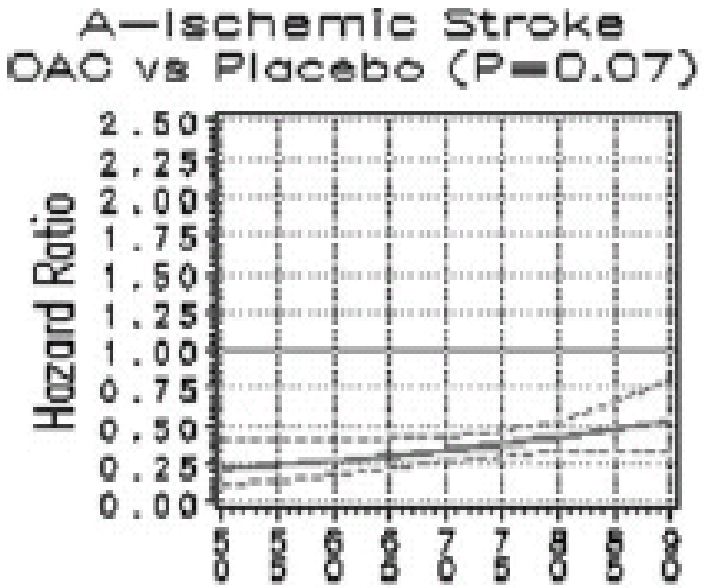
Mant et al; Lancet 2007

Effect of Age on Stroke Prevention Therapy in Patients With Atrial Fibrillation

The Atrial Fibrillation Investigators

Conclusions—As patients with atrial fibrillation age, the relative efficacy of AP to prevent ischemic stroke appears to decrease, whereas it does not change for OAC. Because stroke risk increases with age, the absolute benefit of OAC increases as patients get older. (*Stroke*. 2009;40:1410-1416.)





Stroke 2009

Methods

Patients ≥80 years suffering from atrial fibrillation (AF) or venous thromboembolism (VTE) were prospectively followed-up from the start of treatment.

Clinical characteristics of patients, quality of anticoagulation and adverse events occurring during follow-up were recorded.

Poli D et al Circulation, 2011

Clinical Characteristics of patients

N	4093
Males n (%)	1762 (43)
Median (IQR) age	84 (80-102)
Follow-up period (years)	9603
Mean follow-up period (years) (SD)	2.35 ±2.1
Indication for VKA treatment (%)	
Atrial fibrillation	3015 (73.7)
Venous thrombembolism	1078 (26.3)

Poli D et al Circulation, 2011

Bleeding events

Total, n (rate per 100 patient-y)	179 (1.87)
Mean age (range), y	85 (80–94)
Time elapsed from start of VKA treatment, mo	14.2 (0.1–109)
Median INR (range)	2.5 (1.0–13.8)
Bleeds with INR of 2.0–3.0, n (%)	147 (82.1)
Patients <85 y, n (rate per 100 patient-y)	115 (1.71)
Patients ≥85 y, n (rate per 100 patient-y)	64 (2.22)*

VKA indicates vitamin K antagonist; INR, international normalized ratio.

*Patients ≥85 versus <85 years of age: relative risk, 1.3; 95% confidence interval, 1.0 to 1.65; P=0.048.

Poli D et al Circulation, 2011

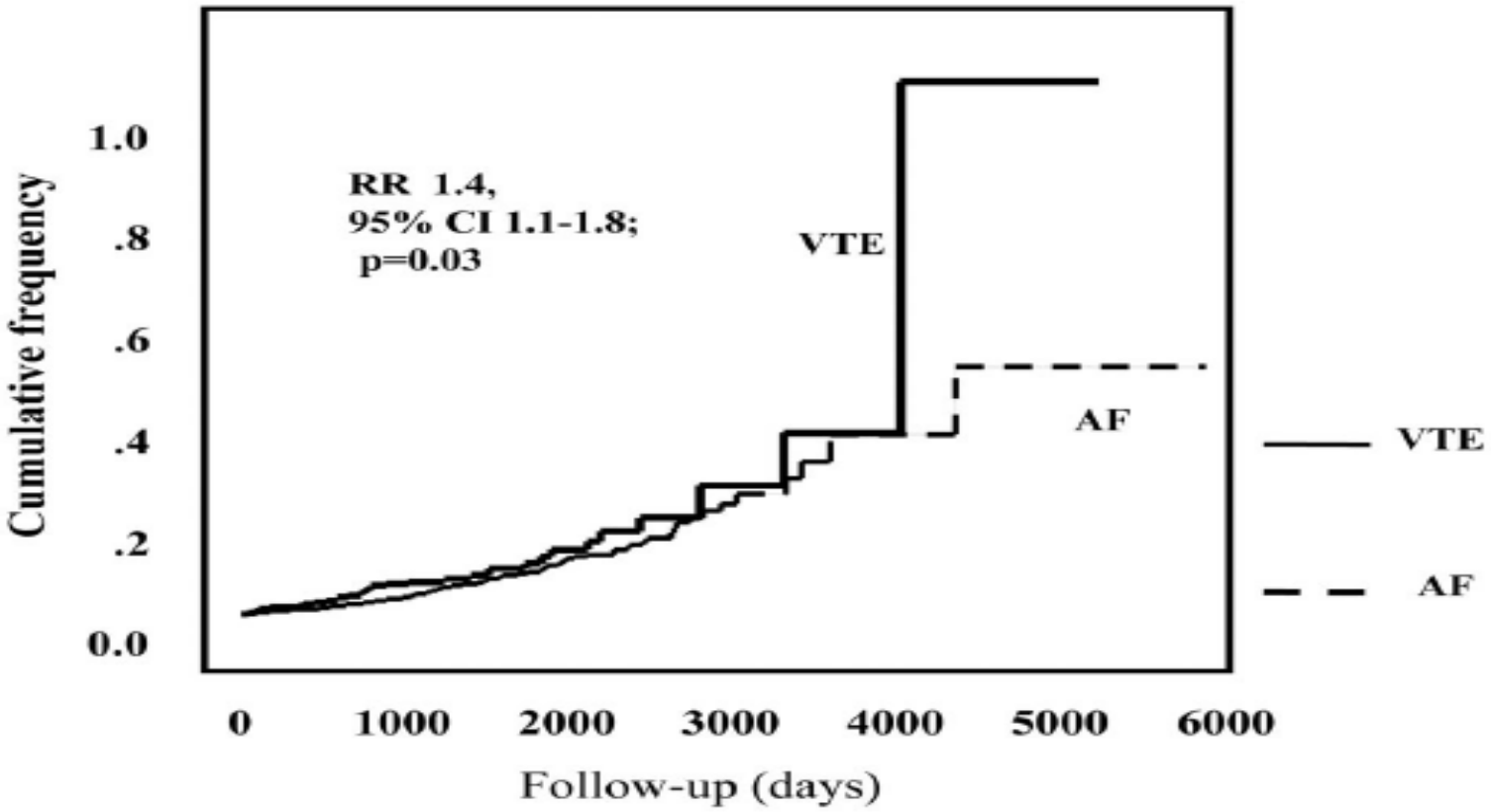


Figure. Cumulative frequency of major bleedings in patients on vitamin K antagonist treatment for venous thromboembolism (VTE) and atrial fibrillation (AF). RR indicates relative risk; CI, confidence interval.

Poli D et al Circulation, 2011

Risk Factors Associated With Bleeding Events: Competing-Risk Regression Analysis

	Hazard Ratio	95% CI	*P*
Male sex	1.42	0.98–2.08	0.06
Age >85 y	1.02	0.71–1.47	0.88
VTE vs AF	1.51	1.01–2.27	0.04
Hypertension	1.30	0.83–2.02	0.23
History of bleeding	5.46	3.29–9.05	<0.0001
Renal failure (serum creatinine ≥1.5 mg/dL)	1.10	0.67–1.79	0.69
Active cancer	2.41	1.47–3.95	<0.0001
History of falls	3.06	1.77–5.27	<0.0001
Comedications (≥3 drugs)	1.32	1.77–5.27	0.16

CI indicates confidence interval; VTE, venous thromboembolism; and AF, atrial fibrillation.

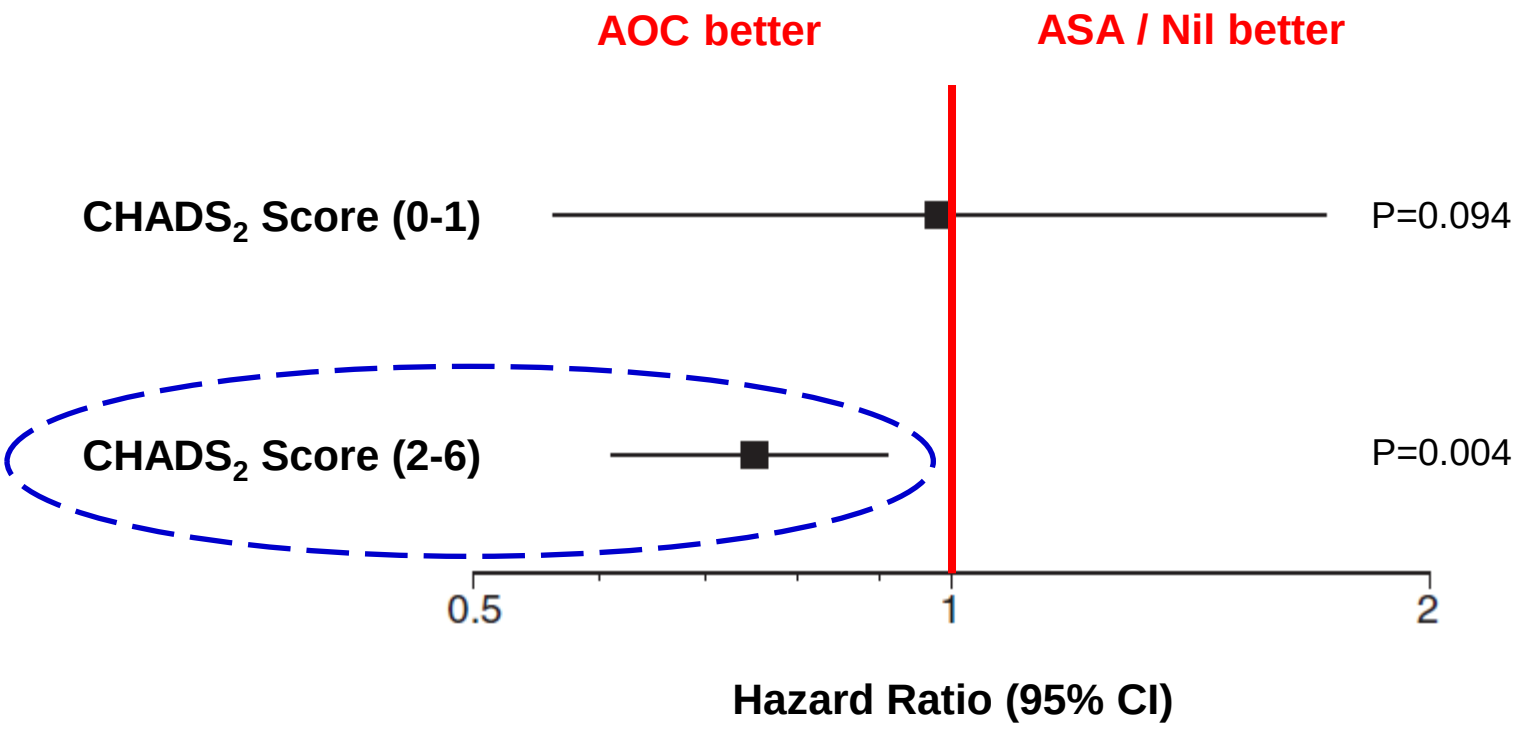
Poli D et al Circulation, 2011

Incidence of intracranial hemorrhage in patients with atrial fibrillation who are prone to fall

Composite outcome:

1. hospitalization for stroke
2. any hemorrhage (including ICH)
3. myocardial infarction
4. out of-hospital death

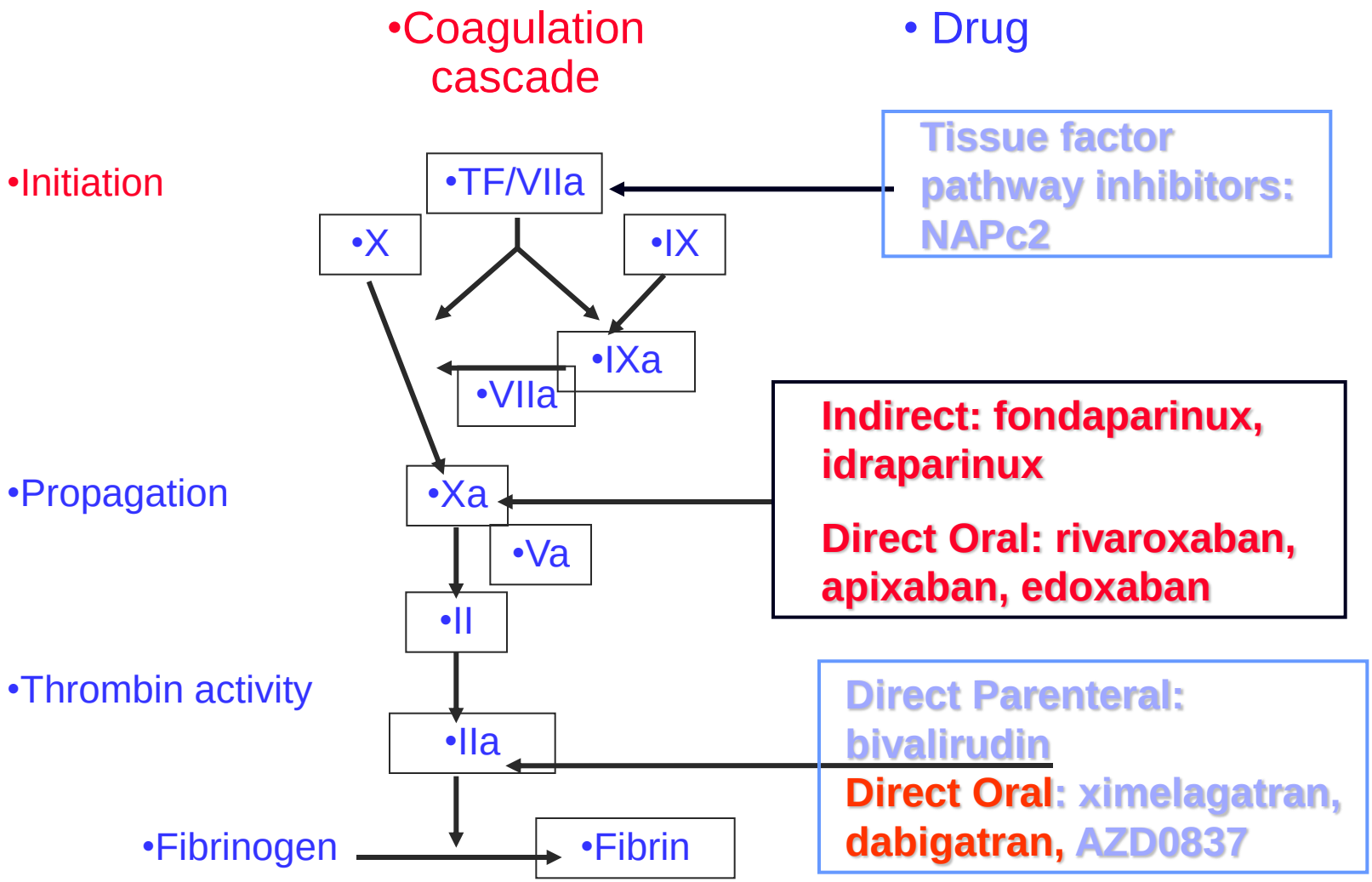
High-fall-risk pts (n=1245)



Sellers MB, 2011

Gage BF, 2005

New Anticoagulants



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

N Engl J Med 2009;361(12):1139-51

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

N Engl J Med August 10, 2011

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., John Eikelboom, M.B., B.S., Campbell Joyner, M.D., Hans-Christoph Diener, M.D., Ph.D., Robert Hart, M.D., Sergey Golitsyn, M.D., Ph.D., Greg Flaker, M.D., Alvaro Avezum, M.D., Ph.D., Stefan H. Hohnloser, M.D., Rafael Diaz, M.D., Mario Talajic, M.D., Jun Zhu, M.D., Prem Pais, M.B., B.S., M.D., Andrzej Budaj, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Petr Jansky, M.D., Patrick Commerford, M.B., Ch.B., Ru San Tan, M.B., B.S., Kui-Hian Sim, M.B., B.S., Basil S. Lewis, M.D., Walter Van Mieghem, M.D., Gregory Y.H. Lip, M.D., Jae Hyung Kim, M.D., Ph.D., Fernando Lanas-Zanetti, M.D., Antonio Gonzalez-Hermosillo, M.D., Antonio L. Dans, M.D., Muhammad Munawar, M.D., Ph.D., Martin O'Donnell, M.B., Ph.D., John Lawrence, M.D., Gayle Lewis, Rizwan Afzal, M.Sc., and Salim Yusuf, M.B., B.S., D.Phil., for the AVERROES Steering Committee and Investigators*

N Engl J Med 2011;364(9): 806-17

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

N Engl J Med August 28, 2011

Trial	RE-LY	ROCKET-AF	ARISTOTLE
n=	18,113 (3 arms)	14,264	18,201
Drug (Brand name)	Dabigatran (Pradaxa) 150 mg bid	Rivaroxaban (Xarelto) 20 mg qd	Apixiban (Eliquis) 5 mg bid
Trial design, randomized	Open label	Double blind, double dummy	Double blind, double dummy
Mean Age (yrs)	71.5	73	70
Efficacy % vs warfarin (CVA or SE)	1.71 vs. 1.11 p<.001 NNT = 167	2.42 vs. 2.12 p=.12	1.60 vs. 1.27 p < .001 NNT = 303
Major Bleeding % **ICH %**	3.57 vs. 3.32 p=0.31 0.74 vs. 0.3 p< .001	3.45 vs. 3.6 p=0.58 0.74 vs. 0.49 p=.019	3.09 vs. 2.13 p<.001 0.47 vs. 0.24 p< .001
Conclusion vs. warfarin	**Superior efficacy, similar bleeding, less ICH**	**Non-inferior on efficacy and safety measures**	**Superior efficacy, less major and ICH, lower mortality**

Health Services and Outcomes Research

Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation

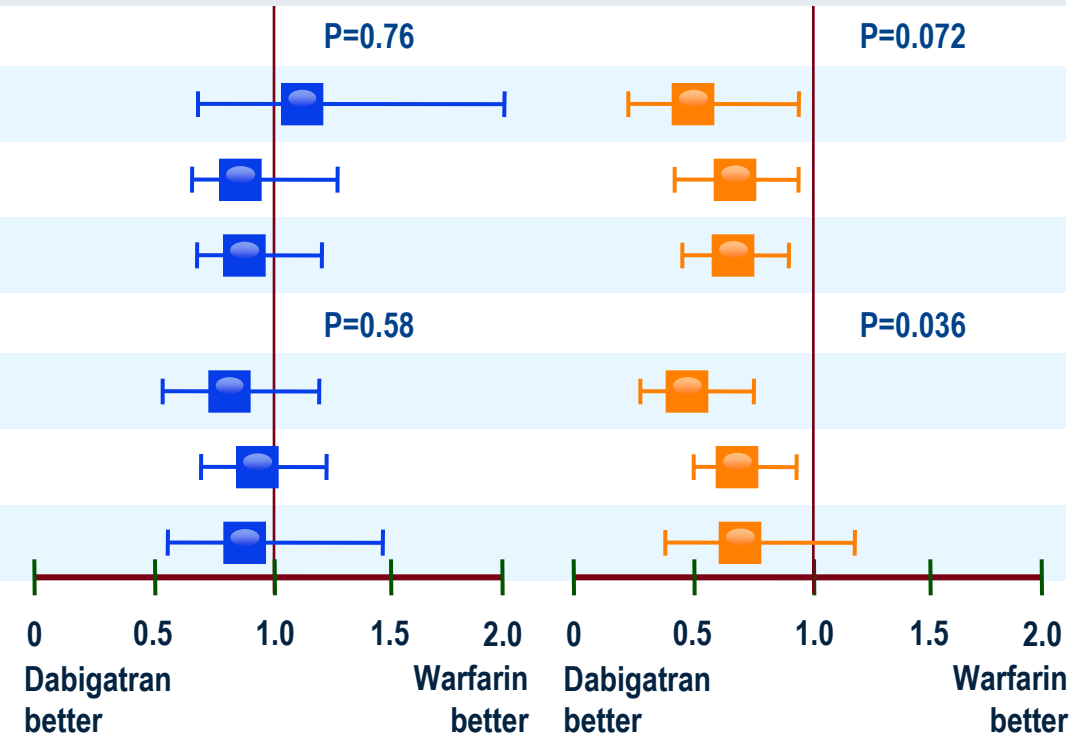
An Analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Trial

John W. Eikelboom, MBBS; Lars Wallentin, MD; Stuart J. Connolly, MD; Mike Ezekowitz, MD; Jeff S. Healey, MD; Jonas Oldgren, MD; Sean Yang, BComSc; Marco Alings, MD; Scott Kaatz, DO; Stefan H. Hohnloser, MD; Hans-Christoph Diener, MD; Maria Grazia Franzosi, PhD; Kurt Huber, MD; Paul Reilly, MD; Jeanne Varrone, MD; Salim Yusuf, MD

Circulation 2011;123:2363-72

AGE AND RENAL FUNCTION SUBGROUP ANALYSIS:
STROKE AND NON-CNS EMBOLISM

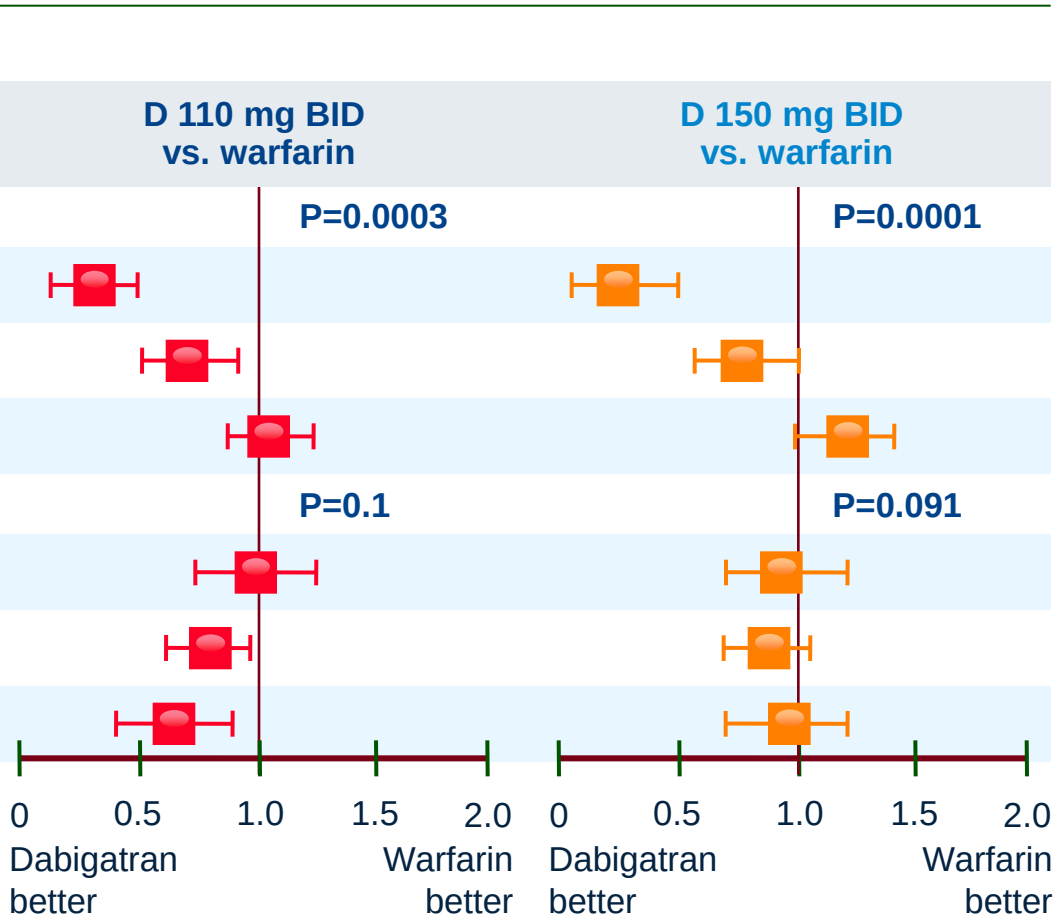
	Annual rate (%)		
	D 110 mg BID	D 150 mg BID	Warfarin
Age (yrs)			
<65	1.48	0.69	1.35
65–74	1.26	0.98	1.43
≥75	1.87	1.43	2.1
Creatinine clearance (mL/min)			
30–50	2.26	1.33	2.65
51–80	1.65	1.24	1.76
>80	0.92	0.72	1



BID = twice daily; CNS = central nervous system; D = dabigatran; P values for interaction.
Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation outside the US and Canada.
Healey JS, et al. ACC 2010; abstr 1078-120.

AGE AND RENAL FUNCTION SUBGROUP ANALYSIS: MAJOR BLEEDING

	Annual rate (%)		
	D 110 mg BID	D 150 mg BID	Warfarin
Age (yrs)			
<65	0.76	0.79	2.32
65–74	2.12	2.45	3.08
≥75	4.21	4.81	4.09
Creatinine clearance (mL/min)			
30–50	5.07	4.85	5.17
51–80	2.62	3.04	3.44
>80	1.36	1.88	2.18



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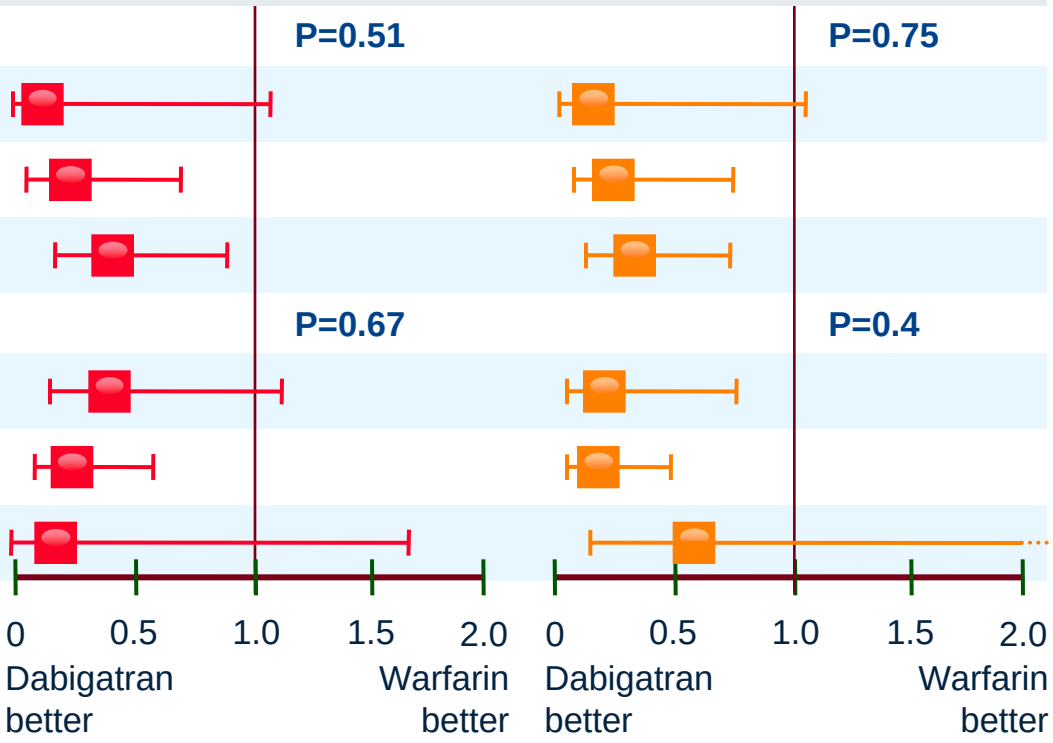
Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation outside the US and Canada.
Healey JS, et al. ACC 2010; abstr 1078-120.

AGE AND RENAL FUNCTION SUBGROUP ANALYSIS: HAEMORRAGIC STROKE

	Annual rate (%)		
	D 110 mg BID	D 150 mg BID	Warfarin
Age (yrs)			
<65	0.05	0.05	0.38
65–74	0.08	0.08	0.31
≥75	0.2	0.15	0.47
Creatinine clearance (mL/min)			
30–50	0.26	0.12	0.58
51–80	0.12	0.09	0.47
>80	0.03	0.08	0.13



FDA approves dabigatran for stroke prevention, embolism, in AF patients

The drug will be available in two doses: 75 mg and 150 mg

EMA approves PRADAXA with the flexibility of two dosing regimens

Overall the 150 mg bid dose is recommended; the 110 mg bid dose is indicated for elderly patients aged 80 years at higher risk of bleeding and for those taking verapamil

INVITED COMMENTARY

New Anticoagulant Drugs Among Elderly Patients Is Caution Necessary?

Arch Intern Med 2011