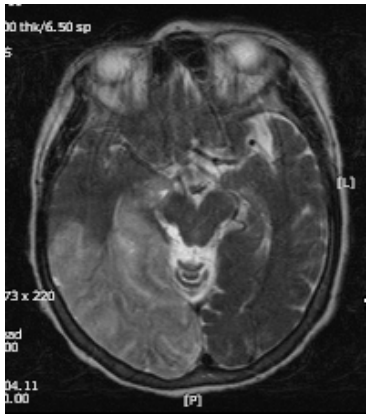


Evaluating **Stroke Risk** *in **Atrial Fibrillation***

오동진
한림의대의료원 강동성심병원
심장내과

To be declared……

- *Investigator* of RE-LY and RELY-ABLE study (*Boehringer Ingelheim*)
- *Investigator* of Borealis-AF study (*Sanofi-aventis*)
- *Investigator* of IV Vernakalant study(MK6621-PN010)(Merck)

- *Attend* the Symposium *sponsored by Boehringer Ingelheim* at Jeju island.
- *Attend* the round table meeting *sponsored by Bayer Healthcare*, 2 times.

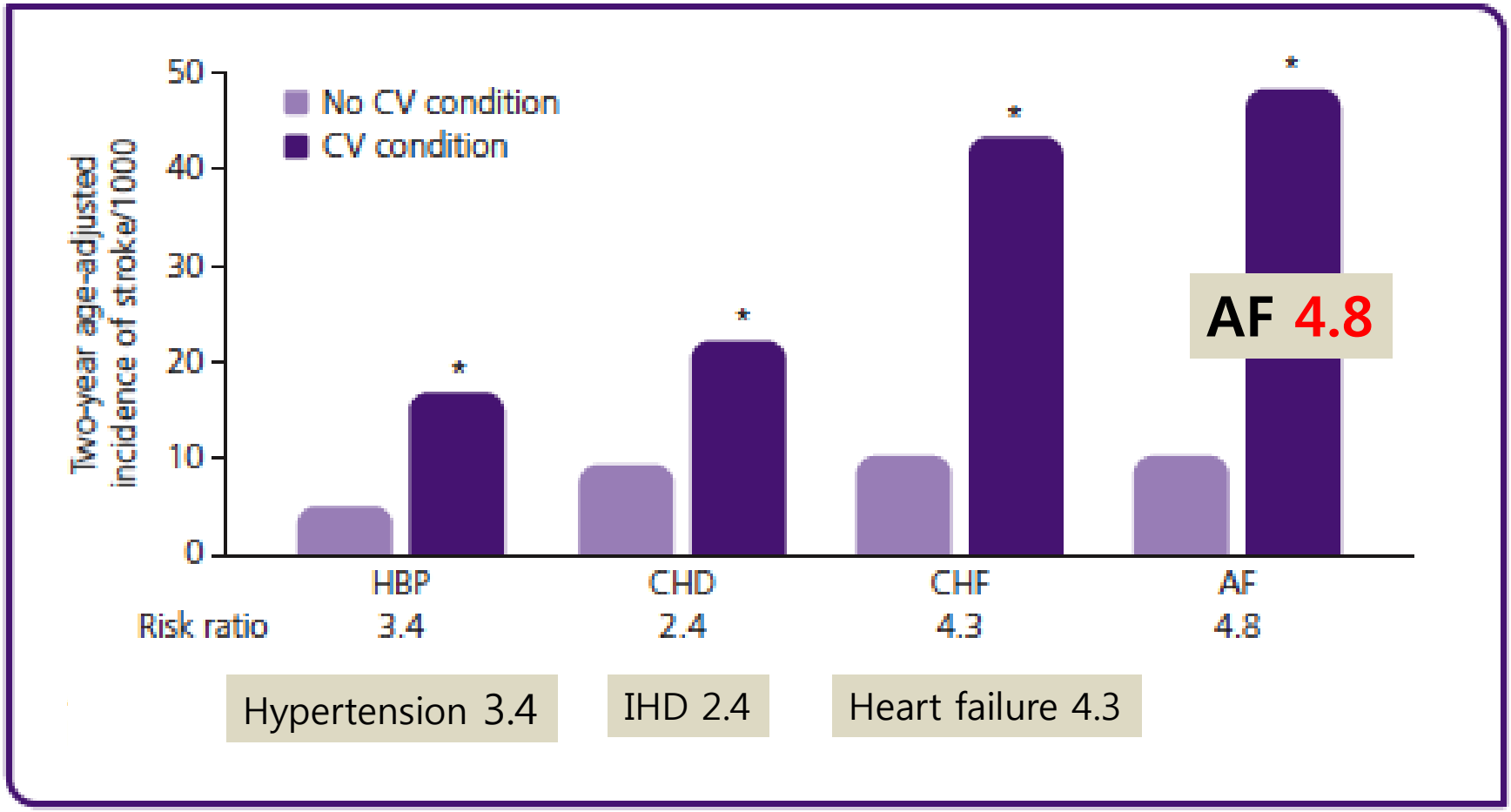
Resources *in talk*

- **2010 ESC Guidelines** for the management of atrial fibrillation(EHRA/EACTS)

- **2011 ACCF/AHA/HRS Focused Updates** incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of Patients with Atrial Fibrillation

- **Focused 2012 update of the Canadian** Cardiovscular Society Atrial Fibrillation Guideleines: Recommendations for Stroke Prevention and Rate/Rhythm Control

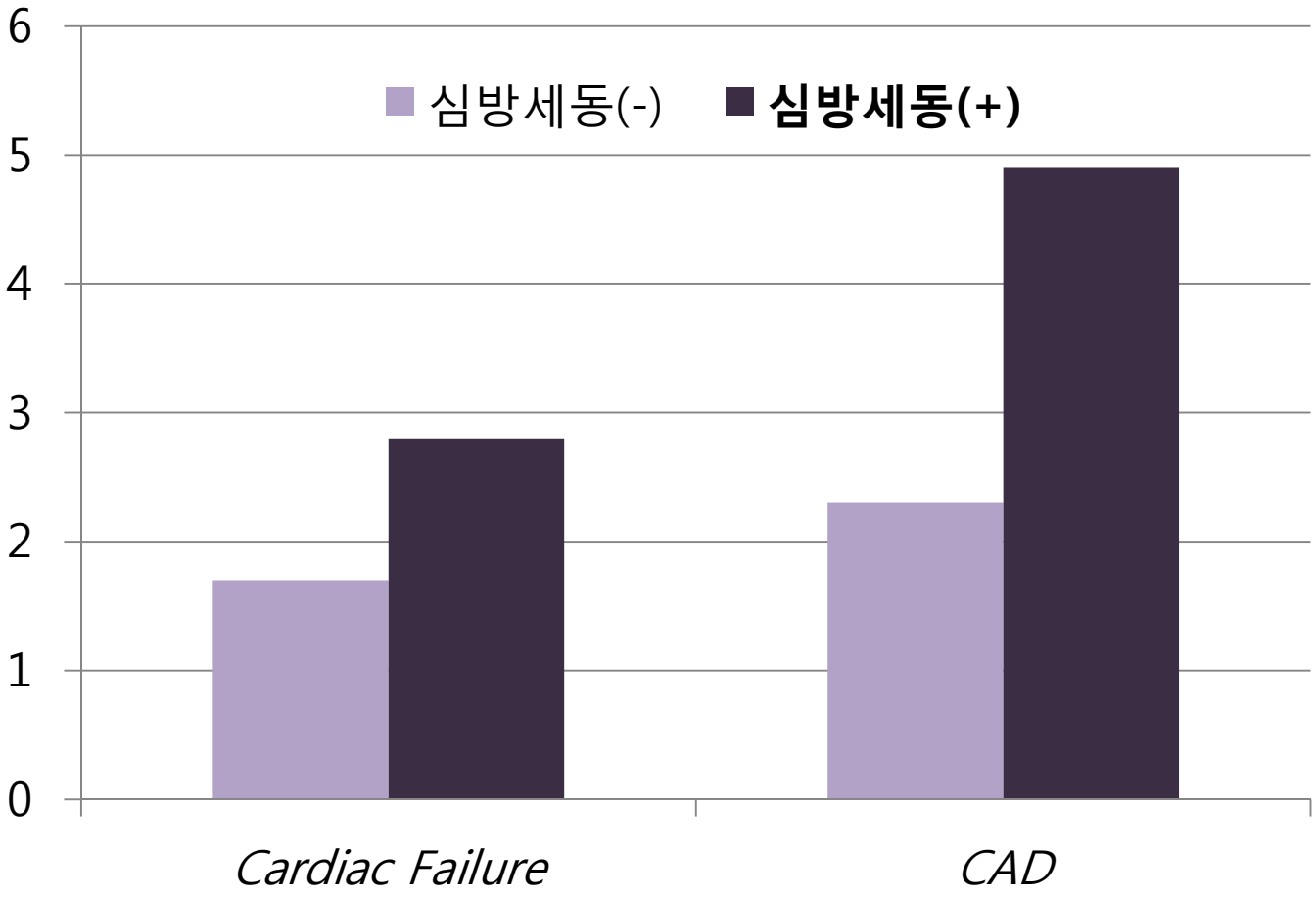
AF *as an Independent* Risk Factor ***for Stroke***



(5,070 participants after 34 years of follow-up, *The Framingham Study*)

(Stroke, 1991 Wolf)

Excess risk of stroke associated with AF



Stroke 1991 Wolf (The Framingham Study)

*PAR: Population Attributable Risk

(2010 Lancet, the INTERSTROKE study)

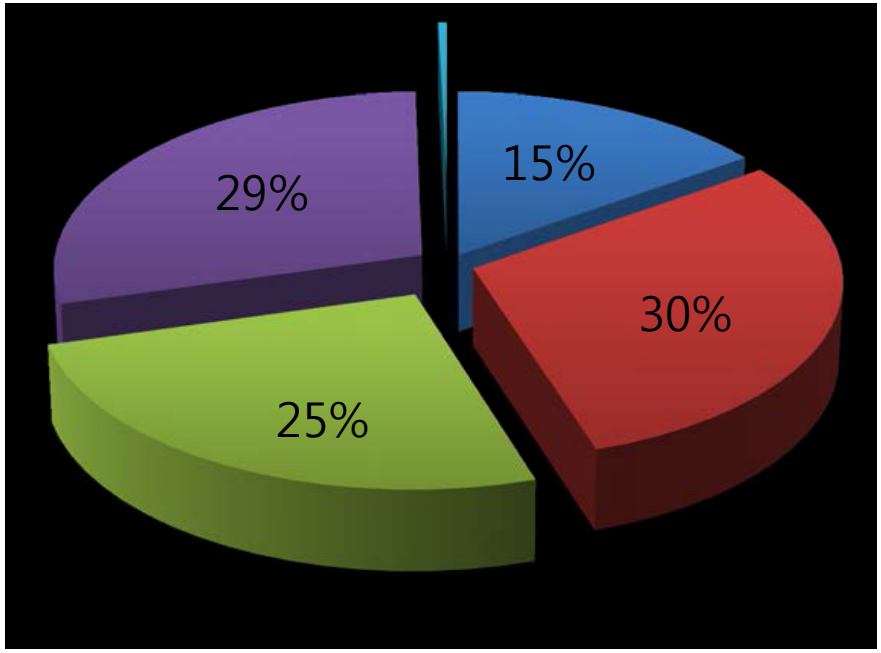
Risk factors *for ischemic* Stroke

	*PAR**	*Odds Ratio*
고혈압	**45.2%** (40.3-50.0)	**3.14** (2.67-3.71)
고지혈증	35.2% (25.5-46.3)	1.30 (1.01-1.67)
규칙적인 운동습관	29.4% (14.5-50.5)	0.68 (0.51-0.91)
복부비만	26.0% (17.7-36.5)	1.34 (1.10-1.64)
흡연	21.4% (17.5-25.8)	2.32 (1.91-2.81)
식이습관	17.3% (9.4-29.6)	1.29 (1.06-1.57)
스트레스	11.5% (5.9-21.6)	2.77 (2.23-3.45)
Cardiac Causes #	**8.5%** (6.4-11.2)	**2.74** (2.03-3.72)
당뇨	7.9% (5.1-12.3)	1.06 (1.29-1.99)
절제된 음주	1.0% (0.0-83.8)	0.79 (0.63-1.00)

(***Cardioembolic Stroke*** ***25%*** *in high-income country*)

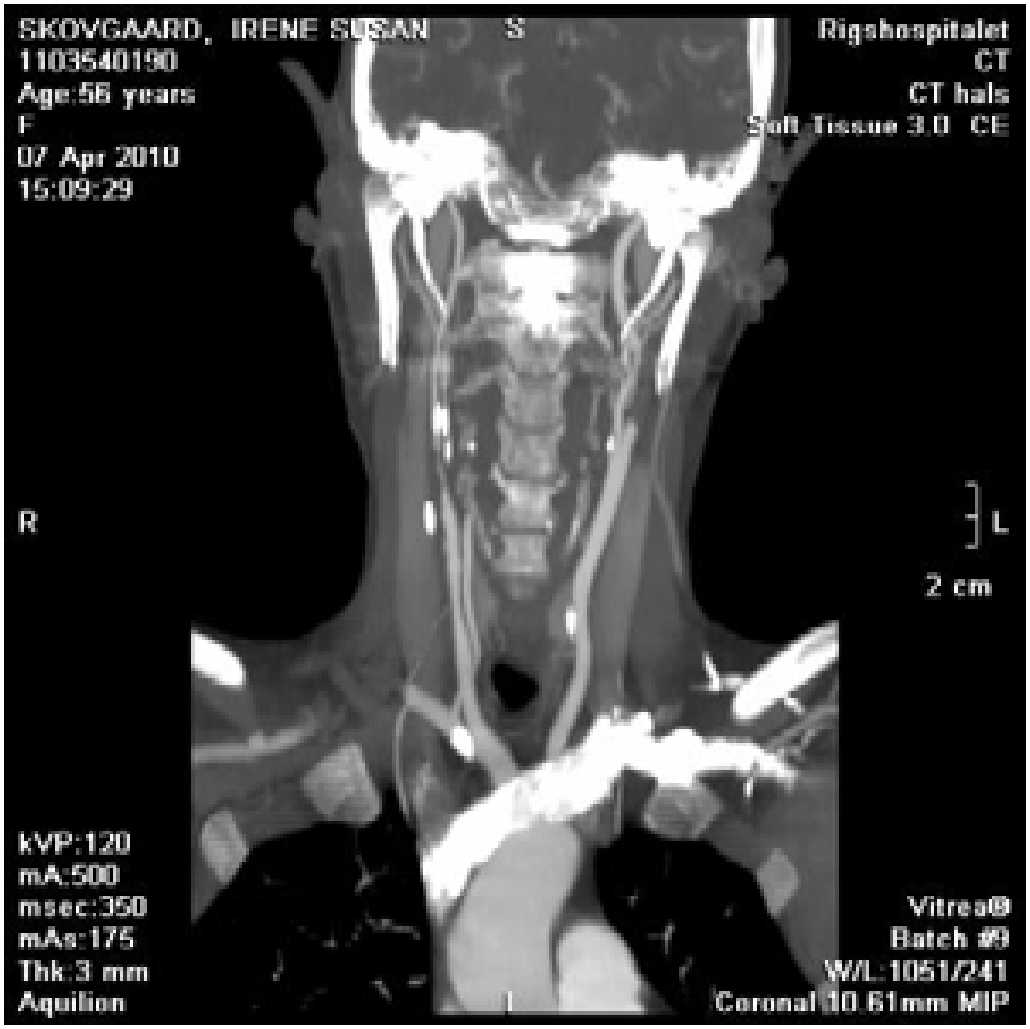
#Cardiac causes; AF/AFL, previous MI, Rheumatic/Prosthetic Valve Disease

(non-hemorrhagic) *Ischemic* Stroke

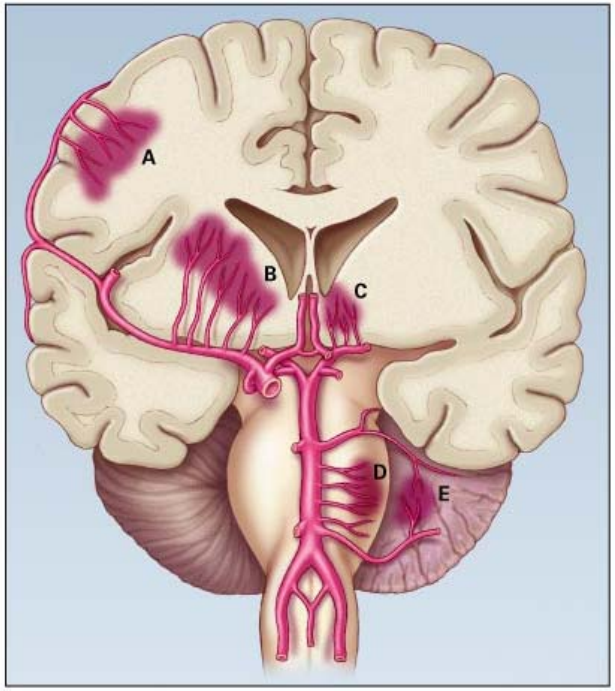


Large Vessel	15%
Cardioembolism	30%
Small vessel	25%
Cryptogenic	29%
Others	<1%

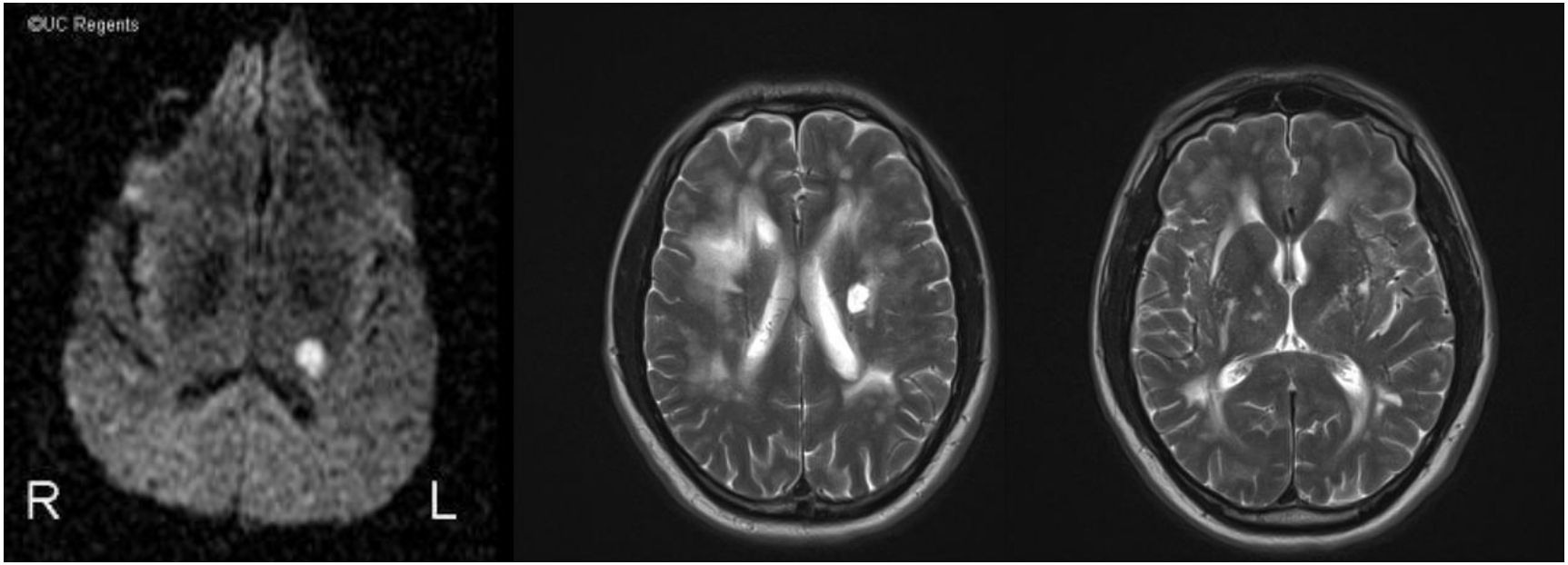
(Stroke 2001, Kolominsky-Rabas PL)



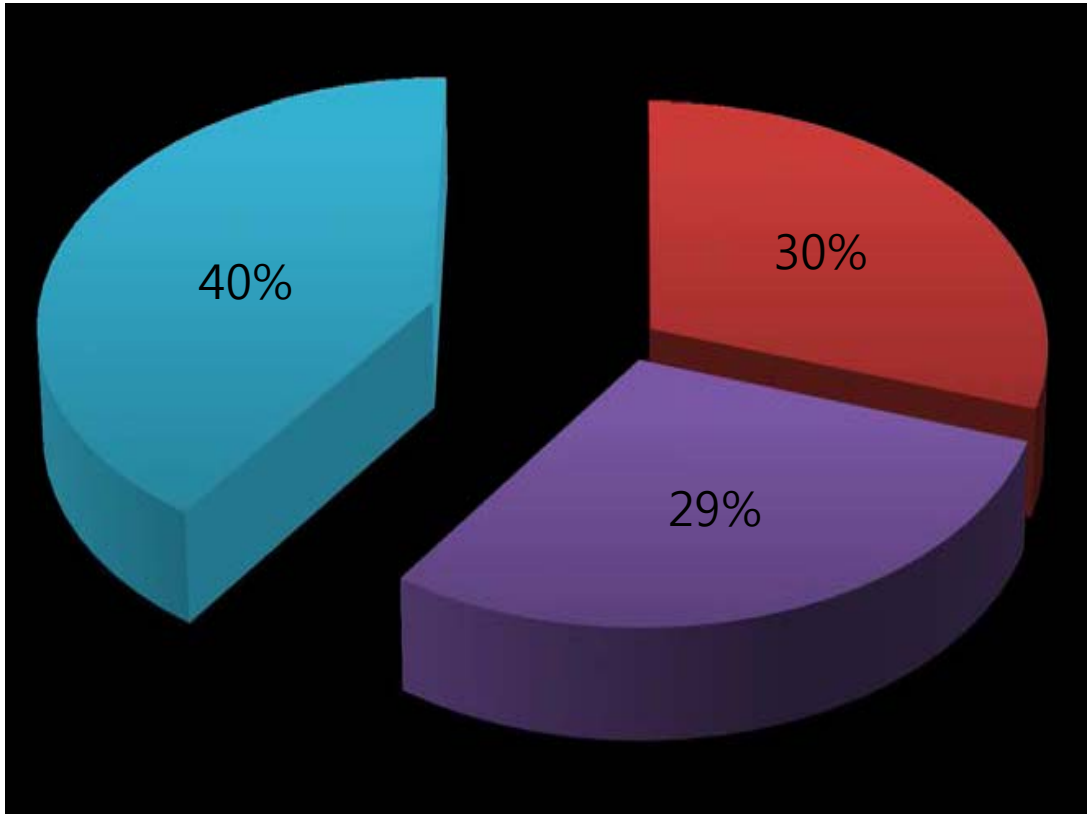
Carotid-embolic stroke
"large vessel" *(15%)*



Small vessel related "lacunar" stroke *(25%)*



1/5 *of stroke related with* AF



Cardioembolism(30%)
>50% AF
(Schneck & Lai 2009)

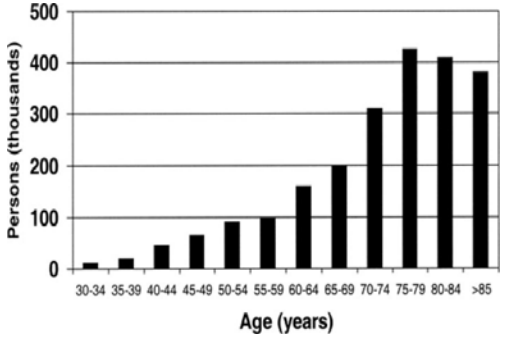
Cryptogenic(29%)
~20% AF #

Other etiologies(40%)
(large & small Vessel disease)

#: Prolonged Monitoring after stroke
(Sobocinski 2012 SURPRISE 2012 Cutter (in prep))

(Stroke 2001, Kolominsky-Rabas PL)

- AF is **Aging process**

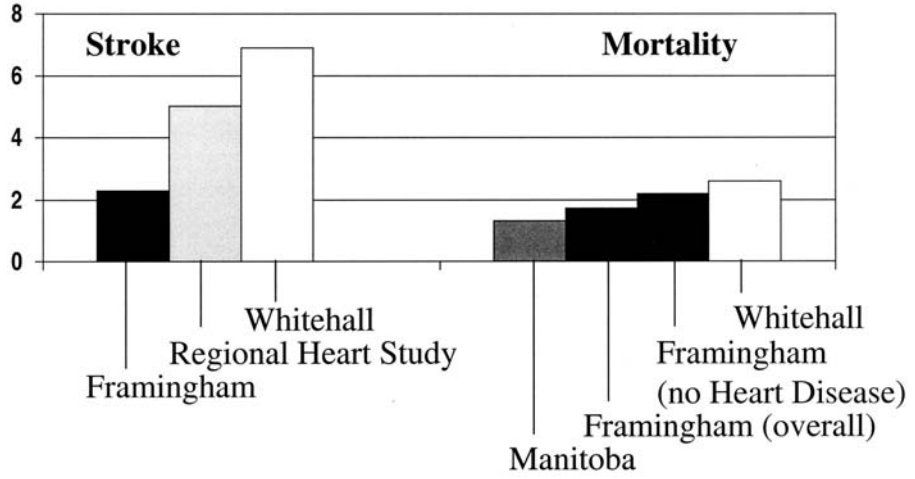


- **Diverse etiology**

Atrial pressure elevation
- **valve disease-** Mitral/tricuspid, Semilunar valvular abnormalities (causing ventricular hypertrophy)
- **Myocardial** disease (primary or secondary, leading to systolic or diastolic dysfunction)
- Systemic or pulmonary **Hypertension** (pulmonary embolism)
- Intracardiac tumors or thrombi

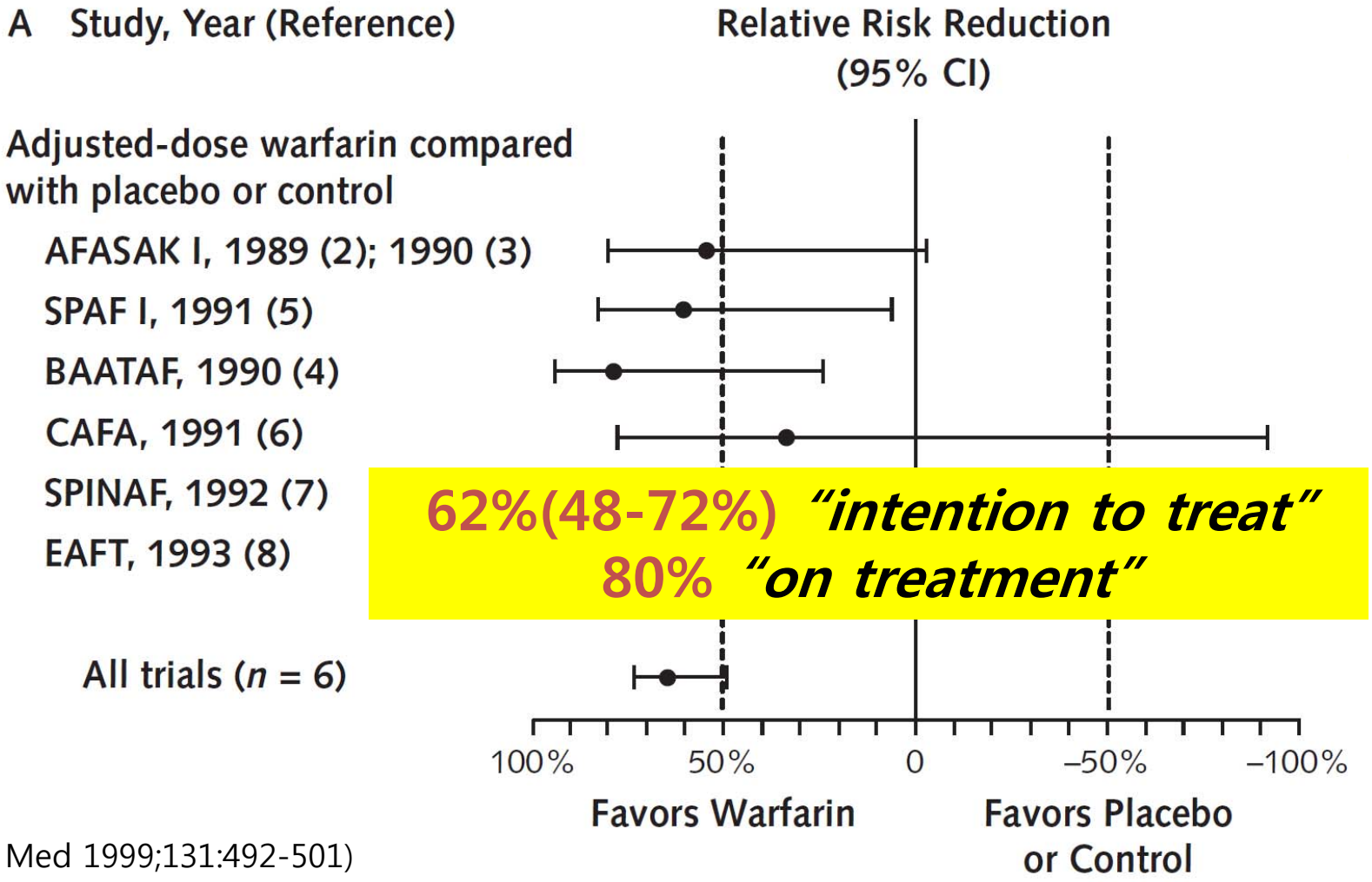
Atrial ischemia **- Coronary artery disease**
Inflammatory /infiltrative atrial disease **– Pericarditis**, Amyloidosis, Myocarditis, Age-induced atrial fibrotic changes
Drugs **– Alcohol**, Caffeine
Endocrine **disorders –Hyperthyroidism**, Pheochromocytoma
Changes in *autonomic tone* - Increased parasympathetic activity, Increased sympathetic activity
Primary or metastatic disease in or adjacent to the atrial wall
Postoperative **-**Cardiac, pulmonary, or esophageal
Congenital **heart disease**
Neurogenic **-** Subarachnoid hemorrhage, Nonhemorrhagic, major stroke
Familial **AF**
Idiopathic **(lone AF)**

- **Stroke/Mortality** risk



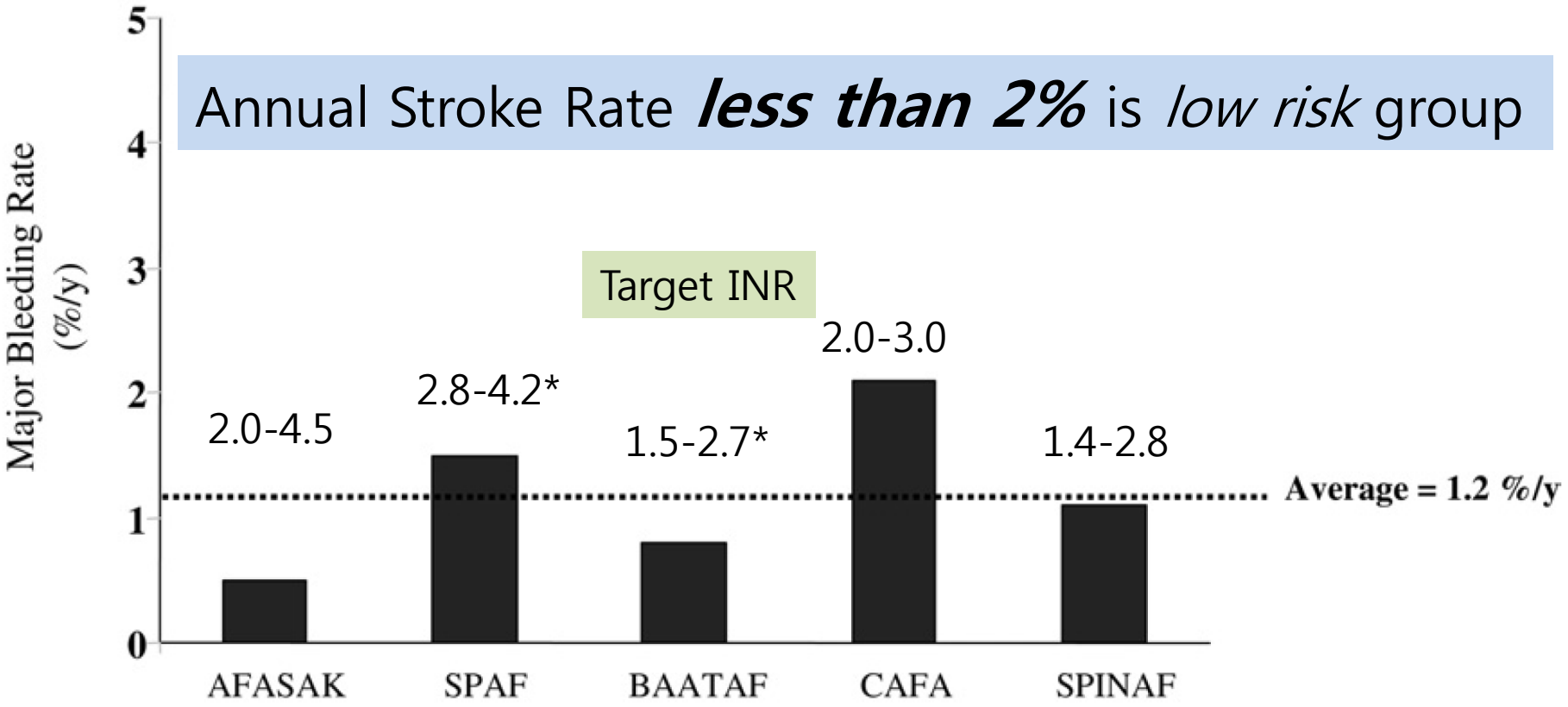
Most common cardiac arrhythmia ***needed to treat***

Anticoagulation *in nonvalvular AF*



(Ann Intern Med 1999;131:492-501)

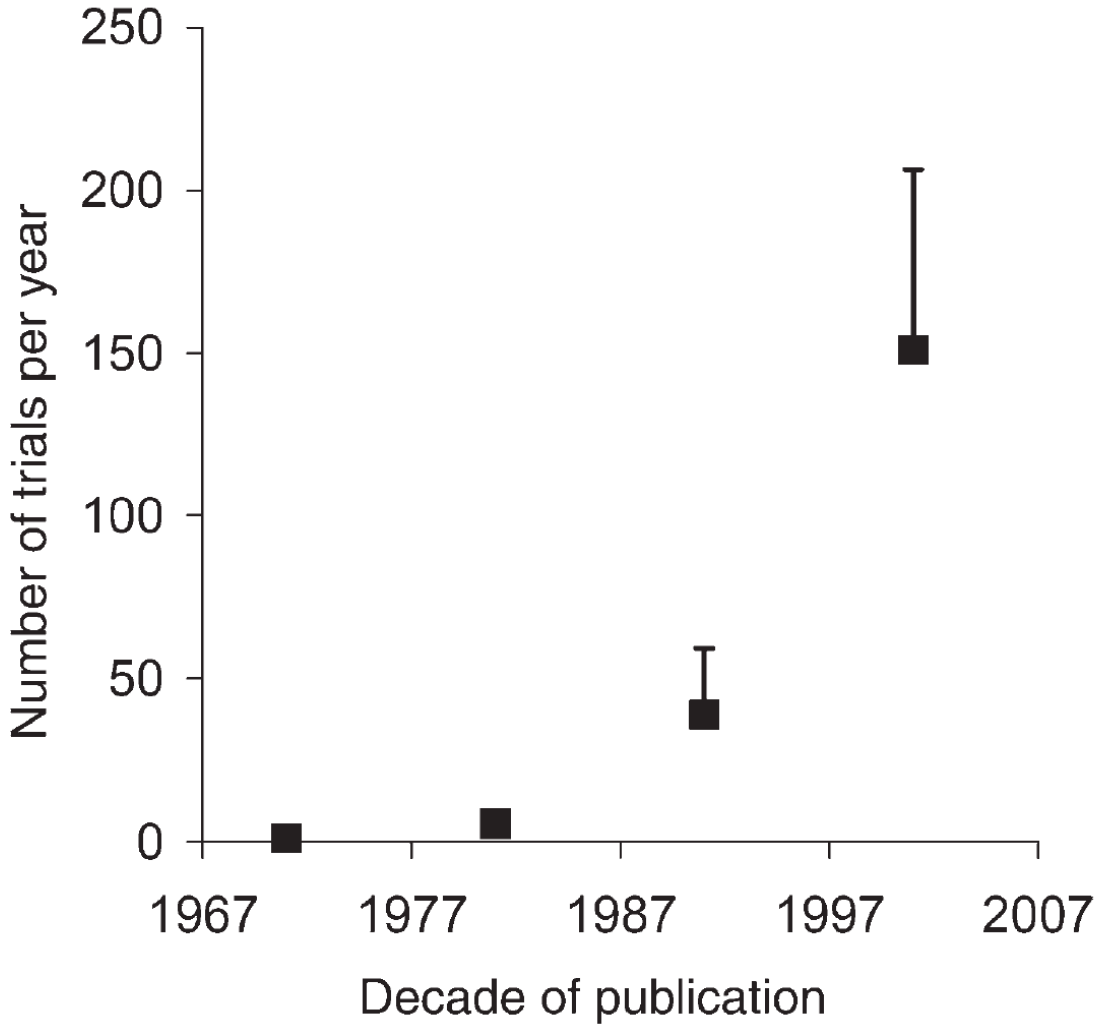
Major Bleeding Rate in RCT



* : *Prothrombin Time Ratio* were used with INR equivalents

Number of randomized trials in AF

published in Medline



2011 ACCF/AHA/HRS *Focused Updates*

Class I.

Antithrombotic therapy to prevent thromboembolism *is recommended* ***for all patients with AF****, except* those with *lone AF* or contraindication *(level of evidence: A)*

Class III.

Long-term anticoagulation with a vitamin K antagonist *is not recommended* for primary prevention of stroke in patients *below the age of 60y* without heart disease (*lone AF*) or any *risk factors* for thromboembolism *(level of evidence: C)*

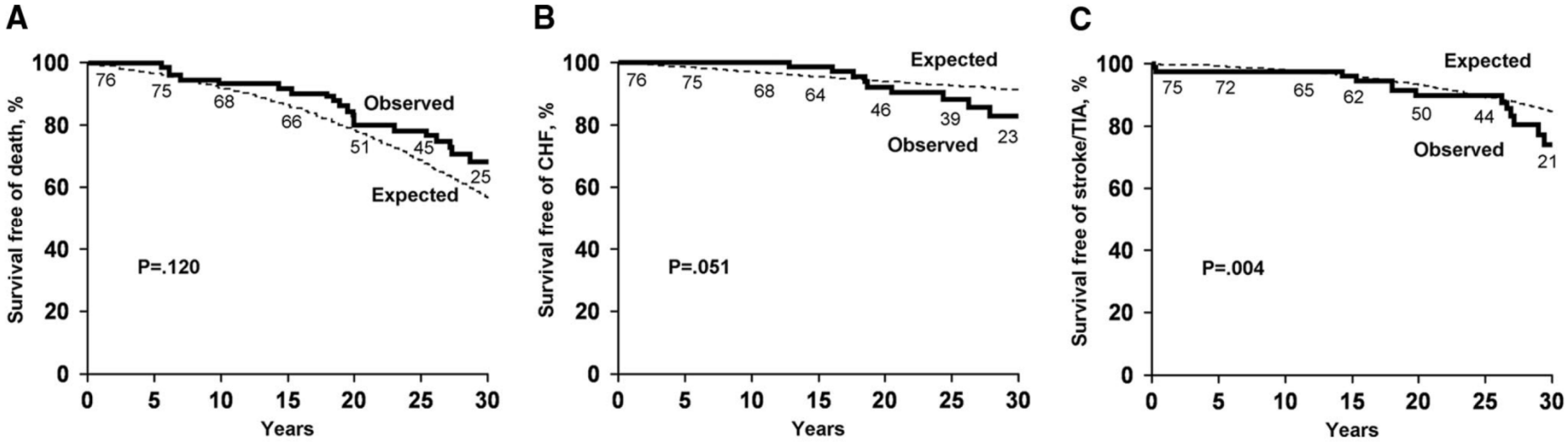
Lone AF

(long-term outcomes with aging)

Survival

CHF

Stroke *or* **TIA**



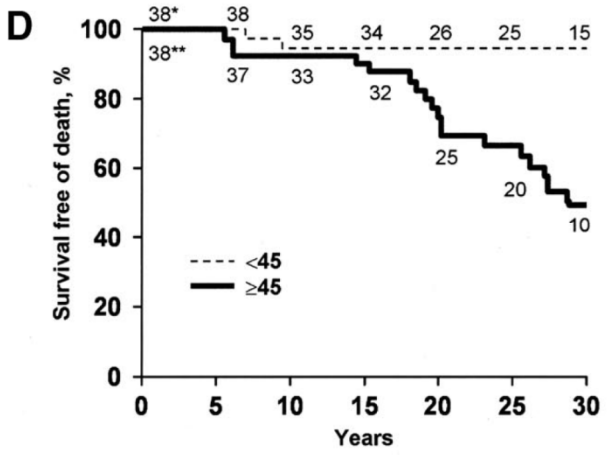
(Olmsted county, Minnesota)

(Circulation 2007, Jahangir)

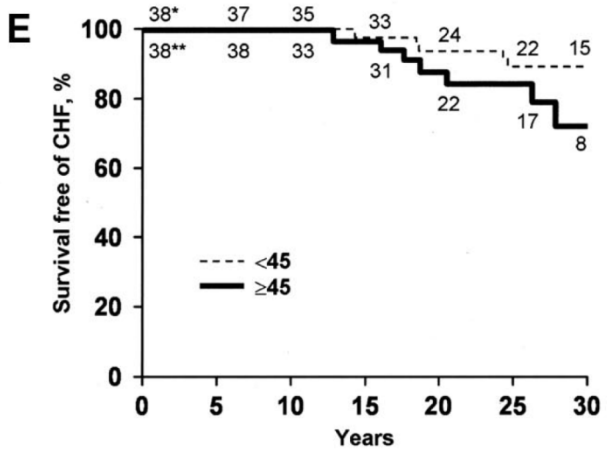
Lone AF

(long-term outcomes with aging)

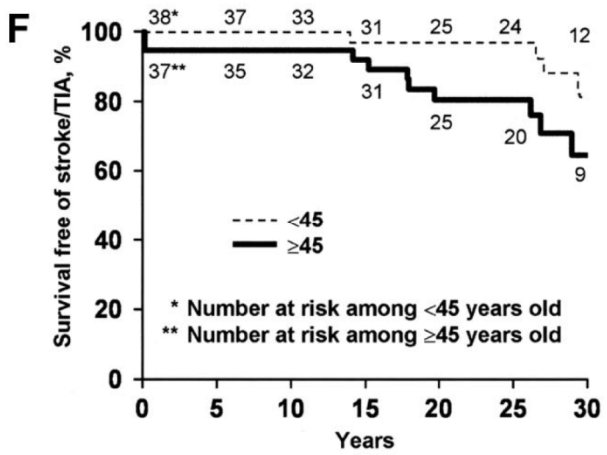
Survival



CHF



Stroke *or* **TIA**

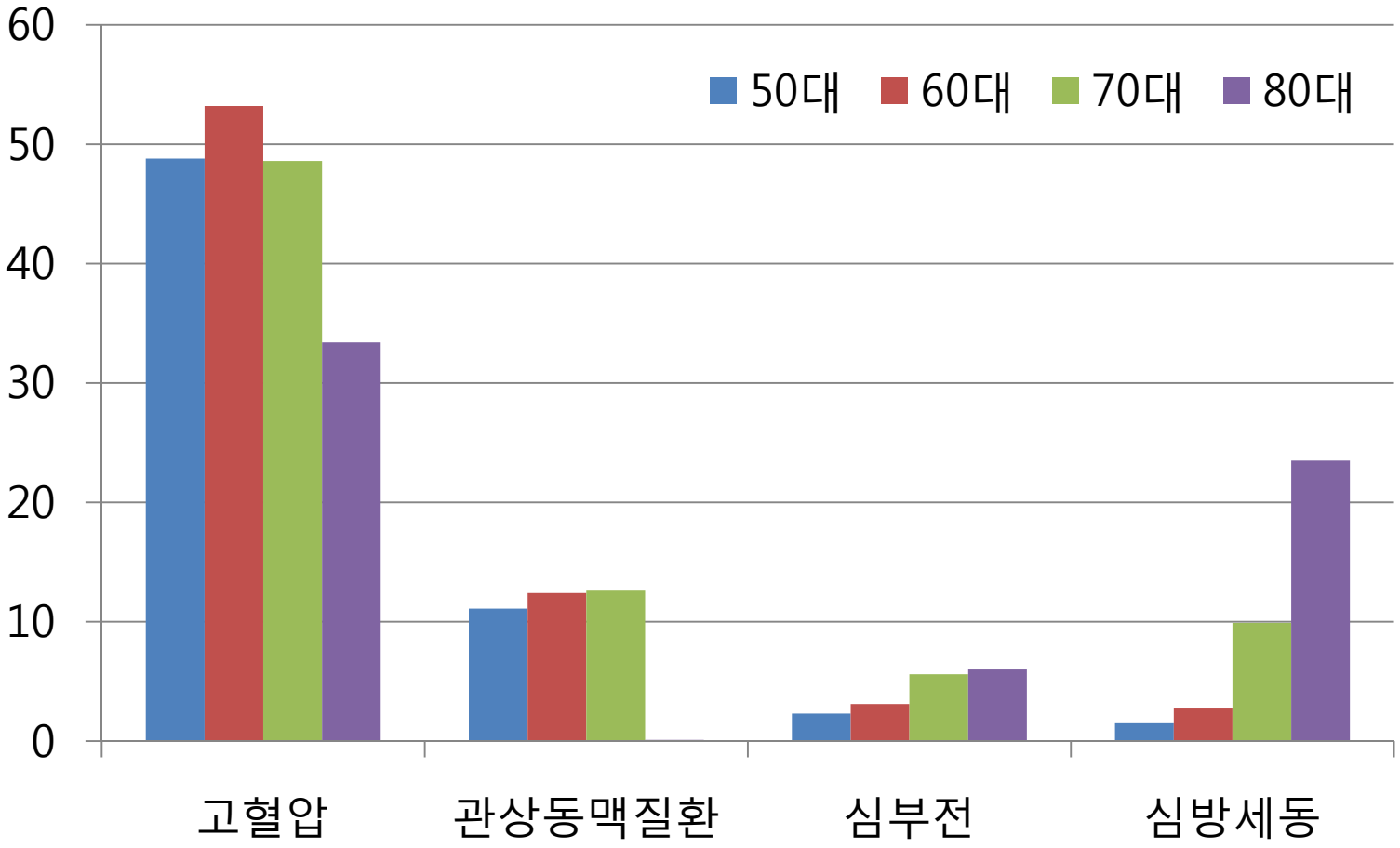


Age *when AF was diagnosed* determined **the prognosis**

(Olmsted county, Minnesota)

(Circulation 2007, Jahangir)

Attributable Risk of Stroke ***by Age***



Stroke 1991 Wolf (The Framingham Study)

Independent predictors of Stroke

in patients with Atrial Fibrillation (systemic review)

	Relative Risk	***Absolute Stroke Rate*** *(observed per year)*
Prior stroke/TIA	2.5 (1.8-3.5)	6-9%
Increasing ***Age***	1.5 (1.3-1.7*)/decade*	1.5-3% *(for >75)*
History of ***HT***	2.0 (1.6-2.5)	1.5-3%
DM	1.7 (1.4-2.0)	2.0-3.5%

Female sex: inconsistently associated
Heart failure, coronary artery disease: inconclusive

(Hart. 2007 Neurology)

Background of ***CHADS$_2$*** *score*

- AFI (*Atrial Fibrillation Investigators*) scheme
  - Hypertension, Prior ischemia, Women > 75years, Recent CHF or LV<25%, SBP>160mmHg
- SPAF (*Stroke Prevention in AF*) III scheme
  - Age >65 years, Prior ischemia, hypertension, DM
- CHADS2 (*a new stroke risk index*)
  - Amalgamate the AFI and SPAF classification schemes
  - Recent CHF, hypertension, age>75, DM, history of stroke or TIA

(Gage JAMA 2001)

Classification Scheme	Scheme Definition
Stroke Prevention in Atrial Fibrillation trial†	
Low risk	None of the following risk factors
Moderate risk	Hypertension
High risk	Prior ischemia, women >75 years, recent CHF or LV ≤25%, SBP >160 mm Hg
Atrial Fibrillation Investigators‡	
Low risk	None of the following risk factors
Moderate risk	Age >65 years
High risk	Prior ischemia, hypertension, DM

(Gage JAMA 2001)

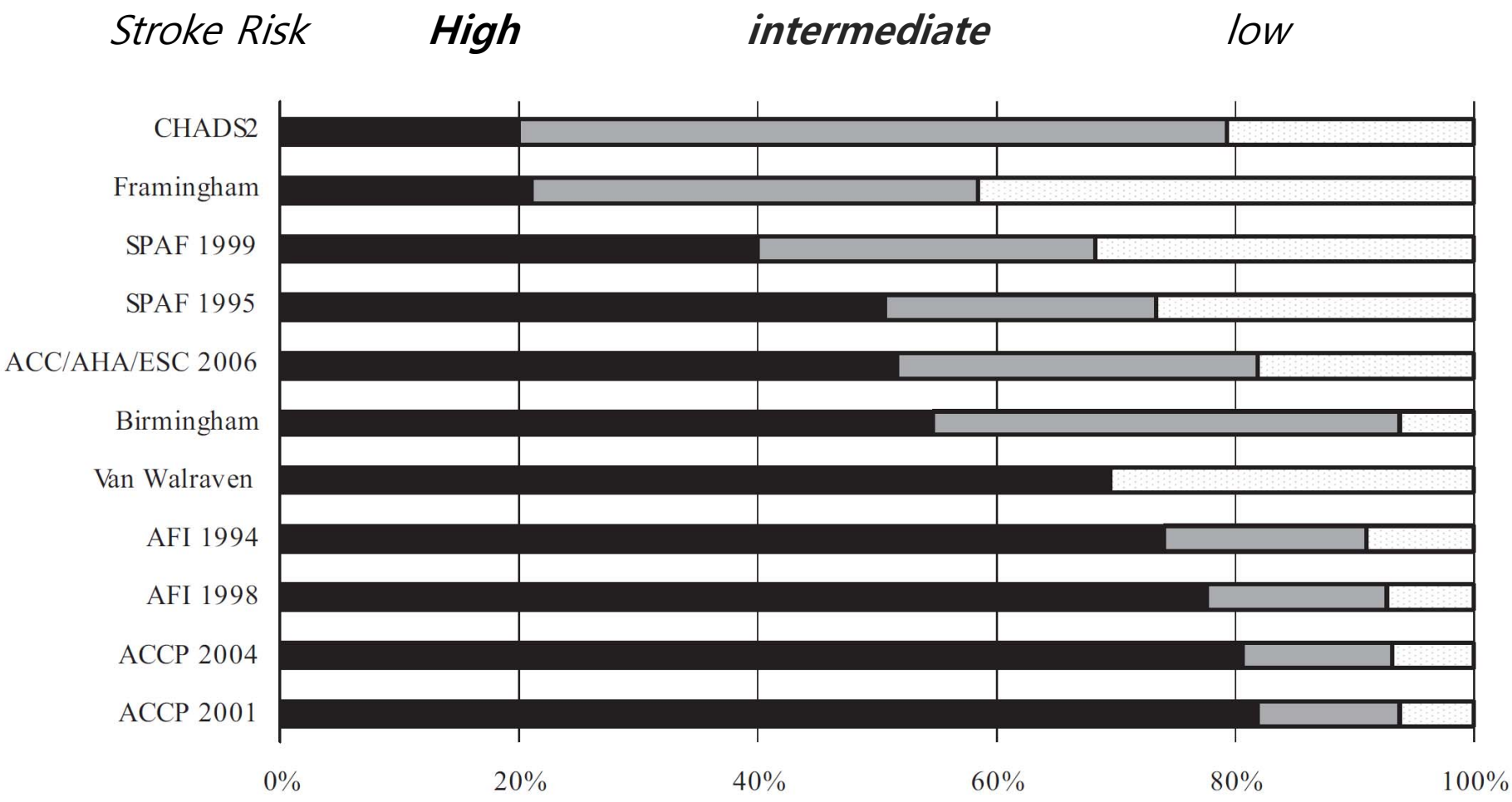
Table 2. Risk of Stroke in National Registry of Atrial Fibrillation (NRAF) Participants, Stratified by $CHADS_2$ Score*

$CHADS_2$ Score	No. of Patients (n = 1733)	No. of Strokes (n = 94)	NRAF Crude Stroke Rate per 100 Patient-Years	NRAF Adjusted Stroke Rate, (95% CI)†
0	120	2	1.2	1.9 (1.2-3.0)
1	463	17	2.8	2.8 (2.0-3.8)
2	523	23	3.6	4.0 (3.1-5.1)
3	337	25	6.4	5.9 (4.6-7.3)
4	220	19	8.0	8.5 (6.3-11.1)
5	65	6	7.7	12.5 (8.2-17.5)
6	5	2	44.0	18.2 (10.5-27.4)

	C statistic
AFI	0.68
SPAF	0.74
$CHADS_2$	**0.82**

(Gage JAMA 2001)

Relative Stroke Risk Distribution



(Stroke Risk in Atrial Fibrillation Working Group. Stroke 2008)

$CHADS_2$ SCORE

	Low	***Intermediate***	*High*
$CHADS_2$-*Classic*	0	**1-2**	≥3
Distribution(%)	(*2.0)*	*(64.0)*	*(34.0)*
$CHADS_2$-*Revised*	0	**1**	≥2
Distribution(%)	(*2.0)*	*(31.1)*	*(66.9)*

Stroke Risk in Patients With Nonvalvular AF Not treated With Anticoagulation According to the CHADS2 Index

CHADS2 Risk Criteria	Score
Prior stroke or TIA	**2**
Age 75 y	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1

Patients (N1733)	***Adjusted Stroke Rate*** (%/y)* (95% CI)	***CHADS2 Score***
120	1.9 *(1.2 to 3.0)*	**0**
463	2.8 *(2.0 to 3.8)*	**1**
523	4.0 *(3.1 to 5.1)*	**2**
337	5.9 *(4.6 to 7.3)*	**3**
220	8.5 *(6.3 to 11.1)*	**4**
65	12.5 *(8.2 to 17.5)*	**5**
5	18.2 *(10.5 to 27.4)*	**6**

0점	No or Aspirin
1점	Warfarin or Aspirin
2점	Warfarin

*The adjusted stroke rate was derived from multivariate analysis assuming no aspirin usage. Data are from van Walraven WC, Hart RG, Wells GA, et al. A clinical prediction rule to identify patients with atrial fibrillation and a low risk for stroke while taking aspirin. *Arch Intern Med* 2003;163:936–43 (415); and Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864–70 (426).

2011 ACCF/AHA/HRS *Focused Updates*

Antithrombotic therapy for patients with AF

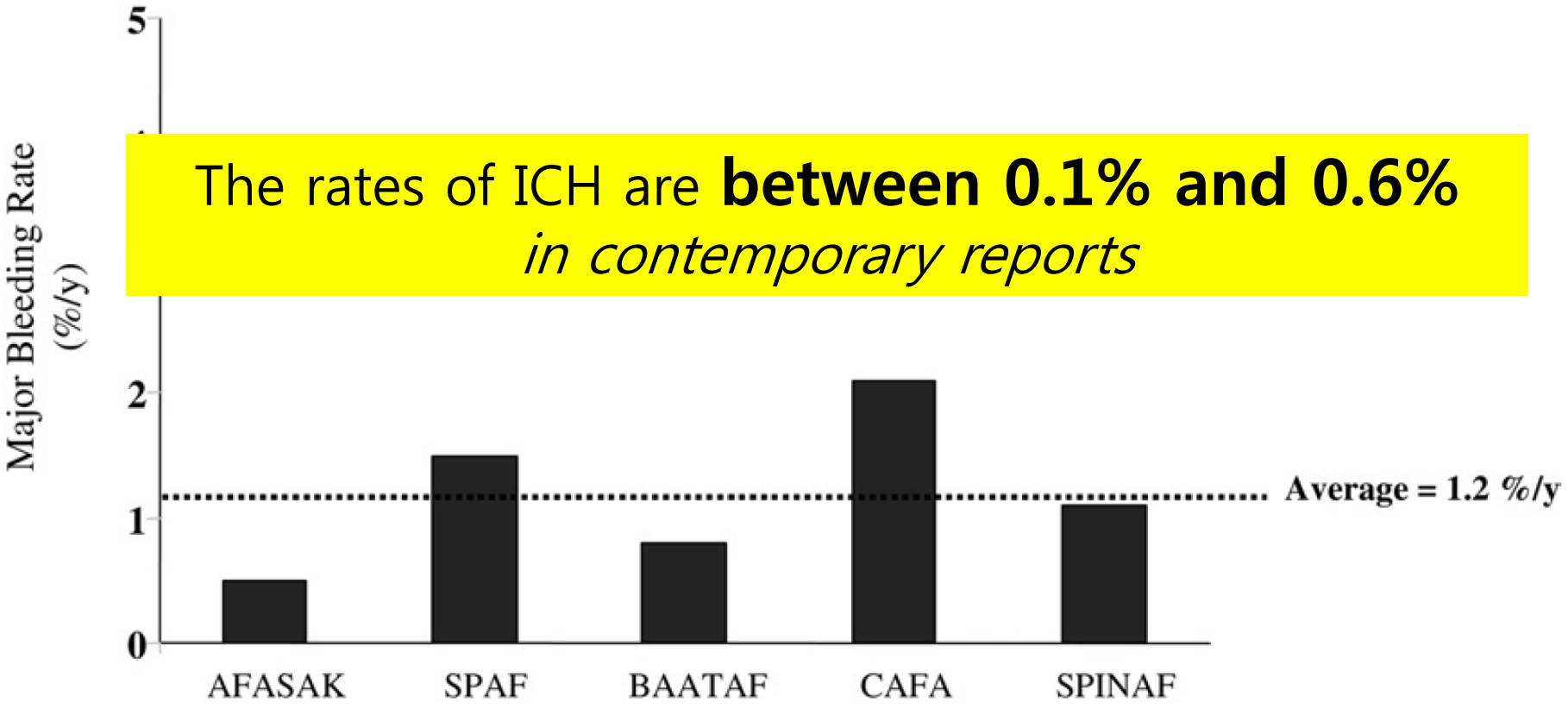
Risk Category	Recommended Therapy
No risk factors	Aspirin, 81 to 325 mg daily
One moderate-risk factor	Aspirin, 81 to 325 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5)
Any high-risk factor or more than 1 moderate-risk factor	Warfarin (INR 2.0 to 3.0, target 2.5)*

Less Validated or Weaker Risk Factors	Moderate-Risk Factors	High-Risk Factors
Female gender	Age greater than or equal to 75 y	Previous stroke, TIA or embolism
Age 65 to 74 y	Hypertension	Mitral stenosis
Coronary artery disease	Heart failure	Prosthetic heart valve*
Thyrotoxicosis	LV ejection fraction 35% or less	
	Diabetes mellitus	

Relatively Conservative *Attitude to* use OAC
and allow the alternatives(anti-platelets)
(more concern about the bleeding risk-benefit)

Major Bleeding Rate of VKA

The rates of ICH are **between 0.1% and 0.6%**
in contemporary reports



(Mant 2007 Lancet)

BAFTA

(the Birmingham AF treatment of the Aged Study)

	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

973 over 75 yo

Stroke Risk in Patients With Nonvalvular AF Not treated With Anticoagulation According to the CHADS2 Index

CHADS2 Risk Criteria	Score
Prior stroke or TIA	**2**
Age 75 y	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1

Patients (N1733)	***Adjusted Stroke Rate*** (%/y)* (95% CI)	***CHADS2 Score***
120	1.9 *(1.2 to 3.0)*	**0**
463	2.8 *(2.0 to 3.8)*	**1**
523	4.0 *(3.1 to 5.1)*	**2**
337	5.9 *(4.6 to 7.3)*	**3**
220	8.5 *(6.3 to 11.1)*	**4**
65	12.5 *(8.2 to 17.5)*	**5**
5	18.2 *(10.5 to 27.4)*	**6**

*The adjusted stroke rate was derived from multivariate analysis assuming no aspirin usage. Data are from van Walraven WC, Hart RG, Wells GA, et al. A clinical prediction rule to identify patients with atrial fibrillation and a low risk for stroke while taking aspirin. *Arch Intern Med* 2003;163:936–43 (415); and Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864–70 (426).

Background of CHA_2DS_2-VASc

Table 5—*Risk Categorization, Incidence of TE,[a] and Predictive Ability for Contemporary Risk Stratification Schema Among Euro Heart Survey Patients Who Did not Receive Anticoagulation at Baseline*

	Categorization of TE Risk			Predictive Ability	
	Low	Intermediate	High	C Statistic (95% CI)	*P* Value
AFI 1994					.209
% in risk category	16.7	12.2	71.1	0.573	
TE events, No. (%)	1 (0.6)	4 (3.0)	20 (2.6)	(0.470-0.676)	
SPAF 1999					.405
% in risk category	26.2	44.8	29.0	0.549	
TE events, No. (%)	5 (1.8)	11 (2.3)	9 (2.9)	(0.435-0.662)	
$CHADS_2$—classic					.296
% in risk category	20.4	61.9	17.7	0.561[b]	
TE events, No. (%)	3 (1.4)	16 (2.4)	6 (3.2)	(0.450-0.672)	
$CHADS_2$—revised					.140
% in risk category	20.4	34.9	44.7	0.586[b]	
TE events, No. (%)	3 (1.4)	7 (1.9)	15 (3.1)	(0.477-0.695)	
Framingham					.018
% in risk category	48.3	41.5	10.2	0.638[b]	
TE events, No. (%)	6 (1.2)	14 (3.2)	5 (4.6)	(0.532-0.744)	
NICE 2006					.094
% in risk category	13.1	39.2	47.7	0.598	
TE events, No. (%)	0 (0.0)	13 (3.1)	12 (2.3)	(0.498-0.698)	
ACC/AHA/ESC 2006					.228
% in risk category	19.6	32.6	47.8	0.571	
TE events, No. (%)	3 (1.4)	7 (2.0)	15 (2.9)	(0.461-0.680)	
ACCP 2008					.204
% in risk category	19.6	33.4	47.0	0.574	
TE events, No. (%)	3 (1.4)	7 (1.9)	15 (3.0)	(0.465-0.683)	
Birmingham 2009					.070
% in risk category	9.2	15.1	75.7	0.606	
TE events, No. (%)	0 (0.0)	1 (0.6)	24 (3.0)	(0.513-0.699)	

$CHADS_2$ -> CHA_2DS_2VASc

CHADS2 Risk	Score
CHF	1
Hypertension	1
Age > 75	1
Diabetes	1
Stroke or TIA	2

CHA2DS2-VASc Risk	Score
CHF or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke/TIA/ Thromboembolism	2
Vascular Disease	1
Age 65 - 74	1
Female	1

$CHADS_2$ vs CHA_2DS_2VASc ***Grading Scale***

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score		
CHA_2DS_2-VASc score	**Patients (n = 7329)**	**Adjusted stroke rate (%/year)[b]**
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

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

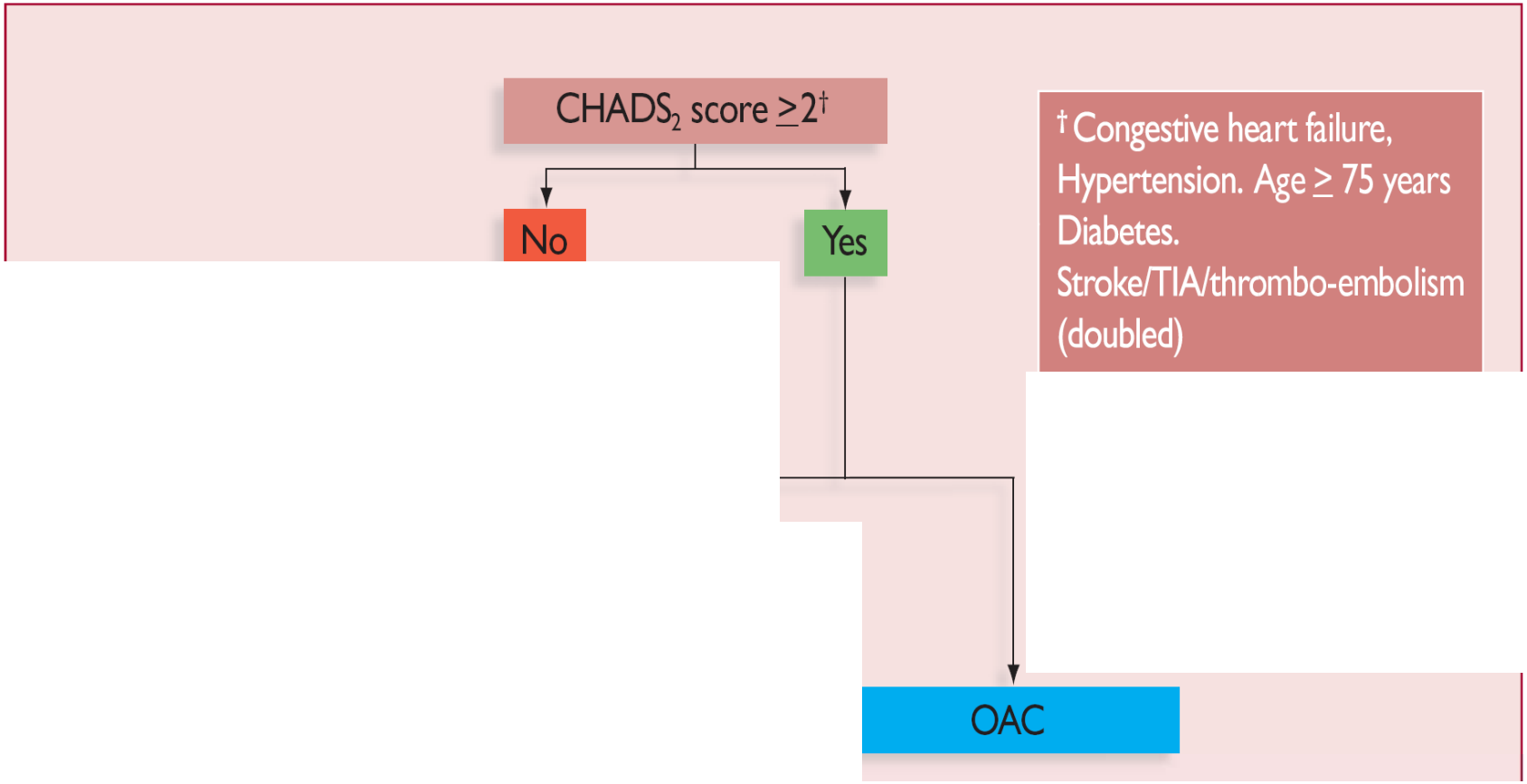
CHA_2DS_2-VASc is *complementary rather than independent* to **$CHADS_2$**

Table 6—*Stroke or Other TE at 1 Year Based on the 2009 Birmingham (CHA_2DS_2-VASc) Scoring System*

CHA_2DS_2-VASc Score	No.	Number of TE Events	TE Rate During 1 y (95% CI)	TE Rate During 1 y, Adjusted for Aspirin Prescription,[a] %
0	103	0	0% (0-0)	0
1	162	1	0.6% (0.0-3.4)	0.7
2	184	3	1.6% (0.3-4.7)	1.9
3	203	8	3.9% (1.7-7.6)	4.7
4	208	4	1.9% (0.5-4.9)	2.3
5	95	3	3.2% (0.7-9.0)	3.9
6	57	2	3.6% (0.4-12.3)	4.5
7	25	2	8.0% (1.0-26.0)	10.1
8	9	1	11.1% (0.3-48.3)	14.2
9	1	1	100% (2.5-100)	100
Total	1,084	25	*P* Value for trend 0.003	

(Chest 2010 Lip)

2010 ESC Guidelines of AF



HAS-BLED bleeding risk score

H	**Hypertension**	**1**
A	Abnormal Renal/ Liver function	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly(>65)	1
D	Drug of Alcohol	1 or 2
		Maximum 9 points

≥ 3 high risk

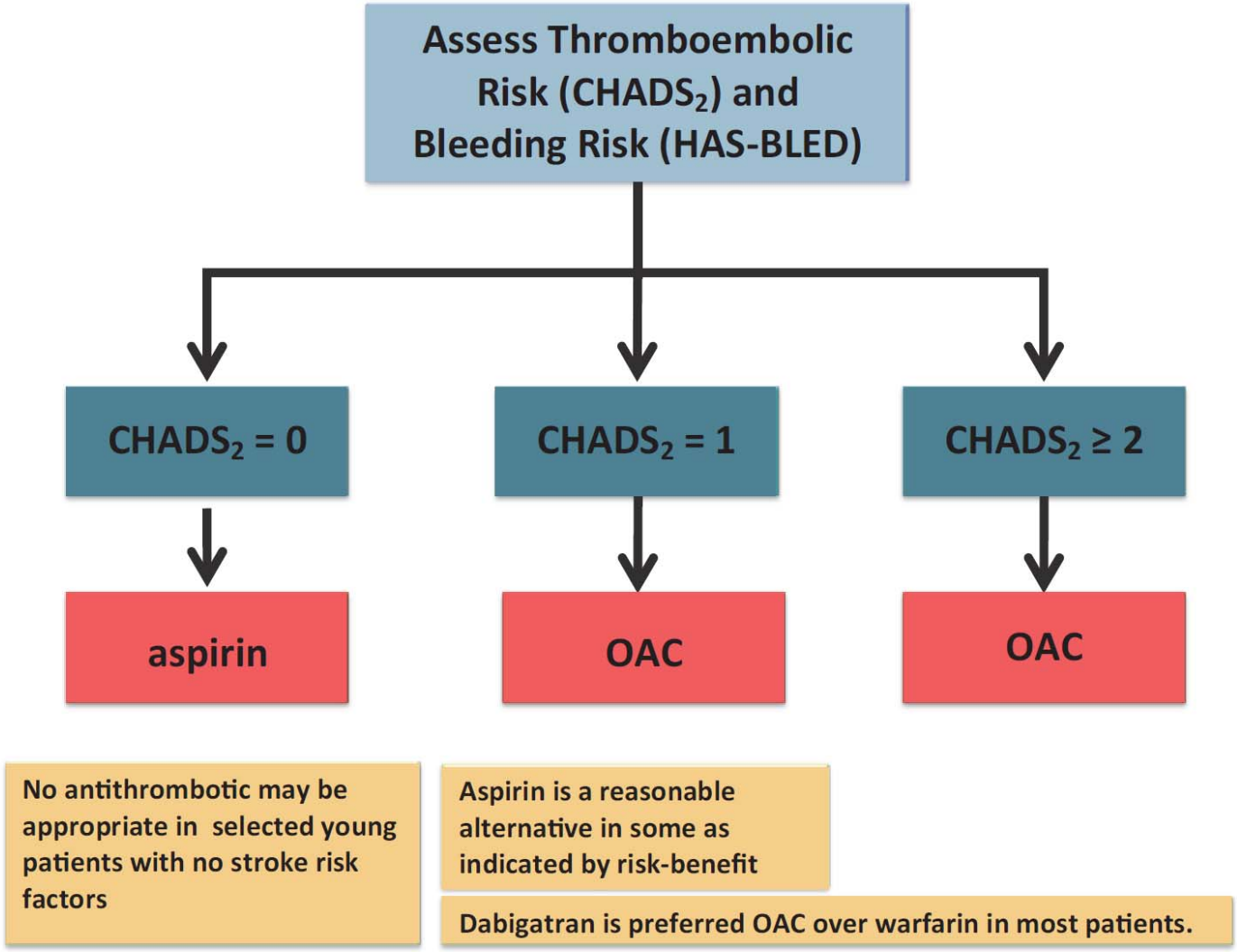
HAS-BLED

	HAS-BLED		
Risk Factors/Score	No.	No. of Bleeds	Bleeds Per 100 Patient-Years
0	798	9	1.13
1	1,286	13	1.02
2	744	14	1.88
3	187	7	3.74
4	46	4	8.70
5	8	1	12.50
6	2	0	0.0
7	0	...	...
8	0	...	...
9	0	...	...
Any score	3,071	48	1.56
P value for trend			0.007

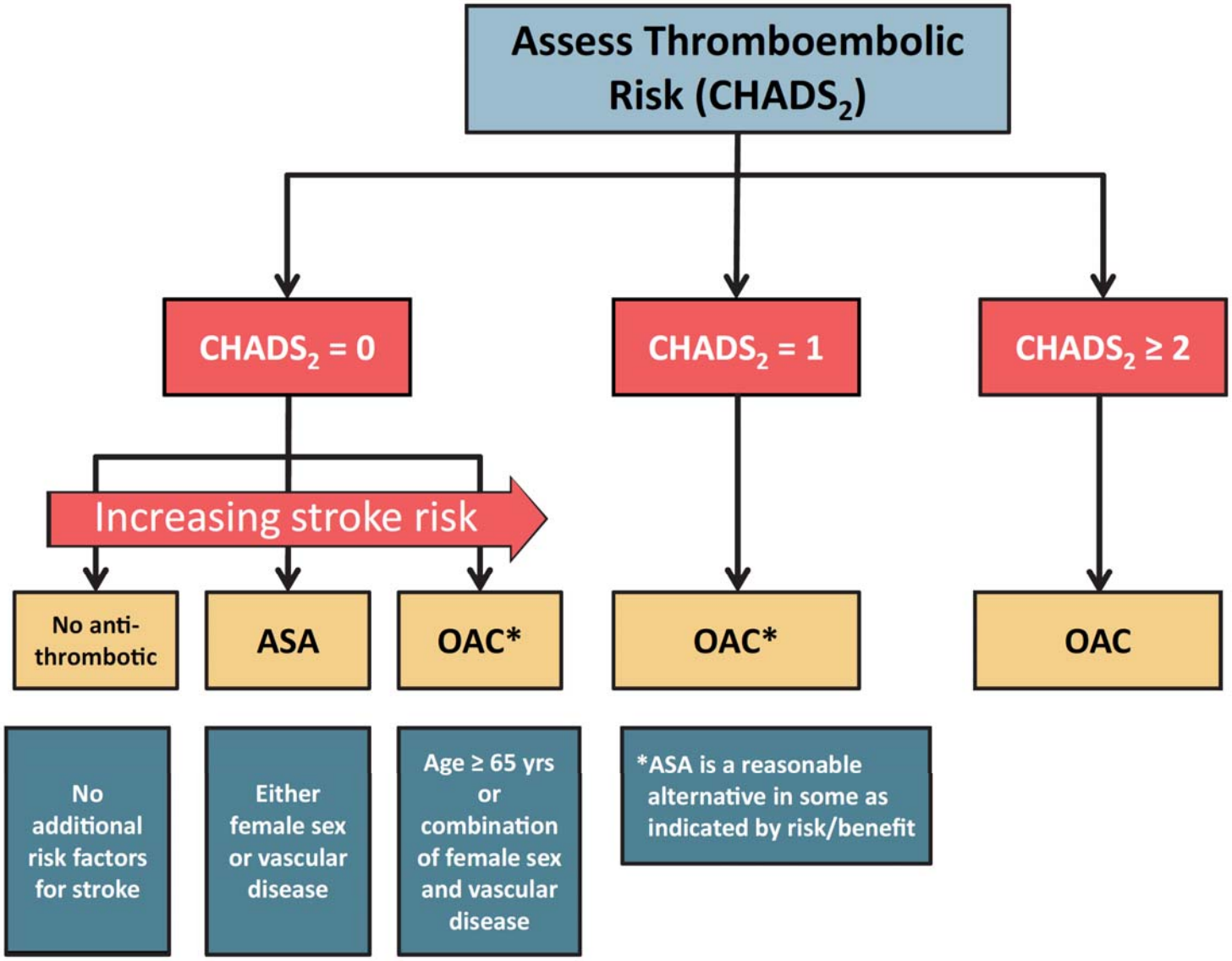
(Pisters Chest 2010)

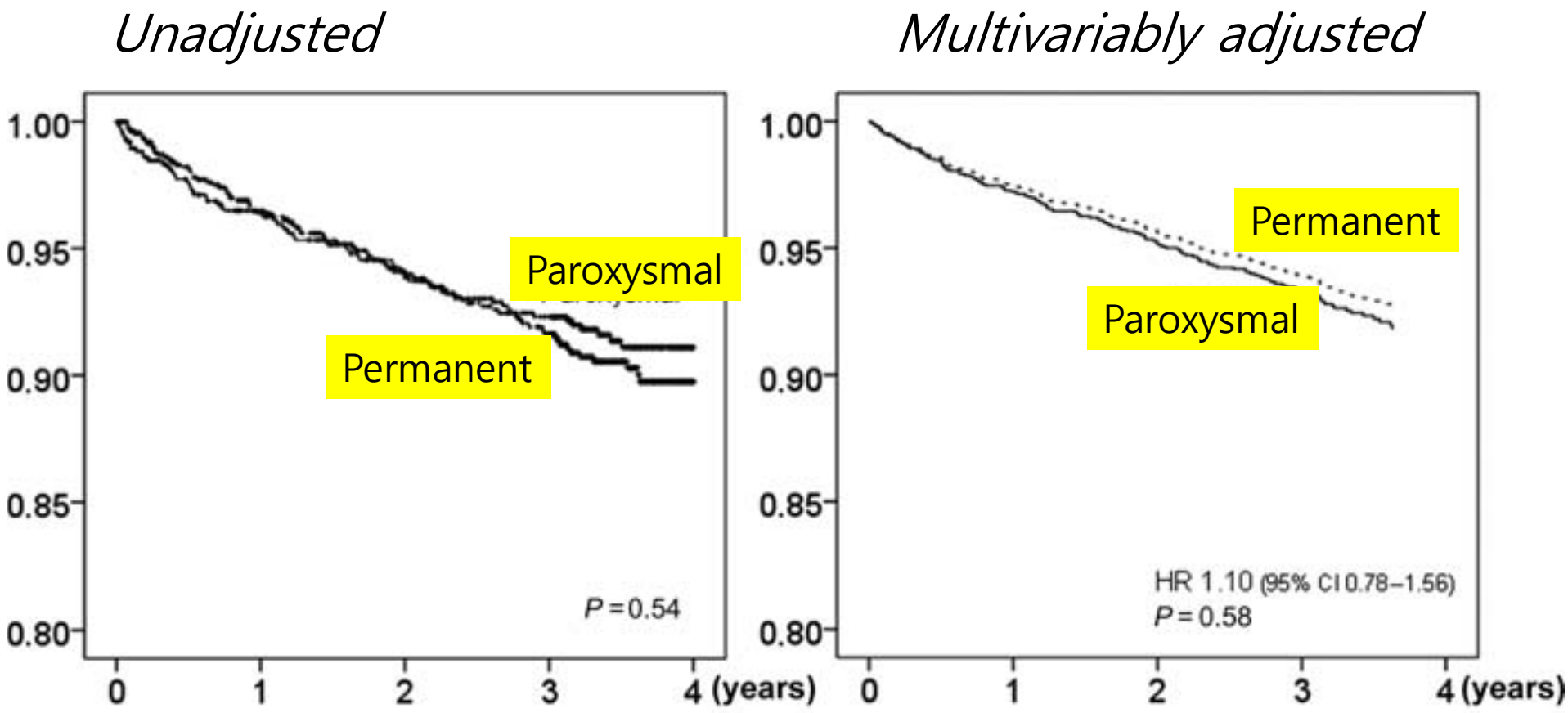
2010 Canadian Cardiovascular Society *AF* Guideline

Overview of Thromboembolic Management



Focused 2012 Update of Canadian AF Guideline





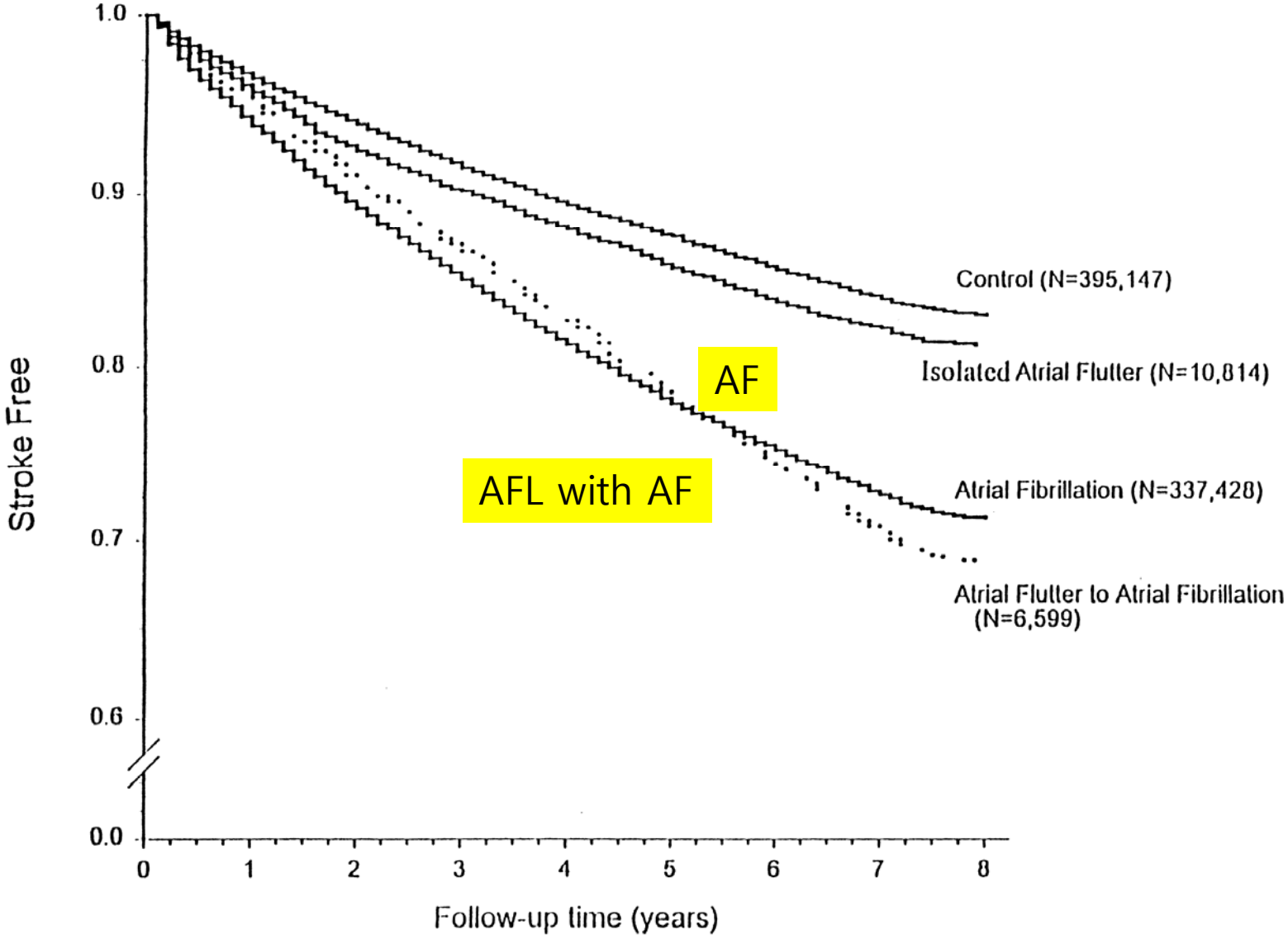
Survival *free from* Ischemic Stroke *in* ***paroxysmal*** AF

(Report from the Stockholm Cohort of Atrial Fibrillation *Friberg L. Eur Heart J 2010)*

Class IIa

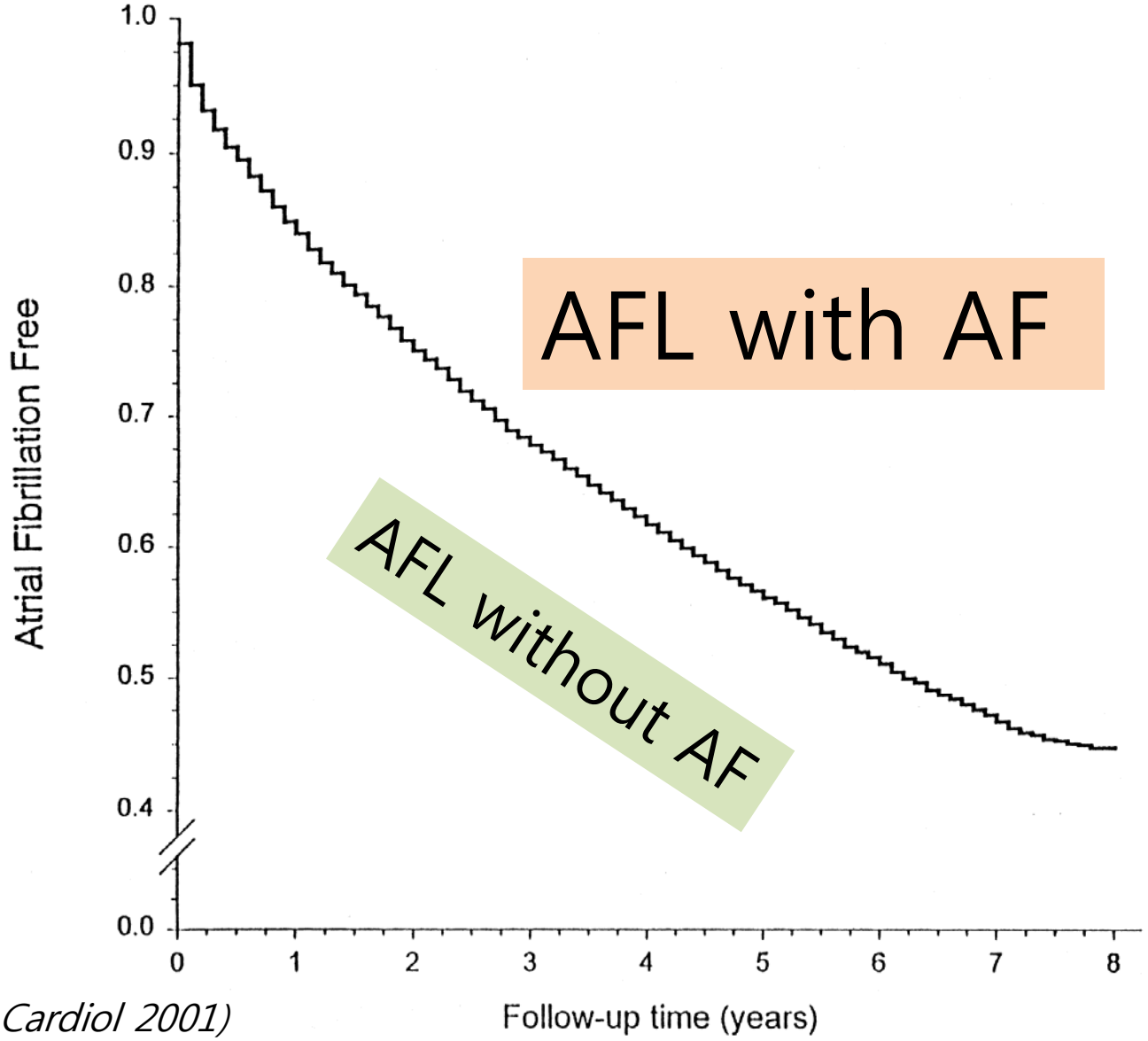
3. It is reasonable to select antithrombotic therapy using the *same criteria irrespective of the pattern* (i.e., ***paroxysmal, persistent, or permanent***) of AF. *(level of Evidence: B)*

Risk of Stroke *in patients with* Atrial Flutter



(Biblo LA Am J Cardiol 2001)

The incidence of AF *after inception of AFL*



(Biblo LA Am J Cardiol 2001)

Class I

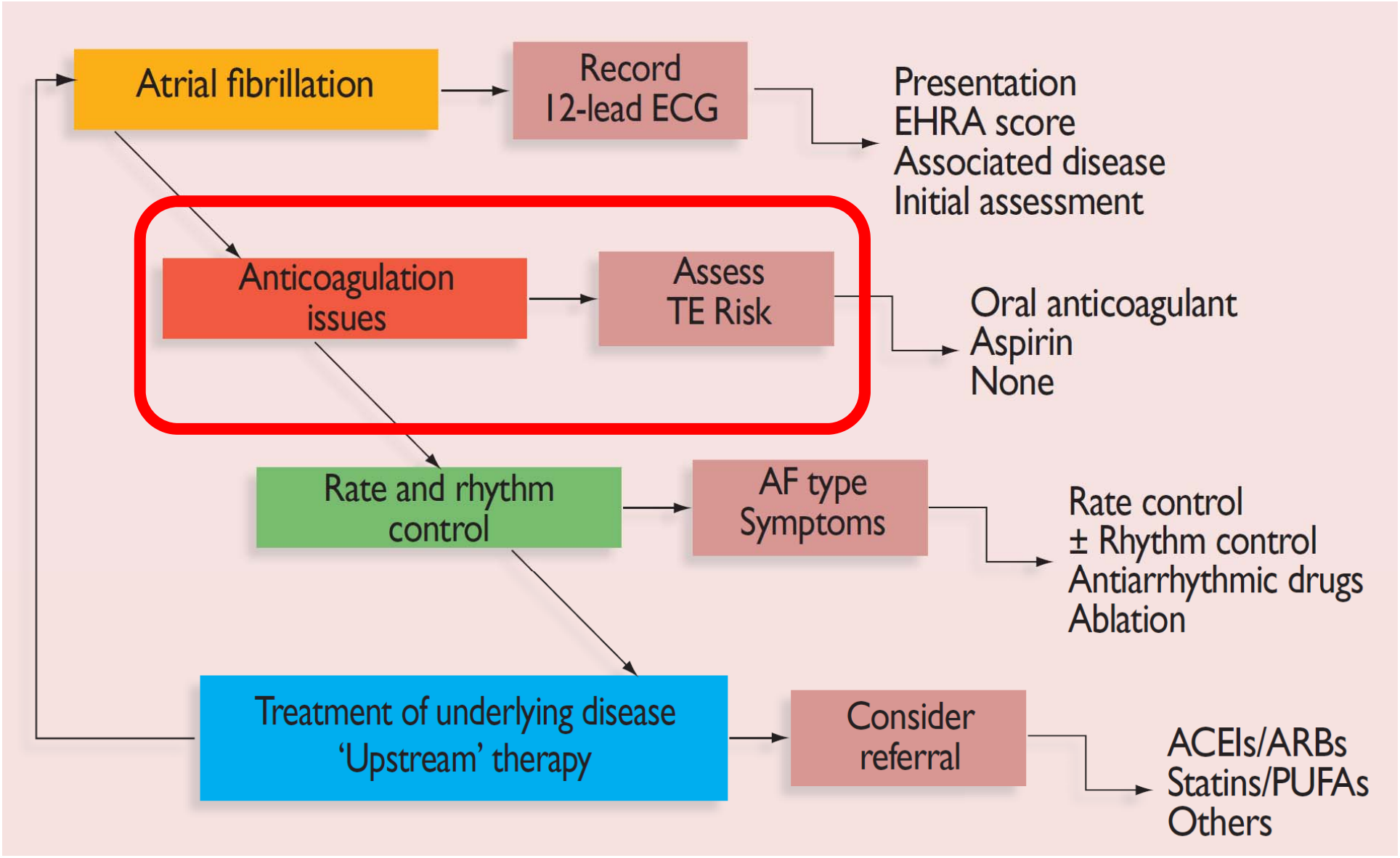
8. Antithrombotic therapy is recommended for patients with ***atrial flutter*** as for those with AF. *(Level of Evidence: C)*

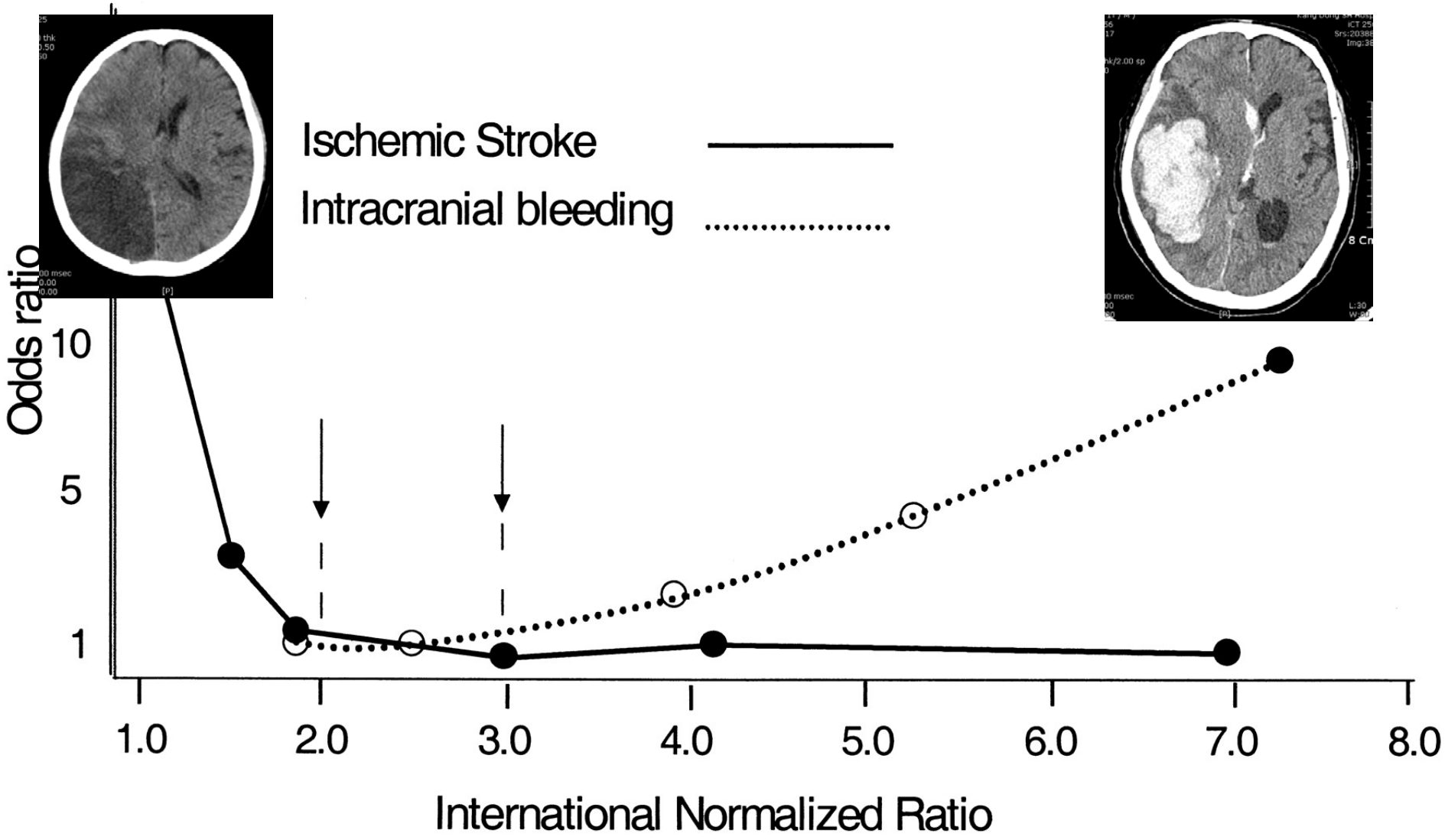
To reduce the **Stroke Risk** *in association with* **AF**, ***what we should consider?***

- ***To Whom?***
- ***By What?***
  - Warfarin (oral vitamin K antagonist)
  - Antiplatelet
  - New OAC
- ***How to?***
  - Adherence to the clinical Guidelines
  - Practical tips
    - *Weekly dosage*
    - ***Education!!*** *and communication*
    - *Self monitoring*

the Management Cascade

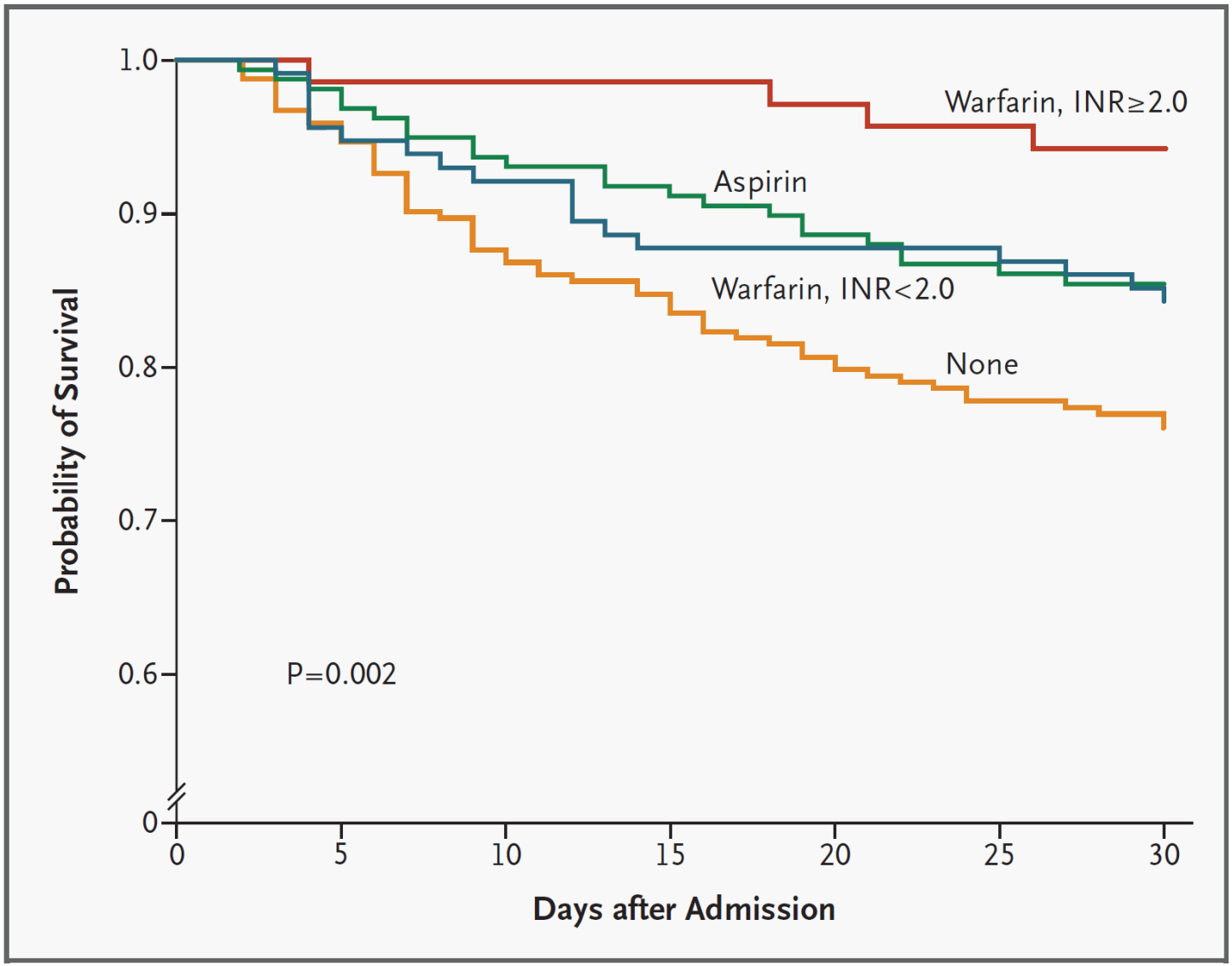
for patients with AF





(INR) **Monitoring is essential!**
Stroke/Embolism Prevention vs Bleeding Risk

(N Engl J Med 2003 Hylek)



(N Engl J Med 2003 Hylek)

INR *and* Stroke/ICH

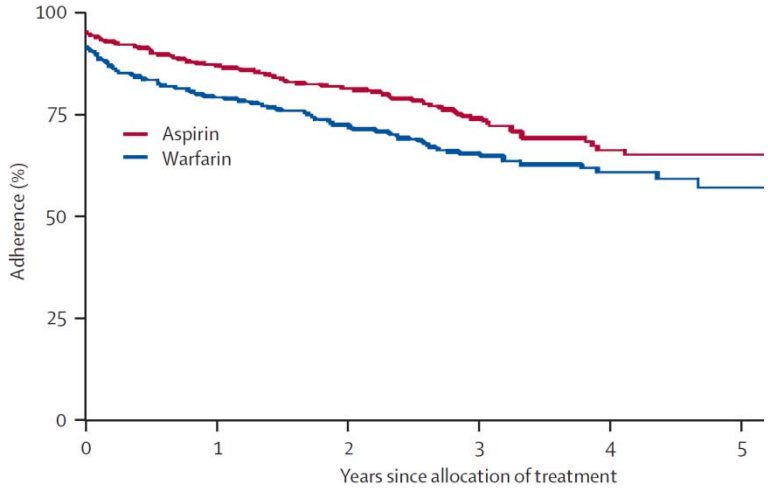
INR	Person-yr†	Stroke (95% CI) (N=152)	Person-yr†	Intracranial Hemorrhage (95% CI) (N=58)
		rate/100 person-yr		*rate/100 person-yr*
<1.5	556	7.7 (5.7–10.4)	561	0.5 (0.2–1.7)
1.5–1.9	2847	1.9 (1.4–2.4)	2867	0.3 (0.1–0.6)
2.0–2.5	5357	0.4 (0.3–0.7)	5400	0.3 (0.2–0.4)
2.6–3.0	2388	0.9 (0.6–1.4)	2409	0.5 (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)

(N Engl J Med 2003 Hylek)

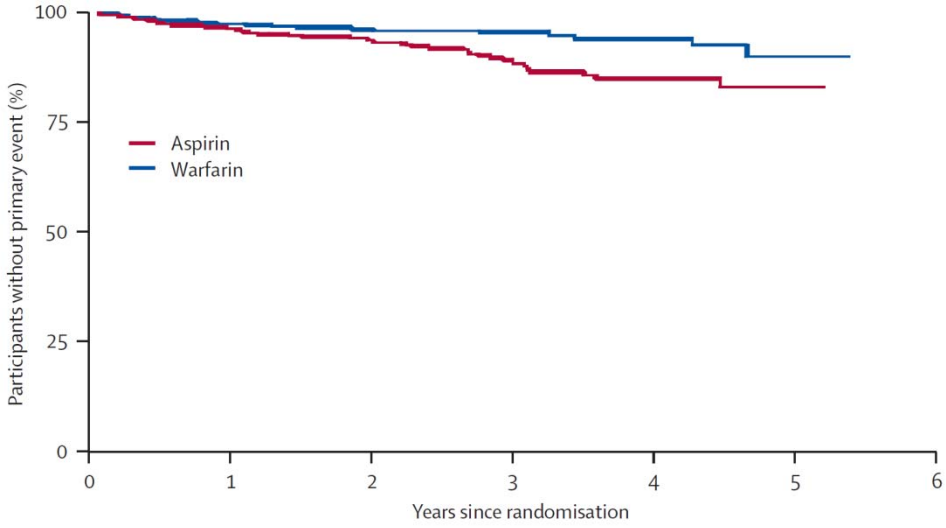
Variable	None (N=248)	Aspirin (N=160)	Warfarin	
			INR <2.0 (N=117)	INR ≥2.0 (N=71)
			percent	
Severity and outcome of stroke				
Fatal in-hospital stroke	14	6	9	1
Severe stroke, total dependence	8	7	6	4
Major stroke, neurologic deficit that prevented independent living	37	36	44	38
Minor stroke, neurologic deficit that did not prevent independent living	36	49	38	55
No neurologic sequelae	5	2	3	2
Total 30-day mortality	24	15	16	6

BAFTA

(the Birmingham AF treatment of the Aged Study)

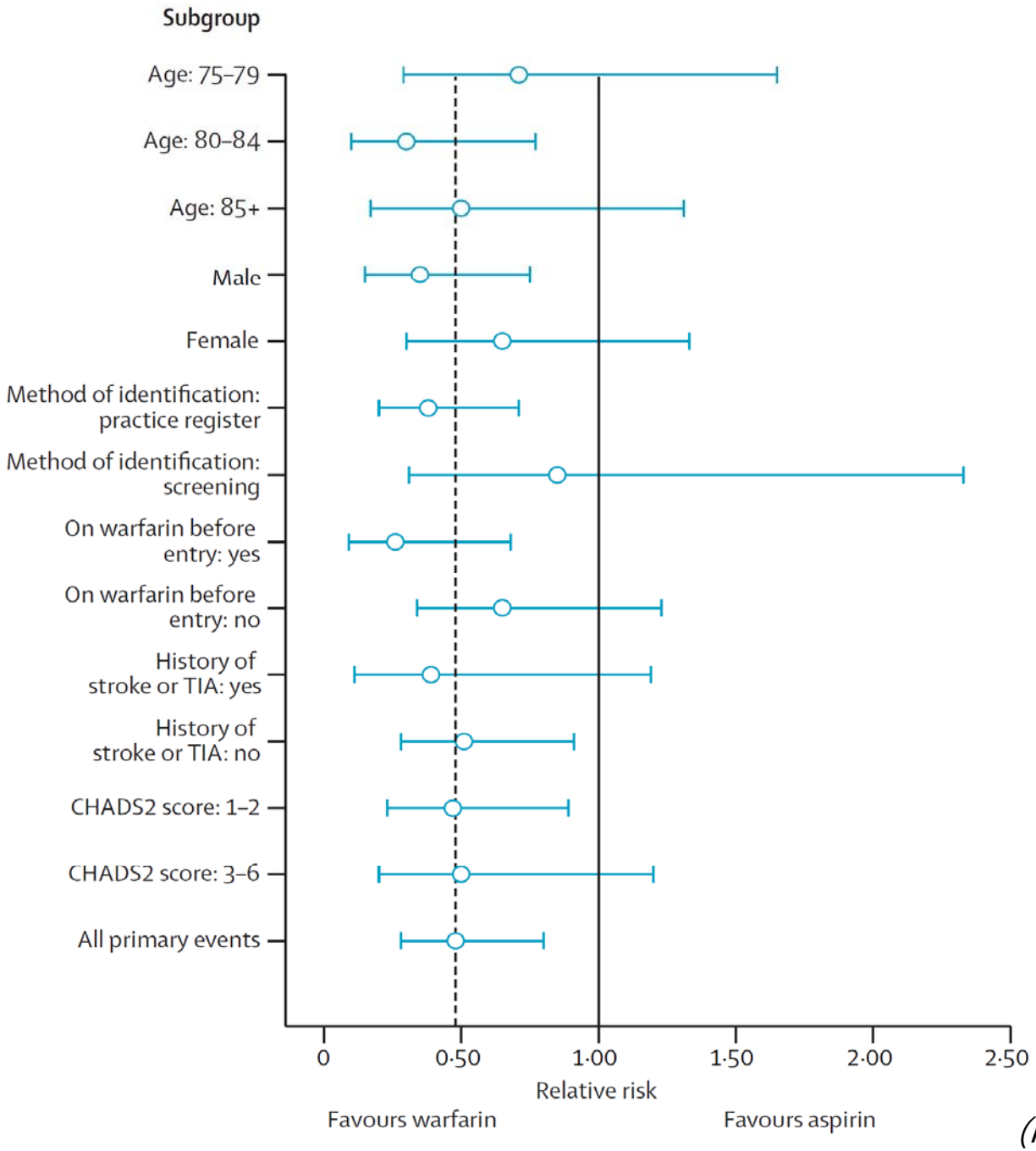


Number at risk						
Warfarin	488	364	289	118	49	10
Aspirin	485	392	313	122	57	12

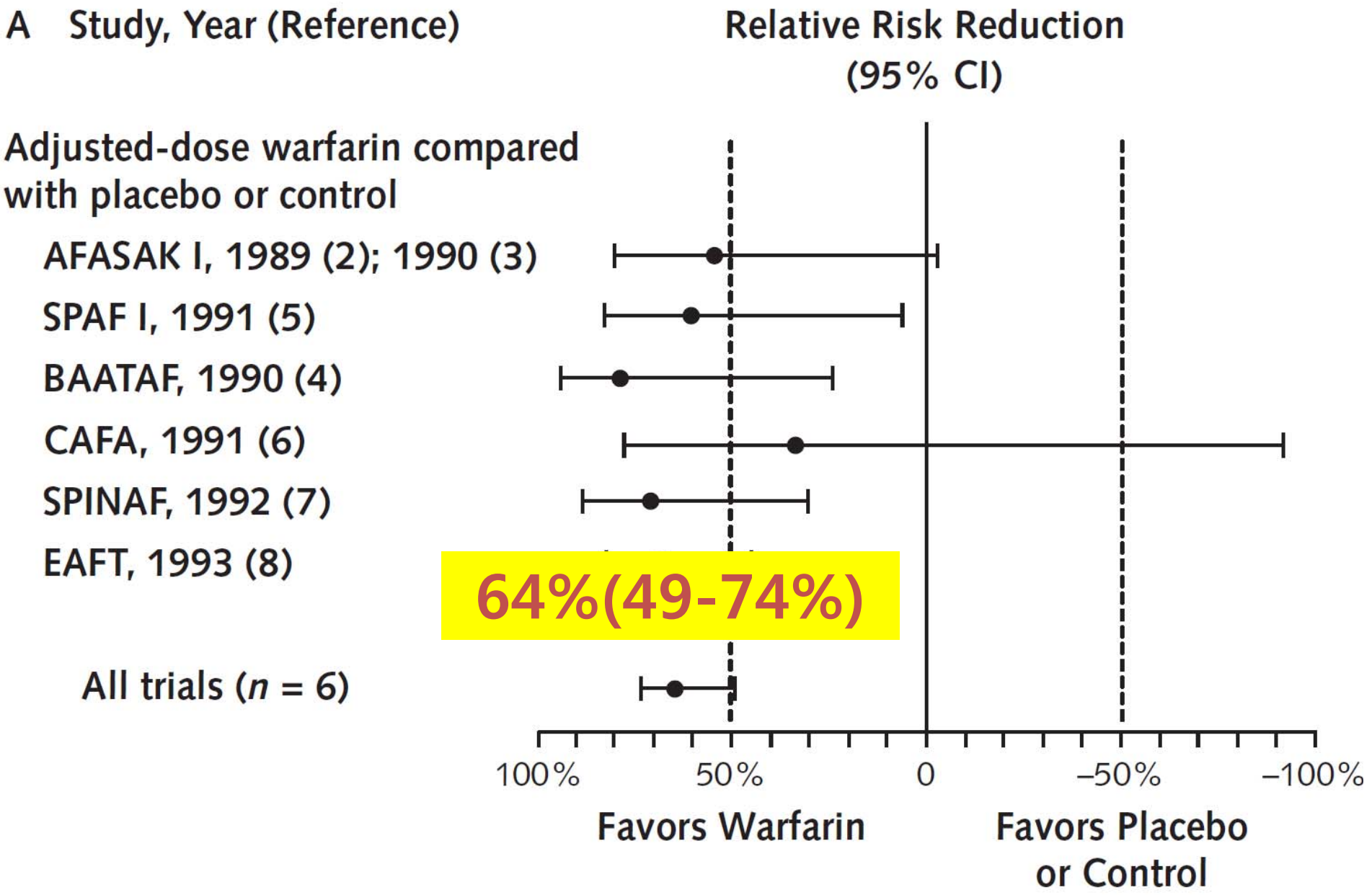


Number at risk						
Warfarin	488	450	383	169	77	19
Aspirin	485	447	378	146	72	14

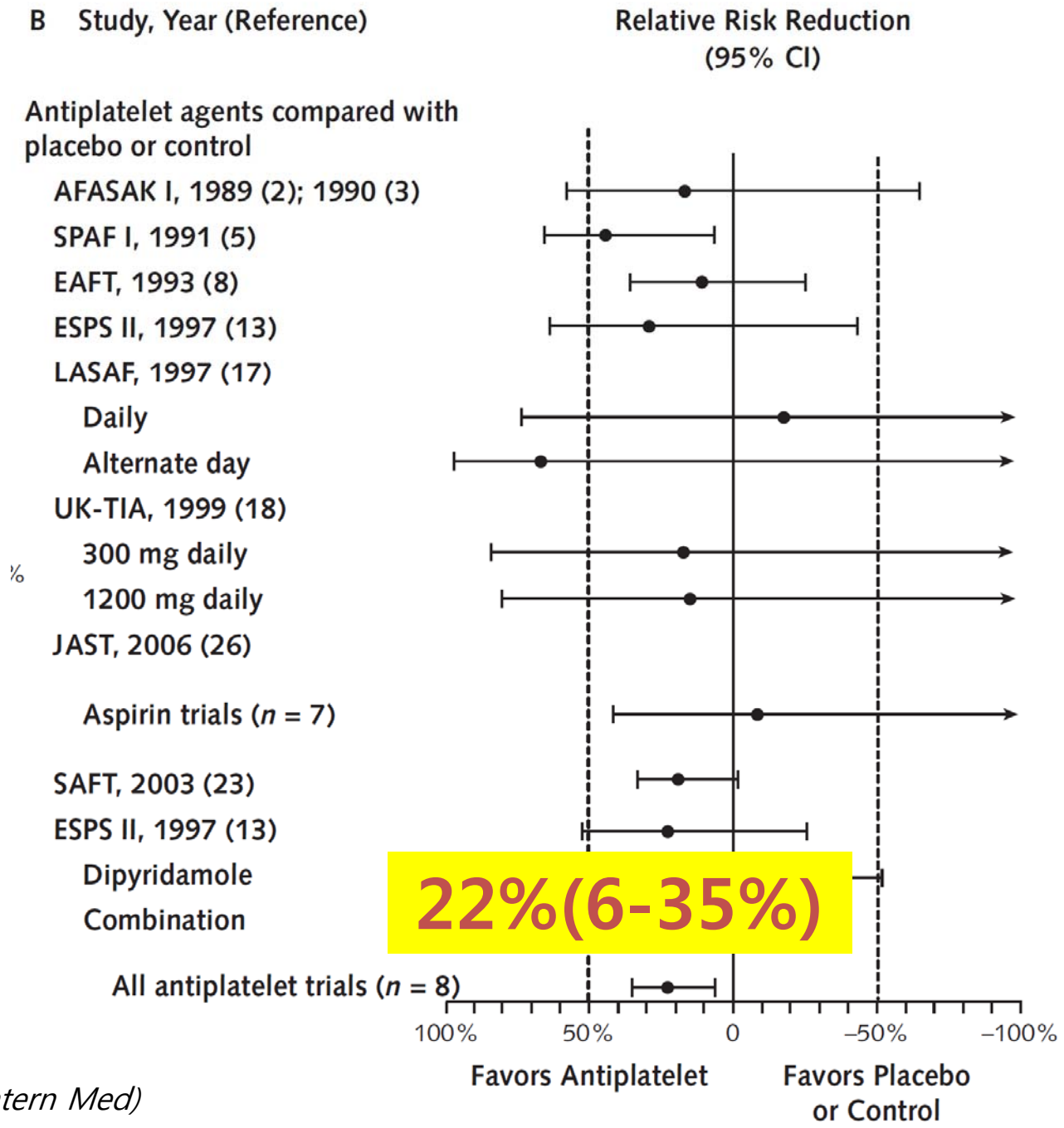
(Mant 2007 Lancet)



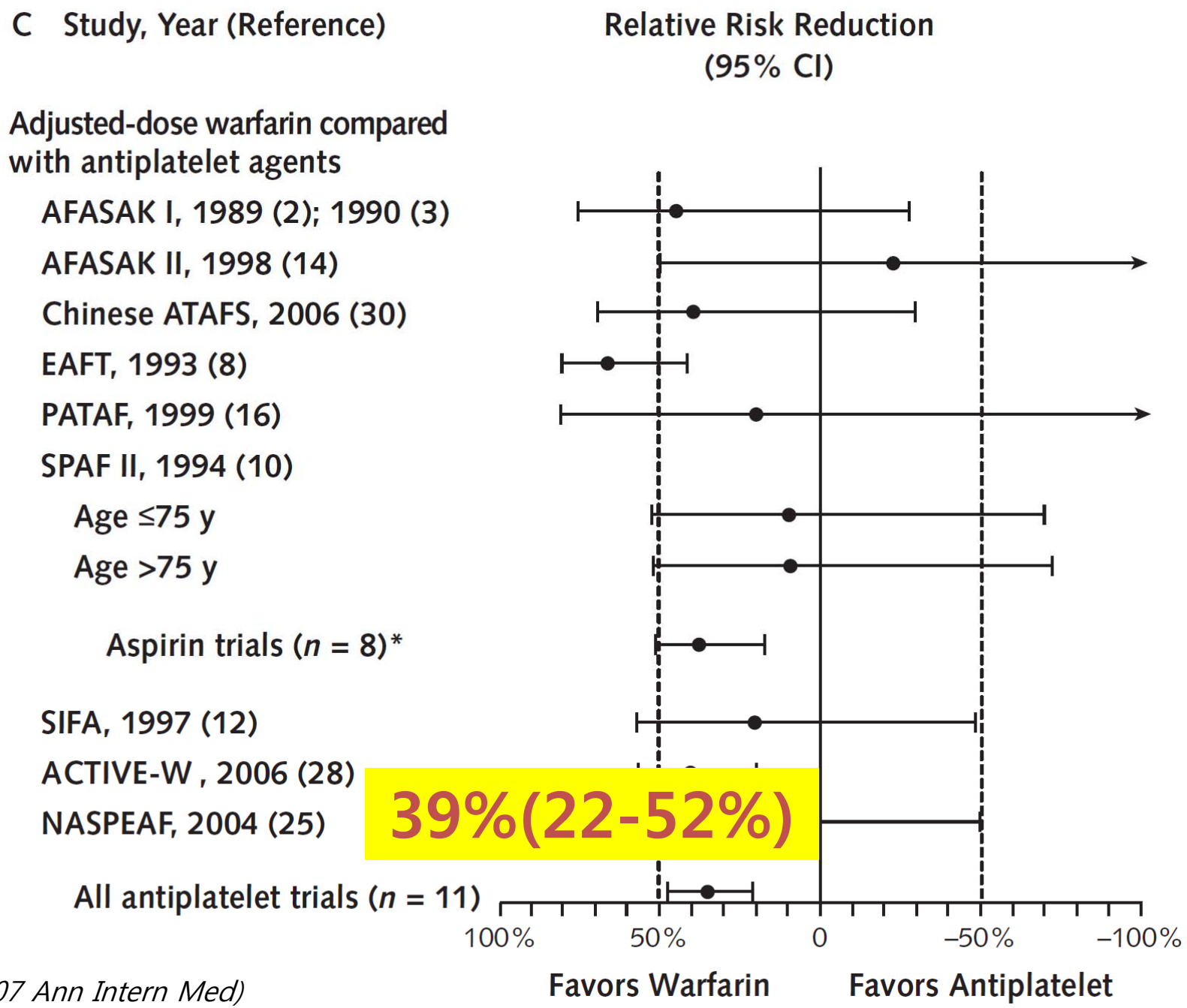
(Mant 2007 Lancet)



(Hart 2007 Ann Intern Med)



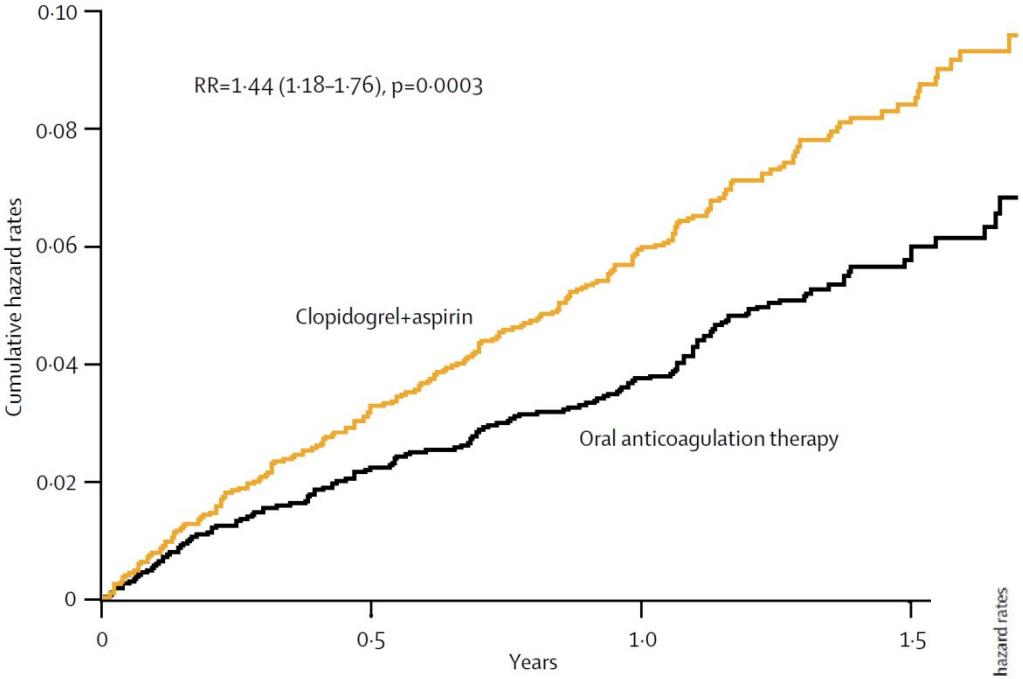
(Hart 2007 Ann Intern Med)



(Hart 2007 Ann Intern Med)

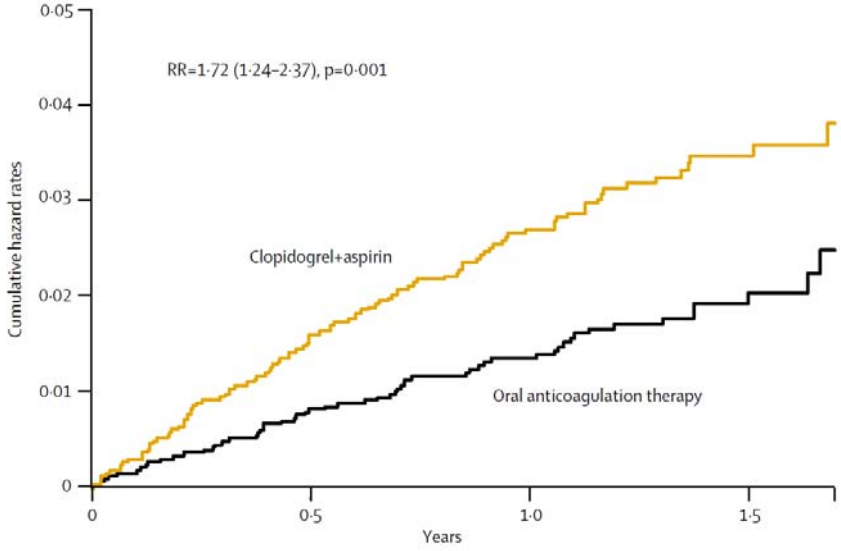
(Lancet 2006, ACTIVE Writing Group)

Active W



Primary Outcome*

Stroke



*: 1st stroke, non-CNS systemic embous, MI, vascular death

To reduce the **Stroke Risk** *in association with* **AF**, ***what we should consider?***

- To Whom ?
- By What ?
  - Warfarin (oral vitamin K antagonist)
  - Antiplatelet
  - New OAC
- How to ?
  - Adherence to the clinical Guidelines
  - Practical tips
    - Weekly dosage
    - Self monitoring