Weighing the risk of stroke vs the risk of bleeding: Which AF patients should be anticoagulated?

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MY CONFLICTS OF INTEREST ARE

Research Contract: Gilead Sciences (Study of new antiarrhythmic compounds in the Canine Sterile Pericarditis Model of Atrial Fibrillation and Atrial Flutter)

Consulting: *St. Jude Medical; #Biosense Webster; #Gilead Sciences; *AtriCure; **Pfizer; **Laguna Pharmaceuticals, **Abbott Cardiovcascular; **Bristol-Myers Squibb

Speaker: Janssen, Pfizer, Bristol-Myers Squibb, Daiichi Sankyo

*clinical trial steering committee; **scientific advisory board; #clinical trial adverse events adjudication committee or data safety monitoring board

# Disclosures: Albert L. Waldo, MD, PhD (Hon)

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Antithrombotic Therapy in AF

bleeding   **thrombosis**
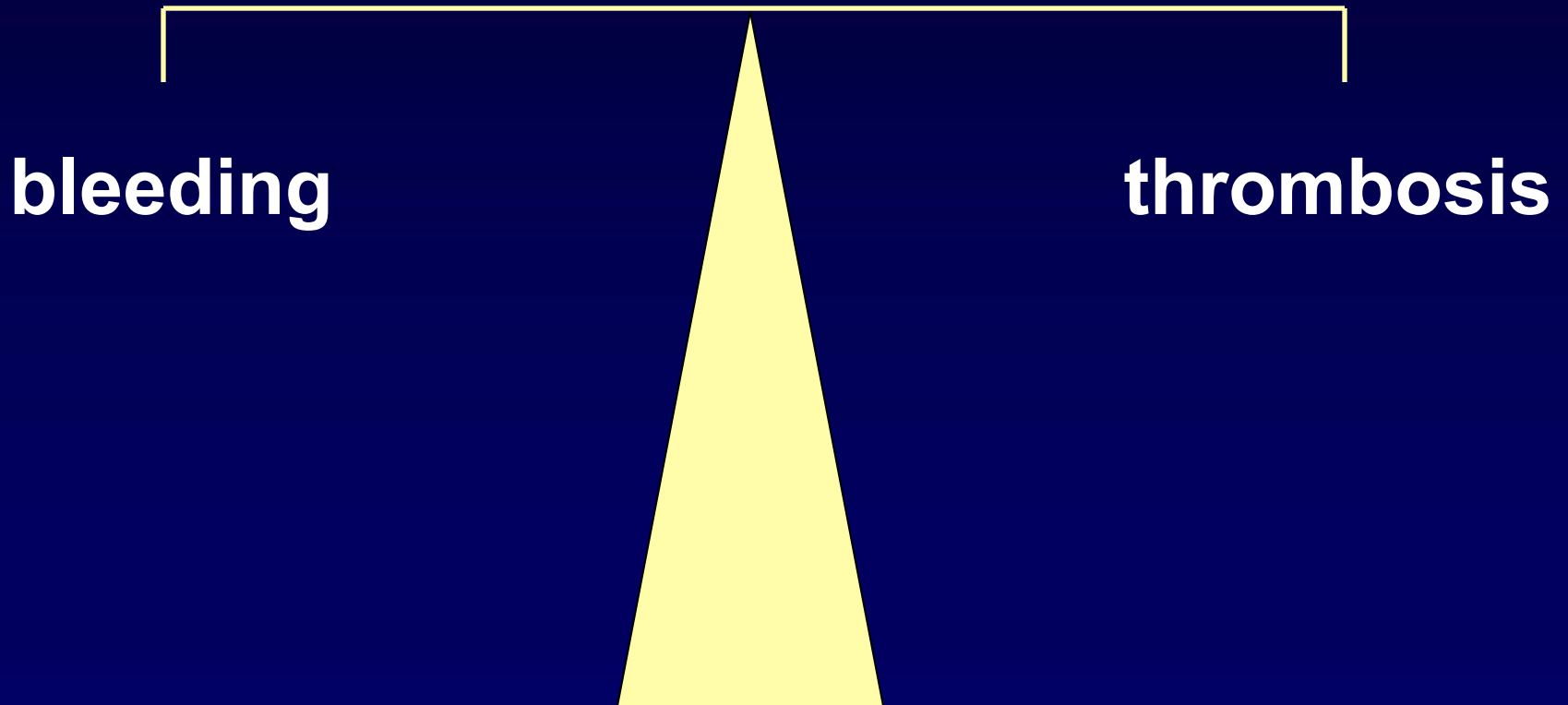
Stroke Risk Stratification in AF

CHADS$_2$

Risk Factor	Score
Cardiac failure	1
HTN	1
Age ≥75 y	1
Diabetes	1
Stroke	2

Total Score	Annual Risk of Stroke (%)	
0	1.9	0
1	2.8	1.3
2	4.0	2.2
3 CHADS$_2$ →	5.9	3.2
4	8.5	4.0
5	12.5	6.7 ← CHA$_2$DS$_2$-VASc
6	18.2	9.8
7		9.6
8		6.7
9		15.2

CHA$_2$DS$_2$-VASc

Risk Factor	Score
Cardiac failure	1
HTN	1
Age ≥75 y	2
Diabetes	1
Stroke	2
Vascular disease (MI, PAD, aortic atherosclerosis)	1
Age 65-74 y	1
Sex **c**ategory (female)	1

CHA$_2$DS$_2$-VASc seems to have 2 major benefits: it more accurately identifies truly low risk pts; it reclassifies many CHADS$_2$ score 0-1 pts to a higher stroke risk

Lip GY, Halperin JL. *Am J Med*. 2010;123:484-8. Camm AJ, et al. *Eur Heart J*. 2010;31:2369-429.

Swedish Cohort Atrial Fibrillation Study: Hazard Ratios for Stroke Risk

182,678 patients with nonvalvular AF

Mean age 76 yrs
53% Male
Average FU 1.5 yrs
53% not on warfarin

	Multivariate hazard ratios (95% CI)
Age (years)	
<65	1.0 (Reference)
65–74	2.97 (2.54–3.48)
≥75	5.28 (4.57–6.09)
Female sex	1.17 (1.11–1.22)
Previous ischaemic stroke	2.81 (2.68–2.95)
Intracranial bleeding	1.49 (1.33–1.67)
Vascular disease (any)	1.14 (1.06–1.23)
• Myocardial infarction	1.09 (1.03–1.15)
• Previous CABG	1.19 (1.06–1.33)
• Peripheral artery disease	1.22 (1.12–1.32)
Hypertension	1.17 (1.11–1.22)
Heart failure (history)	0.98 (0.93–1.03)
Diabetes mellitus	1.19 (1.13–1.26)
Thyroid disease	1.00 (0.92–1.09)
Thyrotoxicosis	1.03 (0.83–1.28)

ATRIA Stroke Risk Model Point Scoring System

Risk Factor	Without Prior Stroke		With Prior Stroke	
Age, y	Points	Hazard Ratio	Points	Hazard Ratio
≥ 85	6	6.38	9	11.92
75 to 84	5	3.79	7	7.61
65 to 74	3	2.10	7	7.89
< 65	0		8	8.99
Female	1	1.52	1	
Diabetes	1	1.40	1	
CHF	1	1.27	1	
Hypertension	1	1.24	1	
Proteinuria	1	1.40	1	
eGFR<45 or ESRD	1	1.33	1	

Possible point scores range from 0 - 12 for those without a prior stroke, and from 7 - 15 for those with a prior stroke.

ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.

Framingham Risk Score
Predicted 5-Year Risk of Stroke in AF

Step 1

Age, y	Pts
55-59	0
60-62	1
63-66	2
67-71	3
72-74	4
75-77	5
78-81	6
82-85	7
86-90	8
91-93	9
>93	10

Step 2

Sex	Pts
Men	0
Women	6

Step 3

Systolic blood pressure, mm Hg	Pts
<120	0
120-139	1
140-159	2
160-179	3
>179	4

Step 4

Diabetes	Pts
No	0
Yes	5

Step 5

Prior stroke or TIA	Pts
No	0
Yes	6

Add up points from steps 1-5

Look up predicted 5 year risk of stroke in table ➡️

Pts	5 yr risk, %
0-1	5
2-3	6
4	7
5	8
6-7	9
8	11
9	12
10	13
11	14
12	16
13	18
14	19
15	21
16	24
17	26
18	28
19	31
20	34
21	37
22	41
23	44
24	48
25	51
26	55
27	59
28	63
29	67
30	71
31	75

Wang et al. JAMA. 2003; 290:1049-56.
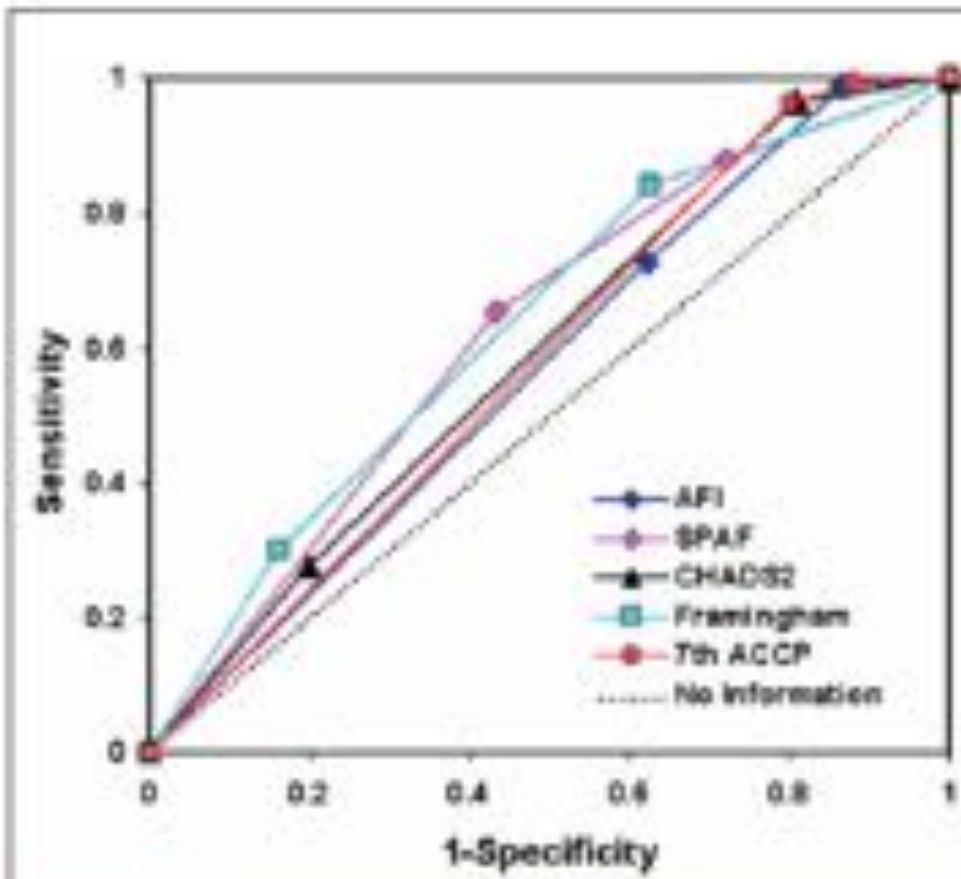
Figure 3: ROC Curves for 5 Risk Stratification Schemes Used to Predict AF-Related Thromboembolism

The 45° dotted line represents the line of no information. ROC = receiver operating characteristic; other abbreviations as in figure 1.
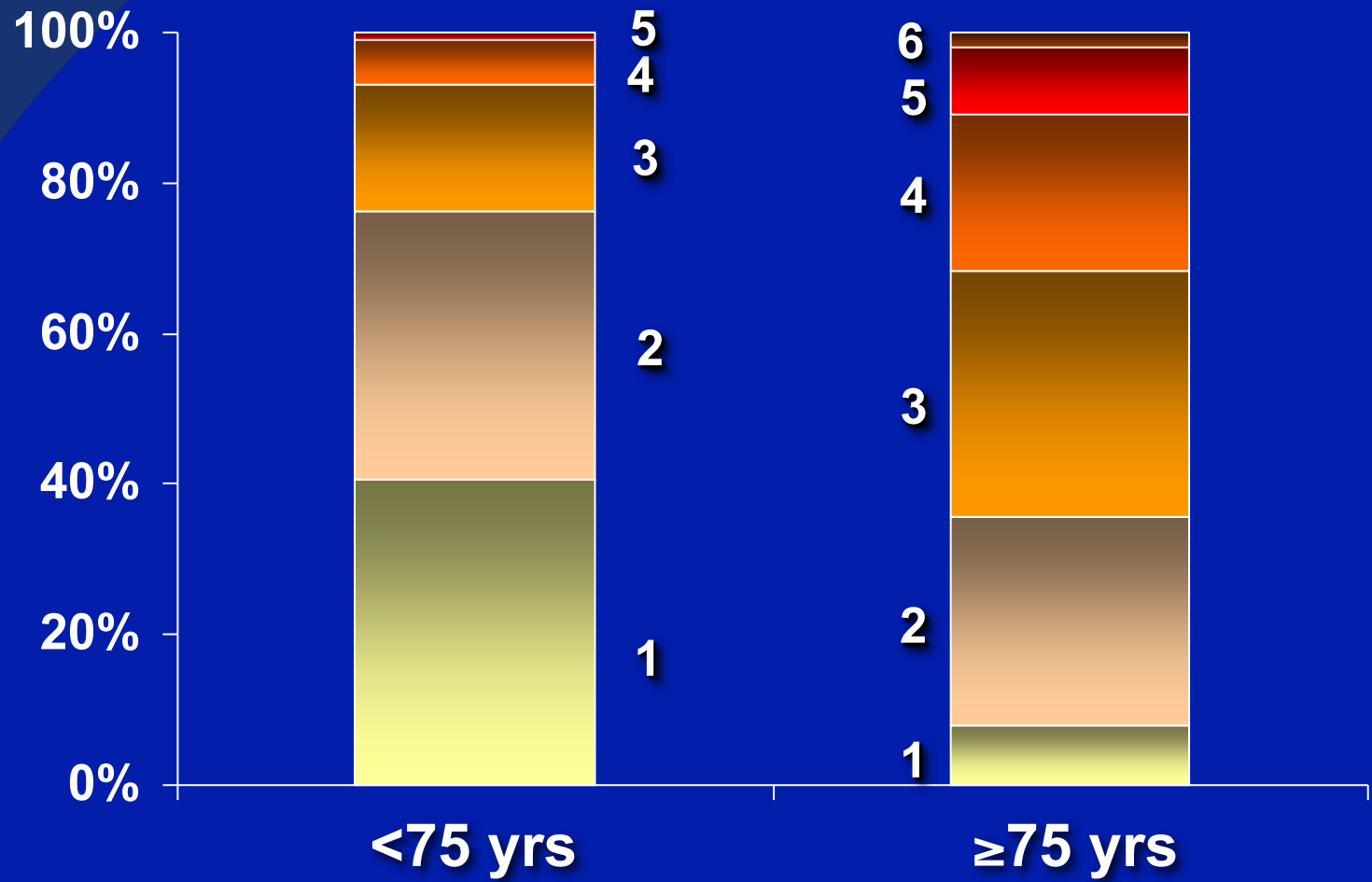
Risk Score	c-Statistic
Atria	0.73*
AFI	0.56
SPAF	0.60
CHADS$_2$ CHA$_2$DS$_2$VaSC	0.58/0.67* 0.70*
Framingham	0.62
7th ACCP	0.56

Oral Anticoagulation in Elderly Patients with AF

White RH et al. Am J Med 1999;106:165-71
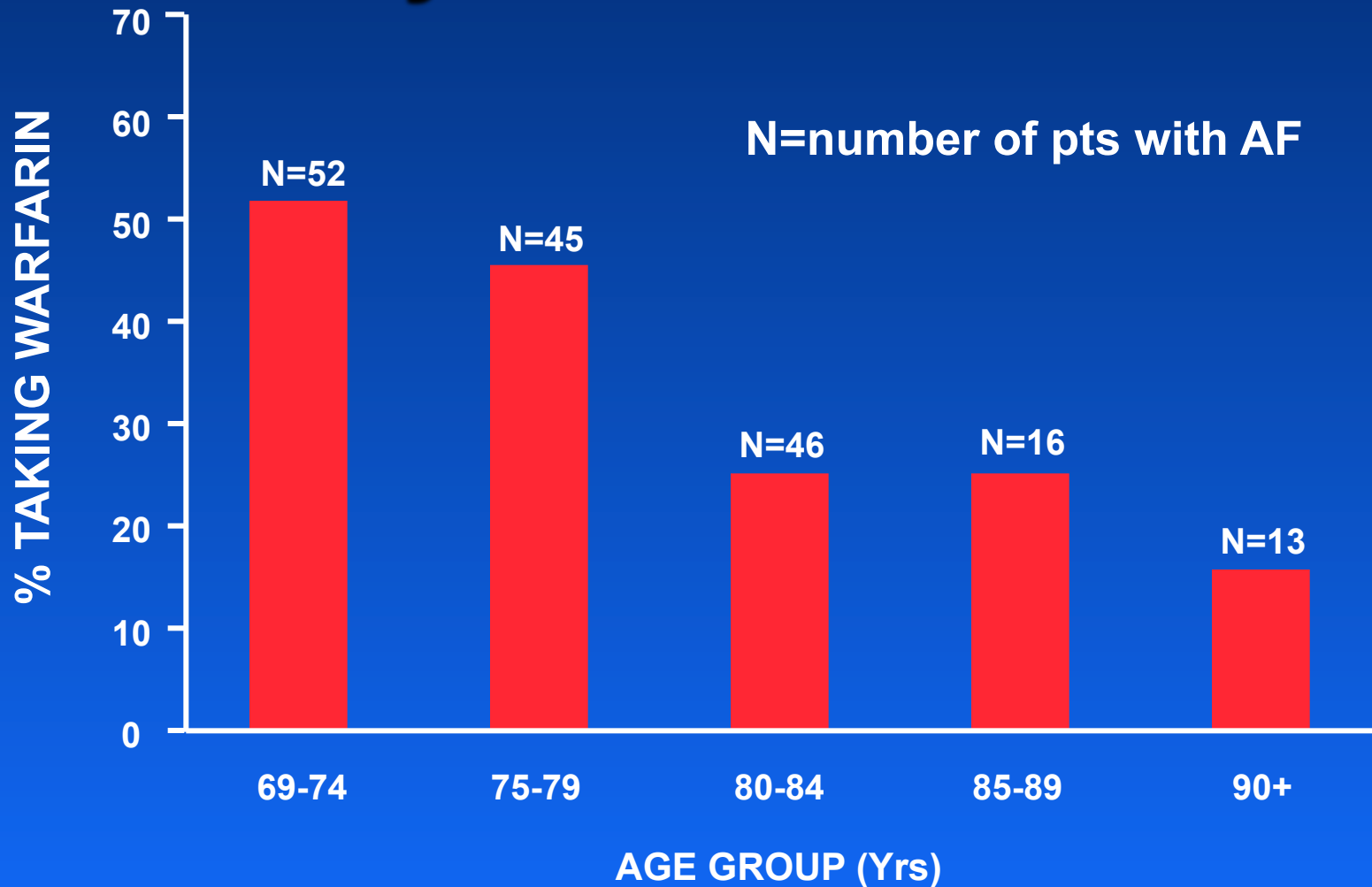
Effect of Age on Bleeding Risk* and Warfarin Use

*Perceived or actual bleeding risk includes fall risk, neuropsychological impairment, past bleeding episode, peptic ulcer disease, and aneurysm history

Legend: ▨ Warfarin Utilization   ■ Perceived or Actual Bleeding Risk

Waldo A. et al. J Am Coll Cardiol. 2005; 46: 1729 - 36.

NABOR

Age-Related Trends in AF

Risk of Stroke

An Unmet Need

OAC Use

The risk of stroke in AF increases dramatically with age.

However, the use of anticoagulation decreases.

Increasing Age

13
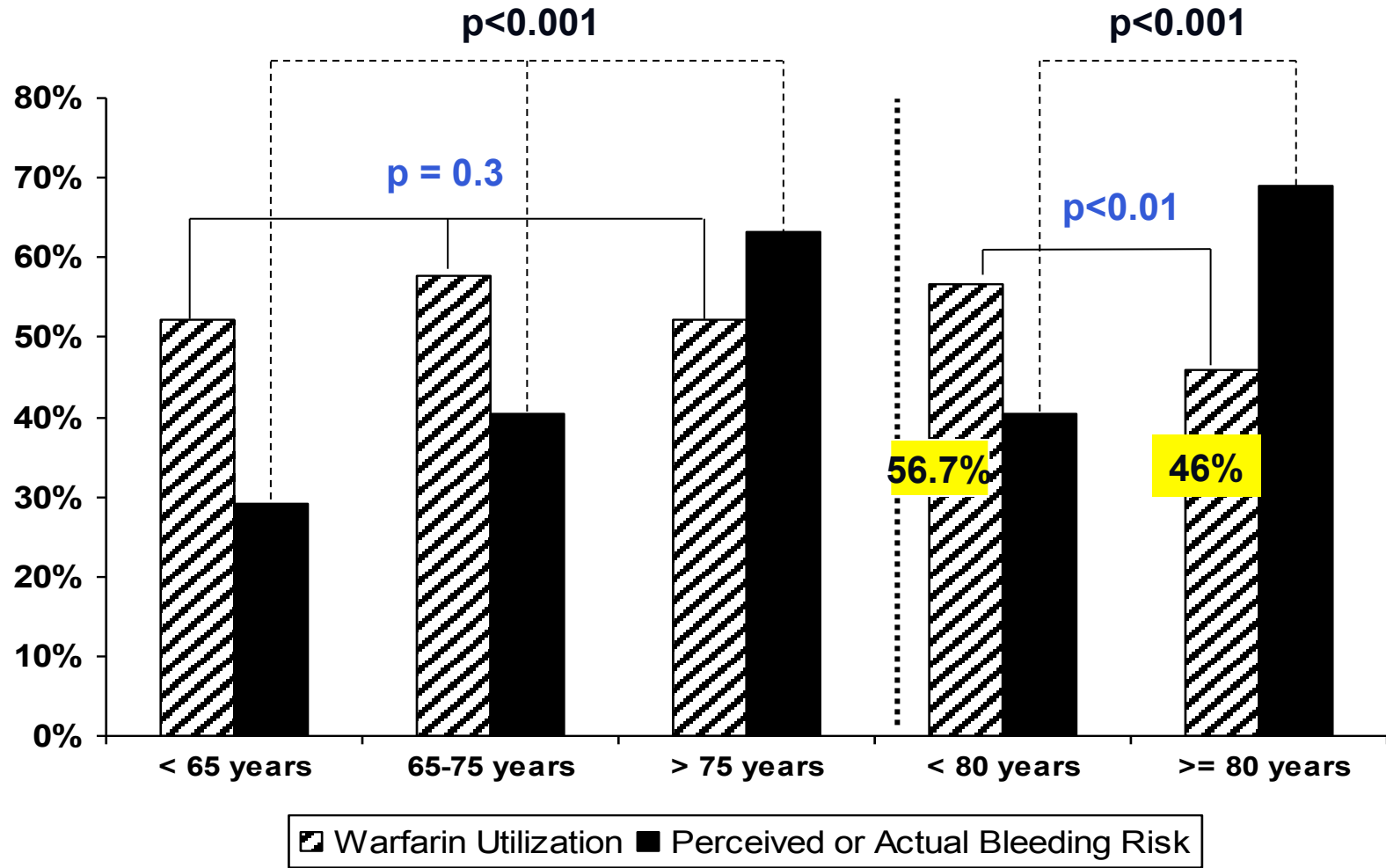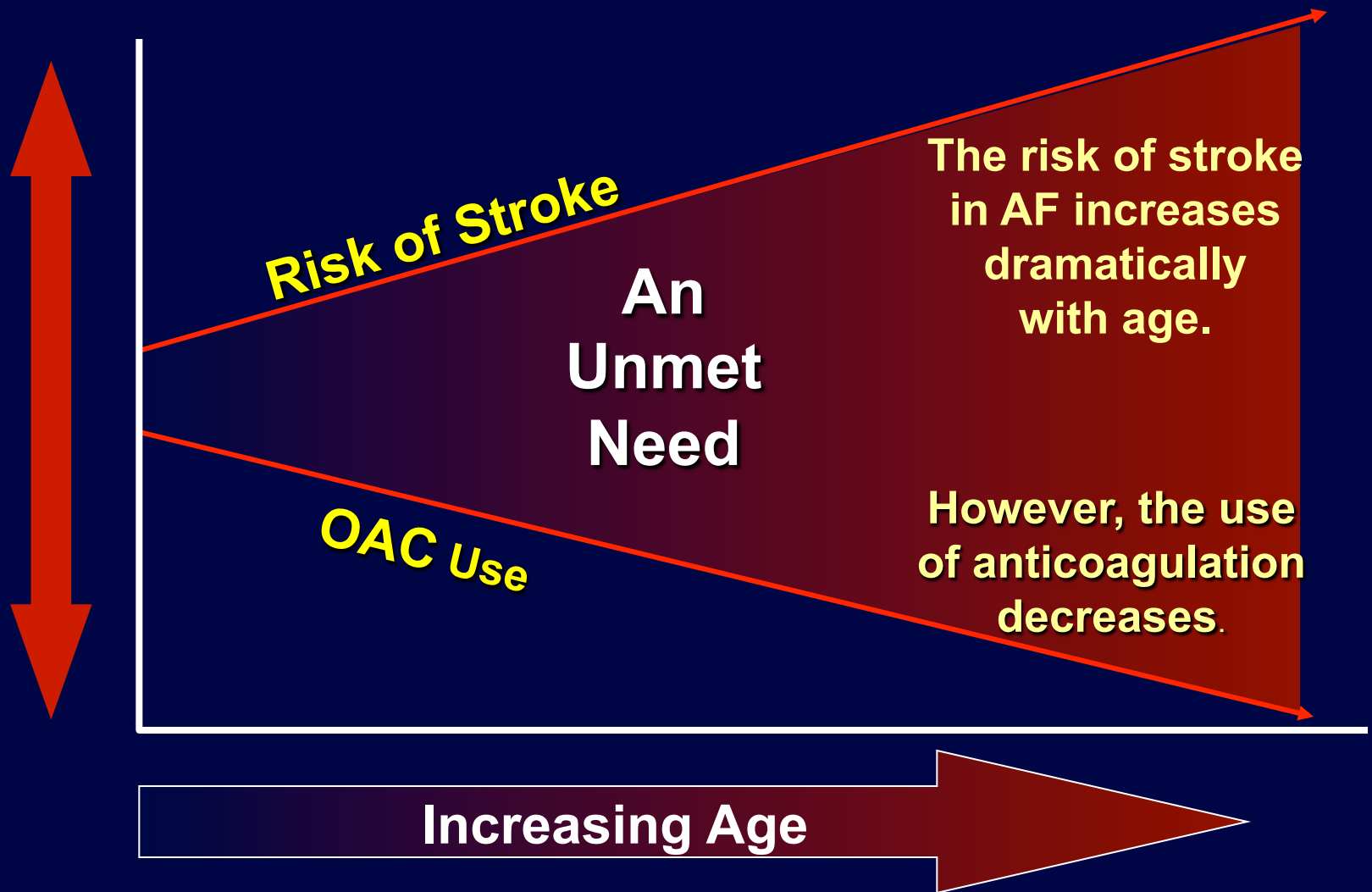
Prevalence of Eligible AF Patients Receiving Warfarin Therapy

Warfarin is prescribed for only 41% to 65% of eligible pts with AF, many of whom are considered "warfarin-unsuitable"

Percent patients treated with warfarin

Study	Percent
ATRIA[1] N=11,082	55
NABOR[2] N=945	54
N=405[3]	51
Medicare[4] N=17,272	65
N=116,969[5]	52
N=50,071[6]	41
Euro Heart Study[7] N=2,706	64
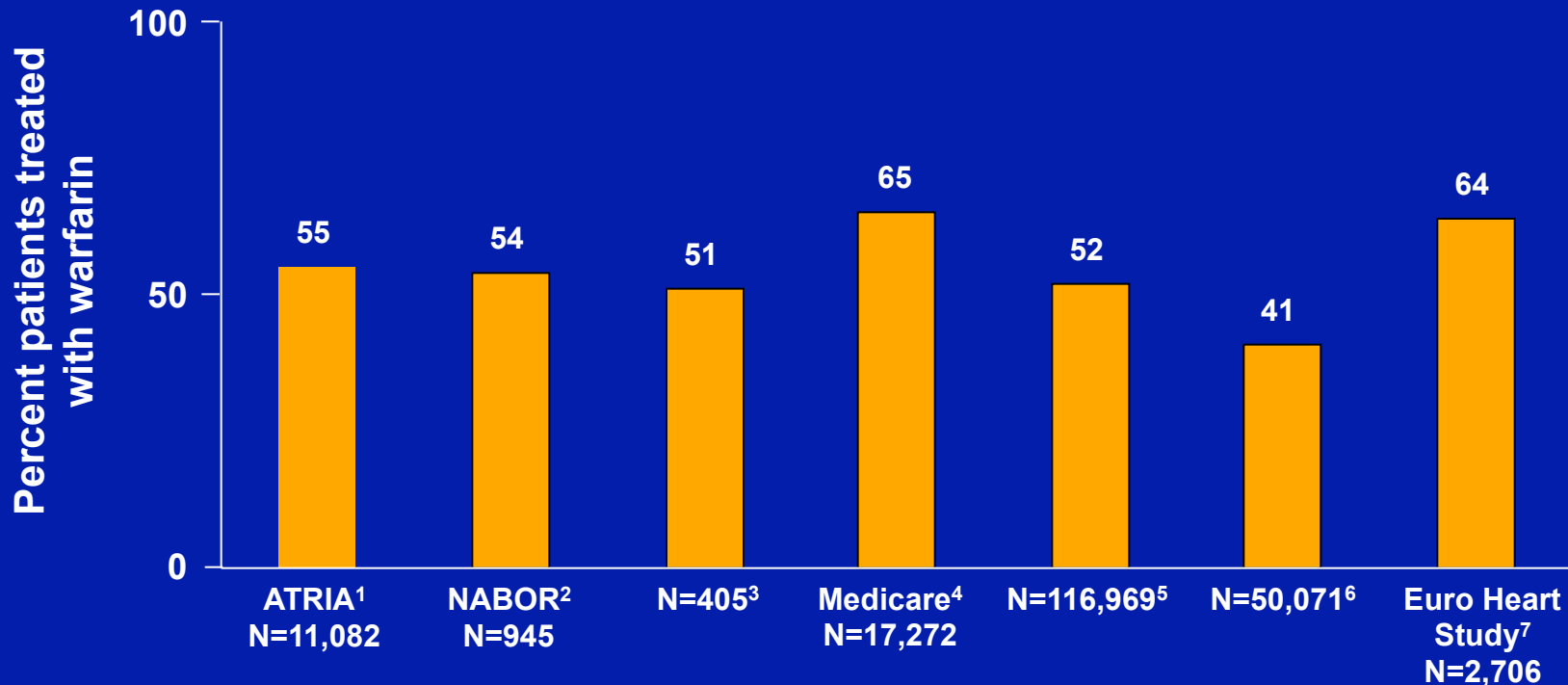
**ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation,
NABOR=National Anticoagulation Benchmark and Outcomes Report**

1. Go AS et al. *Ann Intern Med.* 1999;131:927-934.
2. Waldo AL et al. *J Am Coll Cardiol.* 2005;46:1729-1736.
3. Hylek EM et al. *Stroke.* 2006;37:1075-1080.
4. Birman-Deych E et al. *Stroke.* 2006;37:1070-1074.
5. Walker AM, Bennett D. *Heart Rhythm.* 2008;5:1365-1372.
6. Williams CJ et al. American College of Cardiology 58th Annual Scientific Session; March 29-31, 2009; Orlando, FL.
7. Nieuwlaat R et al. *Eur Heart J.* 2006;27:3018-3026.

Variables Associated with Use or Non Use of Warfarin Therapy (All Patients)

Independent Variable	OR	95%CI	p Value
Perceived/Actual Bleeding Risk	0.724	(0.54–0.95)	0.022
Persistent/Permanent AF	1.799	(1.37–2.34)	<0.001
Stroke/TIA/Embolic Event	1.586	(1.09–2.28)	0.014
Age > 80	0.663	(0.48–0.90)	0.008

NABOR

Analysis of High Risk AF Cohort Who Did <u>Not</u> Receive Warfarin

Perceived or Actual Bleeding Risk	(n) = 814	Frequency
Fall Risk	(339)	41.7%
Neuropsychological Impairment	(137)	16.8%
Past Bleeding Episode	(119)	14.6%
Peptic Ulcer Disease	(103)	12.7%
Aneurysm History	(42)	5.1%
None of these Factors	(351)	43.1%

Note: At least one bleeding risk factor was present in 47.4% of patients receiving warfarin versus 56.9% of patients receiving aspirin or no treatment (p <0.01).

Of those not receiving warfarin, only 2.9% were receiving clopidogrel or ticlopidine.

Waldo AL et al. J Am Coll Cardiol 2005; 46: 1729 - 36

NABOR

HAS-BLED Bleeding Risk Score

Letter	Clinical Characteristic	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	1
D	Drugs or alcohol (1 point each)	1 or 2

Maximum possible score is 9

Lip GY et al. J AM Coll Cardiol 2011;57:173-80.

Absolute Diffs in Hemorrhagic Stroke and Intracranial Bleeding with W vs NOAC are Small

Absolute Diffs:	Hemorrhagic Stroke – 0.19%/y Intracranial Bleed – 0.41%/y		Hemorrhagic Stroke Rate	Intracranial Bleeding Rate
TRIAL	Drug	Dose	%/year	%/year
RE-LY	War		0.38	0.74
	Dab	110 mg	0.12	0.23
	War		0.31	0.70
	Dab	150 mg	0.10	0.30
ROCKET AF	War		0.44	0.74
	Riv	20 mg	0.26	0.49
ARISTOTLE	War		0.47	0.80
	Api	5 mg	0.24	0.39
ENGAGE AF	War		0.47	0.85
	Edox	60 mg	0.26	0.39
	Edox	30 mg	0.16	0.26

Connolly SJ et al. NEJM 2009;361:1139-51; Patel MR et al. NEJM 2011,365:883-91; Granger CB et al. NEJM 2011;365:981-82; Giugliano RP et al. NEJM 2013;369:2093-104

The Swedish AF Cohort Study

- **Friberg et al. investigated how to maximize the net clinical benefit of oral anticoagulation (warfarin) by balancing ischemic stroke against intracranial hemorrhage in 182,678 AF patients enrolled in the Swedish National Hospital Discharge Register followed an average of 1.5 years**

- **Patients were classified according to stroke risk (CHADS$_2$ and CHA$_2$DS$_2$-VASc), and bleeding risk (HAS-BLED [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly])**

The Swedish AF Cohort Study: Net Clinical Benefit

- The net result favored warfarin treatment for all patients except for those at very low risk of ischemic stroke using the CHA_2DS_2-VASc score (score = 0)

- Those who appeared to have the best net benefit from warfarin were patients with the highest risk score with both risk score schemes

- Patients at very low risk of ischemic stroke (CHA_2DS_2-VASc score = 0) and moderately elevated bleeding risk appeared to have a net clinical disadvantage from warfarin treatment (i.e., -1.7%/yr)

- An approach to the anticoagulation issue could be to regard anticoagulation as the general rule for all AF patients except those at very low risk of stroke, those with a CHA_2DS_2-VASc score of 0, and those at extremely high risk of bleeding

- In this study, in only 0.4% of all patients did the risk of bleeding exceed the risk of ischemic stroke

- Conclusion: in almost all patients with AF, the risk of ischemic stroke without anticoagulant treatment is far higher than the risk of intracranial hemorrhage with anticoagulant treatment, and that most AF patients should be offered effective thromboprophylaxis with oral anticoagulation

Friberg L et al. Circulation 2012;125:2298-307

Relation between CHA2DS2-VASc scores and annual event rates of ischemic stroke and intracranial hemorrhage (ICH; left) and more widely defined thromboembolic events and bleeding (right) in relation to use of oral anticoagulation (OAC; n=159 013).

ischemic stroke and intracranial hemorrhage

thromboembolic events and bleeding

Friberg L et al. Circulation. 2012;125:2298-307
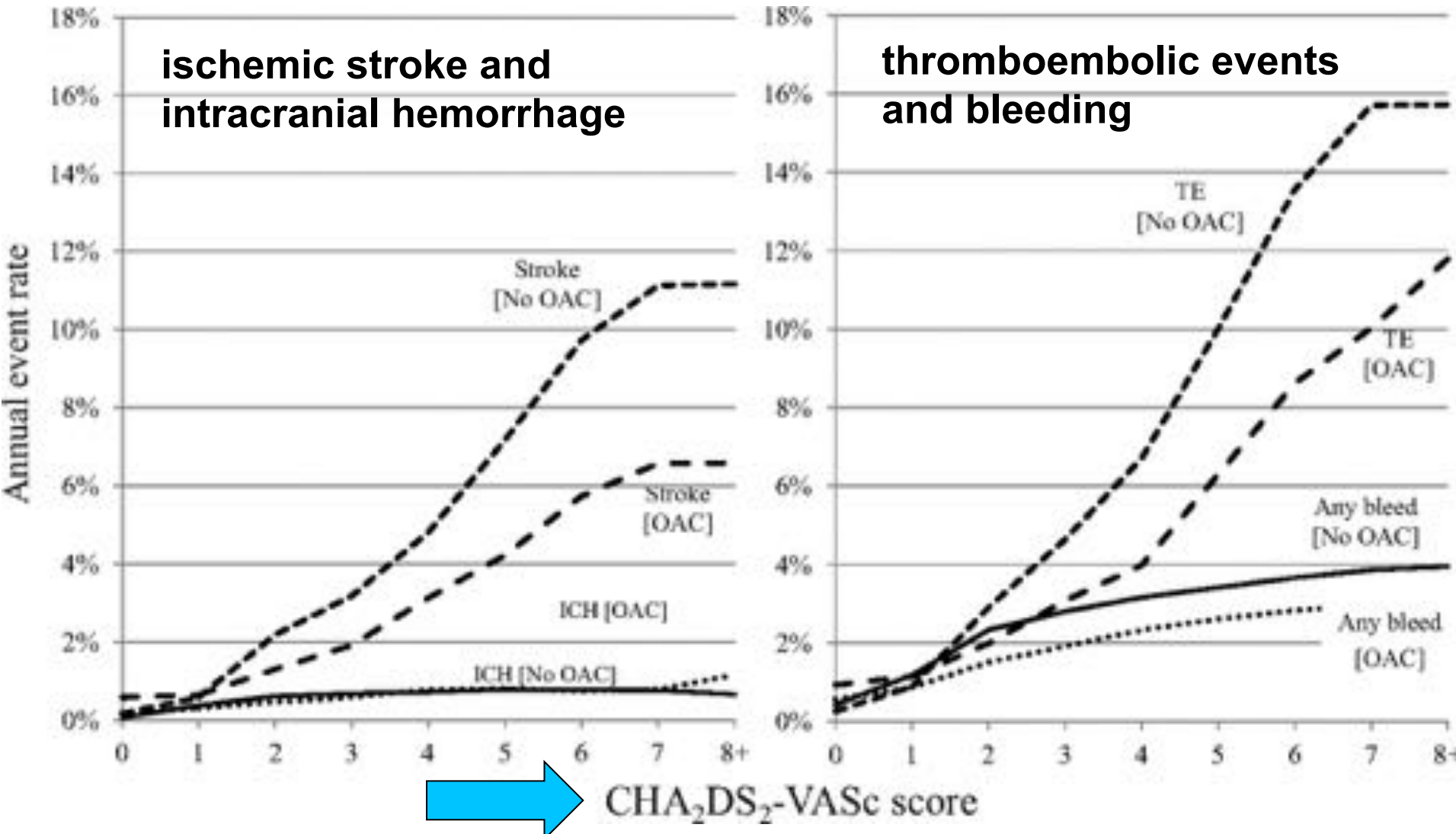
Relation between HAS-BLED scores and annual event rates of ischemic stroke and intracranial hemorrhage (ICH; left) and more widely defined thromboembolic events (TEs) and bleedings (right) in relation to use of oral anticoagulation (OAC; n=159 013).

ischemic stroke and intracranial hemorrhage

thromboembolic events and bleeding

Friberg L et al. Circulation. 2012;125:2298-307
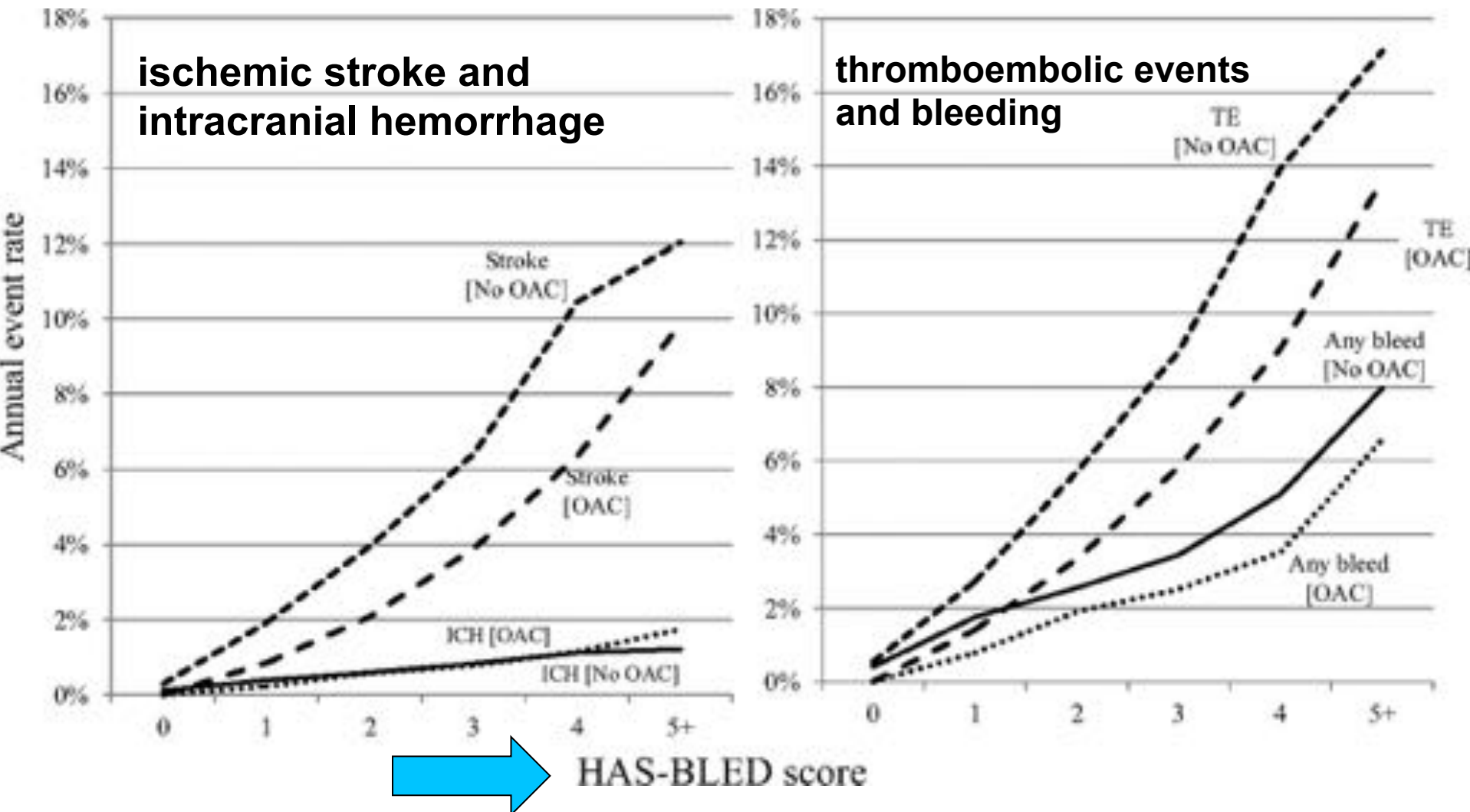
All-cause mortality, ischemic stroke, and intracranial bleeds in relation to OAC Rx in pts with different combos of stroke and bleeding risks using the CHA2DS2-VASc and HAS-BLED risk scores.

Risk for Intracranial bleeding

Risk for embolic stroke

Friberg L et al. Circulation. 2012;125:2298-307
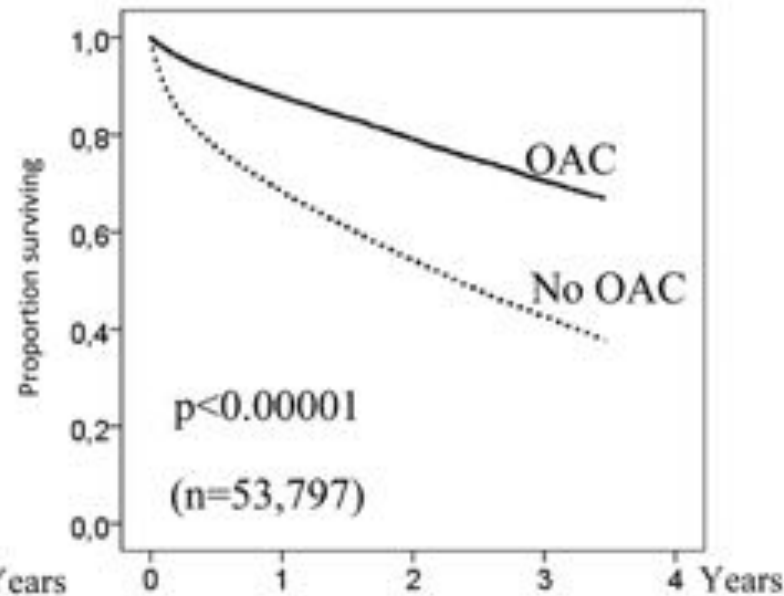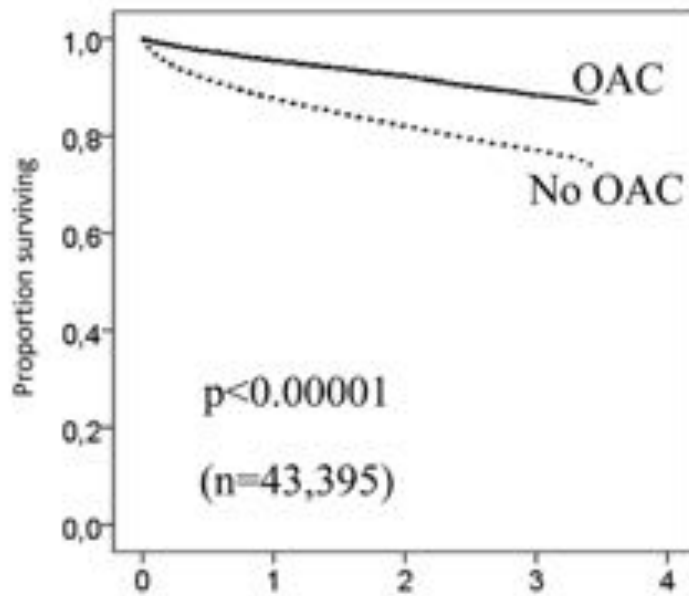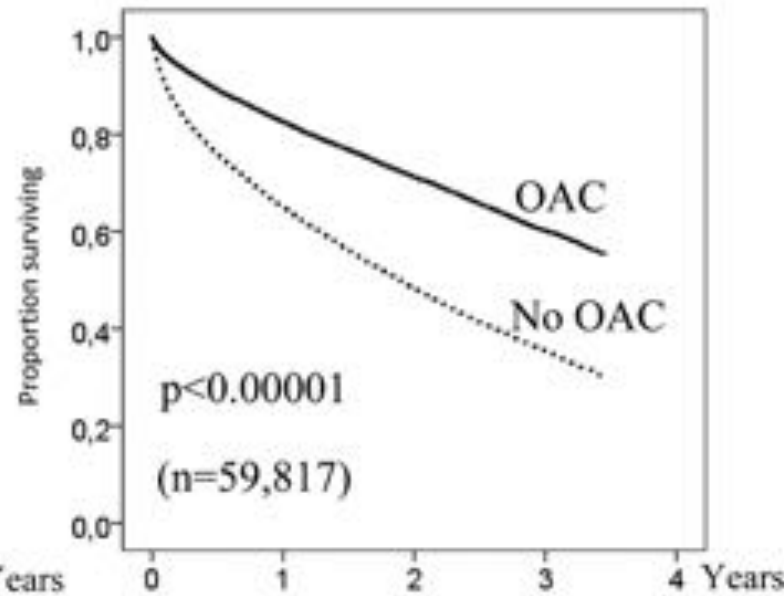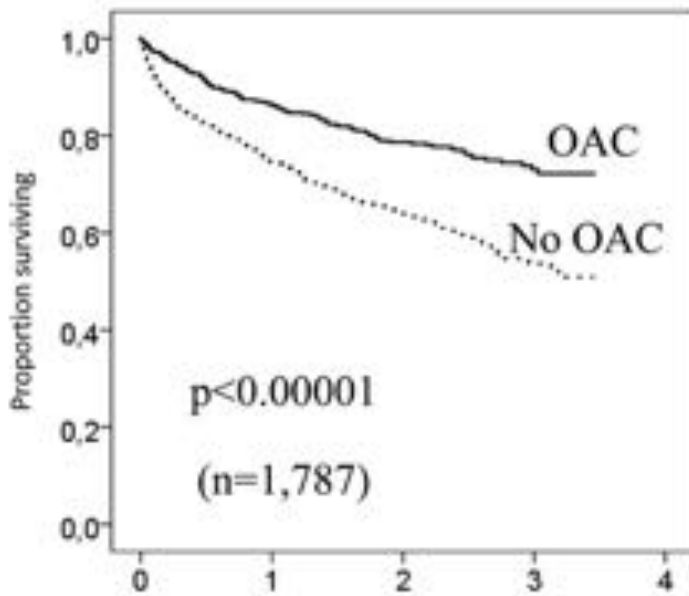
NOAC Phase 3 Bleeding
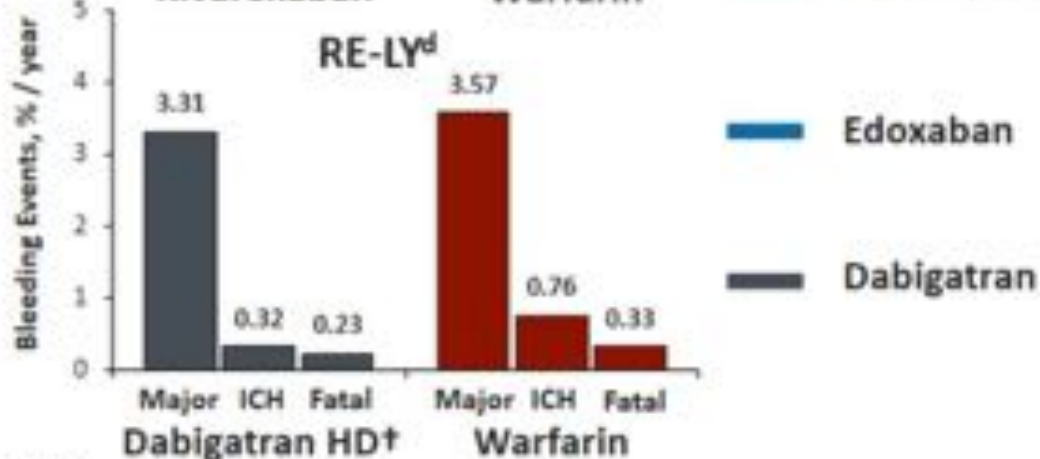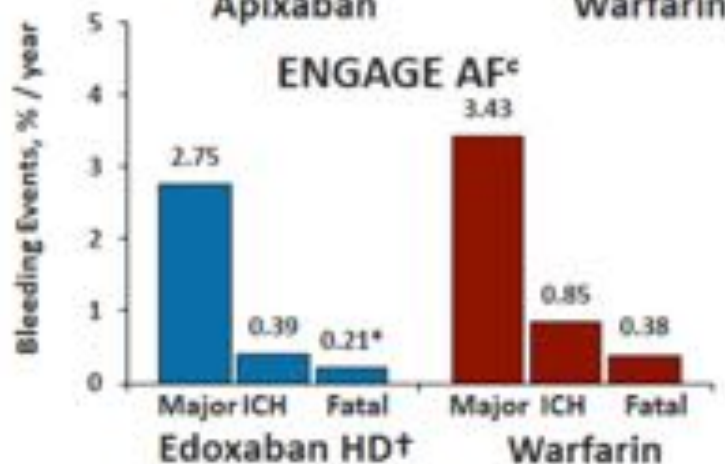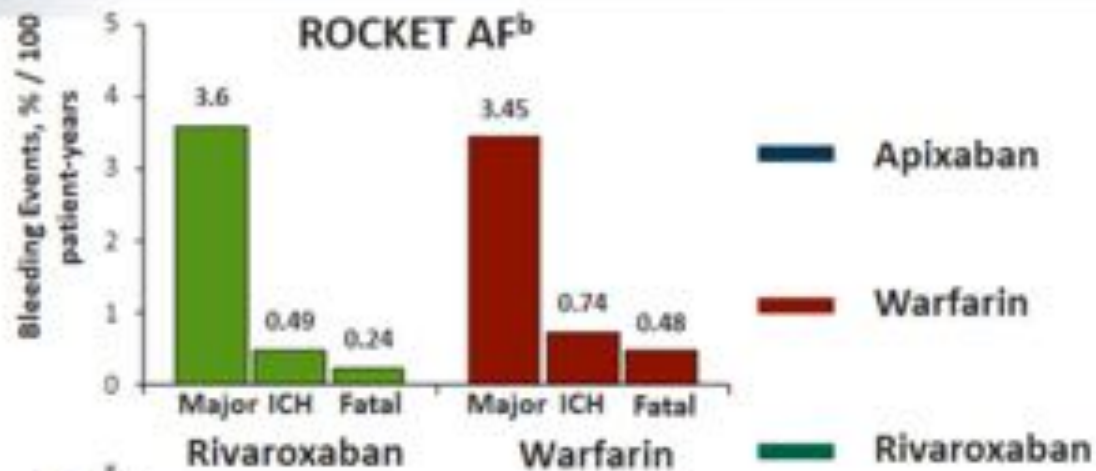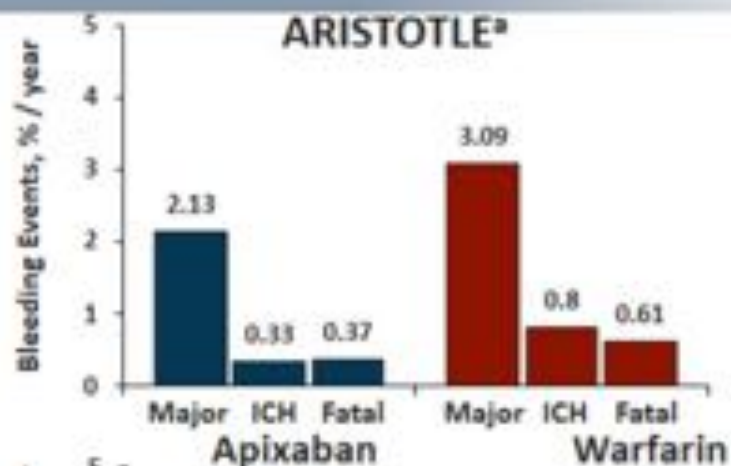
a. Granger CB, et al. N Engl J Med. 2011;365:981-992.
b. Patel MR, et al. N Engl J Med. 2011;365:883-891.
c. Giugliano RP, et al. N Engl J Med. 2013; 369:2093-2104.
d. Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151.

*Total event rate, % per year not reported.
†High dose.

The Swedish AF Cohort Study

- **The main finding of this study is that the risk of ischemic stroke without anticoagulant treatment exceeds the risk of intracranial bleeding with anticoagulant treatment at almost every combination of stroke and bleeding risks that were studied**

- **When the HAS-BLED risk of bleeding is high, the risk of ischemic stroke or of a thromboembolic event is even higher**

- **Indeed, the higher the bleeding risk was, the wider the gap was between the embolic risk and the bleeding risk**

- **Thus, there is more to be gained form OAC treatment**
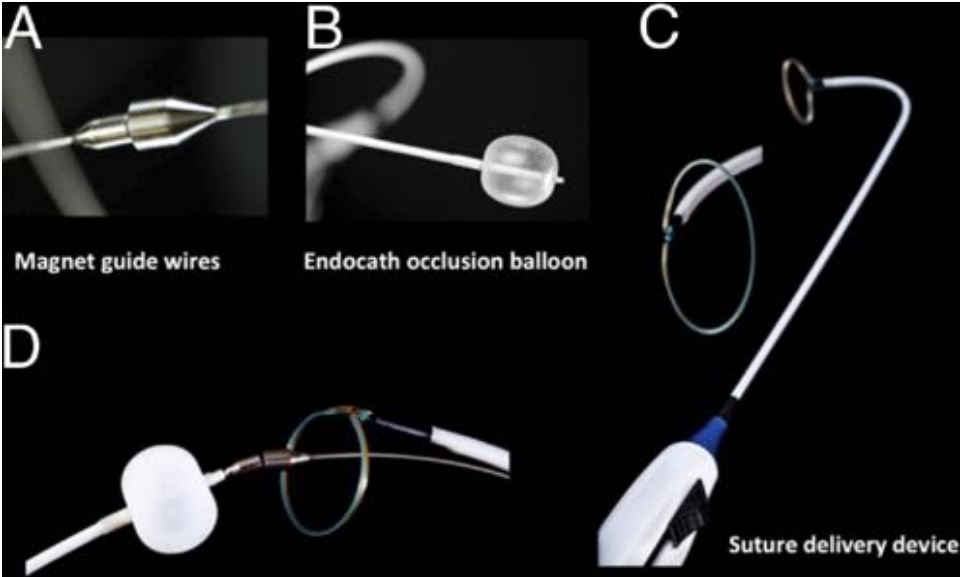
Left Atrial Appendage Occluders

Watchman® Occluder

Amplatzer® Cardiac Plug
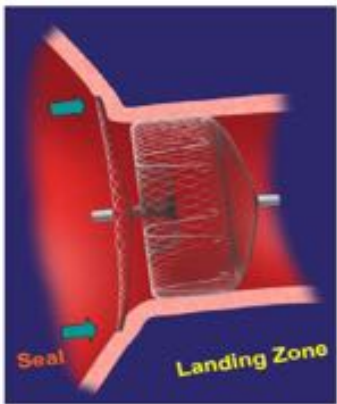
Lariat

**AtriClip**

Silent Cerebral Infarcts Frequently Occur in AF

Study	N		Prevalence (%)	
	AF	Controls	AF	Controls
Petersen, 1987	29	29	58	28
Guidotti, 1990	72	72	44.4	11.1
Feinberg, 1990	141	---	26	---
Ezekowitz, 1995	516	---	14.7	---

Petersen P, et al. *Stroke* 1987;18:1098-1100.

Guidotti M, et al. *Ir J Med Sci* 1990;159:96-7.

Feinberg WM, et al. *Arch Intern Med* 1990;150:2340-4.

Ezekowitz MD, et al. *Circulation* 1995;92:2178-82
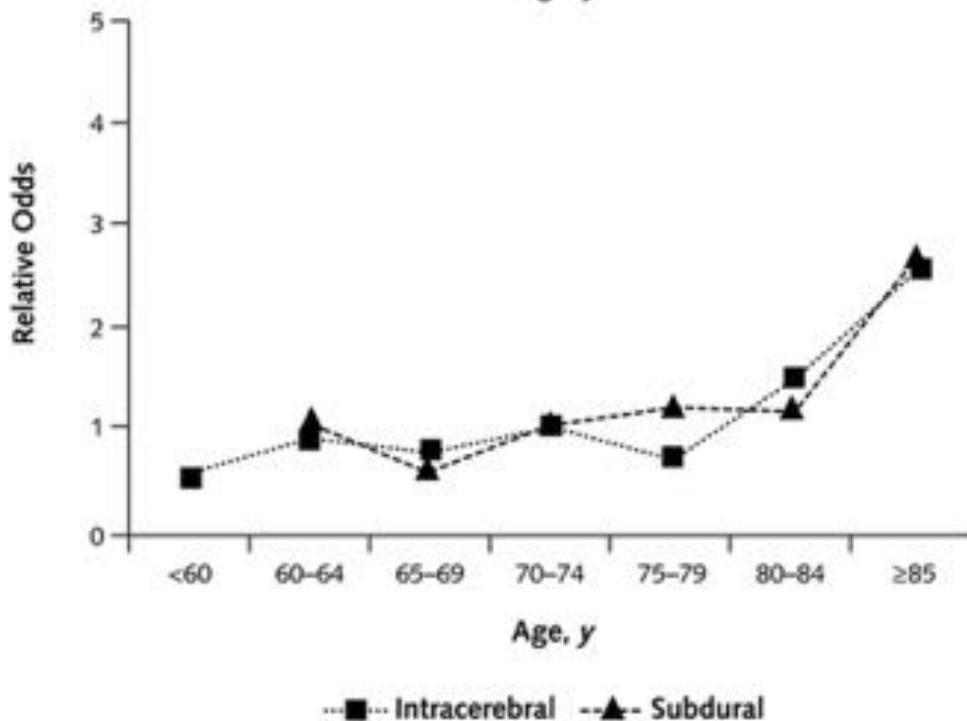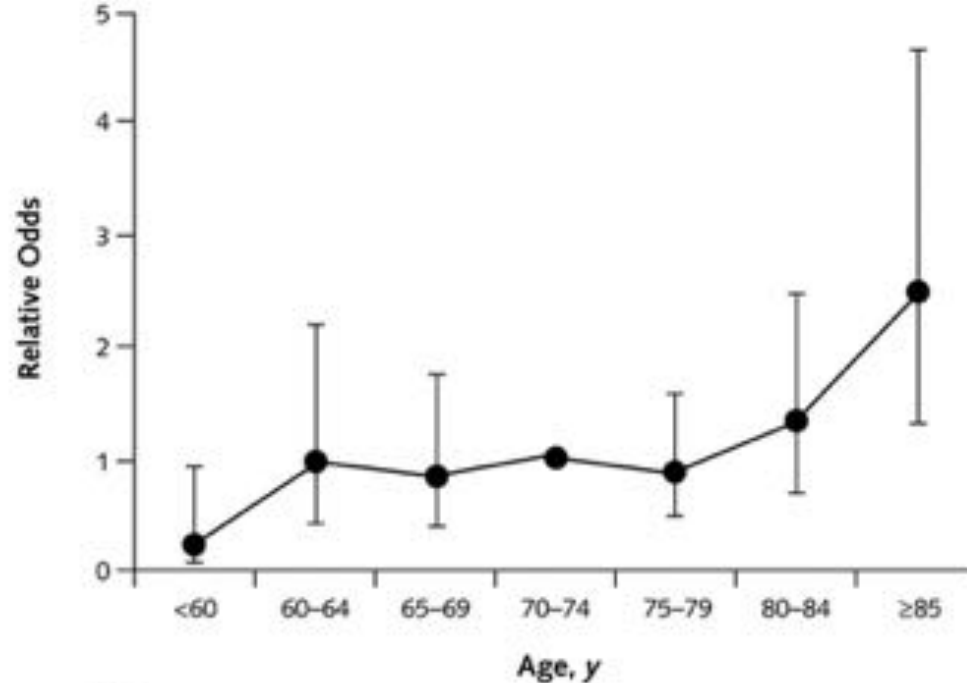
Adjusted relative odds of intracranial hemorrhage by age in 145 case-patients and 870 controls, overall (*top*) and stratified by hemorrhage (*bottom*). **The referent group was patients 70 to 74 years of age.** Data points are plotted at the midpoints of each age interval; vertical bars represent 95% CIs.

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

Adjusted relative odds of intracranial hemorrhage by international normalized ratio (*INR*) in 145 case-patients and 870 controls, overall (*top*) and stratified by hemorrhage (*bottom*). The referent group was patients with an INR of 2.0 to 3.0. Data points are plotted at the midpoints of each INR interval; vertical bars represent 95% CIs.

Fang, MC et al Ann Intern Med 2004;141:745-752