Stroke, bleeding and risk scores in atrial fibrillation

Stefan Bertog, Laura Vaskelyte, Markus Reinartz, Ilona Hofmann, Sameer Gafoor, Horst Sievert

CardioVascular Center

Frankfurt

In Partnership with the ACC
tct2014
CARDIOVASCULAR RESEARCH FOUNDATION

Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support • Consulting Fees/Honoraria • Major Stock Shareholder/Equity • Royalty Income • Ownership/Founder • Intellectual Property Rights • Other Financial Benefit	• CardioRenal LLC

Stroke and atrial fibrillation

- Does atrial fibrillation "*cause*" strokes?

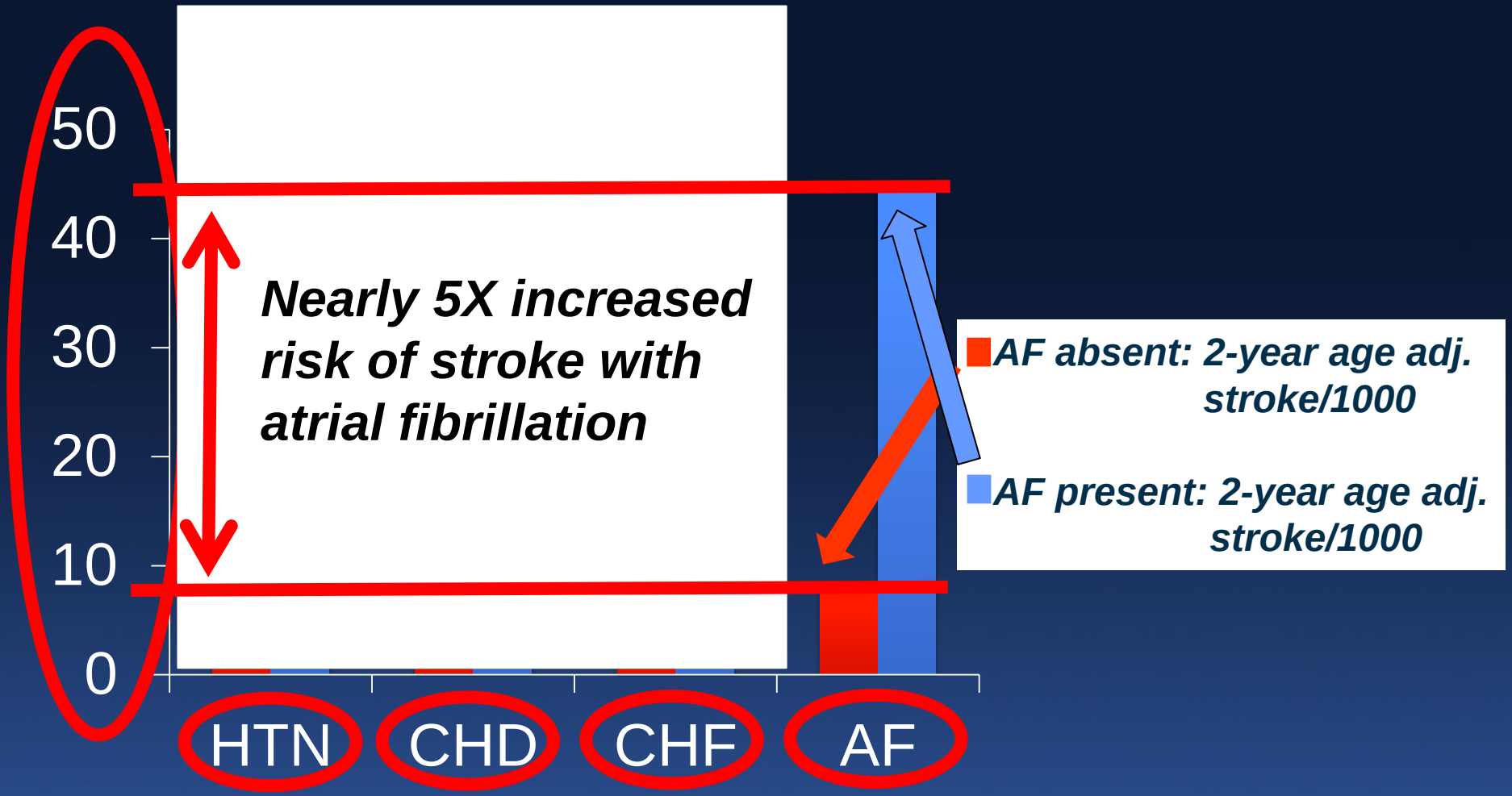
Stroke and atrial fibrillation

- Is atrial fibrillation ***associated with*** an increased stroke risk?
- Is the increased stroke risk in atrial fibrillation the ***result of LAA thrombi***?

Stroke and atrial fibrillation

- Framingham Study
  - ~5K healthy individuals enrolled in 1948
  - Followed biennially
  - Cardiovascular events recorded

Stroke and atrial fibrillation



Wolf et al. Stroke 1991;22:983-988

Stroke and atrial fibrillation

Well, this could just be a reflection of the patients' ages and co-morbidities…..

Stroke and atrial fibrillation

Estimated relative risk adjusted for other stroke risk factors (HTN, CHF, CAD)

	Age group			
	50-59	60-69	70-79	80-89
Atrial fibrillation	4	2.6	3.3	4.5

Wolf et al. Stroke 1991;22:983-988

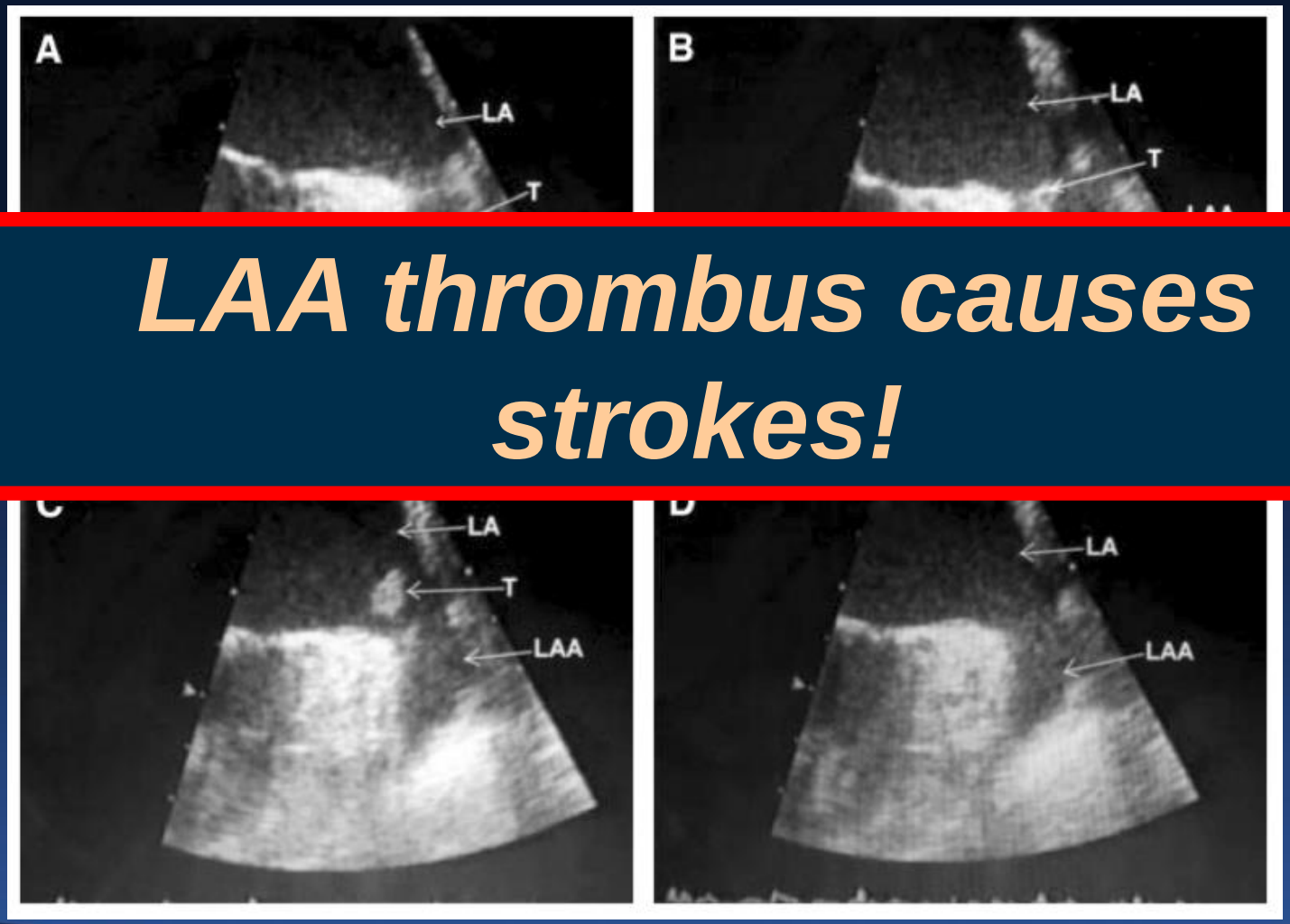
Stroke and atrial fibrillation

- …OK, atrial fibrillation is ***associated with*** an increased stroke risk
- …It appears to be an ***independent risk factor*** for stroke

Stroke and atrial fibrillation

- Is this risk relationship due to thrombi in the LAA?
  - Anatomical and physiological plausibility
  - Echocardiography and pathological specimens

Disappearing thrombus resulting in stroke



LAA thrombus causes strokes!

Parekh et al. Circ 2006;114:e513

Thrombus location

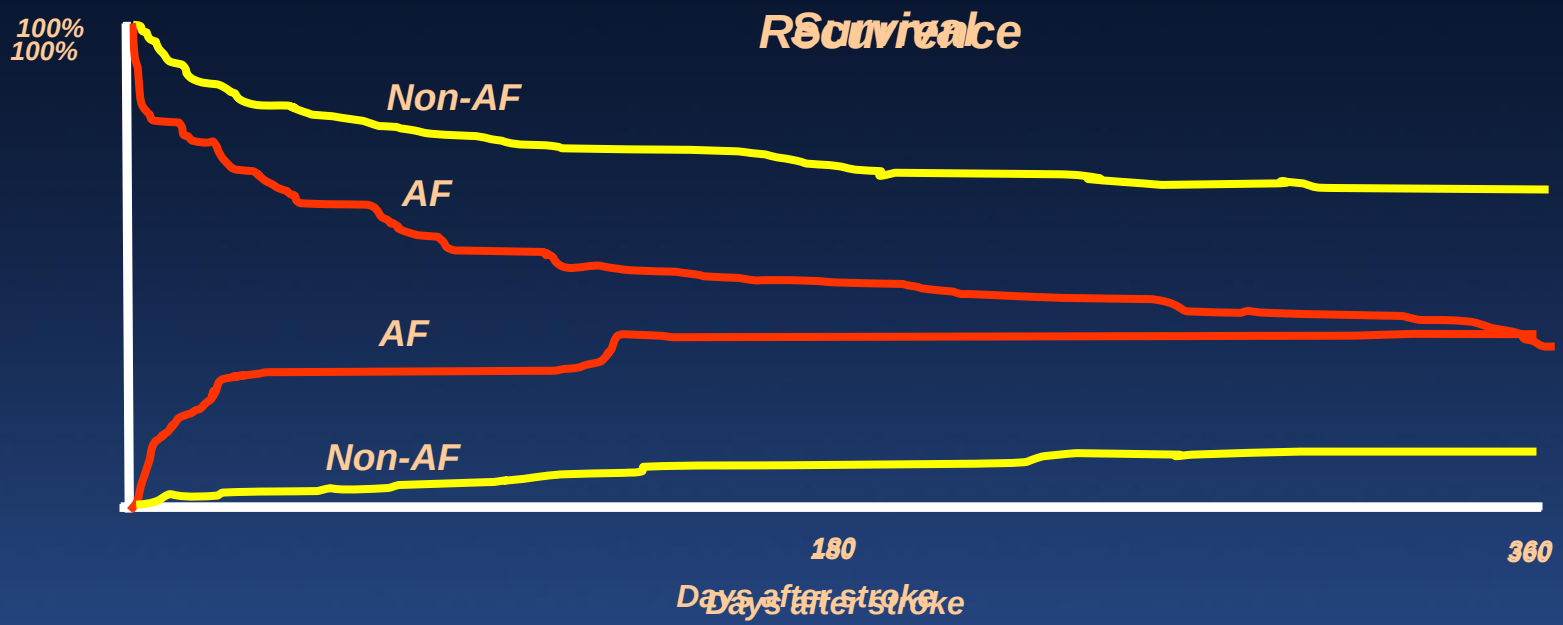
Type of examination	No. of pts	LA appendage	LA cavity
TEE	317	66	1

90% of thrombi in non-valvular atrial fibrillation are in the LAA

TEE and surgery	171	8	3
SPAF III TEE	359	19	1
TEE	272	19	0
TEE	60	6	0
Total	1288	201	21

Blackshear and Odell.Ann Thorac Surg 1996;61:755-9

Stroke size and recurrence in atrial fibrillation



Lin et al. Stroke 1996;27(10:1760-4

Stroke and atrial fibrillation

- Atrial fibrillation is an independent risk factor for strokes
- Thrombi are located overwhelmingly in the LAA
- Strokes attributed to atrial fibrillation are typically larger than strokes of other etiology

Stroke risk

- What is the stroke risk without anticoagulation?
- What is the stroke risk with anticoagulation?

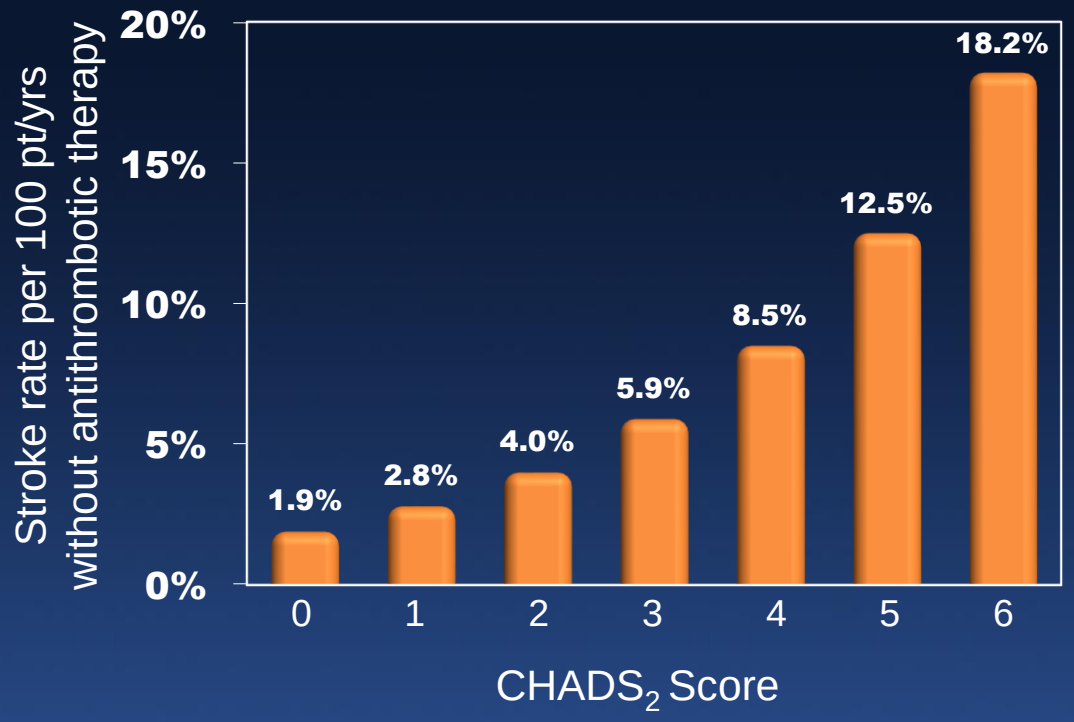
$CHADS_2$

- **$CHADS_2$, developed and validated by Gage et al, is a system for establishing the risk of stroke in patients with non-rheumatic atrial fibrillation[1]**
  - **Patients are awarded points based on comorbidities**

	Condition	Points
C	Congestive heart failure	1
H	Hypertension	1
A	Age ≥75 years	1
D	Diabetes mellitus	1
S_2	Previous stroke or TIA	2

European Society of Cardiology Guidelines[2]

$CHADS_2$ score	Treatment
0	Aspirin
1	Aspirin or warfarin*
≥2	Warfarin



1. Gage BF et al, *JAMA* 2001;285:2864–2870
2. Camm AJ et al, *Eur Heart J* 2010;31, 2369–2429

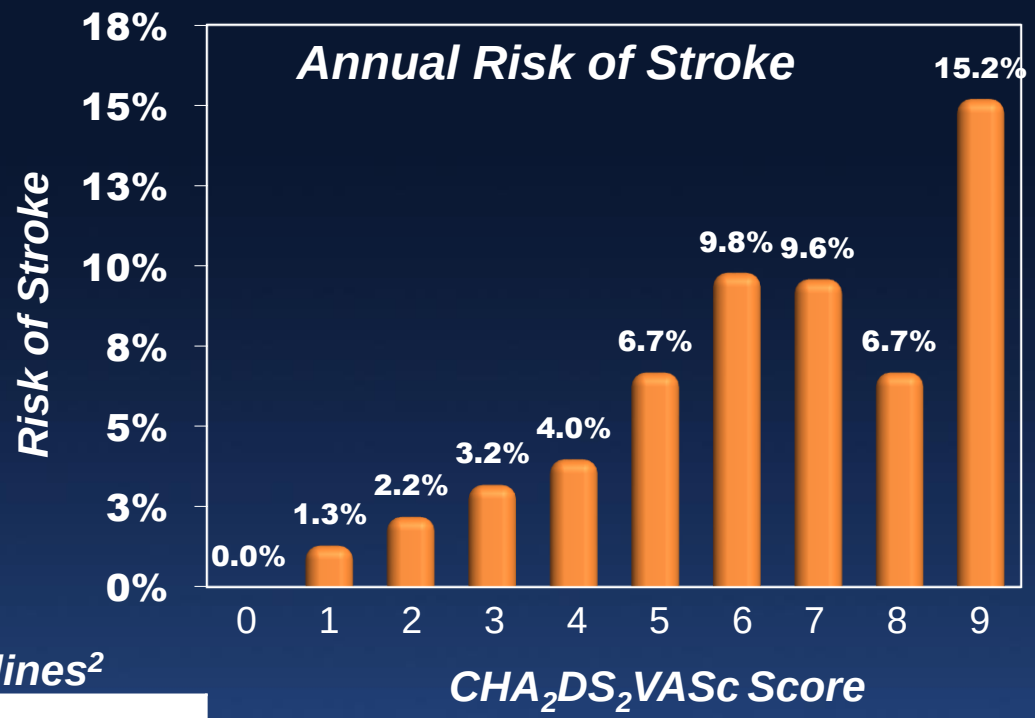
$CHADS_2$

- **Problem:**
  - **It does not perform well in patients with low scores (0-1)**
  - **There are other risk factors that determine stroke risk not accounted for**

CHA_2DS_2VASc

- **CHA_2DS_2VASc, developed by Lip et al, is a refinement of the older $CHADS_2$ Score which includes additional stroke risk factors and puts greater emphasis on age as a risk factor[1]**

	Condition/Risk Factor	Points
C	Congestive heart failure	1
H	Hypertension	1
A_2	Age ≥75 years	2
D	Diabetes Mellitus	1
S_2	Previous stroke or TIA	2
V	Vascular disease	1
A	Age 65-74 years	1
Sc	Sex (female gender)	1



European Society of Cardiology Guidelines[2]

CHA_2DS_2-VASc Score	Treatment
0	Aspirin
1	Aspirin or warfarin or dabigatran
≥2	Warfarin or dabigatran

1. *Lip GY et al, Chest 2010;137(2):263-72*
2. *Camm AJ et al, Eur Heart J 2010;31, 2369–2429*

Added value of CHADSvasc

- Danish registry of “low risks” patients (CHADS-2 score 0-1) with atrial fibrillation not treated with anticoagulation
- ~47K patients included

Added value of CHADSvasc

	Annual stroke risk
CHADS 0	*1.28%*
CHADSvasc 0	*0.76%*
CHADSvasc 1	*1.44%*
CHADSvasc 2	*2.11%*
CHADSvasc 3	*2.10%*
CHADS 1	*3.61%*
CHADSvasc 1	*1.46%*
CHADSvasc 2	*3.26%*
CHADSvasc 3	*4.28%*
CHADSvasc 4	*4.93%*

Olesen et al. Thromb Heamost 2012;107:1172-1179

Step 1

Age, y	Points
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	Points
Men	0
Women	6

Step 3

Systolic Blood Pressure, mm Hg	Points
<120	0
120-139	1
140-159	2
160-179	3
>179	4

Step 4

Diabetes	Points
No	0
Yes	5

Step 5

Prior Stroke or TIA	Points
No	0
Yes	6

Step 6

Add Up Points From Steps 1 Through 5

Look Up Predicted 5-Year Risk of Stroke in Table

Predicted 5-year Risk of Stroke

Total Points	5- Year 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

	No. at Risk	KM Rate at 2 Years
$CHADS_2$		
0	2753	1.0
1	4191	2.5
2	3579	4.7
3	1957	7.3
4	733	8.8
5	288	11.0
6	58	16.0
R_2CHADS_2		
0	2414	0.8
1	3038	2.2
2	2425	4.0
3	2070	4.2
4	1807	6.0
5	1171	9.2
6	445	9.3
7	157	11.6
8	32	11.4

+2 for CrCl of <60

Other prediction models

- SPAF
- AFI
- Community-based risk model based on Framingham
- R2CHADS2
- ATRIA

Risk Factor	Points Without Prior Stroke	Points With Prior Stroke
Age, y		
≥85	6	9
75 to 84	5	7
65 to 74	3	7
<65	0	8
Female	1	1
Diabetes	1	1
CHF	1	1
Hypertension	1	1
Proteinuria	1	1
eGFR<45 or ESRD	1	1

Points	Rate per 100 Person-Years
0	0.08
1	0.43
2	0.99
3	0.73
4	0.64
5	0.99
6	1.91
7	2.50
8	3.86
9	4.33
10	6.35
11	6.18
12	10.95
13	7.52
14	16.36
15	0

Singer et al. J Am Heart Assoc. 2013:21;2(3)

How about LAA morphology?

- Retrospective study
- 932 pts
- Scheduled for Afib ablation
  - 48% chicken wing
  - 30% Cactus
  - 19% Windsock
  - 3% Cauliflower

% with prior stroke

4%

12%

10%

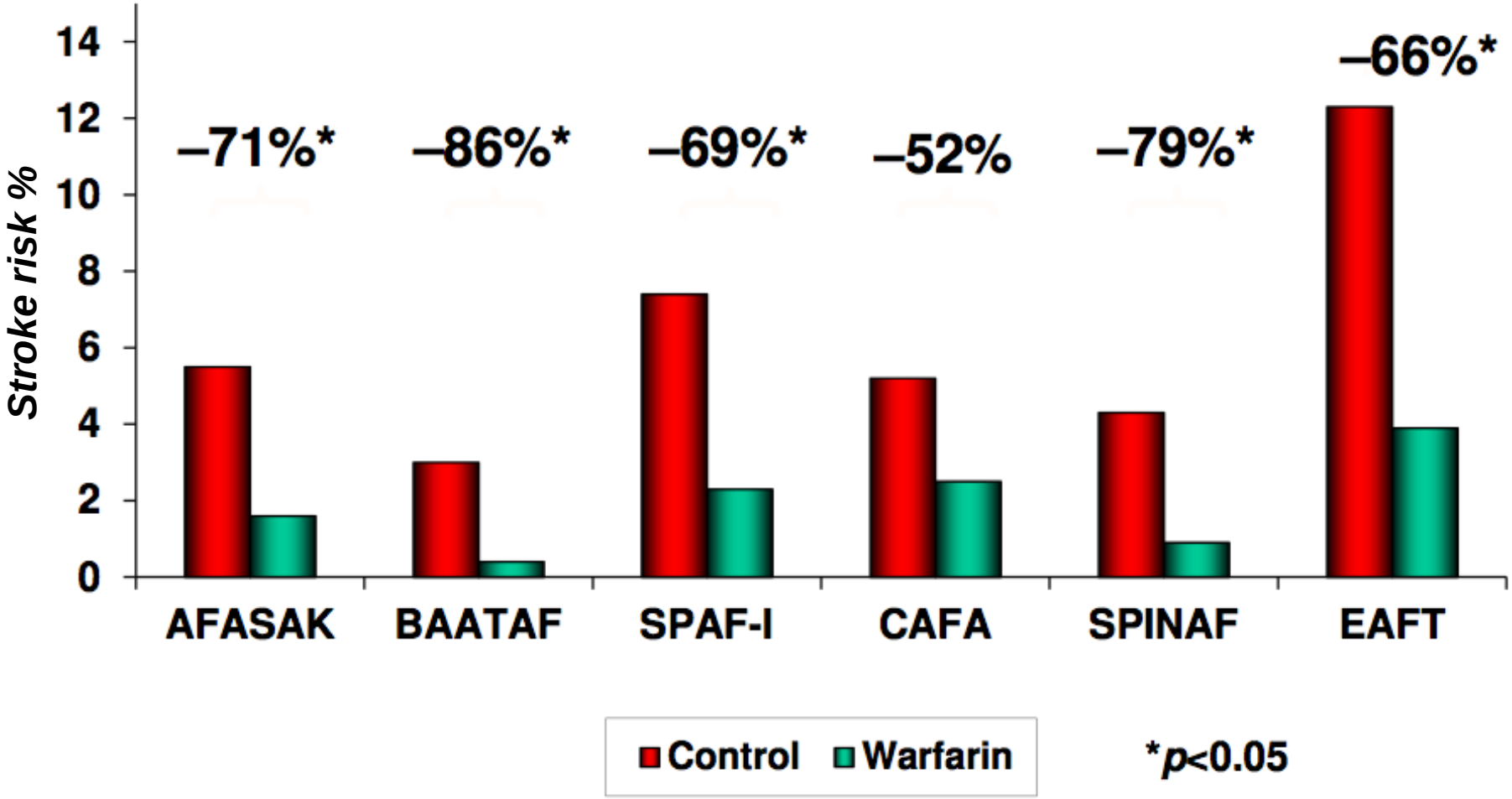
18%

OR 0.21 CI: 0.05-0.91

Stroke risk

- What is the stroke risk without anticoagulation?
- What is the stroke risk with anticoagulation?

Efficacy of warfarin in afib



Hart et al. Ann Intern Med 1999;131:492-501

Bleeding risk

- How about bleeding risk?

Warfarin and bleeding

- Meta-analysis (AFASAK 1, EAFT, PATAF, SPAF 2, AFASAK 2, SPAF 3):
  - Annual major bleeding: 2.2%
  - 15% of all major bleeding was lethal
  - Major bleeding was significantly higher than in control groups

Van Walraven et al. JAMA 2002;288(19):2441-48

Warfarin and bleeding

- **Intracranial hemorrhage?**
  - **Cohort study ~11K patients with atrial fibrillation**
    - **Annual intracranial hemorrhage (0.46% versus 0.23%, OR: 1.94, CI: 1.25-3.03)**
  - **Metanalysis (AFASAK, SPAF, BAATAF, CAFA, SPINAF, EAFT):**
    - **Annual intracranial hemorrhage (0.3% on warfarin versus 0.1% in the placebo group)**

Go et al. JAMA 2003;290(20): 2685-2692)
Hart et al. Ann Intern Med 1999;131:492-501

LAA closure

- **Warfarin is associated with a significant bleeding risk including intracranial hemorrhage**

Quantifying bleeding risk

- **HAS-BLED risk score:**

	Points
HTN	1
Renal failure	1
Liver dysfunction	1
Stroke	1
Bleeding tendency	1
Labile INRs	1
Age >65	1
Drugs (ASA, NSAIDS)	1
ETOH	1
	Max 9

HAS-BLED score (total points)	Bleeds/100 pt-yrs
0	1.13
1	1.02
2	1.88
3	3.74
4	8.7
5 to 9	Insuff. data

Pisters et al. Chest. 2010; 138:1093-100

Quantifying bleeding risk

- **HEMORRH2HAGES risk index:**

HEMORR$_2$HAGES		
Letter	**Clinical Characteristic**	**Points**
H	Hepatic or Renal Disease	1
E	Ethanol Abuse	1
M	Malignancy	1
O	Older Age	1
R	Reduced Platelet Count or Function	1
R	Rebleeding Risk	2
H	Hypertension	1
A	Anemia	1
G	Genetic Factors	1
E	Excessive Fall Risk	1
S	Stroke	1
Maximum Score		12

0-1: low
2-3: intermediate
>3: high

Gage et al. Am Heart J. 2006; 151:713-719

Quantifying bleeding risk

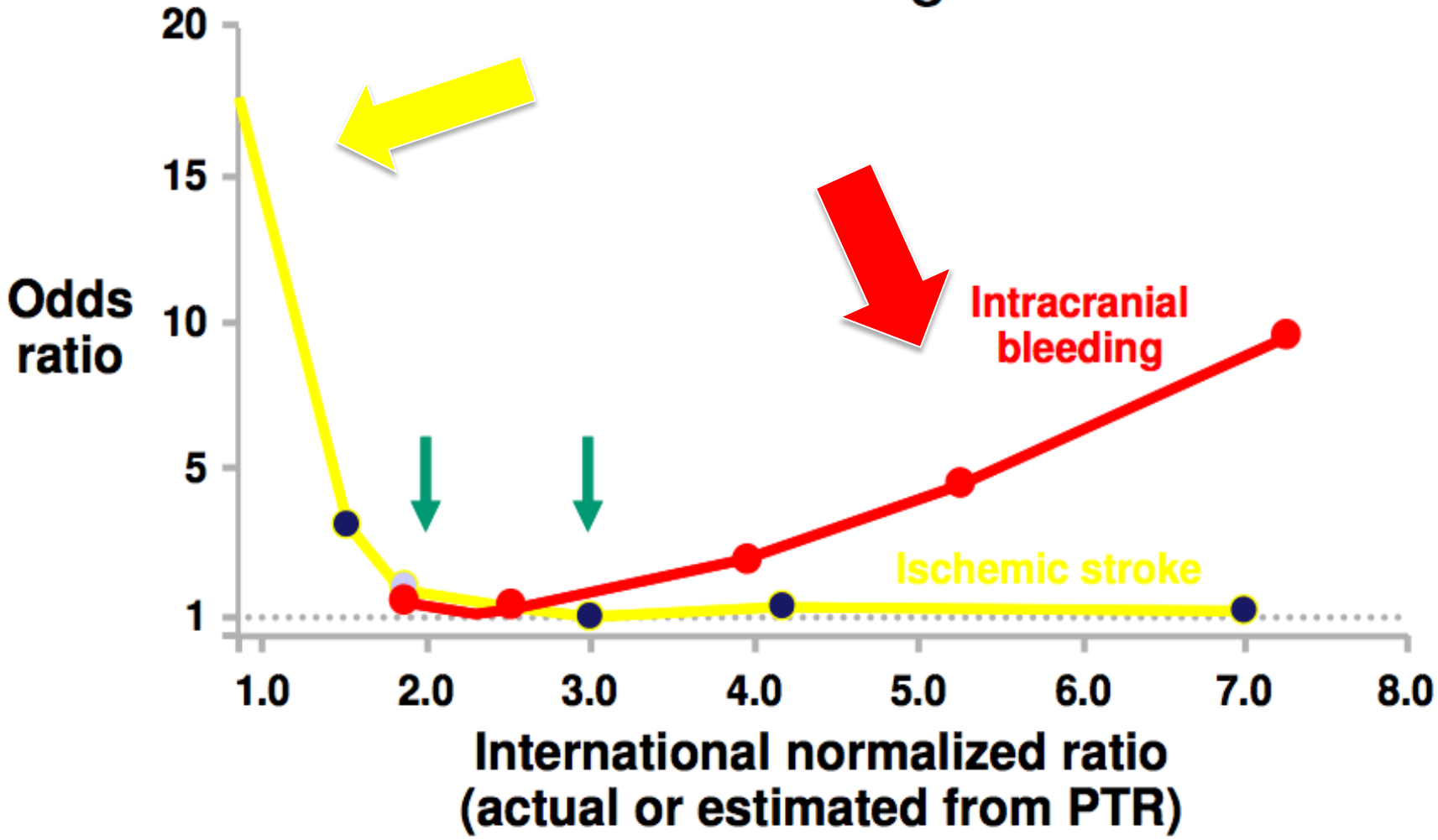
- **ATRIA risk score:**

ATRIA	
Clinical Characteristic	**Points**
Anemia	3
Severe Renal Disease	3
Age ≥75 Years	2
Prior Bleeding	1
Hypertension	1
Maximum Score	10

0-3: low (0.8%)
4: intermediate (2.6%)
>4: high (5.8%)

Fang et al. J Am Coll Cardiol. 2011; 58:395-401

Stroke and bleeding risk depending on INR



Hylek EM and Singer DE: Ann Intern Med 120:897, 1994
Hylek EM et al: N Engl J Med 335:540, 1996

Warfarin and bleeding

- **Importantly, risk factors of stroke also are risk factors for hemorrhage**

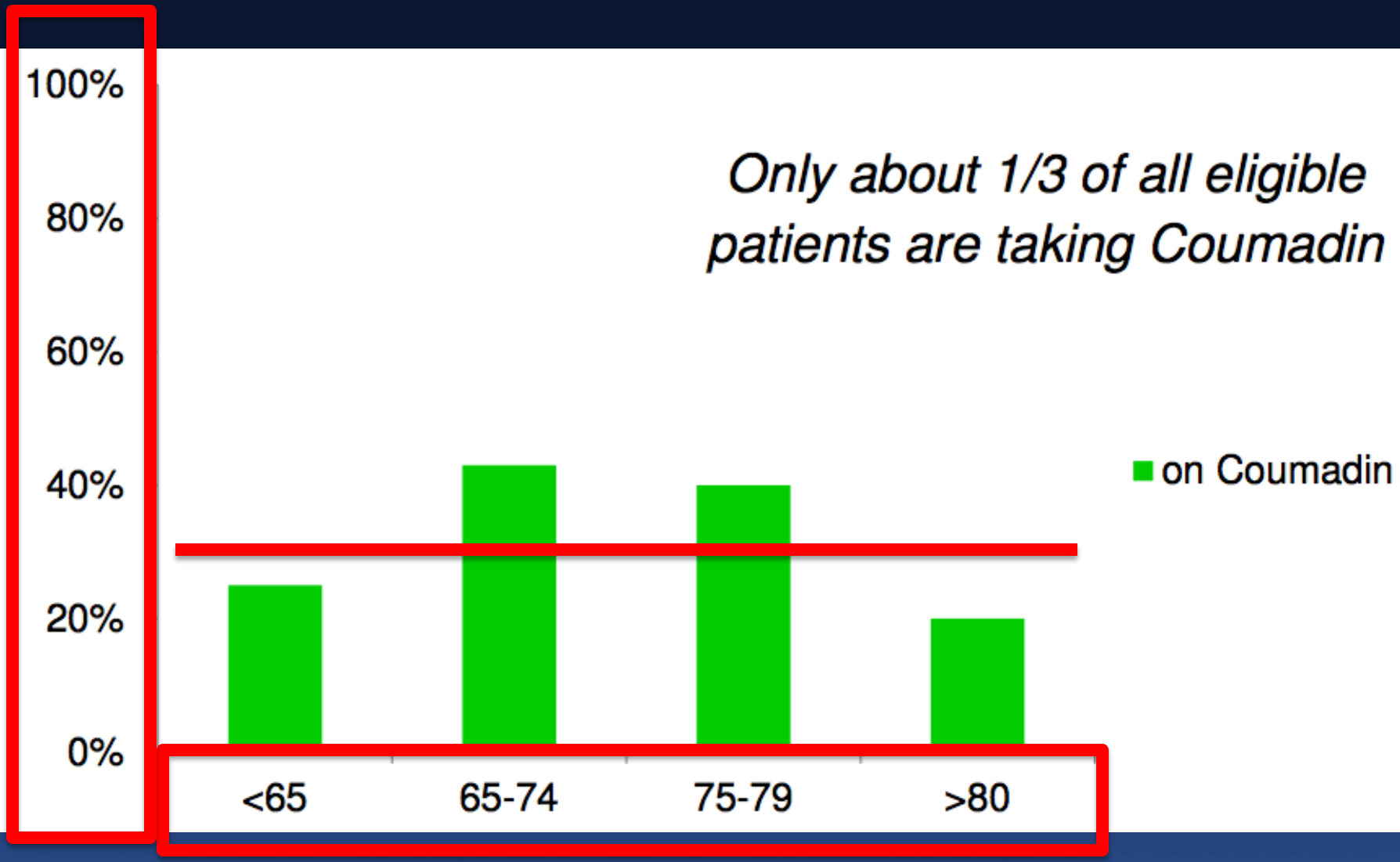
CHADS2VASC

	Condition/Risk Factor	Points
C	Congestive heart failure	1
H	Hypertension	1
A_2	Age ≥75 years	2
D	Diabetes Mellitus	1
S_2	Previous stroke or TIA	2
V	Vascular disease	1
A	Age 65-74 years	1
Sc	Sex (female gender)	1

Renal failure

HAS-BLED

	Points
HTN	1
Renal failure	1
Liver dysfunction	1
Stroke	1
Bleeding tendency	1
Labile INRs	1
Age >65	1
Drugs (ASA, NSAIDS)	1
ETOH	1
	Max 9



Only about 1/3 of all eligible patients are taking Coumadin

Stafford and Singer, Arch Int Med, 1996

Stroke risk reduction

- **Novel anticoagulants and stroke risk reduction**

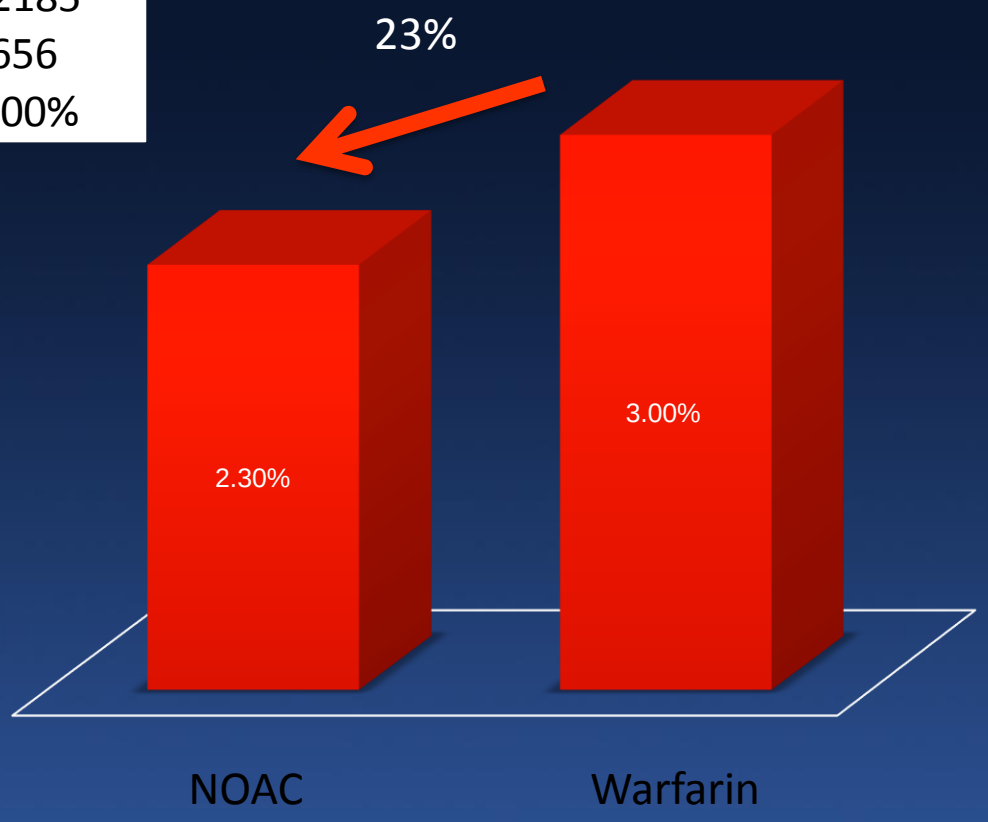
How about: stroke risk reduction: newer anticoagulants vs. warfarin

- **Dabigatran**
  - At 150 mg bid: lower stroke rate
  - At 110 mg bid: equivalent stroke rate
- **Rivaroxaban**
  - Equivalent stroke rate
    - 1.7% versus 2.2% (stroke or systemic embolism)
- **Apixaban**
  - Lower stroke rate (driven by hemorrhagic strokes)
    - 1.2% versus 1.5% annually (p=0.01)

Stroke alone (all cause)

P<0.0001

	NOAC	Warfarin
	22257	22185
Stroke	505	656
	2.30%	3.00%



Risk of major hemorrhage: Newer anticoagulants vs. warfarin

- **Rivaroxaban:**
  - No difference in major bleeding (3.6% versus 3.4% annually)
  - Lower rate of intracranial hemorrhage with rivaroxaban (0.8% versus 1.2%, p=0.02)

Risk of major hemorrhage Newer anticoagulants vs. warfarin

- **Dabigatran:**
  - At 150 mg bid: no difference in major bleeding (3.32% versus 3.57% annually)however, higher major hemorrhage with dabigatran in pts >75 yrs
  - At 110 mg bid: lower rate of major bleeding (2.87% versus 3.57%, p=0.003)
  - Overall lower rate of intracranial hemorrhage (0.10% [0.12%] versus 0.38%, p<0.001)

Risk of major hemorrhage
Newer anticoagulants vs. warfarin

- **Apixaban:**
  - Less major bleeding (2.1% vs. 3.1% annually)
  - Lower rate of intracranial hemorrhage (0.33% versus 0.80%)

Conclusions

- Atrial fibrillation is associated with a substantial stroke risk
- The risk is largely related to LAA thrombi
- Anticoagulation reduces the stroke risk substantially
- Anticoagulation also increases the major bleeding risk substantially
- Due to the risks of anticoagulants only a minority eligible for anticoagulation are actually taking it
- NOACs are also associated with a significant bleeding risk
- Alternatives that reduce stroke risk while avoiding major bleeding are desirable