Identifying Patients for Anticoagulation: While Many Patients Remain Untreated, Who Should NOT be Anticoagulated?

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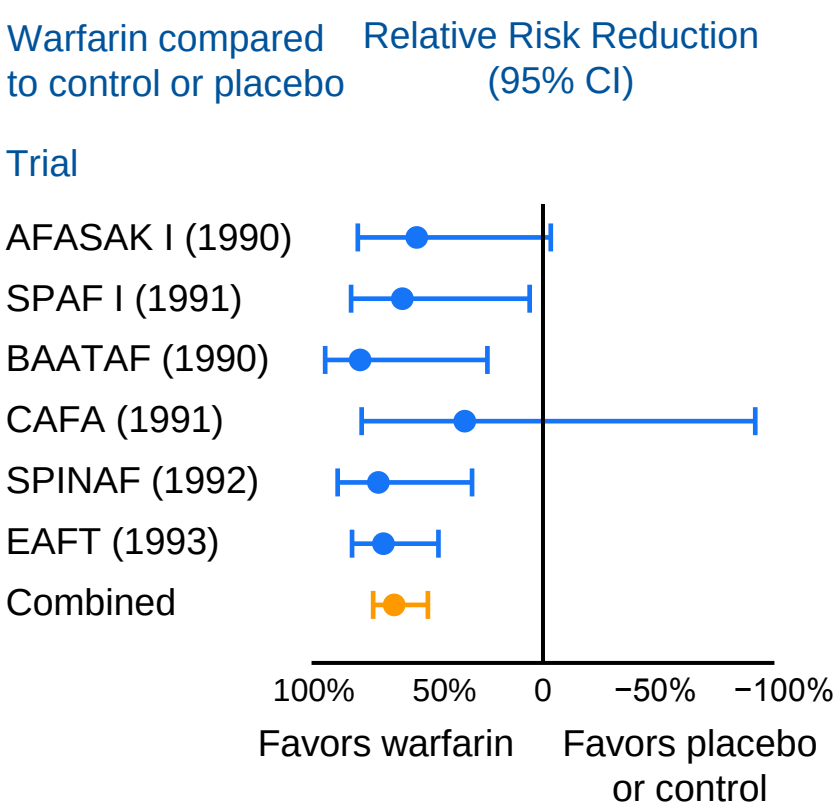
Disclosures

- Conflict of interest disclosures available at http://www.dcri.duke.edu/research/coi

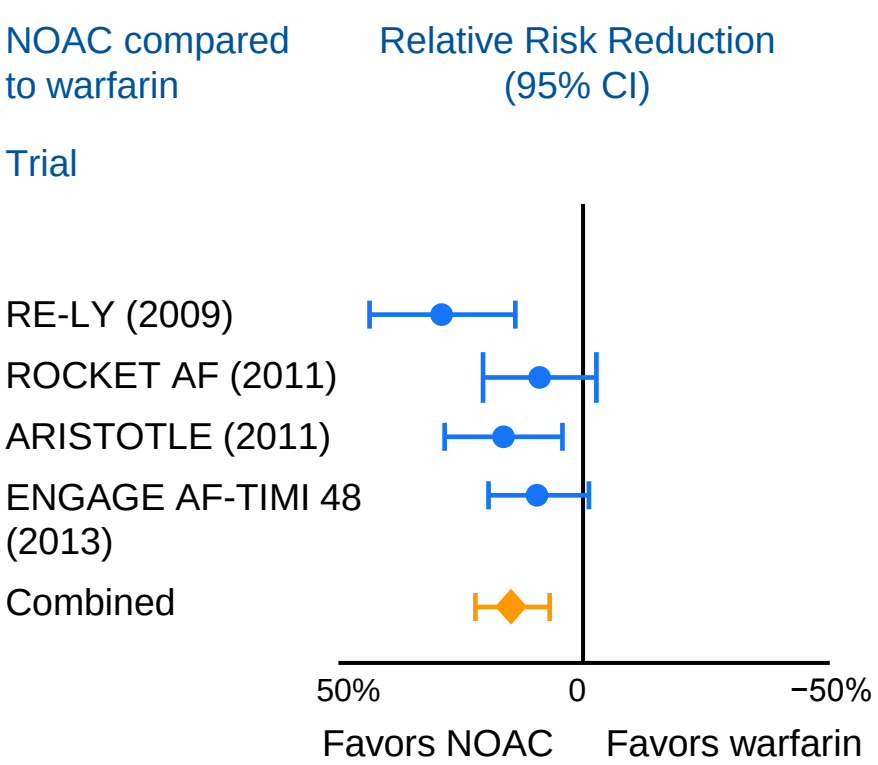
Oral Anticoagulation for stroke prevention



RRR 64%

Warfarin vs. Placebo or Control
(6 trials, total n=2,900)

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

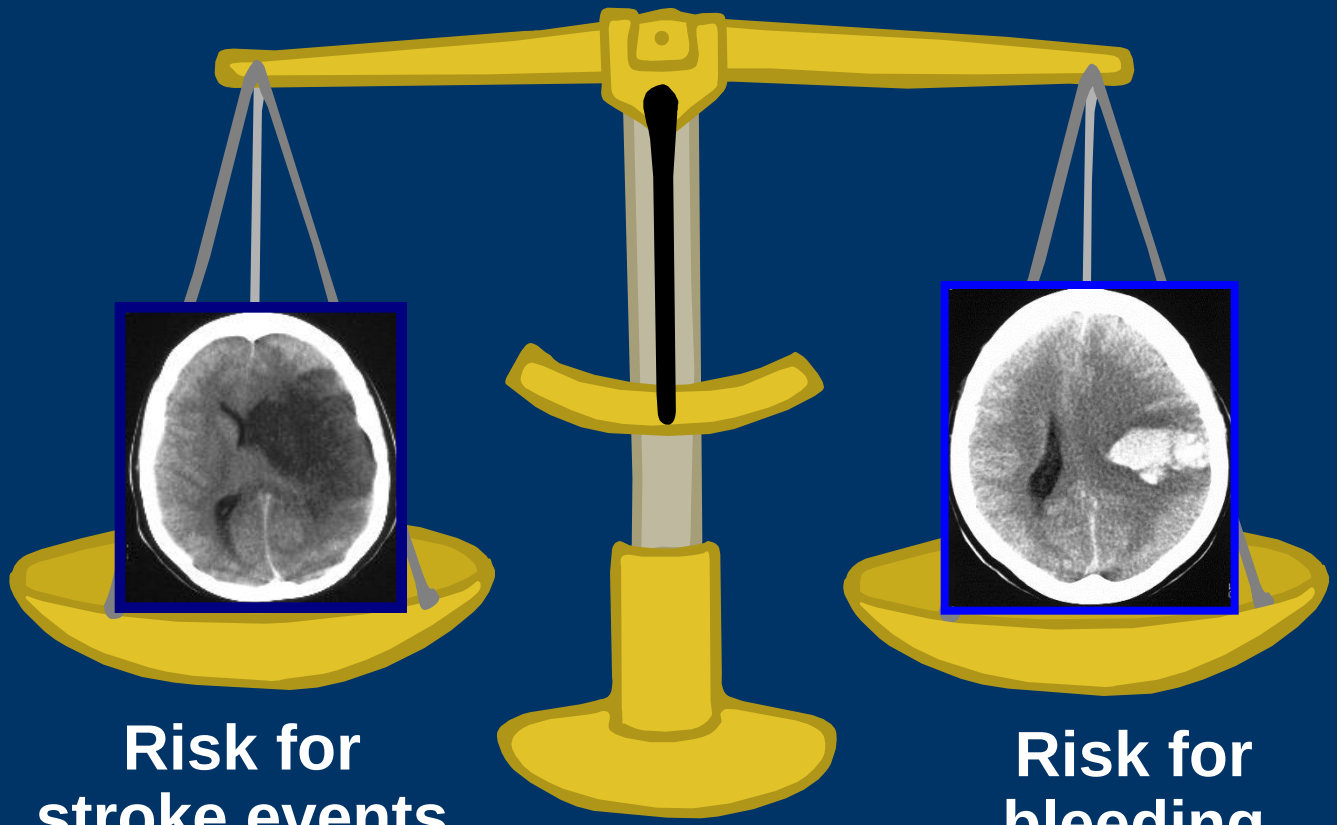


RRR 19%

NOAC vs. Warfarin
(4 trials, total n=71,683)

Ruff C, et al. Lancet. 2014;383:955–962.

Anticoagulant Therapy in Atrial Fibrillation



Risk for stroke events

Risk for bleeding

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Correlation between $CHADS_2$ and HAS-BLED scores

$CHADS_2$	HAS-BLED		
	0–1	**2**	**≥3**
0–1	2980 (43)	2142 (32)	1061 (23)
2	2621 (38)	2549 (38)	1346 (30)
≥3	1275 (19)	2091 (31)	2136 (47)

Lopes et al. Lancet 2012

Contraindications to Anticoagulation

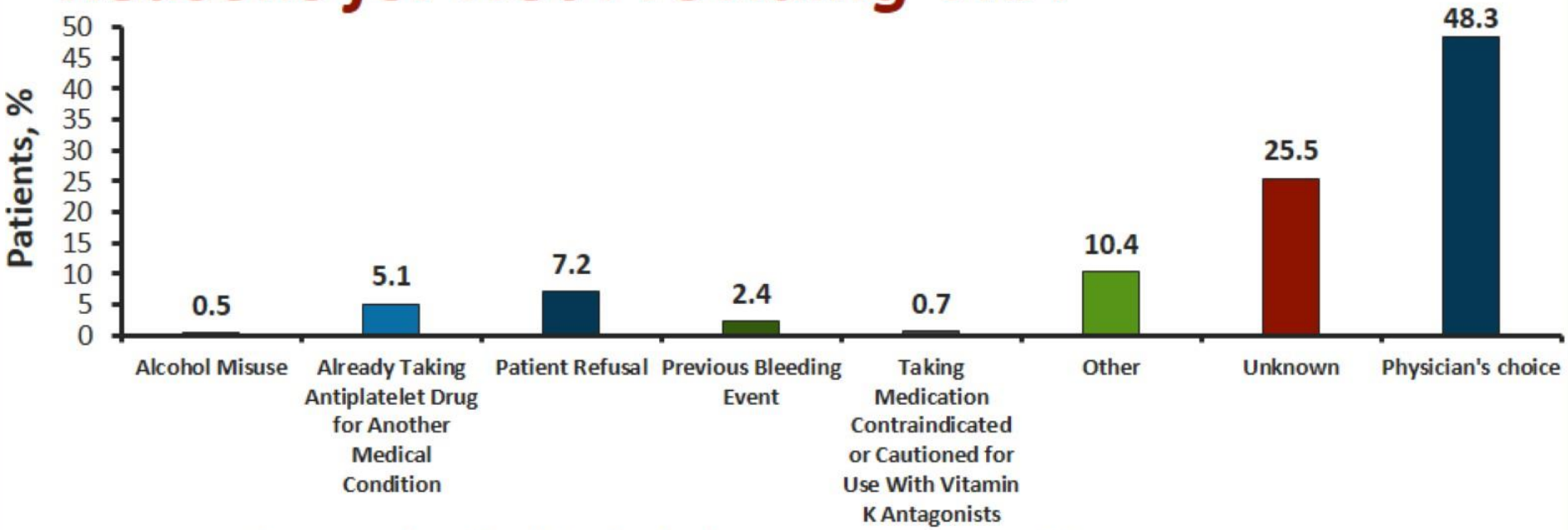
ORBIT AF (n= 10,130; 13% with contraindication)

Contraindication†	Overall (n = 1330)	Age (y) <75 (n = 493)	Age (y) ≥75 (n = 837)	P§
Prior bleed	27.7	21.1	31.7	<.0001
Patient refusal	27.5	31.6	25.1	.01
High bleeding risk	18.0	15.4	19.5	.06
Frequent falls/frailty	17.6	5.9	24.5	<.0001
Need for dual APT	10.4	12.0	9.4	.14
Unable to adhere	6.0	7.3	5.3	.13
Comorbid Illness	5.3	6.1	4.8	.30

Obrien E AHJ 201467:601-609.e1

GARFIELD-AF

*Reasons for Not Providing VKA**



Reasons for Physician's Choice	%
Bleeding risk	7.4
Concern over patient compliance	5.3
Guideline recommendation	1.4
Fall risk	6.5
Low risk of stroke	4.1
Other	23.6

*In patients with $CHADS_2$ score ≥ 2 in cohort 1.

Kakkar AK, et al. *PLoS One*. 2013;8:e63479.

PROSPER

- GWTG National Inpatient Stroke Registry (2007-2011)
- Linkage to CMS claims

Reasons for No Anticoagulation in Afib Patients with a Pre-Stroke CHA_2DS_2-VASc≥2

Documented Reasons	Total N=58,084 (%)
Risk for bleeding	9476 (16.3)
Risk for falls	5968 (10.3)
Allergy to or complication with warfarin or heparins	341 (0.6)
Serious side effect to medication	583 (1.0)
Patient/family refused	2476 (4.3)
Mental status	652 (1.1)
Terminal illness	3616 (6.2)
At least 1 documented reason	19,835 (34.2)
No documented reason	**38,249 (65.8)**

Unpublished data from PROSPER

European Heart Journal
doi:10.1093/eurheartj/ehw054

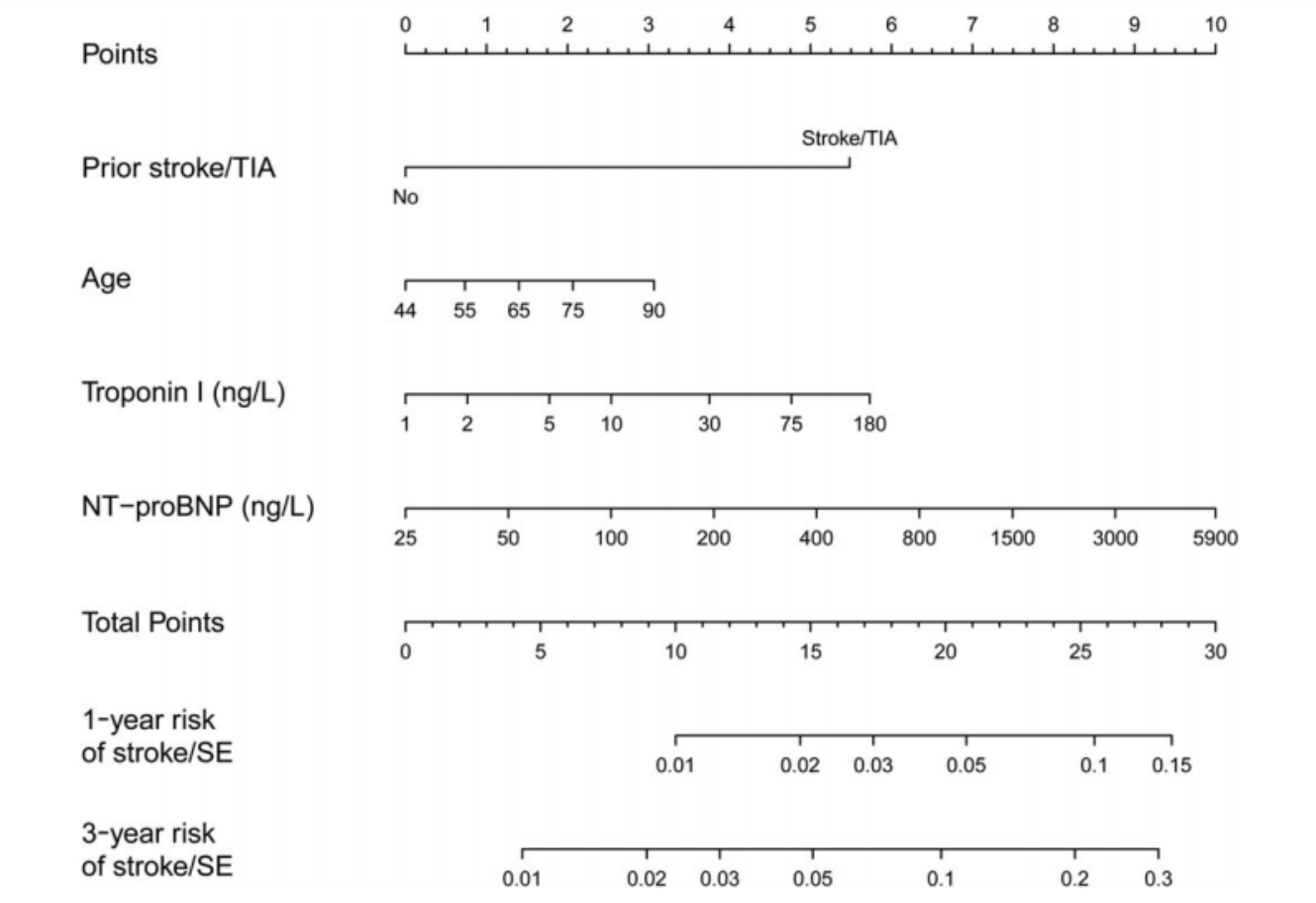
CLINICAL RESEARCH
Atrial fibrillation

The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation

Ziad Hijazi[1,2]*, Johan Lindbäck[2], John H. Alexander[3], Michael Hanna[4], Claes Held[1,2], Elaine M. Hylek[5], Renato D. Lopes[3], Jonas Oldgren[1,2], Agneta Siegbahn[2,6], Ralph A.H. Stewart[7], Harvey D. White[7], Christopher B. Granger[3], and Lars Wallentin[1,2], on behalf of the ARISTOTLE and STABILITY Investigators

New biomarker based risk score in AF

The new score was named ABC stroke score (Age, Biomarkers, Clinical history)



Nomogram for the variables in the ABC risk score proportional to the Cox-model coefficients

Hijazi Z, et al. *Eur Heart J* 2016;37:1582-90.

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Comparison of ABC stroke risk score with other risk scores

C-statistics for prediction of stroke or systemic embolism

Risk score	C-statistic
ABC	0.68
CHA_2DS_2VASc	0.62

	Condition	Points
C	Congestive heart failure	1
H	Hypertension > 140/90 mmHg or treated	1
A_2	Age ≥ 75 years	2
D	Diabetes Mellitus	1
S_2	Prior stroke or TIA	2
V	Vascular disease	1
A	Age 65 – 74 years	1
Sc	Sex category (female)	1

CHA_2DS_2VASc score

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Hijazi Z, et al. *Eur Heart J* 2016;37:1582-90.

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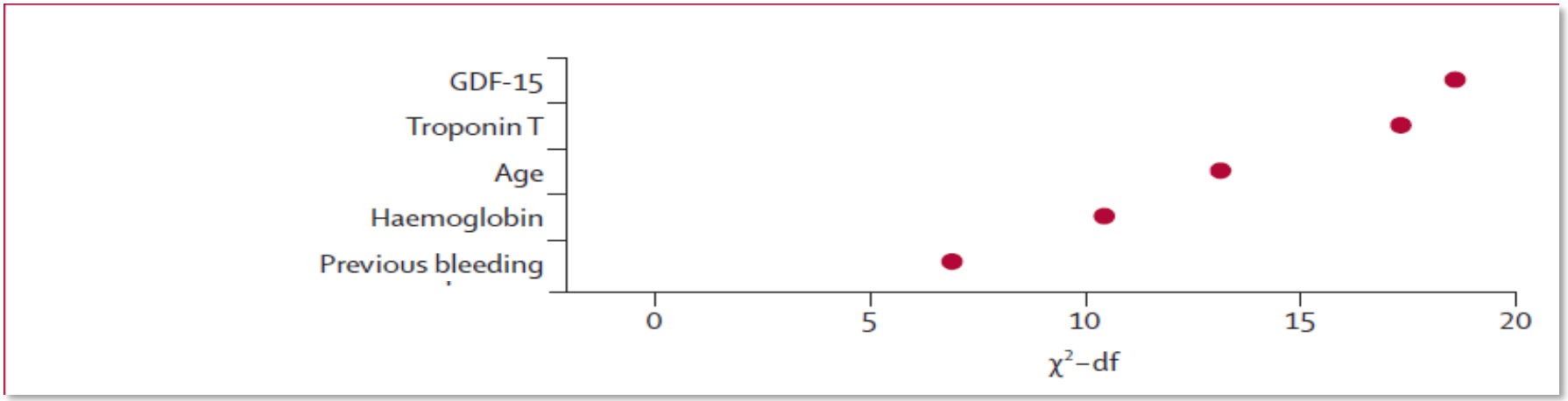
The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study

Ziad Hijazi, Jonas Oldgren, Johan Lindbäck, John H Alexander, Stuart J Connolly, John W Eikelboom, Michael D Ezekowitz, Claes Held, Elaine M Hylek, Renato D Lopes, Agneta Siegbahn, Salim Yusuf, Christopher B Granger, Lars Wallentin, on behalf of the ARISTOTLE and RE-LY Investigators

Hijazi Z, et al. *Lancet.* 2016:S0140-6736.

The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study

ABC-bleeding score (age, biomarkers [GDF-15, cTnT-hs (or creat clearance), and hemoglobin], and clinical history [previous bleeding]) score yielded a higher c-index than HAS-BLED and ORBIT scores for major bleeding in both the derivation (0·68 vs 0·61 vs 0·65) and validation (0·71 vs 0·62 vs 0·68) cohorts



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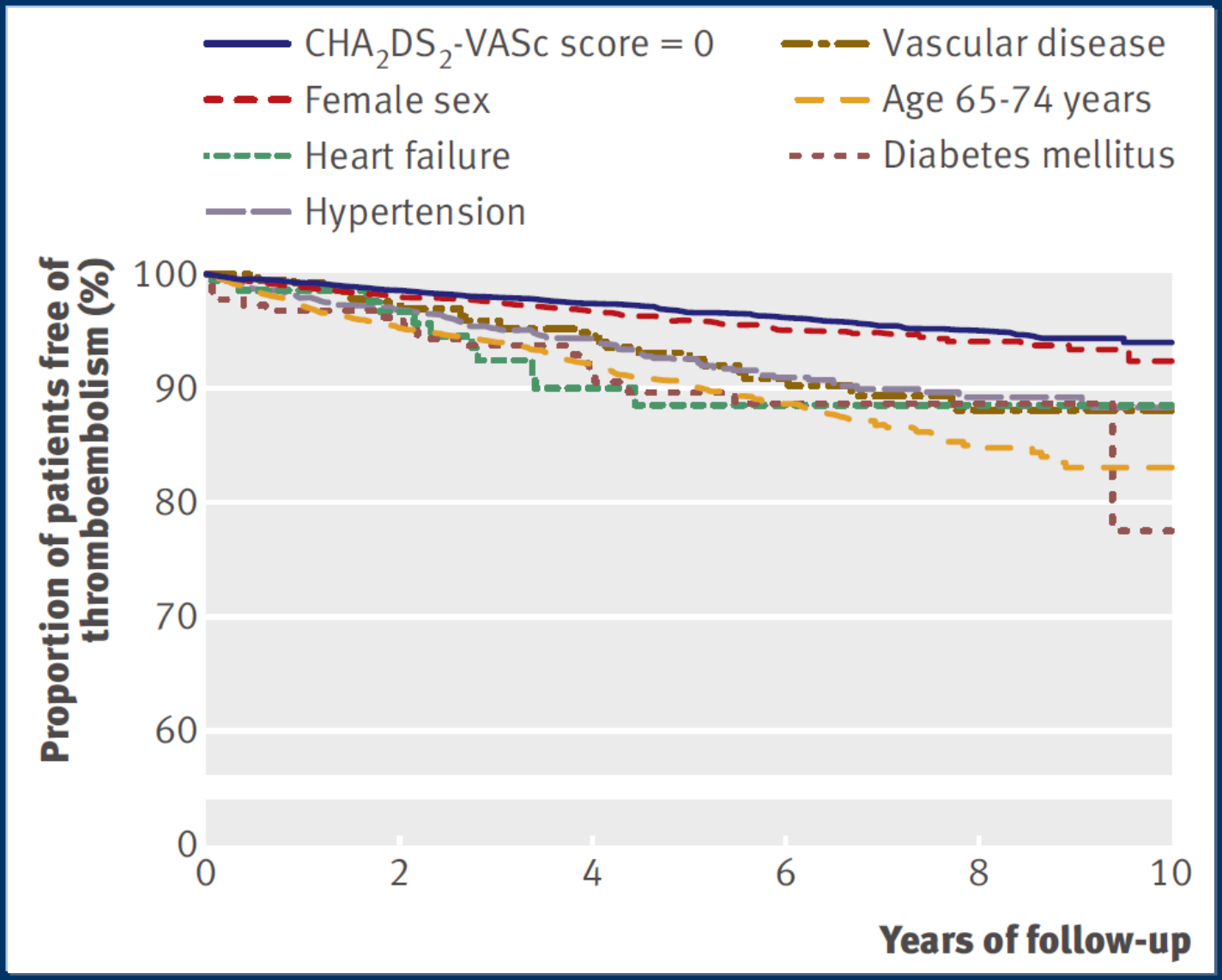
Hijazi et al. Lancet 2016387: 2302–11

Danish Hospital Registry Data 1997-2006
14,572 patients CHADS-VASc 0 or 1

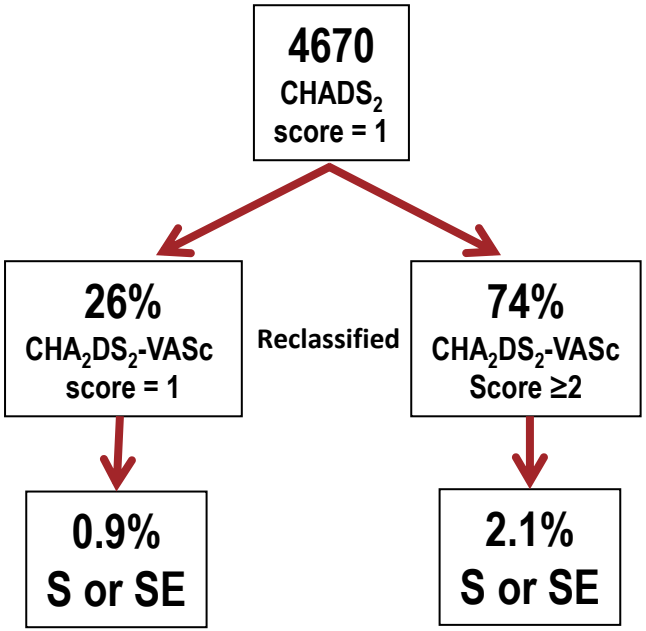


Olesen J. BMJ 2011;342:d124

CHA_2DS_2-VASc Identifies Patients with $CHADS_2$=1 Who May Not Benefit from Anticoagulation

Of 4670 patients from AVERROES & ACTIVE trials with $CHADS_2$ score = 1

- 74% up-classified to CHA_2DS_2-VASc score of ≥2 definitely requiring anticoagulation and
- 26% to score of 1 not requiring anticoagulation



S, stroke; SE, systemic embolus

Coppens M et al. *Eur Heart J*. 2013;34:170-176.

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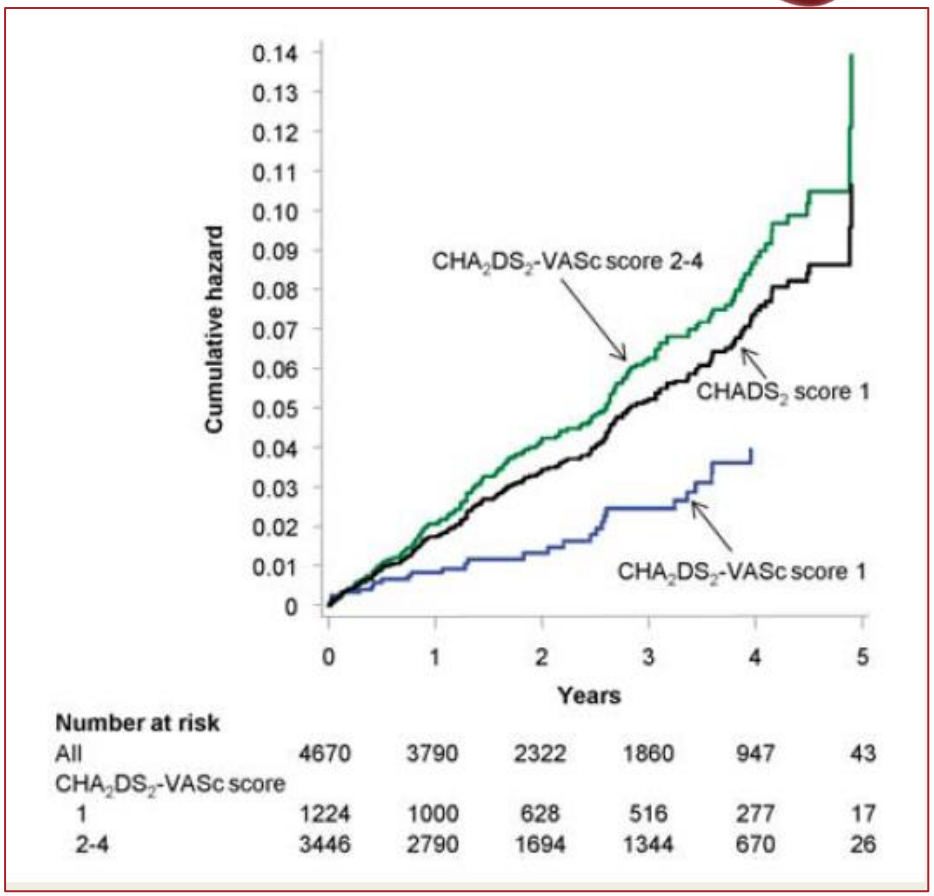

Kaplan-Meier cumulative hazard rates of composite outcome of ischemic or unspecified stroke and non-CNS sys embolism in patients treated with aspirin only or with combined aspirin and clopidogrel.

Should patients with or at risk of falls receive anticoagulation?

Choosing Antithrombotic Therapy for Elderly Patients With Atrial Fibrillation Who Are at Risk for Falls

Malcolm Man-Son-Hing, MD, MSc, FRCPC; Graham Nichol, MD, MPH, FRCPC; Anita Lau; Andreas Laupacis, MD, MSc, FRCPC

- Among older patients, falling is common (about 30% fall at least once a year), and subdural hematomas are uncommon

"… persons taking warfarin must fall about 295 times in 1 year for warfarin to not be the optimal therapy."

Arch Intern Med 1999;159:677-685

Anticoagulation in Patients with AF at Risk for Falls

- ICH rates per 100 patient-years[1]
  - High fall risk: 2.8
  - Other patients: 1.1
  - Traumatic ICH: 2.0 vs 0.34
- Ischemic stroke rates per 100 patient-years
  - High fall risk: 13.7
  - Other patients: 6.9

RISK[1]:
HRs: Independent Predictors of ICH

Factor	HR (95% CI)
Prior stroke	2.1 (1.6-2.7)
Prior major bleed	1.9 (1.4-2.4)
Neuropsychiatric impairment	1.4 (1.0-3.1)

There is no good evidence that quantifies the degree to which "fall risk" or a "history of falls" increases the chance of serious ICH.

CI=confidence interval; HR=hazard ratio

1. Gage BF, et al. *Am J Med.* 2005;118:612-617.

Rates of Intracranial Bleeding by Location, Type and Randomized Treatment

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	Apixaban Rate (n)	Warfarin Rate (n)	Hazard Ratio (95% CI) Apixaban vs. Warfarin	p-value
All Intracranial (n = 174)	0.33 (52)	0.80 (122)	0.417 (0.302 - 0.577)	<.0001
Spontaneous (n = 119)	0.26 (41)	0.51 (78)	0.515 (0.353 - 0.751)	0.0006
Traumatic (n = 47)	0.06 (10)	0.24 (37)	0.264 (0.131 - 0.531)	0.0002
Intracerebral (n = 106)	0.22 (34)	0.47 (72)	0.462 (0.308 - 0.695)	0.0002
Spontaneous (n = 94)	0.20 (31)	0.41 (63)	0.482 (0.314 - 0.741)	0.0009
Traumatic (n = 12)	0.02 (3)	0.05 (8)	0.367 (0.097 - 1.382)	0.1382
Subdural (n = 43)	0.06 (10)	0.22 (33)	0.296 (0.146 - 0.601)	0.0007
Spontaneous (n = 14)	0.02 (3)	0.07 (11)	0.266 (0.074 - 0.953)	0.0419
Traumatic (n = 29)	0.05 (7)	0.14 (22)	0.311 (0.133 - 0.729)	0.0072
Subarachnoid (n = 14)	0.03 (5)	0.06 (9)	0.544 (0.182 - 1.624)	0.2753
Spontaneous (n = 8)	0.03 (5)	0.02 (3)	1.637 (0.391 - 6.849)	0.4999
Traumatic (n = 6)	0.00 (0)	0.04 (6)	--	--

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Lopes RD, et al. Presented at AHA 2015.
Data on file; Lopes RD, et al. (Manuscript under review).

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How much AF is enough to increase the risk for stroke? Studies evaluating risk of stroke vs AF burden

Year	Study	n	AF Burden Measure	HR for stroke
2003	MOST	312	5 min	6.7 p=0.02
2005	Capucci	725	>24 hrs	3.1 p=0.04
2009	Botto	568	CHADS + AF burden	6.2 (5 vs 0.8%)
2009	TRENDS	2486	5.5 hrs	2.2 p=0.06
2012	Home monitor CRT	560	3.8 hrs	9.4 p=0.006
2012	ASSERT	2580	6 min	2.5 p=0.008

Glotzer T, et al. *Circulation* 2003;107:1614-9.
Capucci A, et al. *J Am Coll Cardiol* 2005;46:1913-20.
Botto GL, et al. *J Cardiovasc Electrophysiol* 2009;20:241-8.
Glotzer T. *Circ Arrhythm Electrophysiol* 2009;2:474-80
Shanmugam N, et al. *Europace* 2012;14:230-7..
Healey JS, et al. *N Engl J Med* 2012;366:120-9.
Camm AJ, et al. *Am J Cardiol* 2012;110:270-276.

Should we be looking for and treating subclinical, silent AF? ASSERT

2580 pts w/ PPM or ICD, monitored x 3 mo

Event	Device-Detected Atrial Tachyarrhythmia				Device-Detected Atrial Tachyarrhythmia Present vs. absent		
	Absent N=2319		Present N= 261				
	events	%/year	events	%/ year	RR	95% CI	p
Ischemic Stroke or Systemic Embolism	40	0.69	11	1.69	2.49	1.28 – 4.85	0.007
Vascular Death	153	2.62	19	2.92	1.11	0.69 – 1.79	0.67
Stroke / MI / Vascular Death	206	3.53	29	4.45	1.25	0.85 – 1.84	0.27
Clinical Atrial Fibrillation or Flutter	71	1.22	41	6.29	5.56	3.78 – 8.17	<0.001

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Healy et al. NEJM 2012;366:120-9.

ARTESiA

APIXABAN FOR THE REDUCTION OF THROMBO-EMBOLISM IN PATIENTS WITH DEVICE-DETECTED SUB-CLINICAL ATRIAL FIBRILLATION

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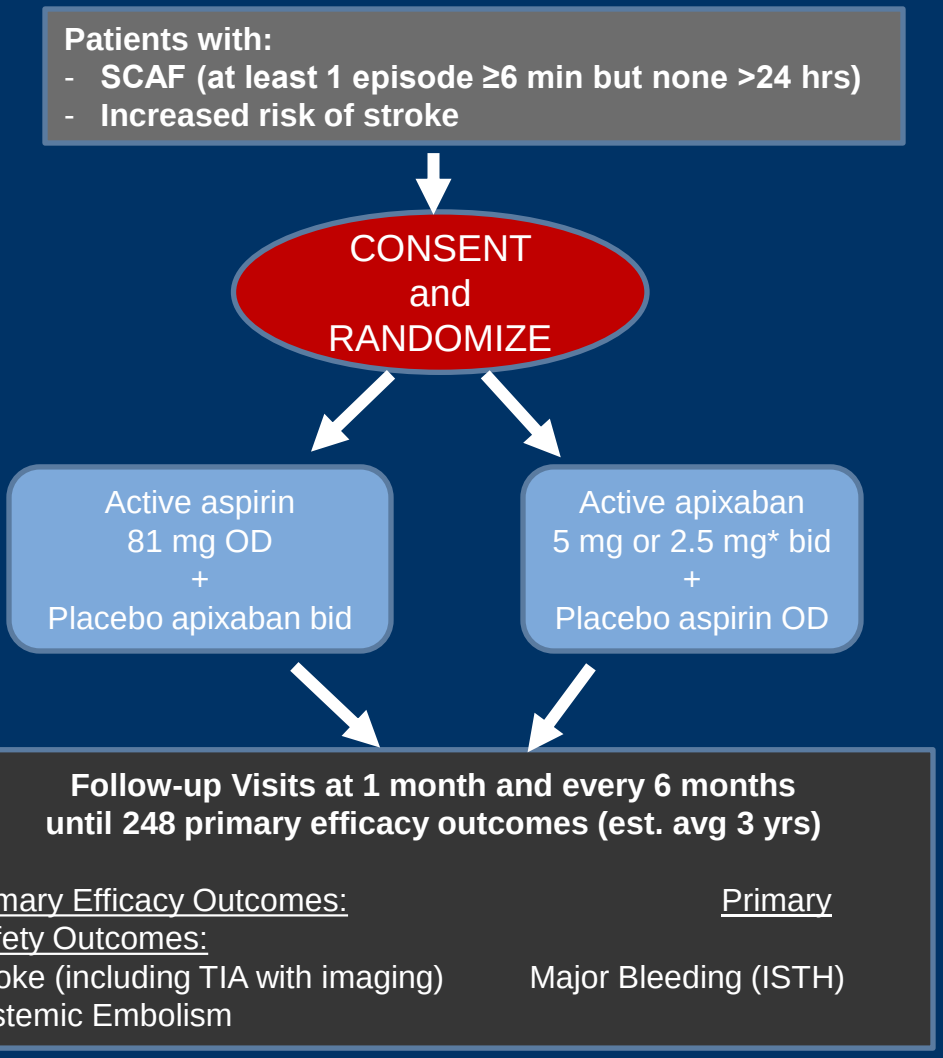
https://clinicaltrials.gov/ct2/show/NCT01938248.

Study Design



Double-blind, double-dummy design

* 2.5 mg if either of the following:

- At least 2 of 3 of:
  - Age ≥ 80
  - Weight ≤ 65 kg
  - Serum Creatinine ≥ 133 µmol/L (1.5 mg/dL)
- Ongoing need for inhibitor of both CYP3A4 and P-glycoprotein

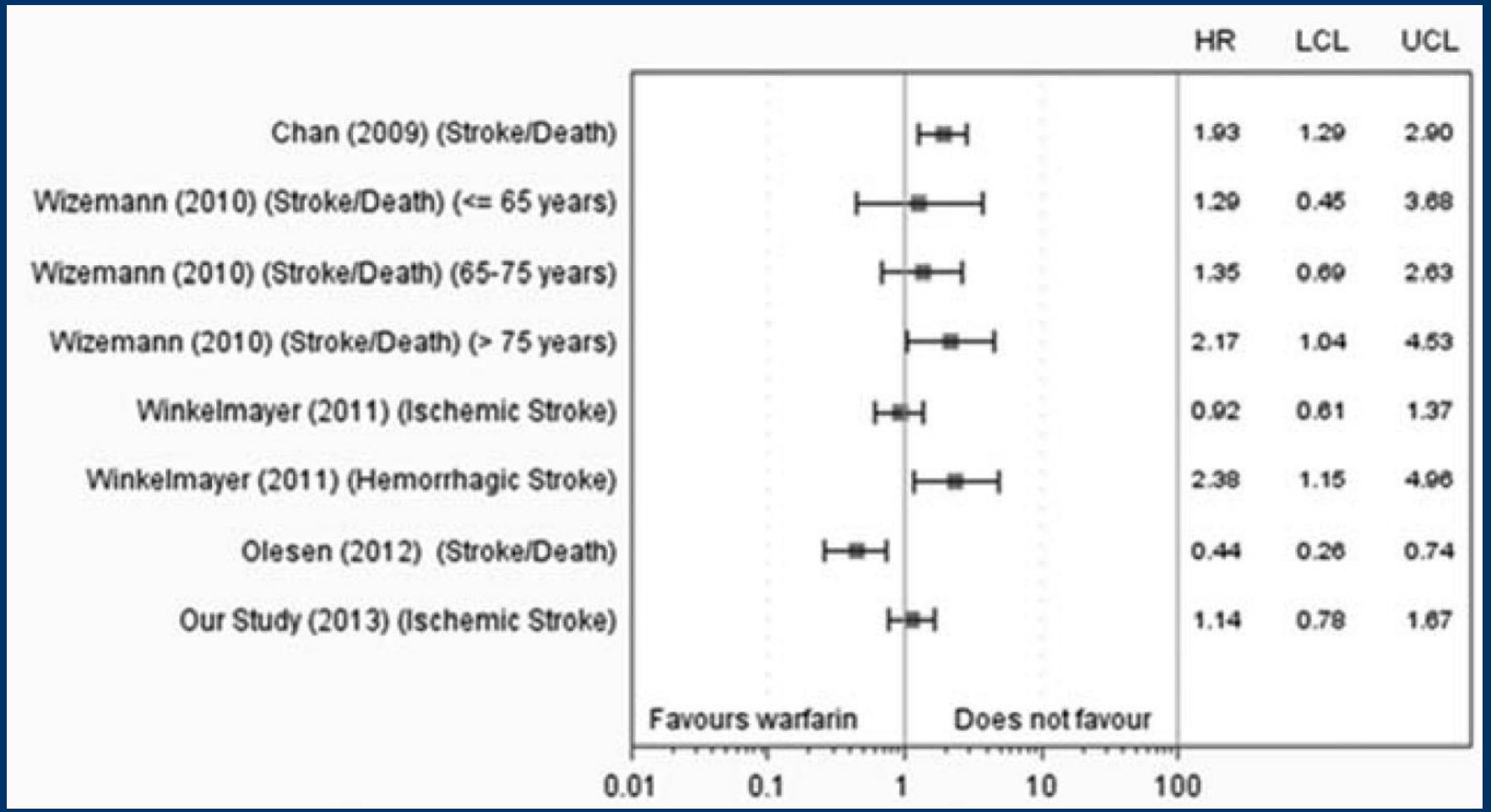
https://clinicaltrials.gov/ct2/show/NCT01938248.

Atrial Fibrillation in Hemodialysis

- AF prevalence reported up to 27% in hemodialysis population, at least twice that of age-matched patients not on HD
- Most strongly related to age; Genovesi found 17% in age 51-60, 37% in 71-80 years
- USRDS/ Medicaid data, increase from 2% to 17% over age range from <55 to >85 years

Genovesi, S. et al. Am. J. Kidney Dis. 2005;46:897–902 .
Wetmore, J. B. et al. Kidney Int. 2012;81:469–476.

AF, dialysis, warfarin use in Ontario and Quebec, 1998 to 2007



Shah M et al. *Circulation* 2014.

Reasons for not using OAC for AF with risk factors

- Very high risk of major/life-threatening bleeding or ICH with low/moderate CHADSVASC score
- Unable to tolerate warfarin and unable to afford NOAC
- CHADSVASC =0 in male or 1 (female)
- CHADSVASC 1 (male) or 2 (female): not everyone (Bleeding risk, chadsvasc criterion)
- Patients with AF and stable CAD/stent and CHADSVASC<2
- SubClinical AF (6 min to 24 hours)
- Dialysis ??
- Patients with *Left* atrial *appendage occlusion device*

"In medicine, therapeutic decisions should be based on science; the 'art' of medicine is in how you interact with the patient."

- Robert M. Califf MD

Thank you!

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