PHAR 451

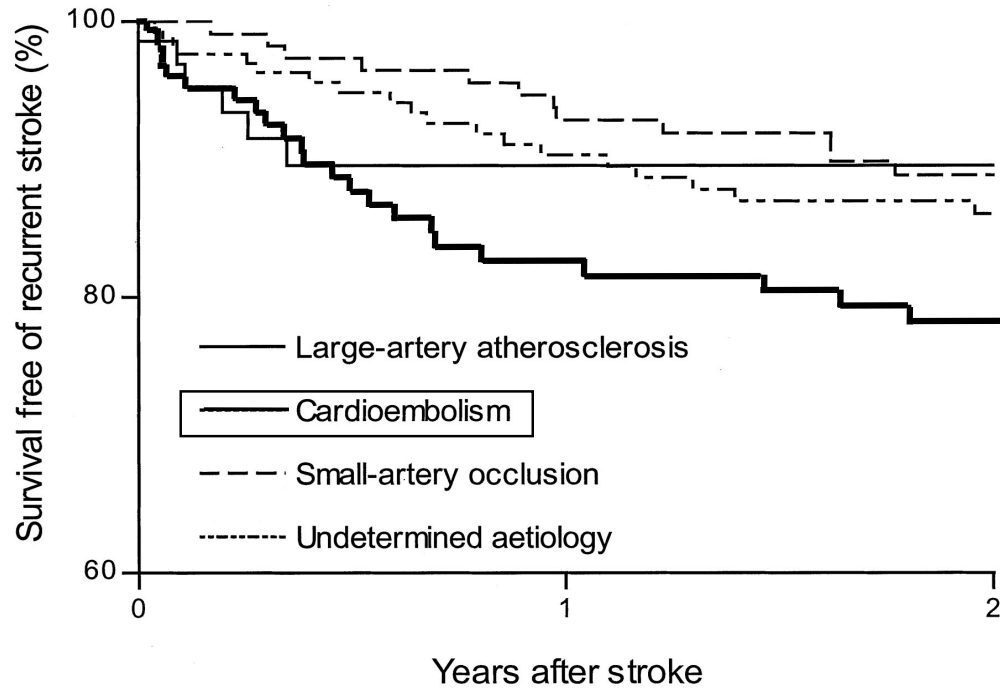# Ischemic Stroke Prevention in patients with Atrial Fibrillation

Peter Loewen, B.Sc.(Pharm), ACPR, Pharm.D., FCSHP

University of British Columbia

Vancouver General Hospital

Objective

After the session, and upon personal reflection & study, students will be able to DESIGN and RATIONALIZE using EVIDENCE, a stroke prevention regimen (drugs, doses, routes, frequency) for a patient with atrial fibrillation which incorporates their stroke risk, bleeding risk, access to coverage, personal values, and ability to be monitored.

2-Year Stroke-free Survival After Ischemic Stroke

Survival free of recurrent stroke (%) vs Years after stroke

- Large-artery atherosclerosis
- Cardioembolism
- Small-artery occlusion
- Undetermined aetiology

Kolominsky-Rabas et al. Stroke 2001;32:2735-40

CASE

78 y/o F with newly-identified asymptomatic atrial fibrillation

PMH:

DM2 (diet-controlled)

TIA in 1999 (receiving ASA 80mg/d since)

MI in 2009

What is the most appropriate antithrombotic therapy for stroke prophylaxis in this patient?

Stroke risk in chronic Atrial Fib

"CHADS2"

LV Dysfunction (CHF)
HTN
| Age > 75 | 1
| Diabetes | 1
| Previous Stroke/TIA | 2

CHADS2 score: **4**

CHADS2 Score	Stroke risk/ year
0	1.2%
1	3.6%
2	5.4%
3	9.9%
4	13.7%
5	12.6%
6	17.2%

1%
per year

✖

risk of hospital admission and death due to peripheral artery embolism, ischaemic stroke, and pulmonary embolism

18%
per year

Olesen JB, et al. BMJ 2011;342:d124

Stroke risk in chronic Atrial Fib

"CHA2DS2-VASc"

LV Dysfunction (CHF)
HTN
| Age > 75 | 2
| Diabetes | 1
| Previous Stroke/TIA | 2
| Prior MI, peripheral artery disease, or aortic plaque | 1
Age 65-75
| Female | 1

CHA2DS2-VASc score: **7**

CHADS2 Score	Stroke risk/ year
0	0.7%
1	1.5%
2	2.9%
3	4.3%
4	6.5%
5	10%
6	12.5%
7	14%
8	14.1%
9	16%

1%
per year

✖

risk of hospital admission and death due to peripheral artery embolism, ischaemic stroke, and pulmonary embolism

18%
per year

Olesen JB, et al. BMJ 2011;342:d124

SPARC - Stroke Prevention in Atrial Fibrillation Risk Tool

for estimating risk of stroke and benefits & risks of antithrombotic therapy in patients with chronic atrial fibrillation

In your patient with atrial fibrillation, which of the following stroke or bleeding risk factors are present?

CHADS2 CRITERIA

CHF/LV dysfunction (diagnosed at any time in the past)	☐
Hypertension (controlled or uncontrolled)	☐
Age > 75	☐
Diabetes Type I or II (controlled or uncontrolled)	☐
TIA or stroke (at any time in the past)	☐

CHADS2 SCORE (0-6):0

CHA2DS2-VASc CRITERIA

Prior MI, peripheral artery disease, or aortic plaque	☐
Age 65-75	☐
Female	☐

CHA2DS2-VASc SCORE (0-9):0

HAS-BLED CRITERIA*

Abnormal renal function (dialysis, SCr>200 mmol/L, or transplant)	☐
Abnormal liver function (cirrhosis or liver enzymes >3x ULN)	☐
History of major bleeding (any cause)	☐
History of labile INR (time in therapeutic range <60%)	☐
Current "excess" use of alcohol	☐
Currently taking antiplatelet drug(s) or NSAID(s)	☐

HAS-BLED SCORE (0-9)*:0

www.sparctool.com

https://itunes.apple.com/ca/
app/anticoagevaluator/
id609795286?mt=8
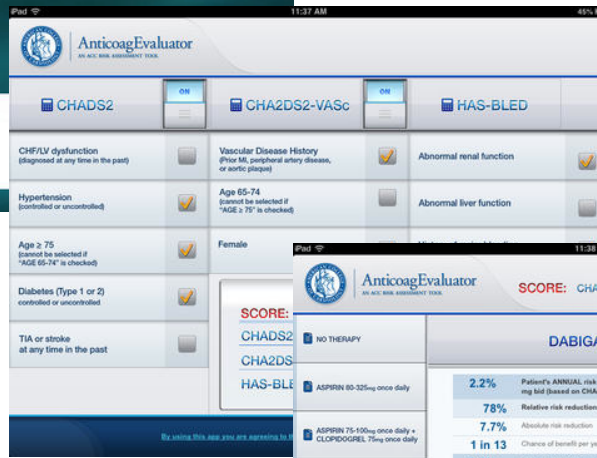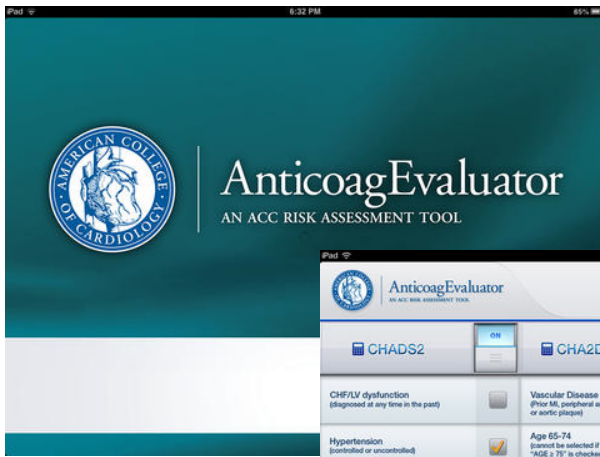
Stroke Prevention in AF

What we do	In whom	Effect vs. placebo	Source
ASA	CHADS2 0-1 OR unable to anticoagulate	RR 0.78	Ann Intern Med. 2007;146:857-867
warfarin	CHADS2 > 1	RR 0.33	
dabigatran	CHADS2 > 1 & if preferred over warfarin, labile INR, coverage available	110mg bid: similar efficacy+less bleeding vs. warfarin 150mg bid: superior efficacy +similar bleeding vs. warfarin	RE-LY
rivaroxaban		efficacy & bleeding similar to warfarin	ROCKET-AF
apixaban		superior efficacy and safety to warfarin	ARISTOTLE
(edoxaban)	not marketed in Canada yet	efficacy similar to warfarin, less bleeding	ENGAGE-AF-TIMI48

EASY THING TO REMEMBER:

WARFARIN in Atrial Fibrillation

RELATIVE RISK OF STROKE = 0.33
vs. no therapy

Hart et al. Ann Intern Med 1999;131:492-501
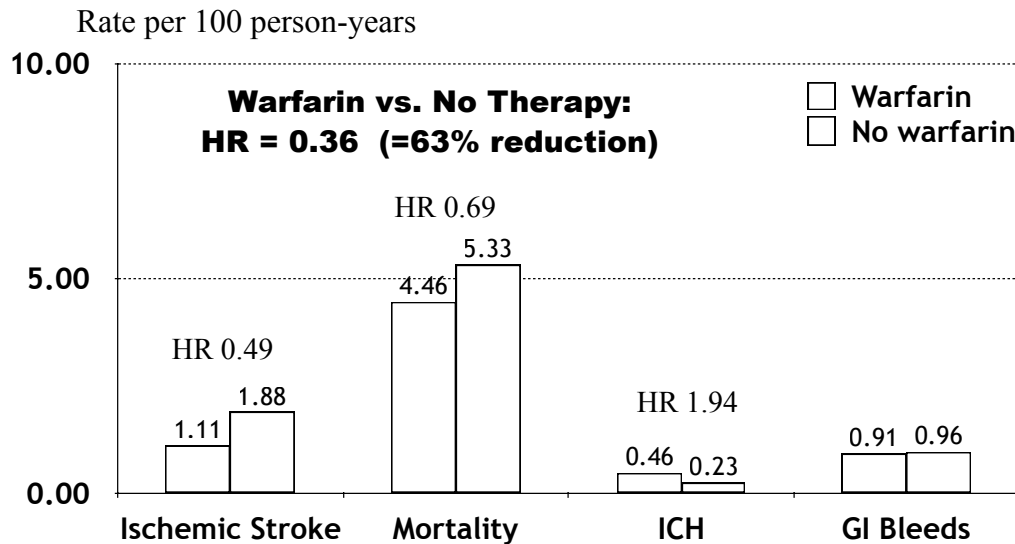Ann Intern Med. 2007;146:857-867

EASY THING TO REMEMBER:

ASPIRIN in Atrial Fibrillation

RELATIVE RISK OF STROKE = 0.78
vs. no therapy

Hart et al. Ann Intern Med 1999;131:492-501
Ann Intern Med. 2007;146:857-867

Effectiveness of Warfarin in AF

Cohort study, N=11,526 wth AF, mean 71 y/o

2.2 years of observation

Go et al. JAMA 2003;290:2685-92

CMAJ   RESEARCH

Rates of hemorrhage during warfarin therapy for atrial fibrillation

Tara Gomes MHSc, Muhammad M. Mamdani PharmD MPH, Anne M. Holbrook MD PharmD, J. Michael Paterson MSc, Chelsea Hellings MSc, David N. Juurlink MD PhD

ABSTRACT

Background: Although warfarin has been extensively studied in clinical trials, little is known about rates of hemorrhage attributable to its use in routine clinical practice. Our objective was to examine incident hemorrhagic events in a large population-based cohort of patients with atrial fibrillation who were starting treatment with warfarin.

Methods: We conducted a population-based cohort study involving residents of Ontario (age ≥ 66 yr) with atrial fibrillation who started taking warfarin between Apr. 1, 1997, and Mar. 31, 2008. We defined a major hemorrhage as any visit to hospital for hemorrhage. We determined crude rates of hemorrhage during warfarin treatment, overall and stratified by CHADS₂ score (congestive heart failure, hypertension, age ≥ 75 yr, diabetes mellitus and prior stroke,

rate of hemorrhage was 3.8% (95% confidence interval [CI] 3.8%–3.9%) per person-year. The risk of major hemorrhage was highest during the first 30 days of treatment. During this period, rates of hemorrhage were 11.8% (95% CI 11.1%–12.5%) per person-year in all patients and 16.7% (95% CI 14.3%–19.4%) per person-year among patients with a CHADS₂ scores of 4 or greater. Over the 5-year follow-up, 10 840 patients (8.7%) visited the hospital for hemorrhage; of these patients, 1963 (18.1%) died in hospital or within 7 days of being discharged.

Interpretation: In this large cohort of older patients with atrial fibrillation, we found that rates of hemorrhage are highest within the first 30 days of warfarin therapy. These rates are considerably higher than the rates of 1%–3% reported in randomized controlled trials of warfarin therapy. Our study provides timely
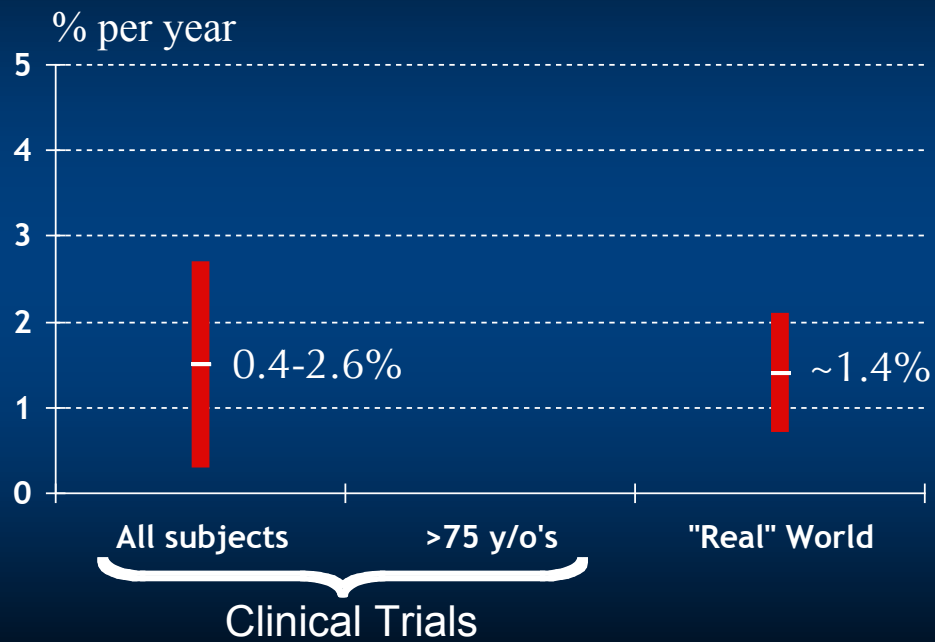
Major Bleeding with warfarin

% per year

All subjects — 0.4-2.6%	"Real" World — ~1.4%

All subjects — **>75 y/o's** — **"Real" World**

Clinical Trials

ICH with warfarin

% per year

SPAF II: INR up to 4.5

0-0.8%

0.3-1.8%

~0.5%

All subjects — **>75 y/o's** — **"Real" World**

Clinical Trials
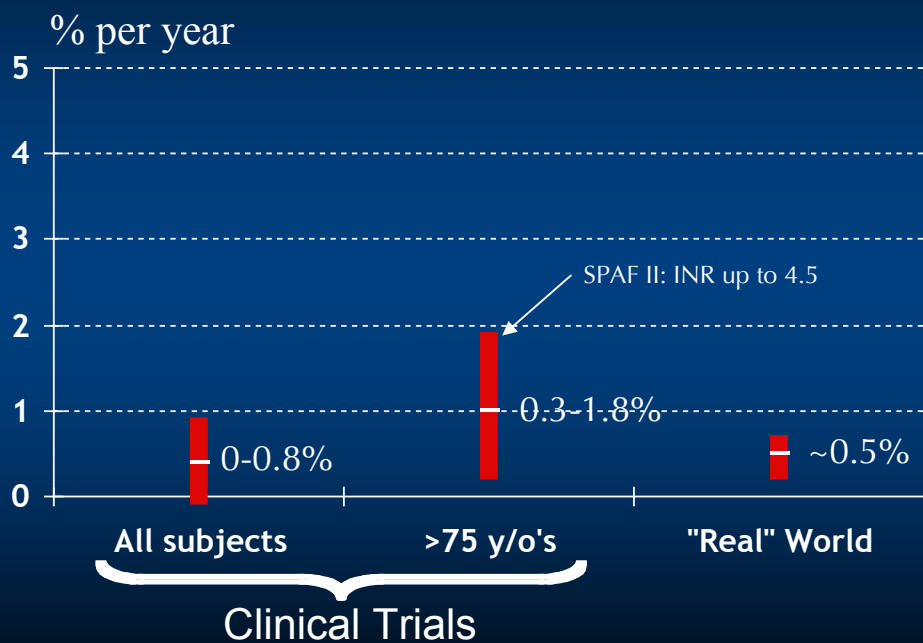
Safety of ASA: Acute GI Bleeds

N=24 trials, 66,000 patients. Average follow-up 28 mos.

OR 1.68
RRI: 73%
NNH (28mos)~100
= ~200 x 1 year

2.47

1.42

Placebo

ASA

%

Acute GI Bleeding
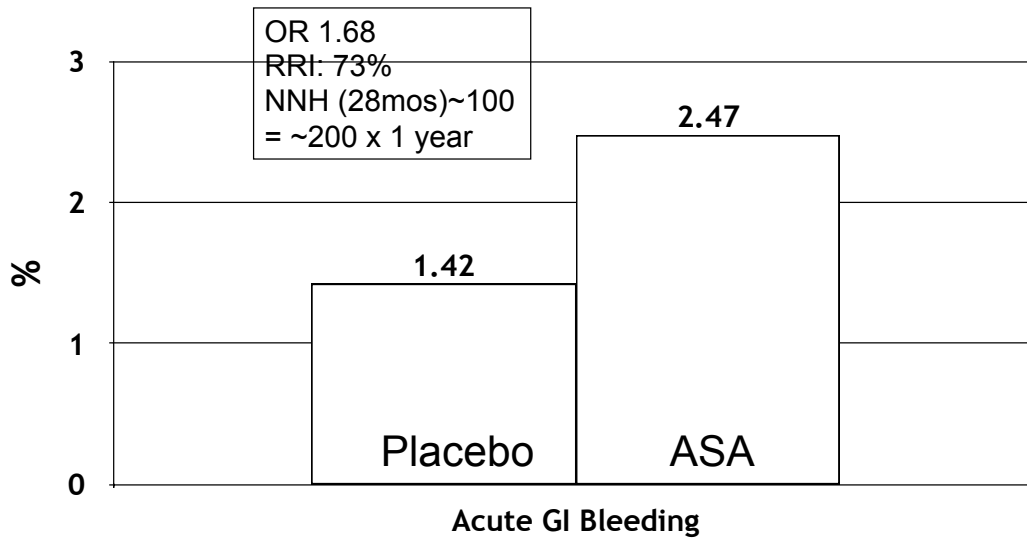
Derry & Loke. BMJ 2000;321:1183-7
consistent with ATTC 2009: Lancet 2009; 373: 1849–60
Lanas et al. Clin Gastro Hepatol 2011;9:762

Safety of low-dose ASA: Bleeding

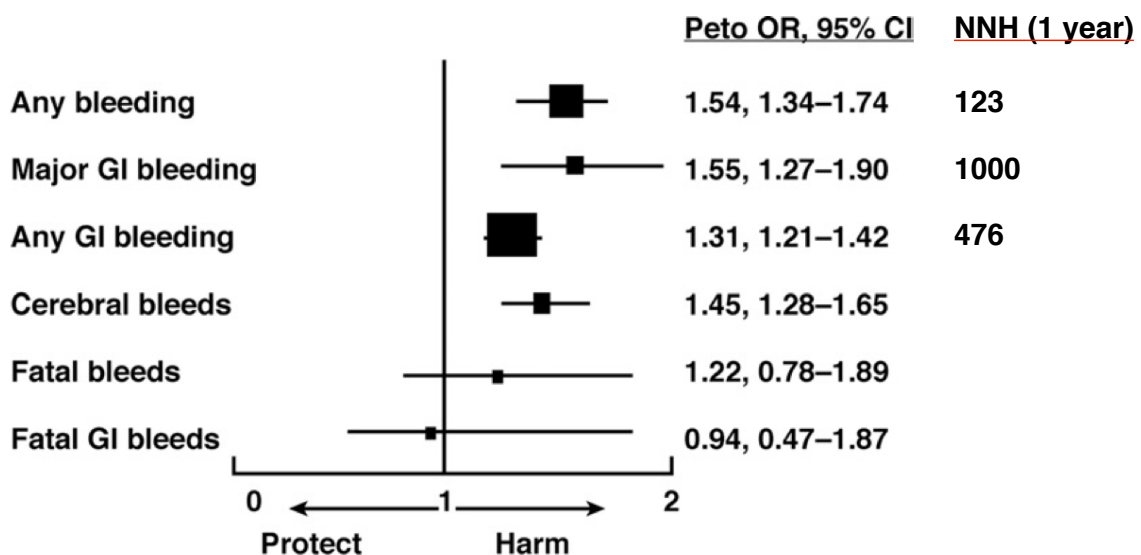N=35 trials, 87,581 patients. 338,735 person-years followup. Average follow-up 3.9 y.

		Peto OR, 95% CI	NNH (1 year)
Any bleeding		1.54, 1.34–1.74	123
Major GI bleeding		1.55, 1.27–1.90	1000
Any GI bleeding		1.31, 1.21–1.42	476
Cerebral bleeds		1.45, 1.28–1.65	
Fatal bleeds		1.22, 0.78–1.89	
Fatal GI bleeds		0.94, 0.47–1.87	

0   1   2

Protect   Harm

Figure 1. Bleeding events associated with low-dose ASA alone vs controls.

Lanas et al. Clin Gastro Hepatol 2011;9:762

Safety of ASA: Intracranial Hemorrhage

N=6 trials. 51,342 women, 44,114 men.
ASA 75mg - 500 mg/d, mean 6.4 years followup.

% over 6.4 years

Legend:
- Placebo/no Tx
- Aspirin

OR 1.69
NNH 803

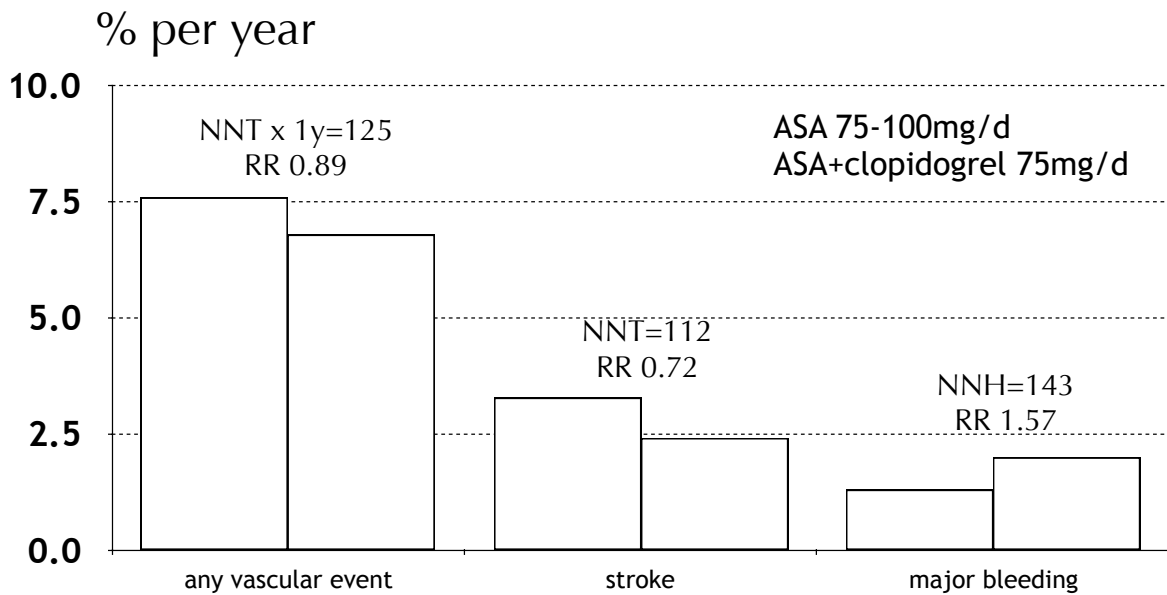FEMALES   MALES
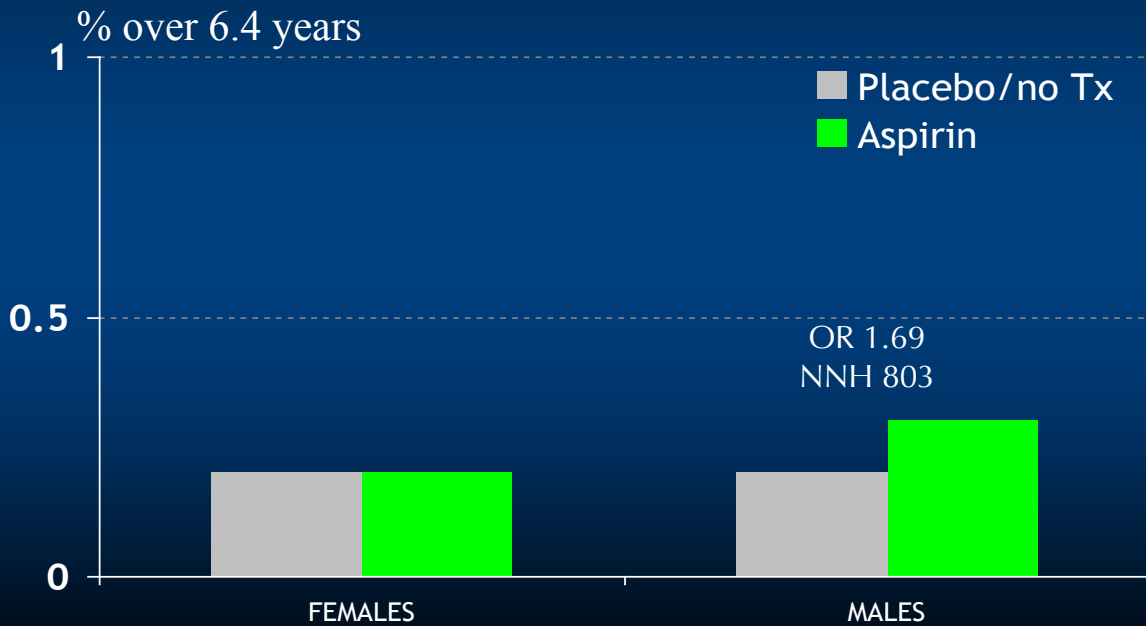
Berger JS et al. JAMA 2006;295:306-13

ACTIVE W

N= 6,707 AF patients with 2+ risk factors for stroke (CHADS + PVD), felt to be candidates for warfarin therapy. 33% >75 y/o. Stopped early.

% per year

warfarin INR 2-3
ASA + clopidogrel 75mg/d

NNT/H=59
RR 1.45

NNT/H=97
RR 1.75

stroke+embolism+MI+vasc death   stroke   major bleeding
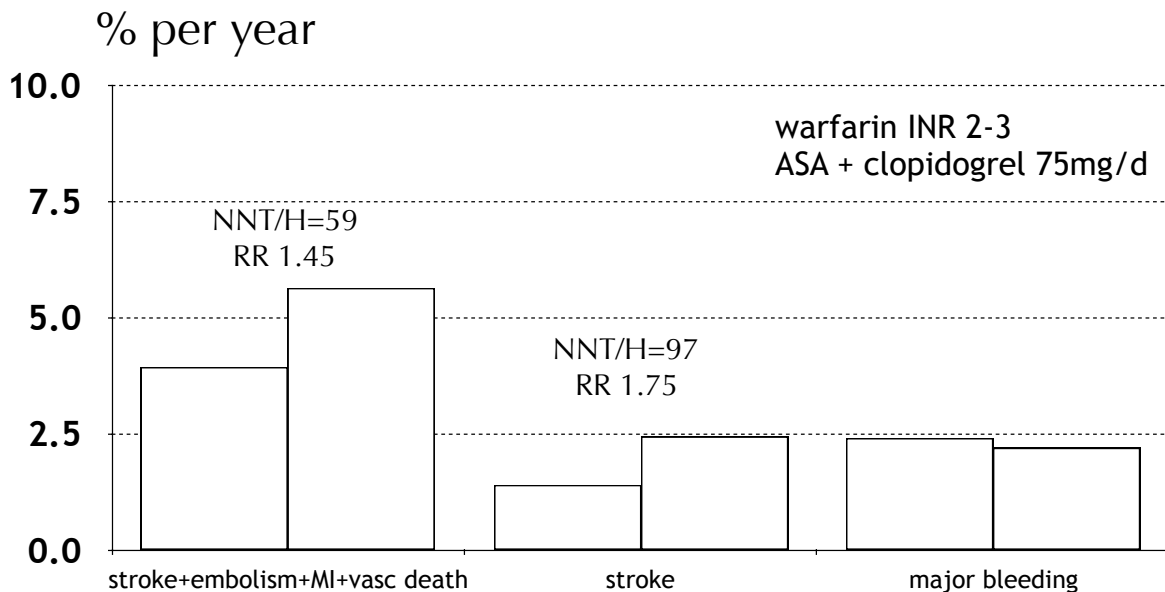
ACTIVE-W. Lancet 2006;367:1903-12

ACTIVE A

N= 7,554 AF patients with 1+ risk factors for stroke (CHADS2+CAD), felt to be "unsuitable" for warfarin therapy. Median 3.6y followup.

% per year

NNT x 1y=125
RR 0.89

ASA 75-100mg/d
ASA+clopidogrel 75mg/d

NNT=112
RR 0.72

NNH=143
RR 1.57

any vascular event   stroke   major bleeding
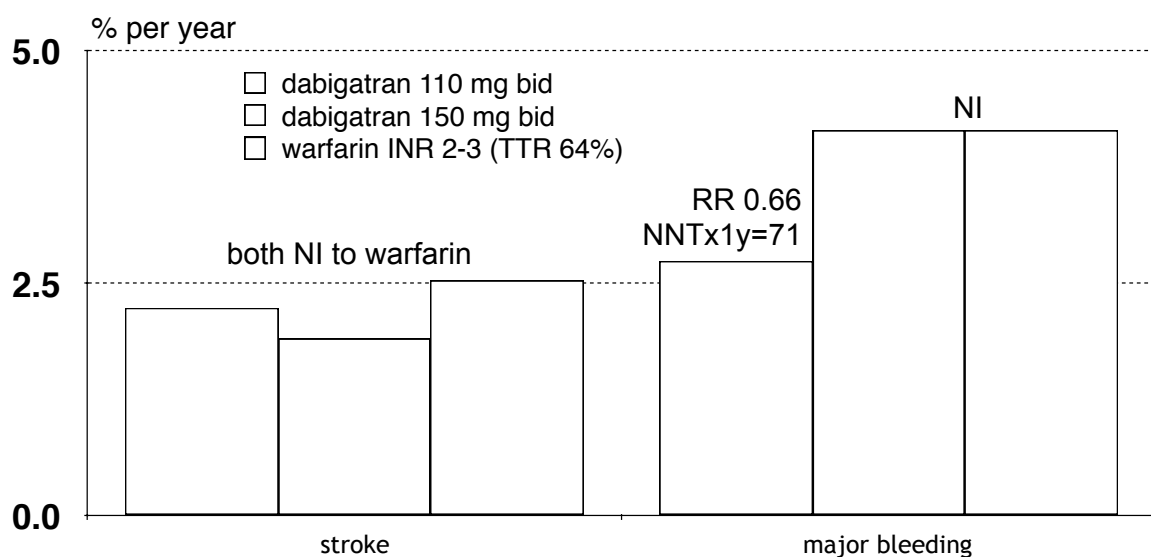
ACTIVE-A. NEJM 2009;360 [1APR09]

RE-LY: dabigatran vs. warfarin in AF

N= 18,113 AF patients with 1+ risk factors for stroke (mean CHADS2 score 2.1). Median 2y followup. Non-inferiority trial.

% per year

☐ dabigatran 110 mg bid
☐ dabigatran 150 mg bid
☐ warfarin INR 2-3 (TTR 64%)

NNHx1y=154
RR 0.8

both NI to warfarin

NNTx1y=172
RR 0.66

NNTx1y=179
RR 0.64

stroke or embolism   stroke   major bleeding
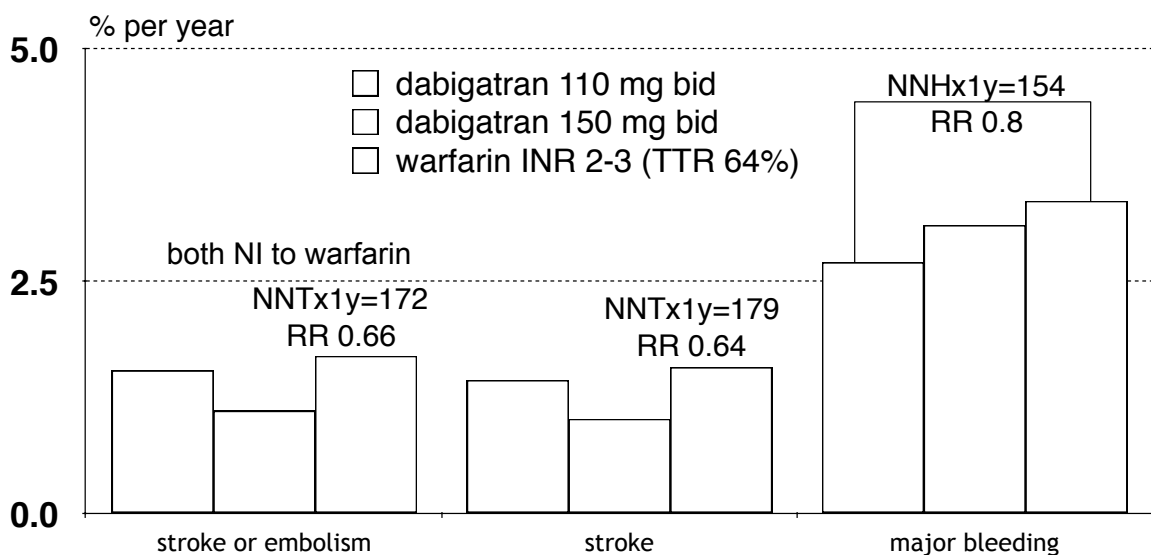
RE-LY. NEJM 2009;361

RE-LY: dabigatran vs. warfarin in AF - other endpoints

N= 18,113 AF patients with 1+ risk factors for stroke (mean CHADS2 score 2.1). Median 2y followup. Non-inferiority trial.

% per year

- ☐ dabigatran 110 mg bid
- ☐ dabigatran 150 mg bid
- ☐ warfarin INR 2-3 (TTR 64%)

NNT ~370
RR ~0.28

*

NS

NNH=476
RR 1.38 (1.0-1.91)

hemorrhagic stroke   MI

RE-LY: dabigatran vs. warfarin in AF - SECONDARY prevention

N= 3,623 AF patients with prior stroke/TIA. Median 2y followup. Pre-specified secondary analysis

% per year

- ☐ dabigatran 110 mg bid
- ☐ dabigatran 150 mg bid
- ☐ warfarin INR 2-3 (TTR 64%)

NI

RR 0.66
NNTx1y=71

both NI to warfarin

stroke   major bleeding

RE-LY® Trial

Primary Endpoints: All Strokes and Systemic Embolic Events
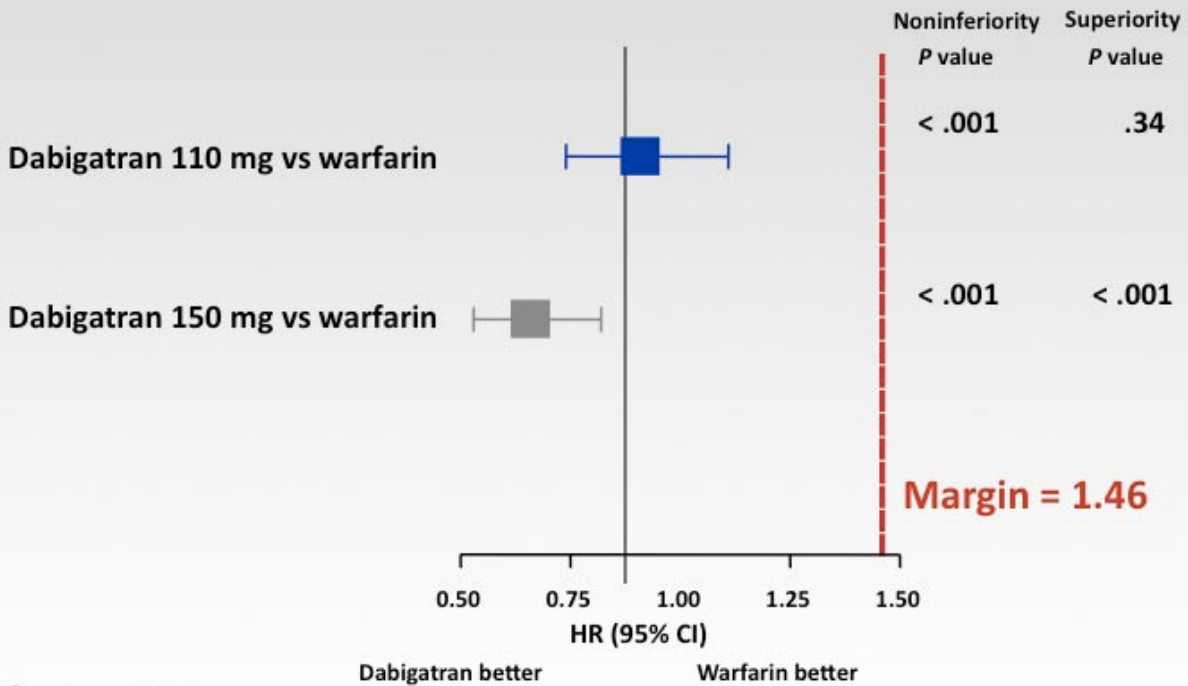
Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151.

Rivaroxaban: ROCKET-AF

N= 14,264 AF patients, 87% with CHADS2 >2.
Median 20 months followup. DB, Non-inferiority trial.

% per year

- ☐ rivaroxaban 20mg once daily
- ☐ warfarin INR 2-3 (TTR 55%)

HR 1.04 (0.90–1.20)

HR 0.79 (0.66–0.96)
NNTx1y=200

HR 0.88 (0.74–1.03)

5.0

2.5

0.0

stroke or embolism
(on-treatment)

stroke or embolism (ITT)

major bleeding
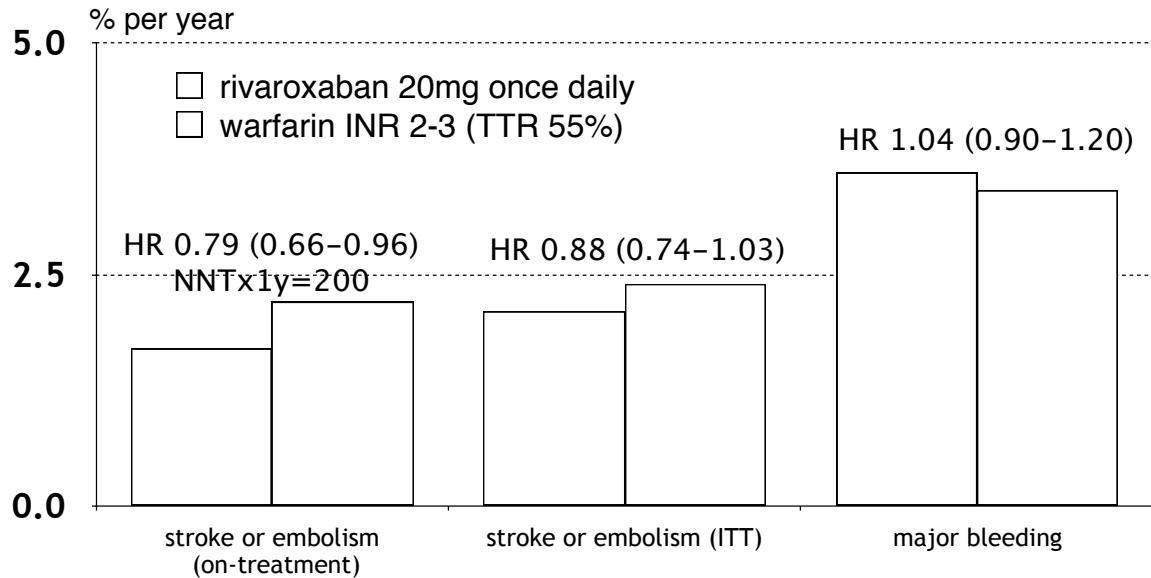
ROCKET-AF. NEJM 2011;10.1056/NEJMoa1009638 (10AUG11)

Rivaroxaban: ROCKET-AF - bleeding breakdown

N= 14,264 AF patients, 87% with CHADS2 >2.
Median 20 months followup. DB, Non-inferiority trial.

% per year

- ☐ rivaroxaban 20mg once daily
- ☐ warfarin INR 2-3 (TTR 55%)

HR 1.39 (1.19–1.61)
NNHx1y=100

HR 1.26
(1.20–1.55)
NNHx1y=278

HR 0.50
(0.31–0.79)
NNTx1y=250

HR 0.67
(0.47–0.93)
NNHx1y=500

5.0

2.5

0.0

GI bleeding

fatal bleeding

ICH

non-major clinically relevant GI
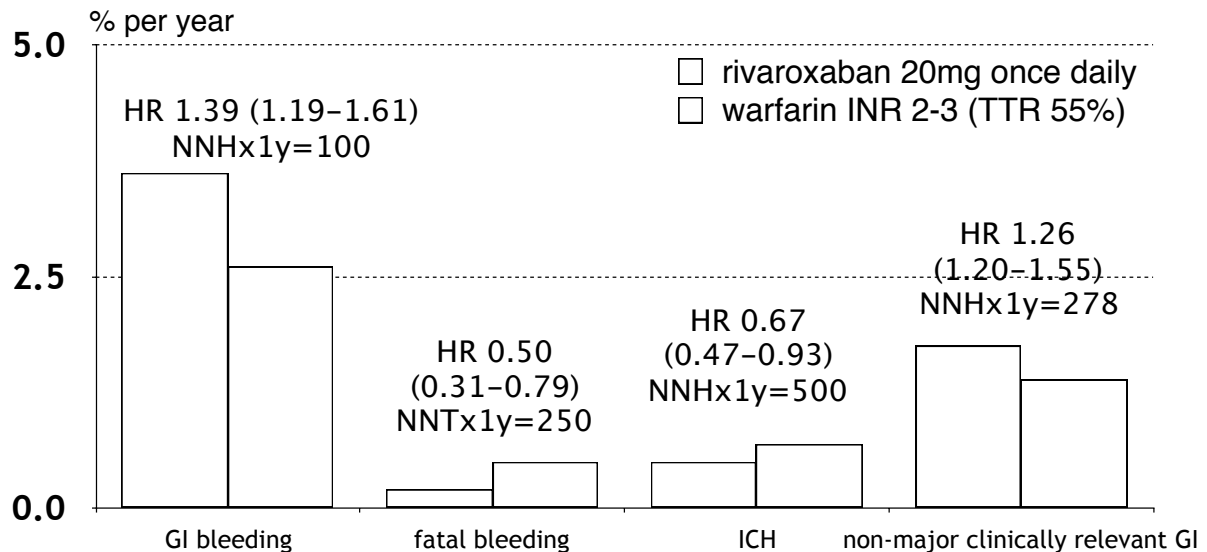
ROCKET-AF. CHEST.October 2012;142(4_MeetingAbstracts):84A-84A

Apixaban: AVERROES

N= 5,599 AF patients with AF + intolerant or "unsuitable" for warfarin.
Max 3y followup, mean 1.1 years (stopped early). Superiority trial.

% per year

NNTx1y=48
HR 0.46

☐ apixiban 5 bid
☐ ASA 81-325 mg daily
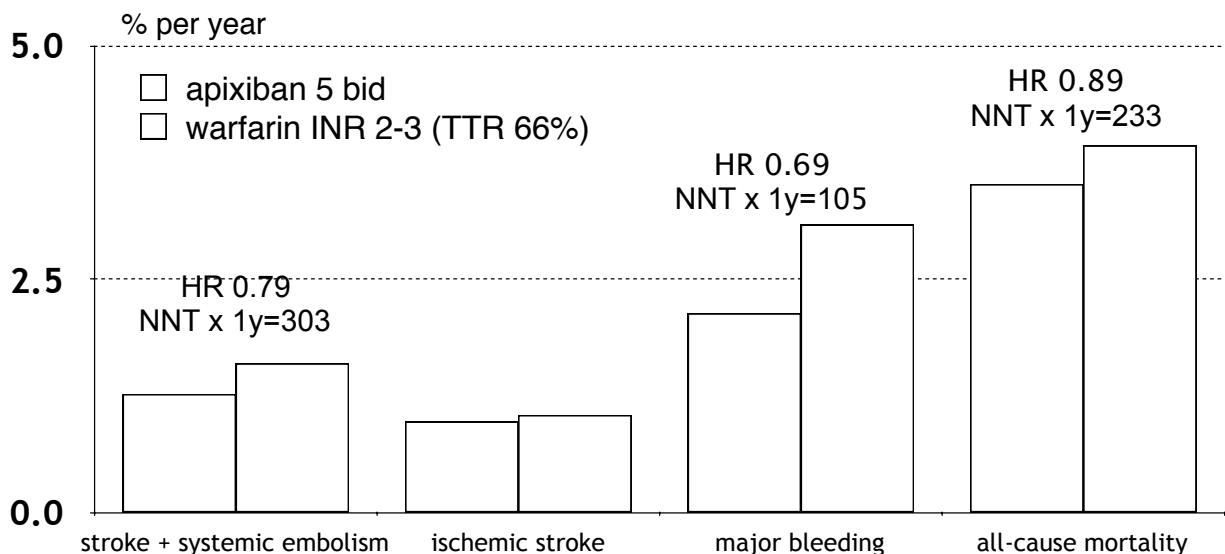
HR 1.14 (0.74–1.75)

- 5.0
- 2.5
- 0.0

stroke (hemorrhagic or ischemic) + systemic embolism

major bleeding
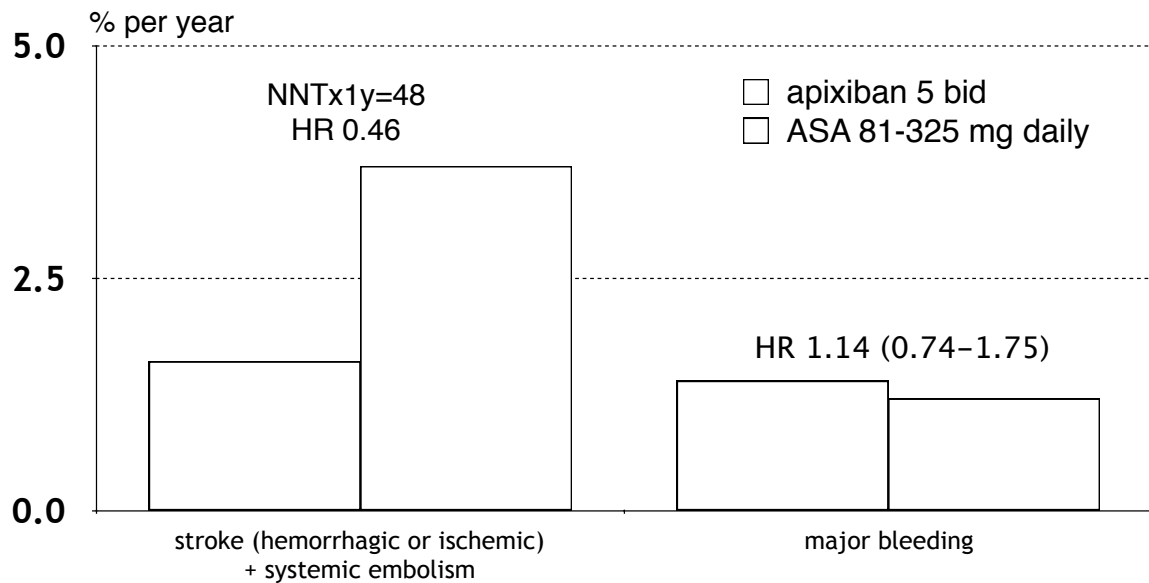
Apixaban: ARISTOTLE

N= 18,201 AF patients with AF. ~70 had CHADS2 score >1. Median 1.8y followup. DB non-inferiority trial.

% per year

☐ apixiban 5 bid
☐ warfarin INR 2-3 (TTR 66%)

HR 0.89
NNT x 1y=233

HR 0.69
NNT x 1y=105

HR 0.79
NNT x 1y=303

- 5.0
- 2.5
- 0.0

stroke + systemic embolism   ischemic stroke   major bleeding   all-cause mortality

Edoxaban: ENGAGE AF-TIMI 48

N= 21,105 AF patients with AF & CHADS2 score >1. Median 2.8y followup. DB non-inferiority trial.

% per year

- ☐ edoxaban 30 daily
- ☐ edoxaban 60 daily
- warfarin INR 2-3 (TTR 68.4%)

HR 1.41 — ischemic stroke
HR 0.35 — (stroke + systemic embolism)
HR 0.55 — major bleeding
HR 0.87 — all-cause mortality

Y-axis: 5.0, 2.5, 0.0

X-axis: stroke + systemic embolism, ischemic stroke, major bleeding, all-cause mortality
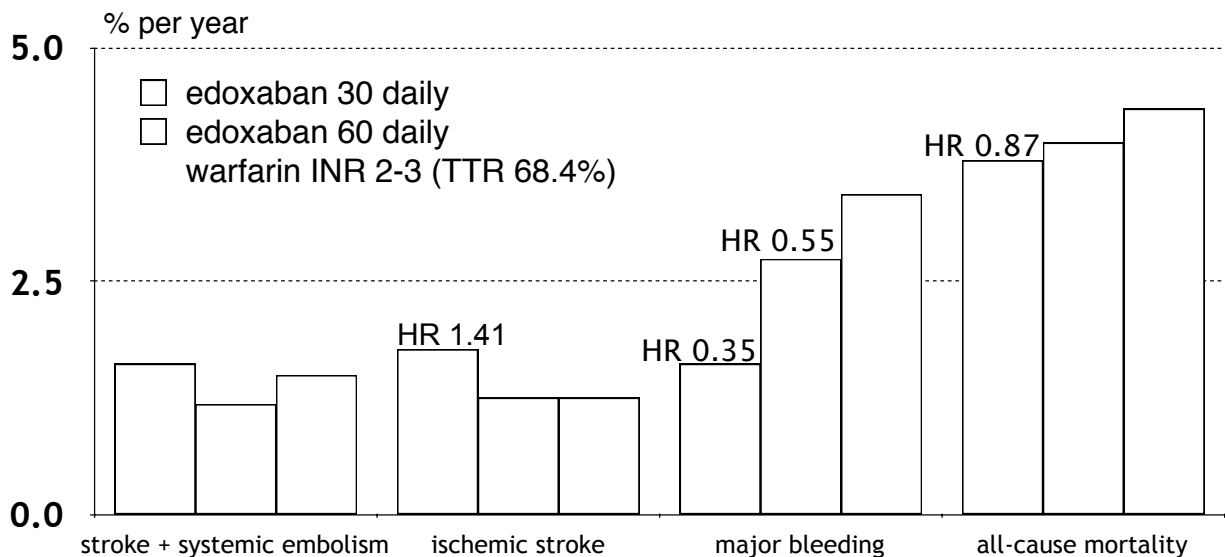
ENGAGE AF-TIMI 48. NEJM 2013; 19NOV13

NOAC PharmaCare Coverage in BC

Dabigatran
http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/limited-coverage-drug-program/limited-coverage-drugs-dabigatran

Rivaroxaban
http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/limited-coverage-drug-program/limited-coverage-drugs-rivaroxaban-for-atrial-fibrillation-af

Apixaban
http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/limited-coverage-drug-program/limited-coverage-drugs-apixaban-for-atrial-fibrillation-af

http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare
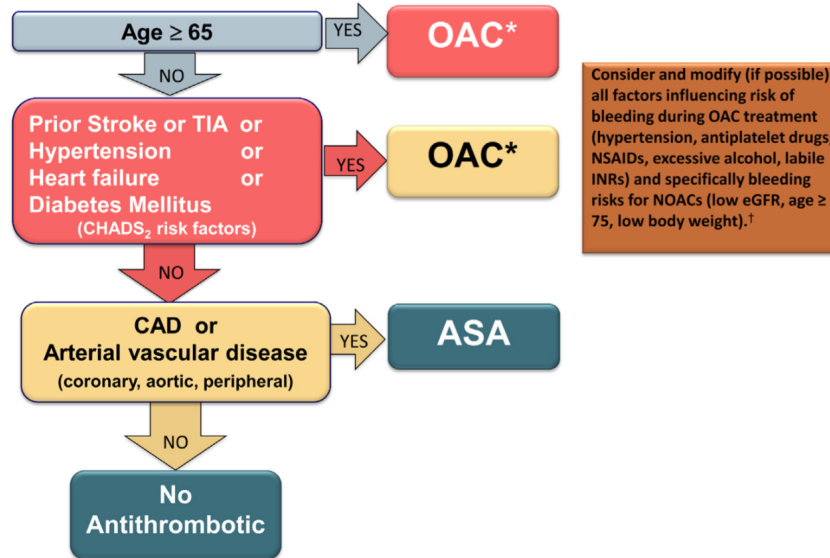
The "CCS Algorithm" for OAC Therapy in AF

Figure 1. The simplified "CCS algorithm" for deciding which patients with atrial fibrillation (AF) or atrial flutter (AFL) should receive oral anti-coagulation (OAC) therapy. * We suggest that a NOAC be used in preference to warfarin for non-valvular AF. [†] Might require lower dosing. ASA, acetylsalicylic acid; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CHADS2, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; NOAC, novel oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drug; TIA, transient ischemic attack.

CCS 2014 AF Guideline Update: Canadian Journal of Cardiology 2014;30:1114-30