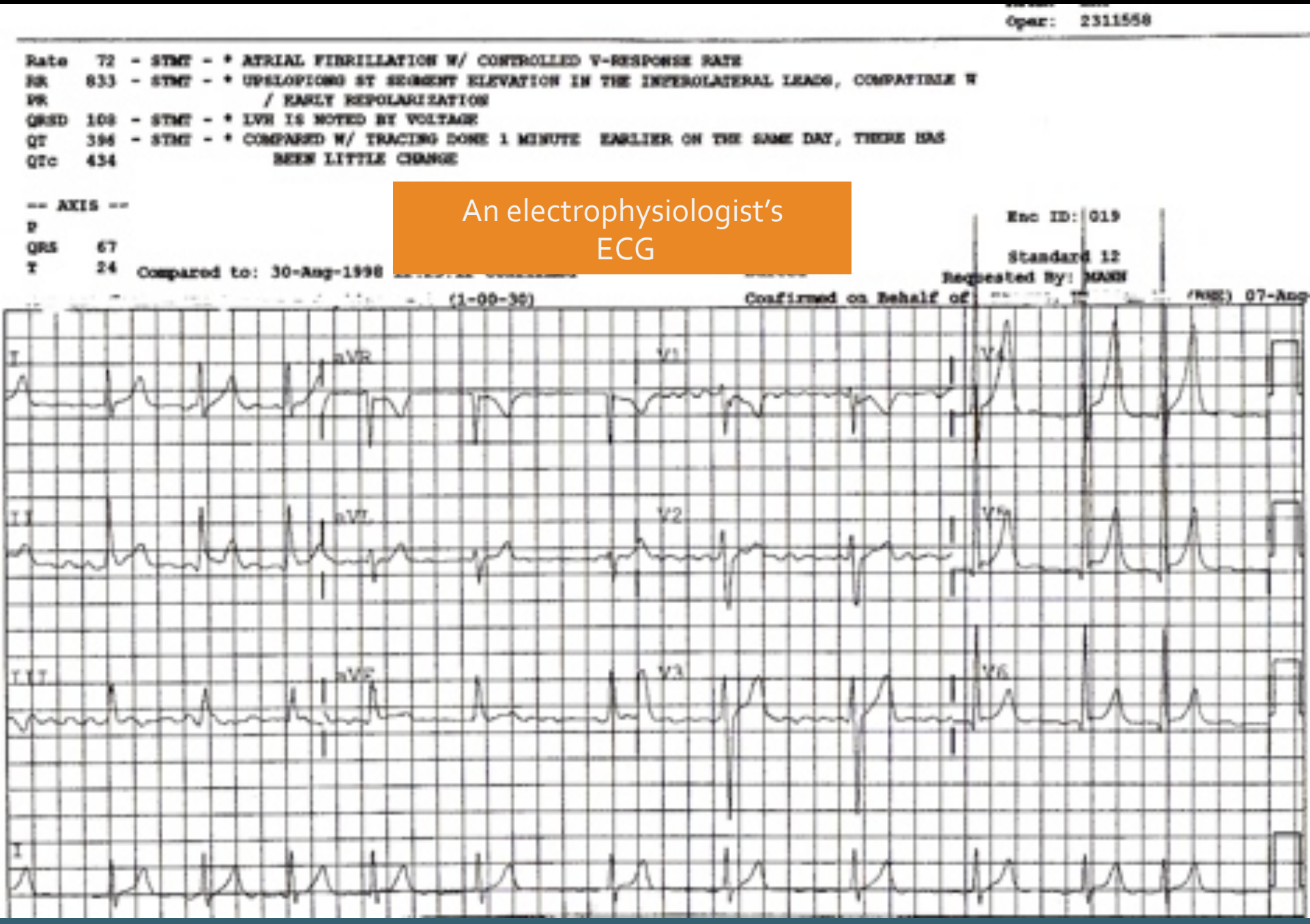
Atrial Fibrillation Treatment 2011

John Mandrola

Disclosures

None

PART 1: INTRO



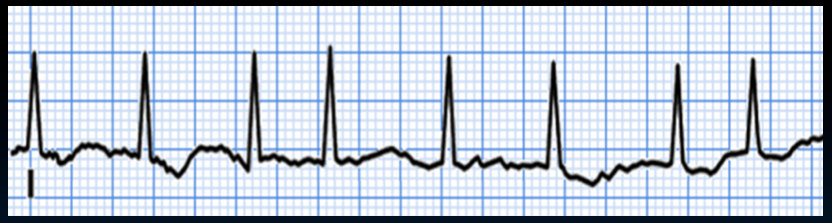
An electrophysiologist's ECG

Topics for today

1. The best tool to treat AF
2. A new way to risk stratify for stroke
   - A better CHADS score?
3. The new blood thinners
4. The expanding role of AF ablation
5. Future directions

Approach to AF treatment

(after making the diagnosis, and exclusion of obvious causes)



Treat Symptoms

Rhythm Control

Drugs v.AF-Ablation

Prevent Heart Failure

Rate Control

Prevent Stroke

Anticoagulants

What's the best tool for treating AF?

- Drugs?
- Devices?
- Ablation?

Education
Knowledge

AF Education

Things that I explain

- What is AF?
- What causes AF?
- What are the goals of treatment?
  - Cures are rare
- What are the possible treatments?
- The importance of treating associated conditions
  - TLC – *Therapeutic Lifestyle Changes*
- The Quandary
- The Rule

The Quandary

AF AF RX

AF Treatment…Bad?

- **Prolonged QT and VF**
  - Sotalol, Dofetilide, Amiodarone, Dronedarone
- **1:1 Atrial Flutter and syncope and SCD**
  - Propafenone, Flecanide
- **Organ toxicity (Liver, Lung and Thyroid)**
  - Amiodarone, Dronedarone
- Bleeding as a complication of blood thinners
- **Severe bradycardia warranting an implantable intravascular device**
  - All AF drugs except dofetilide
- **Fatigue, exercise Intolerance and shortness of breath**
  - All AF drugs except dofetilide
- **Complications from catheter ablation**
  - Death, Stroke, Pericardial tamponade, Phrenic nerve paralysis, PV stenosis, Pulmonary emboli, pneumonia, vascular complications

The ‘Rule’

No matter what…

Never…

Ever…

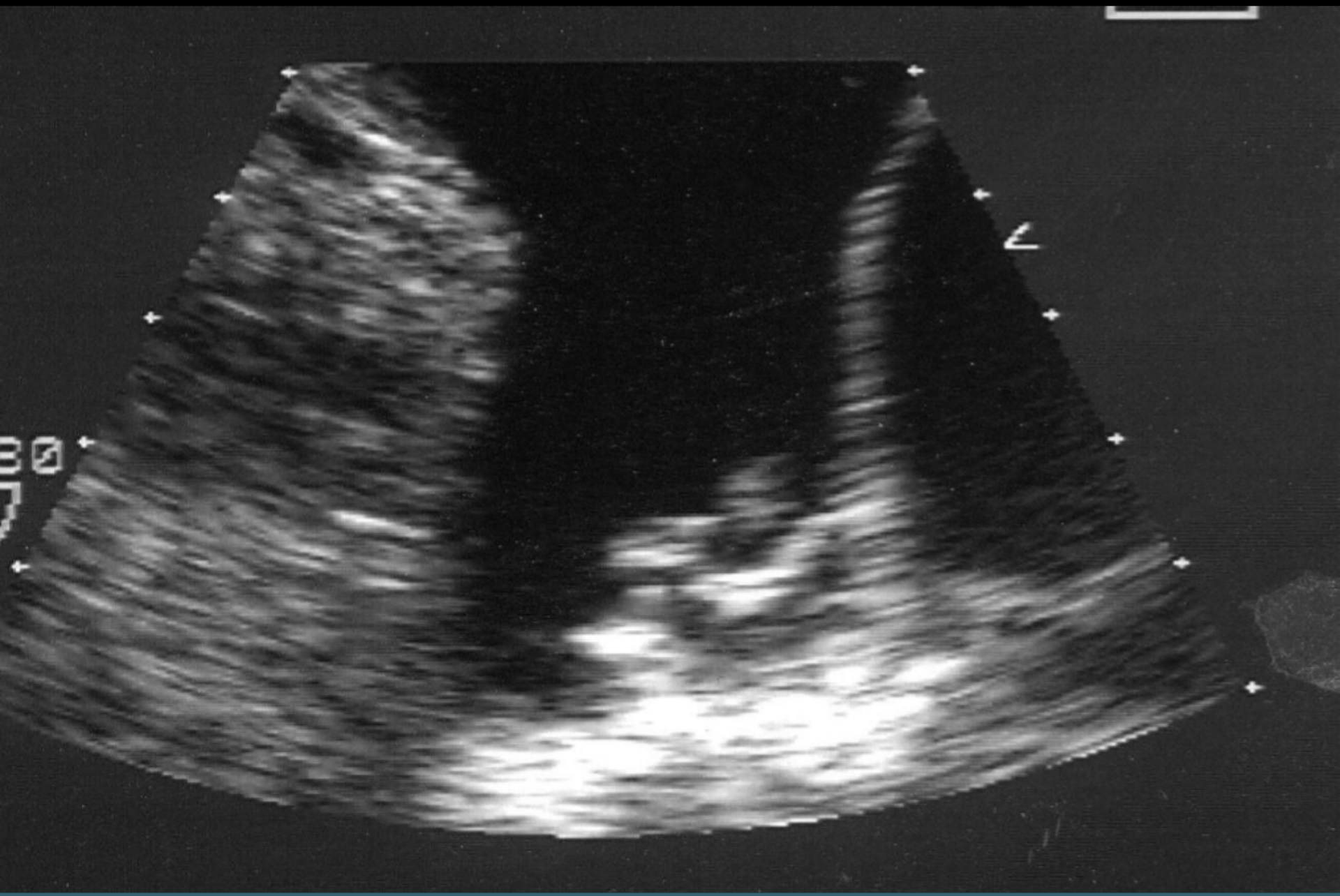
Make AF treatment worse than the disease

PART 2: AF COMPLICATIONS STROKE

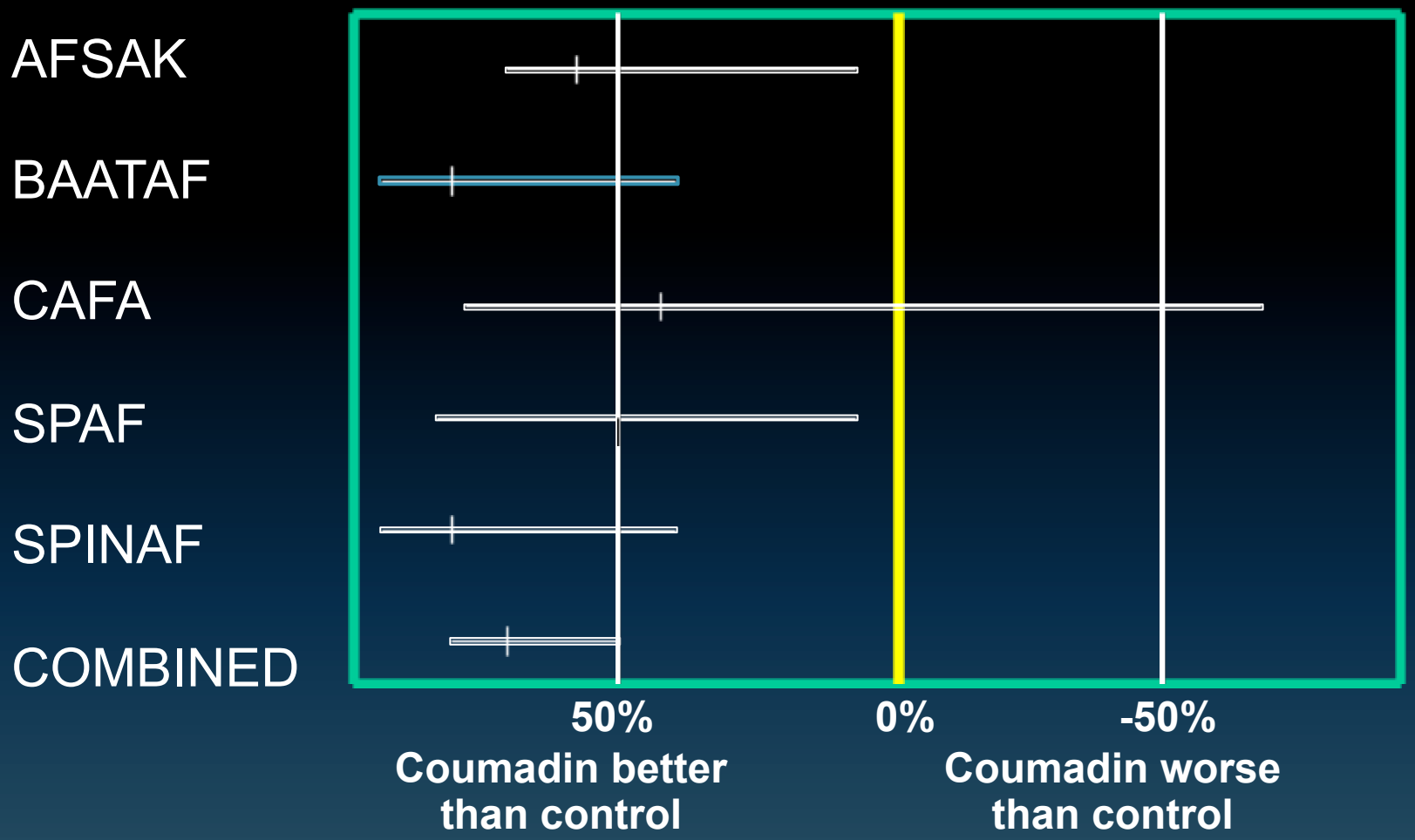
Possible Mechanisms for Stroke in AF

- Loss of mechanical systole
- Stasis of blood
- Atrial fibrosis
- Platelet activation
- (E) All of the above

Left Atrial Appendage clot in AF



Plot of 5 Randomized trials of Thrombo-embolic Prevention with Warfarin



Stroke in AF
Myths

1. Rhythm-control strategies (with drugs) prevent stroke
2. **Running the INR on the low side** (< 2) is an effective strategy for lowering risk of bleeding and still getting some stroke prevention
3. Intermittent AF confers less stroke risk than permanent AF
4. **Aspirin** offers the elderly AF patient a safer and effective strategy of stroke prevention

    -BAFTA

    -AVEROS

    -Danish Registry study (10-11)

Does rhythm control prevent stroke?

AFFIRM lessons

Event	Overall (N=4060)	Rate-Control Group (N=2027)	Rhythm-Control Group (N=2033)	P Value
		no. of patients (%)		
Primary end point (death)	666 (26.3)	310 (25.9)	356 (26.7)	0.08†
Secondary end point (composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest)	861 (32.3)	416 (32.7)	445 (32.0)	0.33
Torsade de pointes	14 (0.5)	2 (0.2)‡	12 (0.8)	0.007
Sustained ventricular tachycardia	15 (0.6)	9 (0.7)	6 (0.6)	0.44
Cardiac arrest followed by resuscitation				
Ventricular fibrillation or ventricular tachycardia	19 (0.6)	10 (0.7)	9 (0.5)	0.83
Pulseless electrical activity, bradycardia, or other rhythm	10 (0.3)	1 (<0.1)	9 (0.6)	0.01
Central nervous system event				
Total	211 (8.2)	105 (7.4)	106 (8.9)	0.93
Ischemic stroke§	157 (6.3)	77 (5.5)	80 (7.1)	0.79
After discontinuation of warfarin	69	25	44	
During warfarin but with INR <2.0	44	27	17	
Concurrent atrial fibrillation	67	42	25	
Primary intracerebral hemorrhage	34 (1.2)	18 (1.1)	16 (1.3)	0.73
Subdural or subarachnoid hemorrhage	24 (0.8)	11 (0.8)	13 (0.8)	0.68

AFFIRM Trial NEJM 2002

Stroke in AF
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Ischemic Stroke and ICH in AF

Table 5. Incidence Rates of Ischemic Stroke and Intracranial Hemorrhage among Patients with Nonvalvular Atrial Fibrillation Who Were Taking Warfarin, According to the International Normalized Ratio (INR) at the Time of the Stroke.*

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)

* CI denotes confidence interval.
† Differences in the numbers of person-years between stroke and intracranial hemorrhage reflect differences in the time at which data were censored.

- 13K patients with AF and stroke
  - Kaiser Permanente Northern CA
- SubRx INR assoc with Inc stroke severity, inc mortality and no fewer ICH

Threshold of Increased ICH

Hylek EM et al. N Engl J Med 2003;349:1019-1026.

The NEW ENGLAND JOURNAL of MEDICINE

Severity of stroke, according to the intensity of blood-thinner

Table 2. Severity of the Neurologic Deficit at Discharge and 30-Day Mortality Rates, According to the Antithrombotic-Medication Status and International Normalized Ratio (INR) at Admission.

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

Adequate blood-thinning assoc with less severe neurologic events

Hylek EM et al. N Engl J Med 2003;349:1019-1026.

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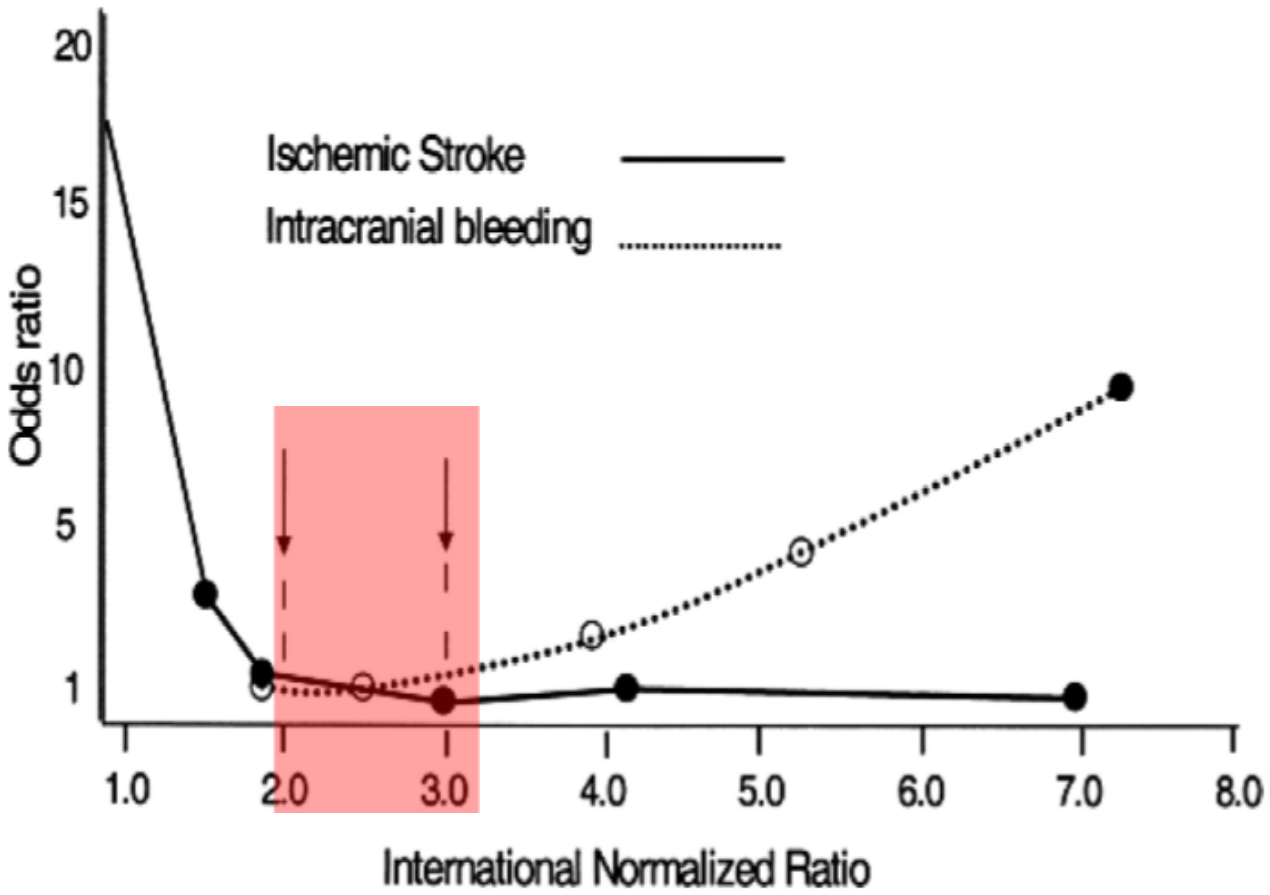
Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to inter of anticoagulation



Fuster, V. et al. J Am Coll Cardiol 2006;48:e149–e246

JACC Journal of the American College of Cardiology

Stroke in AF
Myths

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    -BAFTA

    -AVEROS

    -Danish Registry study (10-11)

Stroke Risk: Intermittent AF versus Persistent/Permanent

European Guidelines

- *Patients with paroxysmal AF should be regarded as having a stroke risk similar to those with persistent or permanent AF, in the presence of risk factors.*

Stroke in AF
Myths

1. **Rhythm-control strategies** prevent stroke
2. **Running the INR on the low side** (< 2) is an effective strategy for lowering risk of bleeding and still getting some stroke prevention
3. Intermittent AF confers less stroke risk than permanent AF
4. **Aspirin** offers the (elderly) AF patient a safer and equally effective strategy for preventing stroke

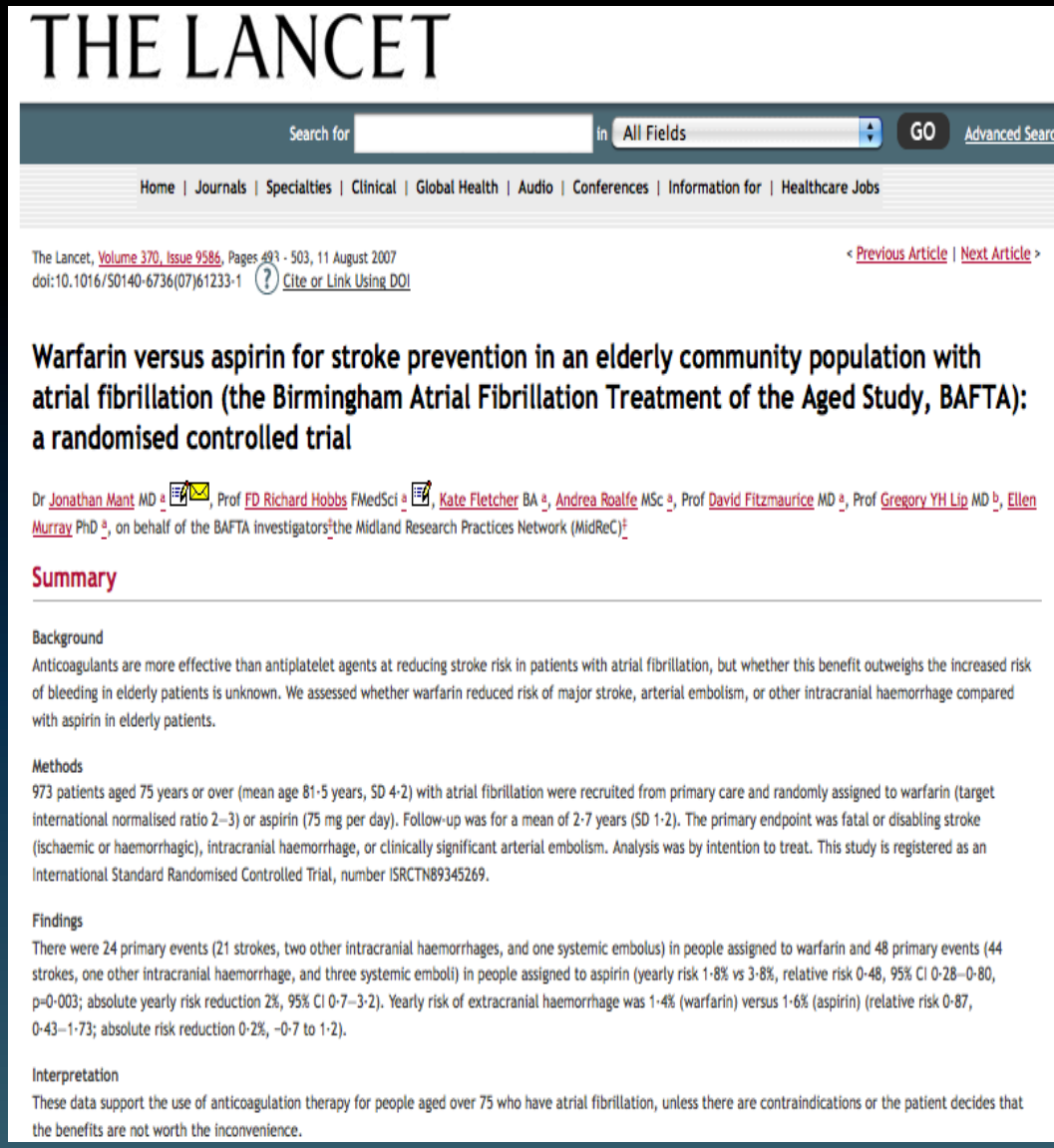
    -BAFTA

    -AVEROS

    -Danish Registry study (October 2011)

BAFTA Trial (2007)

- Real-world cohort of 975 elderly patients (>75 years) w/AF (Private practice)
- Warfarin vs ASA
- Far fewer s trokes with warfarin (RR dec by 50%)
- *No differences in ICH or bleeding*



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The Lancet, Volume 370, Issue 9586, Pages 493 - 503, 11 August 2007
doi:10.1016/S0140-6736(07)61233-1 Cite or Link Using DOI

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Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial

Dr Jonathan Mant MD [a], Prof FD Richard Hobbs FMedSci [a], Kate Fletcher BA [a], Andrea Roalfe MSc [a], Prof David Fitzmaurice MD [a], Prof Gregory YH Lip MD [b], Ellen Murray PhD [a], on behalf of the BAFTA investigators[‡]the Midland Research Practices Network (MidReC)[‡]

Summary

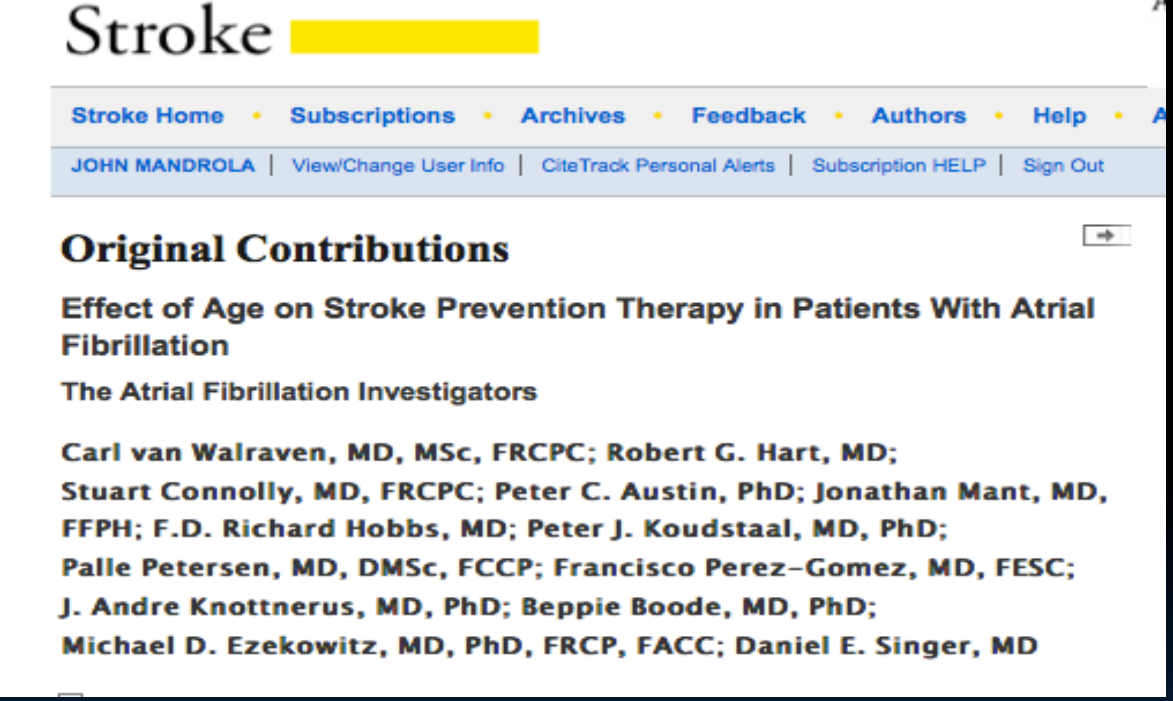
Background
Anticoagulants are more effective than antiplatelet agents at reducing stroke risk in patients with atrial fibrillation, but whether this benefit outweighs the increased risk of bleeding in elderly patients is unknown. We assessed whether warfarin reduced risk of major stroke, arterial embolism, or other intracranial haemorrhage compared with aspirin in elderly patients.

Methods
973 patients aged 75 years or over (mean age 81·5 years, SD 4·2) with atrial fibrillation were recruited from primary care and randomly assigned to warfarin (target international normalised ratio 2–3) or aspirin (75 mg per day). Follow-up was for a mean of 2·7 years (SD 1·2). The primary endpoint was fatal or disabling stroke (ischaemic or haemorrhagic), intracranial haemorrhage, or clinically significant arterial embolism. Analysis was by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN89345269.

Findings
There were 24 primary events (21 strokes, two other intracranial haemorrhages, and one systemic embolus) in people assigned to warfarin and 48 primary events (44 strokes, one other intracranial haemorrhage, and three systemic emboli) in people assigned to aspirin (yearly risk 1·8% *vs* 3·8%, relative risk 0·48, 95% CI 0·28–0·80, p=0·003; absolute yearly risk reduction 2%, 95% CI 0·7–3·2). Yearly risk of extracranial haemorrhage was 1·4% (warfarin) versus 1·6% (aspirin) (relative risk 0·87, 0·43–1·73; absolute risk reduction 0·2%, −0·7 to 1·2).

Interpretation
These data support the use of anticoagulation therapy for people aged over 75 who have atrial fibrillation, unless there are contraindications or the patient decides that the benefits are not worth the inconvenience.

Effect of Age on Stroke Prevention RX in AF (2009-Stroke)



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Original Contributions

Effect of Age on Stroke Prevention Therapy in Patients With Atrial Fibrillation

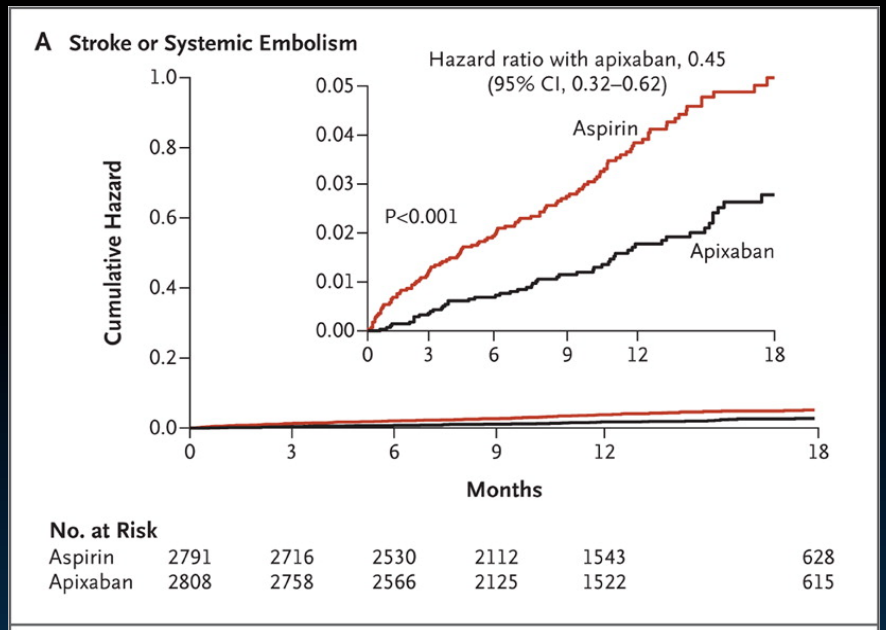
The Atrial Fibrillation Investigators

Carl van Walraven, MD, MSc, FRCPC; Robert G. Hart, MD; Stuart Connolly, MD, FRCPC; Peter C. Austin, PhD; Jonathan Mant, MD, FFPH; F.D. Richard Hobbs, MD; Peter J. Koudstaal, MD, PhD; Palle Petersen, MD, DMSc, FCCP; Francisco Perez–Gomez, MD, FESC; J. Andre Knottnerus, MD, PhD; Beppie Boode, MD, PhD; Michael D. Ezekowitz, MD, PhD, FRCP, FACC; Daniel E. Singer, MD

- Meta-Analysis of 8000+ patients from RCT of OAC and ASA
- Results:
  - Relative benefit of OAC did not vary by age
  - Increased bleeding risk with OAC was far smaller than beneficial reduction in stroke
  - Relative benefit of ASA decreased with increasing age.
- Conclusion:

Because stroke risk increases with age, the absolute benefit of OAC increases as patients age

AVEROS Trial (NEJM 2010)



- 5000+ warfarin-unsuitable AF patients randomized to Apixaban or ASA
- Apixaban sig reduced risk of stroke without an increase in bleeding

Connolly SJ et al. N Engl J Med 2011;364:806-817.

The NEW ENGLAND JOURNAL of MEDICINE

Thromb Haemost. 2011 Sep 27;106(4):739-49. Epub 2011 Jul 20.

Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: A net clinical benefit analysis using a 'real world' nationwide cohort study.

Olesen JB, Lip GY, Lindhardsen J, Lane DA, Ahlehoff O, Hansen ML, Raunsø J, Tolstrup JS, Hansen PR, Gislason GH, Torp-Pedersen C.

Jonas Bjerring Olesen, Department of Cardiology, Post 635, Copenhagen University Hospital Gentofte, Niels Andersens Vej 65, 2900 Hellerup, Denmark, Tel.: +45 2361 7139, Fax: +45 7020 1283, E-mail: jo@heart.dk.

Abstract

It was the aim of this study to determine the efficacy and safety of vitamin K antagonists (VKAs) and acetylsalicylic acid (ASA) in patients with non-valvular atrial fibrillation (AF), with separate analyses according to predicted thromboembolic and bleeding risk. By individual level-linkage of nationwide registries, we identified all patients discharged with non-valvular AF in Denmark (n=132,372). For every patient, the risk of stroke and bleeding was calculated by CHADS2, CHA2DS2-VASc, and HAS-BLED. During follow-up, treatment with VKA and ASA was determined time-dependently. VKA consistently lowered the risk of thromboembolism compared to ASA and no treatment; the combination of VKA+ASA did not yield any additional benefit. In patients at high thromboembolic risk, hazard ratios (95% confidence interval) for thromboembolism were: 1.81 (1.73-1.90), 1.14 (1.06-1.23), and 1.86 (1.78-1.95) for ASA, VKA+ASA, and no treatment, respectively, compared to VKA. The risk of bleeding was increased with VKA, ASA, and VKA+ASA compared to no treatment, the hazard ratios were: 1.0 (VKA; reference), 0.93 (ASA; 0.89-0.97), 1.64 (VKA+ASA; 1.55-1.74), and 0.84 (no treatment; 0.81-0.88), respectively. There was a neutral or positive net clinical benefit (ischaemic stroke vs. intracranial haemorrhage) with VKA alone in patients with a CHADS2 score of ≥ 0, and CHA2DS2-VASc score of ≥ 1. This large cohort study confirms the efficacy of VKA and no effect of ASA treatment on the risk of stroke/thromboembolism. Also, the risk of bleeding was increased with both VKA and ASA treatment, but the net clinical benefit was clearly positive, in favour of VKA in patients with increased risk of stroke/thromboembolism.

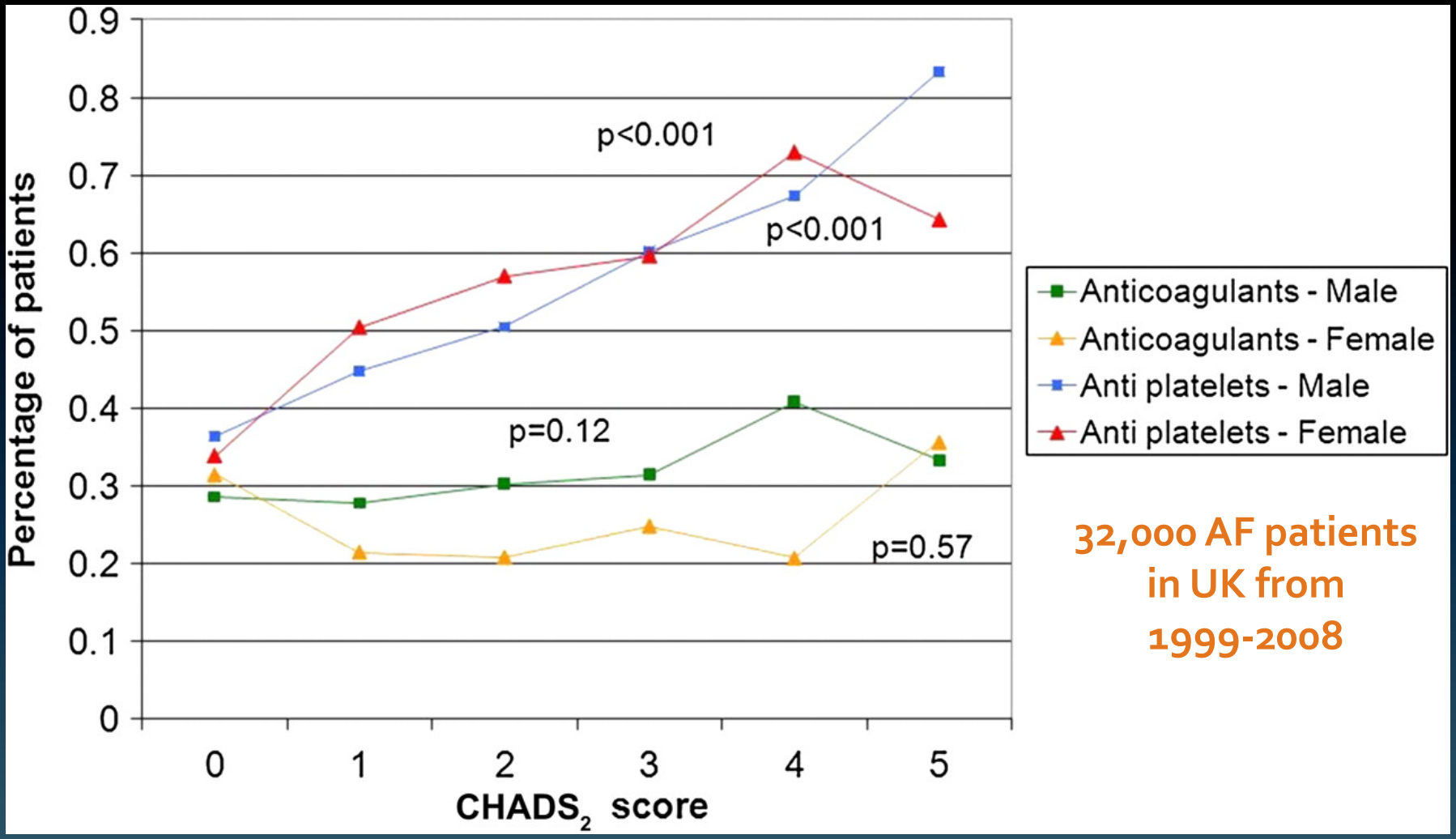
Risk of stroke and bleeding in patients with AF: A net clinical benefit analysis using a 'real world' nationwide cohort study. (2011)

- 132,000 Danish AF patients
  - F/U 7 days to 12 years
- Warfarin consistently decreased stroke risk
  - Except in very low risk patients (CHADS2 = 0)
- ASA ineffective compared to warfarin
- Bleeding risk increased with ASA, Warfarin, Combination
  - Highest bleeding risk w/combination

Despite all the data on anticoagulation in AF

- ASA is overused
- Anticoagulants underused
- Patients at highest risk are not being anti-coagulated
- Females less aggressively treated

Percentage of AF patients treated with anticoagulant and antiplatelet therapy *prior to* stroke.



32,000 AF patients in UK from 1999-2008

Lee S et al. BMJ Open 2011

PART 3: NEW STROKE-RISK SCORE

Deciding on anticoagulation…

Which AF patients benefit?

CHADS2 versus *CHA_2DS_2-VASc*

Stratification of stroke risk in AF

CHADS2

	Points
• Congestive Failure – (LV dysfunction)	1
• HTN	1
• Age > 75	1
• Diabetes	1
• Stroke (previous stroke /TIA)	2

JAMA 2001

$CHADS_2$ score and stroke rate

$CHADS_2$ score	Patients (n = 1733)	Adjuste stroke rate (%/y)* (95% confidence interval)
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)

Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of AF JAMA 2001;285:2864 – 2870.

North American (AHA/ACC/HRS) guidelines for stroke prevention

- CHADS2 = 0 → Nothing or ASA
- CHADS2 = 1 → Anticoag or ASA
- CHADS2 >= 2 → Anticoag (INR 2-3)

Advantages of CHADS2

- Simple
- Concrete
- Easy to remember
- Validated with a good evidence base

Two major downsides of CHADS2

Could it be too simple?

1. How low risk is CHADs zero?
2. Intermediate Risk is broad:

   CHADS2 = 1 rep-resents a diverse and large cohort

→ Risk of underusing warfarin

CHADS2 Cases

- CHADS2 = 0 :
  - 74 year-old female smoker with severe CAD
  - 34 year old medical student
- CHADS2 = 1:
  - 74 year-old female with severe CAD and diabetes
  - 34 year-old medical student w/HTN

CHA_2DS_2-VASc

Adds three criteria to CHADS2

- Female Gender
- Age 65-74
- Vascular disease
  - CAD
  - PAD
  - Aortic Plaque

$CHADS_2$ -> 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

From ESC AF Guidelines

http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-afib-FT.pdf

$CHADS_2$ -> CHA_2DS_2VASc

CHADS2 score	Patients (*n* = 1733)	Adjusted stroke rate %/ year
0	120	1.9
1	463	2.8
2	523	4.0
3	337	5.9
4	220	8.5
5	65	12.5
6	5	18.2

CHA2DS2-VASc score	Patients (*n* = 7329)	Adjusted stroke rate (%/ year)
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

From ESC AF Guidelines: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-afib-FT.pdf

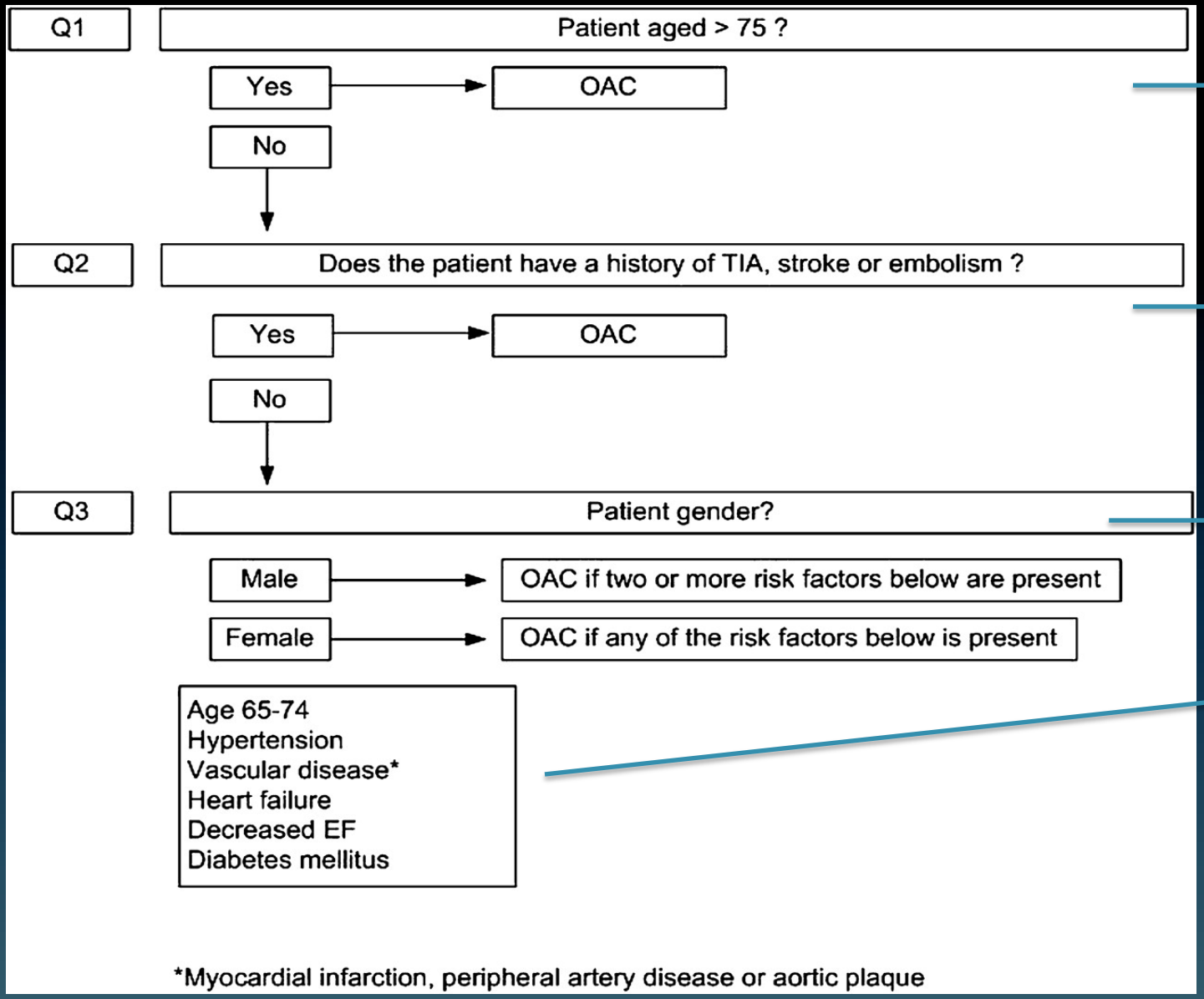
European approach to AF stroke prevention

Risk category	CHA_2DS_2-VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥ 2 'clinically relevant non-major' risk factors	≥ 2	OAC
One 'clinically relevant non-major' risk factor	1	Either OAC or aspirin 75-325 mg daily. Preferred: OAC rather than aspirin.
No risk factors	0	Either aspirin 75-325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.

Advantages of CHA2DS2-VASc "Euro-CHADS"

- ***Low Risk is truly low risk:***
  - CHA2DS2-VASc (0) patients are at very low risk.
  - No anticoag needed
- ***Intermediate Risk (gives docs a choice) more narrow***
  - With CHADS (1)– 32% patients fall in ASA or Warfarin
  - With CHA2DS2-VASc (1)– only 11% fall in ASA or Warfarin group
- Euro-CHADs has slightly improved c-statistic

Proposed clinical flowchart for stroke prevention in AF



2 points

2 points

1 point

+

1 point

Lip G Y H et al. Chest 2010;137:263-272

Table 8 CHA_2DS_2VASc score and stroke rate

(a) Risk factors for stroke and thrombo-embolism in non-valvular AF	
'Major' risk factors	**'Clinically relevant non-major' risk factors**
Previous stroke, TIA, or systemic embolism Age ≥75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤40%) Hypertension - Diabetes mellitus Female sex - Age 65–74 years Vascular disease[a]
(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)	

Table 2

Event rate (95% CI) of hospital admission and death due to thromboembolism* per 100 person years

Score/risk category	1 year's follow-up	5 years' follow-up	10 years' follow-up
$CHADS_2$:			
0	1.67 (1.47 to 1.89)	1.28 (1.19 to 1.38)	1.24 (1.16 to 1.33)
1	4.75 (4.45 to 5.07)	3.70 (3.55 to 3.86)	3.56 (3.42 to 3.70)
2	7.34 (6.88 to 7.82)	5.58 (5.35 to 5.83)	5.40 (5.18 to 5.63)
3	15.47 (14.62 to 16.36)	10.29 (9.87 to 10.73)	9.89 (9.50 to 10.31)
4	21.55 (20.03 to 23.18)	14.00 (13.22 to 14.82)	13.70 (12.95 to 14.48)
5	19.71 (16.93 to 22.93)	12.98 (11.52 to 14.63)	12.57 (11.18 to 14.14)
6	22.36 (14.58 to 34.30)	16.75 (11.91 to 23.56)	17.17 (12.33 to 23.92)
$CHADS_2$:			
Low risk (0)	1.67 (1.47 to 1.89)	1.28 (1.19 to 1.38)	1.24 (1.16 to 1.33)
Intermediate risk (1)	4.75 (4.45 to 5.07)	3.70 (3.55 to 3.86)	3.56 (3.42 to 3.70)
High risk (2-6)	12.27 (11.84 to 12.71)	8.30 (8.08 to 8.51)	7.97 (7.77 to 8.17)
CHA_2DS_2-VASc:			
0	0.78 (0.58 to 1.04)	0.69 (0.59 to 0.81)	0.66 (0.57 to 0.76)
1	2.01 (1.70 to 2.36)	1.51 (1.37 to 1.67)	1.45 (1.32 to 1.58)
2	3.71 (3.36 to 4.09)	3.01 (2.83 to 3.20)	2.92 (2.76 to 3.09)
3	5.92 (5.53 to 6.34)	4.41 (4.21 to 4.61)	4.28 (4.10 to 4.47)
4	9.27 (8.71 to 9.86)	6.69 (6.41 to 6.99)	6.46 (6.20 to 6.74)
5	15.26 (14.35 to 16.24)	10.42 (9.95 to 10.91)	9.97 (9.53 to 10.43)
6	19.74 (18.21 to 21.41)	12.85 (12.07 to 13.69)	12.52 (11.78 to 13.31)
7	21.50 (18.75 to 24.64)	13.92 (12.49 to 15.51)	13.96 (12.57 to 15.51)
8	22.38 (16.29 to 30.76)	14.07 (10.80 to 18.33)	14.10 (10.90 to 18.23)
9	23.64 (10.62 to 52.61)	16.08 (8.04 to 32.15)	15.89 (7.95 to 31.78)
CHA_2DS_2-VASc:			
Low risk (0)	0.78 (0.58 to 1.04)	0.69 (0.59 to 0.81)	0.66 (0.57 to 0.76)
Intermediate risk (1)	2.01 (1.70 to 2.36)	1.51 (1.37 to 1.67)	1.45 (1.32 to 1.58)
High risk (2-9)	8.82 (8.55 to 9.09)	6.01 (5.88 to 6.14)	5.72 (5.60 to 5.84)

*Includes peripheral artery embolism, ischaemic stroke, and pulmonary embolism.

$CHADS_2$ vs CHA_2DS_2-VASc

- 73,000 AF patients in Denmark registry, not treated with warfarin and followed clinically from 1997-29006
- How did the two validation schemes compare?

BMJ 2011; 342:d124

Table 2

Event rate (95% CI) of hospital admission and death due to thromboembolism* per 100 person years

Score/risk category	1 year's follow-up	5 years' follow-up	10 years' follow-up
$CHADS_2$:			
0	1.67 (1.47 to 1.89)	1.28 (1.19 to 1.38)	1.24 (1.16 to 1.33)
1	4.75 (4.45 to 5.07)	3.70 (3.55 to 3.86)	3.56 (3.42 to 3.70)
2	7.34 (6.88 to 7.82)	5.58 (5.35 to 5.83)	5.40 (5.18 to 5.63)
3	15.47 (14.62 to 16.36)	10.29 (9.87 to 10.73)	9.89 (9.50 to 10.31)
4	21.55 (20.03 to 23.18)	14.00 (13.22 to 14.82)	13.70 (12.95 to 14.48)
5	19.71 (16.93 to 22.93)	12.98 (11.52 to 14.63)	12.57 (11.18 to 14.14)
6	22.36 (14.58 to 34.30)	16.75 (11.91 to 23.56)	17.17 (12.33 to 23.92)
$CHADS_2$:			
Low risk (0)	1.67 (1.47 to 1.89)	1.28 (1.19 to 1.38)	1.24 (1.16 to 1.33)
Intermediate risk (1)	4.75 (4.45 to 5.07)	3.70 (3.55 to 3.86)	3.56 (3.42 to 3.70)
High risk (2-6)	12.27 (11.84 to 12.71)	8.30 (8.08 to 8.51)	7.97 (7.77 to 8.17)
CHA_2DS_2-VASc:			
0	0.78 (0.58 to 1.04)	0.69 (0.59 to 0.81)	0.66 (0.57 to 0.76)
1	2.01 (1.70 to 2.36)	1.51 (1.37 to 1.67)	1.45 (1.32 to 1.58)
2	3.71 (3.36 to 4.09)	3.01 (2.83 to 3.20)	2.92 (2.76 to 3.09)
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High risk (2-9)	8.82 (8.55 to 9.09)	6.01 (5.88 to 6.14)	5.72 (5.60 to 5.84)

*Includes peripheral artery embolism, ischaemic stroke, and pulmonary embolism.

CHA_2DS_2-VASc was better:

Low risk is lower

Intermediate risk more defined

BMJ 2011; 342:d124

Clopidogrel vs VKA: *ACTIVE-W*

THE LANCET

The Lancet, Volume 367, Issue 9526, Pages 1903 - 1912, 10 June 2006
doi:10.1016/S0140-6736(06)68845-4 Cite or Link Using DOI

< Previous Article | Next Article

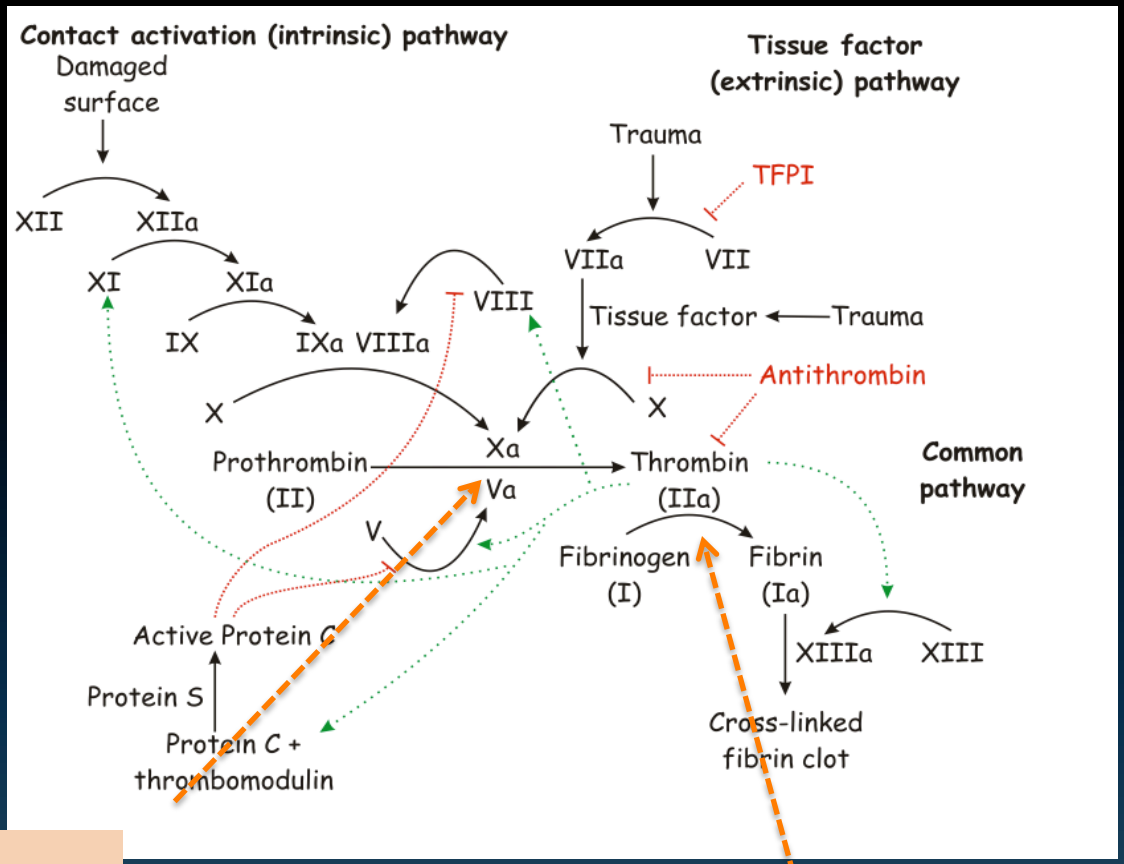
Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial

The ACTIVE Writing Group on behalf of the ACTIVE Investigators ‡

- Clear superiority of warfarin over clopidogrel (40% Risk reduction)
- Study stopped prematurely due to warfarin benefit

PART 4: NEW BLOOD THINNERS

The new oral blood thinners



Factor Xa-Inhibitors

Rivaroxaban

Apixaban

Direct Thrombin Inhibitor

Dabigatran

The then and now…

Dabigatran and Rivaroxaban

- Data
- Clinical caveats
- Limitations

RE-LY Trial

2009

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

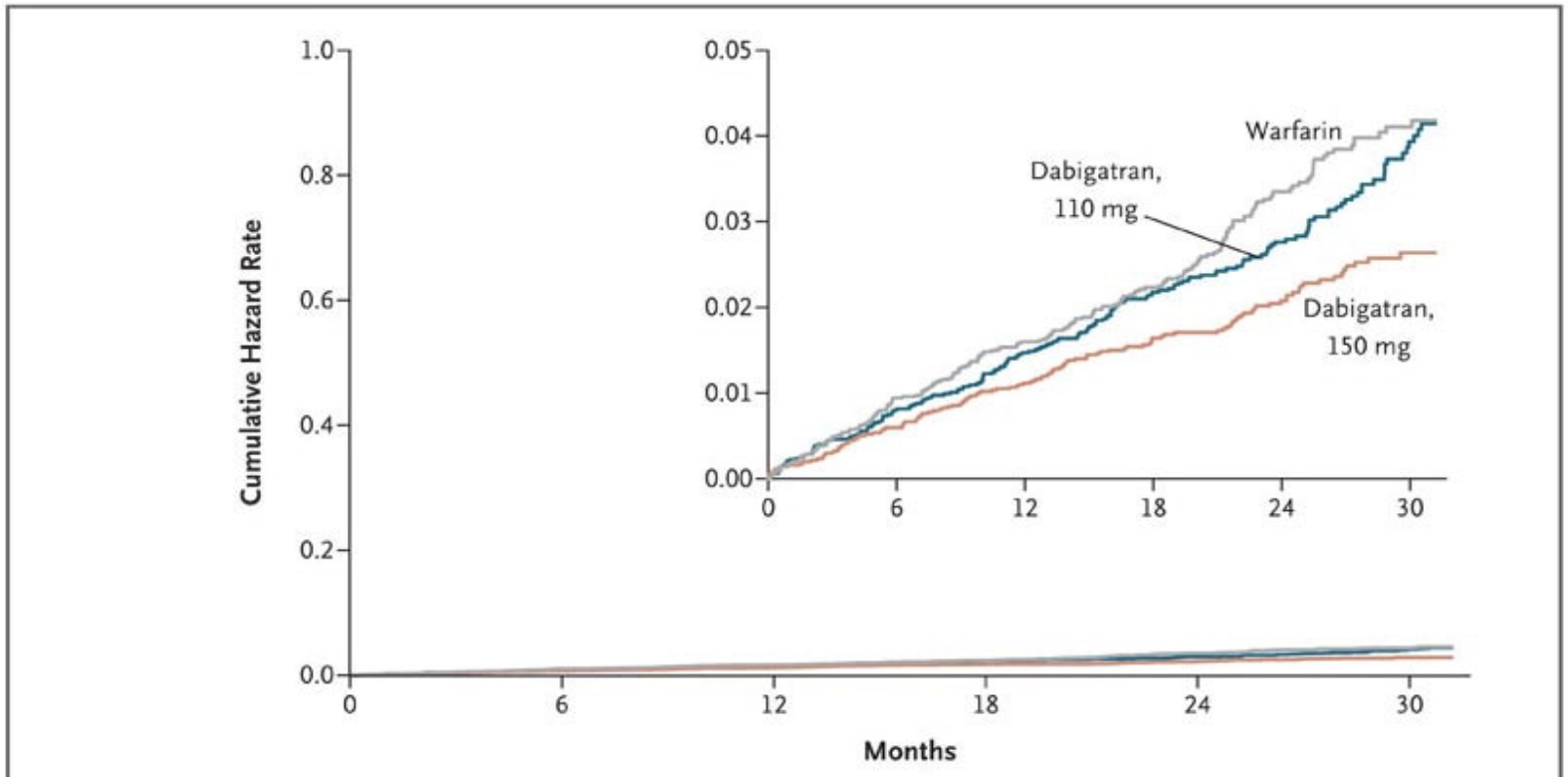
Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

RE-LY
NEJM 2009

- Methods:
  - 18, 000 AF patients randomized to dabigatran 110mg bid, dabigatran 150mg bid or warfarin
- Results:
  - Average CHADS2 score =2; mean age 71
  - Mean f/u 2 years
  - Warfarin TTR 64%

RE-LY: Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism



No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Connolly SJ et al. N Engl J Med 2009;361:1139-1151.

The NEW ENGLAND JOURNAL of MEDICINE

RE-LY Bleeding Data

	Warfarin (n= 6022)	Dabigatran 150 (n=6076)	P-Value
Major Bleeds	397	375	p=0.31
Life-threatening bleeds	212	175	p=0.04
ICH	87	36	p < 0.001
GI Bleeds**	129	182	p< 0.001

Dabigatran Facts

- Mechanism of Action
  - Direct Thrombin inhibitor (Final pathway)
- Pharmacology
  - Rapid onset of action (1 hour) and half life 12-14 hours
  - Cleared primarily through kidneys; dose adjustments required when GFR < 30
  - BID dosing
  - No significant drug interactions
  - No dietary interactions
- Adverse Effects
  - 12% reported "dyspepsia."
- Convenience Factors
  - No INR testing

Dabigatran

Positives

- Superior to warfarin
  - Fewer strokes
  - Less ICH
  - Trend toward lower mortality
- No drug interactions
- No dietary interaction
- Convenience
  - No INRs
  - Can be used to acutely anticoagulate: oral "lovenox"

Negatives

- Increased cost
  - May be cost-effective (Annals paper)
- GI Side effects are real
- BID dosing requires compliance
- Trust factor
  - Personal responsibility
- Superiority in low risk patients or those with good INR control is debatable
- Renal adjustments

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

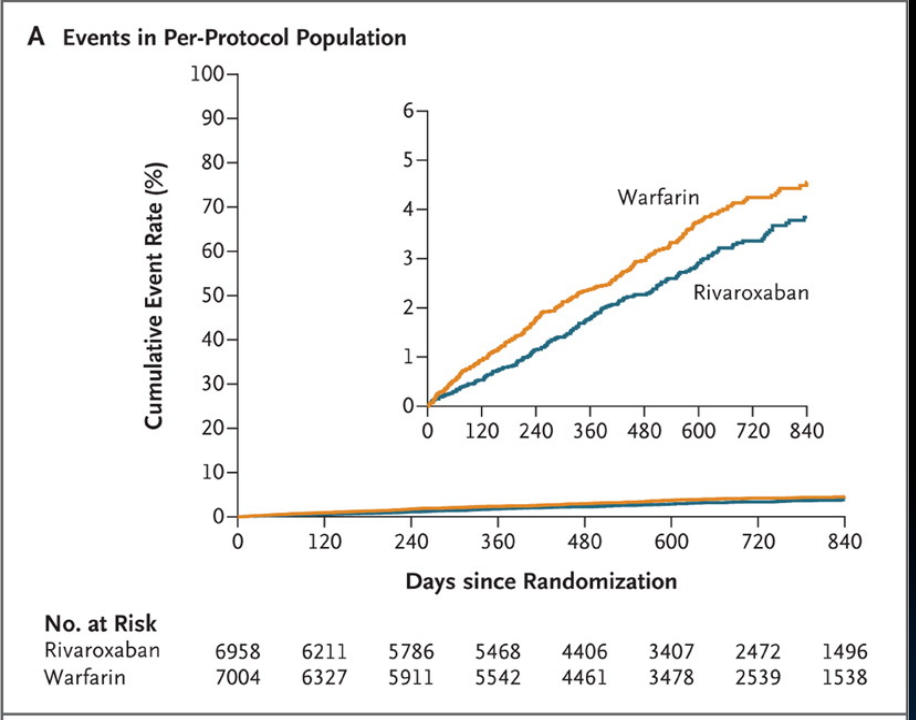
Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

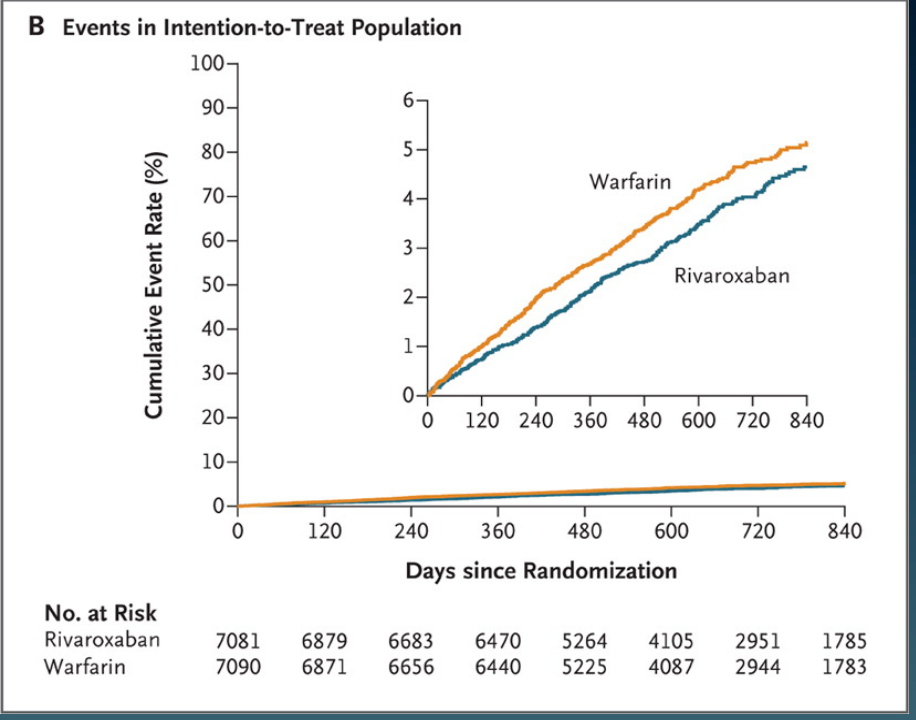
Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

Multi-center randomized controlled clinical trial of rivaroxaban 20 mg once daily to warfarin (INR 2-3) in patients with AF

- 14,000 patients
- Double blinded
- Average age = 73
- Mean CHADS = 3.4

Rocket-AF Trial: Rivaroxaban versus Warfarin





Cumulative Rates of the Primary End Point (Stroke or Systemic Embolism) in the Per-Protocol Population and in the Intention-to-Treat Population.

Patel MR et al. N Engl J Med 2011;365:883-891.

The NEW ENGLAND JOURNAL of MEDICINE

Rocket-AF Trial: Rivaroxaban versus Warfarin

Primary End Point of Stroke or Systemic Embolism.

Table 2. Primary End Point of Stroke or Systemic Embolism.*

Study Population	Rivaroxaban			Warfarin			Hazard Ratio (95% CI)†	P Value	
	No. of Patients	No. of Events	Event Rate	No. of Patients	No. of Events	Event Rate		Noninferiority	Superiority
			no./100 patient-yr			*no./100 patient-yr*			
Per-protocol, as-treated population‡	6958	188	1.7	7004	241	2.2	0.79 (0.66–0.96)	<0.001	
Safety, as-treated population	7061	189	1.7	7082	243	2.2	0.79 (0.65–0.95)		0.02
Intention-to-treat population§	7081	269	2.1	7090	306	2.4	0.88 (0.75–1.03)	<0.001	0.12
During treatment		188	1.7		240	2.2	0.79 (0.66–0.96)		0.02
After discontinuation		81	4.7		66	4.3	1.10 (0.79–1.52)		0.58

* The median follow-up period was 590 days for the per-protocol, as-treated population during treatment; 590 days for the safety, as-treated population during treatment; and 707 days for the intention-to-treat population.
† Hazard ratios are for the rivaroxaban group as compared with the warfarin group.
‡ The primary analysis was performed in the as-treated, per-protocol population during treatment.
§ Follow-up in the intention-to-treat population continued until notification of study termination.

Patel MR et al. N Engl J Med 2011;365:883-891.

The NEW ENGLAND JOURNAL of MEDICINE

Rocket-AF Trial: Rivaroxaban versus Warfarin

Rates of Bleeding Events

Table 3. Rates of Bleeding Events.*

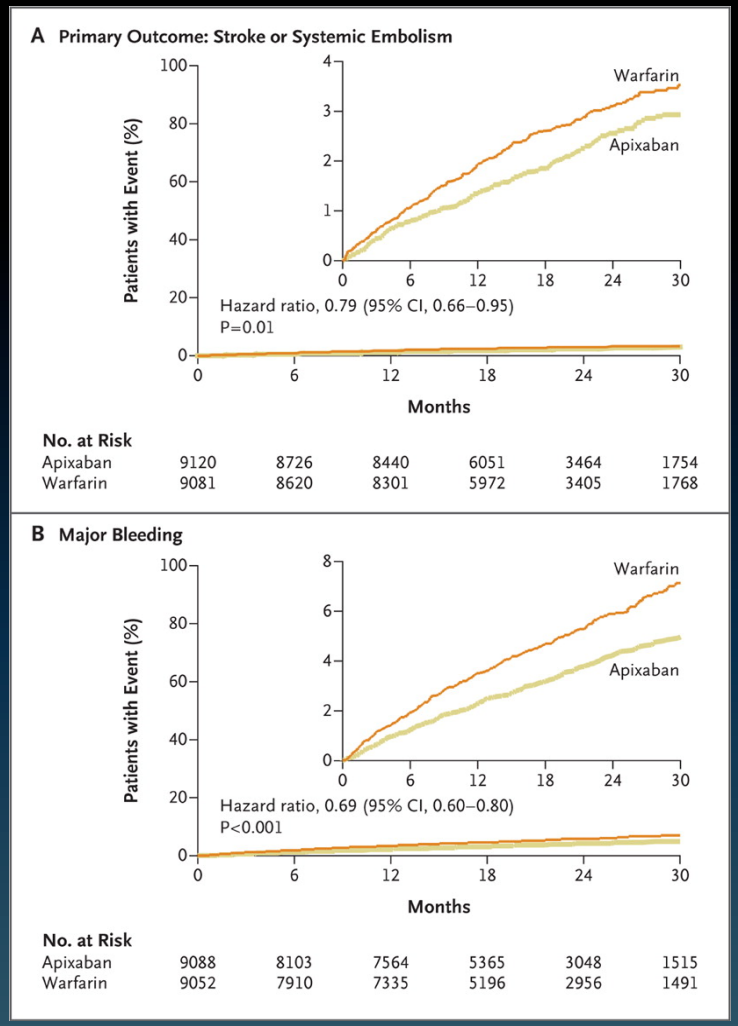
Variable	Rivaroxaban (N=7111)		Warfarin (N=7125)		Hazard Ratio (95% CI)†	P Value‡
	Events	Event Rate	Events	Event Rate		
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*		
Principal safety end point: major and nonmajor clinically relevant bleeding§	1475 (20.7)	14.9	1449 (20.3)	14.5	1.03 (0.96–1.11)	0.44
Major bleeding						
Any	395 (5.6)	3.6	386 (5.4)	3.4	1.04 (0.90–1.20)	0.58
Decrease in hemoglobin ≥2 g/dl	305 (4.3)	2.8	254 (3.6)	2.3	1.22 (1.03–1.44)	0.02
Transfusion	183 (2.6)	1.6	149 (2.1)	1.3	1.25 (1.01–1.55)	0.04
Critical bleeding¶	91 (1.3)	0.8	133 (1.9)	1.2	0.69 (0.53–0.91)	0.007
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5	0.50 (0.31–0.79)	0.003
Intracranial hemorrhage	55 (0.8)	0.5	84 (1.2)	0.7	0.67 (0.47–0.93)	0.02
Nonmajor clinically relevant bleeding	1185 (16.7)	11.8	1151 (16.2)	11.4	1.04 (0.96–1.13)	0.35

* All analyses of rates of bleeding are based on the first event in the safety population during treatment.
† Hazard ratios are for the rivaroxaban group as compared with the warfarin group and were calculated with the use of Cox proportional-hazards models with the study group as a covariate.
‡ Two-sided P values are for superiority in the rivaroxaban group as compared with the warfarin group.
§ Minimal bleeding events were not included in the principal safety end point.
¶ Bleeding events were considered to be critical if they occurred in intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular (with compartment syndrome), or retroperitoneal sites.

Three Critiques of ROCKET-AF
Rivaroxaban

- Robustness of warfarin superiority was less than dabigatran
- Increased number of CV events after discontinuation of rivaroxaban
  - Related to higher-risk patients or short half-life of Rivaroxaban, or both?
- Warfarin TTR was only 58% (versus 65% percent in other clinical trials)
  - *Did the 'un-skillful' use of warfarin bias the results?*

ARISTOTLE Trial: Apixaban



NEJM Sept 15, 2011

- RCT of 18,000 AF patients
- Apixaban versus warfarin
- Apixaban clearly superior:
  - Marked reduction in stroke
  - Fewer bleeds,
  - Far fewer ICH
  - Statistically sig decrease mortality

Apixaban is not yet FDA-approved