Will Apixaban change practice in atrial fibrillation?

A Patient Unsuitable for VKA Treatment

Professor Yoseph Rozenman

The E. Wolfson Medical Center

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Disclosures

I have the following potential conflicts of interest to report:

- Consulting and or lecture fees: Abott, Boston-Scientific, Medtronic, Pfizer, Sanofi-Aventis, MSD, AstraZeneca, Elli-Lilly, Bayer, Boehringer Ingelheim

Case Presentation

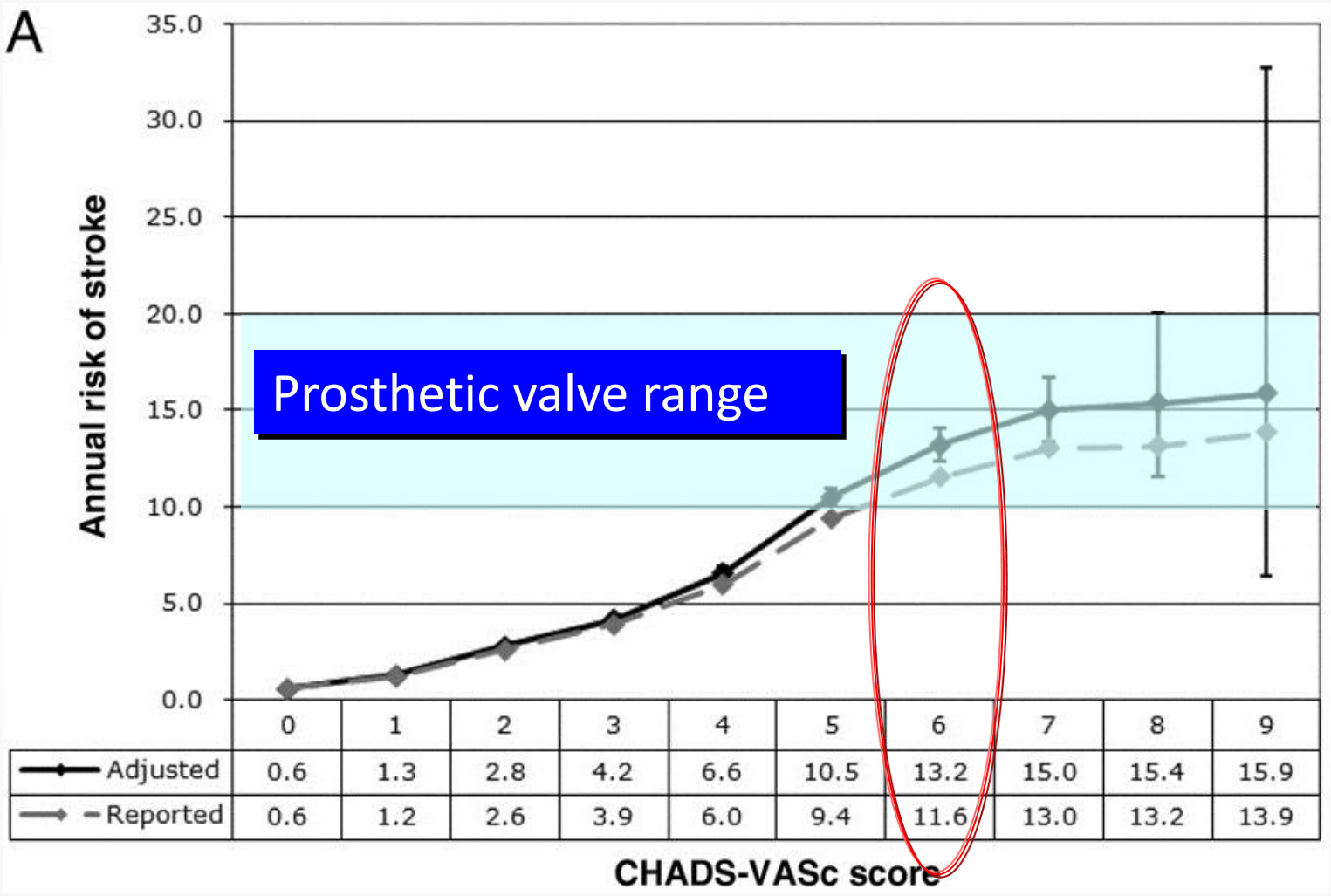
- 82 YO Female with Permanent Atrial Fibrillation (3 years)
- PMH: HTN, NIDDM, CAD (Inf MI 8 years ago)
  - **Recurrent hemorrhoidal bleeding**
- Current Medications:
  - **Aspirin**
  - Enalapril, Bisoprolol, Simvastatin, Metformin
- $CHADS_2$ = 3, CHA_2DS_2VASc = 6

Rectal Bleeding on Warfarin

- 2009 - Pt. complaining on bright red blood in stools
  - 6 months after initiation of warfarin therapy
  - INR – 2.8, No drop in Hb
  - Warfarin therapy was held temporarily

- What to do next:
  1. Colonoscopy, identify and treat source of bleeding and restart warfarin
  2. Restart warfarin after few days when bleeding stops (target INR: 2 – 2.5)
  3. Start ASA
  4. No antithrombotic therapy

Thromboembolic Risk: AFib and Prosthetic Valve



	0	1	2	3	4	5	6	7	8	9
Adjusted	0.6	1.3	2.8	4.2	6.6	10.5	13.2	15.0	15.4	15.9
Reported	0.6	1.2	2.6	3.9	6.0	9.4	11.6	13.0	13.2	13.9

Risk of thromboembolism according to CHA_2DS_2VASc Score

Hospital admission and death due to thromboembolism* at one year in 73,538 patients with NVAF who did not receive VKA or heparin (Danish registry cohort study, 1997-2006)

CHA_2DS_2VASc score	No. of patients (%)	Thromboembolism* per 100 person years at 1 year follow-up
0	6,369 (8.7)	**0.78**
1	8,203 (11.2)	**2.01**
2	12,771 (17.4)	**3.71**
3	17,371 (23.6)	**5.92**
4	13,887 (18.9)	**9.27**
5	8,942 (12.2)	**15.26**
6	4,244 (5.8)	**19.74**
7	1,420 (1.9)	**21.50**
8	285 (0.4)	**22.38**
9	46 (0.1)	**23.64**

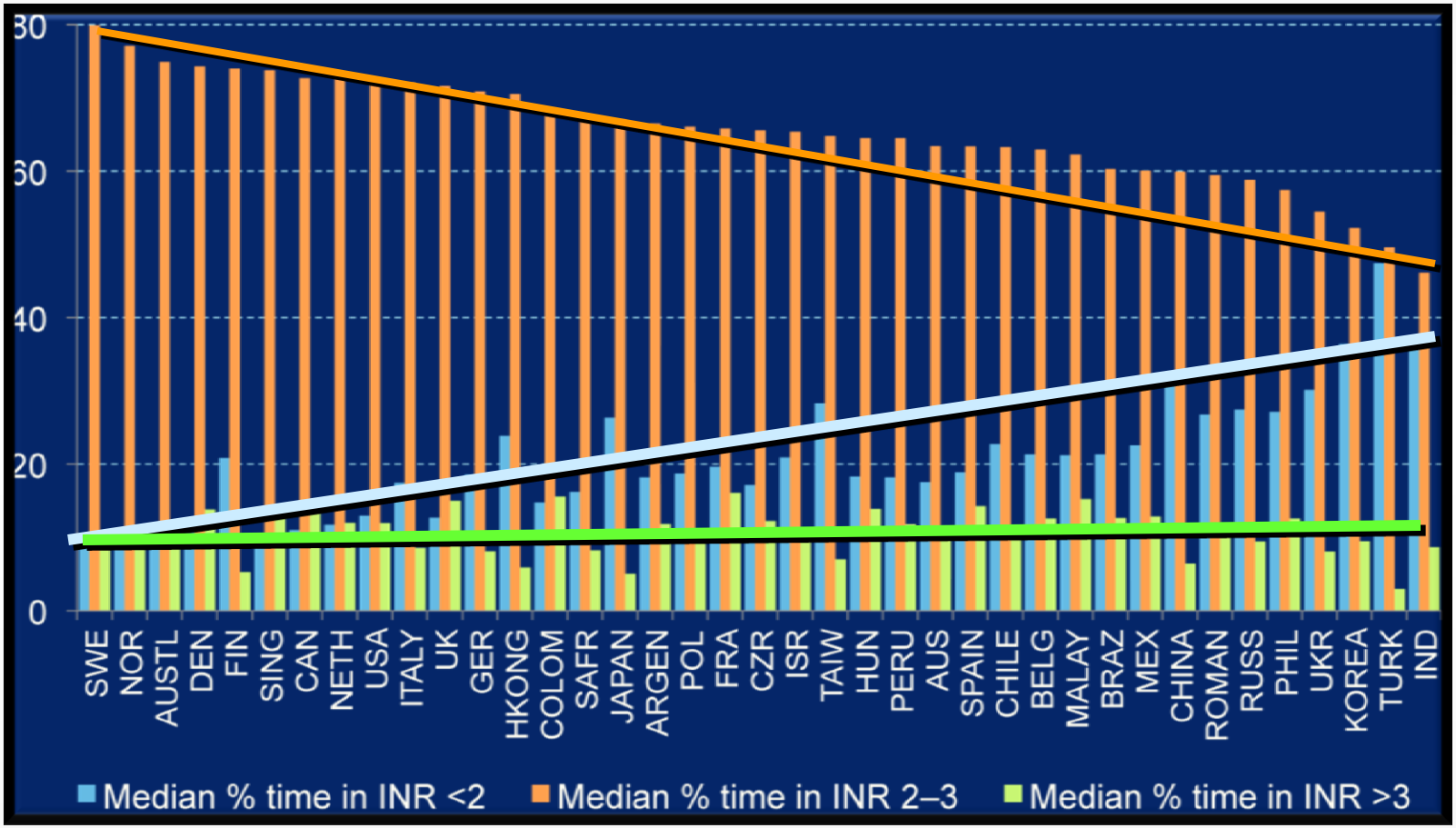
**Thromboembolic events: Ischaemic stroke, peripheral artery or pulmonary embolism*

Olesen et al. BMJ 2011;342:d124. doi:10.1136/bmj.d124

Rectal Bleeding on Warfarin

- Colonoscopy: bleeding hemorrhoids
  - local therapy
  - warfarin therapy was restarted after 1 week
- Unstable INR
  - Undertreatment and overtreatment
  - Occasional, self limiting, recurrent rectal bleeding
  - Warfarin dose decreased to maintain INR of ~2

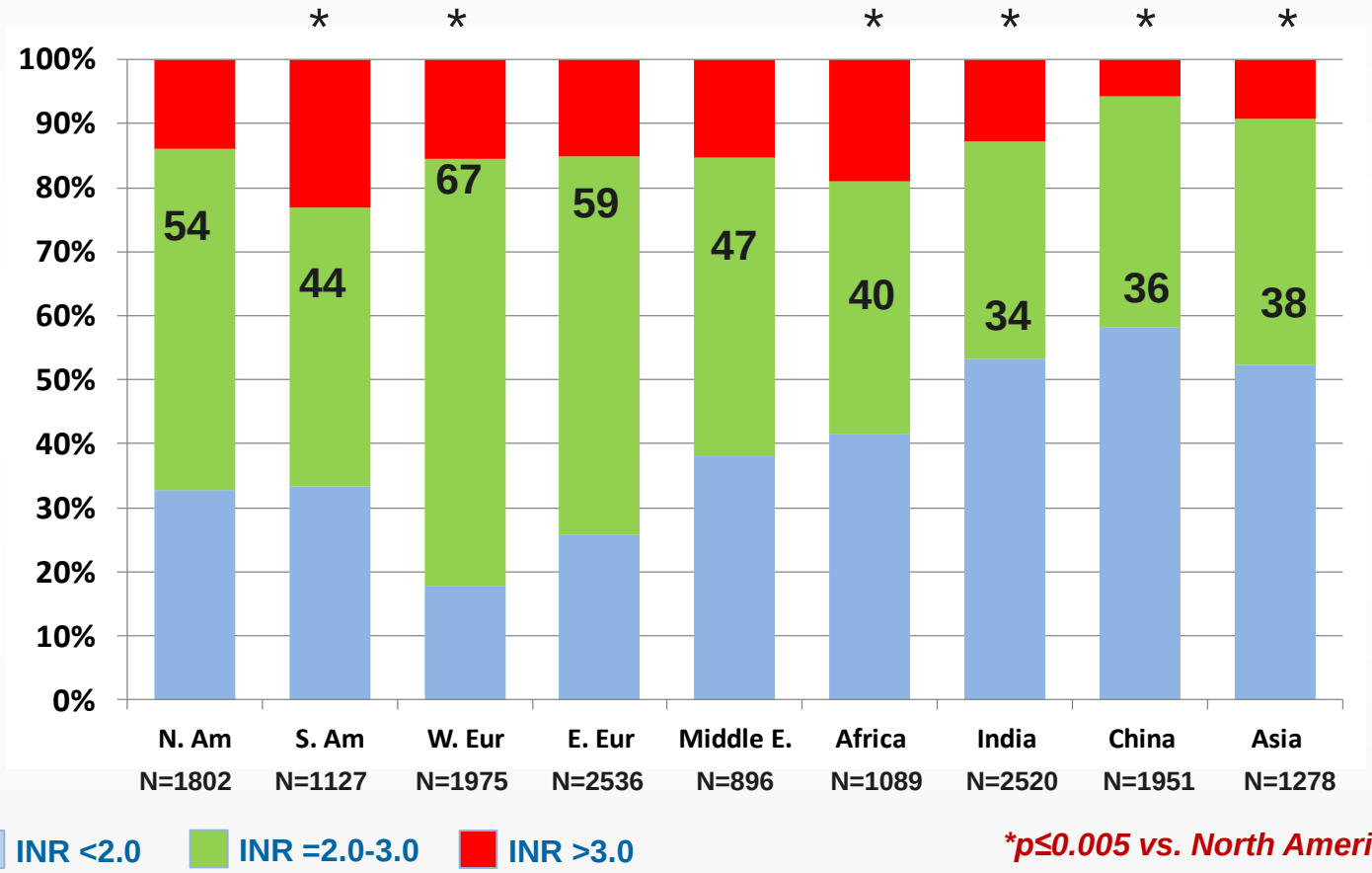
Median of Patients TTR in Different Countries ARISTOTLE Study



- Regional difference mainly due to INR time <2.0
- May be caused by targeting INR <2.5 within 2.0–3.0 range

Suboptimal INR control worldwide (2008-2011)

The TTR is only ~50% in a global AF registry



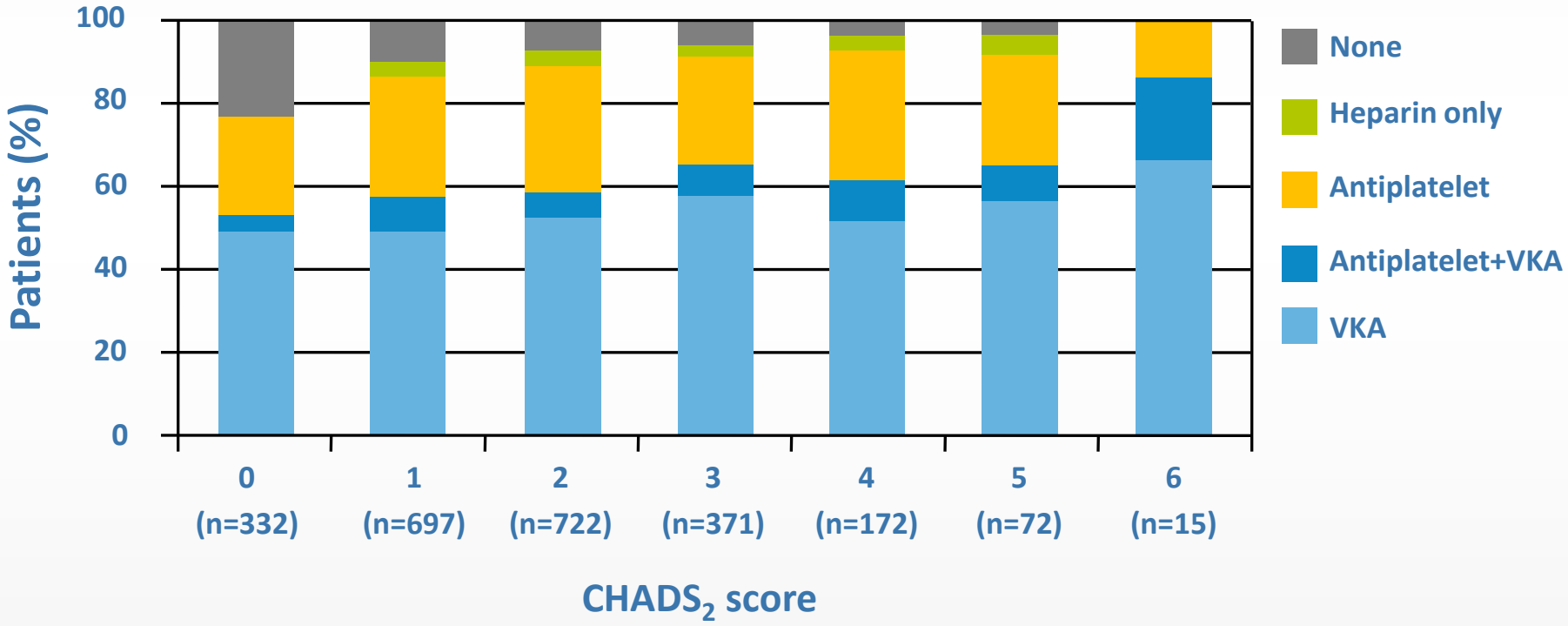
**p≤0.005 vs. North America*

Adapted from Healey et al. Presented at the ESC meeting on Sunday August 28, 2011 - http://spo.escardio.org/eslides/view.aspx?eevtid=48&fp=1355

- 2011 – Admission for rectal bleeding
  - INR – 3.0, no drop in Hb
  - Switched to ASA
  - Occasional episodes of self limiting rectal bleeding
  - No ischemic stroke/ TIA for 2 years

Antiplatelet agents remain widely used in patients with AF

Euro Heart Survey: ~15-20% of AF patients receive antiplatelet agents even among high-risk groups



Adapted from Nieuwlaat et al. Eur Heart J 2006;27:3018-26.

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Regular clinic visit, Stable patient, What to do?

1. Continue current therapy
   - Patient is stable
2. Restart warfarin – better INR control
   - Risk of stroke is very high
3. Start NOAC
   - Dabigatran 110/ 150 mg bid
   - Rivaroxaban 15/ 20 mg qd
   - Apixaban 2.5/ 5 mg bid

NOAC’s Tolerability

General and Gastrointestinal

NOAC: Treatment discontinuation at the end of follow-up

Trial	Warfarin	NOAC	P value
RE-LY - dabigatran 110 mg	16.6%	20.7%	NR
RELY - dabigatran 150 mg	16.6%	21.2%	NR
ROCKET-AF - rivaroxaban	22.2%	23.7%	NR
ARISTOTLE - apixaban	27.5%	25.3%	0.001

NR: not reported

Not head to head comparisons – For illustrative purpose only – adapted from references 1-4

1. Connolly et al. N Engl J Med 2009; 361: 1139-51. 2. Patel et al. N Engl J Med 2011; 365: 883-91.
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ARISTOTLE - apixaban	27.5%	25.3%	0.001
Trial	**ASA**	**NOAC**	**P value**
AVERROES - apixaban	20.5% /yr	17.9% / yr	0.03

NR: not reported

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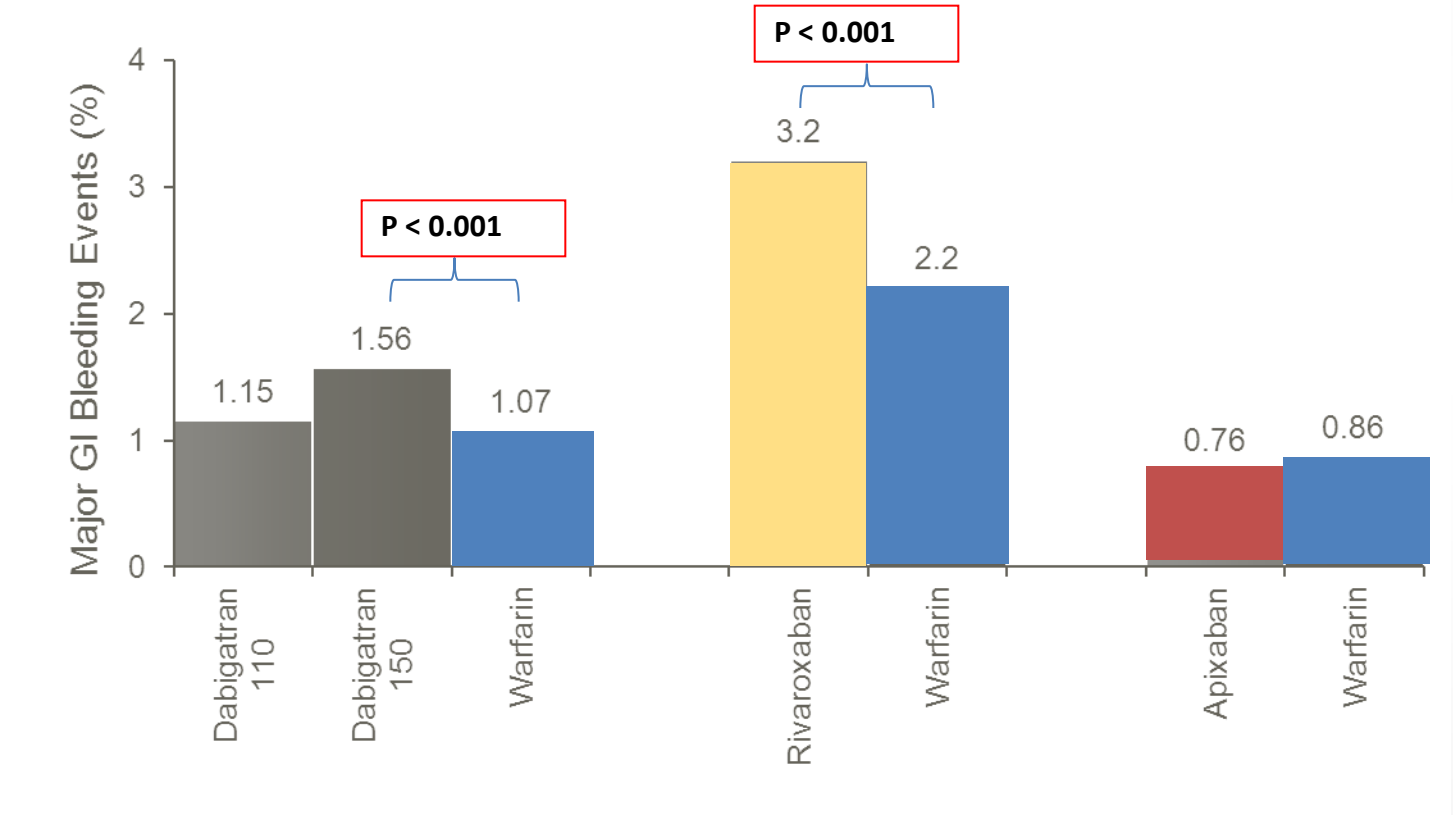
SPAF Trials—Major GI bleeding

- Dabigatran 150 mg and rivaroxaban demonstrated a statistically significant increase in major GI bleeding compared to warfarin

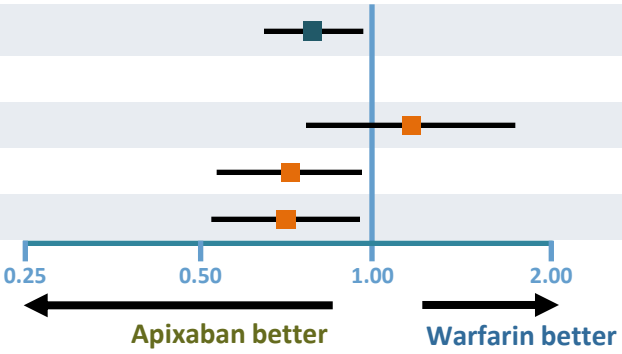


1. Connolly SJ et al. *N Engl J Med*. 2010;363(19):1875-1876.
2. Patel MR et al. *N Engl J Med*. 2011;365(10):883-891:Supp appendix
3. Granger CB et al. *N Engl J Med*. 2011;365(11):981-992.

ARISTOTLE: Efficacy and safety according to age*

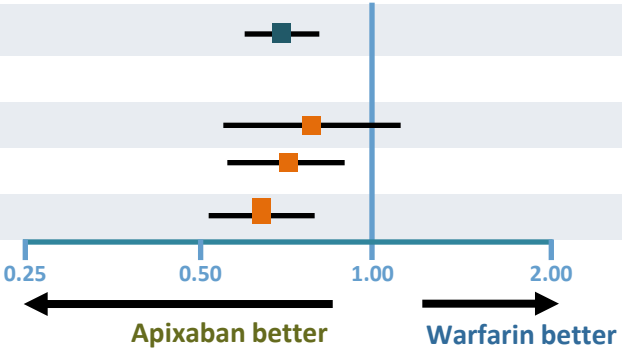
A. Primary Efficacy Outcome: Stroke and Systemic Embolism

Subgroup	No. of patients	Apixaban	Warfarin	Hazard Ratio (95% CI)	P value for interaction
		No. of events (%/yr)			
All patients	18,201	212 (1.27)	265 (1.60)		
Age					0.12
< 65 yr	5,471	51 (1.0)	44 (0.9)		
65 to < 75 yr	7,052	82 (1.3)	112 (1.7)		
≥ 75 yr	5,678	79 (1.6)	109 (2.2)		



B. Major Bleeding

Subgroup	No. of patients	Apixaban	Warfarin	Hazard Ratio (95% CI)	P value for interaction
		No. of events (%/yr)			
All patients	18,140	327 (2.13)	462 (3.09)		
Age					0.64
< 65 yr	5,455	56 (1.2)	72 (1.5)		
65 to < 75 yr	7,030	120 (2.0)	166 (2.8)		
≥ 75 yr	5,655	151 (3.3)	224 (5.2)		



*Relative Risks of the Primary Efficacy and Safety Outcomes,

Adapted from Granger et al. N Engl J Med 2011;365:981-92.

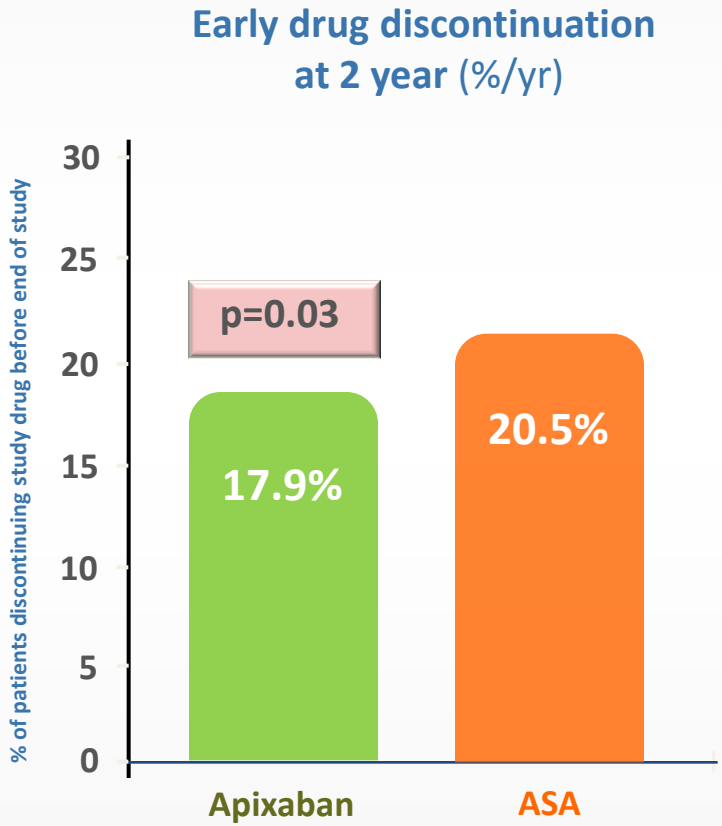
AVERROES: Baseline clinical characteristics

Characteristic	Apixaban (n=2808)	ASA (n=2791)
Mean age±SD	**70 ±9 yrs**	**70±10 yrs**
Male sex	**59%**	**58%**
Mean $CHADS_2$ ±SD	**2.0±1.1**	**2.1±1.1**
≤1	**36%**	**37%**
2	**37%**	**34%**
≥ 3	**27%**	**29%**
Risk factors		
Prior stroke or TIA	**14%**	**13%**
VKA within 30 days before screening	**14%**	**15%**
ASA within 30 days before screening	**76%**	**75%**

Connolly et al. N Engl J Med 2011;364:806-17.

AVERROES: Trial metrics

- DSMB recommended early study termination due to a clear benefit in favour of apixaban:
  - Treatment benefit >4 SD in favour of apixaban
  - Long-term open-label apixaban follow-up*
- 94% patients received apixaban 5 mg BD
- 91% patients received ASA≤162 mg/day
- Median duration of follow-up: 1.1 year
- Fewer patients in the apixaban group than in the ASA group discontinued study drug before the end of the study

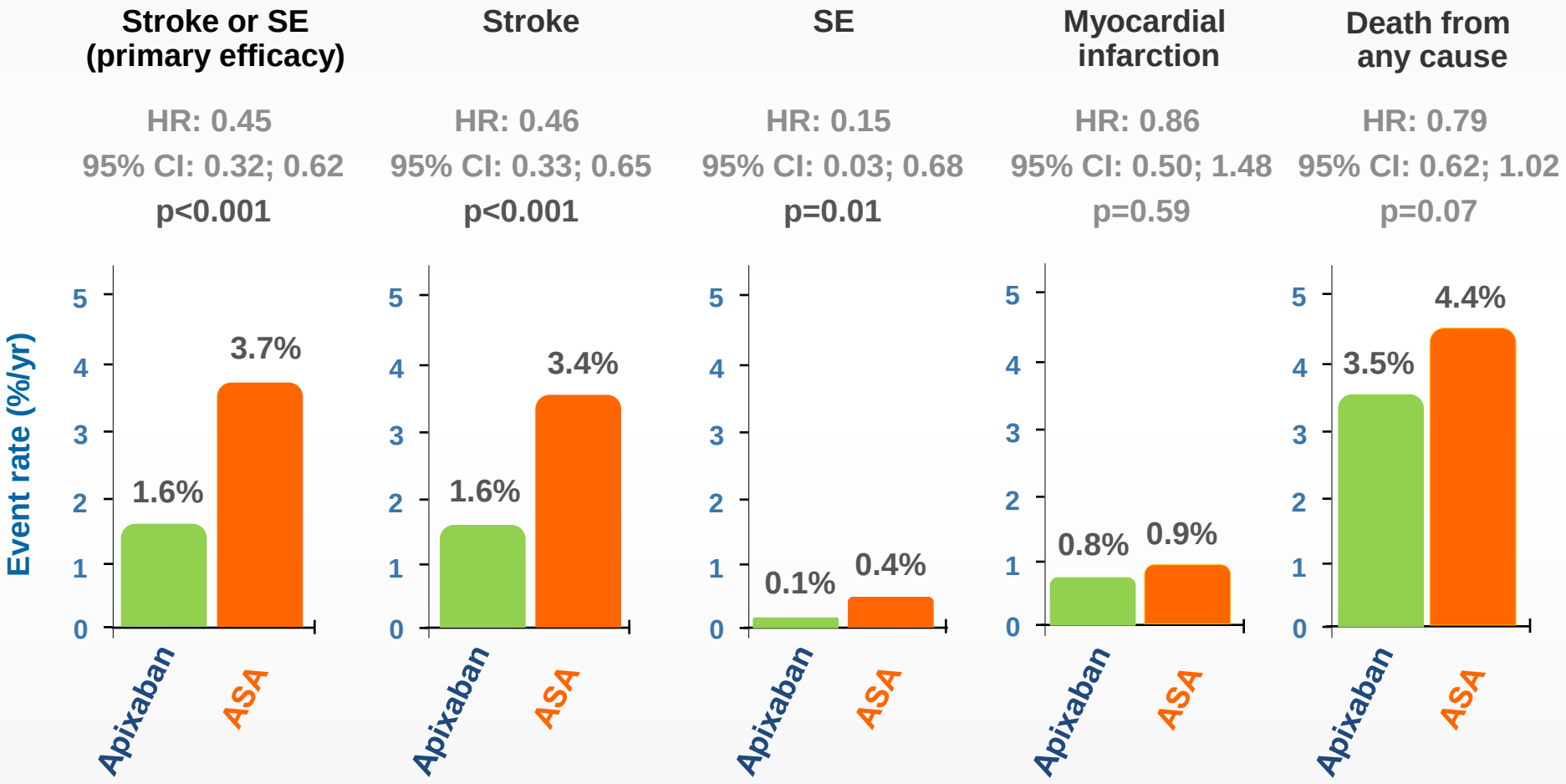


*Clinicaltrials.gov NCT00496769

Adapted from Connolly SJ et al. N Engl J Med 2011;364:806–817.

DSMB: Data safety monitoring board
SD: Standard Deviations

AVERROES: Main efficacy outcomes



Adapted fromConnolly et al. N Engl J Med 2011;364:806-17.

AVERROES: Main safety outcomes

Outcome	Apixaban (N=2808) Event Rate (%/yr)	ASA (N=2791) Event Rate (%/yr)	HR (95% CI)	P value
Primary safety outcome: Major bleeding	1.4	1.2	1.13 (0.74, 1.75)	0.57
Intracranial	0.4	0.4	0.85 (0.38, 1.90)	0.69
Extracranial or unclassified	1.1	0.9	1.23 (0.74, 2.05)	0.42
Gastrointestinal	0.4	0.4	0.86 (0.40, 1.86)	0.71
Non-gastrointestinal	0.6	0.4	1.55 (0.77, 3.12)	0.22
Fatal	0.1	0.2	0.67 (0.19, 2.37)	0.53
Clinically relevant non-major bleeding	3.1	2.7	1.15 (0.86, 1.54)	0.35
Minor bleeding	6.3	5.0	1.24 (1.00, 1.53)	0.05
Hospitalisation for cardiovascular cause	12.6	15.9	**0.79** (0.69, 0.91)	**<0.001**

Connolly et al. N Engl J Med 2011;364:806-17.

What to do?

Continue current therapy

- Patient is stable

1. Restart warfarin – better INR control
   - Risk of stroke is very high
2. Start NOAC
   - Dabigatran 110/ 150 mg bid
   - Rivaroxaban 15/ 20 mg qd
   - Apixaban 2.5/ 5 mg bid

My recommendation: **Start Apixaban 2.5mg bid**

- Best efficacy / safety balance
- Highest likelihood for tolerability

Thanks