Risk Benefit of Apixaban and Other New Oral Anticoagulants Compared with Standard of Care for the Prevention of Stroke

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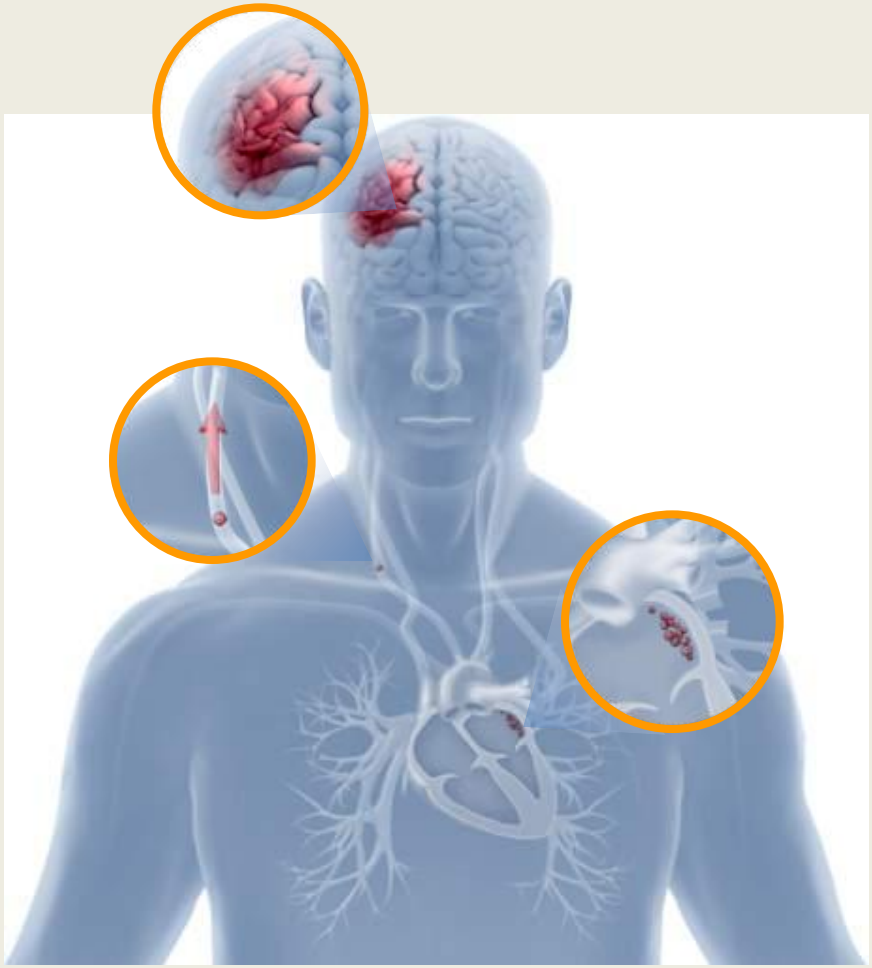
Content

- Unmet needs in atrial fibrillation (AF)
- 2012 ESC Guidelines
- AVERROES study
- ARISTOTLE study
- Potential differences among new oral anticoagulants (NOACs)

AF confers an increased thromboembolic risk, notably in the brain

- AF confers a **near 5-fold risk increase** of stroke[1]
- It is estimated that 20% of all strokes are caused by AF[2]
- AF is often asymptomatic[3]
- The absence of symptoms (e.g. palpitations) does not imply a lower risk of thromboembolism[3]

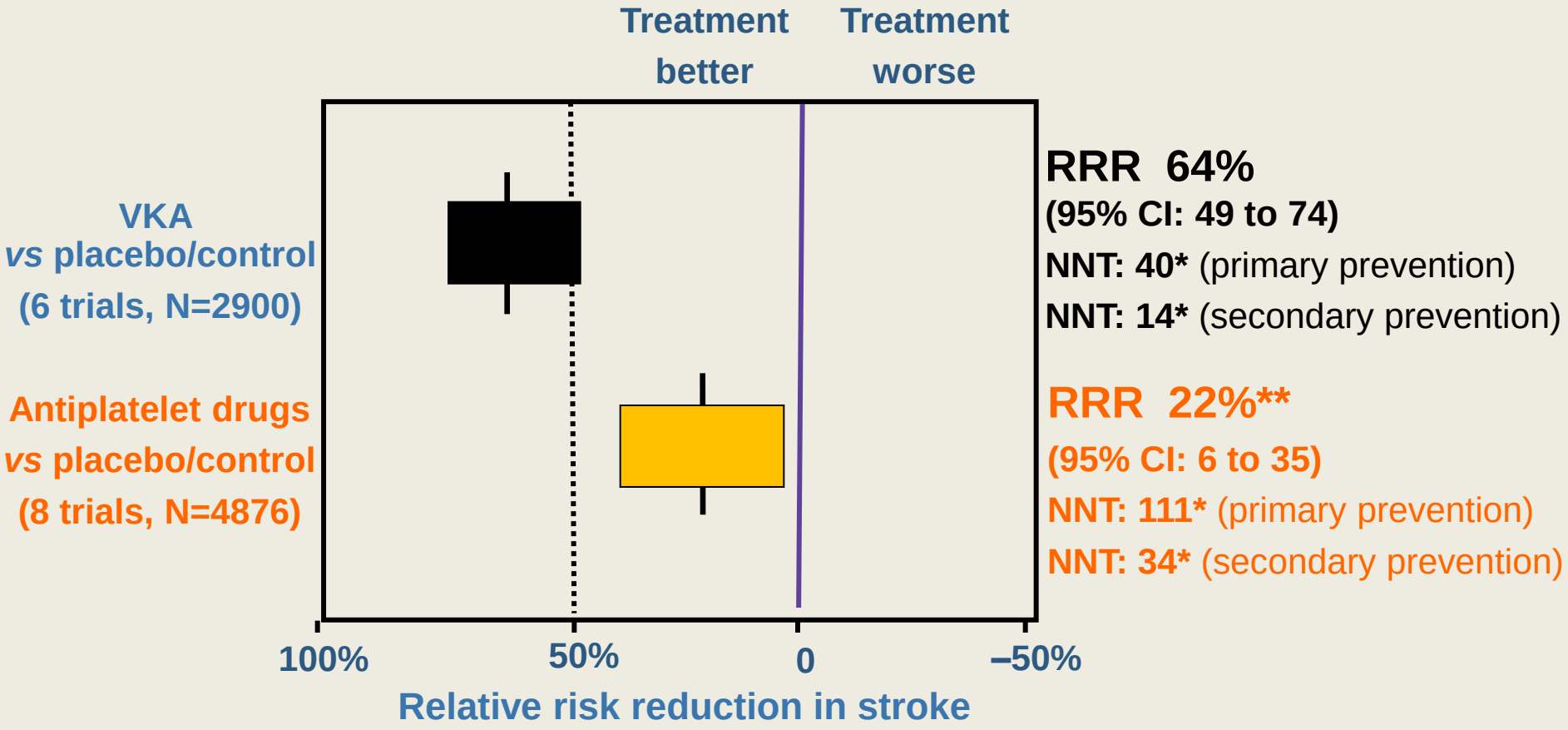


1. Wolf et al. Stroke 1991;22:983-8.

2. Friedman et al. Circulation 1968;38:533-541.

3. Flaker et al. Am Heart J 2005;149:657-63.

In historical trials in AF patients, vitamin K antagonists (VKA) and antiplatelet agents reduced stroke by ~60% and ~20%, respectively.

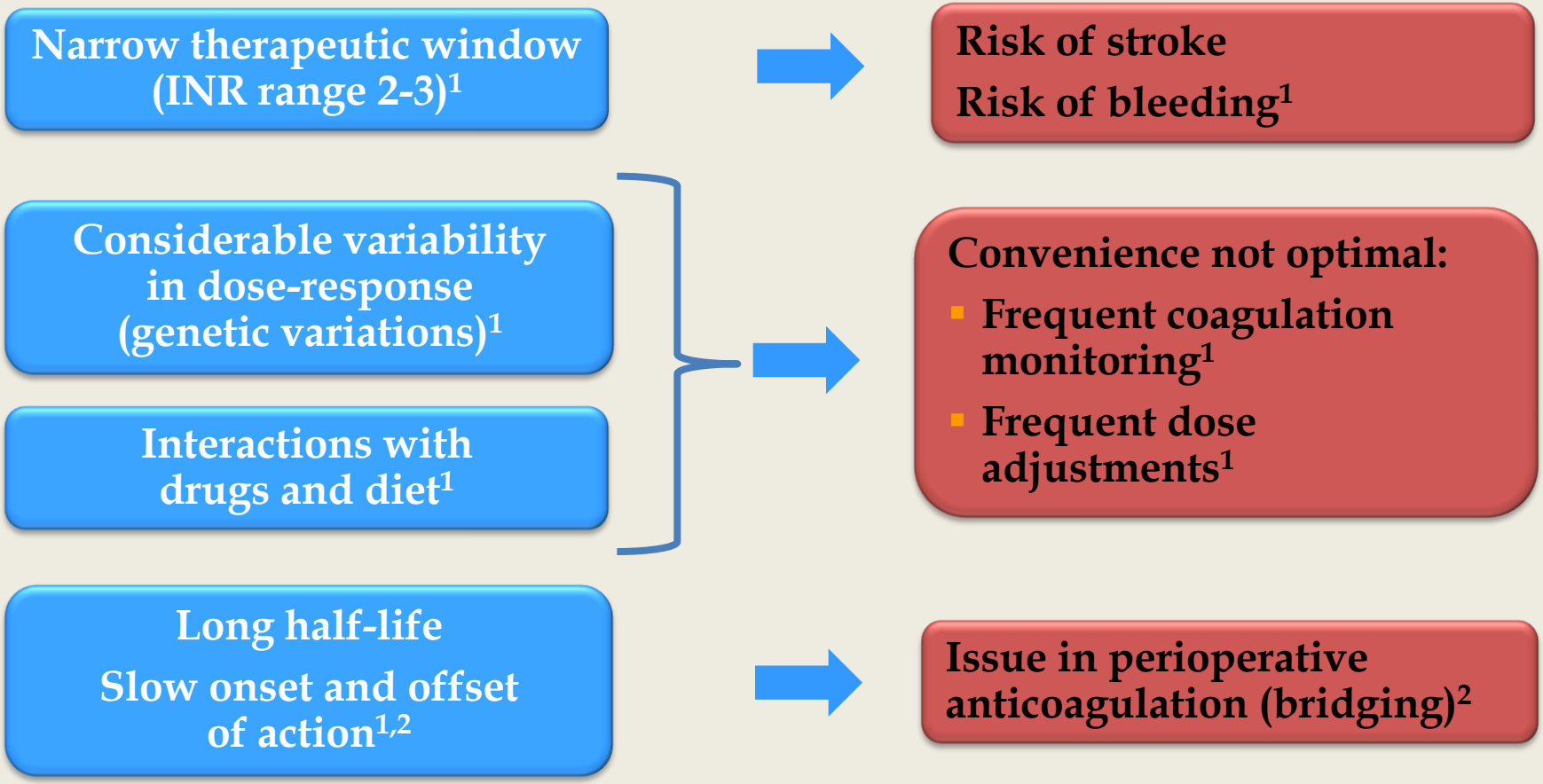


*NNT for one year to prevent one stroke

**If data confined to ASA, the RRR is 19% (95% CI: -1 to 35, NS)

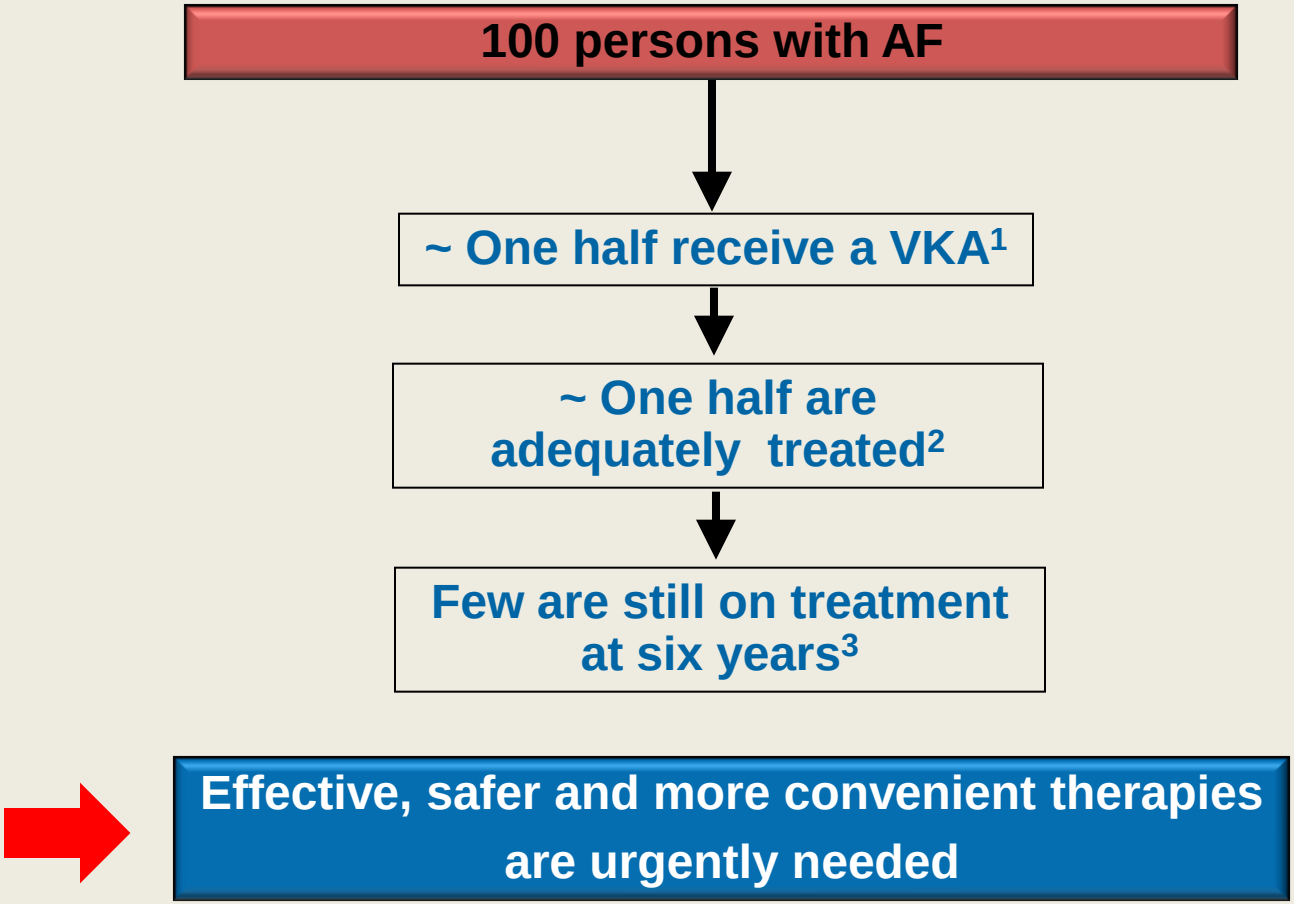
Hart et al. Ann Intern Med 2007;146:857-67.

VKA therapy has several limitations



1. Weitz et al. Eur J Haematol 2010;85 (Suppl 72);1-28.
2. Camm et al. Eur Heart J 2010;31:2369-429.

Summary of the global unmet needs

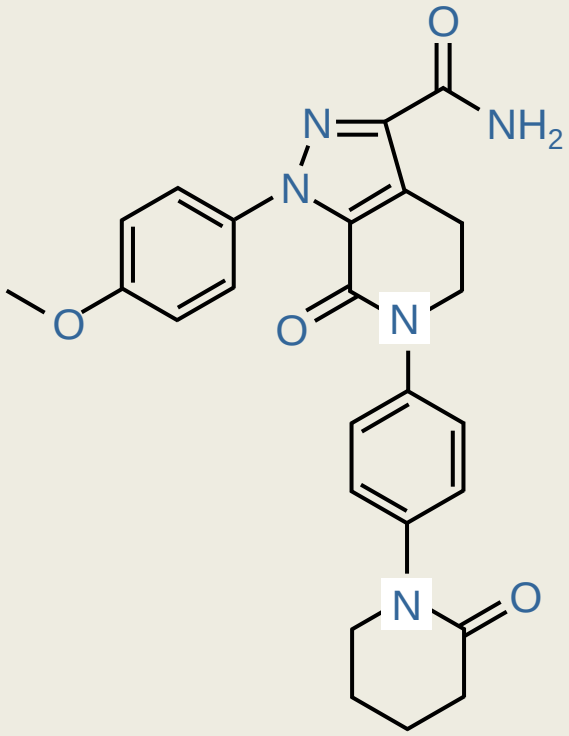


1. Nieuwlaat et al. Eur Heart J 2006;27:3018-26.

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

3. Gallagher et al. J Thromb Haemost 2008;6:1500–1506

Apixaban: a novel direct factor Xa inhibitor



Apixaban

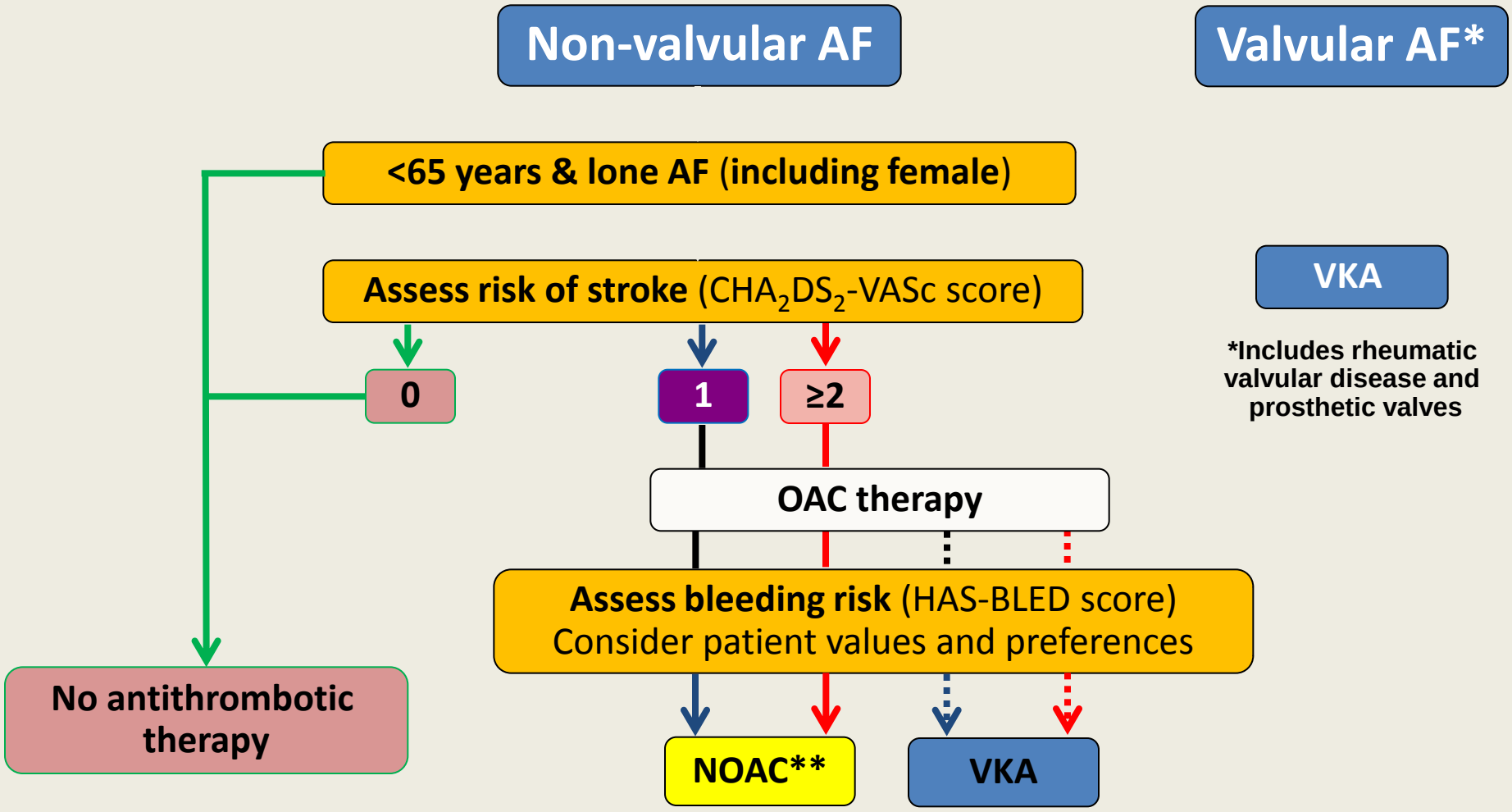
Apixaban, a structurally novel and neutral bicyclic pyrazole, was rationally designed and selected for the following qualities:

- Not a prodrug
- Oral bioavailability: **~50%**
- T_{max}: **3–4 h**
- **~87% bound** to plasma proteins
- $T_{1/2}$: **~12 h**
- Multiple elimination/excretion pathways: **~27% renally excreted**
- **No active circulating metabolites**

$T_{1/2}$ = elimination half-life;
T_{max} = time to reach maximum plasma concentration

Apixaban SmPC 2012.
Pinto et al. J Med Chem. 2007;50(22):5339-56.

ESC 2012 recommendations – Choice of anticoagulant



**NOAC should be considered instead of VKA (INR 2–3) for most patients with AF.

Adapted from Camm et al. Eur Heart J 2012;e-published August 2012, doi:10.1093/eurheartj/ehs253.

ESC 2012 recommendations – NOACs in NVAF

Recommendations	Class	Level
When adjusted-dose VKA (INR 2-3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs* is recommended.	**I**	**B**
Where OAC is recommended, one of the NOACs* should be considered rather than adjusted-dose VKA (INR 2-3) for most patients with NVAF, based on their net clinical benefit.	**IIa**	**A**

Camm et al. Eur Heart J 2012;e-published August 2012, doi:10.1093/eurheartj/ehs253.

Clinical program to demonstrate the efficacy & safety of apixaban for the prevention of stroke & SE in NVAF patients[1]

A total of 23,799 patients were randomised in the clinical program, including 11,927 randomised to apixaban[1]

ARISTOTLE[2]	AVERROES[3]
Randomised, double-blind, double-dummy, active control, multinational trial	Randomised, double-blind, double-dummy, active control, multinational trial
In more than **18,000 patients** with NVAF	In more than **5500 patients** with NVAF
Who were **suitable** for VKA therapy	Who were **unsuitable** for VKA therapy
Receive either **apixaban** 5.0 mg BD (or 2.5 mg BD in selected patients*) or **warfarin** (INR, target: 2.0-3.0)	Receive either **apixaban** 5.0 mg BD (or 2.5 mg BD in selected patients*) or **ASA** 81-324 mg

**Patients with ≥2 of the following: age ≥80 years, body weight ≤60 kg, or a serum creatinine level ≥1.5 mg/dL (133 µmol/L)*

1. Apixaban SmPC 2012. 2. Granger et al. N Engl J Med 2011;365:981-92. 3. Connolly et al. N Engl J Med 2011;364:806-17.

Apixaban Clinical Trial Data

ASA IS NOT RECOMMENDED ANY LONGER AS ALTERNATIVE TO VKA

- **RESULTS FROM AVERROES**

AVERROES: Study Design[1,2]

Mean follow-up: 1.1 years

Patient Population

- Patients ≥50 years with NVAF and ≥1 risk factors for stroke
- Not receiving VKA therapy (demonstrated or expected to be unsuitable for VKA)

N=5599

Randomised, double-blind, double-dummy

Event Driven

Apixaban 5.0 mg BD
(2.5 mg in select patients* [6.4%])

ASA 81-324 mg OD**

**Patients with ≥2 of the following: age ≥80 years, weight ≤60 kg, serum creatinine ≥1.5 mg/dL (133 µmol/L).*

***The selection of an ASA dose of 81, 162, 243, or 324 mg was at the discretion of the investigator with 91% of subjects receiving either an 81-mg (64%) or 162-mg (27%) dose at randomization.*

The primary objective of the trial was to determine if apixaban was superior to ASA for the prevention of the composite outcome of stroke or systemic embolism.

- Primary efficacy outcome: Stroke or systemic embolism
- Primary safety outcome: Major bleeding

1. Apixaban SmPC 2012. 2. Connolly et al. N Engl J Med 2011;364:806-817.

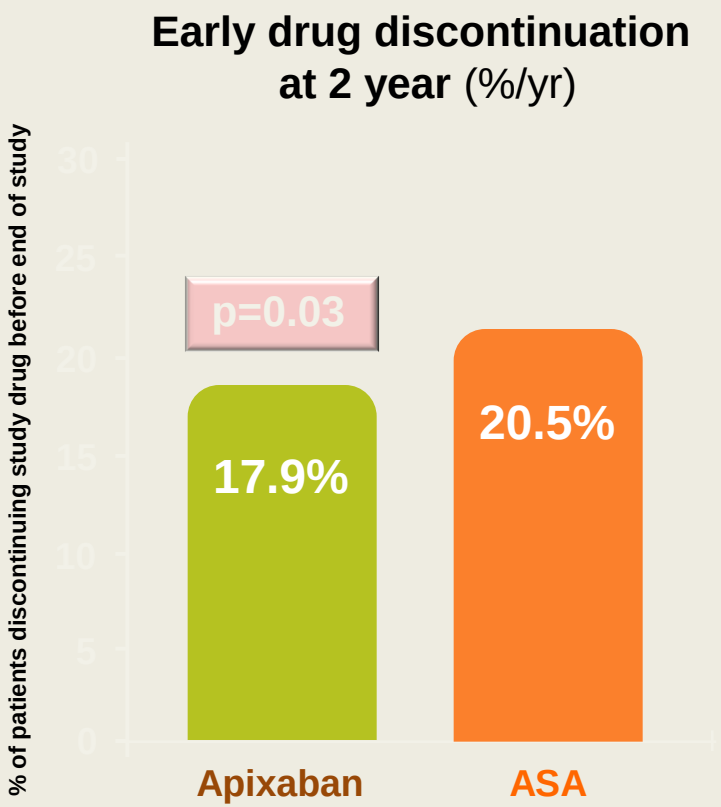
AVERROES: Main reasons for unsuitability to VKA

	Apixaban (n=2808)	ASA (n=2791)
Assessment that INR could not or was unlikely to be measured at requested intervals	43%	43%
Patient's refusal to take VKA	38%	37%
$CHADS_2$ score of 1 and VKA therapy not recommended by physician	21%	22%
Assessment that INR could not be maintained in therapeutic range	17%	17%
Uncertainty about patient's ability to adhere to instruction regarding VKA therapy	16%	15%
Patient's refusal to take VKA as only reason for unsuitability	15%	14%
$CHADS_2$ score of 1 as only reason for unsuitability of VKA therapy	11%	12%
Expected difficulty in contacting patient for urgent change in dose of VKA	11%	12%
Multiple reasons	51%	52%

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***
- **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

DSMB: Data safety monitoring board
SD: Standard Deviations

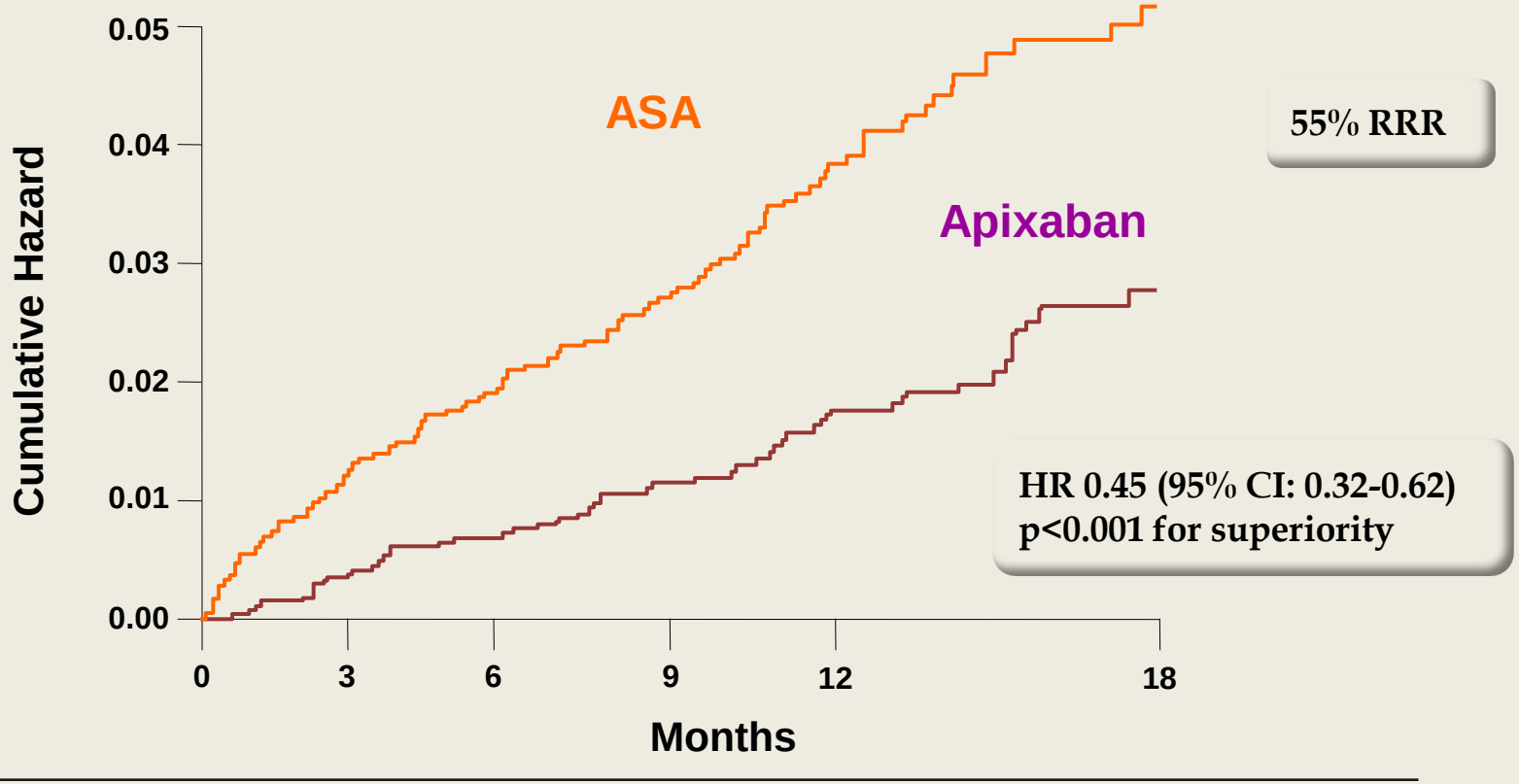
Adapted from Connolly SJ et al. N Engl J Med 2011;364:806–817.

AVERROES: Baseline clinical characteristics were well balanced between the two study groups

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.

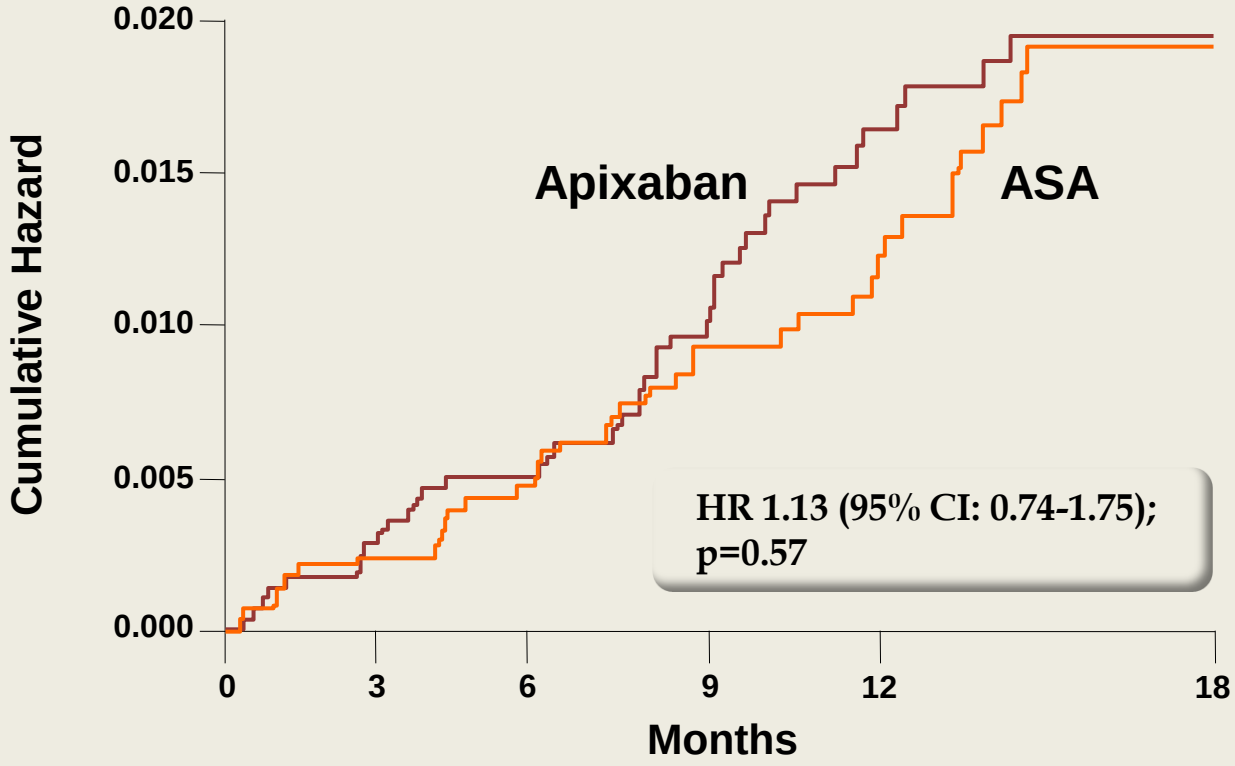
AVERROES: Apixaban was superior to ASA in preventing stroke or systemic embolism*



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

***Primary efficacy outcome**

AVERROES: There was no difference in the risk of major bleeding* between apixaban and ASA

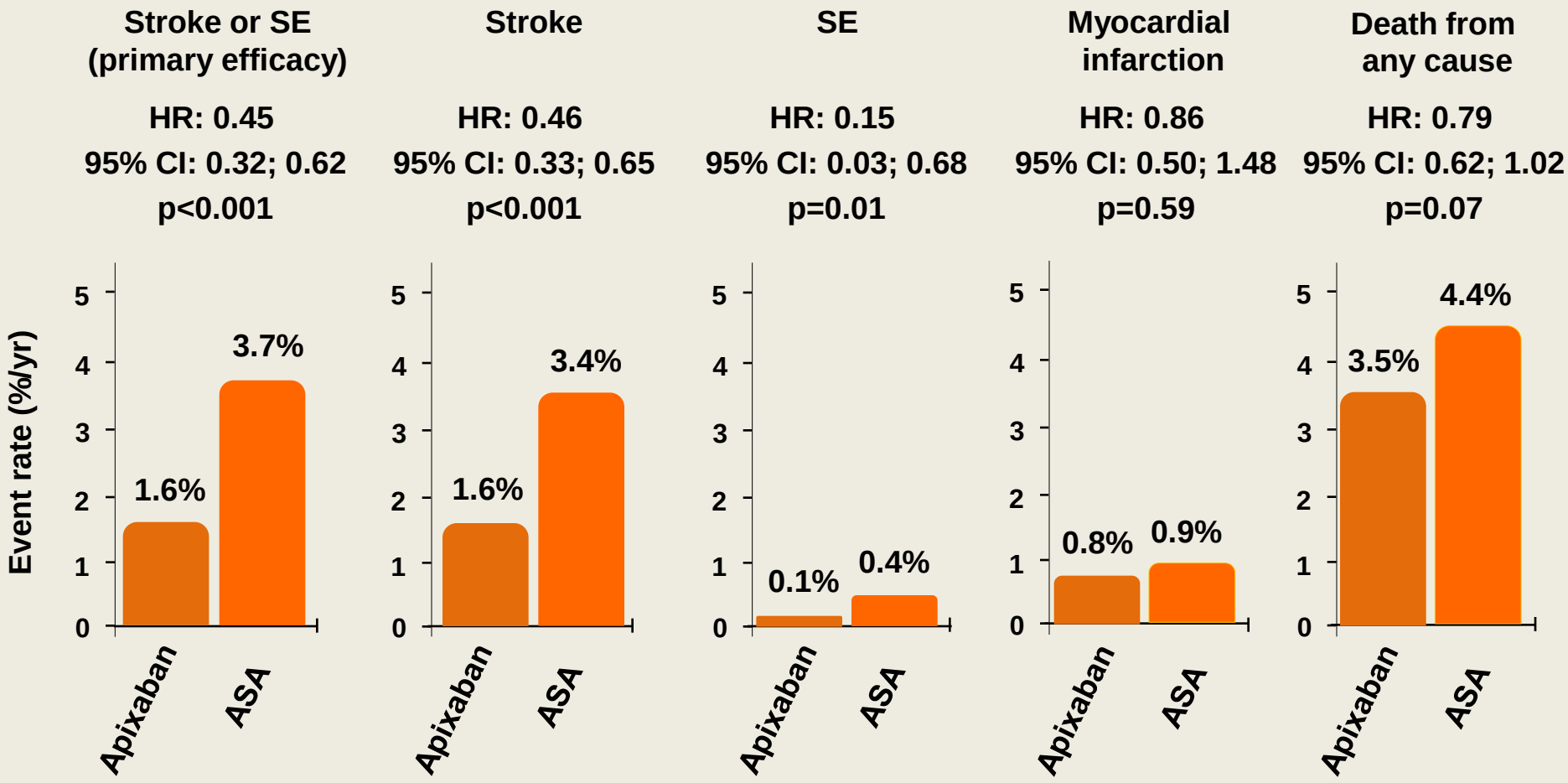


No. at Risk						
Apixaban	2808	2759	2566	2120	1521	622
ASA	2791	2738	2557	2140	1571	642

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

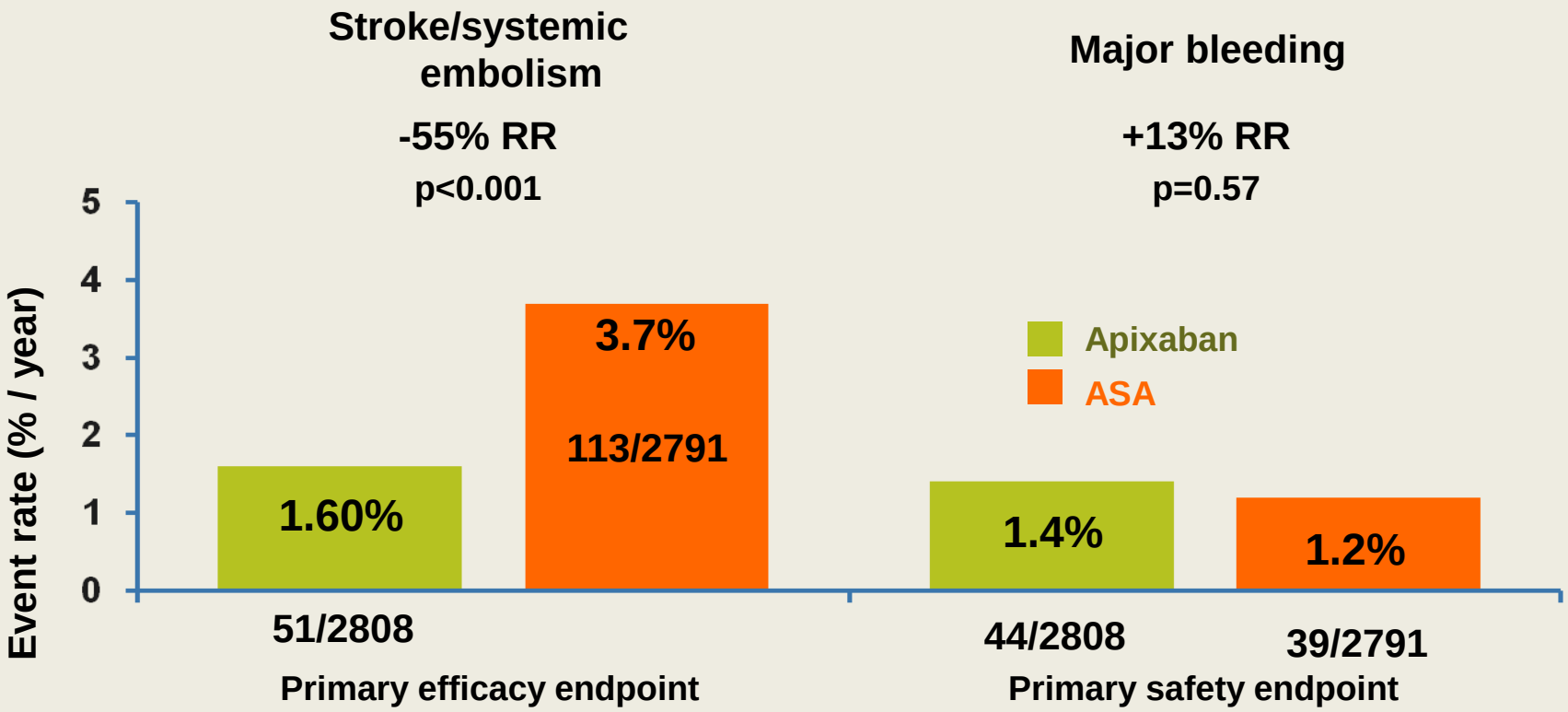
***Primary safety outcome**

AVERROES: Main efficacy outcomes



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

Apixaban demonstrated superior efficacy *vs*. ASA without significantly increasing the risk of major bleeding



AVERROES confirms that oral anticoagulation should be the preferred option in all AF patients at risk

The ESC recommends that antiplatelet therapy should be considered only when patients refuse any OAC, or cannot tolerate OAC for reasons unrelated to bleeding.

Adapted from Connolly et al. N Engl J Med 2011;364:806-17.^Camm et al. Eur Heart J 2012;e-published August 2012, doi:10.1093/eurheartj/ehs253.

Apixaban Clinical Trial Data

COMPARISON OF APIXABAN WITH THE STANDARD OF CARE

- **RESULTS FROM ARISTOTLE**

ARISTOTLE: Study design and objectives[1]

Patient Population[2]

- Aged ≥18 years
- Patients with NVAF and ≥1 risk factors for stroke

Randomised, double-blind, double-dummy

Event Driven*

Apixaban 5.0 mg oral BD
(2.5 mg oral BD in select patients† [4.7%])

Warfarin
(adjusted to an INR of 2–3)

The primary objective of the trial was to determine if apixaban was non-inferior to warfarin for the prevention of stroke and systemic embolism.

If non-inferiority was met, the following endpoints were tested for superiority[1,3]

- Stroke or systemic embolism (primary efficacy endpoint)
- ISTH major bleeding (primary safety endpoint)
- Death due to any cause (key secondary endpoint)

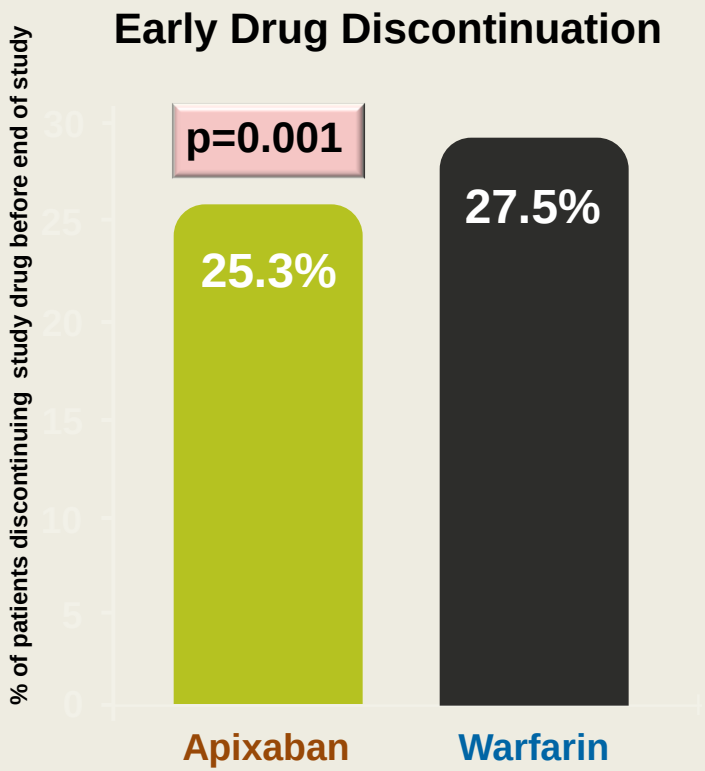
**448 primary study events were needed.*

†≥2 of the following: age ≥80 years, weight ≤60 kg, serum creatinine level ≥1.5 mg/dL

1. Granger et al. N Engl J Med 2011;365:981-992. 2. Lopes et al. Am Heart J 2010;159:331-9. 3. Apixaban SmPC 2012.

ARISTOTLE: Trial metrics

- **Median duration of follow-up: 1.8 years**
- **Median TTR among warfarin- treated patients: 66.0%**
- **Fewer patients in the apixaban group than in the warfarin group discontinued a study drug before the end of the study.**



TTR = Time in Therapeutic Range

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

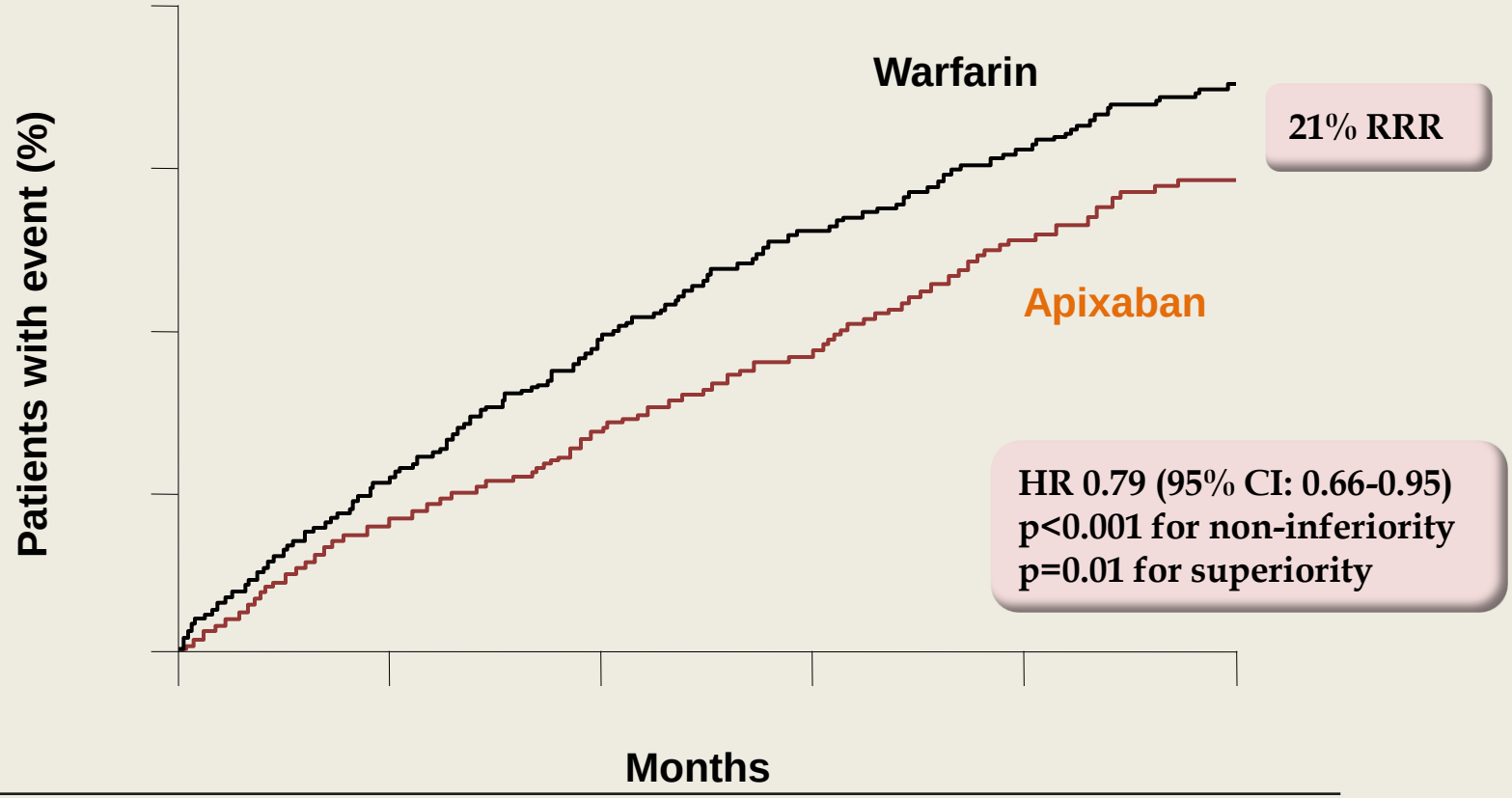
ARISTOTLE: Baseline characteristics were well balanced

Characteristic	Apixaban (n=9,120)	Warfarin (n=9,081)
Median age (25th, 75th percentile)	**70 yrs (63, 76)**	**70 yrs (63, 76)**
Women	**35.5%**	**35.0%**
Region		
North America	**24.7%**	**24.5%**
Latin America	**19.1%**	**19.0%**
Europe	**40.3%**	**40.4%**
Asian Pacific	**16.0%**	**16.1%**
Prior use of VKA	**57.1%**	**57.2%**
Mean $CHADS_2$ (SD)	**2.1 (1.1)**	**2.1 (1.1)**
≤ 1	**34.0%**	**34.0%**
2	**35.8%**	**35.8%**
≥ 3	**30.2%**	**30.2%**

Characteristic	Apixaban (n=9,120)	Warfarin (n=9,081)
Qualifying risk factors		
Age ≥75 yrs	**31.2%**	**31.1%**
Prior stroke, TIA or systemic embolism	**19.2%**	**19.7%**
Heart failure or reduced LVEF	**35.5%**	**35.4%**
Diabetes	**25.0%**	**24.9%**
Hypertension requiring treatment	**87.3%**	**87.6%**
Creatinine clearance		
> 80 mL/min	**41.2%**	**41.4%**
50–80 mL/min	**41.9%**	**41.5%**
> 30–50 mL/min	**15.0%**	**15.2%**
≤ 30 mL/min	**1.5%**	**1.5%**

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

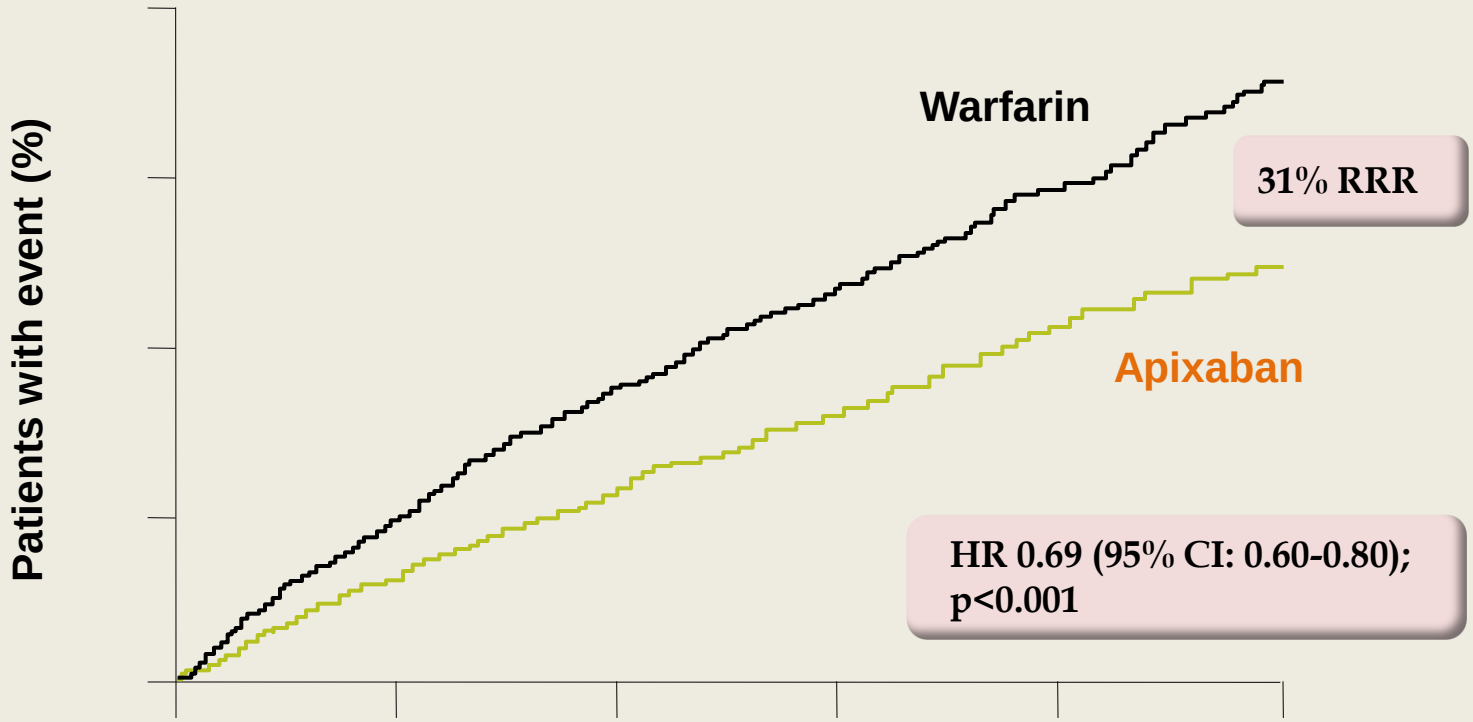
ARISTOTLE: Apixaban was superior to warfarin in preventing stroke or systemic embolism



No. at risk						
Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

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

ARISTOTLE: Apixaban significantly reduced the risk of major bleeding* *vs*. warfarin



No. at Risk						
Apixaban	9088	8103	7564	5365	3048	1515
Warfarin	9052	7910	7335	5196	2956	1491

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

**** Major bleeding was defined according to ISTH criteria***

ARISTOTLE: Apixaban was superior to warfarin in reducing all-cause mortality

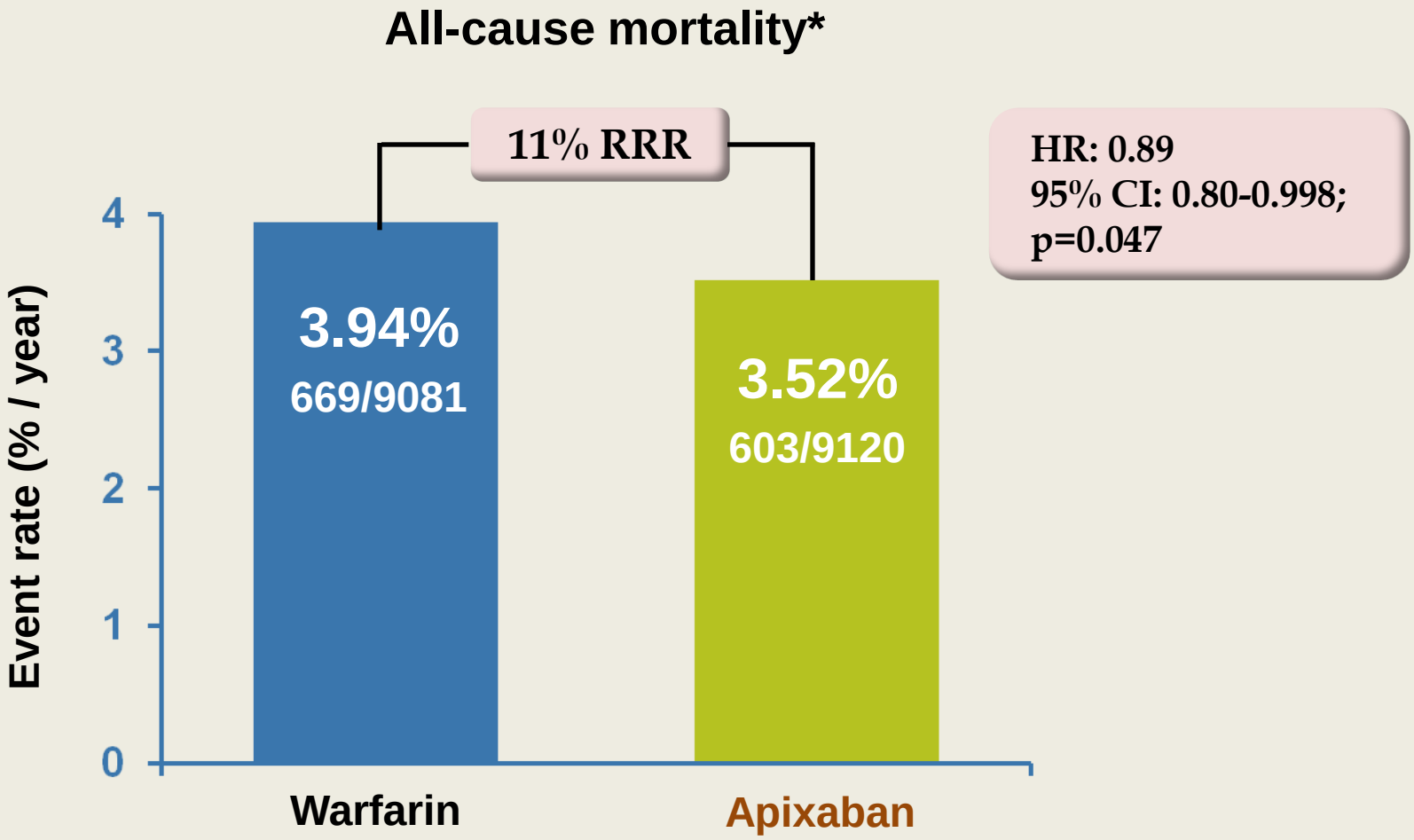
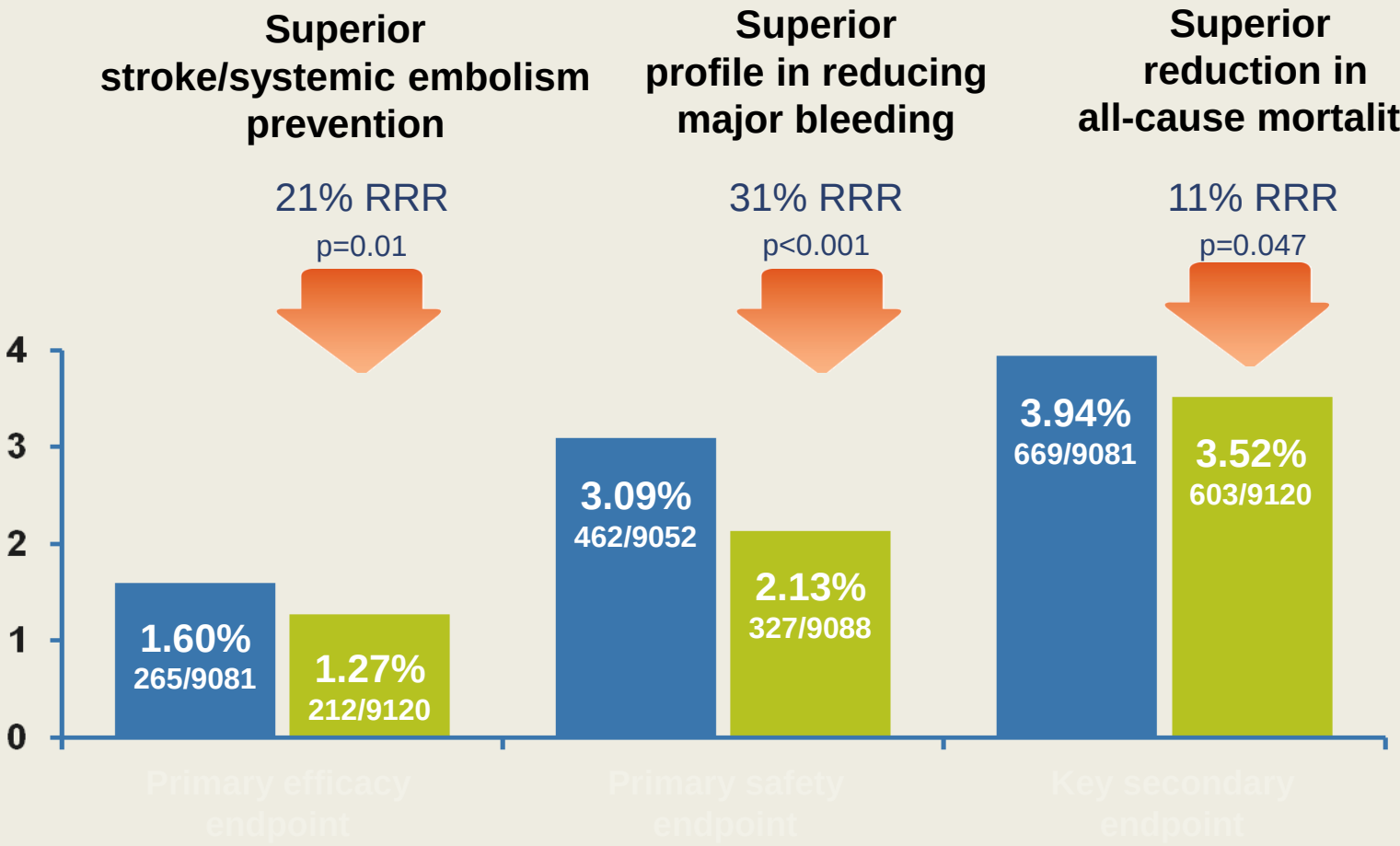


Figure created from data in Granger et al. N Engl J Med 2011;365:981-92.

*Key secondary efficacy endpoint

Apixaban is the only oral anticoagulant to demonstrate superiority *vs*. warfarin in all of the following 3 outcomes



- **Median duration of follow-up 1.8 years**

Figure created from data in Granger et al. N Engl J Med 2011;365:981-92.

For every 1000 AF patients treated for 1.8 years, apixaban, as compared with warfarin, prevented:

6
strokes

15
major bleeds

8
deaths

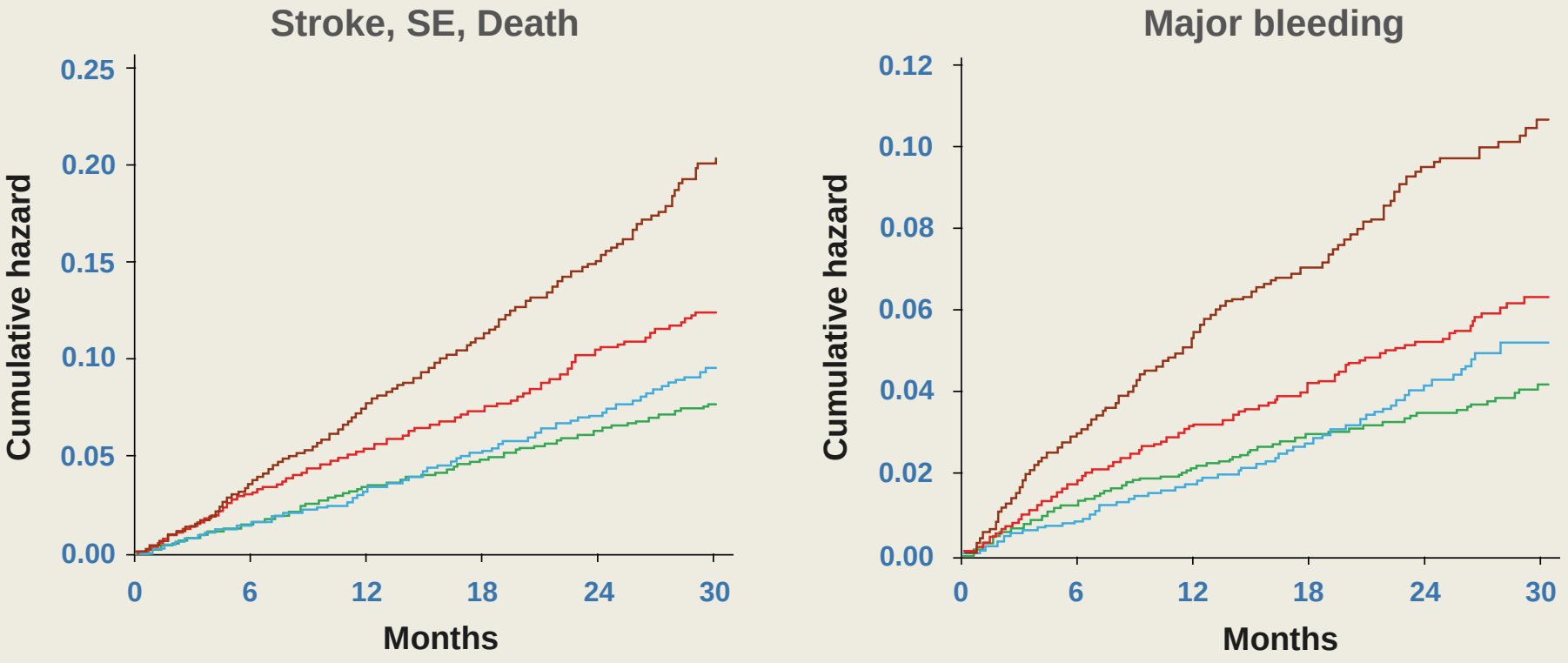
Granger et al. N Engl J Med 2011;365:981-92.

Apixaban in Context

Impaired renal function

Time in therapeutic range

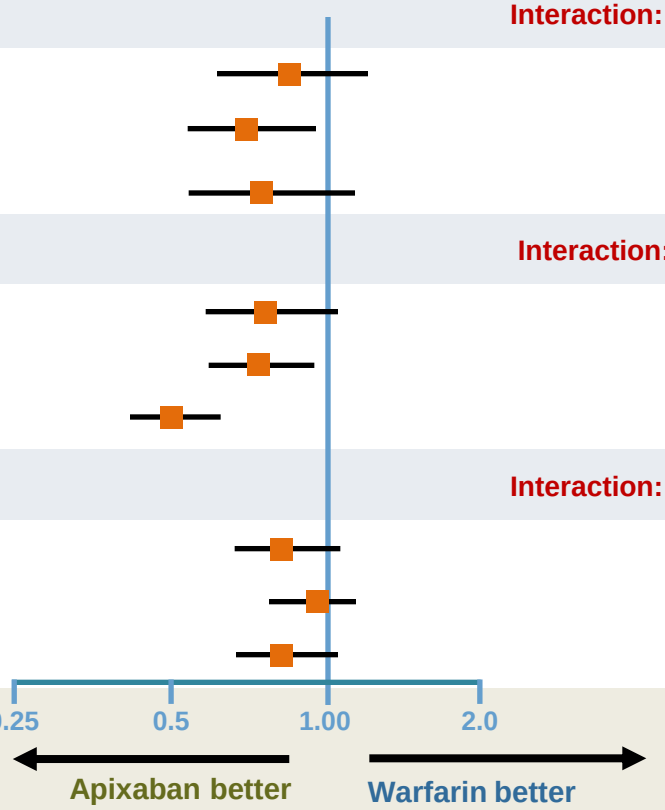
ARISTOTLE: The risk of stroke, SE or death, and major bleeding increased with decreasing **renal function**



Adapted from Honhloser et al. Presented at the ESC meeting on Wednesday August 29, 2012 - http://spo.escardio.org/eslides/view.aspx?eevtid=54&fp=5172

ARISTOTLE: Efficacy and safety according to creatinine clearance (Cockcroft-Gault)

	Apixaban	Warfarin	Hazard Ratio (95% CI)	P value
	%/yr (No. of events)			
Stroke / SE				**Interaction: 0.705**
eGFR >80 mL/min[1]	0.99% (70)	1.12% (79)		
eGFR >50-80 mL/min[2]	1.24% (87)	1.69% (116)		
eGFR ≤50 mL/min[3]	2.11% (54)	2.67% (69)		
Major Bleeding				**Interaction: 0.03**
eGFR >80 mL/min[1]	1.46% (96)	1.84% (119)		
eGFR >50-80 mL/min[2]	2.45% (157)	3.21% (199)		
eGFR ≤50 mL/min[3]	3.21% (73)	6.44% (142)		
All-cause death				**Interaction: 0.627**
eGFR >80 mL/min[1]	2.33% (169)	2.71% (195)		
eGFR >50-80 mL/min[2]	3.41% (244)	3.56% (251)		
eGFR ≤50 mL/min[3]	7.12% (188)	8.30% (221)		



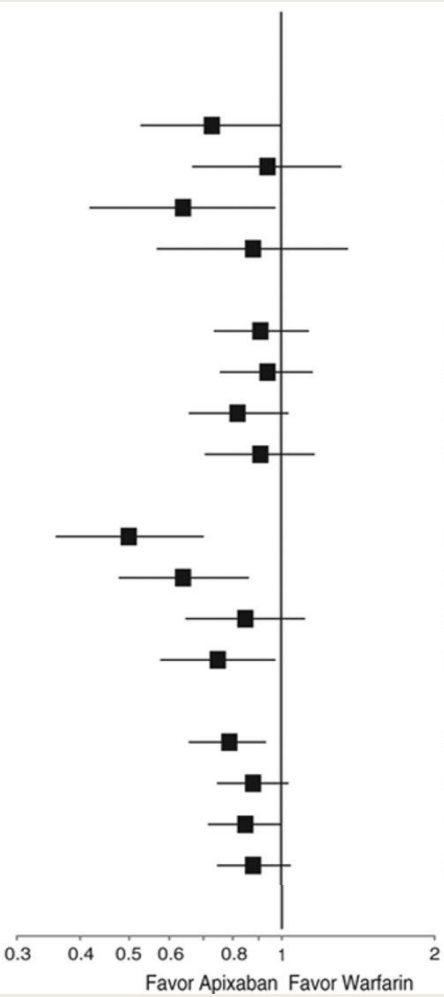
[1]n=7518 (41%); [2]n=7587 (42%); [3]n=3017 (17%)

Results were consistent regardless of methods for GFR estimation

Adapted from Hohnloser et al. Eur Heart J 2012; 2012;e-published August 29, doi:10.1093/eurheartj/ehs274.

Outcome with apixaban vs warfarin in relation to quartiles of predicted centers' **time in therapeutic range (cTTR).**

Predicted cTTR	Apixaban N	Apixaban Events (%/yr)	Warfarin N	Warfarin Events (%/yr)	HR (95% CI)	P Interaction
Primary outcome (SSE)						0.078
24.3 - 60.5	2243	68 (1.72)	2251	92 (2.36)	0.73 (0.53-1.00)	
60.6 - 66.3	2287	68 (1.61)	2266	72 (1.72)	0.94 (0.67-1.31)	
66.4 - 71.1	2301	36 (0.86)	2301	56 (1.35)	0.64 (0.42-0.97)	
71.2 - 83.2	2289	40 (0.91)	2263	45 (1.04)	0.88 (0.57-1.35)	
All cause death						0.34
24.3 - 60.5	2243	163 (4.00)	2251	178 (4.39)	0.91 (0.74-1.13)	
60.6 - 66.3	2287	175 (4.04)	2266	185 (4.30)	0.94 (0.76-1.15)	
66.4 - 71.1	2301	140 (3.29)	2301	170 (4.01)	0.82 (0.66-1.03)	
71.2 - 83.2	2289	125 (2.81)	2263	136 (3.10)	0.91 (0.71-1.16)	
Major bleeding						0.095
24.3 - 60.5	2232	52 (1.44)	2245	102 (2.89)	0.50 (0.36-0.70)	
60.6 - 66.3	2284	77 (1.97)	2261	116 (3.07)	0.64 (0.48-0.86)	
66.4 - 71.1	2290	99 (2.61)	2292	113 (3.06)	0.85 (0.65-1.11)	
71.2 - 83.2	2282	99 (2.48)	2254	131 (3.31)	0.75 (0.58-0.97)	
Net clinical benefit						0.70
24.3 - 60.5	2243	241 (6.19)	2251	301 (7.91)	0.79 (0.66-0.93)	
60.6 - 66.3	2287	284 (6.86)	2266	318 (7.85)	0.88 (0.75-1.03)	
66.4 - 71.1	2301	260 (6.44)	2301	304 (7.61)	0.85 (0.72-1.00)	
71.2 - 83.2	2289	258 (6.13)	2263	290 (6.95)	0.88 (0.75-1.04)	



Wallentin L et al. Circulation 2013;127:2166-2176

American Heart Association
Learn and Live

Baseline co-medication in relation to centers' TTR

Centre TTR	<58.0	58.0–65.7	65.7–72.2	≥72.2	p-value
Randomised	4538	4535	4533	4538	
ASA	31.2%	35.2%	29.3%	28.2%	<0.0001
ARB	24.0%	21.5%	23.6%	26.5%	<0.0001
ACEI/ARB	70.6%	74.7%	70.2%	69.3%	<0.0001
β-blocker	60.3%	63.9%	64.5%	65.9%	<0.0001
Amiodarone	14.7%	13.9%	11.1%	5.8%	<0.0001
Digoxin	36.5%	33.9%	30.9%	28.1%	<0.0001
Lipid-lowering	34.0%	41.2%	47.2%	59.2%	<0.0001

Wallentin L. European Society of Cardiology Congress, Paris, France, 28 August 2011.
http://www.escardio.org/congresses/esc-2011/congress-reports/Documents/28-8-CTU/ARISTOTLE-presenter-Wallentin-slides.pdf

Conclusions from subgroup analyses

- The results were **consistent in predefined subgroups.**
- When compared with warfarin, apixaban treatment reduced the rate of stroke and death **regardless of renal function**.
  - Patients with moderately impaired renal function seemed to have the greatest reduction in major bleeding with apixaban compared to warfarin.
- The benefit of apixaban *vs*. warfarin[4] is maintained **irrespective of centres' quality of INR control**.
  - However, these subgroup analyses have to **be interpreted with caution** as baseline characteristics were quite different across the strata of INR control.

Wallentin L. European Society of Cardiology Congress, Paris, France, 28 August 2011.
http://www.escardio.org/congresses/esc-2011/congress-reports/Documents/28-8-CTU/ARISTOTLE-presenter-Wallentin-slides.pdf

Comparison of NOACs
To Do or Not to Do?

- Do it!
  - Clinically relevant – we need to make a choice!
  - NOACs have different effects – they are not the same!
- Don´t do it!
  - No head-to-head comparisons available
  - Indirect comparisons between studies are limited by
    - differences in study populations
    - differences in study design

NOAC – Study Design

	Pradaxa® (dabigatran)	Xarelto® (rivaroxaban)	Eliquis® (apixaban)
Study	RE-LY	ROCKET AF	ARISTOTLE
Design	PROBE	double-blind, double-dummy	
Drug intake	Twice daily	Once daily	Twice daily
Standard dose	2x150mg	1x20mg	2x5mg
Safety dose	2x110mg	1x15mg	2x2.5 mg
$CHADS_2$-Score (mean)	2.1	3.5	2.1
TTR (median)	67.3%	57.8%	66.0%
Drug discontinuation	21.2%*	23.7%	25.3%**

* Significantly higher in dabigatran group, ** significantly lower in apixaban group

Efficacy

	Pradaxa® (dabigatran)		Xarelto® (rivaroxaban)	Eliquis® (apixaban)
Study	RE-LY 110mg	RE-LY 150mg	ROCKET AF	ARISTOTLE
Stroke and systemic embolism	non-inferior	**superior**	non-inferior	**superior**
	- 9% (p=n.s.)	**- 34% (p<0.001)**	- 12% (p=0,12)	**- 21% (p=0.01)**
Ischemic stroke	+11% (p=0,35)	**- 24% (p=0.03)**	- 01% (p=0,92)	- 08% (p=0.42)
Hemorrhagic stroke	**-69% (p<0.001)**	**- 74% (p<0.001)**	**- 42% (p=0.012)**	**- 49% (p<0.001)**

No head-to-head studies, indirect comparisons!

Safety and Net benefit

	Pradaxa® (Dabigatran)		Xarelto® (Rivaroxaban)	Eliquis® (Apixaban)
Study	RE-LY 110mg	RE-LY 150mg	ROCKET AF	ARISTOTLE
Safety				
Major Bleed	**- 20% (p=0.003)**	- 07% (p=n.s.)	+ 04% (p=0.58)	**- 31% (p<0.001)**
Intracranial Bleed	**- 77% (p<0.001)**	**- 60% (p<0.001)**	**- 33% (p=0.02)**	**- 58% (p<0.001)**
GI Bleed	+12% (p=0.43)	**+50% (p<0.001)**	**+ 45% (p<0.001)**	-11% (p=0.37)
MCI	+ 29% (p=0.09)	+27 (p=0.12)	- 19% (p=0.12)	-12% (p=0.37)
Net benefit				
Mortality	-09% (p=0.13)	**- 12% (p=0.051)**	- 08% (p = 0.152)*	- **11% (p=0.047)**
Net benefit	-08% (p=0.10)	**- 09% (p=0.04)**	???	**- 15% (p<0.001)**

No head-to-head studies, indirect comparisons!

* ITT analysis

Conclusions

- All **NOACs** fulfill unmet needs in AF patients
  - at least as effective and safe as VKA
  - reduce intracranial bleedings
  - are given with a fixed dose
  - do not require regular laboratory monitoring
- **Apixaban** is superior to VKA
  - improved efficacy
  - improved safety
  - particularly safe in vulnerable patients

Thank you for your attention!

Back-up

ESC recommendations – Management of bleeding

Patients on NOAC presenting with bleeding

Check haemodynamic status, basic coagulation tests to assess anticoagulation effect (e.g. aPTT for dabigatran, PT or anti Xa activity for rivaroxaban), renal function, etc.

Minor	**Delay next dose or discontinue treatment**
Moderate-severe	**Symptomatic/supportive treatment** **Mechanical compression** **Fluid replacement** **Blood transfusion** **Oral charcoal if recently ingested[a]**
Very severe	**Consider rFVIIa or PCC** **Charcoal filtration[a] / haemodialysis[a]**

Adapted from Camm et al. Eur Heart J 2012;e-published August 2012, doi:10.1093/eurheartj/ehs253.

[a]With dabigatran

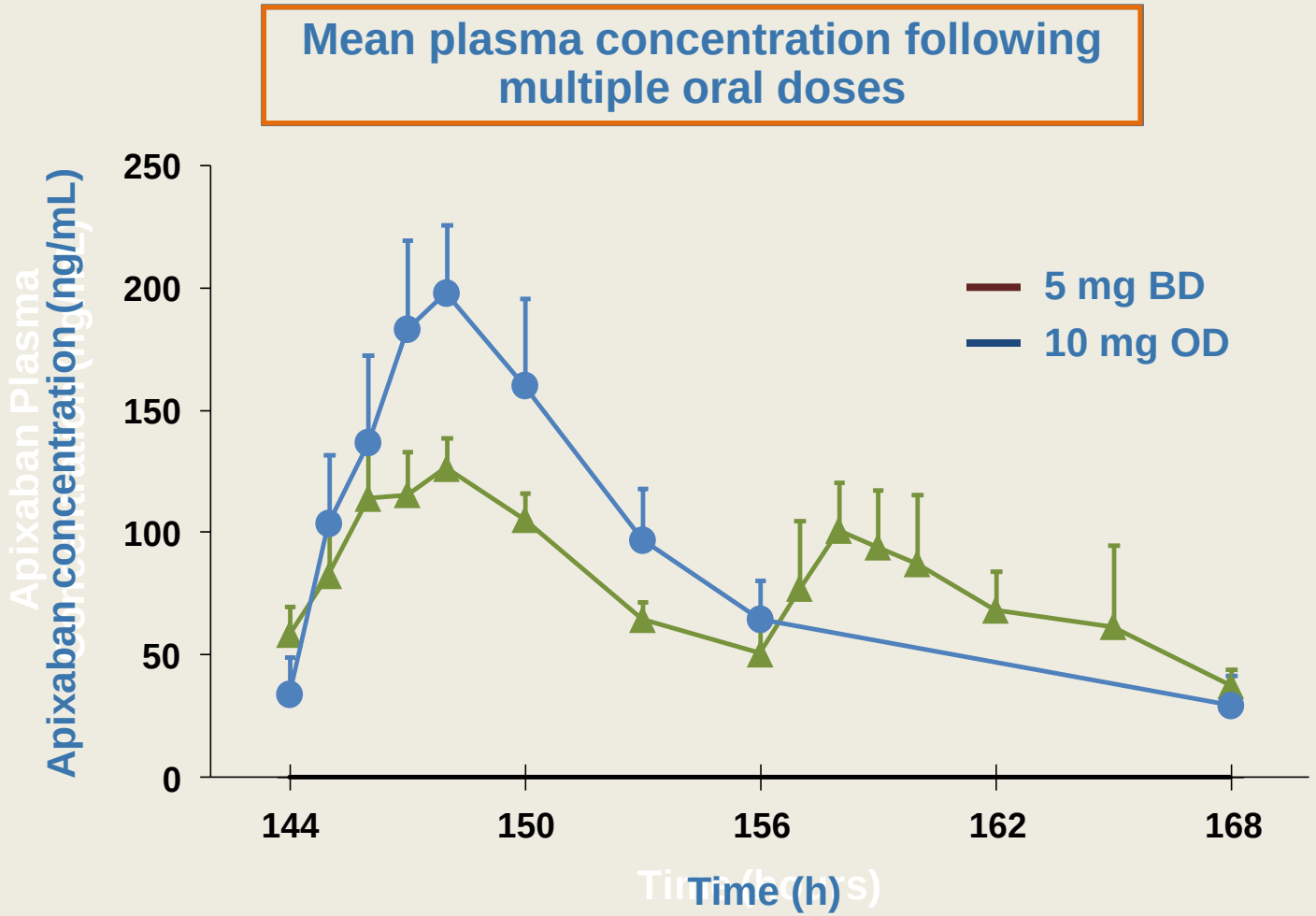
Management of bleeding complications: Prothrombin Complex Concentrates

- Prothrombin complex concentrates (PCC) contains coagulation factors **II, VII, IX, X**.[1]
- An *in vitro* study suggests that PCC or activated PCC reverses the anticoagulant action of apixaban.[2]
- So far, there are no studies with apixaban with PCC or activated PCC in humans.
- Some animal studies suggest a beneficial effect of PCCs for the reversal of bleeding with rivaroxaban.[1]
- PCC immediately and completely reversed the anticoagulant effect of rivaroxaban in healthy subjects.[1]

1. Eerenberg et al. Circulation 124:1573-9.
2. Escolar et al. Thromb Res 2012;130 (Suppl 1):S113, abstract no. C0122.

PCC= Prothrombin Complex Concentrate

The apixaban 5 mg BD regimen demonstrates a lower peak:trough ratio compared with apixaban 10 mg OD



Frost et al. J Thromb Haemost 2007; 5 Supplement 2: P-M-664.

Data on File API-001

Concomitant use of apixaban with antiplatelet agents increases the

Apixaban SmPC recommendations

- In patients with AF and a condition that warrants mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risks should be made before combining this therapy with apixaban.
- Apixaban should be used with caution when co-administered with NSAIDs (including ASA) because these medicinal products typically increase the bleeding risk

ARISTOTLE	APPRAISE II
In a clinical trial of patients with **AF**, concomitant use of **ASA** increased the major bleeding risk: ▪ On apixaban from 1.8% to 3.4% per year ▪ On warfarin from 2.7% to 4.6% per year ▪ There was limited (2.1%) use of concomitant dual antiplatelet therapy	In a clinical trial of **high-risk post ACS** patients, characterised by multiple cardiac and non-cardiac comorbidities, who received **ASA** or the combination of **ASA and clopidogrel:** A significant increase in risk of ISTH major bleeding was reported: ▪ Apixaban: 5.13% per year ▪ Placebo: 2.04% per year

Apixaban SmPC 2012.

The CHA_2DS_2-VASc scheme was adopted by the ESC to complement the $CHADS_2$ scoring system

$CHADS_2$	*Score*	*CHA_2DS_2-VASc*	*Score*
Congestive heart failure	1	Congestive heart failure/left ventricular dysfunction	1
Hypertension	1	Hypertension	1
Aged ≥75 years	**1**	**Aged ≥75 years**	**2**
Diabetes mellitus	1	Diabetes mellitus	1
Stroke/TIA/TE	2	Stroke/TIA/TE	2
Maximum score	**6**	**Vascular disease (prior MI, PAD, or aortic plaque)**	**1**
		Aged 65-74 years	**1**
		Sex category (i.e. female gender)	**1**
		Maximum score	**9**

CHA_2DS_2-VASc:

- In patients with a $CHADS_2$ score of 0-1, or
- When a more detailed stroke risk assessment is indicated

Camm et al. Eur Heart J 2010;31:2369-429.

The 2010/2012 ESC Guidelines recommend the use of a simple bleeding risk score: HAS-BLED

Letter	Clinical characteristic	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

HAS-BLED ≥3:

- **Indicates "high risk", and**
- **Some caution and regular review of the patient is needed following the initiation of antithrombotic therapy, whether with OAC or ASA**

Camm et al. Eur Heart J 2010;31:2369-429.

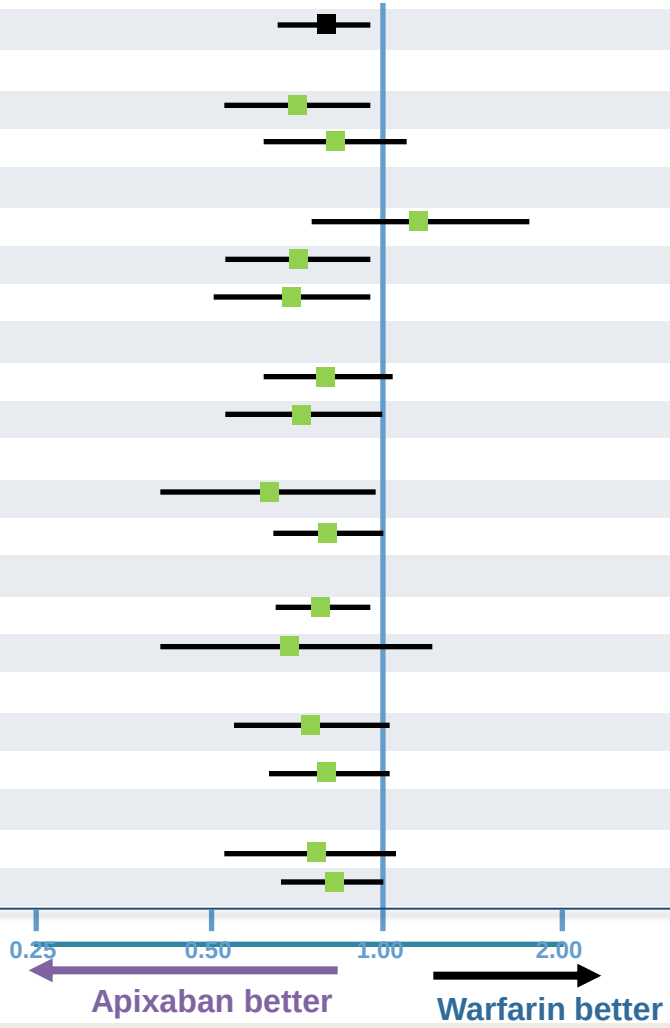
Camm et al. Eur Heart J 2012;e-published August 2012, doi:10.1093/eurheartj/ehs253.

Pisters et al. Chest 2010;138:1093-1100.

Further apixaban data

Primary efficacy results for apixaban were consistent across major subgroups in ARISTOTLE

Characteristics	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)**		
Prior warfarin/VKA					**0.39**
Yes	10,401	102 (1.1)	138 (1.5)		
No	7,800	110 (1.5)	127 (1.8)		
Age					**0.12**
< 65 yrs	5,471	51 (1.0)	44 (0.9)		
65 to < 75 yrs	7,052	82 (1.3)	112 (1.7)		
≥ 75 yrs	5,678	79 (1.6)	109 (2.2)		
Sex					**0.60**
Male	11,785	132 (1.2)	160 (1.5)		
Female	6,416	80 (1.4)	105 (1.8)		
Weight					**0.26**
≤ 60 kg	1,985	34 (2.0)	52 (3.2)		
> 60 kg	16,154	177 (1.2)	212 (1.4)		
Type of AF					**0.70**
Permanent/Persistent	15,412	191 (1.4)	235 (1.7)		
Paroxysmal	2,786	21 (0.8)	30 (1.1)		
Prior stroke or TIA					**0.71**
Yes	3,436	73 (2.5)	98 (3.2)		
No	14,765	139 (1.0)	167 (1.2)		
Diabetes mellitus					**0.71**
Yes	4,547	57 (1.4)	75 (1.9)		
No	13,654	155 (1.2)	190 (1.5)		

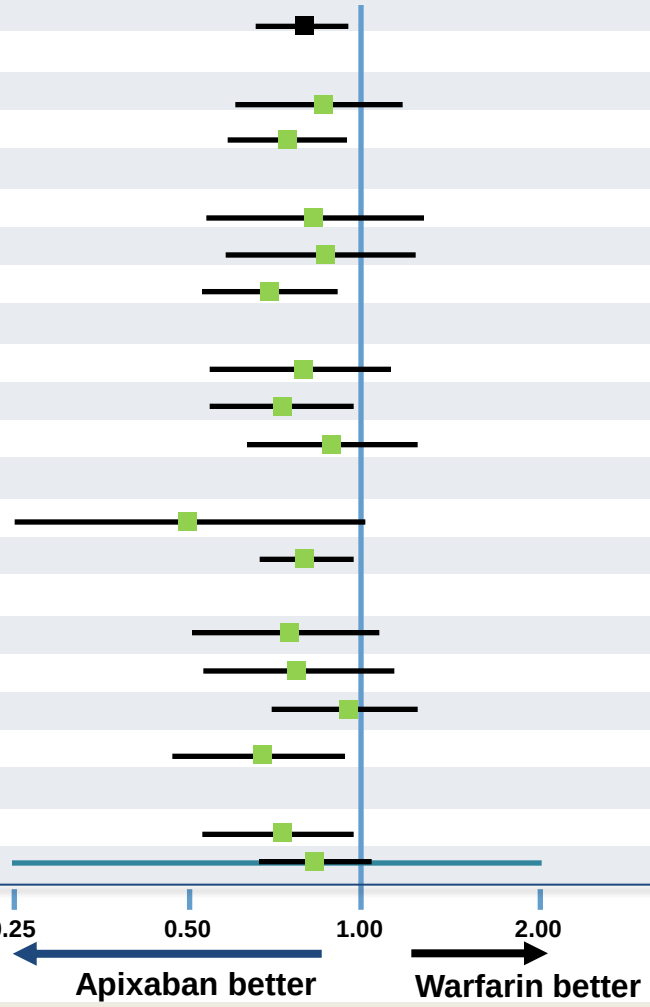


Primary efficacy endpoint: stroke or systemic embolism

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

Primary efficacy results for apixaban were consistent across major subgroups in ARISTOTLE (cont)

Characteristics	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)**		
Heart failure					0.50
Yes	5,541	70 (1.4)	79 (1.6)		
No	12,660	142 (1.2)	186 (1.6)		
$CHADS_2$ score					0.45
≤ 1	6,183	44 (0.7)	51 (0.9)		
2	6,516	74 (1.2)	82 (1.4)		
≥ 3	5,502	94 (1.9)	132 (2.8)		
Level of renal impairment					0.72
Severe or Moderate	3,017	54 (2.1)	69 (2.7)		
Mild	7,587	87 (1.2)	116 (1.7)		
No impairment	7,518	70 (1.0)	79 (1.1)		
Apixaban dose					0.22
2.5 mg BID or placebo	831	12 (1.7)	22 (3.3)		
5 mg BID or placebo	17,370	200 (1.3)	243 (1.5)		
Geographic region					0.44
North America	4,474	42 (1.0)	56 (1.3)		
Latin America	3,468	43 (1.4)	52 (1.8)		
Europe	7,343	75 (1.1)	77 (1.1)		
Asian Pacific	2,916	52 (2.0)	80 (3.1)		
ASA use at randomisation					0.44
Yes	5,632	70 (1.3)	94 (1.9)		
No	12,569	142 (1.2)	171 (1.5)		

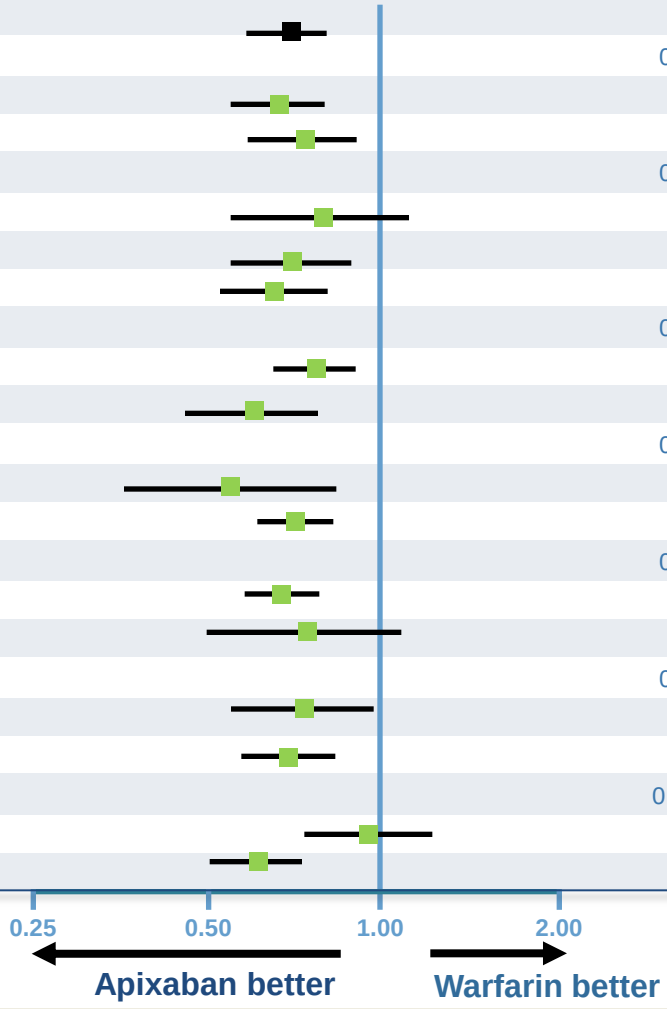


Primary efficacy endpoint: stroke or systemic embolism

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

Apixaban provided generally consistent major bleeding results across subgroups in ARISTOTLE

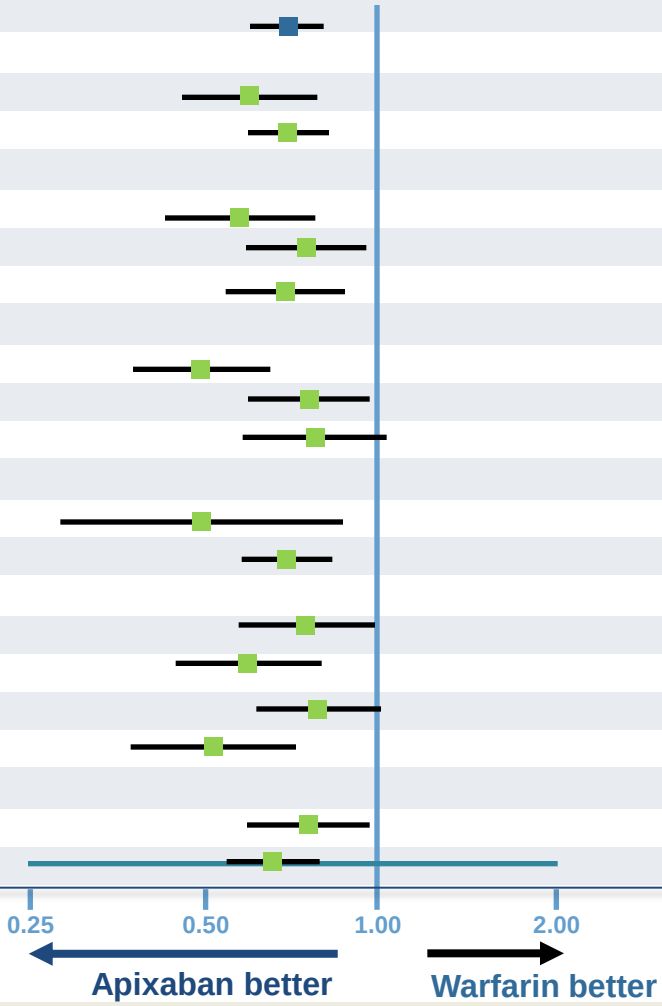
Characteristics	No. of patients	Apixaban	Warfarin	Hazard Ratio (95% CI)	P value for interaction
		No. of events (%/yr)			
All patients	**18,140**	**327 (2.13)**	**462 (3.09)**		
Prior warfarin/VKA					0.50
Yes	10,376	185 (2.1)	274 (3.2)		
No	7,764	142 (2.2)	188 (3.0)		
Age					0.64
< 65 yrs	5,455	56 (1.2)	72 (1.5)		
65 to < 75 yrs	7,030	120 (2.0)	166 (2.8)		
≥ 75 yrs	5,655	151 (3.3)	224 (5.2)		
Sex					0.08
Male	11,747	225 (2.3)	294 (3.0)		
Female	6,393	102 (1.9)	168 (3.3)		
Weight					0.22
≤ 60 kg	1,978	36 (2.3)	62 (4.3)		
> 60 kg	16,102	290 (2.1)	398 (3.0)		
Type of AF					0.75
Permanent/Persistent	15,361	283 (2.2)	402 (3.2)		
Paroxysmal	2,776	44 (1.9)	60 (2.6)		
Prior stroke or TIA					0.71
Yes	3,422	77 (2.8)	106 (3.9)		
No	14,718	250 (2.0)	356 (2.9)		
Diabetes mellitus					0.003
Yes	4,526	112 (3.0)	114 (3.1)		
No	13,614	215 (1.9)	348 (3.1)		



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

Apixaban provided generally consistent major bleeding results across subgroups in ARISTOTLE (cont)

Characteristics	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)**		
Heart failure					0.30
Yes	5,527	87 (1.9)	137 (3.1)		
No	12,613	240 (2.2)	325 (3.1)		
$CHADS_2$ score					0.40
≤ 1	6,169	76 (1.4)	126 (2.3)		
2	6,492	125 (2.3)	163 (3.0)		
≥ 3	5,479	126 (2.9)	173 (4.2)		
Level of renal impairment					0.03
Severe or Moderate	3,005	73 (3.2)	142 (6.4)		
Mild	7,565	157 (2.5)	199 (3.2)		
No impairment	7,496	96 (1.5)	119 (1.8)		
Apixaban dose					0.21
2.5 mg BID or placebo	826	20 (3.3)	37 (6.7)		
5 mg BID or placebo	17,314	307 (2.1)	425 (3.0)		
Geographic region					0.16
North America	4,463	106 (2.8)	137 (3.6)		
Latin America	3,460	60 (2.1)	94 (3.5)		
Europe	7,313	110 (1.7)	135 (2.2)		
Asian Pacific	2,904	51 (2.1)	96 (4.1)		
ASA use at randomisation					0.40
Yes	5,608	129 (2.7)	164 (3.7)		
No	12,532	198 (1.9)	298 (2.8)		



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

ARISTOTLE: Apixaban significantly reduced the rate of bleeding irrespective of the bleeding definition used

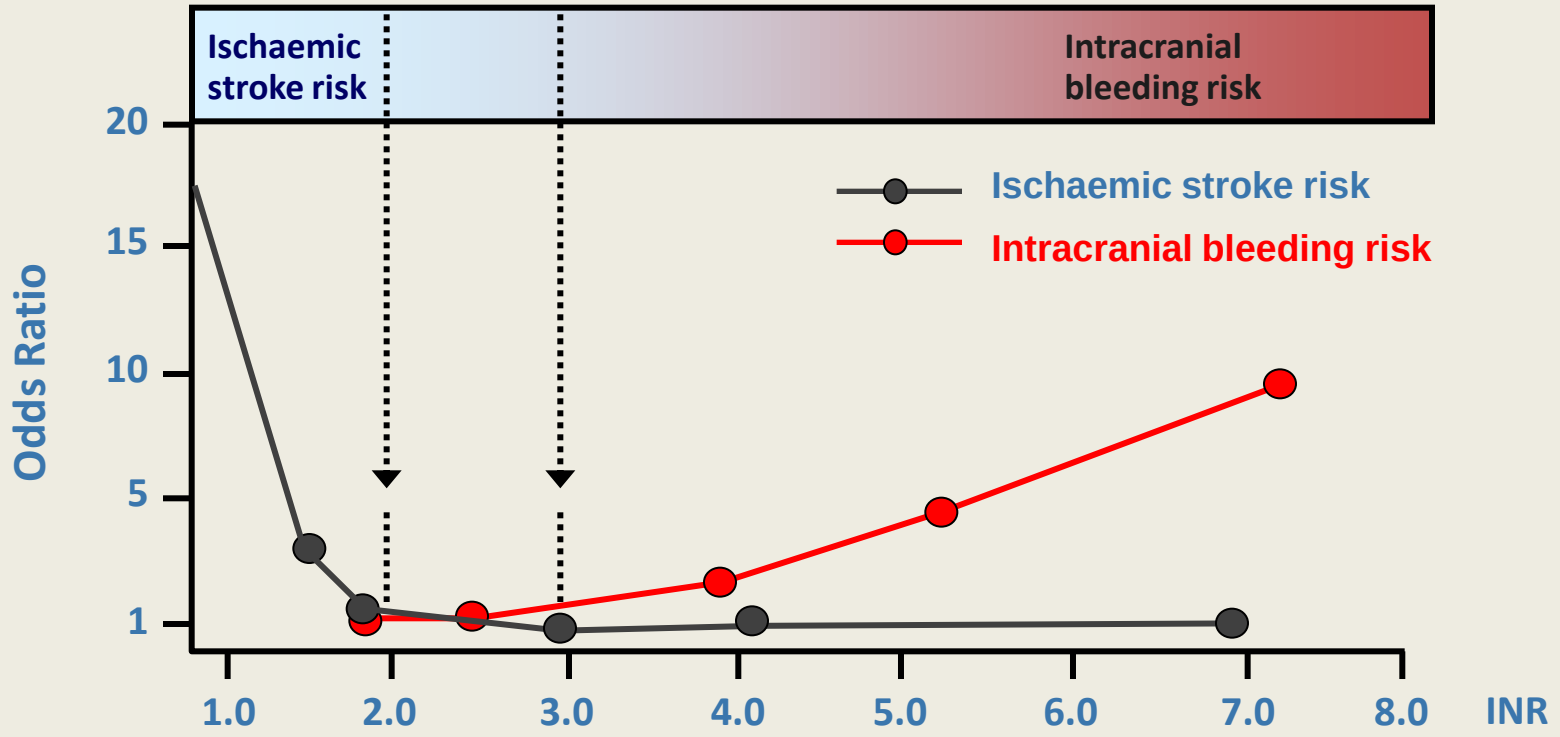
Outcome	Apixaban (N=9,088) Event Rate (%/yr)	Warfarin (N=9,052) Event Rate (%/yr)	HR (95% CI)	P value
Primary safety outcome: ISTH major bleeding	**2.13**	**3.09**	**0.69** (0.60, 0.80)	**<0.001**
Intracranial	**0.33**	**0.80**	**0.42** (0.30, 0.58)	**<0.001**
Other location	**1.79**	**2.27**	**0.79** (0.68, 0.93)	**0.004**
Gastrointestinal	**0.76**	**0.86**	0.89 (0.70, 1.15)	0.37
Major or clinically relevant non-major bleeding	**4.07**	**6.01**	**0.68** (0.61, 0.75)	**<0.001**
GUSTO severe bleeding	**0.52**	**1.13**	**0.46** (0.35, 0.60)	**<0.001**
TIMI major bleeding	**0.96**	**1.69**	**0.57** (0.46, 0.70)	**<0.001**
Any bleeding	**18.1**	**25.8**	**0.71** (0.68, 0.75)	**<0.001**

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

OAC in AF

The risks of ischaemic stroke or intracranial bleed are high outside a narrow INR range

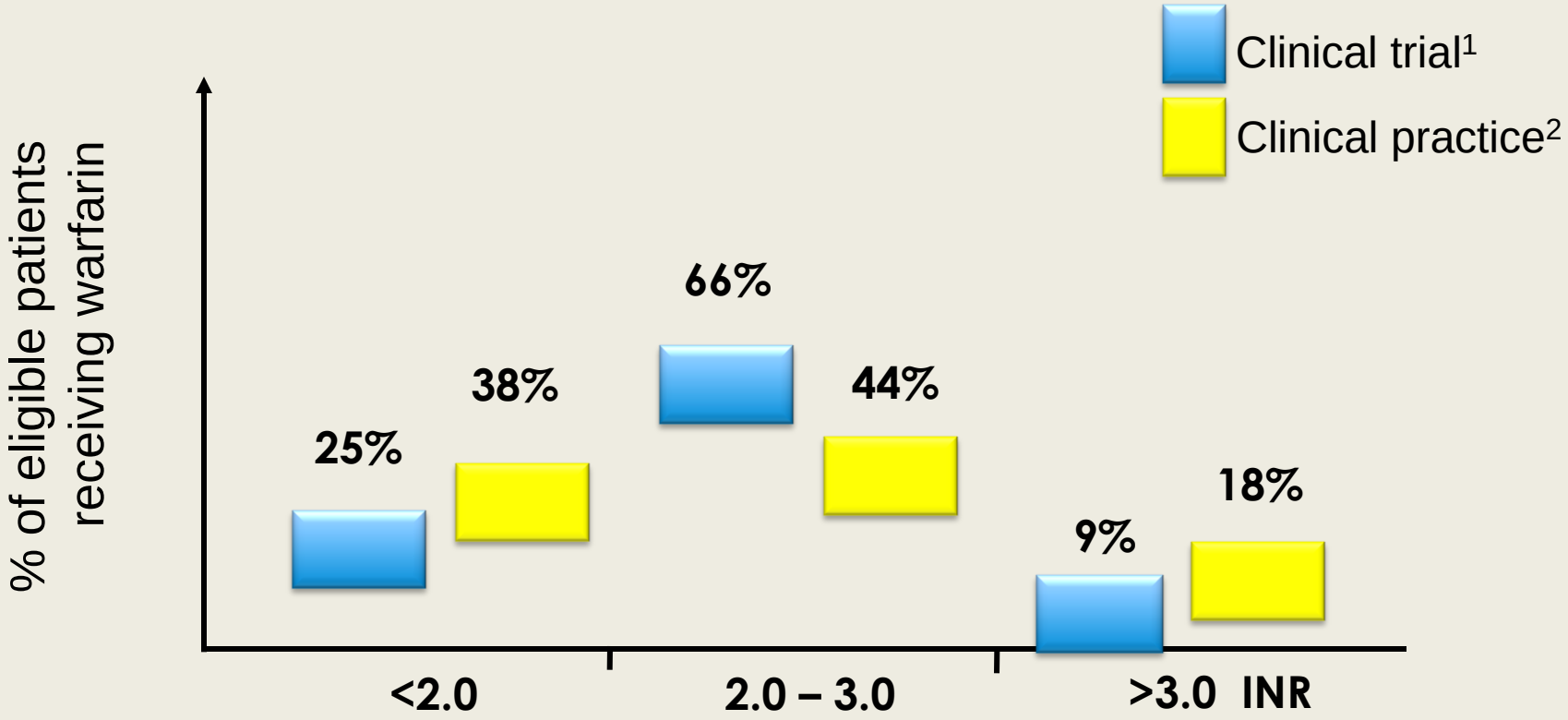
Adjusted odds-ratio for ischaemic stroke and intracranial bleeding in relation to intensity of anticoagulation



Adapted from: *Fuster et al. Circulation 2011;123:e269-e367.*
Hylek and Singer. Ann Intern Med 1994;120:897-902.
Oden et al. Thromb Res 2006;117:493-9.

INR control: clinical trials v. clinical practice

INR control in clinical trial versus clinical practice (TTR*)



* TTR = Time in Therapeutic Range (INR2.0-3.0)

1. Kalra L, et al. *BMJ* 2000;320:1236-1239 * Pooled data: up to 83% to 71% in individualized trials; 2. Matchar DB, et al. *Am J Med* 2002; 113:42-51.

Clinical pharmacology of various new oral anticoagulants

	Apixaban[1,2]	Rivaroxaban[1,3]	Dabigatran[1,4]
Mechanism of action	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct thrombin inhibitor
Oral bioavailability	~50%	80-100%	~6.5%
Pro-drug	No	No	Yes
Food effect	No	Yes (20 mg and 15 mg doses taken with food)	No
Renal clearance	~27%	~33 % *	85%
Dialysis	Not recommended	Not dialysable	Dialysable
Mean half-life ($t_{1/2}$)	~12 h	5-13 h	12-14 h
T_{max}	3-4 h	2-4 h	0.5-2 h

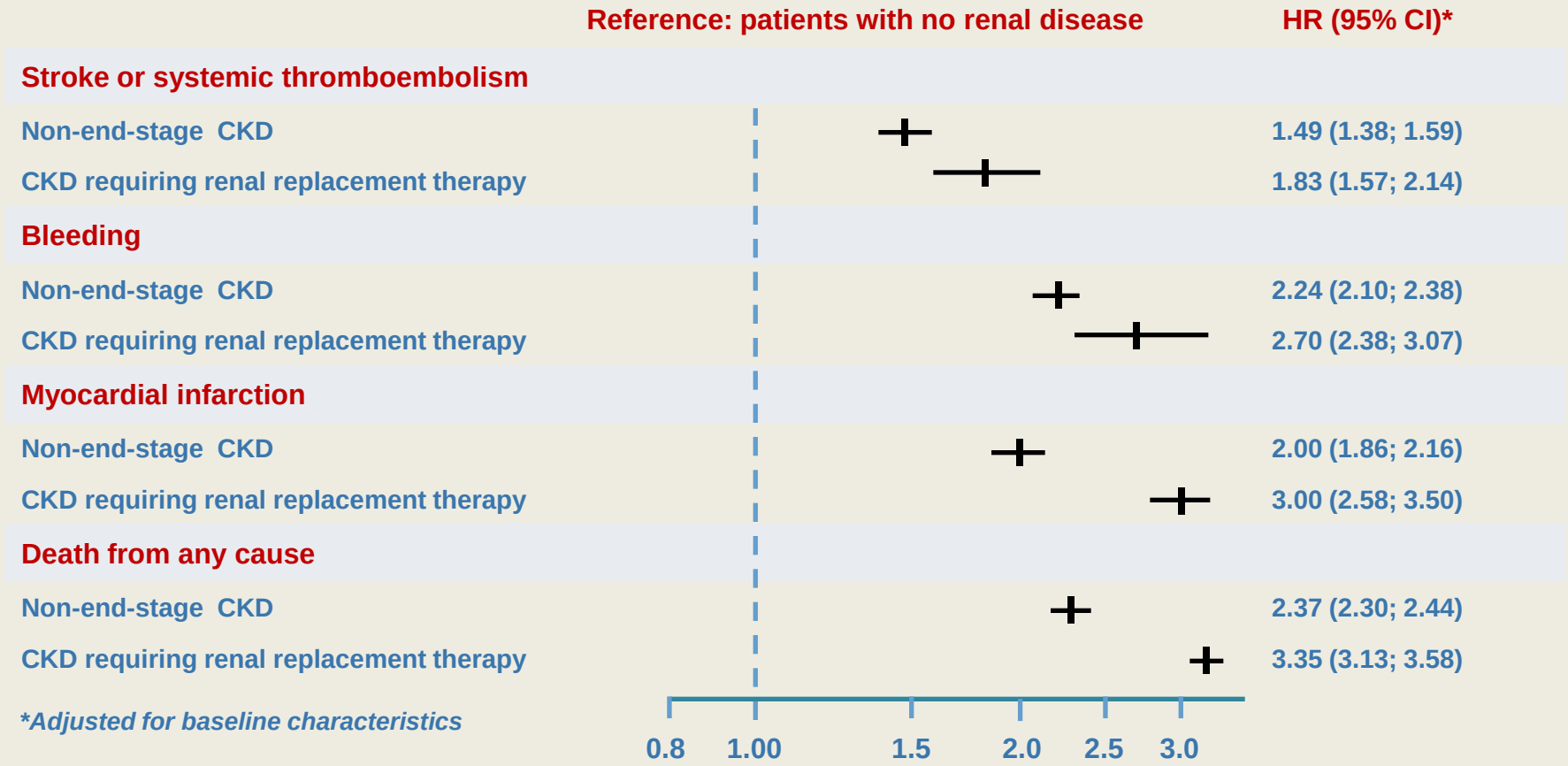
•direct renal excretion as unchanged active substance

The information in this table is based on the SmPC for apixaban, rivaroxaban and dabigatran.
Please refer to the SmPC for further information.

1. Ansell J. Hematology Am Soc Hematol Educ Program 2010:221-8. 2. Apixaban SmPC 2012
3. Rivaroxaban SmPC 2012. 4. Dabigatran SmPC 2012.

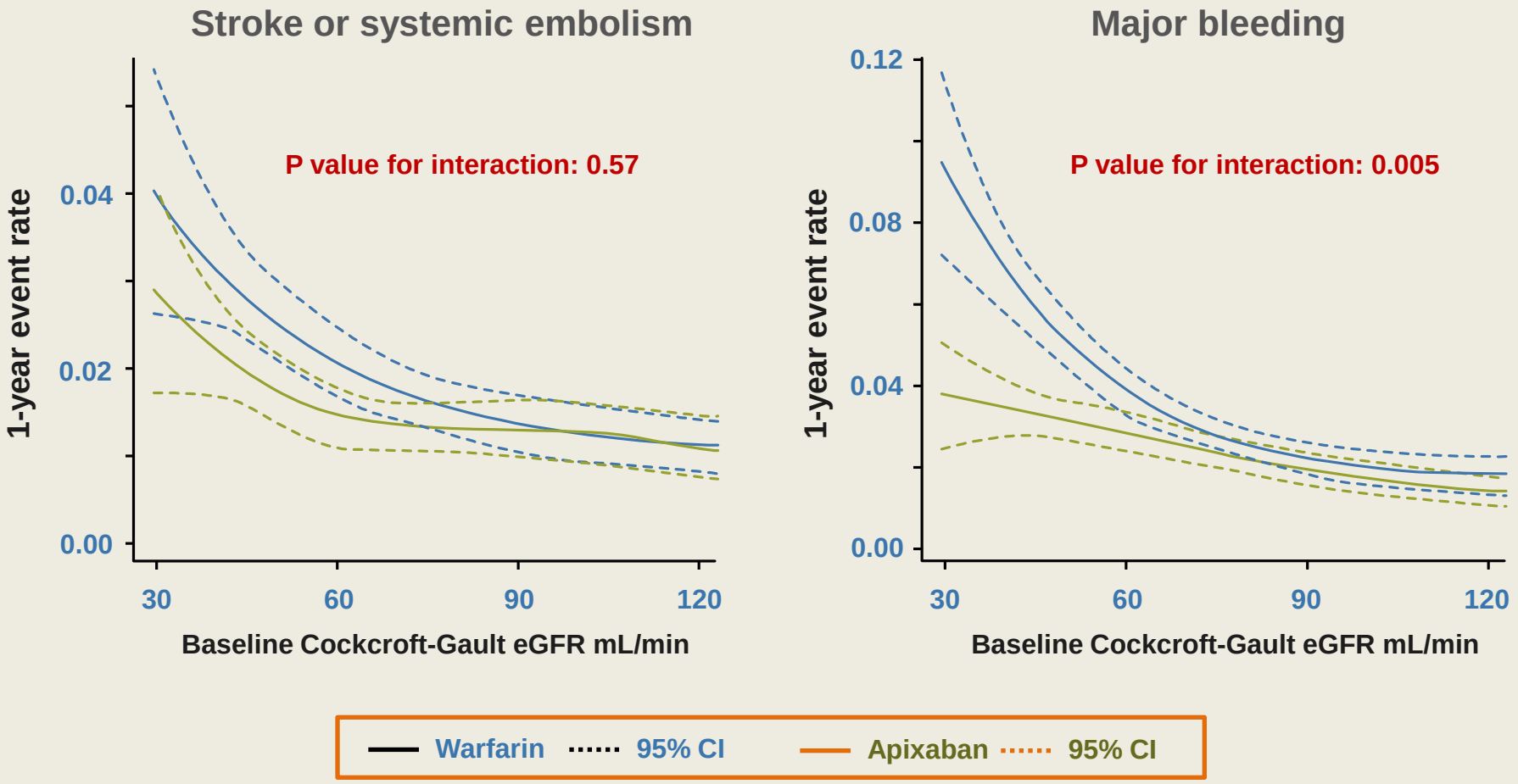
Chronic kidney disease increases the risk of bleeding and all-cause death in AF patients

Risk of events in NVAF patients with non-end-stage CKD (n=3587) or with CKD requiring renal replacement therapy (n=901) compared with NVAF patients with no renal disease (n=127,884) - Danish registry (1997-2008)



Adapted from Olesen et al. N Engl J Med 2012;367:625-35.

ARISTOTLE: Apixaban was more effective and was associated with less major bleeding events than warfarin in patients with impaired renal function



Adapted from Hohnloser et al. Eur Heart J 2012; 2012;e-published August 29, doi:10.1093/eurheartj/ehs274.

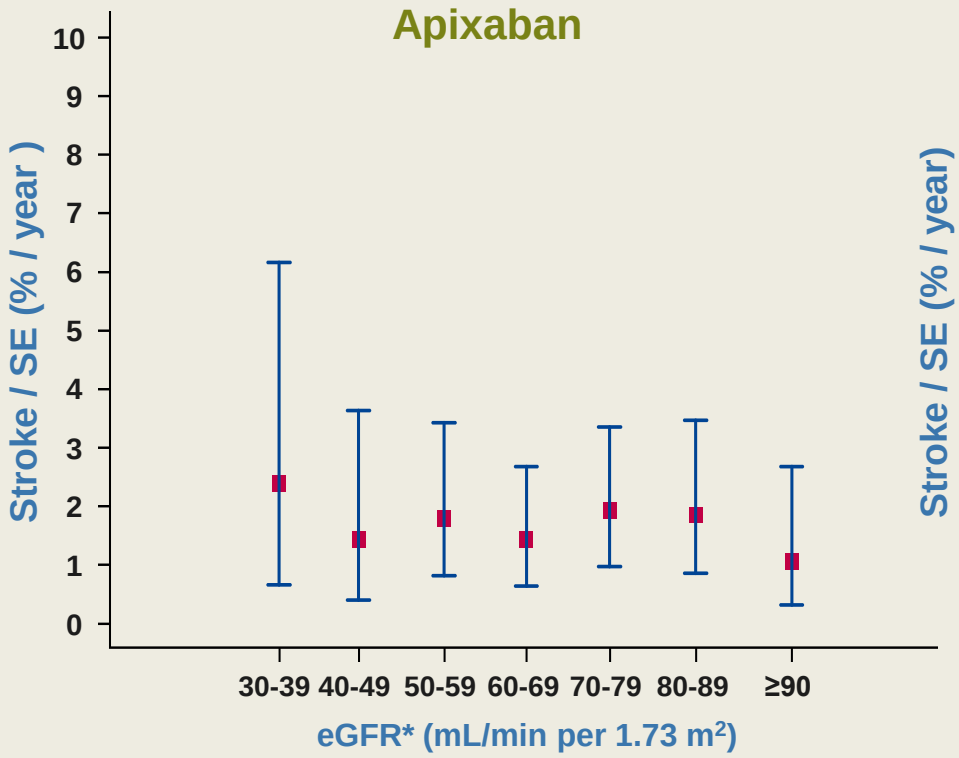
Chronic Kidney Disease in AVERROES

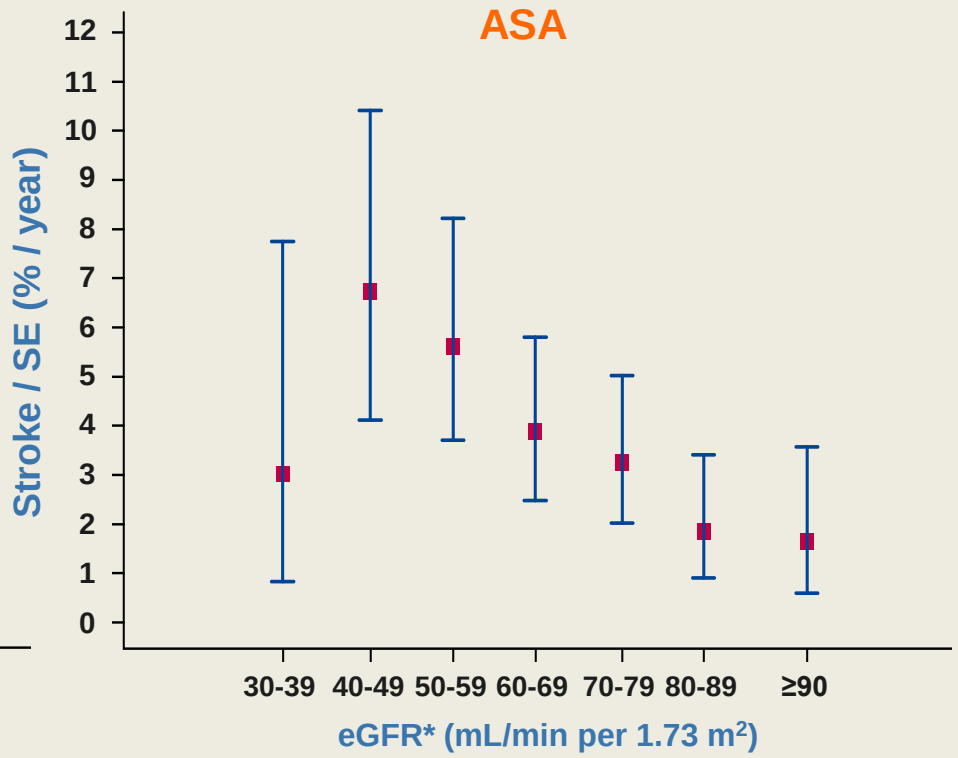
AVERROES: Efficacy and safety of apixaban *vs*. ASA according to renal function

- Because of the prolongation of half-lives of most novel anticoagulants in CKD patients, the antithrombotic effects may be enhanced for these agents when given to patients with CKD, but this may be counterbalanced by a higher risk of bleeding.
- Therefore, the efficacy and safety of new oral anticoagulants merit assessment in patients with CKD.
- The AVERROES study allowed to assess whether CKD status predicts stroke and major bleeding during ASA therapy and analyse the efficacy and safety of apixaban relative to ASA in participants with stage III CKD.
- In AVERROES, serum creatinine >2.5 mg/dL (221µmol/L) or an estimated creatinine clearance <25 mL/min per 1.73m^2 by the Cockcroft–Gault equation was an exclusion criterion.

Eikelboom et al. J Stroke Cerebrovasc Dis 2012;21:429-35.

AVERROES: The rate of stroke/systemic embolism was inversely related to eGFR with ASA but not with apixaban





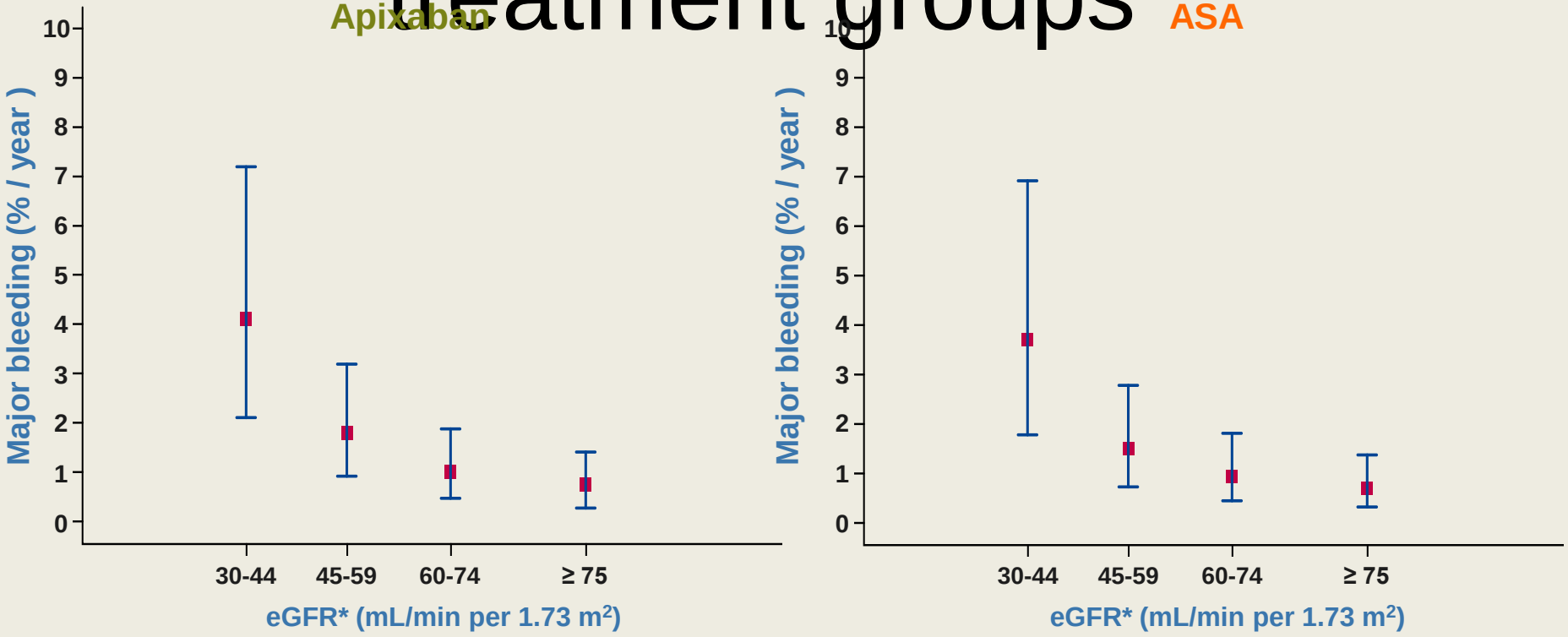
***eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.**

eGFR: estimated glomerular filtration rate

Lower-dose apixaban (2.5 mg twice daily) was assigned to 12% of participants with stage III CKD (eGFR of 30 to 59 mL/min per 1.73 m2) vs. 3% of those with eGFRs ≥60 mL/min per 1.73 m2 (p <0.001).

Adapted from Eikelboom et al. J Stroke Cerebrovasc Dis 2012;21:429-35.

bleeding was inversely related to eGFR in both treatment groups



*eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

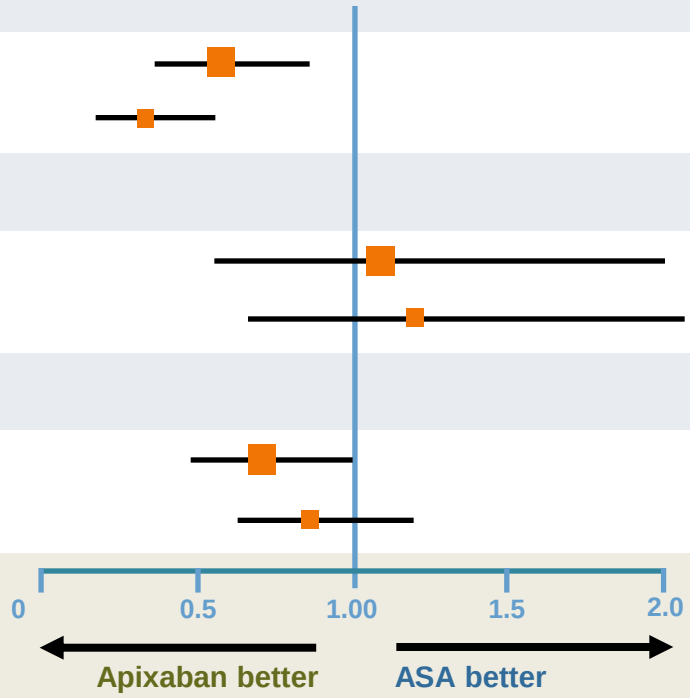
eGFR: estimated glomerular filtration rate

Lower-dose apixaban (2.5 mg twice daily) was assigned to 12% of participants with stage III CKD (eGFR of 30 to 59 mL/min per 1.73 m2) vs. 3% of those with eGFRs ≥60 mL/min per 1.73 m2 (p <0.001).

Adapted from Eikelboom et al. J Stroke Cerebrovasc Dis 2012;21:429-35.

effect of apixaban *vs*. ASA was maintained in stage III CKD patients

	Apixaban	ASA	Hazard Ratio (95% CI)	P value
	%/yr (No. of events / No. of patients)			
Stroke / SE				Interaction: 0.10
eGFR ≥60 mL/min/1.73 m²	1.7% (34/1917)	2.8% (60/1911)		0.009
eGFR 30-59 mL/min/1.73 m²*	1.8% (17/857)	5.6% (51/840)		<0.001
Major Bleeding				Interaction: 0.82
eGFR ≥60 mL/min/1.73 m²	0.9% (19/1917)	0.8% (18/1911)		0.85
eGFR 30-59 mL/min/1.73 m²*	2.5% (24/857)	2.2% (20/840)		0.58
All-cause death				Interaction: 0.39
eGFR ≥60 mL/min/1.73 m²	2.3% (49/1917)	3.3% (71/1911)		0.05
eGFR 30-59 mL/min/1.73 m²*	6.2% (59/857)	7.1% (66/840)		0.42



*eGFR 30-59 mL/min/1.73 m² : stage III CKD patients

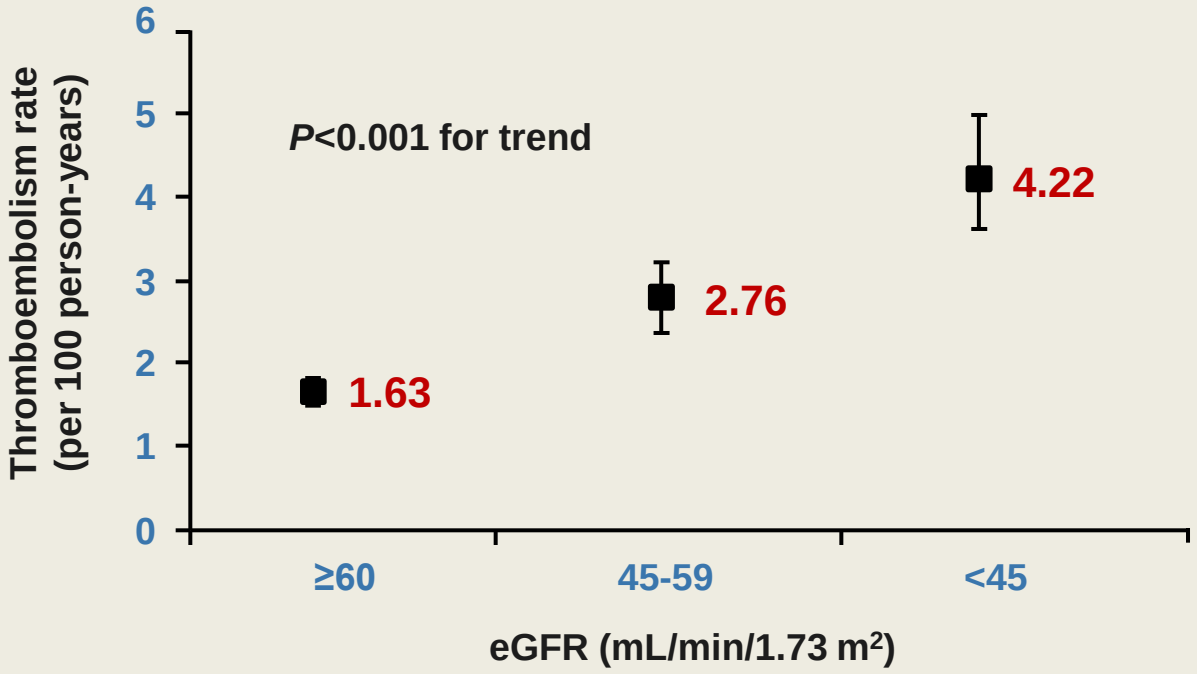
Adapted from Eikelboom et al. J Stroke Cerebrovasc Dis 2012;21:429-35.

Renal function - Conclusions from AVERROES in stage III CKD patients

- Apixaban significantly reduced the risk of stroke relative to ASA without a significant increase in major bleeding in these patients.
- For patients with AF who are not deemed suitable candidates for adjusted dose warfarin, apixaban is an attractive option that is substantially more efficacious than ASA with comparable safety.
- Because of the higher rates of stroke, the absolute reduction in stroke by apixaban *versus* ASA was 3 times as large as for those with higher eGFRs.

Chronic kidney disease increases the risk of thromboembolism in AF Patients not receiving warfarin

Crude rate of thromboembolism (% person-year)* - ATRIA cohort (n=10,908 NVAF patients off warfarin – 1995-2003)



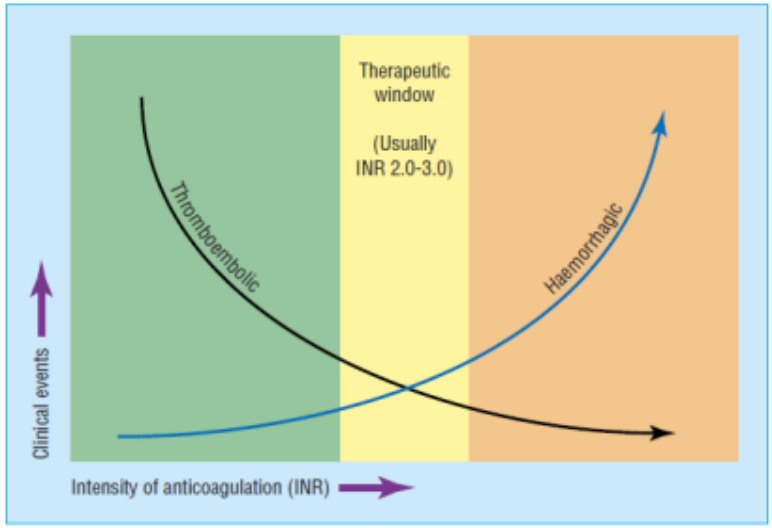
ATRIA: Assembly of the Anticoagulation and Risk Factors in Atrial Fibrillation
eGFR: estimated glomerular filtration rate
MDRD: modification of diet in renal disease

***676 validated thromboembolic events (637 ischaemic strokes, 39 other thromboembolism)**

Go AS et al. Circulation. 2009;119:1363-1369

Time within the Therapeutic range (TTR)

- The benefit of VKA for reducing the risk of stroke in patients with AF depends on the time in which patients remain in the optimum therapeutic range (INR 2.0-3.0)[1]
- There are large variations in TTR between individuals, sites, and countries[1]
- In well monitored clinical trials, patients remain in the therapeutic window only between about 50% and 80% of the time[2-5]
- Observational data from usual clinical practice often show lower means[6]



Blann et al. BMJ 2003;326:153-6.

In ARISTOTLE, patients in the warfarin group had an INR in the therapeutic range (2.0-3.0) for a median of 66.0%[7]

1. Wallentin et al. Lancet 2010;376:975-83.
2. Executive Steering Committee for the SPORTIF III Investigators. Lancet 2003;362:1691-8.
3. Executive Steering Committee for the SPORTIF V Investigators. JAMA 2005;293:690-8.
4. The ACTIVE Writing Group on behalf of the ACTIVE Investigators. Lancet 2006;367:1903-12.
5. Connolly et al. Circulation 2008;118:2029-37. 6. Samsa et al. Arch Intern Med 2000;160:967-73.
7. Granger et al. N Engl J Med 2011;365:981-92.

ARISTOTLE: Treatment effect by quartiles of centres' TTR

- Individual TTR was calculated for each warfarin-treated patient by the Rosendaal method excluding the first 7 days after randomisation and treatment interruptions, until 2 days after the last dose of warfarin
- Patients with less than two INR levels were excluded
- The centres' TTR was calculated as the median of the individual TTRs during the whole study in its warfarin patients
- The centres' TTR was assigned as a proxy for centres' quality of INR control for all its patients
- The interquartile cut-off limits for centres' TTR were identified to keep the patient numbers within each quartile approximately balanced

Wallentin L. European Society of Cardiology Congress, Paris, France, 28 August 2011.
http://www.escardio.org/congresses/esc-2011/congress-reports/Documents/28-8-CTU/ARISTOTLE-presenter-Wallentin-slides.pdf

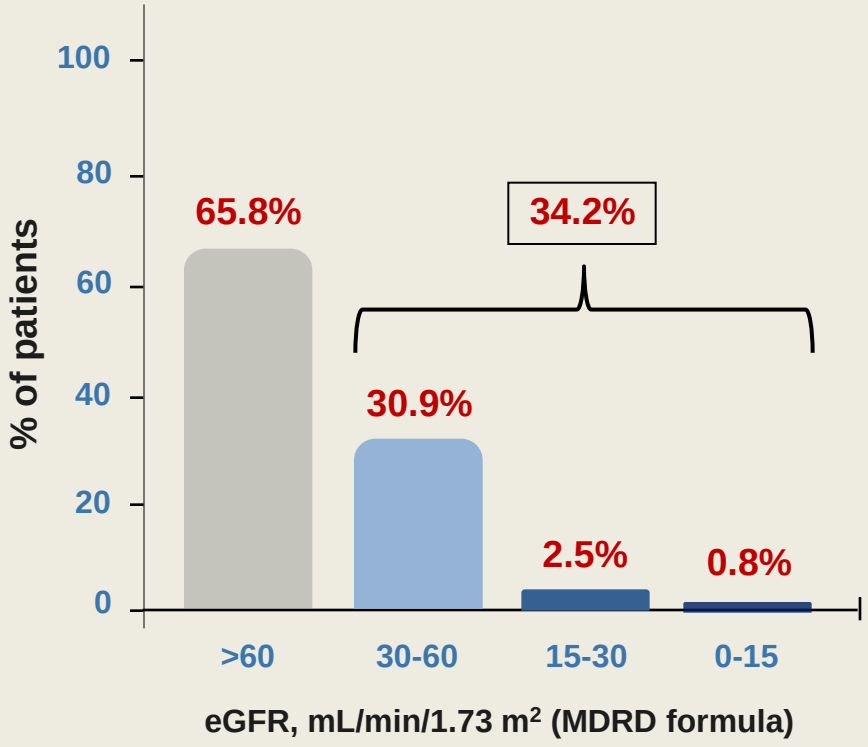
ARISTOTLE: Baseline characteristics and centers' TTR

Centre TTR	<58.0	58.0–65.7	65.7–72.2	≥72.2	p-value
Randomised	4538	4535	4533	4538	-
TTR	50.7%	62.5%	69.3%	76.7%	-
Warfarin-naive	57.4%	50.3%	35.4%	28.4%	<0.0001
Age (yrs), median	68.0	69.0	71.0	72.0	<0.0001
Male	61.8%	61.8%	65.4%	70.1%	<0.0001
Weight (kg), median	76.3	81.0	83.3	87.0	<0.0001
$CHADS_2$, mean	2.2	2.2	2.1	2.0	<0.0001
$CHADS_2$ score 3-6	32.6%	31.1%	30.0%	27.0%	<0.0001
Age ≥75 yrs	24.0%	28.1%	33.1%	39.5%	<0.0001
Prior stroke	13.4%	12.0%	11.5%	9.8%	<0.0001
Heart failure	41.8%	36.5%	27.2%	16.4%	<0.0001
Diabetes mellitus	23.8%	23.9%	25.1%	27.0%	<0.0001
Hypertension	86.2%	89.8%	88.1%	85.7%	<0.0001
Prior MI	12.6%	15.3%	13.0%	15.9%	<0.0001

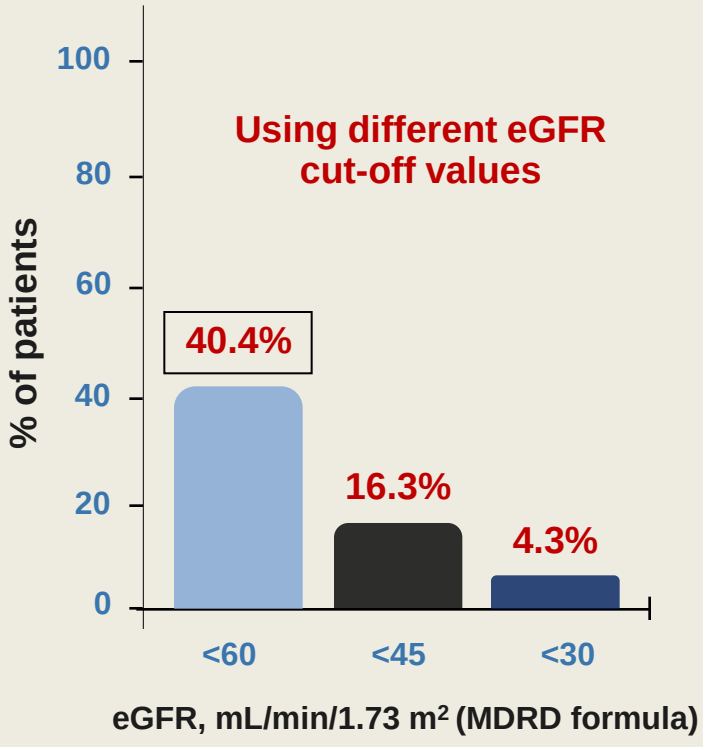
Wallentin L. European Society of Cardiology Congress, Paris, France, 28 August 2011.
http://www.escardio.org/congresses/esc-2011/congress-reports/Documents/28-8-CTU/ARISTOTLE-presenter-Wallentin-slides.pdf

Chronic kidney disease is common among AF patients

Leiden anticoagulation clinic (n=5039; 1997-2005)[1]



AURICULA registry, Malmö (n=2603; 2007-2008)

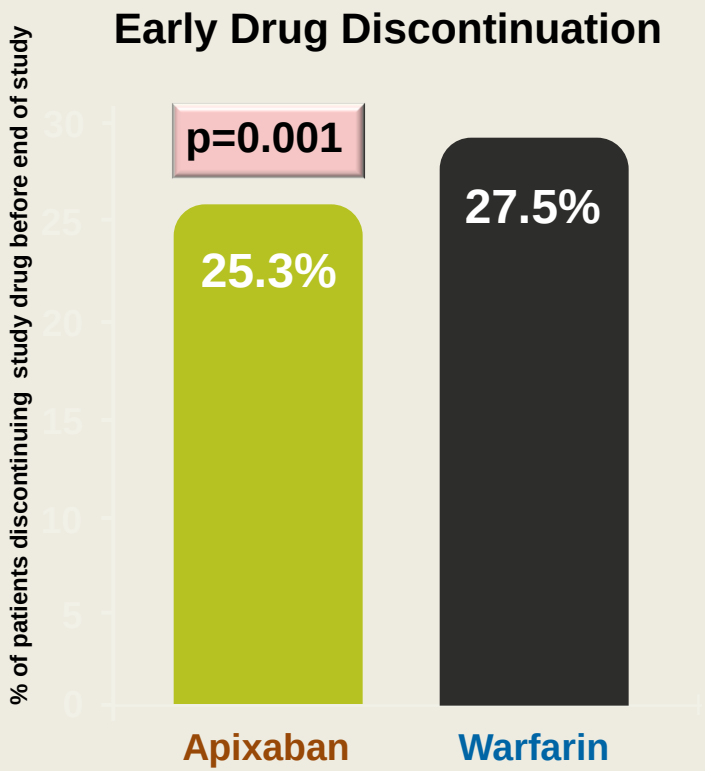


eGFR: estimated glomerular filtration rate; MDRD: modification of diet in renal disease

1. Kooiman et al. J Thromb Haemost 2011;9:1652-3. 2. Jönsson et al. Thromb Res 2011;128:341-5.

ARISTOTLE: Trial metrics

- **Median duration of follow-up: 1.8 years**
- **Median TTR among warfarin- treated patients: 66.0%**
- **Fewer patients in the apixaban group than in the warfarin group discontinued a study drug before the end of the study.**

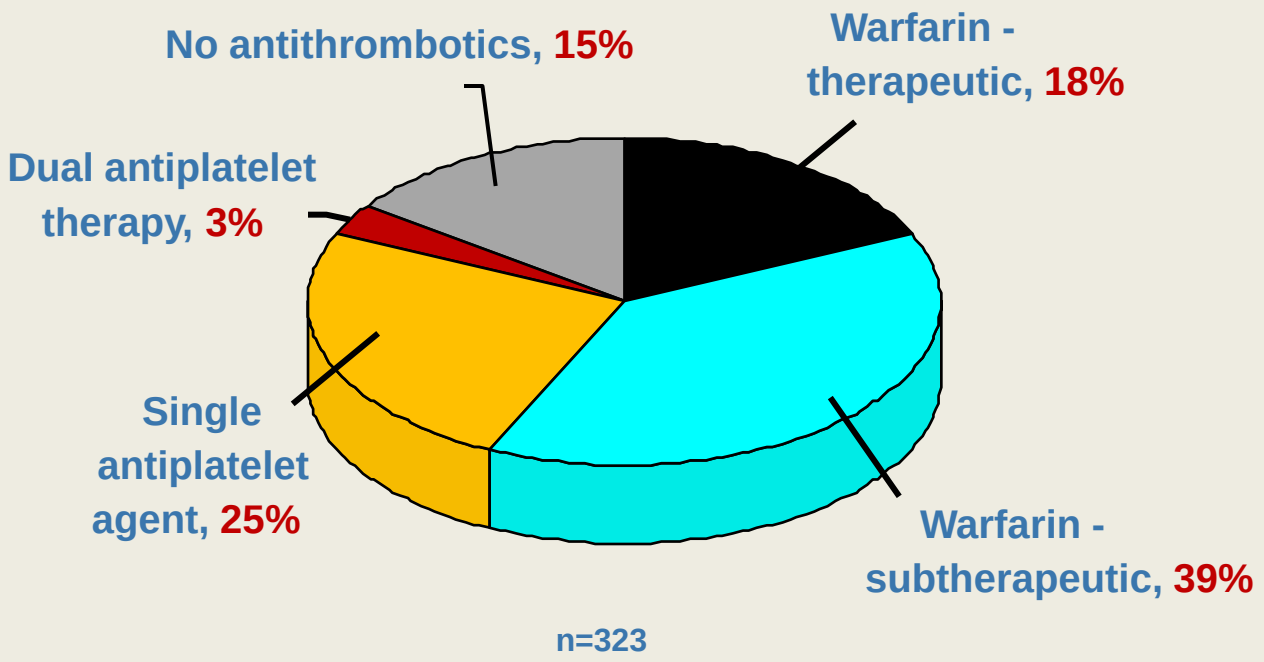


TTR = Time in Therapeutic Range

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

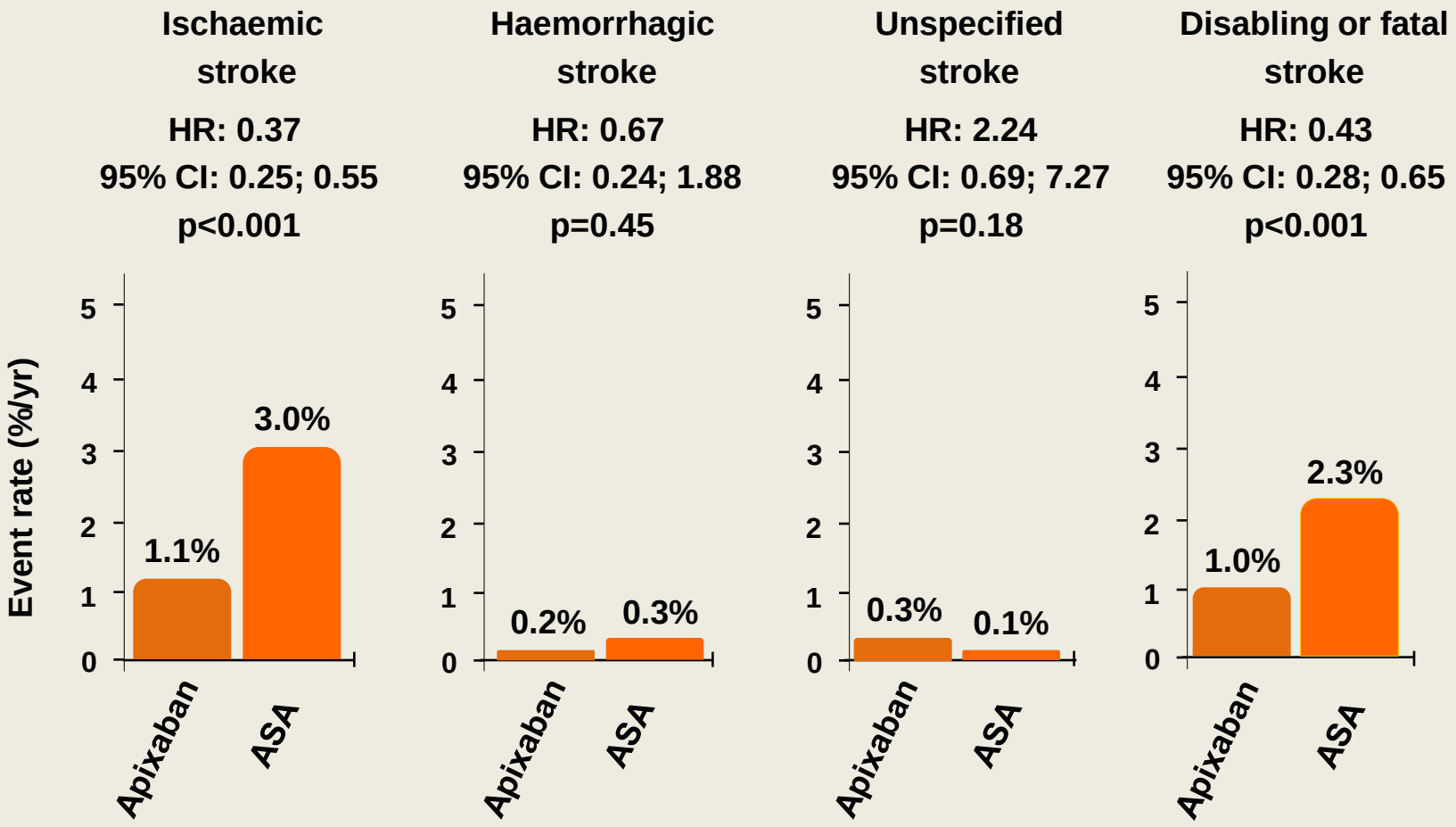
Underutilisation of VKA despite prior TIA or stroke

AF patients with previous TIA or ischaemic stroke, considered to be suitable for anticoagulation and admitted with acute ischaemic stroke (Ontario 2003-2007)



Adapted from Gladstone et al. Stroke 2009;40:235-40.

AVERROES: Type of stroke



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

For every 1000 AF patients treated for 1 year, apixaban, as compared with ASA:

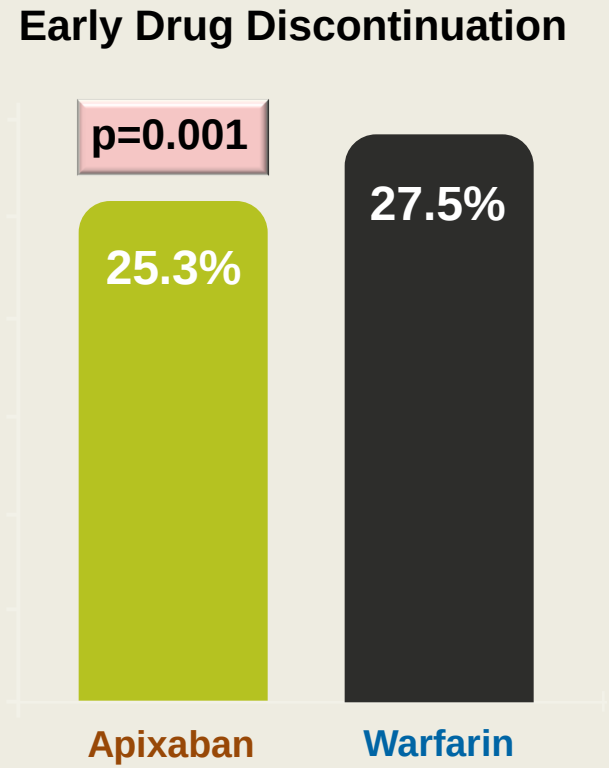
- **Would prevent**
  - **Strokes or systemic emboli in 21 patients,**
  - **Death in 9 patients,***
  - **Hospitalizations for cardiovascular causes in 33 patients,**
- **At the cost of 2 major bleeding events***

*The difference between the two groups was not statistically significant

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

Side effects and drug discontinuation

Outcome	Apixaban (N=9,088)	Warfarin (N=9,052)
Total patients with an adverse event*	81.5%	83.1%
Total patients with a serious adverse event*	35.0%	36.5%
Discontinuations due to an adverse event*	7.6%	8.4%
ALT or AST > 3X ULN and total bilirubin > 2X ULN*	0.3%	0.4%
ALT or AST > 3X ULN, total bilirubin > 2X ULN and alkaline phosphatase <2X ULN*	0.2%	0.2%
ALT elevation*		
> 3X ULN	1.1%	1.0%
> 10X ULN	0.2%	0.2%



**In the safety population of patients receiving at least 1 dose of study drug*

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN, upper limit of normal

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

SUMMARY I. AVERROES

- **Compared with ASA, apixaban significantly reduced the risk of**:
  - Stroke or systemic embolism by 55%
  - Stroke by 54%, and ischaemic stroke by 63%
- **Apixaban did not increase the risk of bleeding compared with ASA**
- **AVERROES confirms that oral anticoagulation should be the preferred option in all AF patients at risk**

The ESC recommends that antiplatelet therapy should be considered only when patients refuse any OAC, or cannot tolerate OAC for reasons unrelated to bleeding.

Connolly et al. N Engl J Med 2011;364:806-17.
Camm et al. Eur Heart J 2012;e-published August 2012, doi:10.1093/eurheartj/ehs253.