NOC comparison. Where are we coming from and where are we going

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No disclosures

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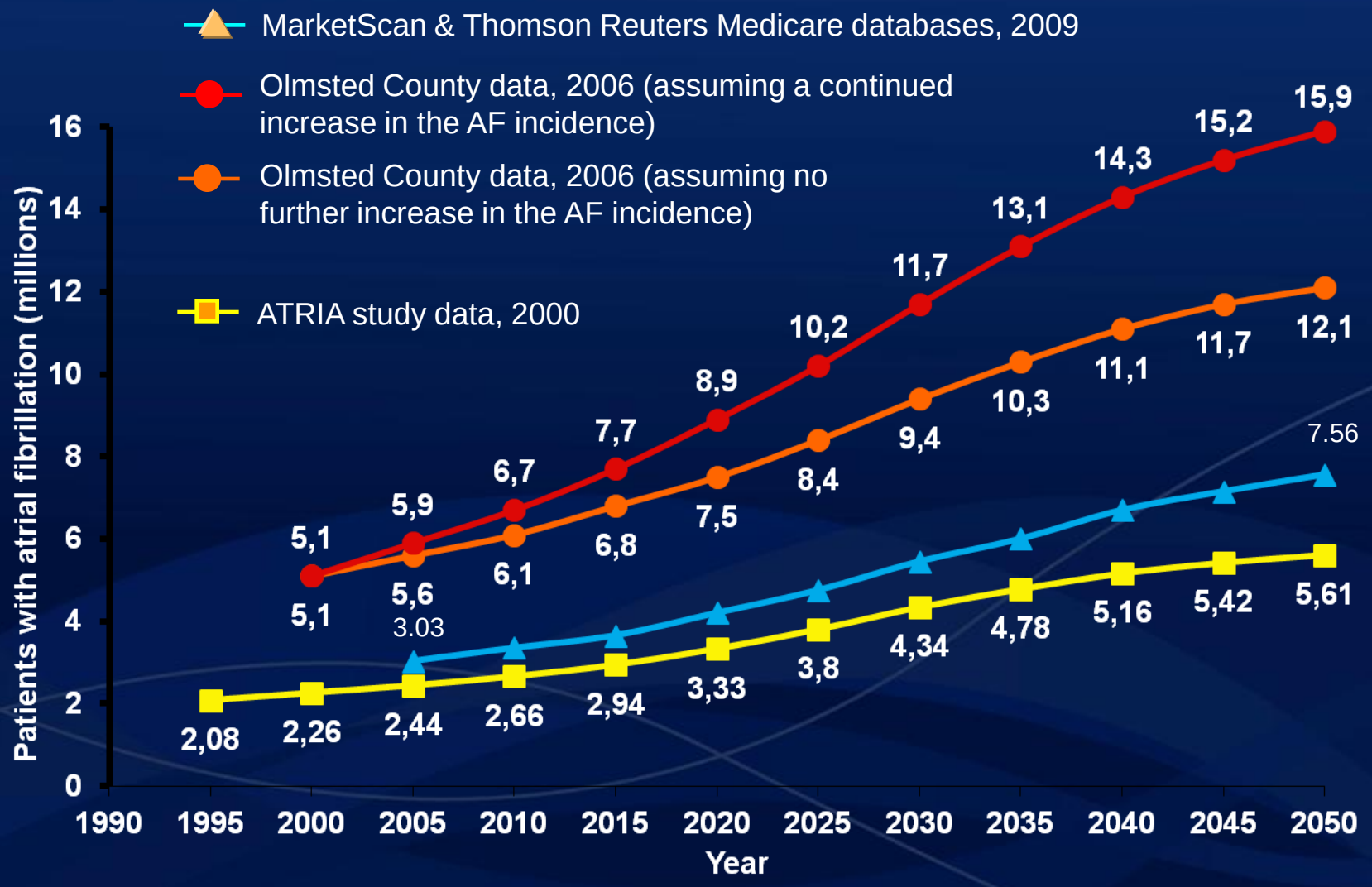
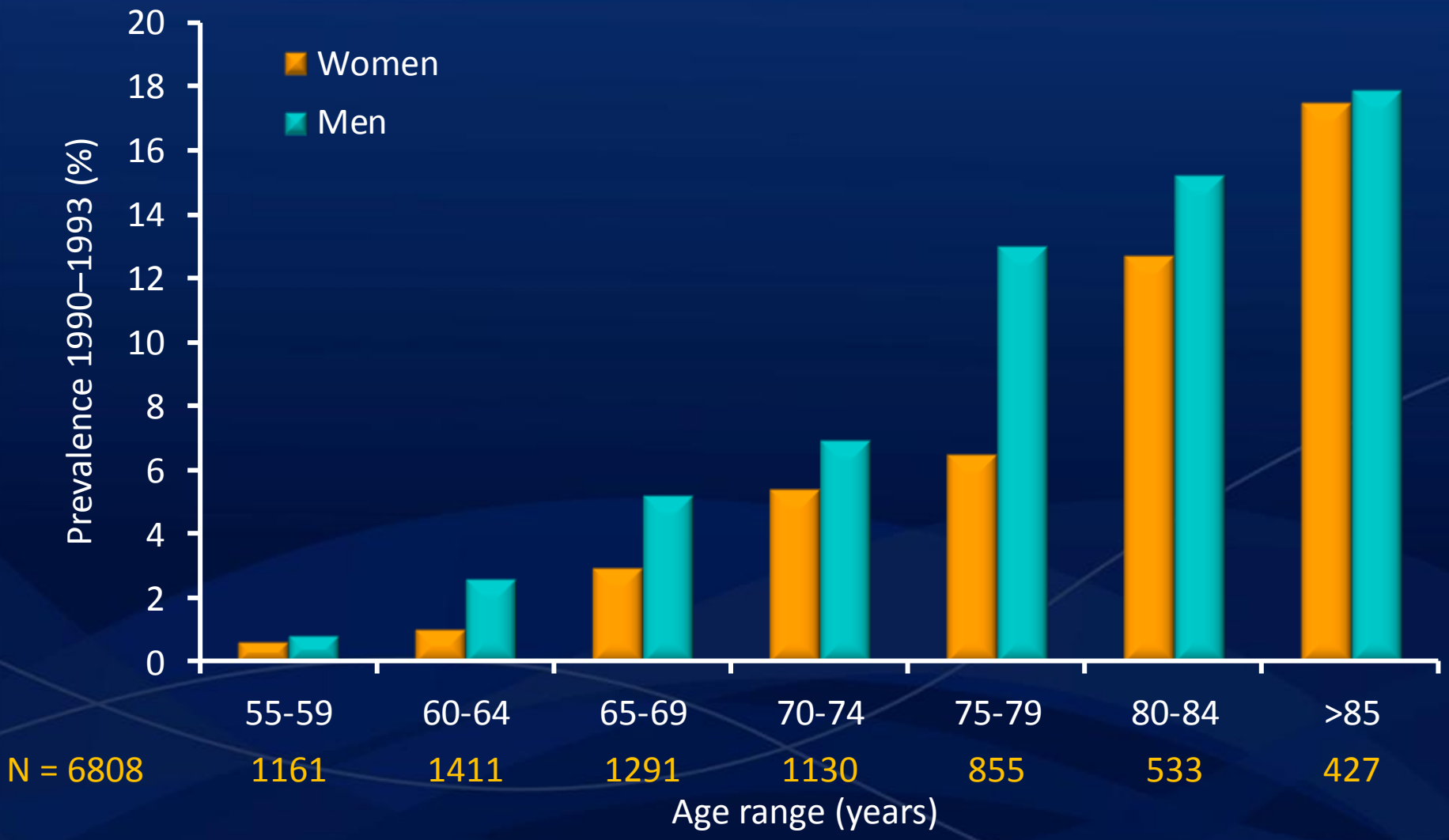
Projected Number of Patients With AF by 2050

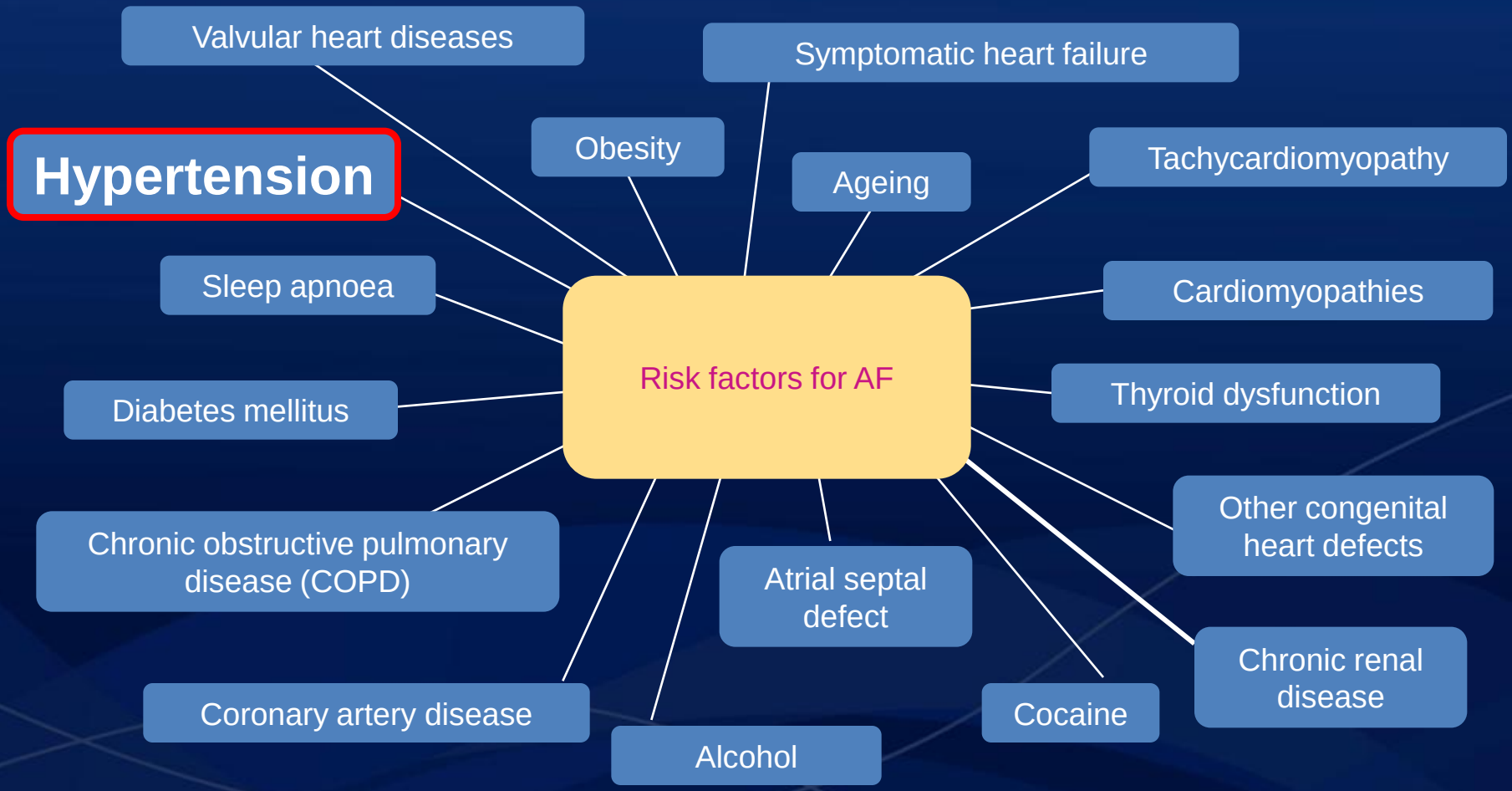


Increasing Prevalence of AF with age



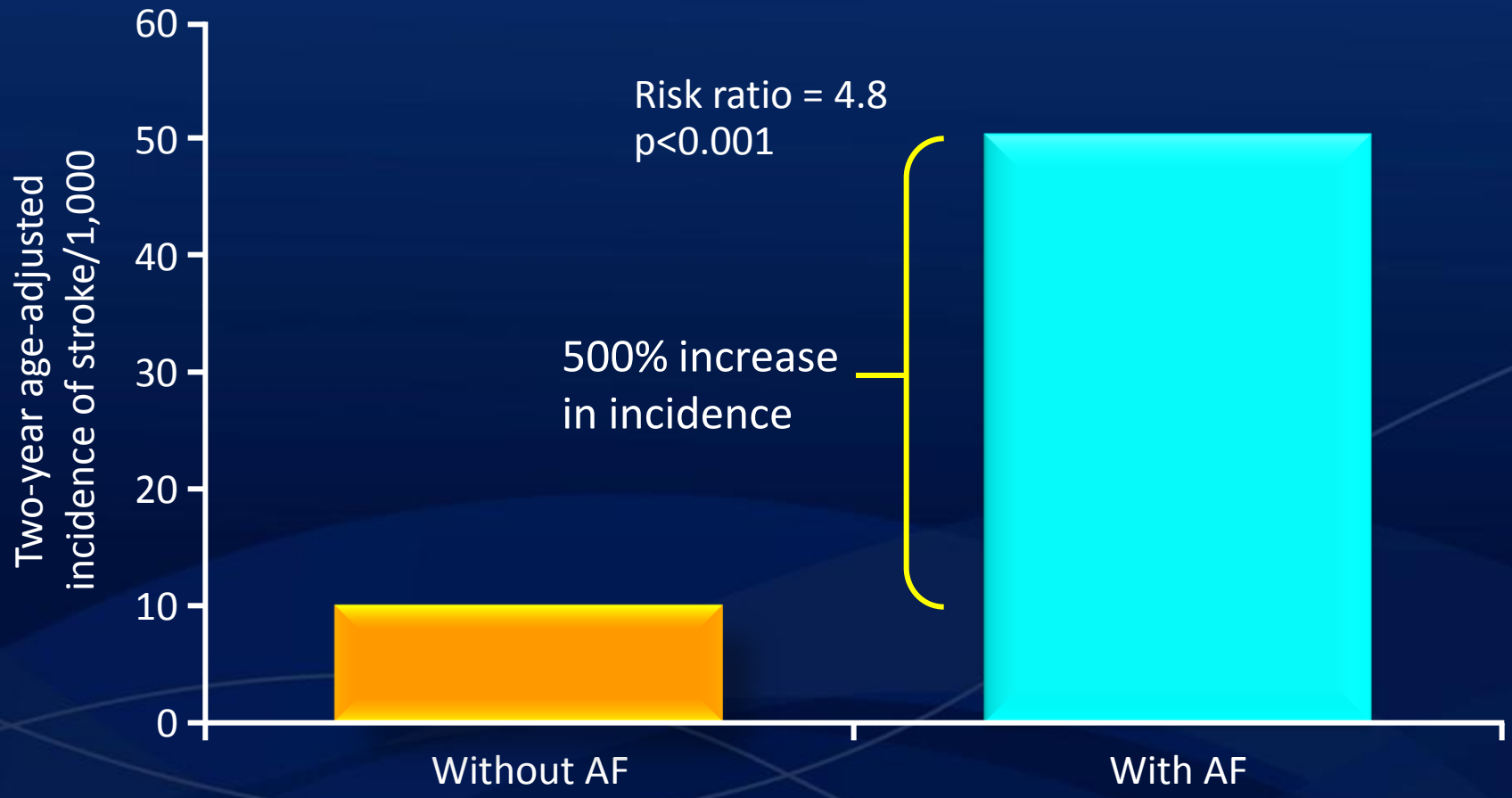
Heeringa et al. Eur Heart J 2006;27:949–53

Risk factors for AF



ESC Guidelines. Eur Heart J 2010;31:2369–429; Heart Rhythm Society. What is atrial fibrillation? http://www.hcahamilton.com/downloads/documentdownloads/AtrialFibrillationOvervie_1.pdf, last accessed 13 January 2012; Ettinger et al. Am Heart J 1978;95:555–62

The incidence of ischaemic stroke is increased fivefold in AF patients

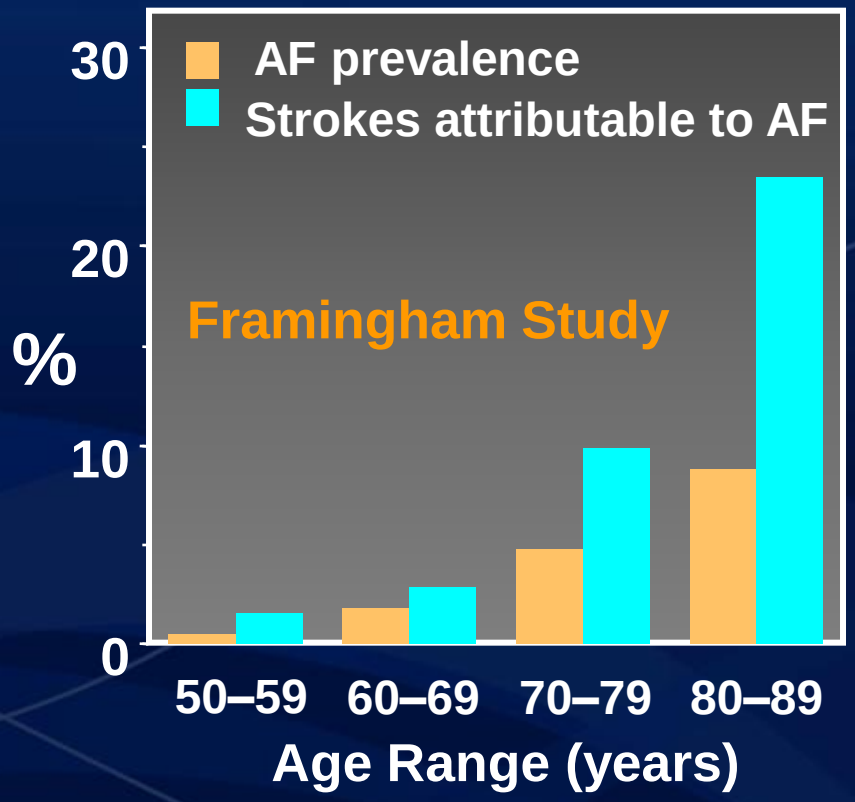


Wolf et al. Stroke 1991;22:983–8

Risk of Stroke in Atrial Fibrillation

Placebo Stroke Rate – 4.5%/yr
1 of 6 strokes attributable to AF

- Previous stroke/TIA 2.5
- History of hypertension 1.6
- Advanced age (continuous)1.4/10 yr
- Diabetes mellitus 1.7
- History of CHF 1.4



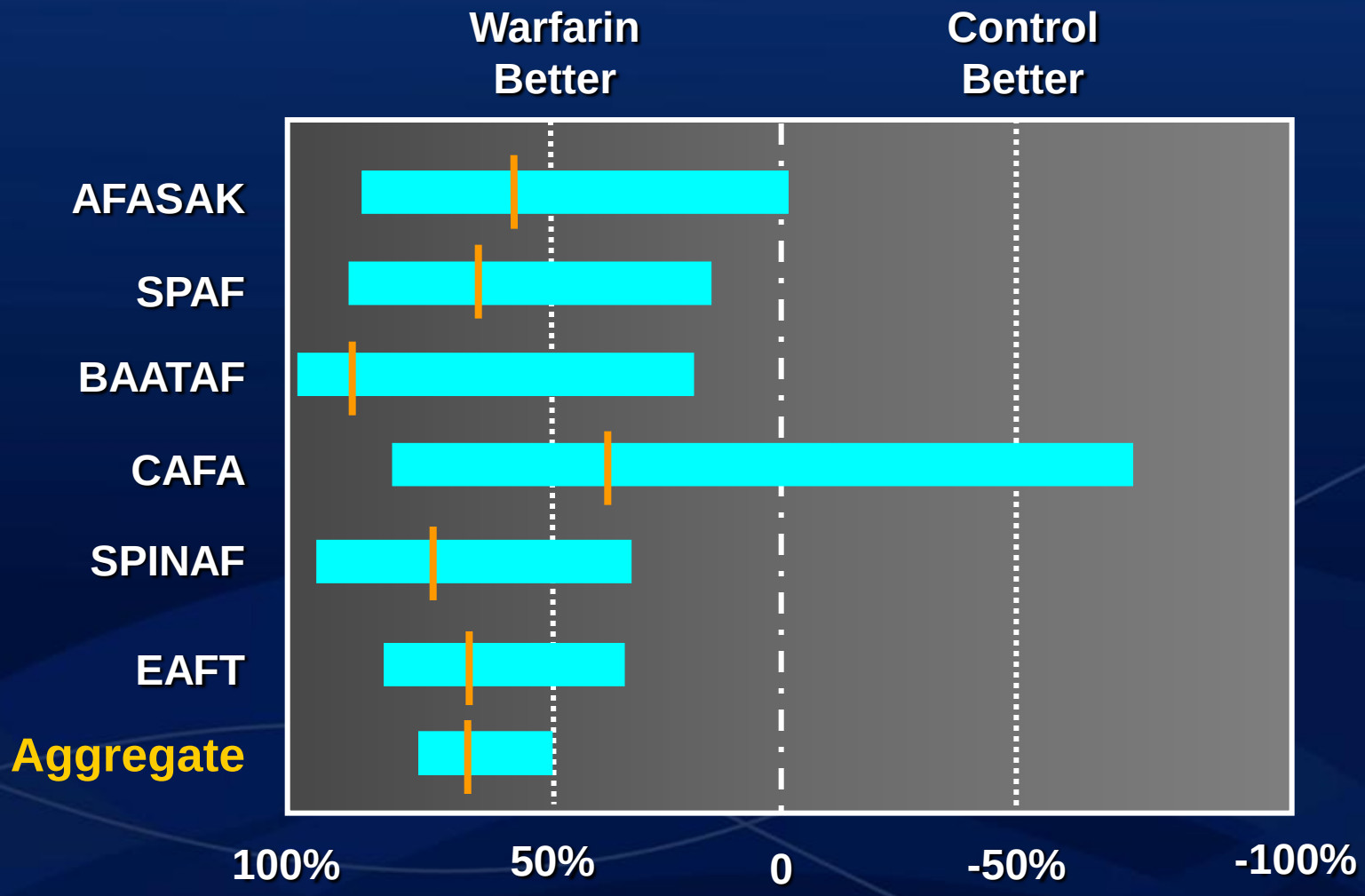
Collaborative Analysis–AFib Investigators. Arch Intern Med. 1994;154:1449-1457.

Wolf et al. Stroke 1991;22:983-988.

Stroke - Europe

- 2 million strokes each year
- €38 billion per annum
  - will double by 2050
- 20% of all strokes attributable to AF
- 6 million Europeans have AF
  - will double by 2050
- AF increases the risk of stroke five fold
- Stroke with AF is 50% fatal within one year
  - others remain severely disabled

Warfarin Anticoagulation in Atrial Fibrillation Stroke Risk Reduction



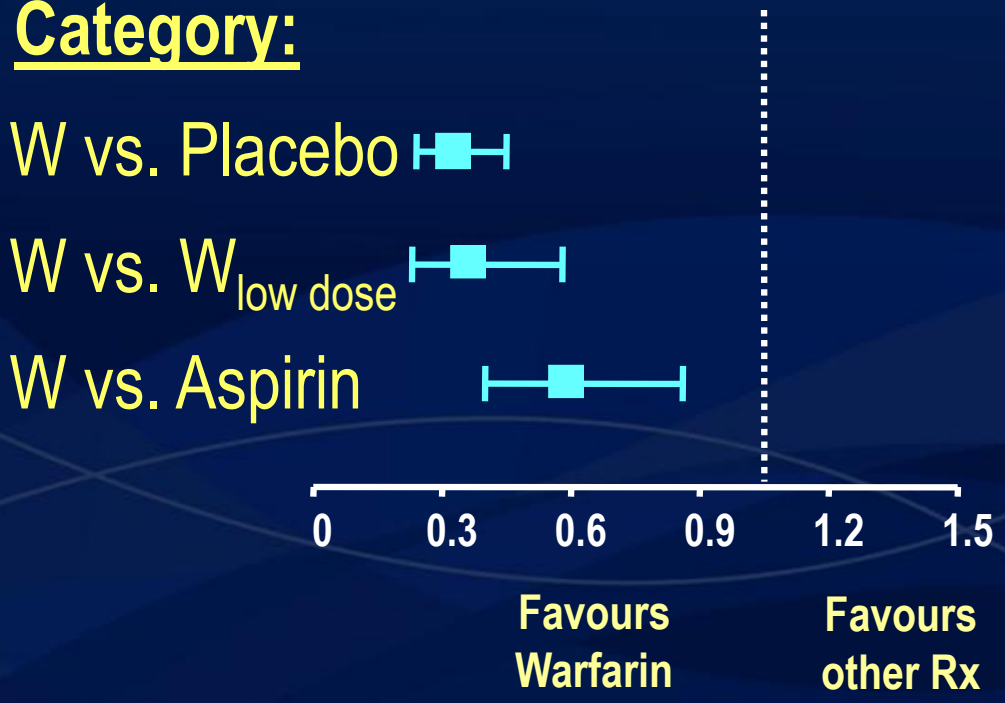
Hart R, et al. Ann Intern Med 1999;131:492

Stroke Prevention with Aspirin and Warfarin

Meta-analysis

Meta-analysis of ischaemic stroke or systemic embolism

Category:

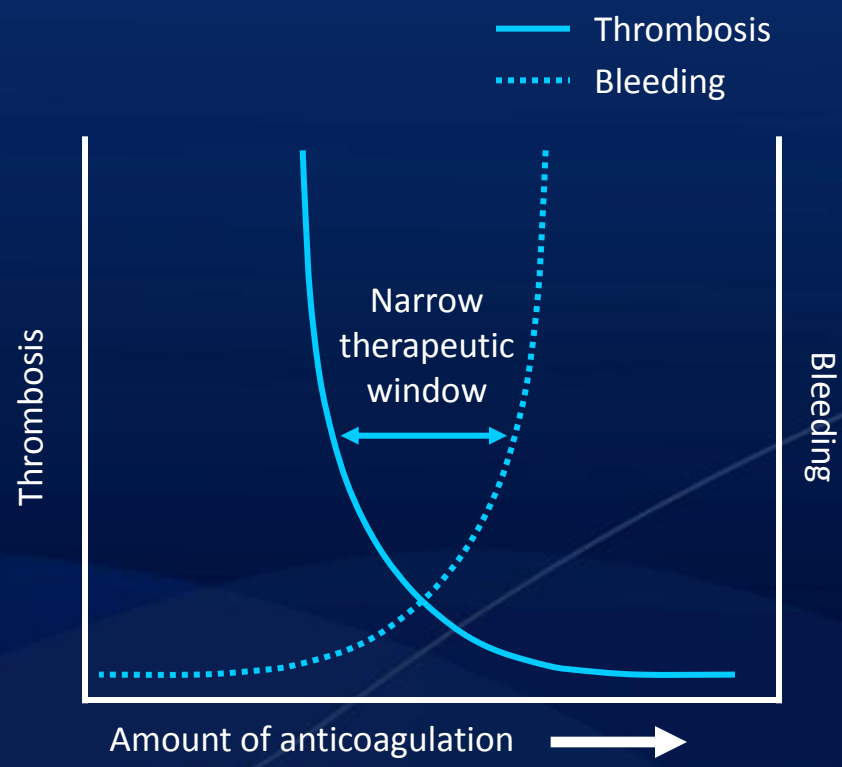


Study	Year	Size	Comparator	IS/SE
AFASAK-I	1989	1007	W, A, P	44
BAATAF	1990	420	W, P	15
CAFA	1991	378	W, P	18
SPAF I	1991	421	W, P	24
SPINAF	1992	525	W, P	30
EAFT	1993	439	W, P	75
SPAF II	1994	715	W, A	35
SPAF II eld.	1994	385	W, A	32
SPAF III	1996	1044	W, W_{ld}+A	55
AFASAK II	1998	677	W, A, W_{ld}, W_{ld}+A	26
MWNAF	1998	303	W, W_{ld},	7
PATAF	1999	394	W, A, W_{ld}	14
Evans	2001	386	W, A	52

Lip GYH et al, 2005

Limitations of vitamin K antagonists (VKAs)

- Unpredictable pharmacology and physiologic response
- Narrow therapeutic window
  - Difficult to keep within therapeutic INR range
- Multiple drug–drug and food–drug interactions
- Frequent dose adjustments in the initial phase of therapy



Adapted from Ansell et al. Chest 2008 133:160S–198S; Eriksson. Annu Rev Med 2011;62:41–57; Turpie. Eur Heart J 2007;29:155–165

Selecting appropriate antithrombotic therapy for a patient is an important management decision in AF

BALANCING RISK

Stroke

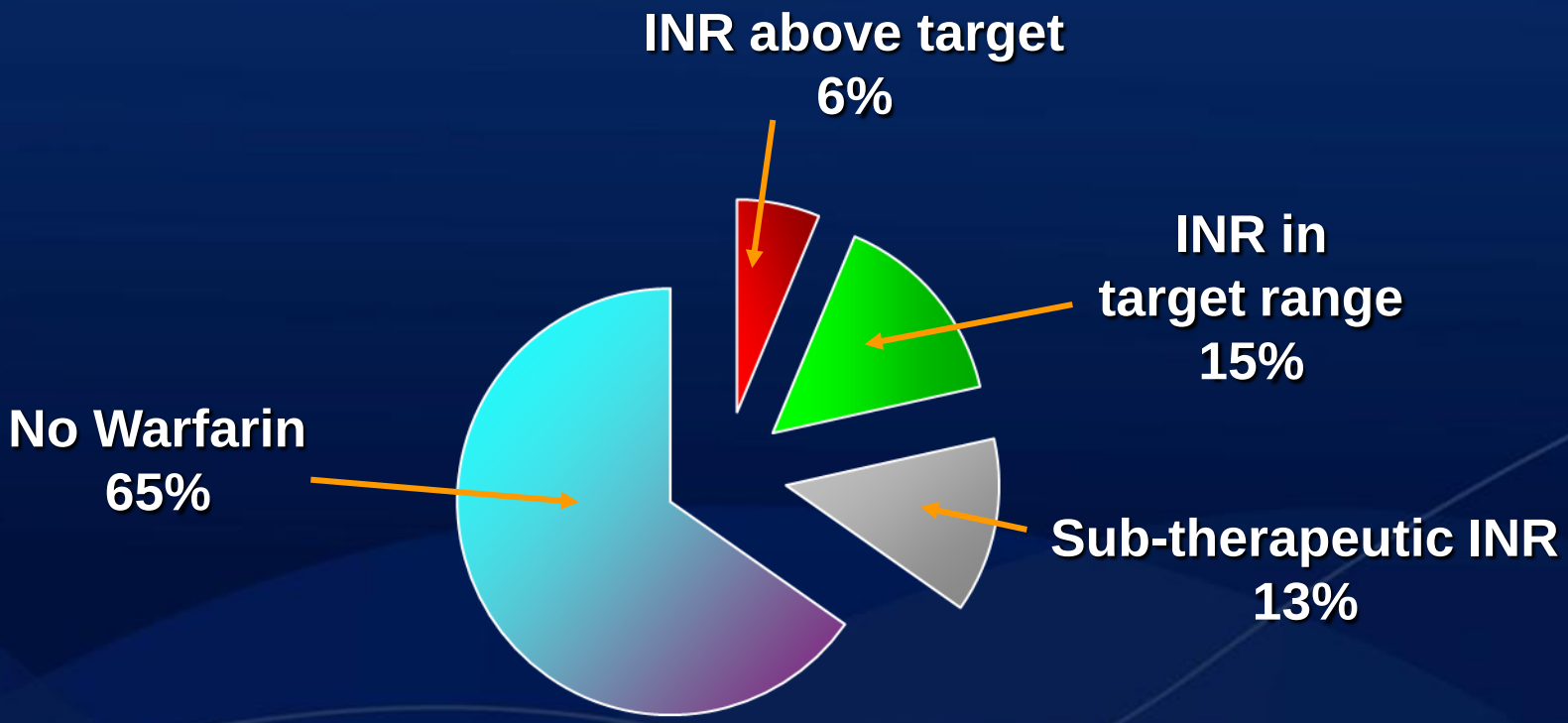
Bleeding

Aim: reducing the risk of thrombotic events with an acceptable increase in bleeding complications

Fang MC. Ann Intern Med 2011;155:636-7.

Inadequate VKA Treatment for AF

Adequacy of Anticoagulation in Patients with AF in Primary Care Practice



50:50:50 Rule

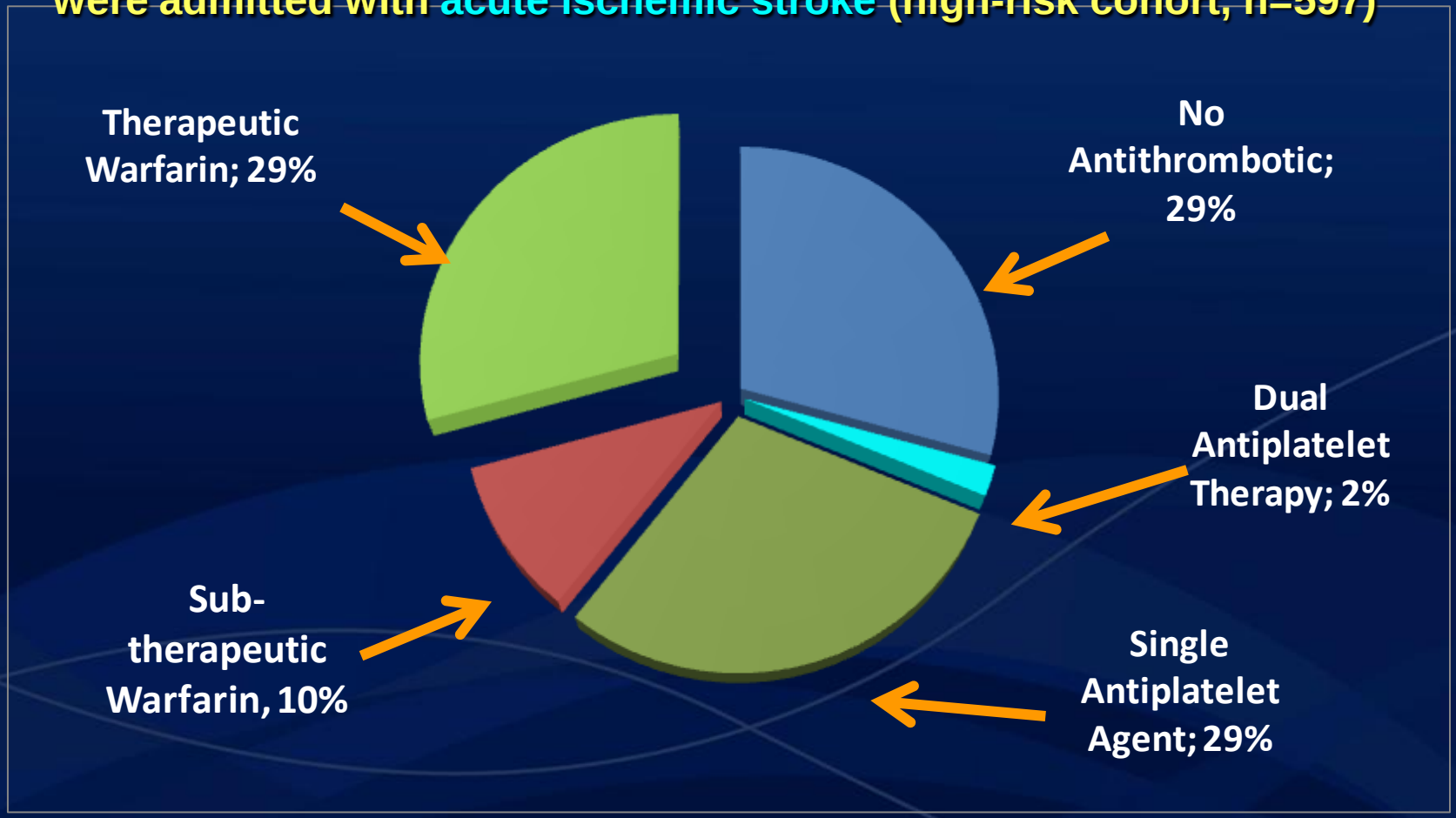
50% of eligible are prescribed warfarin; 50% discontinue; only 50% in therapeutic range

50% → 25% → 12.5%

Samsa GP, et al. Arch Intern Med 2000;160:967.

Missed Opportunities for Stroke Prevention in Atrial Fibrillation

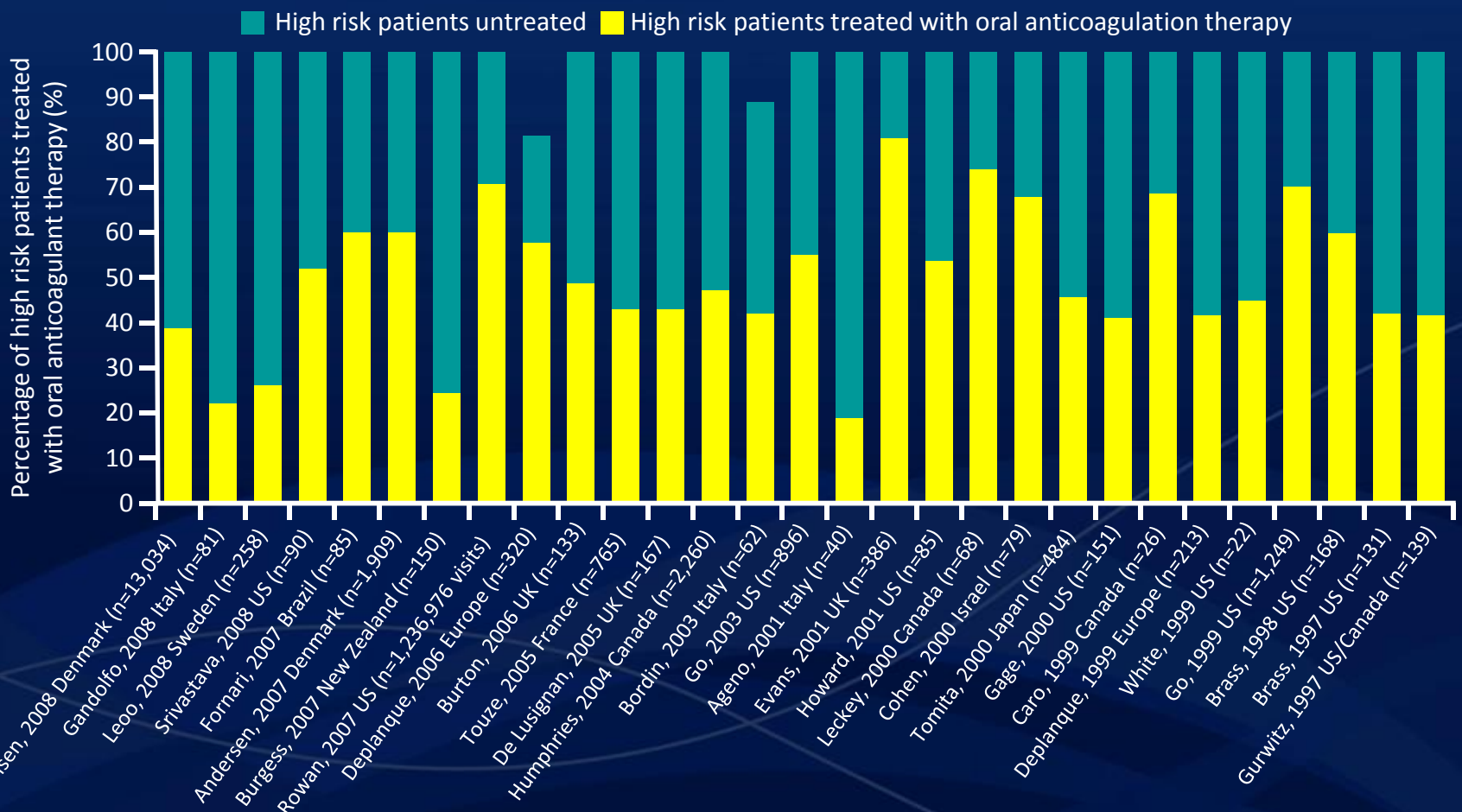
Preadmission medications in patients with known atrial fibrillation who were admitted with acute ischemic stroke (high-risk cohort, n=597)



Gladstone, D. J. et al. Stroke 2009;40:235-240

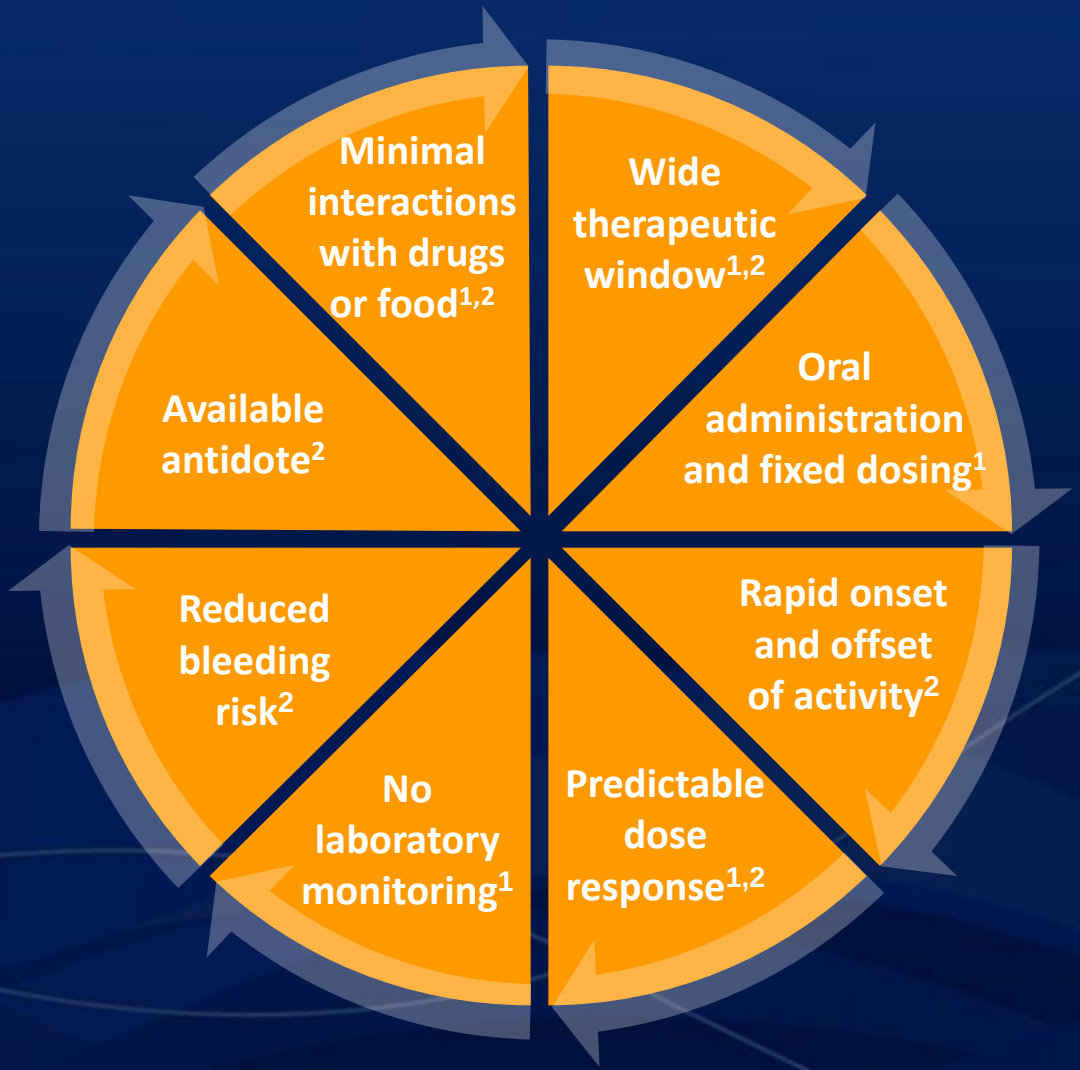
Underutilization of VKA is a global issue

- A recent systematic literature review showed that OAC use was underutilized among patients with AF and prior stroke/TIA without contradictions to OACs



Ogilvie et al. Am J Med 2010;123;638–645

Profile of the ideal anticoagulant: the clinicians view

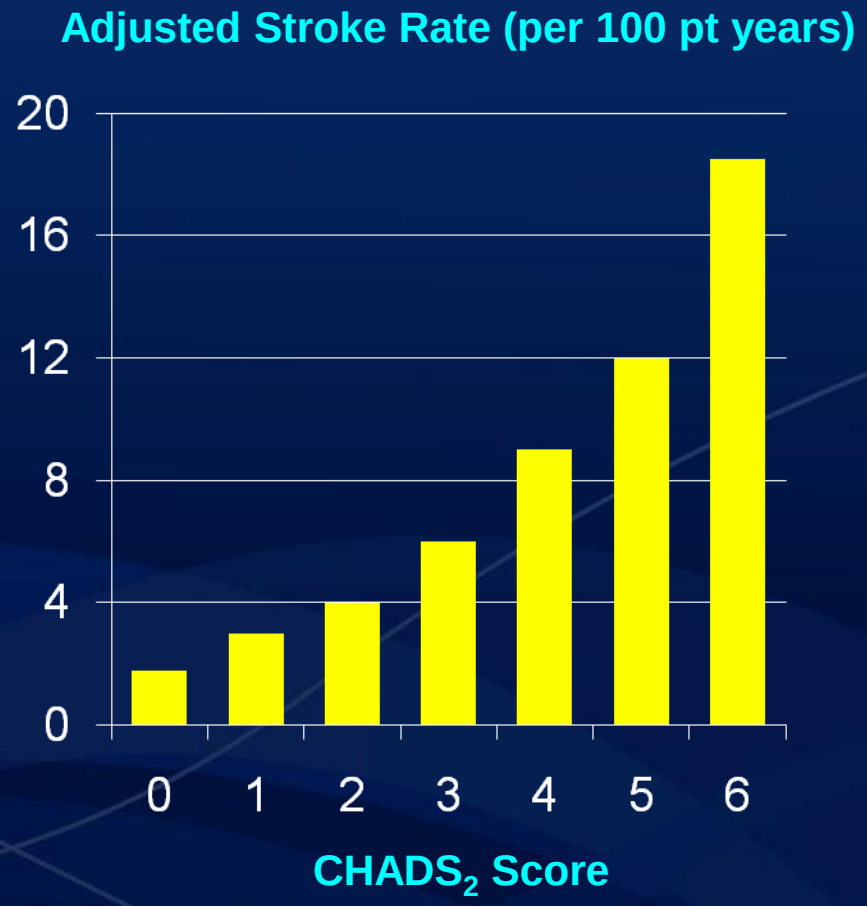


Adapted from 1. Turpie. Eur Heart J 2007;29:155–165; 2. Bauer et al. J Thromb Thrombolysis 2006;21:67-72

Atrial Fibrillation

Stratification of stroke risk: $CHADS_2$ score

	Score
CHF or LV dysfunction	1
Hypertension	1
Age > 75 years	1
Diabetes	1
Stroke/TIA	2



Gage BF et al. JAMA 2001;285: 2864–2870

Antithrombotics in Atrial Fibrillation

Stroke 4 - 5 x more common in patients with atrial fibrillation
One sixth of all strokes are attributable to atrial fibrillation

$CHADS_2$ Score	Situation	Recommendations
0	No known risk factors	None or aspirin
1	One moderate RF (age> 75, HF (or LVEF <35%), hypertension (?LVH), diabetes mellitus	Aspirin or Warfarin
≥ 2	More than one moderate RF	Warfarin

High risk factors: rheumatic mitral stenosis, previous thromboembolism

Less well validated risk factors = age 65-74 years, coronary artery disease, thyrotoxic basis, female gender

Other factors: peripheral vascular disease, chronic renal failure

CHA_2DS_2-VASc

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease	1
Age 65-74	1
Sex category (i.e. female sex)	1
Maximum score	9

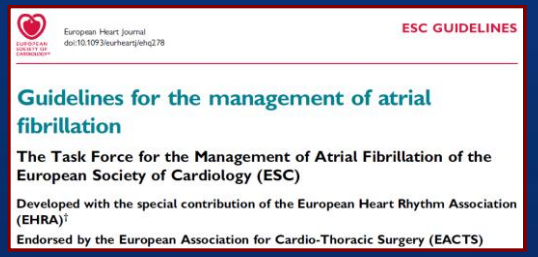
The HAS-BLED bleeding risk score

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

*Hypertension is defined as systolic blood pressure > 160 mmHg.

INR = international normalized ratio.

Fibrilación auricular. ESC 2010



Highlights

1. Presentación clínica y diagnóstico
2. Refinamiento riesgo tromboembolismo y hemorragia
3. Nuevas recomendaciones de tratamiento
4. Ablación como método de tratamiento

CHA_2DS_2-VASc	Score
CHF	1
HTA	1
Age ≥ 75	2
Diabetes	1
Stroke/AIT/TE	2
Enfermedad Vascular	1
Age 65-75	1
Sexo (i.e. femenino) < 75	1

CHA_2DS_2-VASc		Tasa ACV (% año)
0	Nada/AAS	0
1	ACO/AAS	1.3
2	ACO	2.2
3		3.2
4		4.0
5		6.7
6		9.8
7		9.6
8		6.7
9		15.2

H	Hypertension	1
A	Abnormal renal/liver	1 ó 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly (>75)	1
D	Drugs/Alcohol	1 ó 2

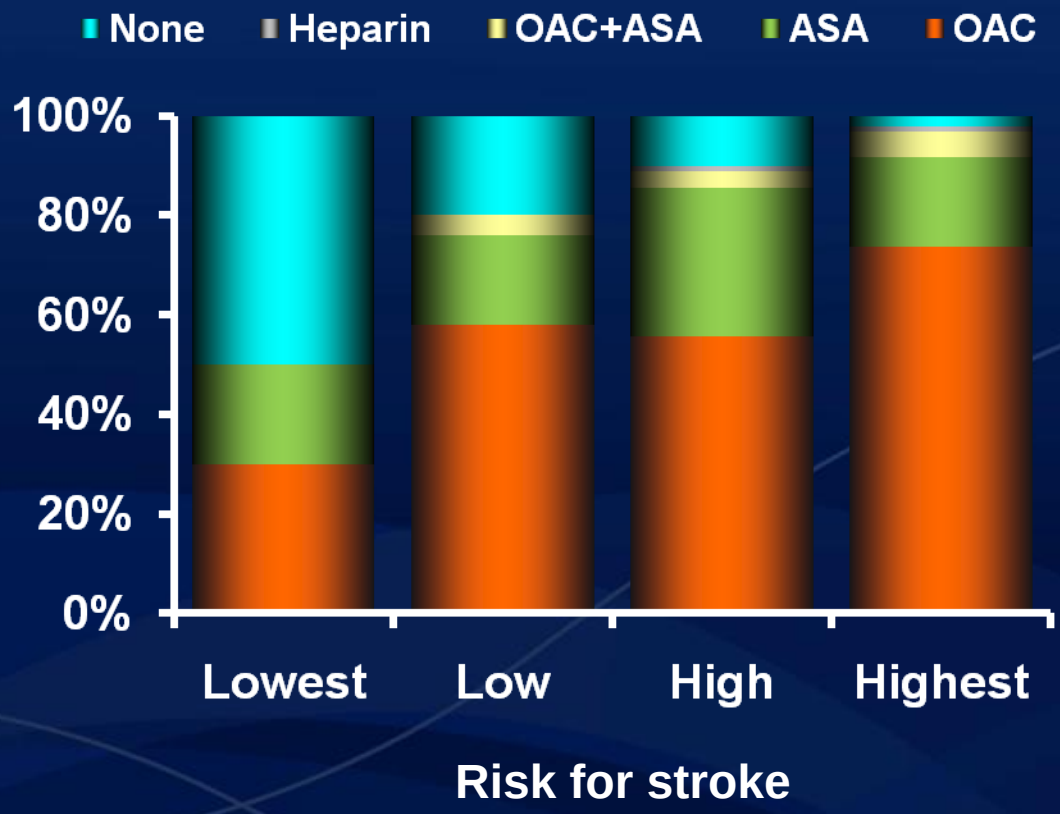
HAS-BLED ≤ 2: Dabigatran 150 mgs bid
HAS-BLED > 2: Dabigatran 110 mgs bid

Clase I nivel evidencia A

Antithrombotic Treatment in AF

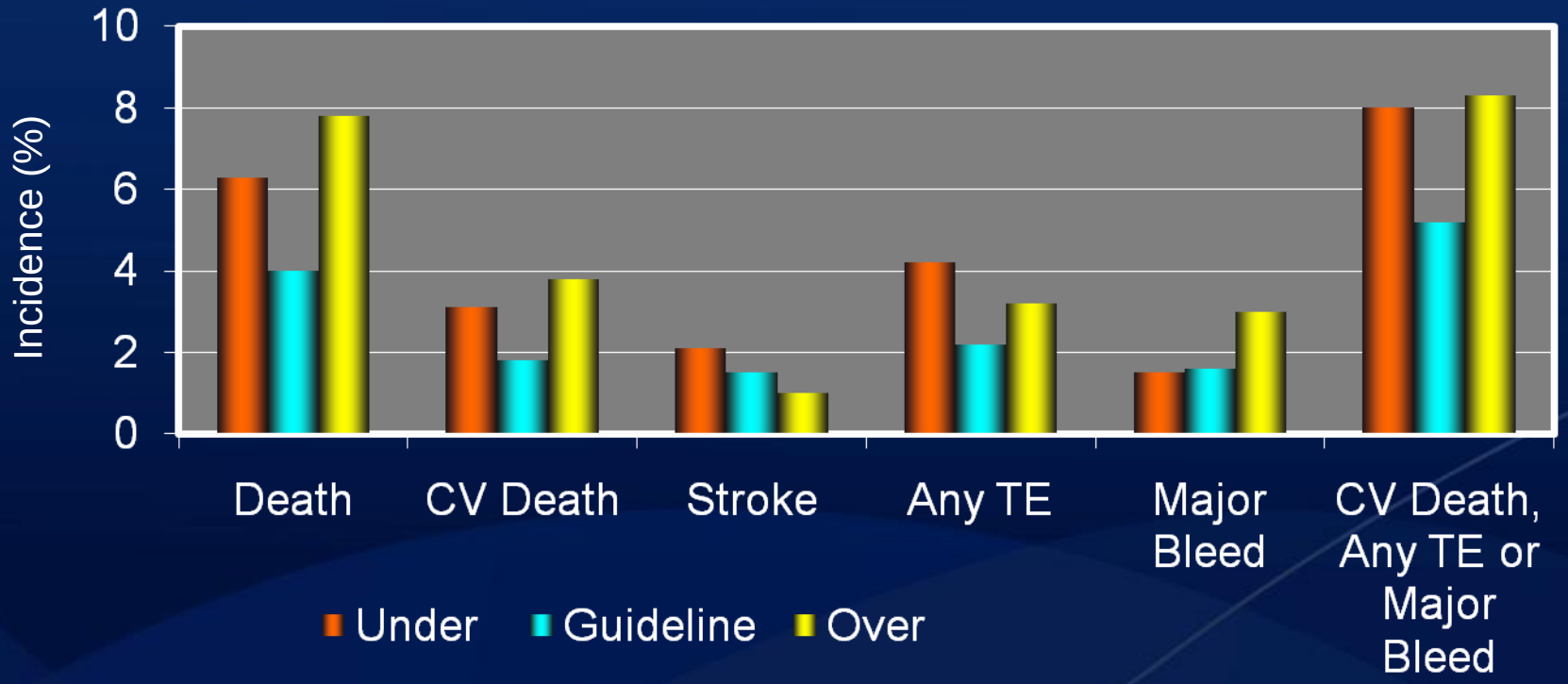
The Euro Heart Survey

- 182 hospitals
- 35 countries
- n = 5333
- 2706 (52%)
- no intervention planned



Nieuwlaat R et al EHJ 2007

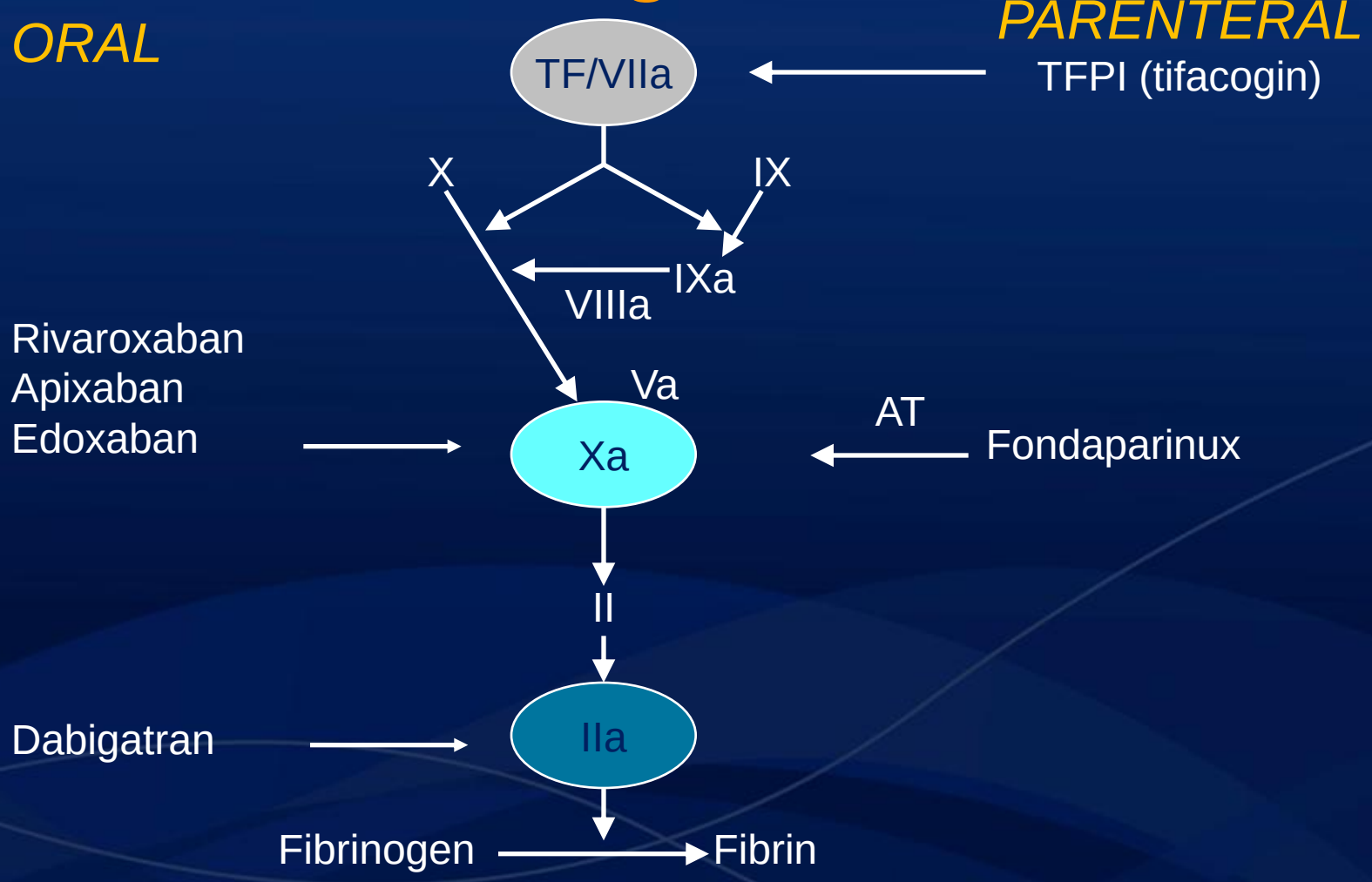
Consequences of Non-Adherence to AC Guidelines



Euro Heart Survey

Nieuwlaat R et al EHJ 2007

Mechanisms of action of existing and novel anticoagulants



AT, antithrombin; TF, tissue factor;
TFPI, tissue factor pathway inhibitor

Adapted from Weitz et al. J Thromb Haemost 2005;3:1843-1853
Agnelli et al. Thromb Res 2009;123:488-497

New Direct Thrombin Inhibitors and Factor Xa Inhibitors for AF

Medication	Action	Phase III Trial	Comparator	Design	n
Dabigatran	**DTI**	**RE-LY**	**Warfarin**	**Non-inferiority**	**18 113**
Apixaban	Anti Xa	**AVERROES**	**Aspirin**	**Superiority**	**5 600**
		ARISTOTLE	Warfarin	Non-inferiority	18 206
Rivaroxaban	Anti Xa	ROCKET AF	Warfarin	Non-inferiority	14 266
Edoxaban	Anti Xa	ENGAGE AF	Warfarin	Non-inferiority	20 500
Biotinylated Idraparinux	Anti Xa	BOREALIS AF	Warfarin	Non-inferiority	~ 9 600

Others include: Betrixaban, YM 150

PK/PD of 5 Novel Oral Agents

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Target	IIa (thrombin)	Xa	Xa	Xa	Xa
Hrs to Cmax	2	2-4	1-3	1-2	NR
CYP metabolism	None	32%	15%	<4%	None
Bioavailability	7%	80%	66%	>45%	34-47%
Transporters	P-gp	P-gp/BCRP	P-gp	P-gp	P-gp
Protein binding	35%	>90%	87%	55%	NR
Half-life	12-14h	9-13h	8-15h	8-10h	19-20h
Renal elimination	80%	66%	25%	35%	<5%
Linear PK	Yes	No	Yes	Yes	Yes

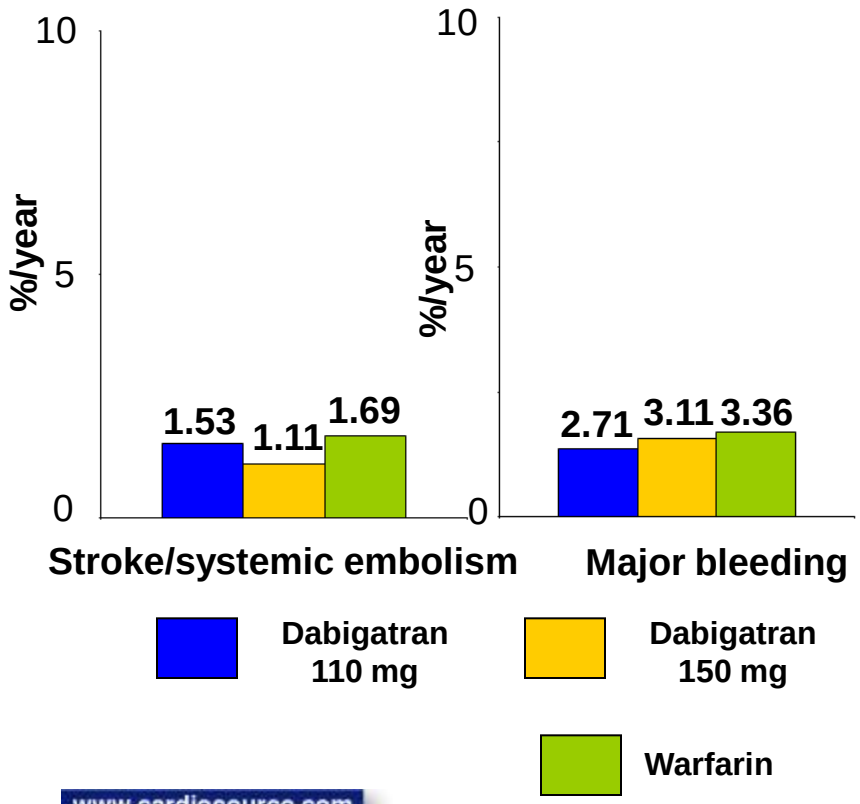
BCRP = breast cancer resistance protein; CYP = cytochrome P450; NR = not reported; P-gp = P-glycoprotein

Ruff CR and Giugliano RP. Hot Topics in Cardiology 2010;4:7-14
Ericksson BI et al. Clin Pharmacokinet 2009; 48: 1-22
Ruff CR et al. Am Heart J 2010; 160:635-41

RE−LY: Dabigatran

Trial design: Patients with AF were randomized to either dabigatran 110 mg, 150 mg, or open-label warfarin. Patients were followed for a mean of 2 years.

*Dabigatran 150 mg vs. warfarin; †Dabigatran 110 mg vs. warfarin



Results

- Dabigatran 150 mg superior to warfarin for stroke/systemic embolism; dabigatran 110 mg was non-inferior
- Stroke ↓ in dabigatran 150 mg arm ($p < 0.001$)
- Major bleeding was higher in warfarin arm compared with dabigatran 110 mg, but was similar to dabigatran 150 mg

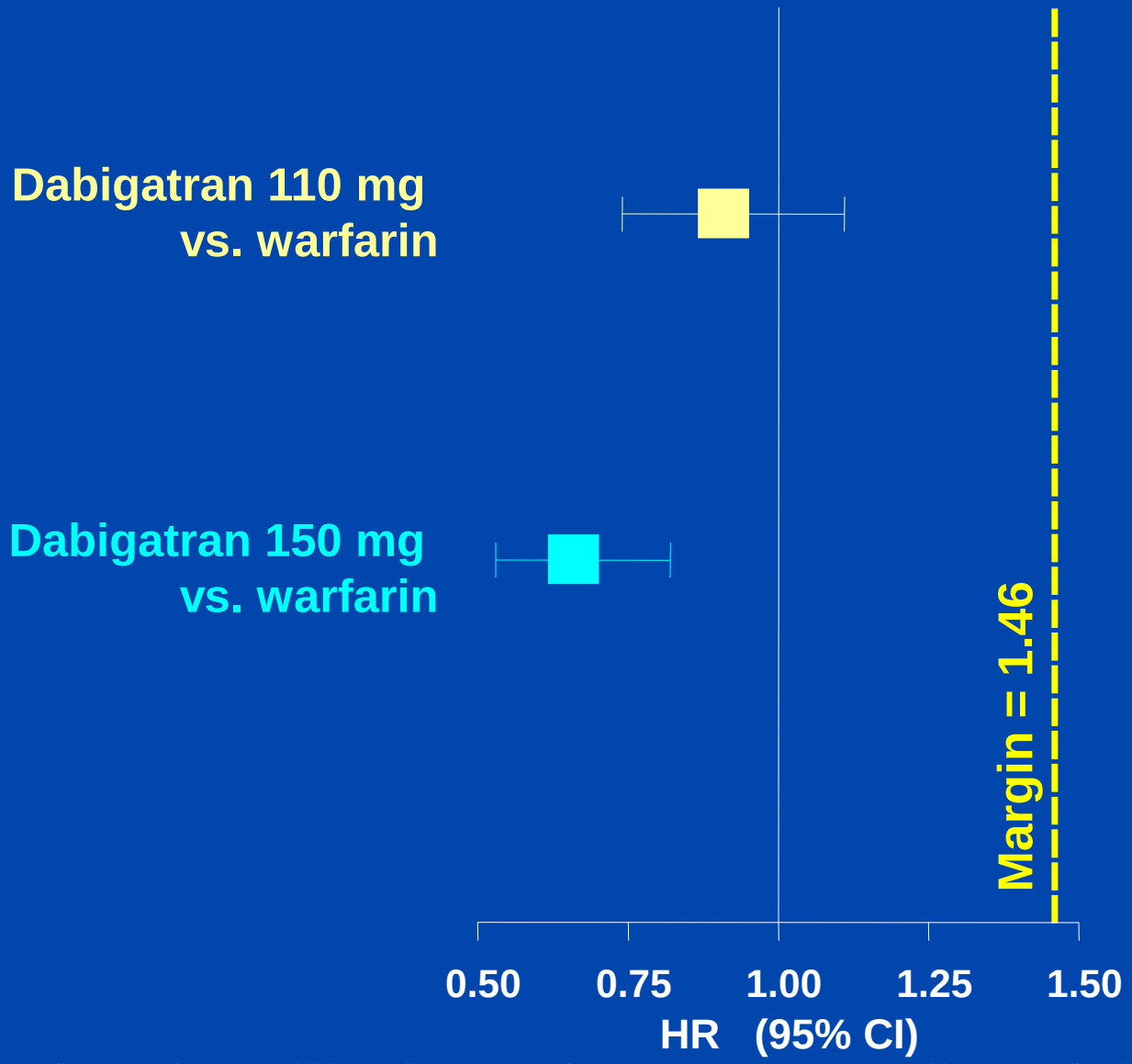
Conclusions

- Dabigatran 150 mg superior to warfarin in reducing stroke or systemic embolism, with a similar bleeding profile. The 110 mg dose was non-inferior for efficacy, associated with lower bleeding compared with warfarin
- Could prove to be alternative to warfarin for chronic anticoagulation; further data are awaited

Connolly SJ, et al. N Engl J Med 2009;Aug 30:[Epub]

Stroke or systemic embolism (SSE)

RELY®
Study of stroke prevention in atrial fibrillation



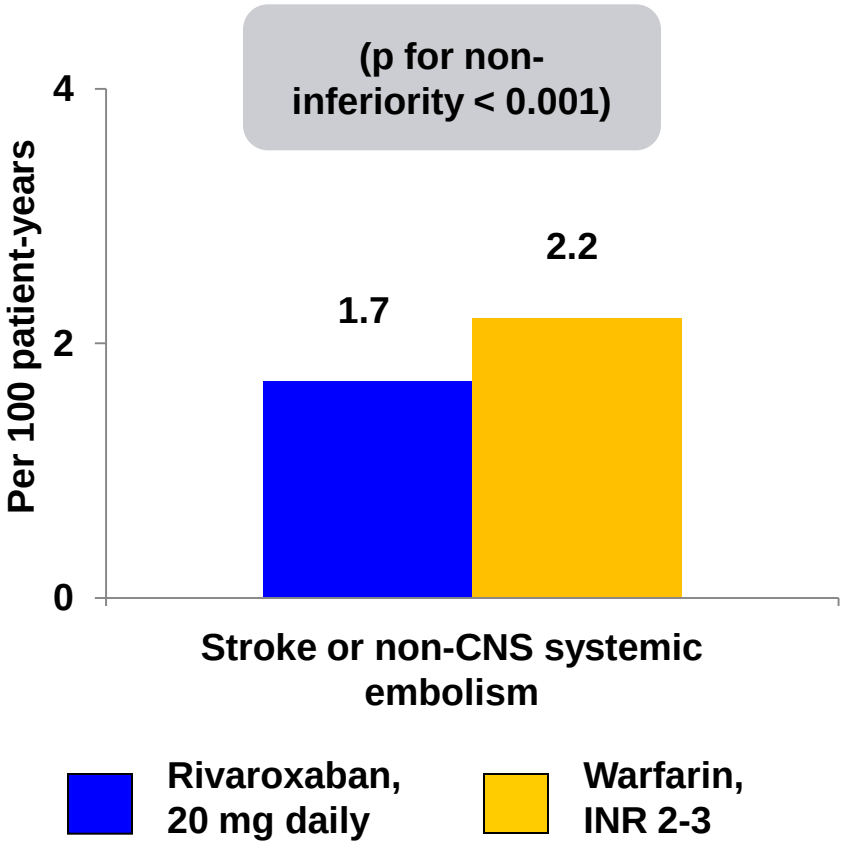
	Noninferiority p-value	Superiority p-value
Dabigatran 110 mg vs. warfarin	<0.001	0.34
Dabigatran 150 mg vs. warfarin	<0.001	<0.001

Connolly SJ., et al. *NEJM* published online on Aug 30th 2009.
DOI 10.1056/NEJMoa0905561

Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation

ROCKET AF – Rivaroxaban

Trial design: Patients with atrial fibrillation at increased risk for stroke were randomized to the direct factor Xa inhibitor rivaroxaban 20 mg oral daily (n = 7,131) vs. warfarin with target INR 2-3 (n = 7,133).



Results

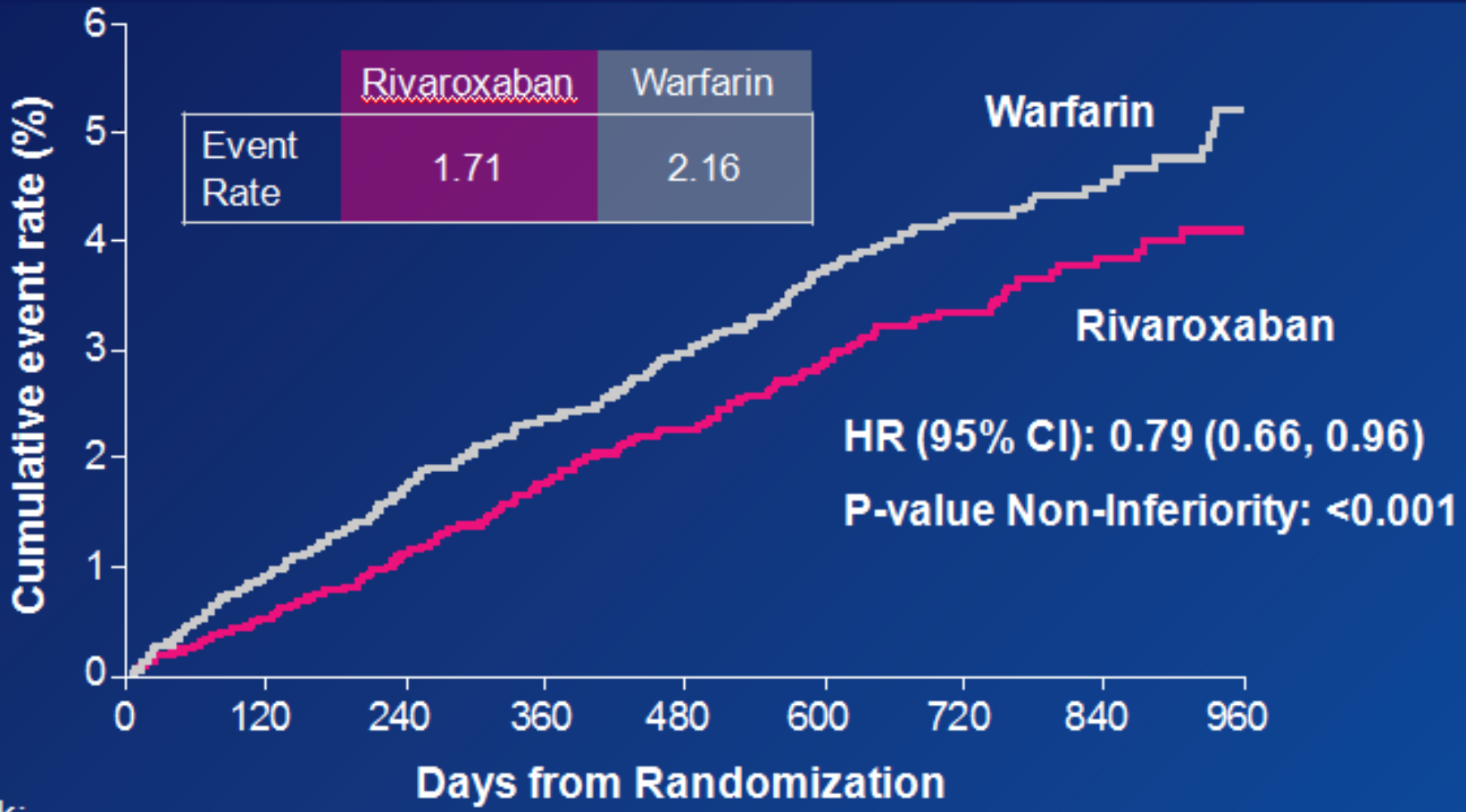
- Stroke or non-CNS systemic embolism (per 100 patient-years): 1.7 with rivaroxaban vs. 2.2 with warfarin (p for noninferiority < 0.001, p for superiority = 0.12 by intention to treat analysis, p for superiority = 0.015 by on-treatment analysis)
- Major and nonmajor clinically relevant bleeding (per 100 patient-years): 14.9 vs. 14.5 (p = 0.44)
- Intracranial hemorrhage (per 100 patient-years): 0.5 vs. 0.7 (p = 0.019)

Conclusions

- Among atrial fibrillation patients with high stroke risk, rivaroxaban was noninferior to warfarin
- Rivaroxaban (on-treatment analysis) was associated with a reduced incidence of the primary outcome without an excess of major bleeding or intracranial hemorrhage

Patel MR, et al. N Engl J Med 2011;Aug 10:[Epub]

Primary Efficacy Outcome
Stroke and non-CNS Embolism



No. at risk:

Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

ROCKET AF

Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

ARISTOTLE

Inclusion risk factors
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Randomize
double blind, double dummy
(n = 18,201)

Major exclusion criteria
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

Apixaban 5 mg oral twice daily
(2.5 mg BID in selected patients)

Warfarin
(target INR 2-3)

Warfarin/warfarin placebo adjusted by INR/sham INR
based on encrypted point-of-care testing device

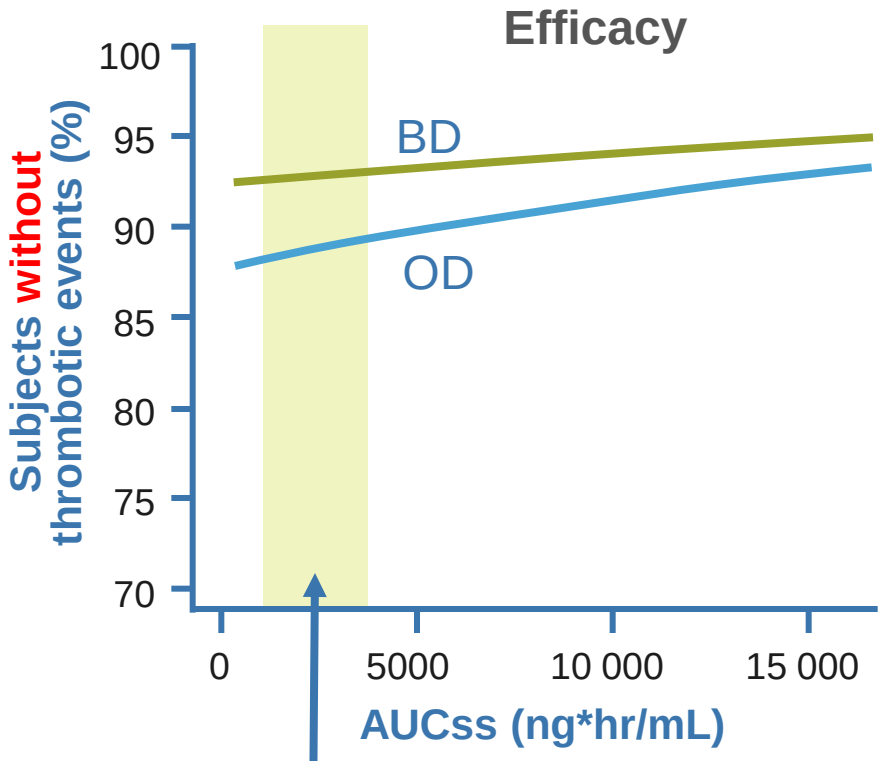
Primary outcome: stroke or systemic embolism

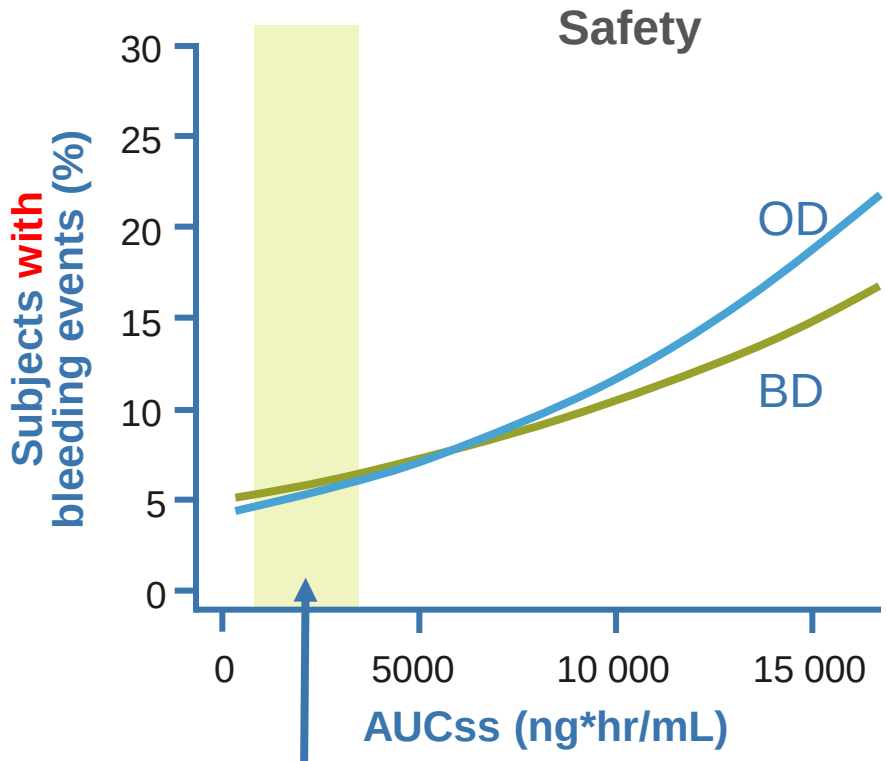
Hierarchical testing: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

Lopes RD, Am Heart J 2010;159:331-9

The choice of the apixaban BD dosage regimen in all studied indications is based on a clear rationale:

to maximise efficacy without increasing bleeding risk



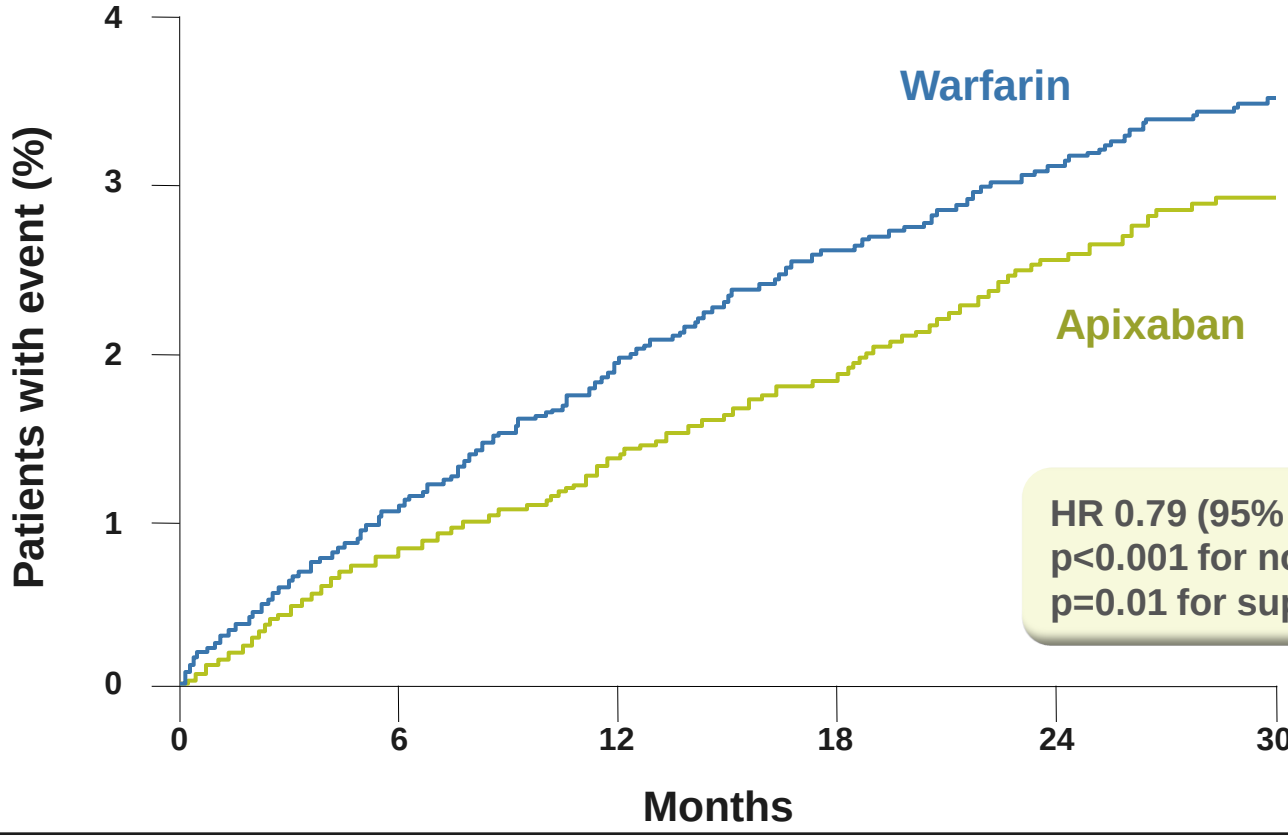


Exposure range (2.5th-97.5th percentile) for 2.5 mg BD dosing regimen

AUCss: Area under the plasma concentration-time curve at steady state

Adapted from Feng Y et al. Poster presented at: 21st Congress of ISTH; July 2007; Geneva, Switzerland. Poster P-M-663.

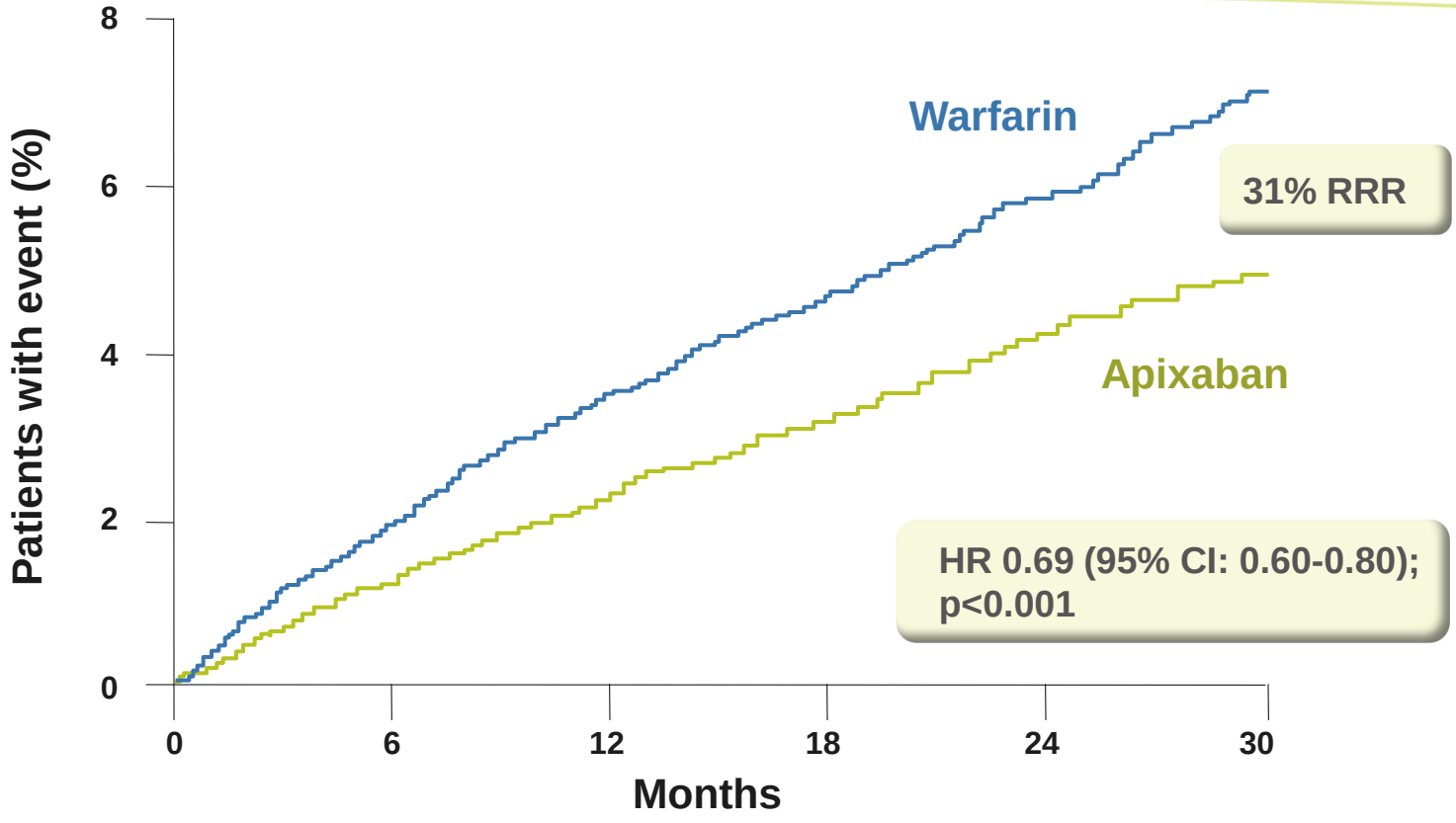
ARISTOTLE: Apixaban was superior to warfarin in preventing stroke or systemic embolism



No. at risk						
Apixaban	9,120	8,726	8,440	6,051	3,464	1,754
Warfarin	9,081	8,620	8,301	5,972	3,405	1,768

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

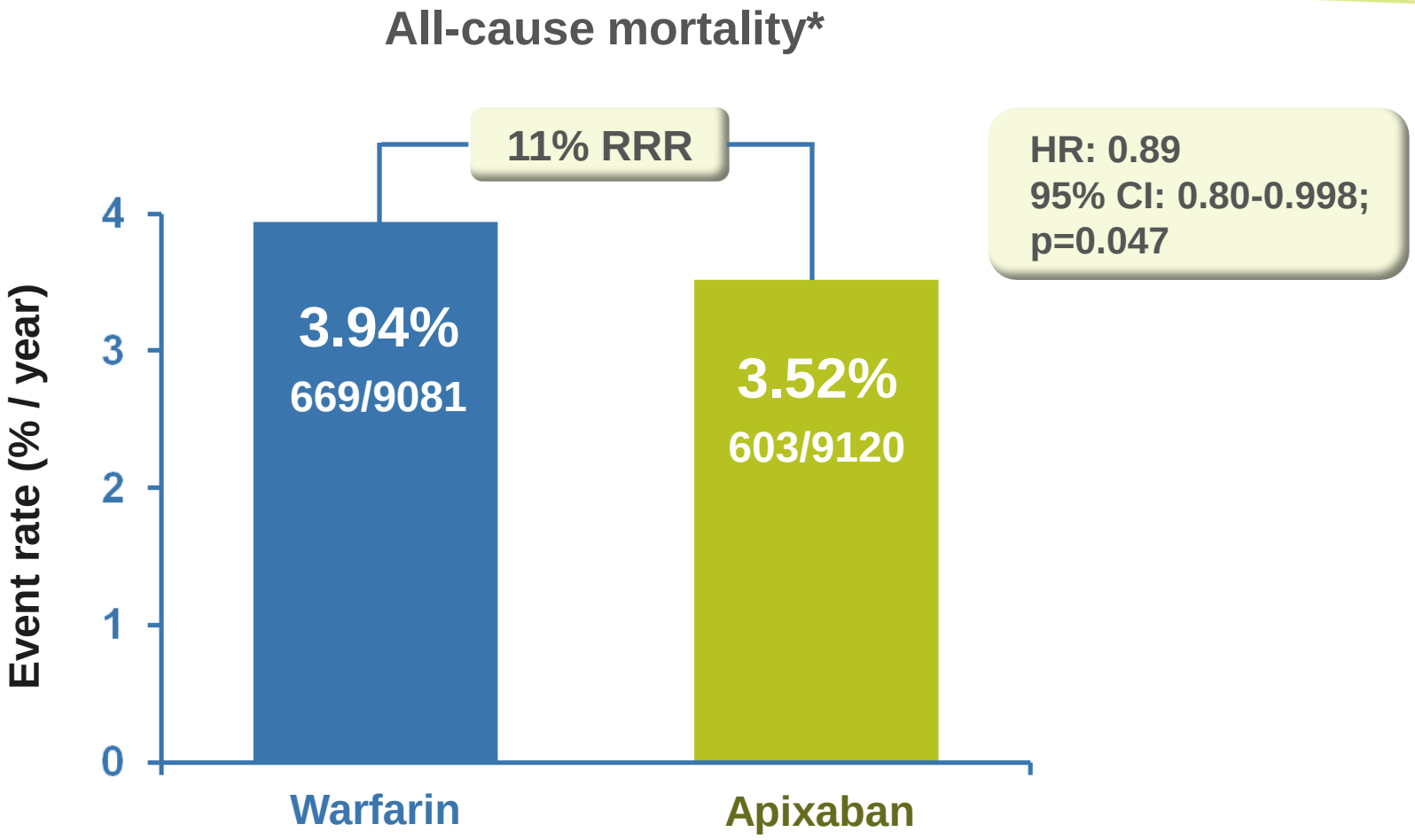
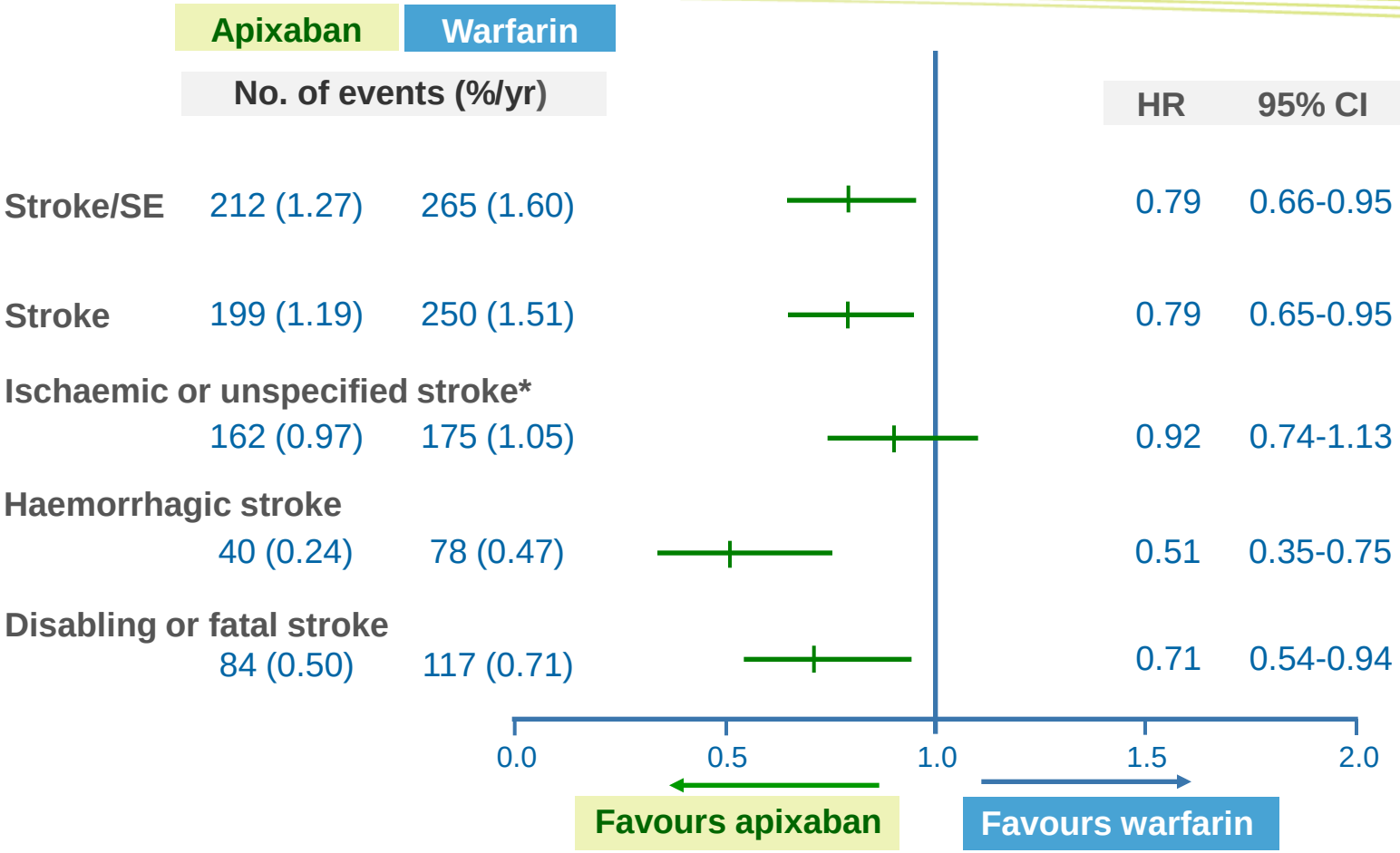


Figure created from data in Granger et al. N Engl J Med 2011;365:981-92.

*Key secondary efficacy endpoint

ARISTOTLE: Efficacy according to type of stroke



**Unknown type of stroke occurred in 14 patients in the apixaban group and 21 patients in the warfarin group. Among patients with ischemic strokes, hemorrhagic transformation occurred in 12 patients with apixaban and 20 with warfarin.*

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

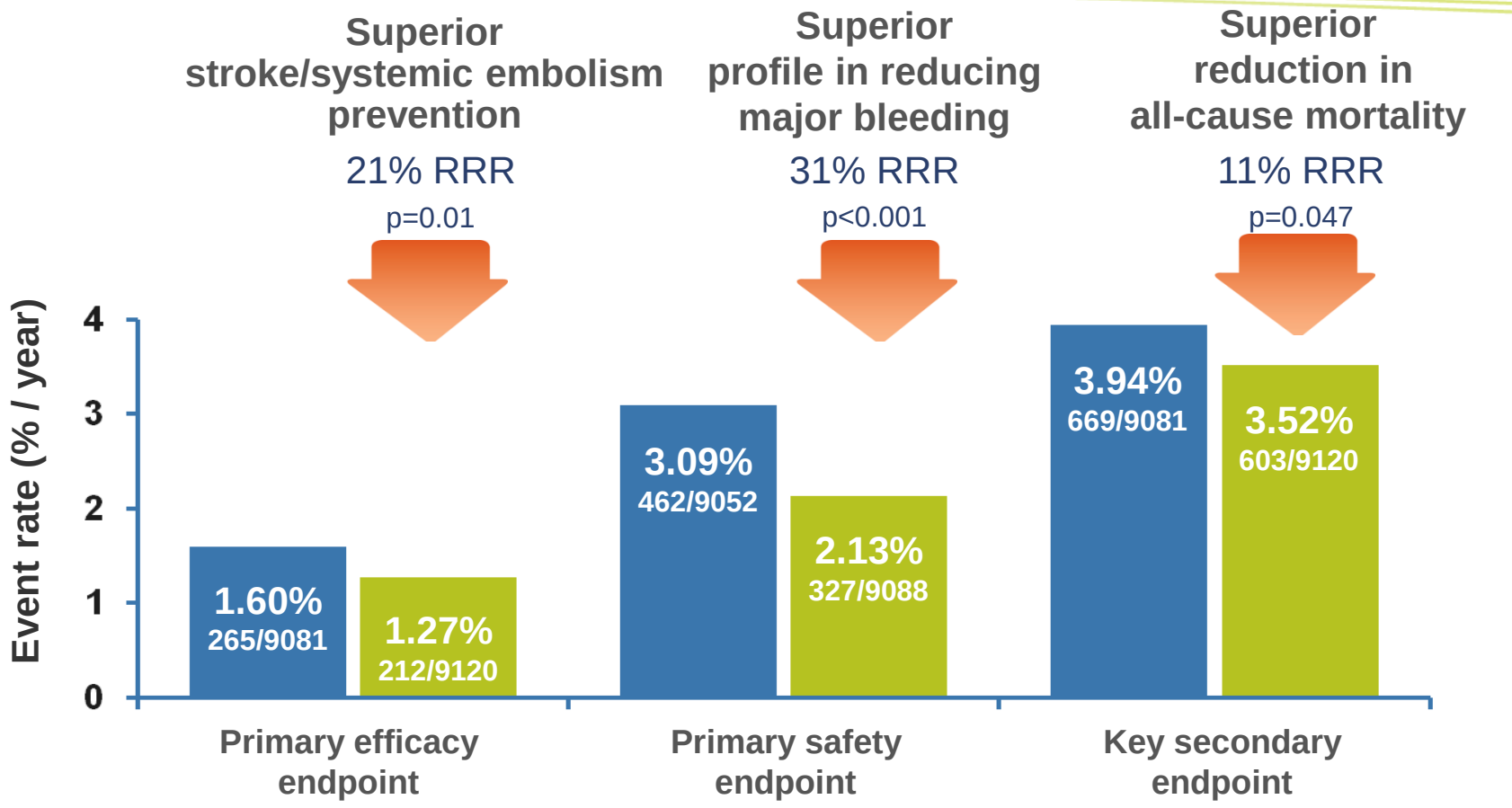
Bleeding Outcomes

Outcome	Apixaban (N=9088) Event Rate (%/yr)	Warfarin (N=9052) 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
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

* Part of sequential testing sequence preserving the overall type I error

Granger CB, NEJM 2011;365:981-92

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.

ARISTOTLE: Conclusion

- In patients with AF and at least one additional risk factor for stroke, **the use of apixaban, as compared with warfarin, significantly reduced** the risk of:
  - Stroke or systemic embolism by 21% (p=0.01)
  - Major bleeding by 31% (p<0.001)
  - Death by 11% (p=0.047)
- The results were **consistent in subgroups** according to geographic region, status with respect to previous warfarin exposure, age, sex, and risk factors for stroke, as well as in other predefined subgroups
- Apixaban had an **acceptable side-effect profile** and a lower rate of study drug discontinuation than in the warfarin group

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

Phase III AF Trials – Results Scorecard

	Re-LY	ROCKET-AF	ARISTOTLE
Drug	Dabigatran	Rivaroxaban	Apixaban
Stroke + SEE	150 mg superior 110 mg non-inferior	ITT cohort: non-infer. On Rx cohort: superior	superior
Bleeding	150 mg: similar 110 mg: lower	similar	lower
Mortality	150 mg: p = 0.051 110 mg: similar	similar	Superior: p = 0.047
Ischemic stroke	150 mg: lower 110 mg: similar	similar	similar
Mean TTR	62%	55%	62%
Stopped drug WD consent	21% 2.3%	23% 8.7%	23% 1.1%

TTR = time in therapeutic range, a measure of the quality of warfarin titration

WD consent = withdrawal of consent, no further data available

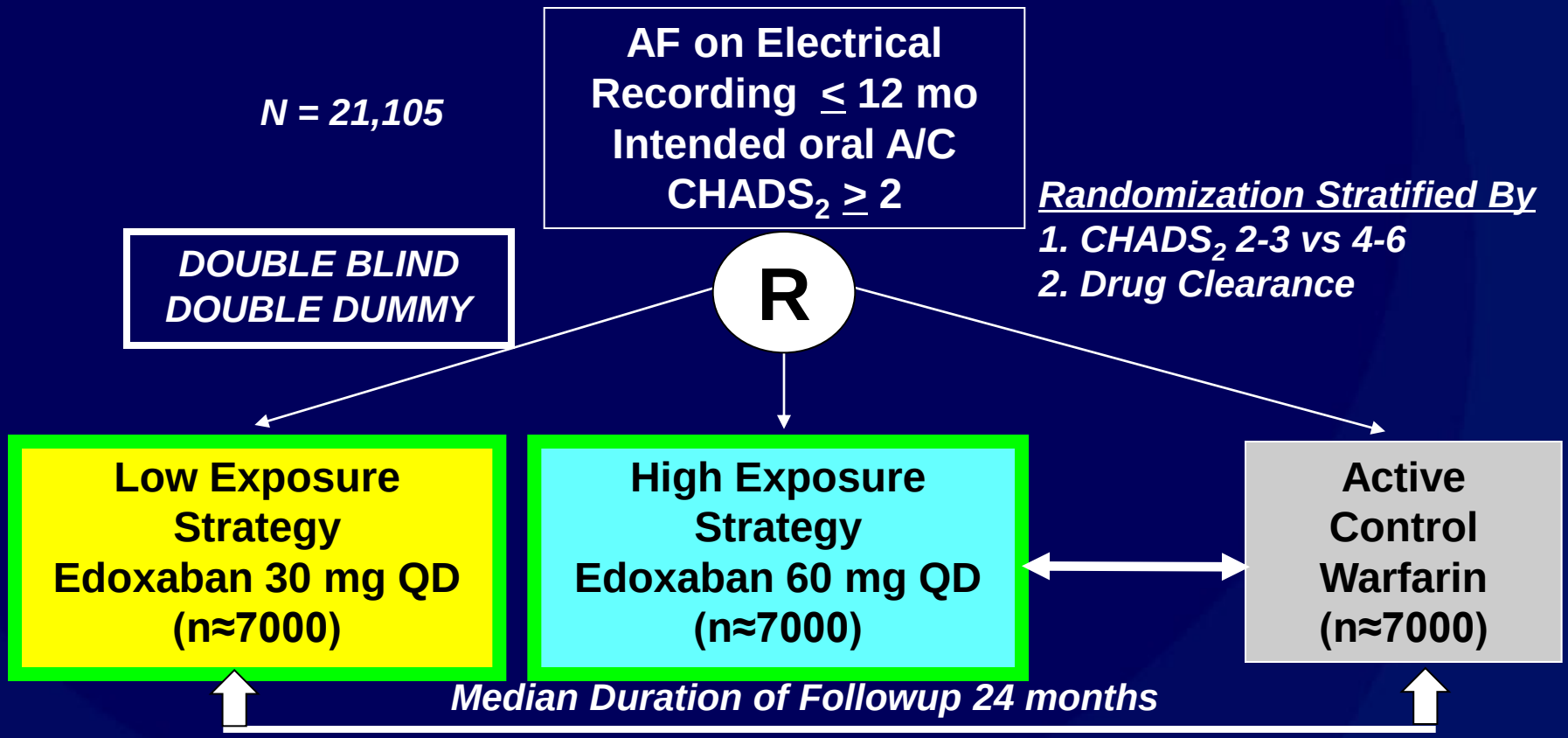
New oral anticoagulants in AF – pharmacological properties –

Property	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Route of administration	Oral	Oral	Oral	Oral
Target	Thrombin	FXa	FXa	FXa
Dosing	Twice daily	Once daily	Twice daily	Once daily
Monitoring required	No	No	No	No
Half-life (hrs)	12–17	9–12	8–15	8–11
Mode of elimination	Renal 80%	Renal ~66% Hepatic ~ 28%	Renal ~25% Hepatic ~ 75%	Renal ~35%

Fxa = Factor Xa

Eriksson BI et al. Annu Rev Med 2011;62:41−57; Pradaxa® SmPC, 2011

Protocol Schema



Primary Objective
Edoxaban: Therapeutically as Good as Warfarin

1º EP = Stroke or SEE (Noninferiority Boundary HR 1.38)
2º EP = Stroke or SEE or All-Cause Mortality
Safety EP's = Major Bleeding, Hepatic Function

SEE = systemic embolic event

EVENT DRIVEN

Ruff CR et al. Am Heart J 2010; 160:635-41

Baseline Characteristics in 3 AF Trials

	RE-LY (Dabigatran)	ARISTOTLE (Apixaban)	ENGAGE AF-TIMI 48* (Edoxaban)	ROCKET-AF (Rivaroxaban)
Number enrolled	18,113	18,201	21,105	14,264
Age (yrs)	72 ± 9	70 [63-76]	72 [64-77]	73 [65-78]
Female	36%	35%	38%	40%
$CHADS_2$ score ≥ 3	32%	30%	52%	87%
VKA naive	50%	43%	41%	38%
Paroxysmal AF	33%	15%	25%	18%
Prior stroke/TIA	20%	19%	18% / 12%	55%**
Diabetes	23%	25%	36%	40%
Prior CHF	32%	35%	56%	62%
Hypertension	79%	87%	90%	91%

*Preliminary data

**includes prior systemic embolism

Conclusions

- Atrial fibrillation (AF) is common and ischemic stroke is a major complication
- Of the current anticoagulants warfarin is the best and reduces stroke rate by 64%
- Warfarin is difficult to use, narrow therapeutic window, food alcohol and medication interactions
- A common and sometimes fatal complication is haemorrhage
- Warfarin is badly and inconsistently used
- Something better is urgently needed

Conclusions

- Several excellent alternatives to VKA on the horizon for AF
- These agents have meaningful differences in PK/PD properties