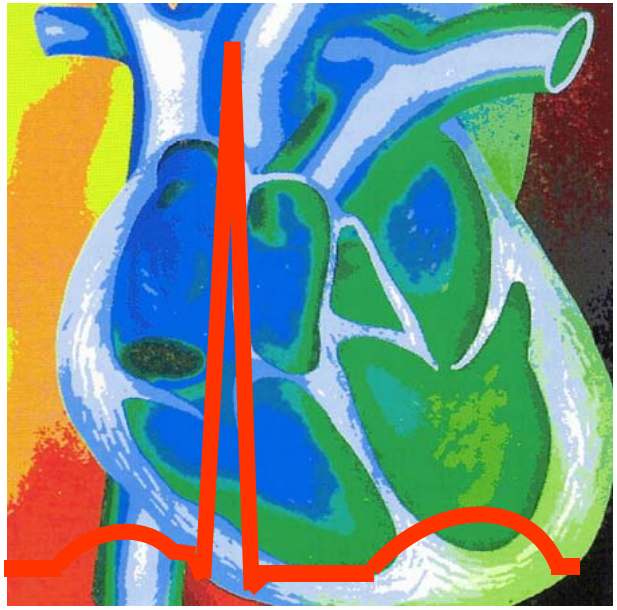
Atrial fibrillation



Antoni Martínez-Rubio, MD, FESC, FACC

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Atrial fibrillation: Key points

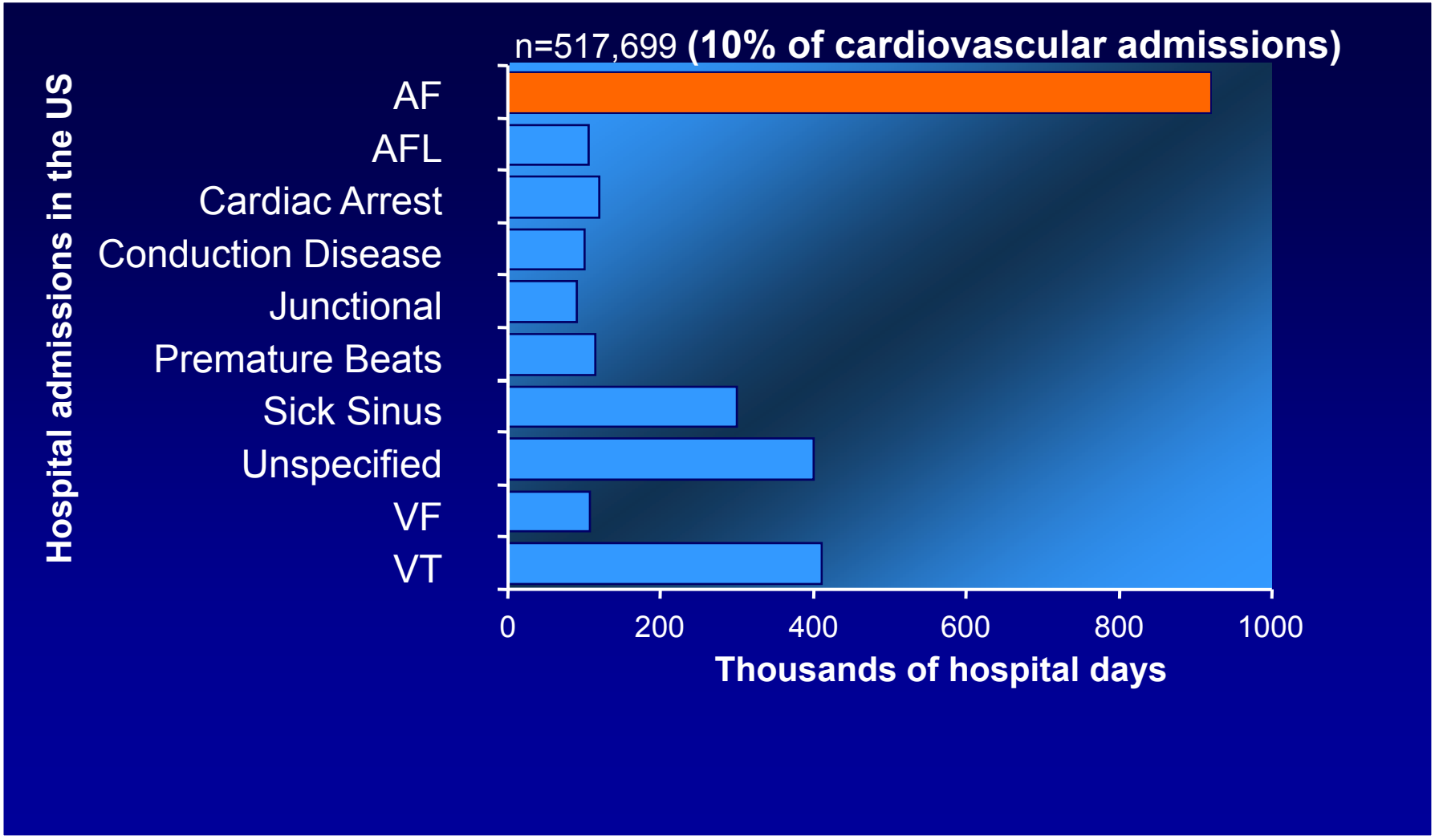
Is it relevant ?

Are antiarrhythmic strategies effective ?

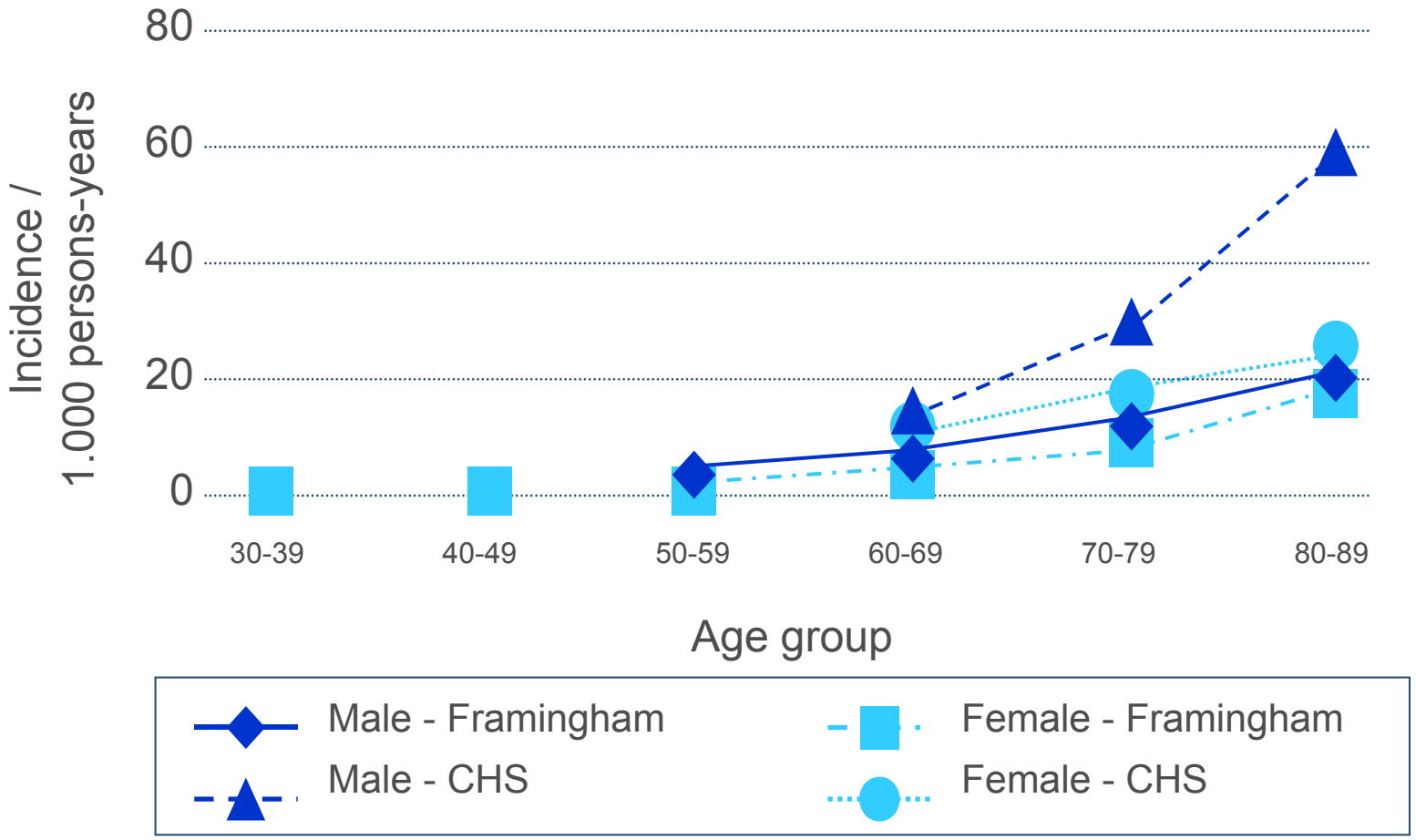
Anticoagulation after ESC 2009 ?

The future ?

AF is the leading cause for hospitalizations for arrhythmia

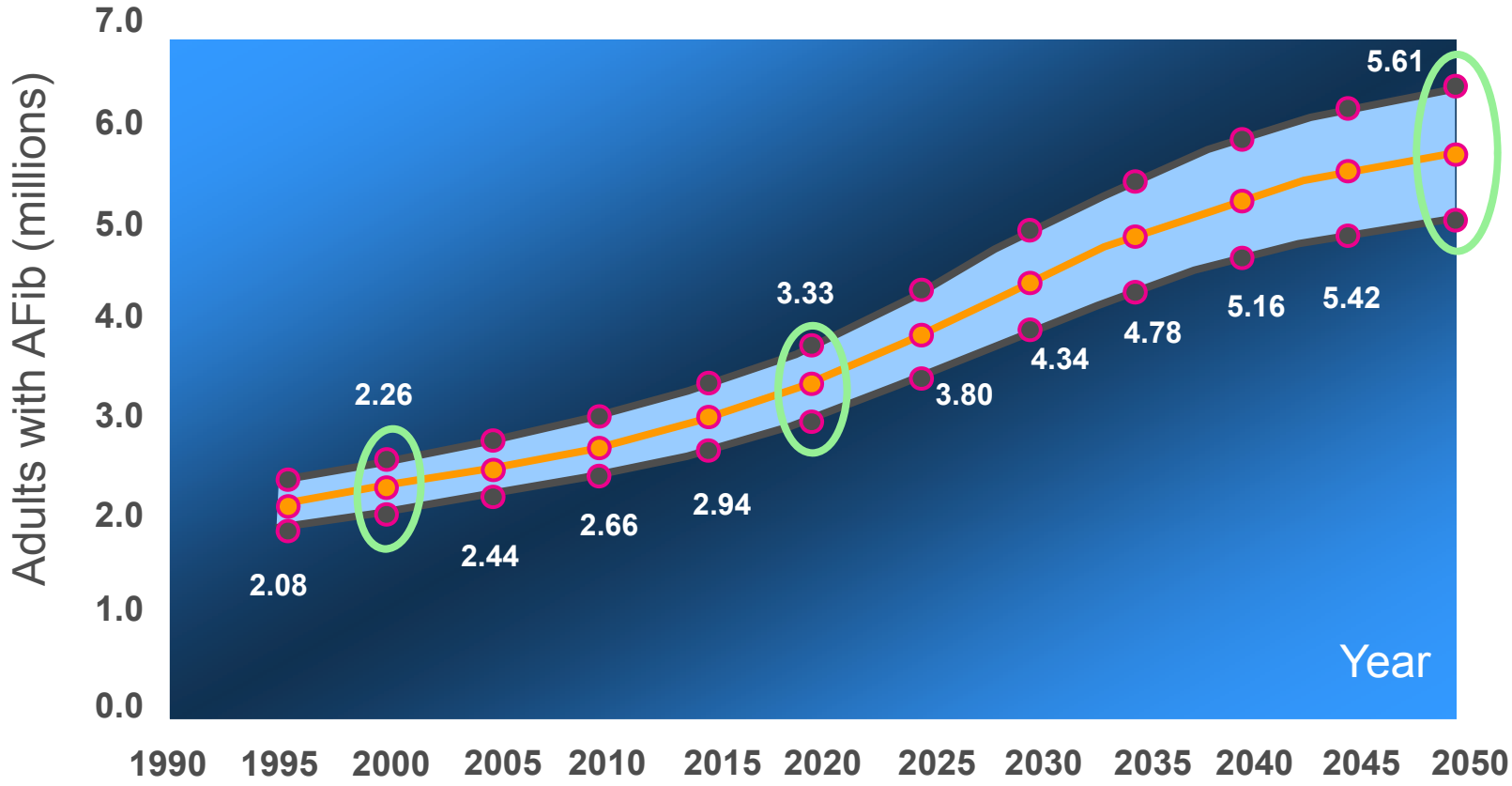


Atrial fibrillation: incidence



Wolf PA et al. The Framingham Study. Arch Intern Med 1987; 147: 1561-4.
Psaty BM et al. Circulation 1997; 96: 2455-61.

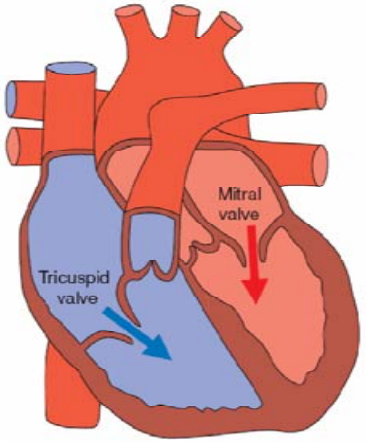
Projected Adults with AF in the USA between 1995 and 2050

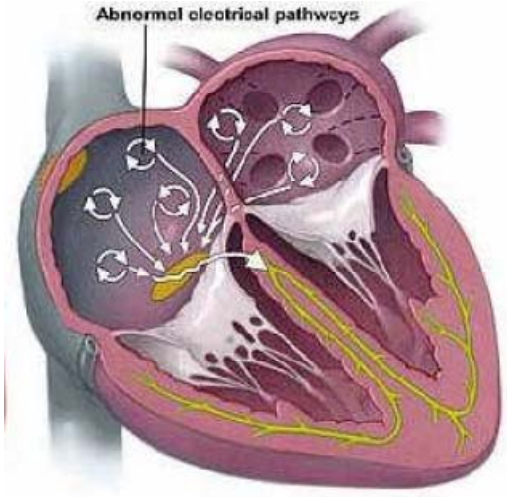


Go: JAMA, 2000

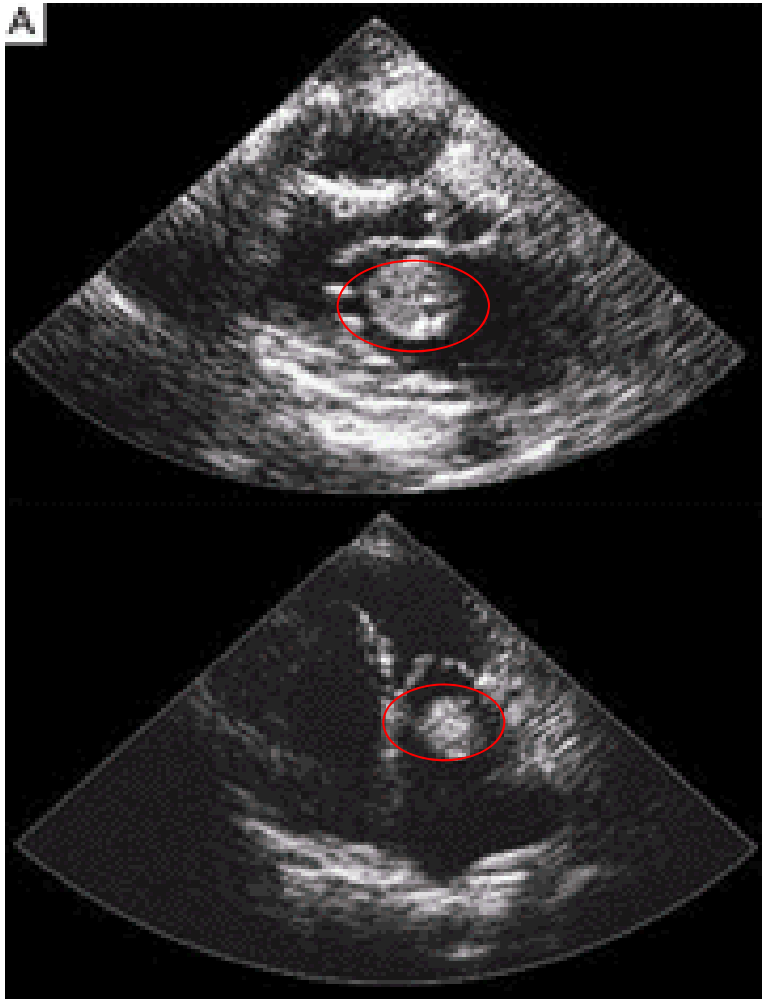
Key Consequences of AF

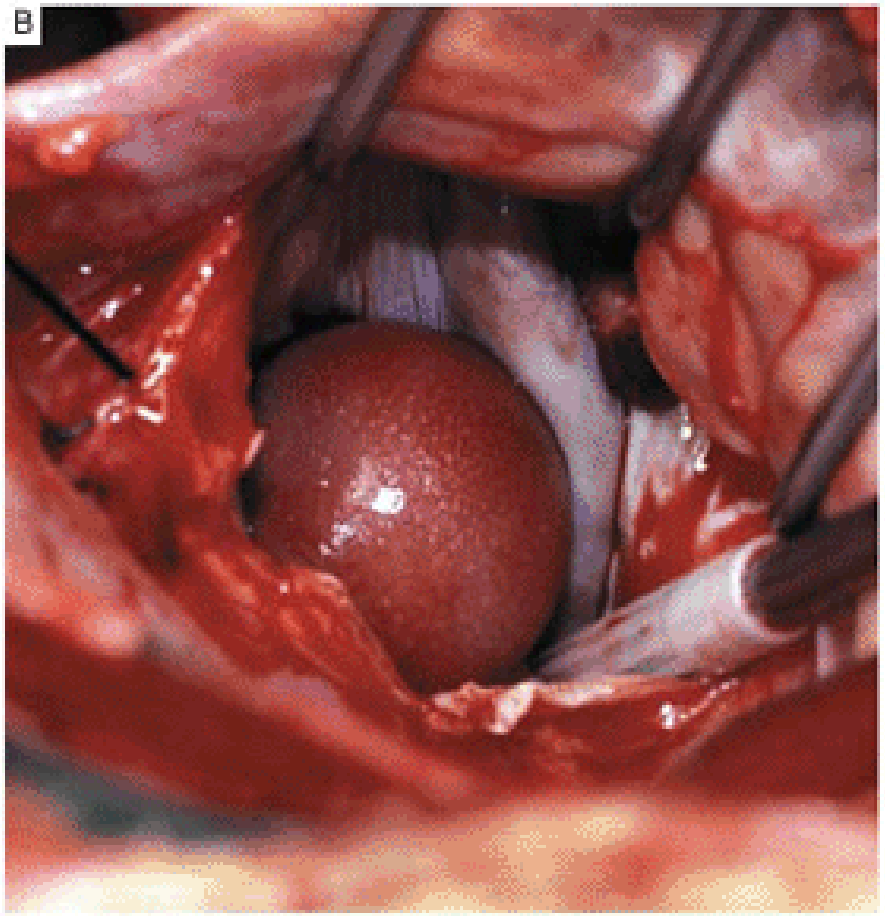
- **Loss of atrial contraction (atrial systole)**
  - Atrial stasis
    - Thromboembolism
  - ↓ in ventricular filling: ≃ 20%
    - Fatigue / dizziness
    - Shortness of breath
- **Rapid and irregular ventricular rate**
  - Palpitations
  - Chest discomfort or angina



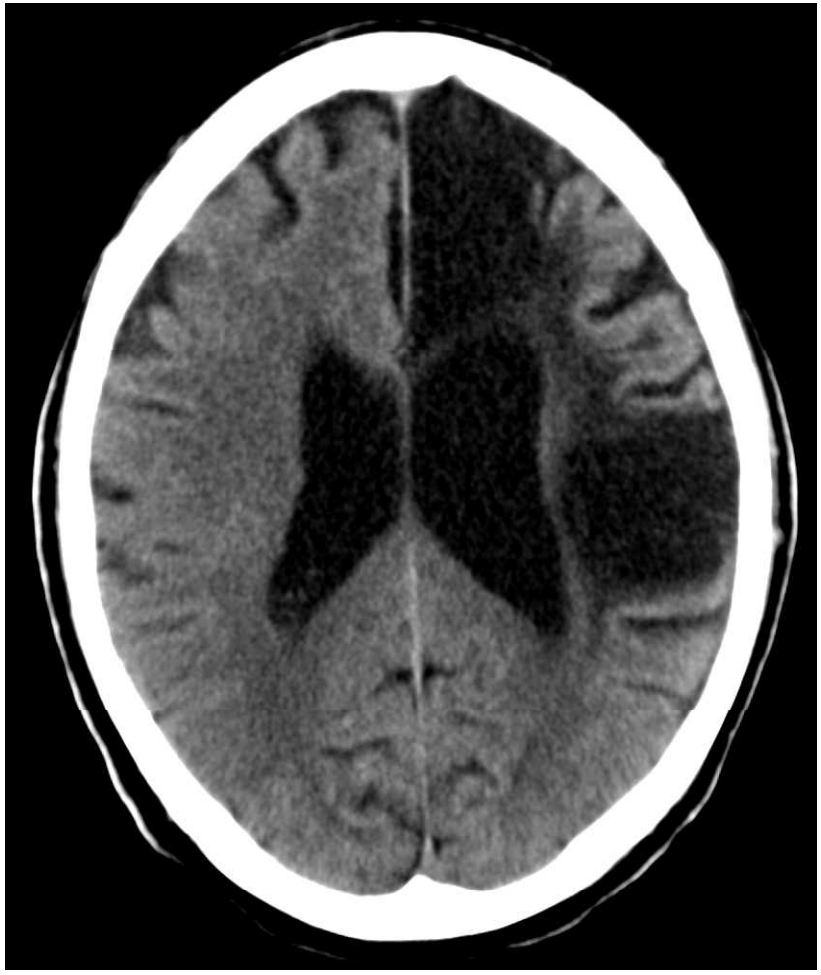


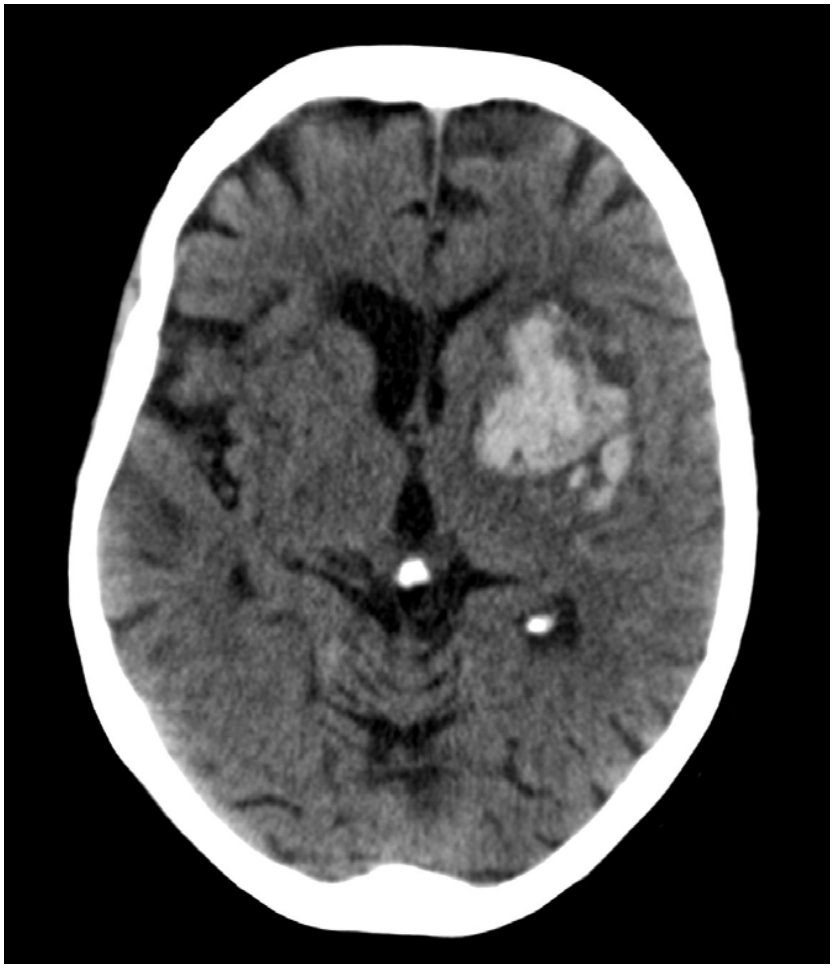
A major complication of AF: the atrial thrombus





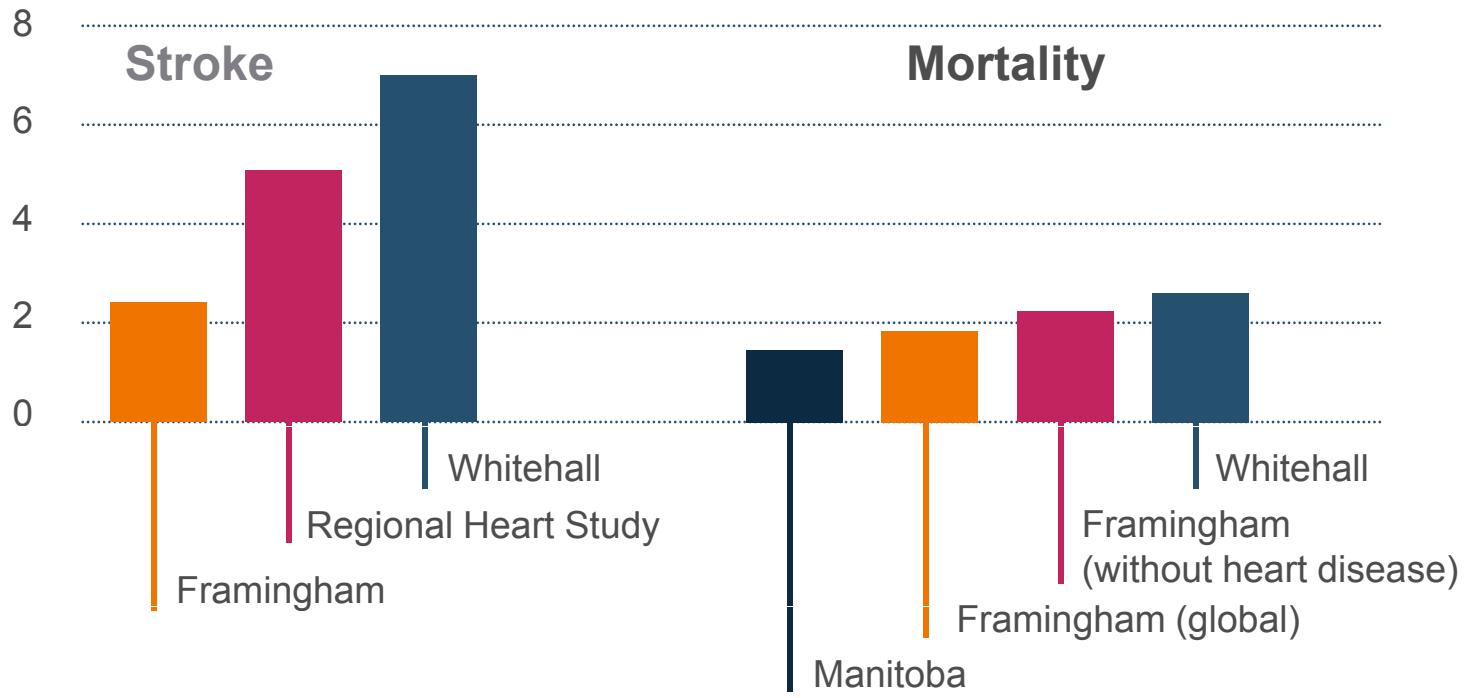
Major complications of AF treatment: stroke





Atrial fibrillation

Relative risk compared to patients without AF



Wolf PA et al. The Framingham Study. Arch Intern Med 1987; 147: 1561-4.
Regional Heart Study.
Framingham et al. Framingham Heart Study.

Flegel KM et al. Whitehall study.
Krahn AD et al. Manitoba study.

Atrial fibrillation: Key points

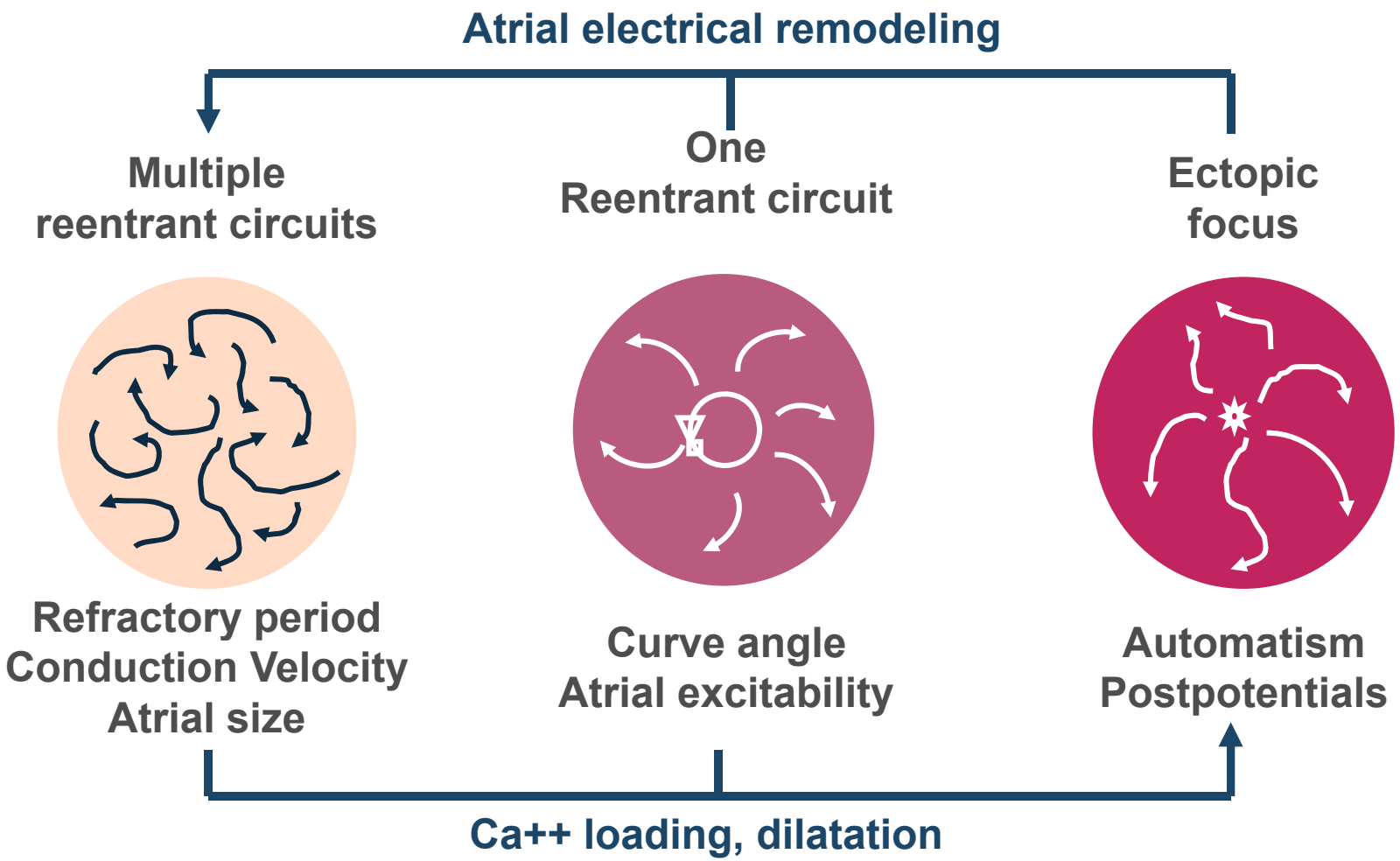
Is it relevant ?

Are antiarrhythmic strategies effective ?

Anticoagulation after ESC 2009 ?

The future ?

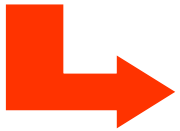
Atrial fibrillation: mechanisms



Atrial fibrillation: Rhythm vs. Rate Control

- PIAF[1], STAF[2], RACE[3], AFFIRM[4], HOT CAFE[5]

1. ≃ **mortality / HF /stroke / thromboembolism / QoL.**
2. **Tendency to increased mortality in rhythm control group patients with CAD, HF or >65 years [4].**
3. **Hospital admissions & adverse events with ADD more frequent in rhythm control group patients [2,4,5]**



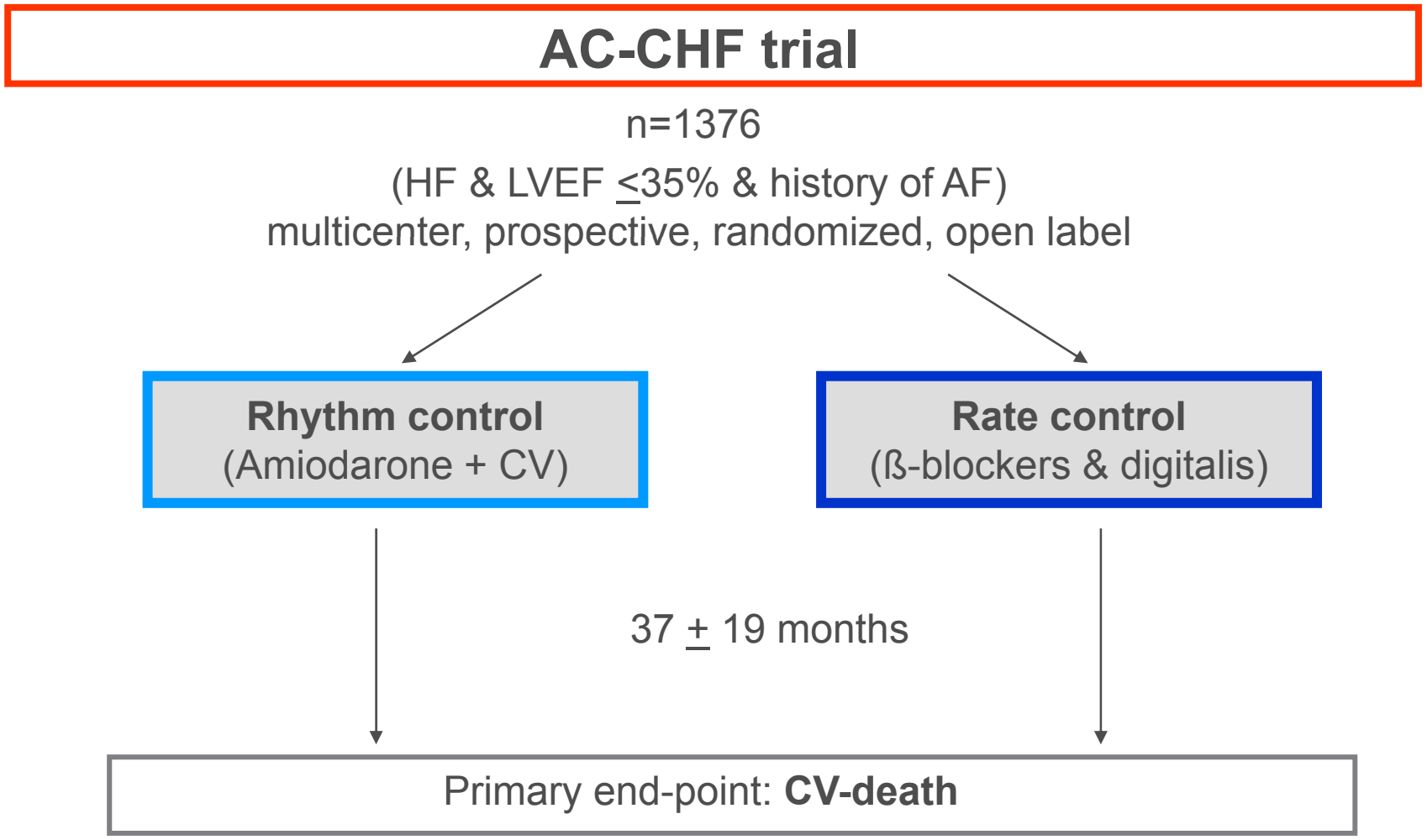
↓ benefit of SR maintenance

Limitations of the trials

- **Patients > 65 years, short follow-up; not randomized**

1. Gronefeld et al. Eur Heart J 2003. **2.** Carlsson et al. JACC 2003. 3. Van Gelder et al. New Engl J Med 2002.
4. Wyse et al. New Engl J Med 2002. **5.** Opolski et al. Kardiol Polska 2003.

Atrial fibrillation: Rhythm vs. Rate Control



Atrial fibrillation: Rhythm vs. Rate Control

AC-CHF trial

Main results:

* Routine **rhythm control** did not improve patients' outcomes as compared to **rate control** strategy (CV death, symptoms, exercise capacity, QoL)

* More admissions in the **rhythm control** strategy group

Atrial fibrillation: Rhythm vs. Rate Control

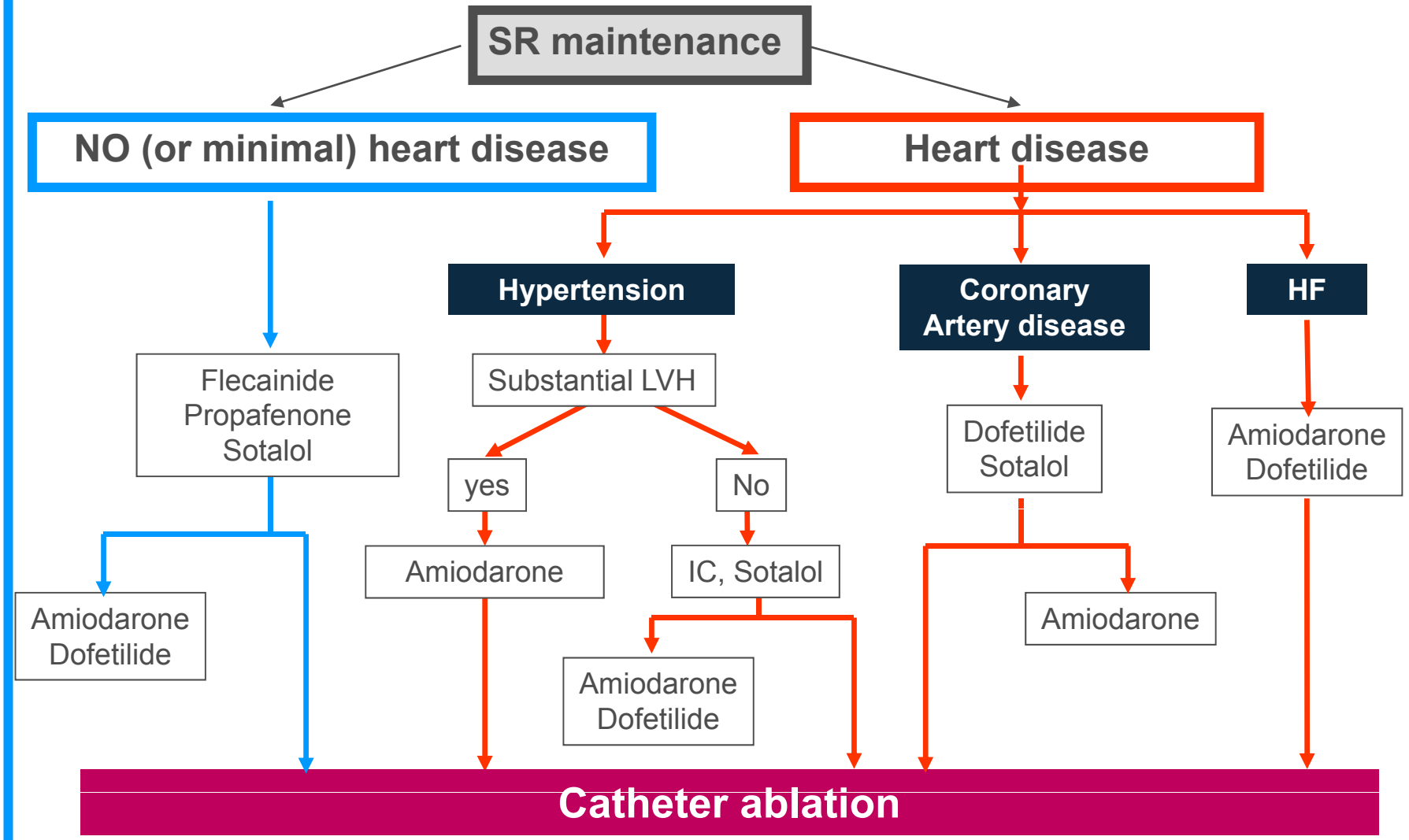
AC-CHF trial

Were treatments effective ?

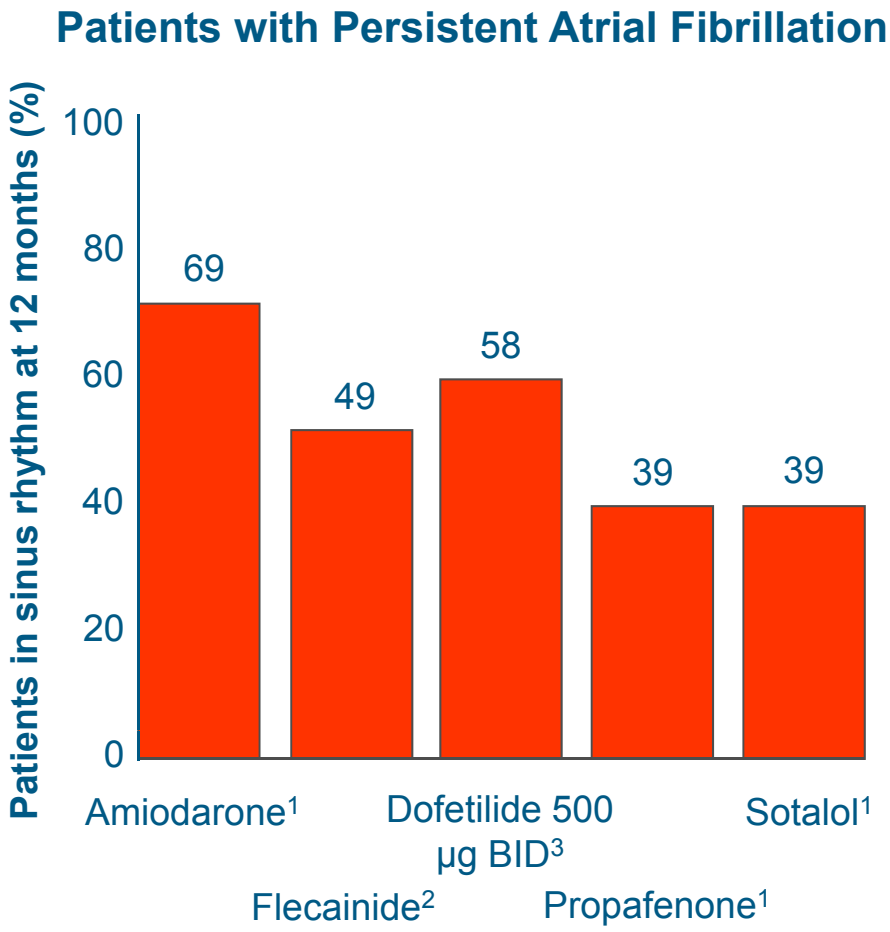
- SR documented in 75-80% of **Rhythm-control** group.
- In the **Rate-control** group, targets (<80/<110 bpm at rest/6MWT) achieved in 82-88% patients during follow-up.

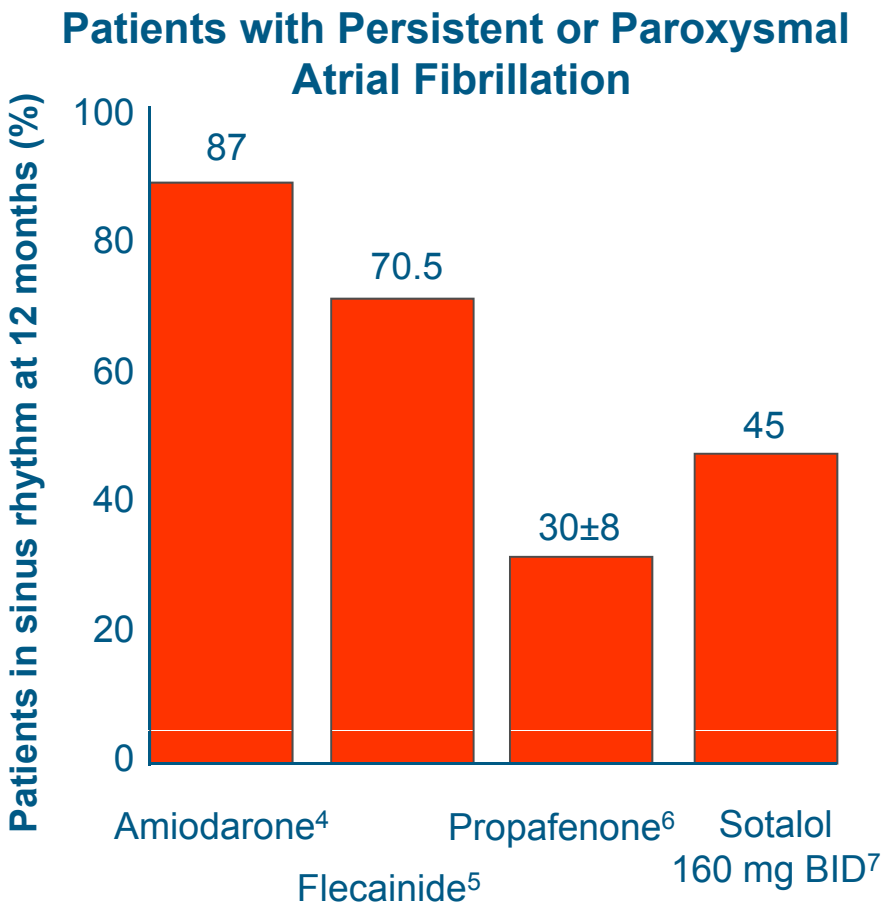
- ***However***:
  - 58% of **Rhythm control** group had ≥1 AF recurrence
  - 40% of **Rate control** group had no AF during follow-up

Atrial fibrillation: management



SR Maintenance at 12 Months with AADs



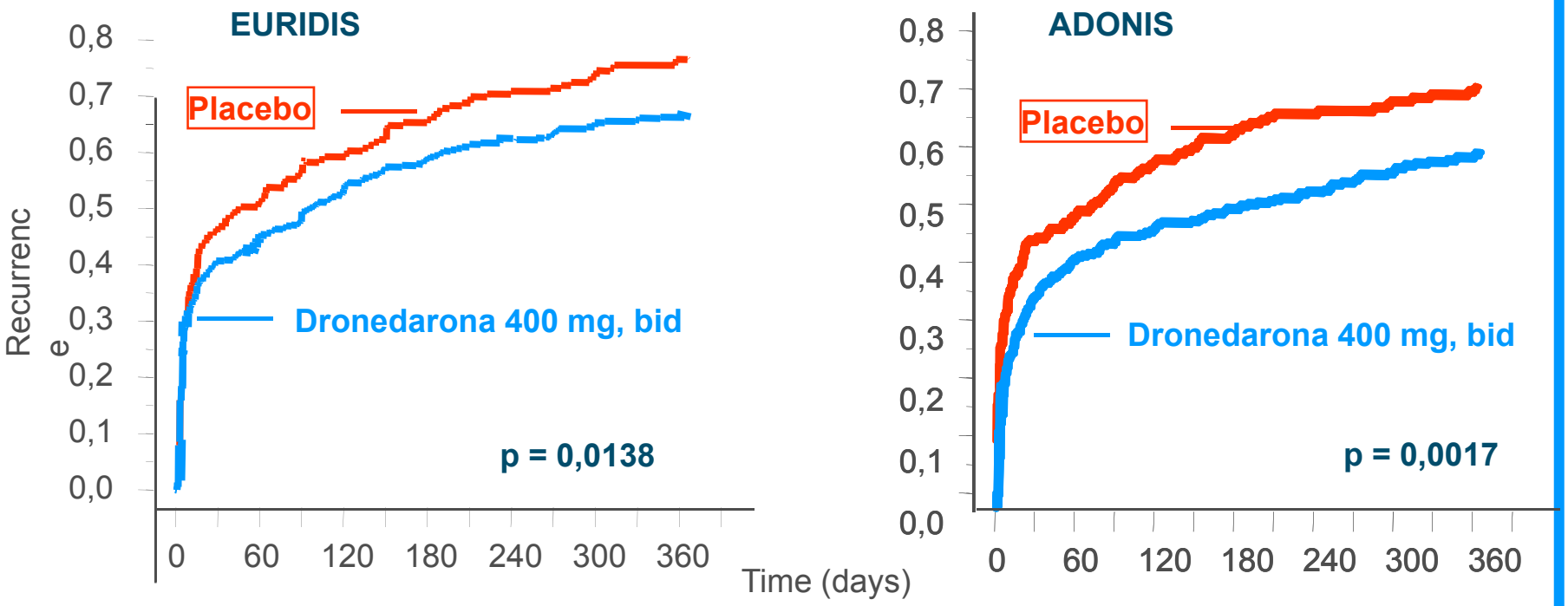


1. Roy D, *et al. N Engl J Med* 2000;**342**:913–920. 2. Van Gelder IC, *et al. Am J Cardiol* 1989;**64**:1317–1321. 3. Capucci, *et al. Int J Cardiol* 1999;**68(2):**187–196. 4. Chun Sh, *et al. Am J Cardiol* 1995;**76**:47–50. 5. Naccarelli GV, *et al. Am J Cardiol* 1996;**77**:53A–59A. 6. Reimold SC, *et al. Am J Cardiol* 1993;**71**:558–563. 7. Benditt DG, *et al. Am J Cardiol* 1999;**84**:270–277

Atrial fibrillation: other AAD

Dronedarone:

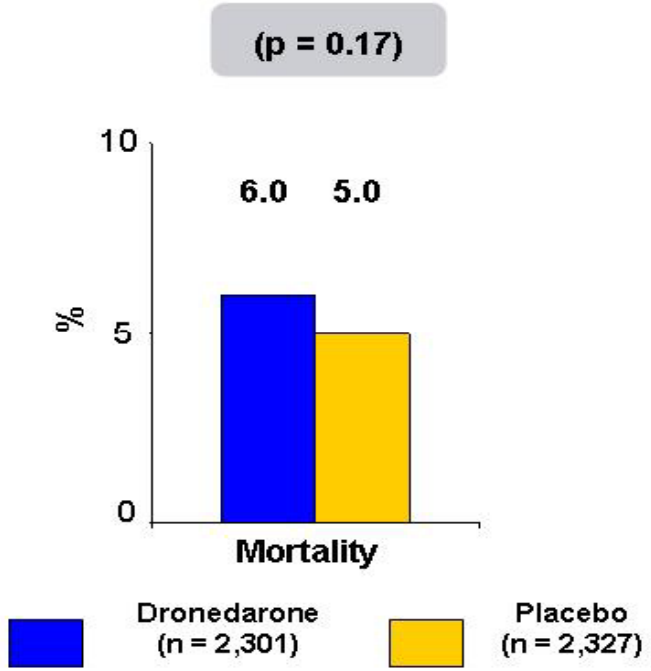
- EP-properties ≃ to amiodarone
- Prolongs recurrence free periods (DAFNE, ADONIS, EURIDIS).
- $T_{1/2}$: 24 h.
- **No thyroidal - pulmonary toxicity o proarrhythmia.**



Atrial fibrillation: role of dronedarone

ATHENA

Trial design: High-risk patients with paroxysmal or persistent atrial fibrillation or flutter were randomized to dronedarone 400 mg twice daily or placebo. Patients were followed for a mean of 21 months.



Results

- Dronedarone associated with a 24% ↓ in cardiac hospitalizations or death vs. placebo ($p < 0.001$)
- Overall mortality similar ($p = 0.17$); cardiovascular mortality lower with dronedarone ($p = 0.03$)
- Higher GI side effects and increased creatinine with dronedarone; other side effects similar

Conclusions

- Dronedarone is safe and effective in the chronic management of atrial fibrillation in high-risk patients
- Head-to-head comparison with amiodarone is awaited

www.cardiosource.com

Presented by Dr. Stefan Hohnloser at Heart Rhythm 2008

Atrial fibrillation: physiology

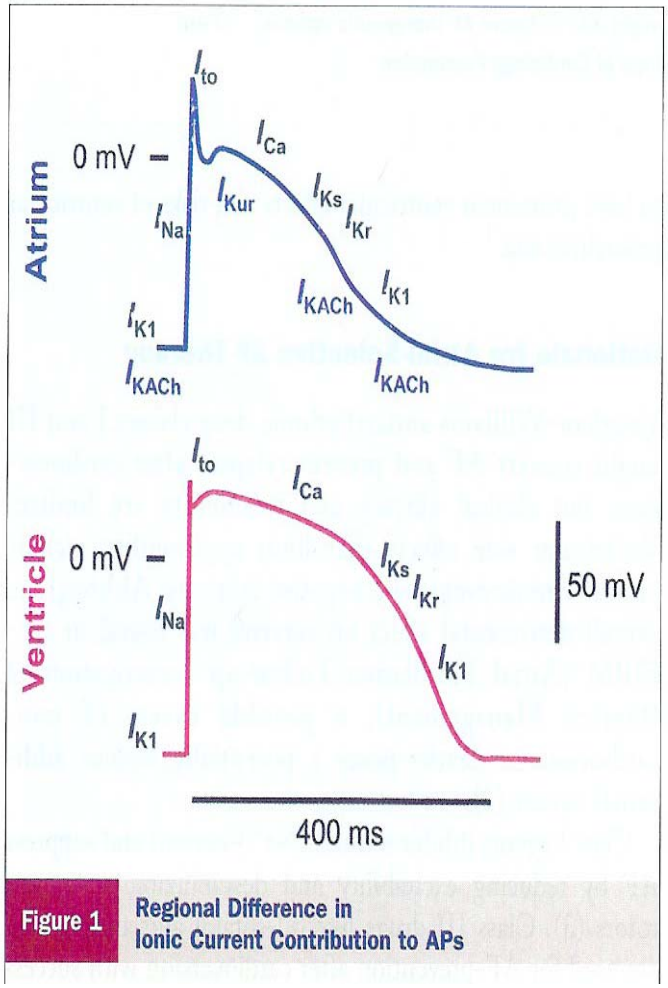
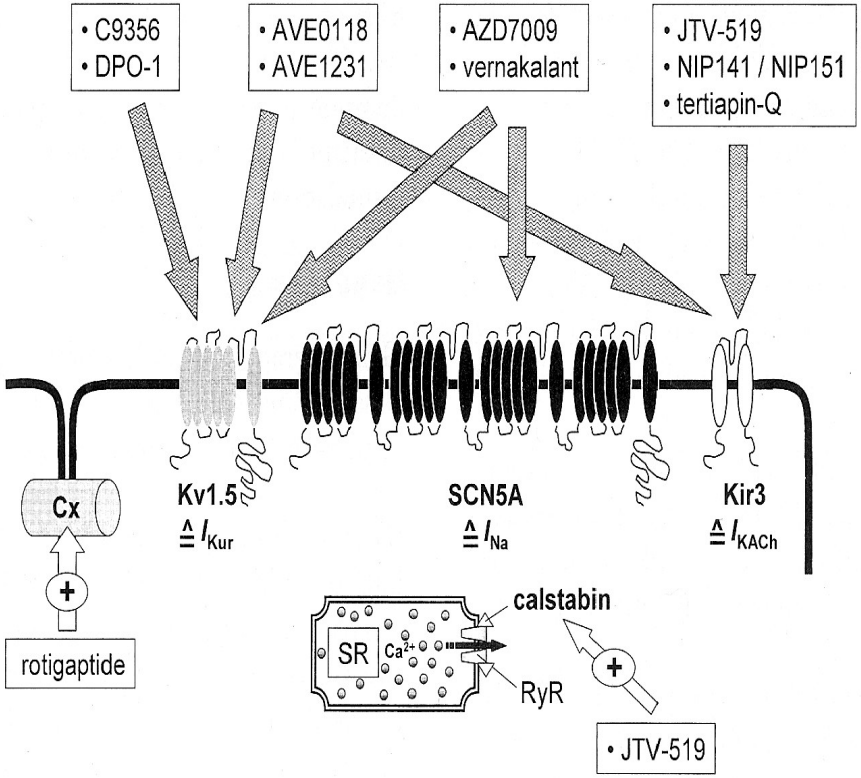


Figure 1 Regional Difference in Ionic Current Contribution to APs



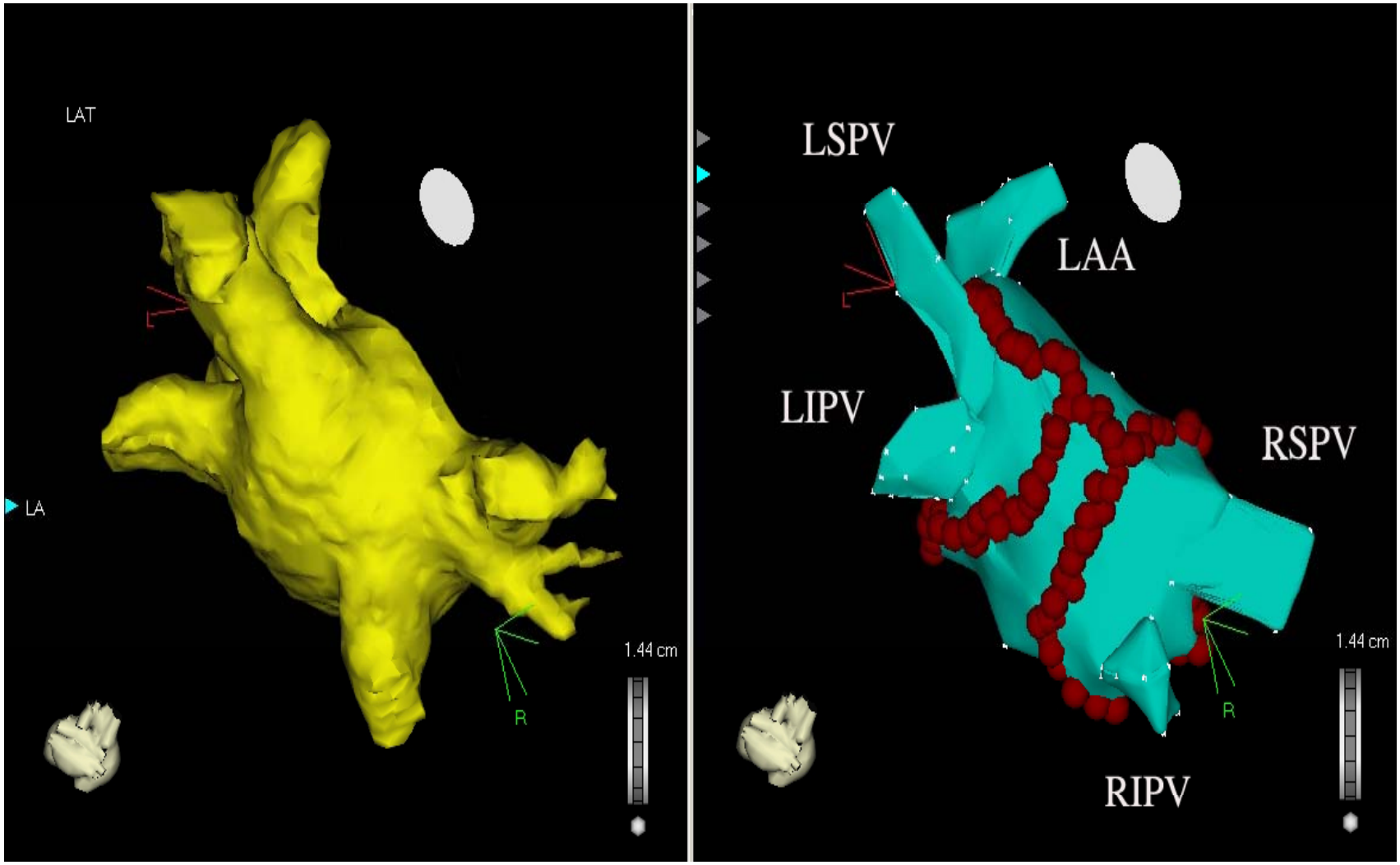
HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation

Indications for Catheter Ablation for AF

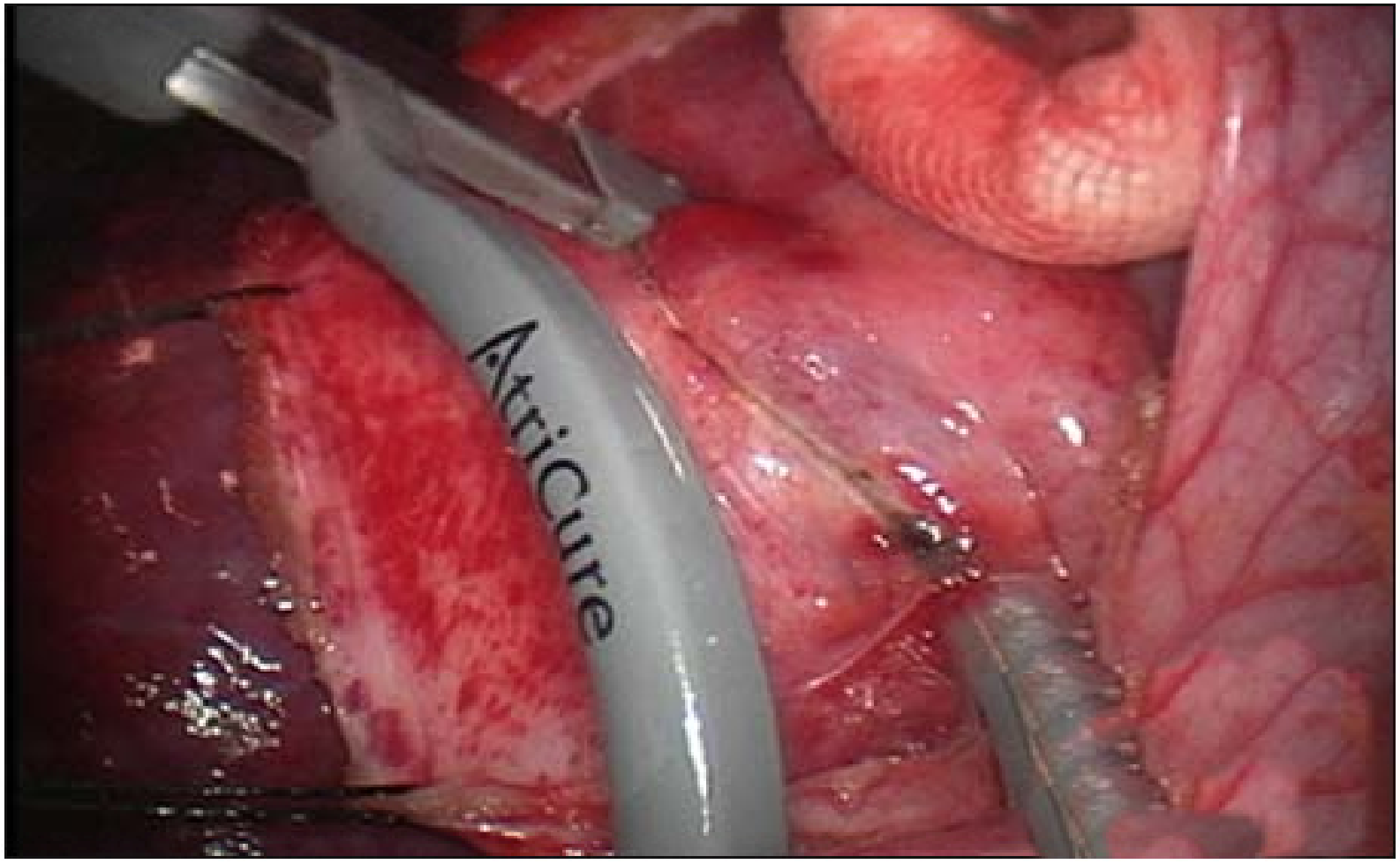
- Symptomatic AF refractory or intolerant to at least one Class 1 or 3 antiarrhythmic agents.
- **In rare clinical situations, it may be appropriate to perform AF ablation as first line therapy.**
- Selected symptomatic patients with heart failure and/or reduced ejection fraction.

Calkins et al. Europace 2007. 9 (6): 335-379.

Atrial fibrillation: ablation



Atrial fibrillation: surgery



Atrial fibrillation: RF-ablation

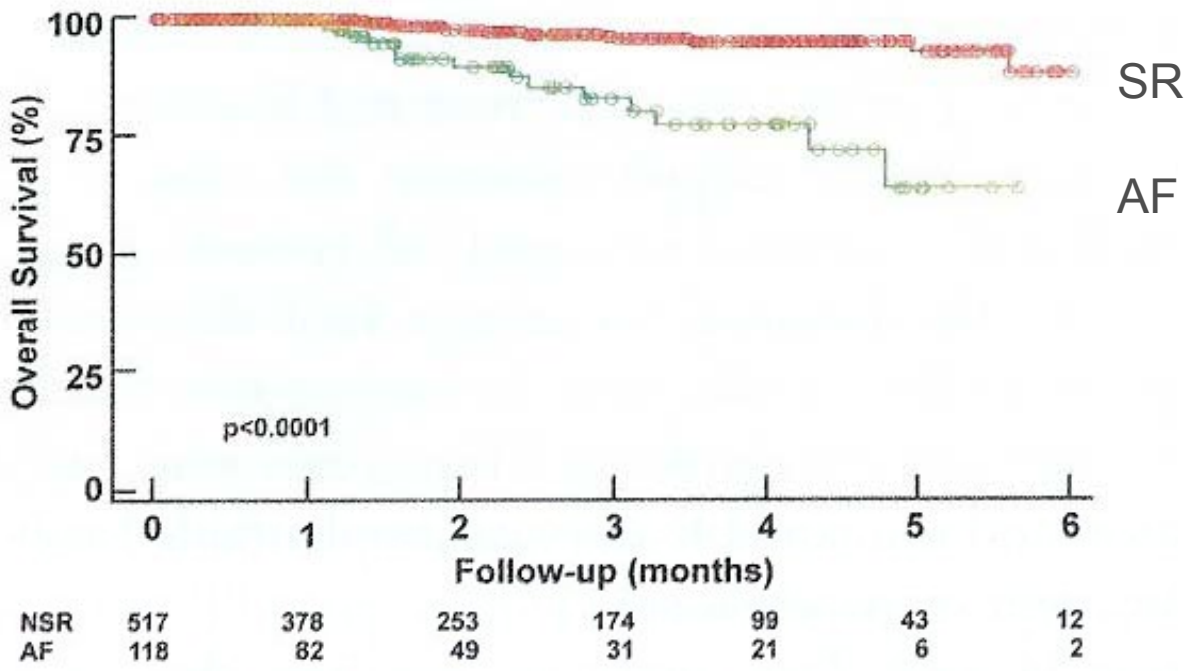


Figure 1 **Effects of Maintaining NSR After AF Ablation on Survival**

Nademanee K, *et al*., JACC 2008; 51: 843-9

HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation

- Pre-procedure Management
  - Patients with persistent AF who are in AF at the time of ablation "should have a TEE" performed to screen for thrombus.
- Post-procedure Management
  - LMWH or i.v. heparin → OA (warfarin > 2 months). "based on the patient's risk factors for stroke and not on the presence or type of AF"

- **Discontinuation of warfarin therapy post ablation is generally not recommended in patients who have a CHADs score ≥ 2.**

Calkins et al. Europace 2007. 9 (6): 335-379.

Atrial fibrillation: Key points

Is it relevant ?

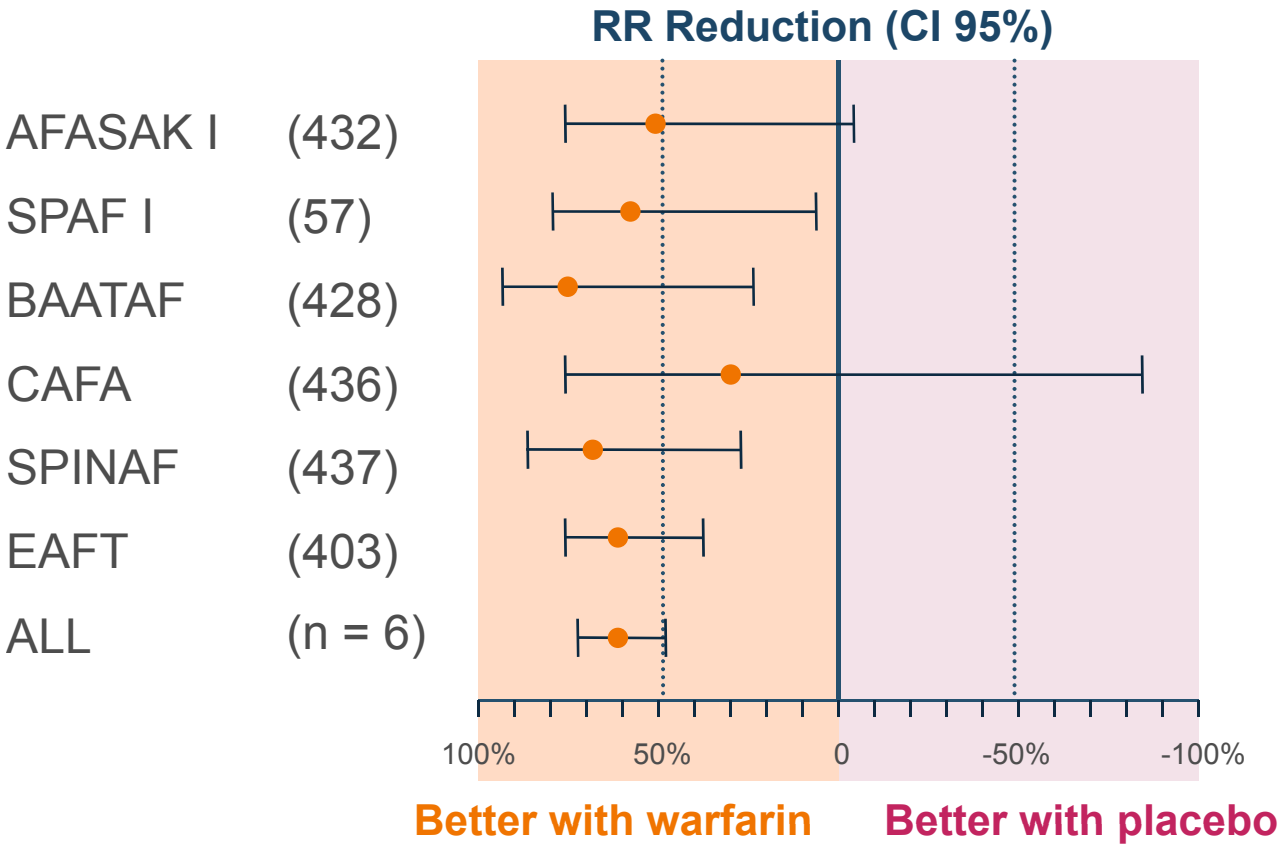
Are antiarrhythmic strategies effective ?

Anticoagulation after ESC 2009 ?

The future ?

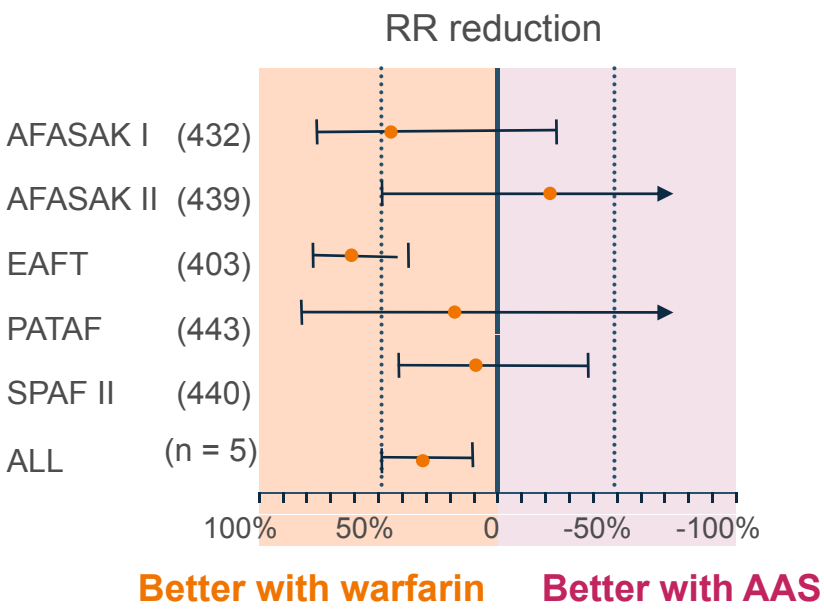
Atrial fibrillation: anticoagulation

Adjusted warfarin dosis compared to placebo



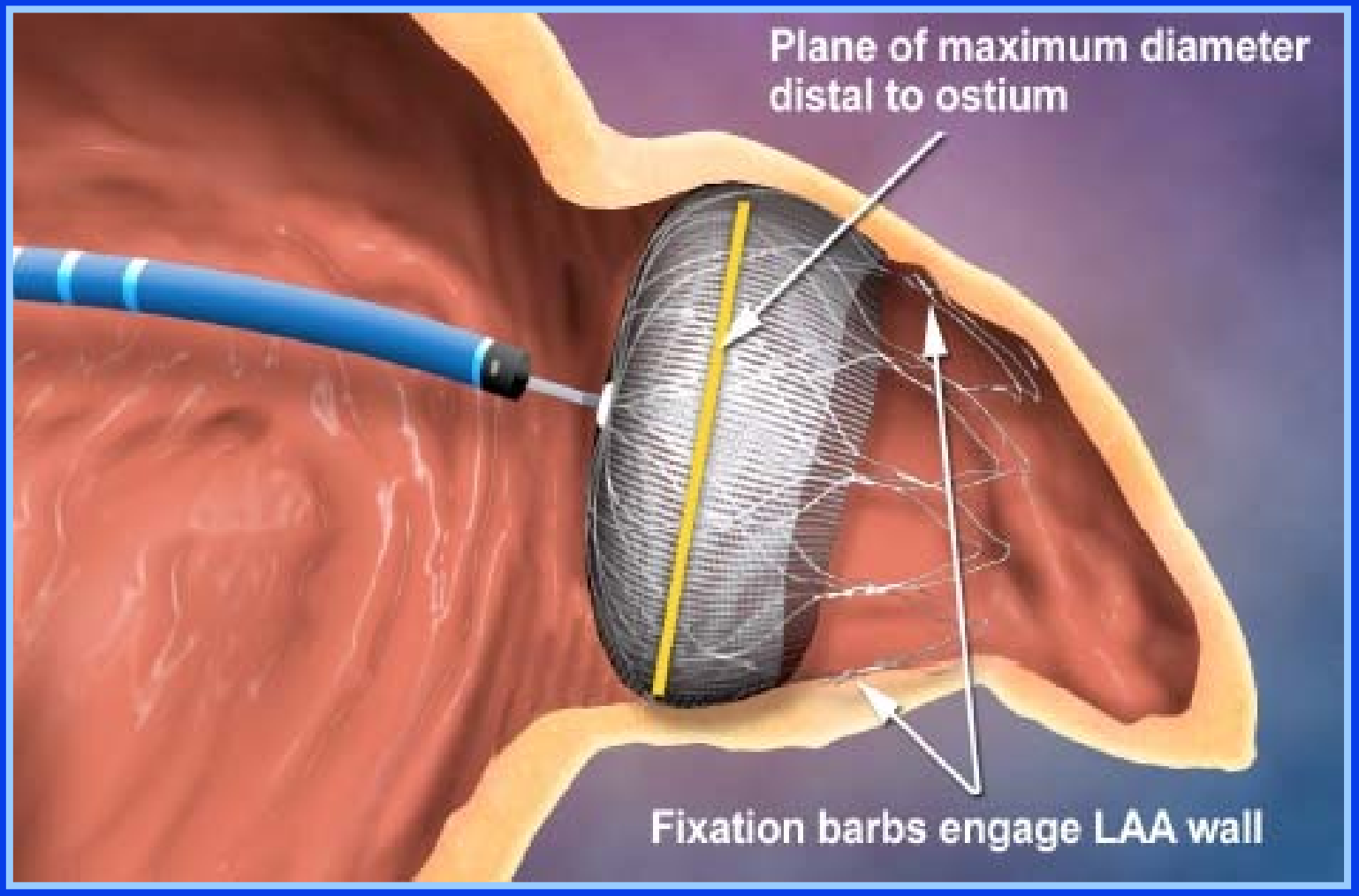
Atrial fibrillation: OAC vs AAS

Warfarina vs. AAS



AAS vs. placebo

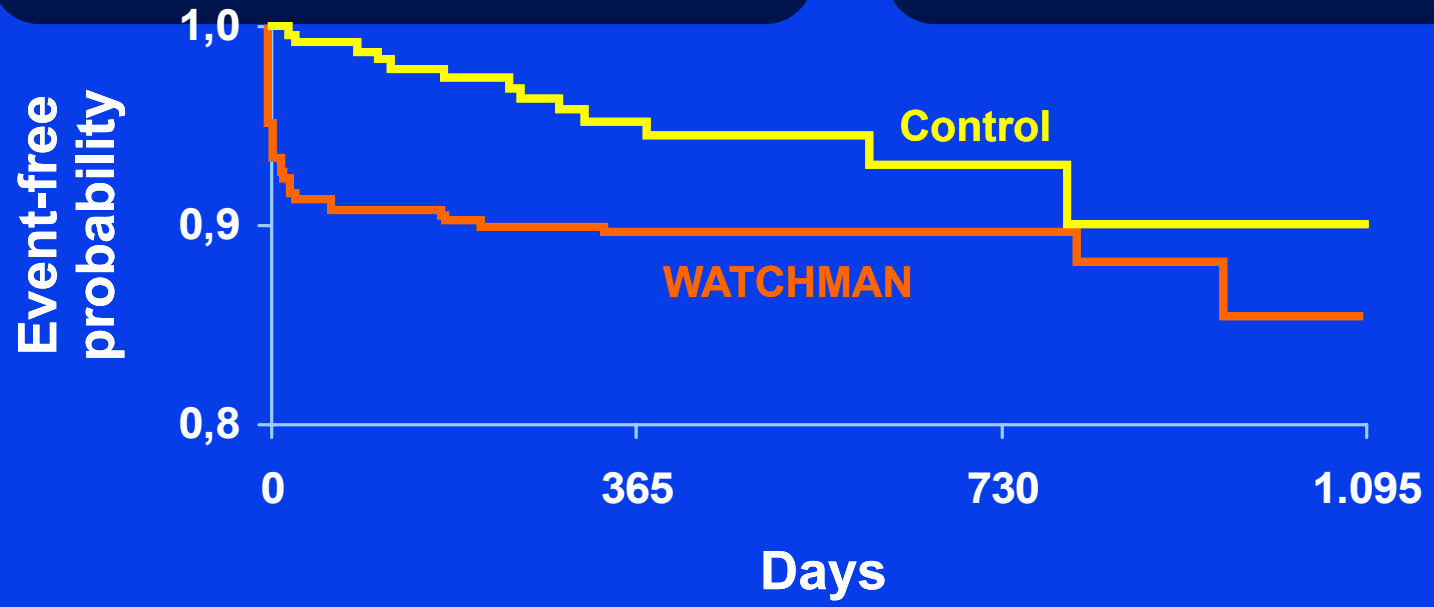
WATCHMAN LAA Closure Device in situ



Intent-to-Treat
Primary Safety Results

Randomization allocation (2 device : 1 control)

Cohort	Device Events (no.)	Device Total pt-yr	Device Rate (95% CI)	Control Events (no.)	Control Total pt-yr	Control Rate (95% CI)	Rel. Risk (95% CI)
900 pt-yr	48	554.2	8.7 (6.4, 11.3)	13	312.0	4.2 (2.2, 6.7)	2.08 (1.18, 4.13)



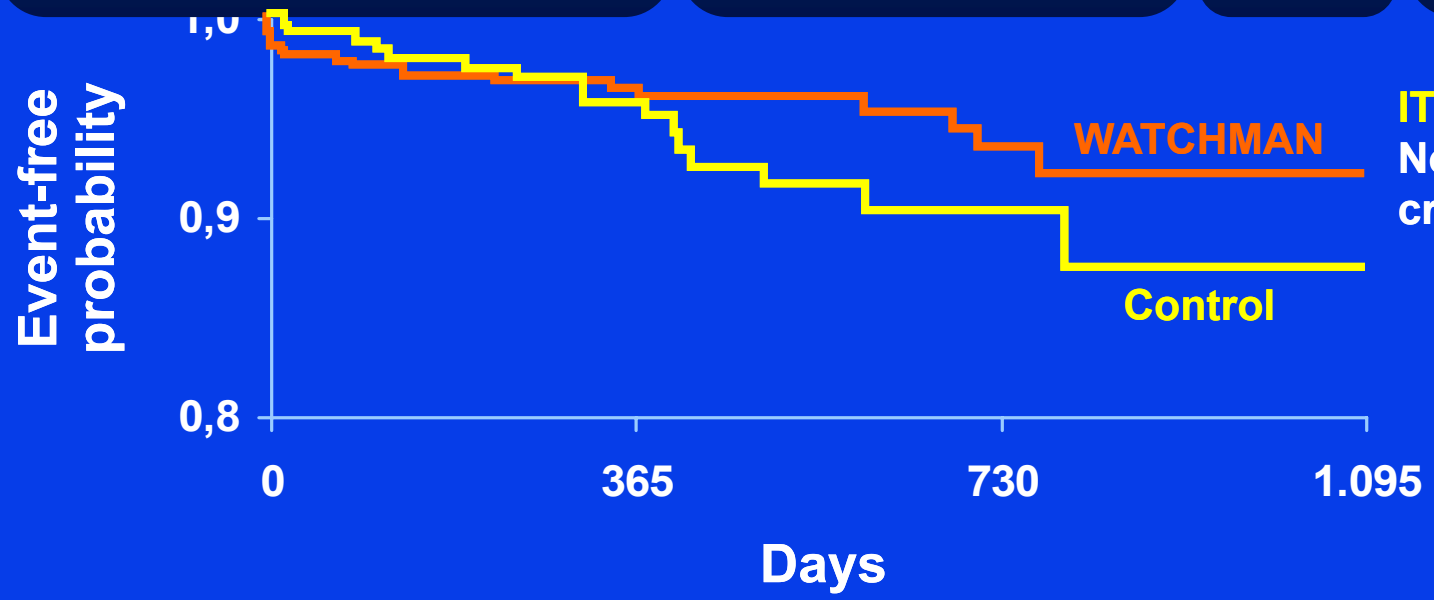
MAYO CLINIC

3001664-1

Intent-to-Treat
Primary Efficacy Results

Randomization allocation (2 device : 1 control)

	Device			Control				Posterior Probabilities	
Cohort	Events (no.)	Total pt-yr	Rate (95% CI)	Events (no.)	Total pt-yr	Rate (95% CI)	Rel. Risk (95% CI)	Non-inferiority	Superiority
900 pt-yr	20	582.3	3.4 (2.1, 5.2)	16	318.0	5.0 (2.8, 7.6)	0.68 (0.37, 1.41)	0.998	0.837



ITT Cohort:
Non-inferiority criteria met

MAYO CLINIC

3001664-2

Other New Antithrombotic Drugs

IIa (Thrombin)	Xa
(Ximelagatran)	**Rivaroxaban** – in Phase III
Dabigatran etexilate – in Phase III	Apixaban – in Phase II
	LY517717 – in Phase II
	YM150 – in Phase II
	Du-176b - in Phase II
	Otamixaban – in Phase II
	Idrabiotaparinux s.c. / 1x/week /reversal agent

RELY®

Study of stroke prevention in atrial fibrillation

The RE-LY Study: Randomized Evaluation of Long-term anticoagulant therapY

Dabigatran Compared to Warfarin in 18,113 Patients with Atrial Fibrillation at Risk of Stroke

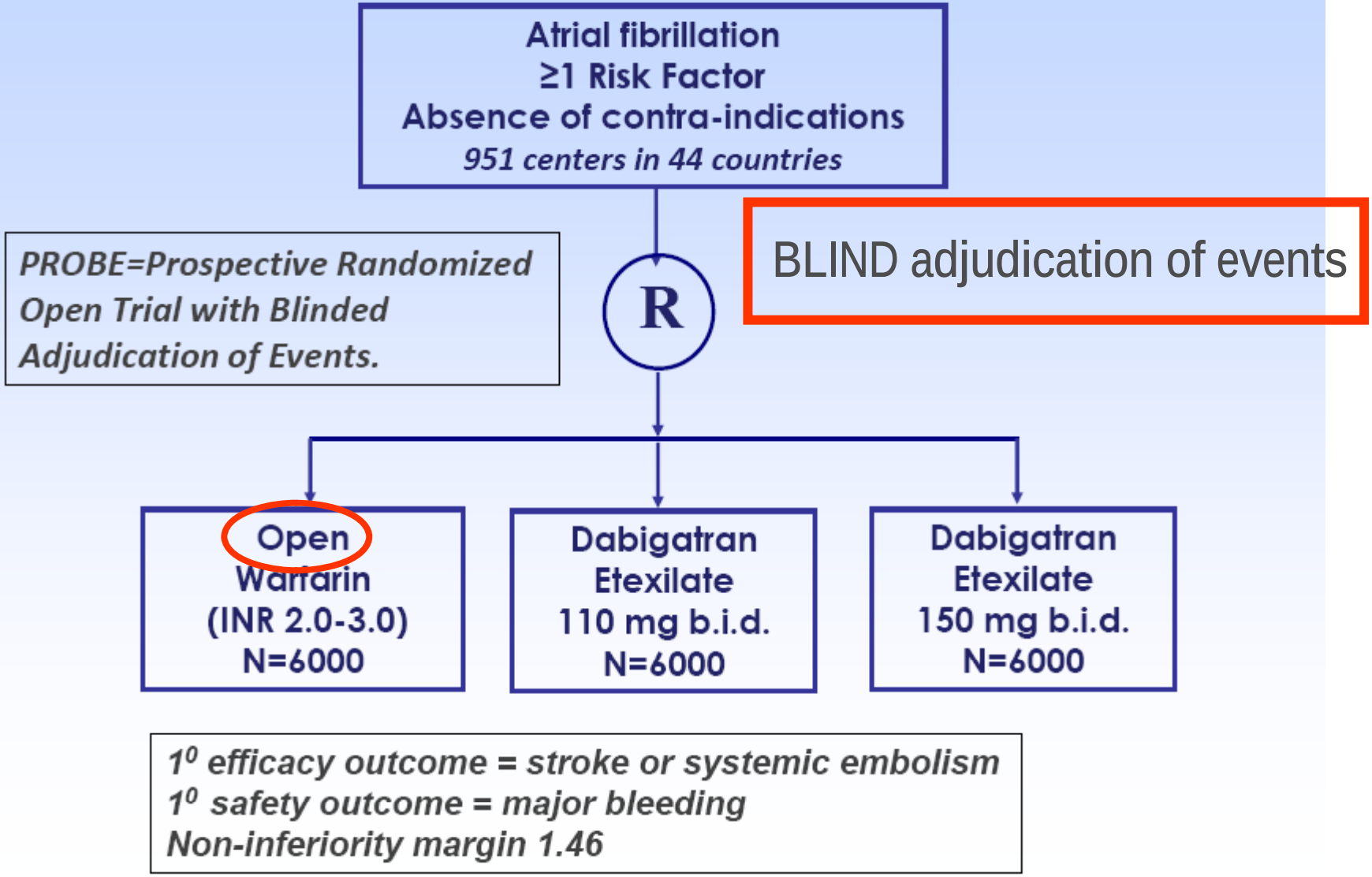
Dabigatran

RELY®
Study of stroke prevention in atrial fibrillation

- Dabigatran Etexilate, a pro-drug, is rapidly converted to dabigatran
- 6.5% bioavailability, 80% excreted by kidney
- Half-life of 12-17 hours
- Phase 2 data identified 220 mg daily and 150 mg BID as target doses

Design of RE-LY

RELY®
Study of stroke prevention in atrial fibrillation



Trial Execution

RELY®
Study of stroke prevention in atrial fibrillation

- Performed December 2005-March 2009
- Median Follow up 2.0 years
- Follow up 99.9% complete
- Mean TTR = 64% (patients on warfarin)

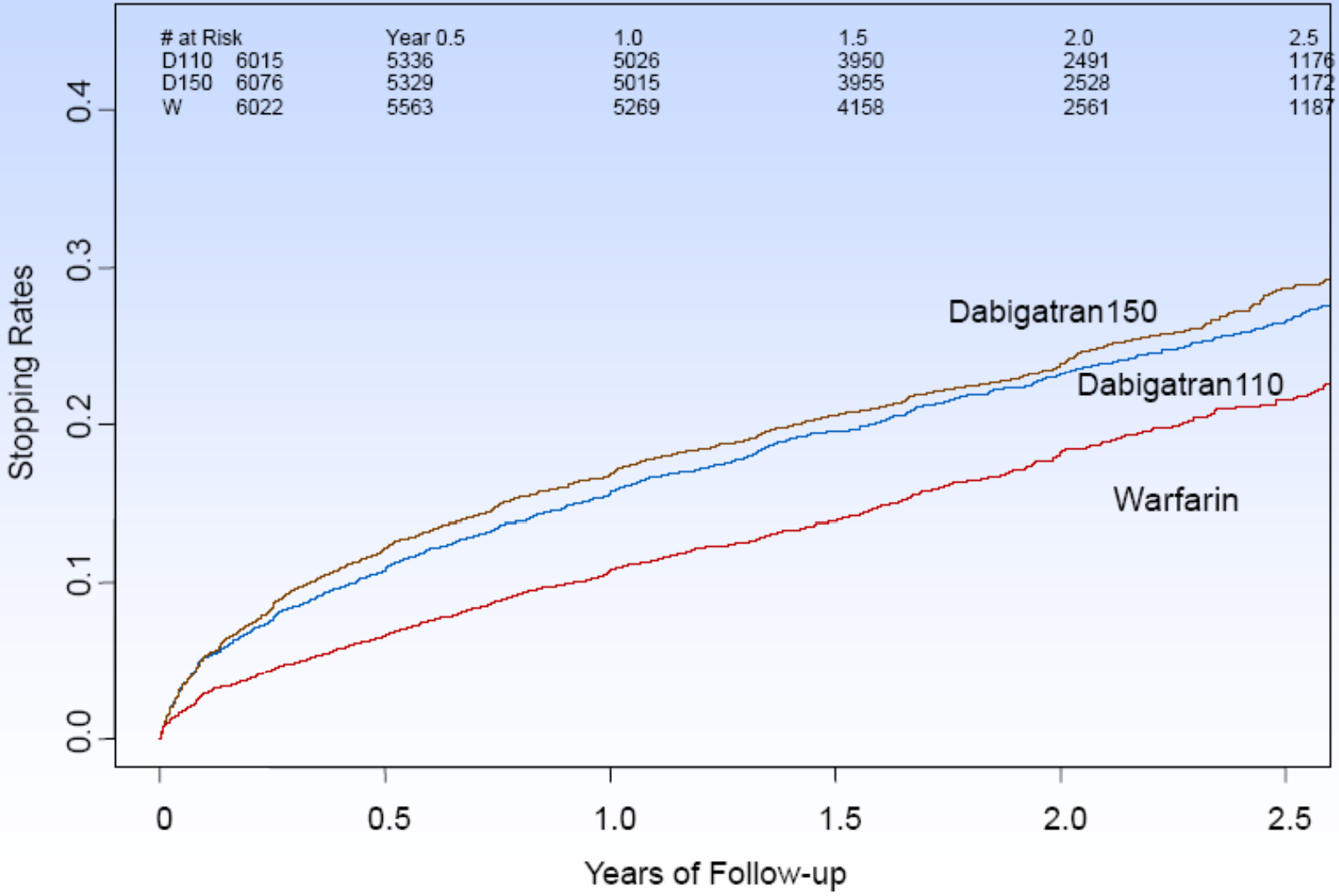
Baseline Characteristics

RELY®
Study of stroke prevention in atrial fibrillation

Characteristic	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
Randomized	6015	6076	6022
Mean age (years)	71.4	71.5	71.6
Male (%)	64.3	63.2	63.3
CHADS2 score (mean)	2.1	2.2	2.1
0-1 (%)	32.6	32.2	30.9
2 (%)	34.7	35.2	37.0
3+ (%)	32.7	32.6	32.1
Prior stroke/TIA (%)	19.9	20.3	19.8
Prior MI (%)	16.8	16.9	16.1
CHF (%)	32.2	31.8	31.9
Baseline ASA (%)	40.0	38.7	40.6
Warfarin Naïve (%)	49.9	49.8	51.4

Permanent Discontinuation

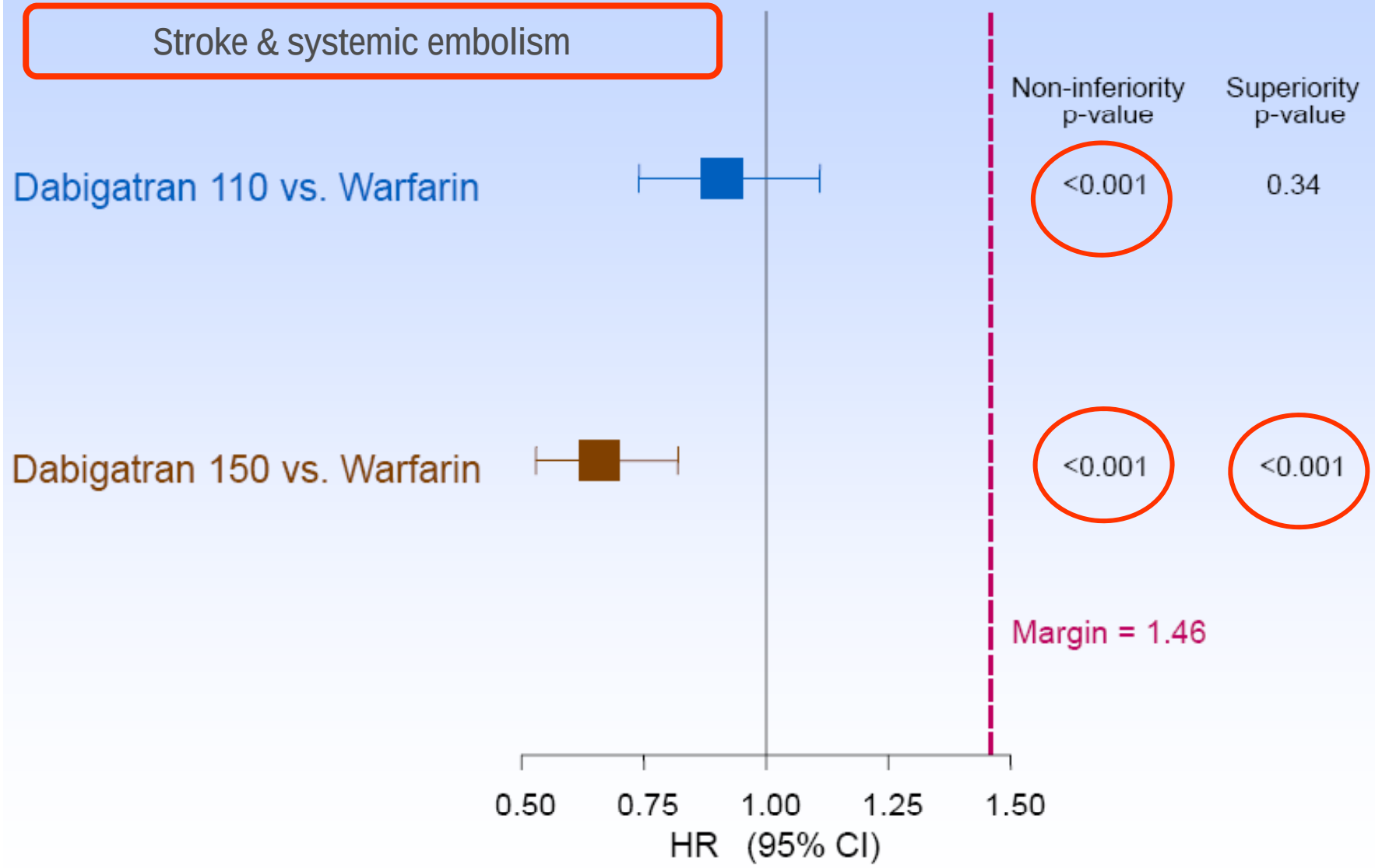
RELY®
Study of stroke prevention in atrial fibrillation



Primary Outcome

RELY®
Study of stroke prevention in atrial fibrillation

Stroke & systemic embolism



Primary Outcome

RELY®
Study of stroke prevention in atrial fibrillation

	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Number rate/yr	Number rate/yr	Number rate/yr	RR 95% CI	p	RR 95% CI	p
Stroke or systemic Embolism	182 1.5 %/yr	134 1.1 %/yr	199 1.7 %/yr	0.91 0.74-1.11	0.34	0.66 0.53-0.82	<0.001
Stroke	171 1.4 %/yr	122 1.0 %/yr	185 1.6 %/yr	0.92 0.74-1.13	0.41	0.64 0.51-0.81	<0.001
Systemic Embolism	14 0.1 %/yr	13 0.1 %/yr	19 0.2 %/yr	0.73 0.37-1.46	0.38	0.67 0.33-1.36	0.27

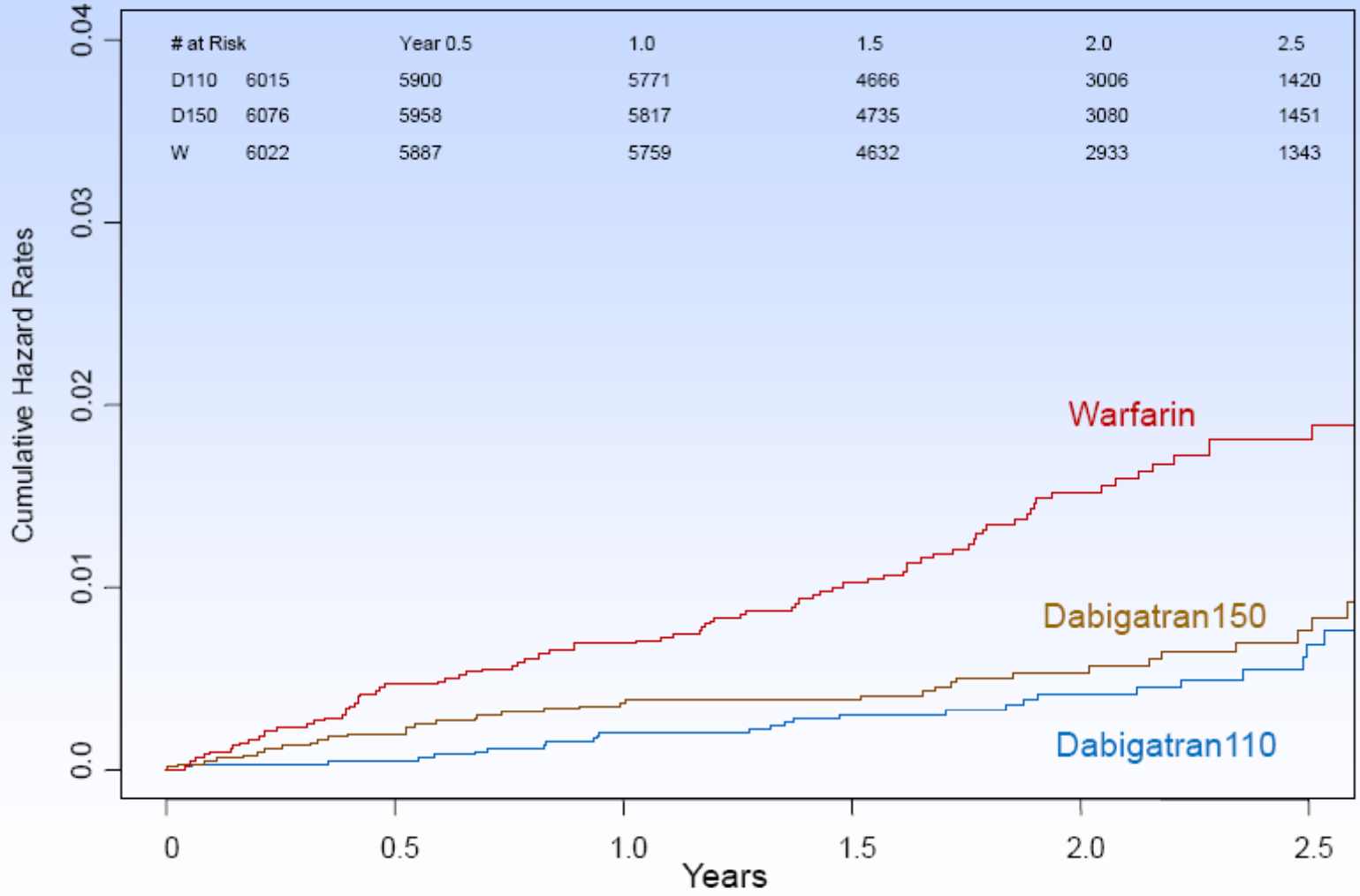
Stroke Classification

RELY®
Study of stroke prevention in atrial fibrillation

	D 110mg	D 150mg	warfarin	D 110 mg vs. Warfarin		D 150 mg vs. Warfarin	
	Number rate/yr	Number rate/yr	Number rate/yr	RR 95% CI	p	RR 95% CI	p
Ischemic	152 1.3 %/yr	103 0.9 %/yr	133 1.1 %/yr	1.14 0.90-1.43	0.28	0.76 0.59-0.98	0.03
Hemorrhagic	14 0.1 %/yr	12 0.1 %/yr	45 0.4 %/yr	0.31 0.17-0.56	<0.001	0.26 0.14-0.49	<0.001
Ischemic/ Unspecified	159 1.3 %/yr	111 0.9 %/yr	142 1.2 %/yr	1.11 0.89-1.40	0.35	0.76 0.60-0.98	0.03

All Intracranial Bleeding

RELY®
Study of stroke prevention in atrial fibrillation



MI, Hospitalization and Death

RELY®
Study of stroke prevention in atrial fibrillation

	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR 95% CI	p	RR 95% CI	p
Myocardial Infarction	0.7%	0.7 %	0.5 %	1.35 0.98-1.87	0.07	1.38 1.00-1.91	0.048
Hospitalization	19.4 %	20.2%	20.8 %	0.92 0.87-0.97	0.003	0.97 0.92-1.03	0.34
Death	3.8 %	3.6 %	4.1 %	0.91 0.80-1.03	0.13	0.88 0.77-1.00	0.05

Bleeding and Net Clinical Benefit

RELY®
Study of stroke prevention in atrial fibrillation

	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR 95% CI	p	RR 95% CI	p
Major Bleeding	2.7 %	3.1 %	3.4 %	0.80 0.69-0.93	0.003	0.93 0.81-1.07	0.31
Life-Threatening major	1.2 %	1.5 %	1.8 %	0.68 0.55-0.83	<0.001	0.81 0.66-0.99	0.04
Minor Bleeding	13.2 %	14.8 %	16.4%	0.79 0.74-0.84	<0.001	0.91 0.85-0.97	0.005
Net Clinical Benefit*	7.1 %	6.9 %	7.6 %	0.92 0.84-1.02	0.10	0.91 0.82-1.00	0.04

* stroke, systemic embolism, myocardial infarction, pulmonary embolism, death and major bleed

Important Sites of Major Bleeding

RELY®
Study of stroke prevention in atrial fibrillation

	Dabigatran 110mg	Dabigatran 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR 95% CI	p	RR 95% CI	p
Gastro-intestinal (GI)	1.1 %	1.5 %	1.0 %	1.10 0.86-1.41	0.43	1.50 1.19-1.89	<0.001
Intracranial (ICH)	0.2 %	0.3 %	0.7 %	0.31 0.20-0.47	<0.001	0.40 0.27-0.60	<0.001
Major Bleed (non-GI, non-ICH)	1.5 %	1.5 %	1.8 %	0.85 0.70-1.04	0.11	0.87 0.71-1.06	0.16

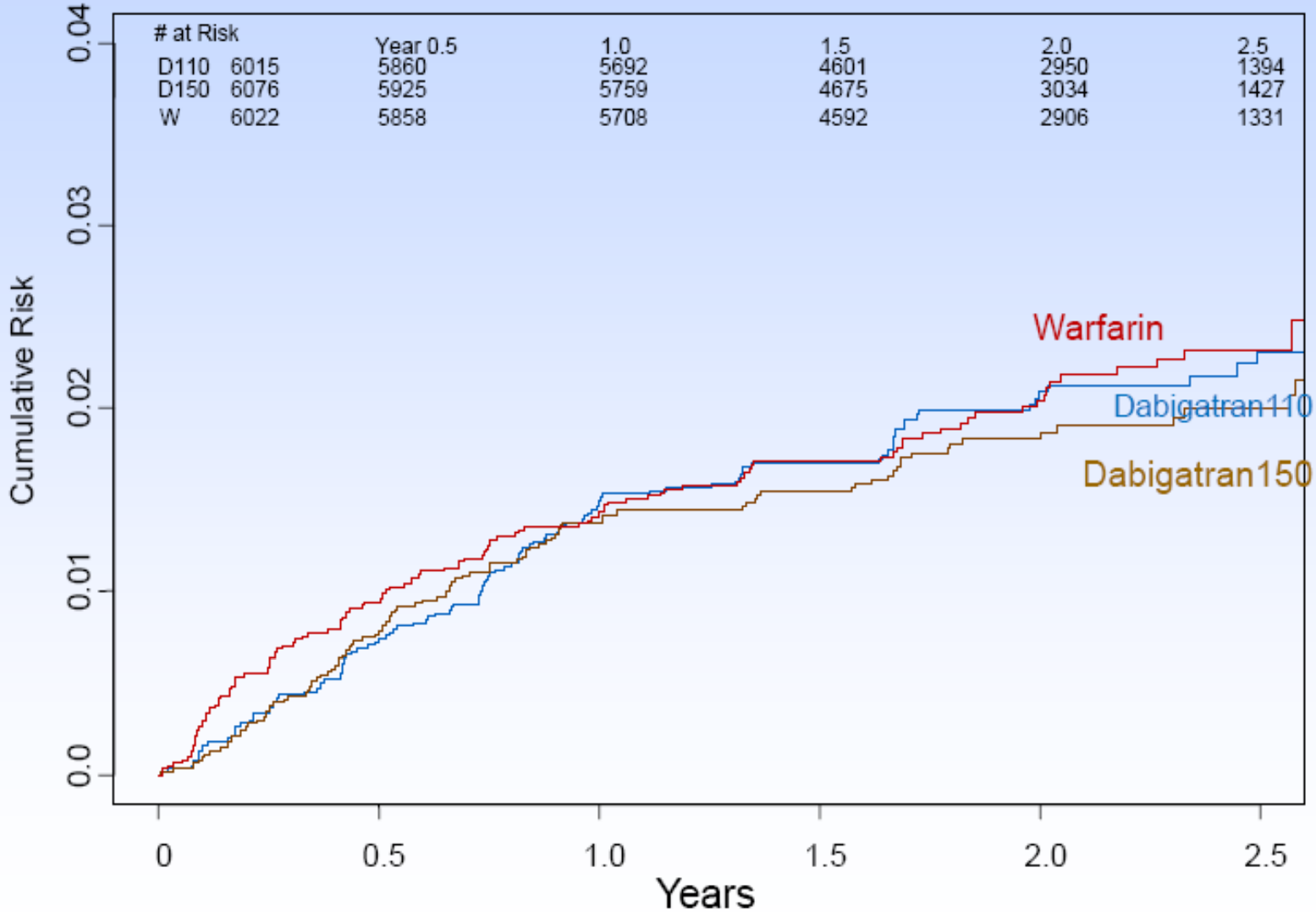
Dabigatran 150 mg vs. 110 mg

RELY®
Study of stroke prevention in atrial fibrillation

	Dabigatran 110mg	Dabigatran 150mg	D 150mg vs. D 110 mg	
	Number rate/yr	Number rate/yr	Relative Risk 95% CI	p
Stroke and systemic embolism	1.53 %	1.11 %	0.73 0.58-0.91	0.005
Ischemic/unspecified stroke	1.34 %	0.92 %	0.69 0.54-0.88	0.002
Hemorrhagic stroke	0.12 %	0.10 %	0.85 0.39-1.83	0.67
Major Hemorrhage	2.67 %	3.11 %	1.17 1.01-1.36	0.04
GI Major Hemorrhage	1.12 %	1.51 %	1.36 1.09-1.70	0.007
Net Clinical Benefit	7.09 %	6.91 %	0.98 0.89-1.08	0.66

ALT or AST >3x ULN

RELY®
Study of stroke prevention in atrial fibrillation



Most common Adverse Events

RELY®
Study of stroke prevention in atrial fibrillation

	Dabigatran 110 mg %	Dabigatran 150 mg %	Warfarin %
Dyspepsia *	11.8	11.3	5.8
Dyspnea	9.3	9.5	9.7
Dizziness	8.1	8.3	9.4
Peripheral edema	7.9	7.9	7.8
Fatigue	6.6	6.6	6.2
Cough	5.7	5.7	6.0
Chest pain	5.2	6.2	5.9
Arthralgia	4.5	5.5	5.7
Back pain	5.3	5.2	5.6
Nasopharyngitis	5.6	5.4	5.6
Diarrhea	6.3	6.5	5.7
Atrial fibrillation	5.5	5.9	5.8
Urinary tract infection	4.5	4.8	5.6
Upper respiratory tract infection	4.8	4.7	5.2

*Occurred more commonly on dabigatran p<0.001

Conclusions

RELY®
Study of stroke prevention in atrial fibrillation

- Dabigatran 110 mg had a similar rate of stroke as warfarin with significantly reduced major bleeding
- Dabigatran 150 mg significantly reduced stoke compared to warfarin with similar risk of major bleeding
- Both doses markedly reduced intra-cranial hemorrhage
- Both doses are free of liver and other major toxicity, although they increase dyspepsia and GI bleeding

Atrial fibrillation: Key points

Is it relevant ?

Are antiarrhythmic strategies effective ?

Anticoagulation after ESC 2009 ?

The future ?

Atrial fibrillation: conclusions (I)

"Disease"

AF is a growing CV disease that ↑ morbidity and mortality

- - - - - - - > triple burden to the society

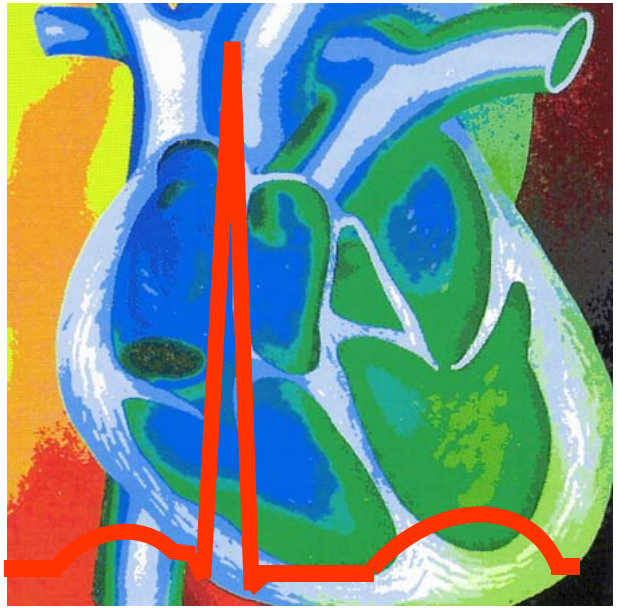
- **Patients**
  - **Increased mortality and morbidity (stroke, heart failure…)**
  - **Impaired quality of life**
- **Physicians**
  - Difficult to treat condition, often not curable
  - No fully satisfactory treatment option available
- **Payers**
  - High risk of hospitalizations & ↑cost
  - Side effects and monitoring needed with existing agents

Atrial fibrillation: conclusions (II)

"Treatment"

- Current Therapeutic Options aim to relieve symptoms and only achieve poor compromises
- Existing AAD are also associated with with toxicities and do not improve clinical outcomes - - - - - > need for new atrium-selective efective & save AAD
- Broad majority of patients will need chronic (NEW) anticoagulation therapy
- Invasive curative approaches are expanding and might change the scenario (universal coverage unlikely)

Atrial fibrillation



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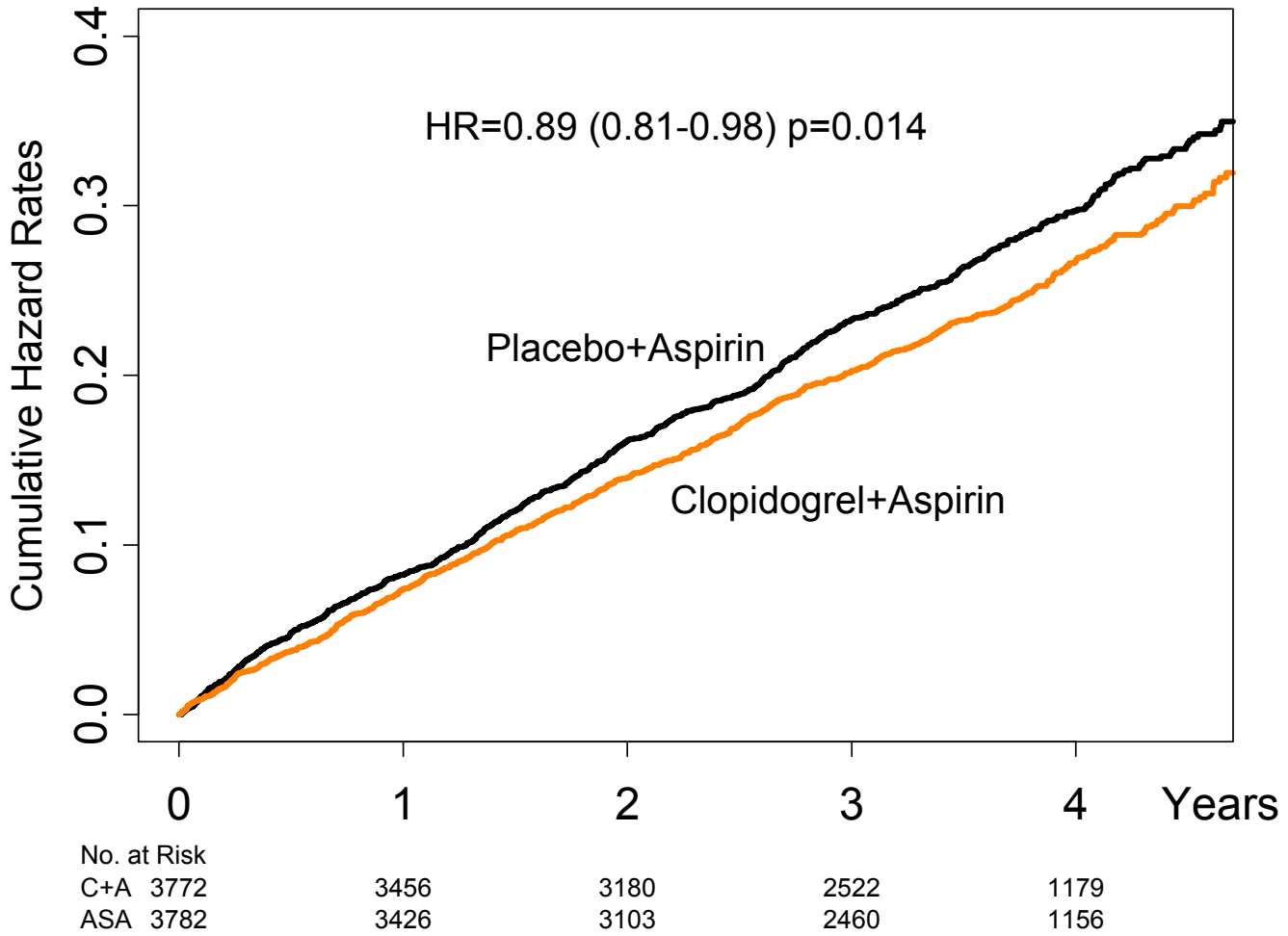
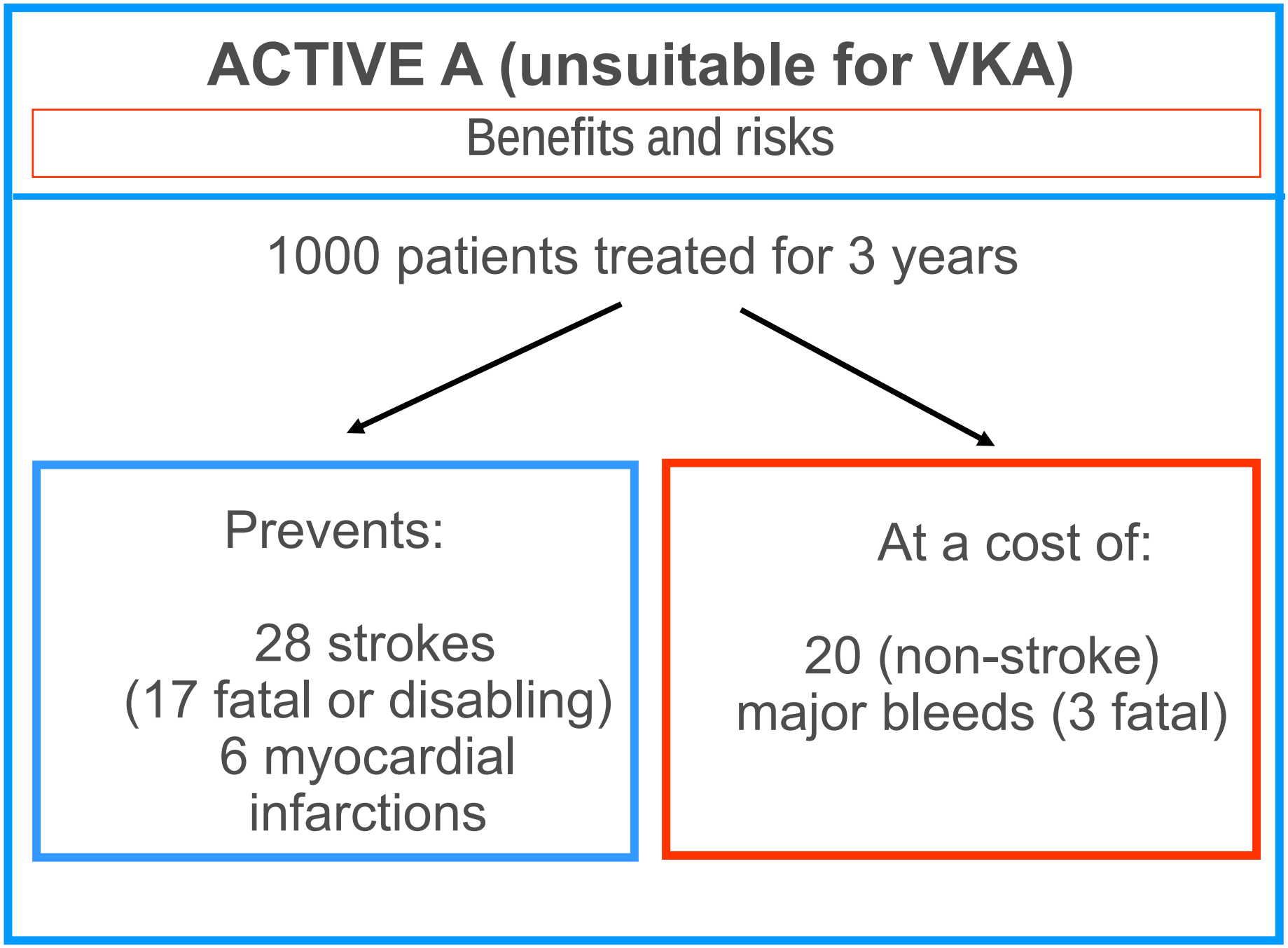
Atrial fibrillation: AAS vs. AAS+Clopidogrel ACTIVE A (unsuitable for VKA)

Outcome	Clopidogrel + Aspirin		Aspirin		Clopidogrel + Aspirin versus Aspirin		
	#	rate/ year	#	rate/ year	RR	95% CI	P
Primary	832	6.8	924	7.6	0.89	0.81-0.98	0.014
Stroke	296	2.4	408	3.3	0.72	0.62-0.83	<0.001
MI	90	0.7	115	0.9	0.78	0.59-1.03	0.08
Vascular Death	600	4.7	599	4.7	1.0	0.89-1.12	0.97
Non-CNS systemic embolism	54	0.4	56	0.4	0.96	0.66-1.40	0.84

ACTIVE A (unsuitable for VKA)

Primary outcome: Stroke + MI + non-CNS systemic embolism + vascular death




ACTIVE A (unsuitable for VKA)
Benefits and risks
1000 patients treated for 3 years
Prevents:
28 strokes
(17 fatal or disabling)
6 myocardial
infarctions
At a cost of:
20 (non-stroke)
major bleeds (3 fatal)

Other New Antithrombotic Drugs

Conclusions

- Otamixaban 0.105-0.140 mg/kg/h assoc w/ up to 40% ↓ in death or ischemic events compared w/ UFH + eptifibatide
- Otamixaban ≤ 0.070 mg/kg/h assoc with ↑ need for bailout GP IIb/IIIa and thrombotic complications during PCI
- Otamixaban 0.175 mg/kg/h assoc with ↑ major & minor bleeding compared with UFH + eptifibatide; doses of 0.105-0.140 mg/kg/h not assoc w/ signif ↑ in major/minor bleeding
- Otamixaban 0.105-0.140 mg/kg/h appears to be best range for further study as a replacement for UFH + GP IIb/IIIa

BUT I.V.

Other New Antithrombotic Drugs

Idrabiotaparinux

Van Gogh: similar efficacy in DVT
less efficacy in PE
less bleeding

AMADEUS (SPAF)
Confirmed efficacy despite low event rate BUT
excess of bleeding (old people & renal failure)

Lancet 2008; 371: 315-21

Borealis-AF (dosis adjusted by age & renal function)

ARISTOTLE Trial Overview

Atrial Fibrillation with At Least One Additional Risk Factor for Stroke

& atrial flutter

- Age = 75 years
- Prior stroke, TIA or SE
- CHF or LVEF = 40%
- Diabetes mellitus
- Hypertension

Randomize
Double blind
(n = 15,000)

Apixaban 5 mg oral twice daily
+
Warfarin placebo

Apixaban placebo twice daily
+
Warfarin (target INR 2-3)

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

Primary outcome: stroke and systemic embolism

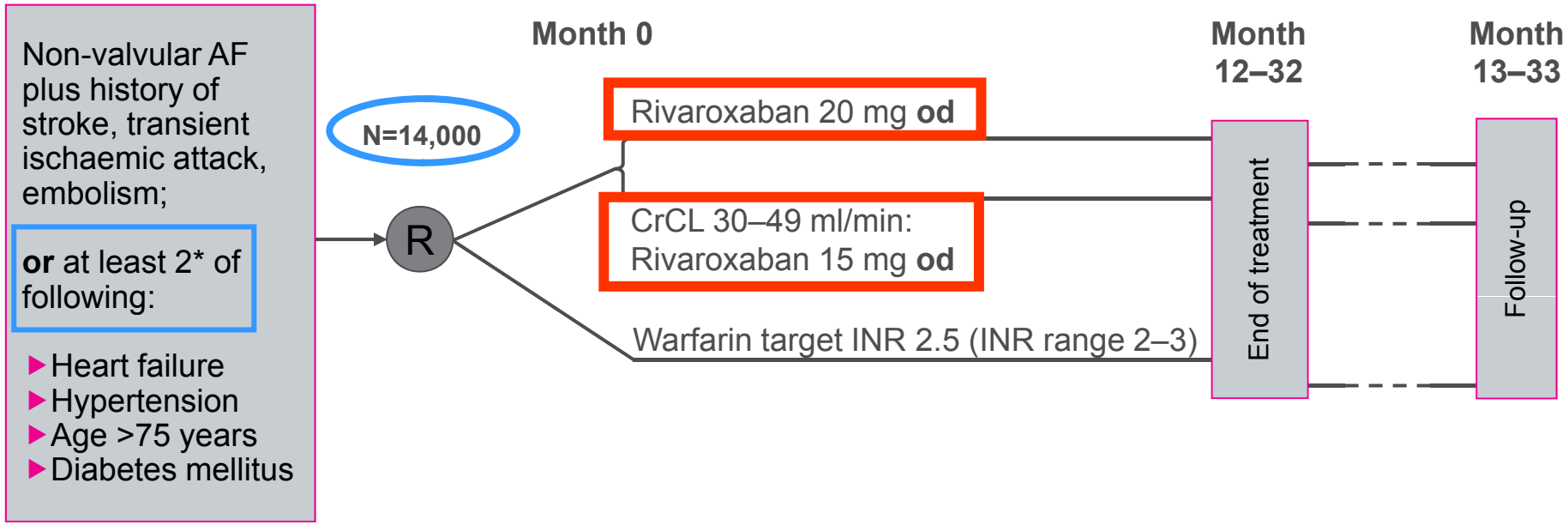
Other outcomes: Death, MI, bleeding

Stratified by warfarin-naïve status

448 events over anticipated 2 year median follow-up;
>90% power to show non-inferiority
(apixaban vs warfarin upper bound of 95% CI <1.38)

ROCKET AF: design

Prospective, randomized, double-blind, double-dummy, parallel-group, active control, multicentre, event-driven, non-inferiority study



*After 10% enrolment with 2 risk factors, this increases to 3

ROCKET AF: design

Statistical assumptions

- Requires 405 adjudicated primary efficacy endpoint events
- Sample Size ~ 14,000 patients
- Estimated warfarin stroke / non-CNS event rate 2.3% per year
- Non-inferiority Margin 1.46
- >95% power

Primary Outcome

RELY®
Study of stroke prevention in atrial fibrillation

	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Number rate/yr	Number rate/yr	Number rate/yr	RR 95% CI	p	RR 95% CI	p
Stroke or systemic Embolism	182 1.5 %/yr	134 1.1 %/yr	199 1.7 %/yr	0.91 0.74-1.11	0.34	0.66 0.53-0.82	<0.001
Stroke	171 1.4 %/yr	122 1.0 %/yr	185 1.6 %/yr	0.92 0.74-1.13	0.41	0.64 0.51-0.81	<0.001
Systemic Embolism	14 0.1 %/yr	13 0.1 %/yr	19 0.2 %/yr	0.73 0.37-1.46	0.38	0.67 0.33-1.36	0.27