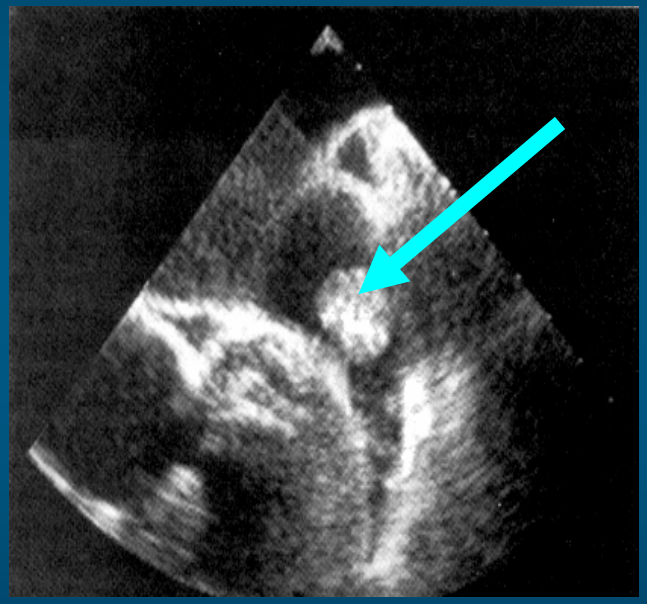
Lisbon, February 2011



New Anticoagulant Strategies in Atrial Fibrillation

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Lisbon, February 2011

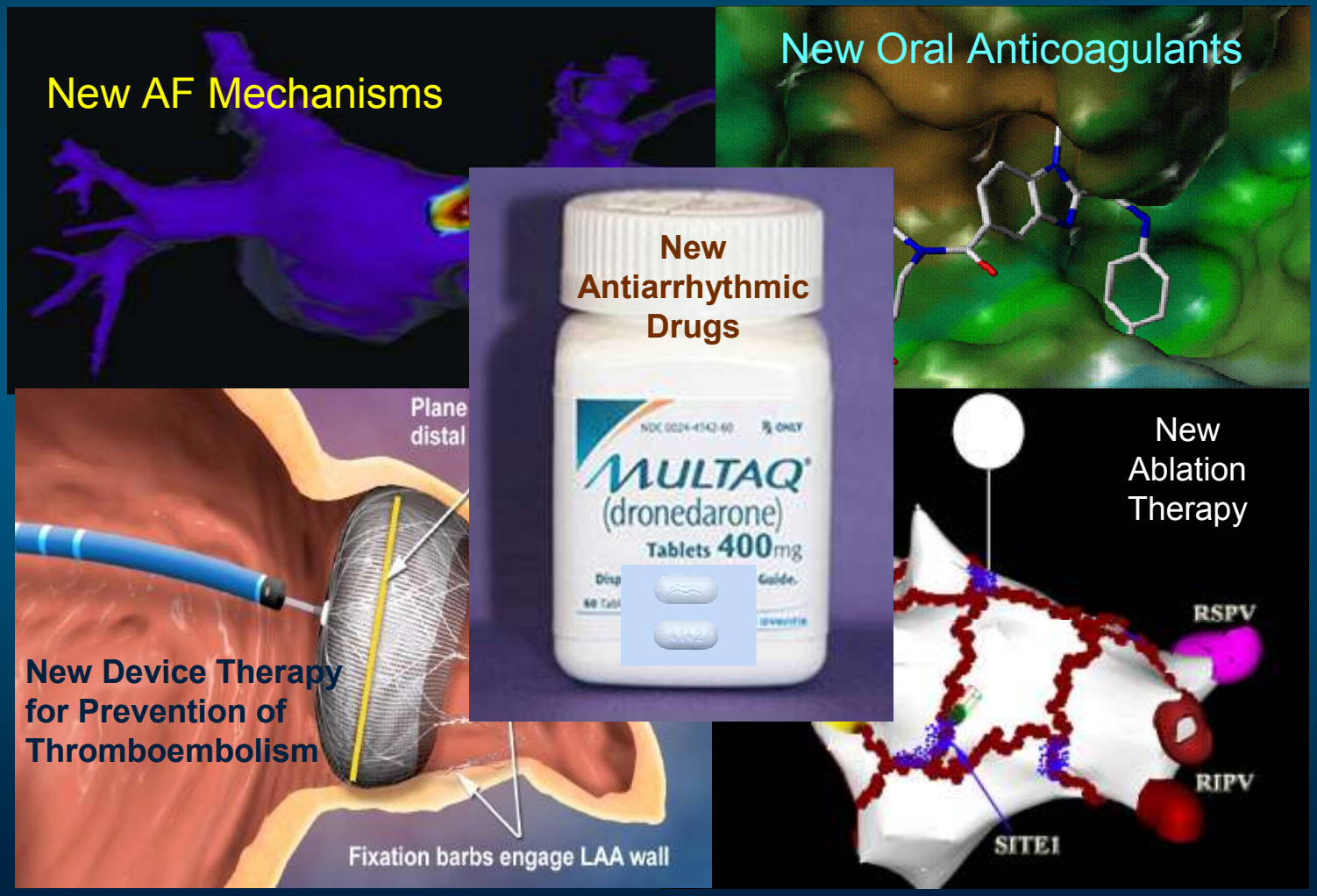
New Anticoagulant Strategies in Atrial Fibrillation

John Camm

Conflicts of Interest: Consultant/Advisor/Speaker

Advisor / Speaker : Ambit, Servier, Novartis, sanofi aventis, Astra Zeneca, Cardiome, Prism, Astellas, Menarini, Xention, ARYx, Bristol Myers Squibb, Daiichi, Bayer, Merck, Medtronic, St. Jude, Biotronik, Boehringer Ingleheim, Takeda, GlaxoSmithKline, Boston Scientific, Pfizer, GlaxoSmithKline, Actelion, Johnson and Johnson, Solvay Pharma

Stoke Reduction in AF
Recent Developments

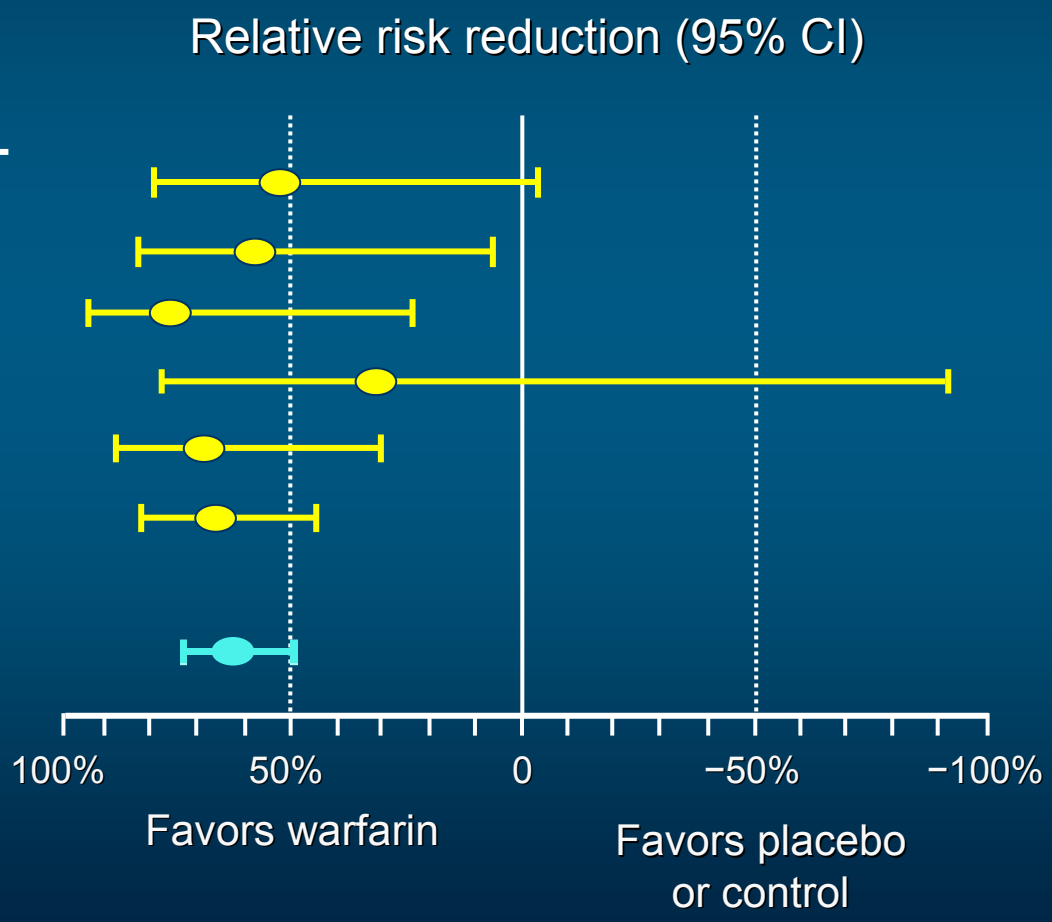


Stroke - Europe

- 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

Efficacy of Warfarin for Stroke Reduction Compared With Placebo or Control in Six Studies

Study	Year
AFASAK I	1989; 1990
SPAF I	1991
BAATAF	1990
CAFA	1991
SPINAF	1992
EAFT	1993
All trials *(n = 6)*	
N = 2,900	

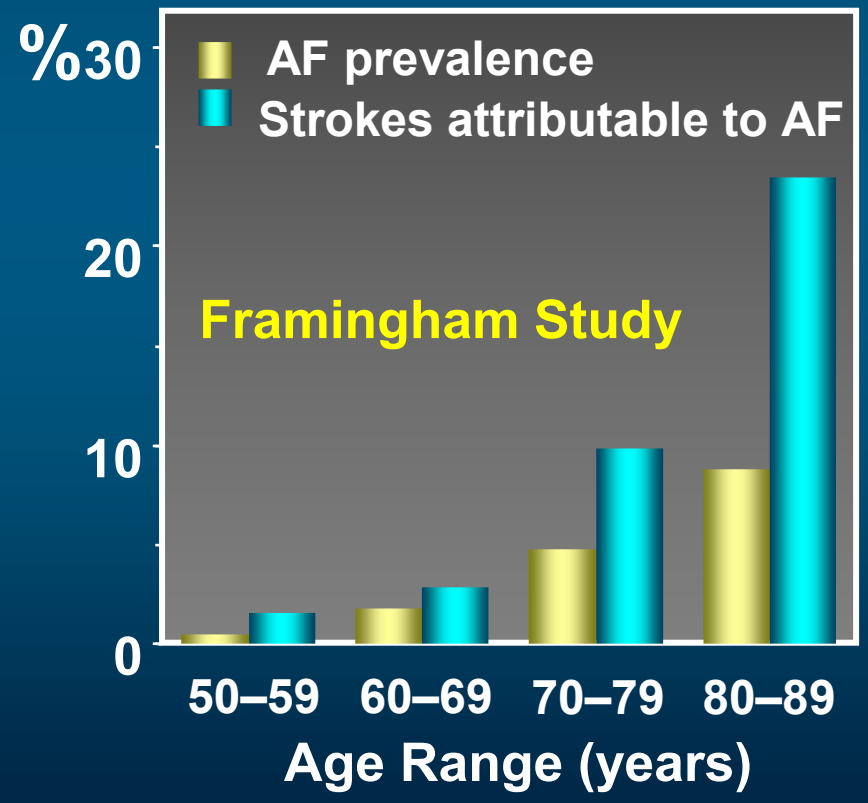


Hart RG, et al. *Ann Intern Med*. 2007;146:857-867.

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



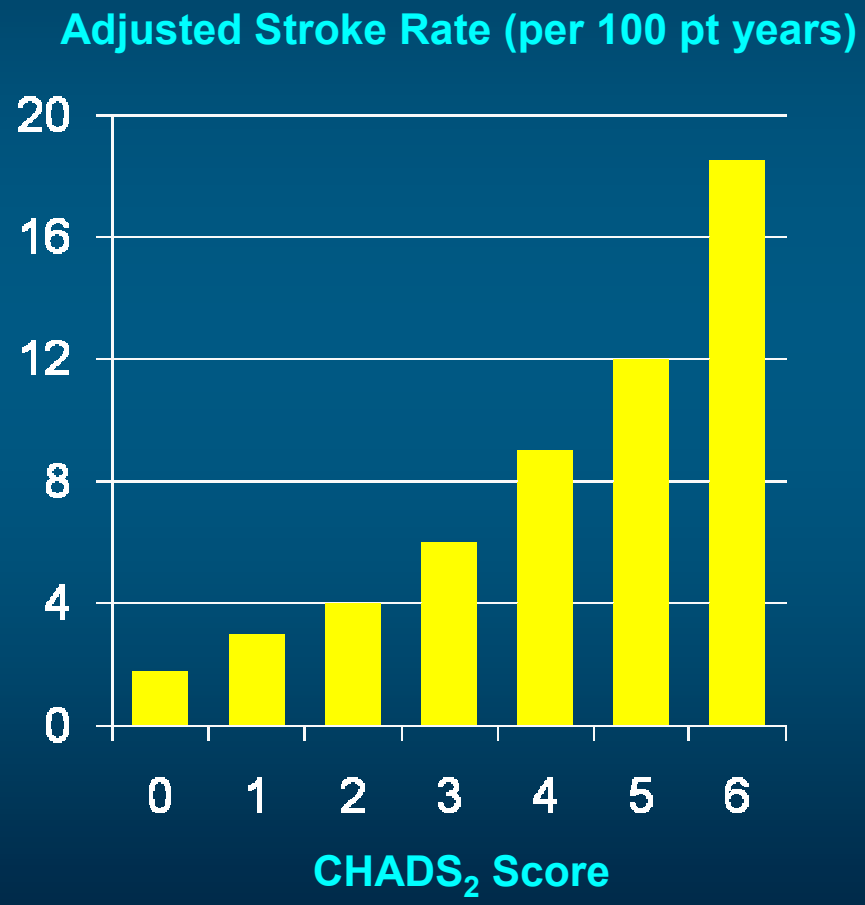
Collaborative Analysis–AFib Investigators. *Arch Intern Med.* 1994;154:1449-1457.

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

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 stokes are attributable to atrial fibrillation

$CHADS_2$ Score	Situation	Remmendation
0	No risk 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 RFs	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

CVA in AF - Risk Models

Model	Risk Factors	Annual Incidence of CVA		
		Low	Intermediate	High
AFI 1994	Age > 65, prior stroke/TIA, HTN, CHF, MI, diabetes, female gender*, PVD*	1%	4.3%	8.1%
SPAF 1998	Age > 75, prior stroke/TIA, women, SBP > 160 mm Hg, CHF or severe LV dysfunction	1%	3%	6%
ACCP 2001	Age ≥ 75, prior stroke/TIA, HTN, VHD, CHF, LVEF ≤ 0.50, thyrotoxicosis	1%	1-4%	8-12%

CVA in AF - Risk Models

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		Low	Intermediate	High
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ACCP 2001	Age ≥ 75, prior stroke/TIA, HTN, VHD, CHF, LVEF ≤ 0.50, thyrotoxicosis	1%	1-4%	8-12%

CHA_2DS_2-VASc

- Congestive heart failure/ LV dysfucntion — 1
- Hypertension — 1
- Age ≥ 75 — 2
- Diabetes mellitus — 1
- Stroke/TIA/TE — 2
- Vascular disease (CAD, CArD, PAD) — 1
- Age 65-74 — 1
- Sex category (female) — 1

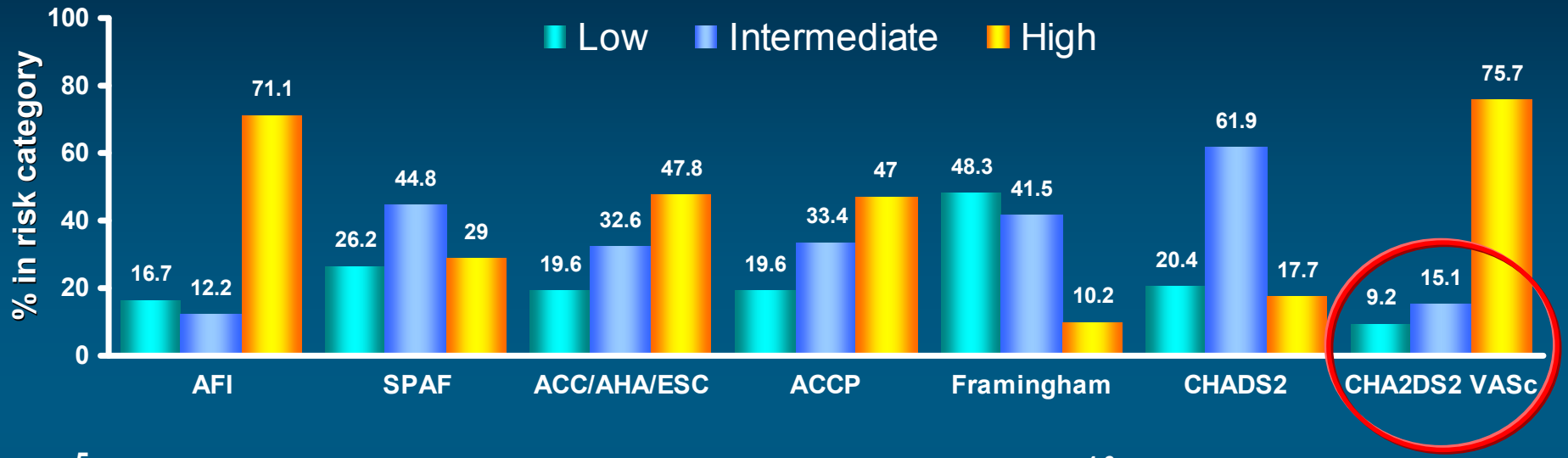
Score 0 – 9

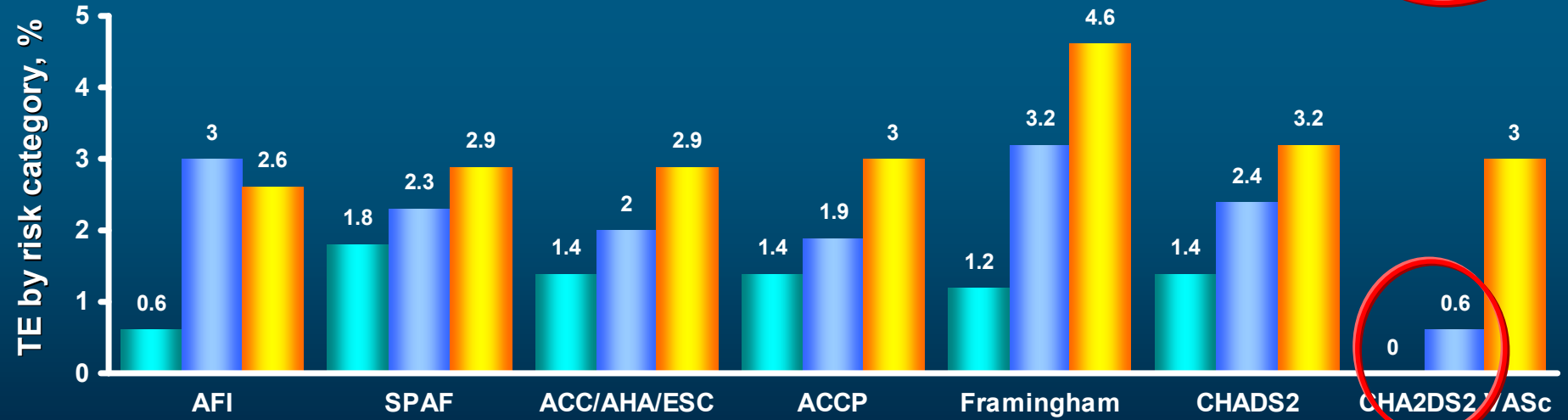
Score	Annual stroke rate, %
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

Validated in 1084 NVAF patients not on OAC with known TE status at 1 year in Euro Heart Survey

OR for stroke if: Female: 2.53 (1.08 – 5.92), p=0.029; Vascular disease: 2.27 (0.94 – 5.46), p=0.063

Validation of CHA_2DS_2VASc in Euro Heart Survey





c-statistic	0.573	0.549	0.571	0.574	0.638	0.561	0.606

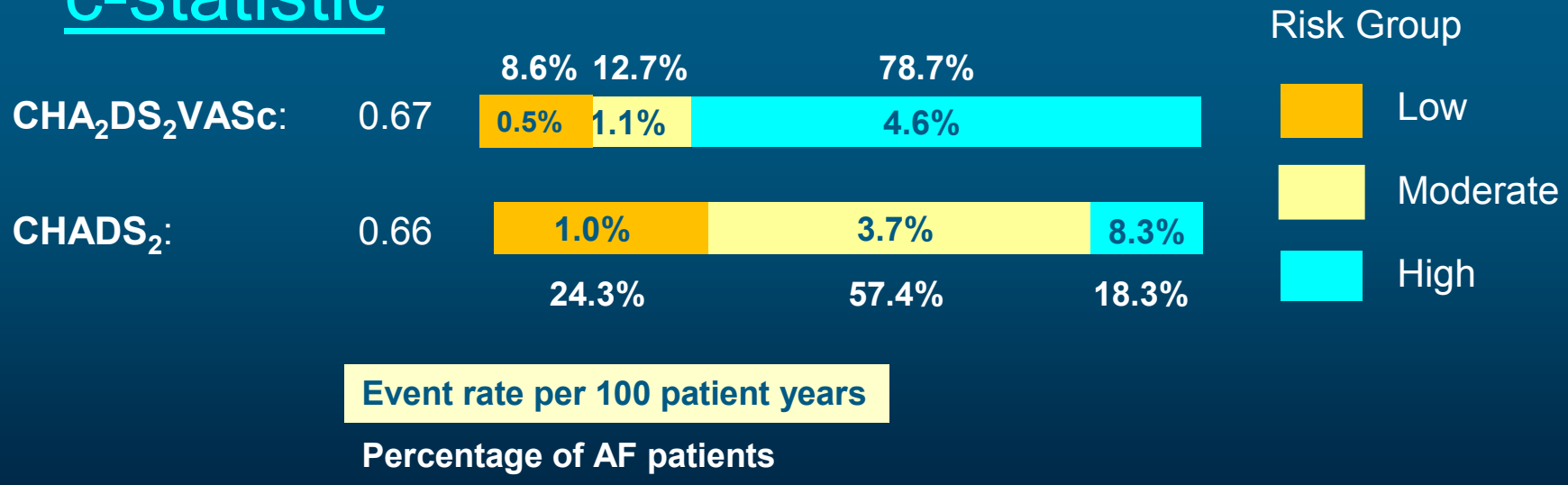
Lip GYH, et al. Chest 2009

CHA_2DS_2VASc - Validation

UK GPR Database

- 79,844 patients
- FU: 4 years
- FU prior to warfarin: 2.4 years

c-statistic



Van Staa TP et al, J Thromb Haemost 2010

Hospital Admission and Fatal Thromboembolism per 100 person years

$CHADS_2$:

Low risk (0)	1.67 (1.47 to 1.89)
Intermediate risk (1)	4.75 (4.45 to 5.07)
High risk (2-6)	12.27 (11.84 to 12.71)

CHA_2DS_2-VASc:

Low risk (0)	0.78 (0.58 to 1.04)
Intermediate risk (1)	2.01 (1.70 to 2.36)
High risk (2-9)	8.82 (8.55 to 9.09)

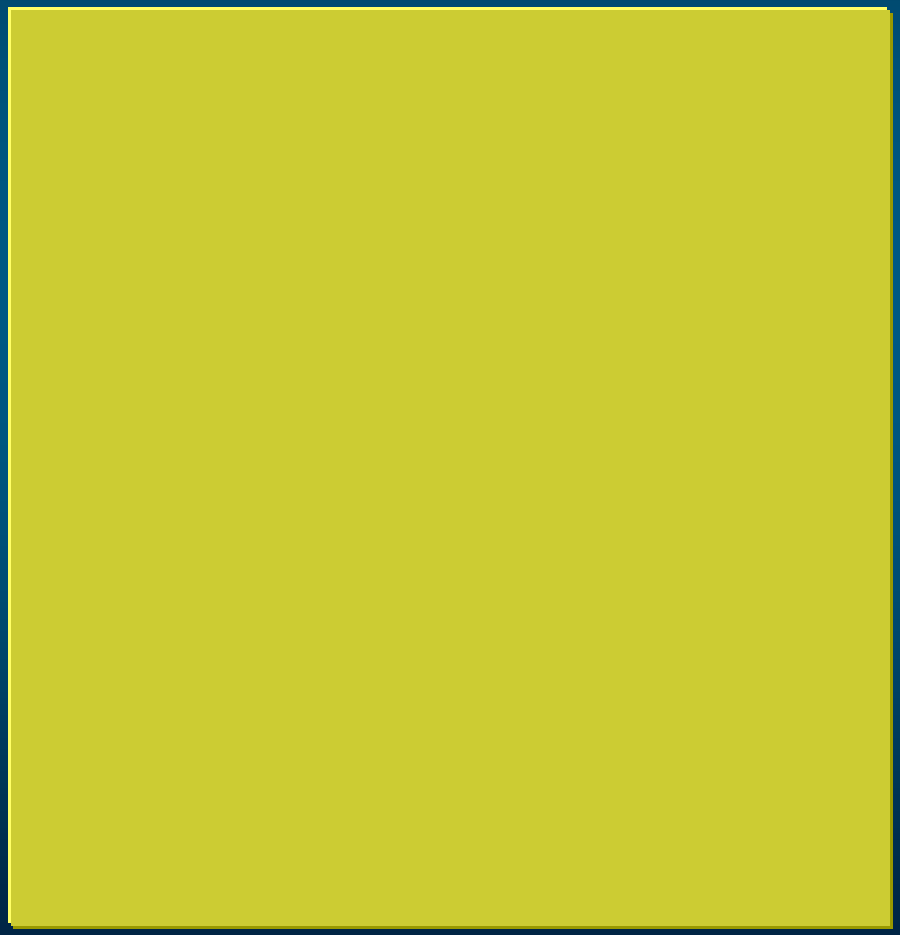
CHA_2DS_2-VASc was clearly superior to $CHADS_2$ for categorisation of patients into risk groups (low, intermediate, and high risk).
At one, five, and 10 years of follow-up, C statistics with $CHADS_2$ were 0.722, 0.796, and 0.812; the corresponding C statistics with CHA_2DS_2-VASc were 0.850, 0.880, and 0.888. The 95% confidence intervals for $CHADS_2$ and CHA_2DS_2-VASc did not overlap.

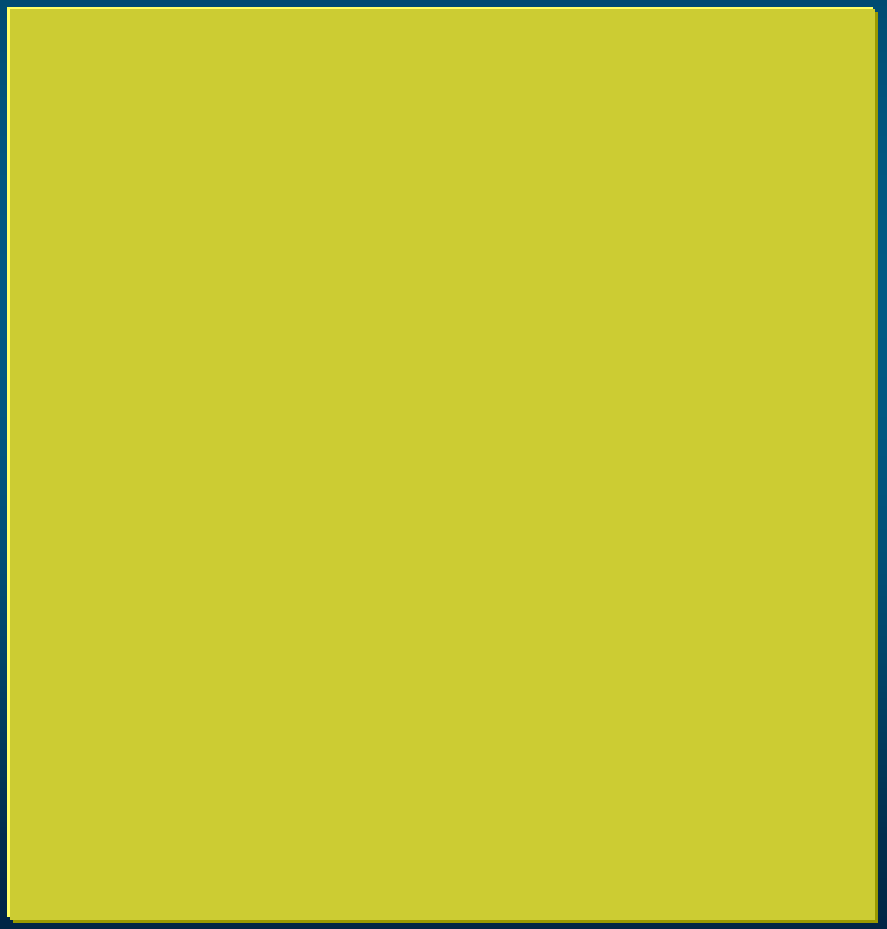
Olesen JB et al, BMJ 2011;342:d124

CHA_2DS_2VASc v $CHADS_2$

All patients with atrial fibrillation not treated with VKAs in Denmark 1997- 2006

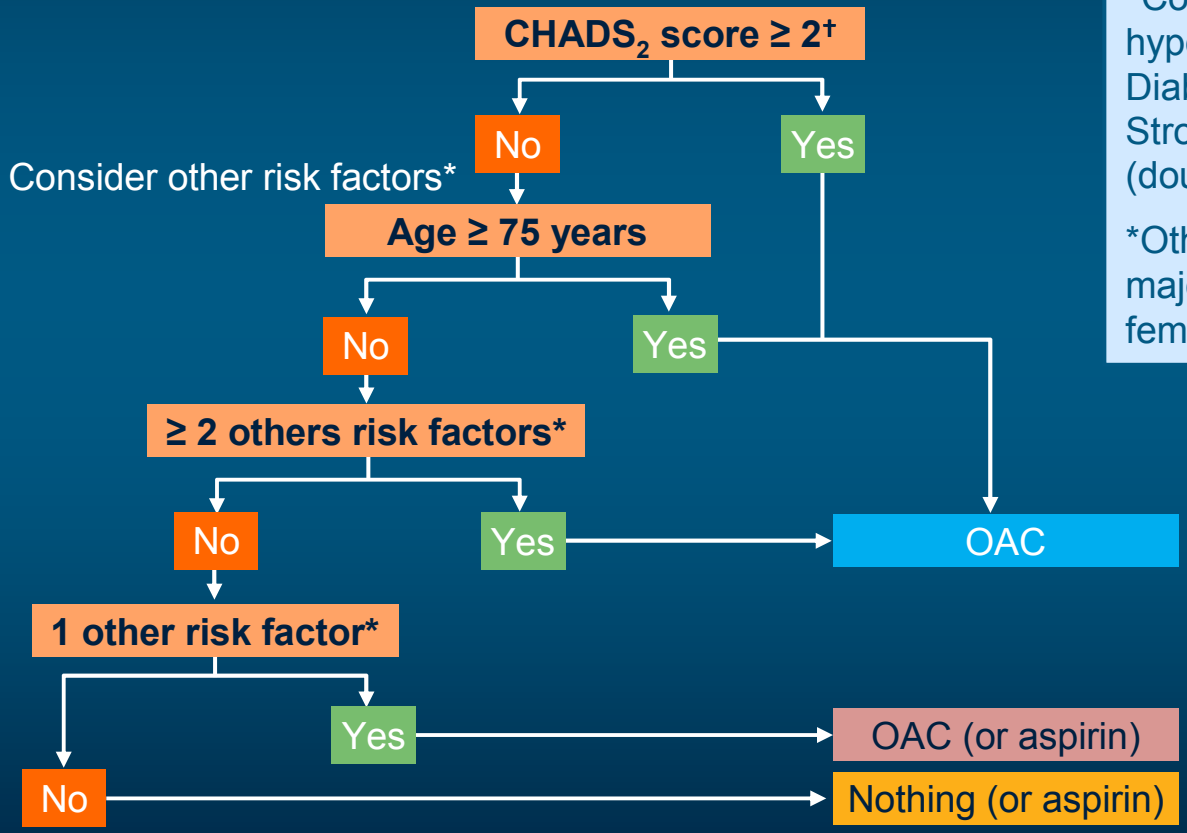
73 538 fulfilled the study inclusion criteria





Olesen JB et al, BMJ 2011;342:d124

Use of Oral Anticoagulation for Stroke Prevention in AF



†Congestive heart failure, hypertension. Age 75 years Diabetes. Stroke/TIA/thromboembolism (doubled)

*Other clinically relevant non-major risk factors: age 65-74, femal sex, vascular disease.

AF = atrial fibrillation; OAC = oral anticoagulant; TIA = transient ischaemic attack.

Prevention of Thromboembolism in AF

Recommendations	Class[a]	Level[b]
Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those at low risk (lone AF, aged < 65 years or with contraindications).	I	A
It is recommended that the selection of the antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the relative risk and benefit for a given patient.	I	A
The $CHADS_2$ (Cardiac failure, Hypertension, Age, Diabetes, Stroke [Doubled]) score is recommended as a simple initial (easily remembered) means of assessing stroke risk in non-valvular AF.	I	A
For the patients with a $CHADS_2$ score of ≥ 2, chronic OAC therapy with a VKA is recommended in a dose-adjusted regimen to achieve an INR range of 2.0-3.0 (target 2.5), unless contraindicated.	I	A
For a more detailed or comprehensive stroke risk assessment in AF (e.g. with $CHADS_2$ score 0-1), a risk factor-based approach is recommended, considering 'major' and 'clinical relevant non-major' stroke risk factors.	I	A
Patients with 1 'major' or ≥ 2 'clinically relevant non-major' risk factors are high risk and OAC therapy [for example, with a VKA, dose adjusted to achieve the target intensity INR of 2.0-3.0] is recommended, unless contraindicated	I	A

[a]Class of recommendation. [b]Level of evidence. AF = atrial fibrillation; CHADS2 = cardiac failure, hypertension, age, diabetes, stroke (doubled); INR = international normalized ratio; LMWH = low molecular weight heparin; OAC = oral anticoagulant; TIA = transient ischaemic attack; VKA = vitamin K antagonist.

Bleeding Risks Scores

Authors	Low	Moderate	High	Risk Factors
Kuijer, et al.	0	1-3	> 3	1.6 x age + 1.3 x sex +2.2 x cancer with 1 point for ≥ 60, female, or malignancy, and 0 if none
Beyth, et al.	0	1-2	≥ 3	≥65 years old; GI bleed in last 2 weeks; previous stroke; comorbidities (recent MI, Hct < 30%, diabetes, creatinine > 1.5) with 1 point for presence of each condition and 0 if absent
Gage, et al.	0-1	2-3	≥ 4	HEMORRHAGES score: liver/renal disease, ETOH abuse, malignancy, > 75 years old, low platelet count or function, re-bleeding risk, uncontrolled HTN, anemia, genetic factors (CYP2C9) risk for fall or stroke, with 1 point for each risk factor present with 2 points for previous bleed
Shireman, et al.	≤1.07	>1.07 - <2.19	> 2.19	(0.49 x age >70) + (0.32 x female) + (0.58 x remote bleed) + (0.62 x recent bleed) + (0.71 x alcohol/drug abuse) + (0.27 x diabetes) + (0.86 x anemia) + (0.32 x antiplatelet drug use) with 1 point for presence of each, and 0 if absent
Pisters, et al.	0	1-2	≥3	HAS-BLED score: Hypertension, Abnormal renal/liver function (1 point each), Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65), Drugs/alcohol concomitantly (1 point each). Maximum 9 points.

Assessment of Risk of Bleeding: HAS-BLED

- Hypertension 1
- Abnormal renal or liver function 1 or 2
- Stroke 1
- Bleeding 1
- Labile INR 1
- Elderly (age > 65 years) 1
- Drugs or alcohol 1 or 2

Score 0 – 9

Validated in 3978 NVAF pts with known TE status at 1 year in Euro Heart Survey

c-statistic 0.72 (similar to $HEMORR_2HAGES$)
0.91 vs 0.85 for patients on ASA or no therapy

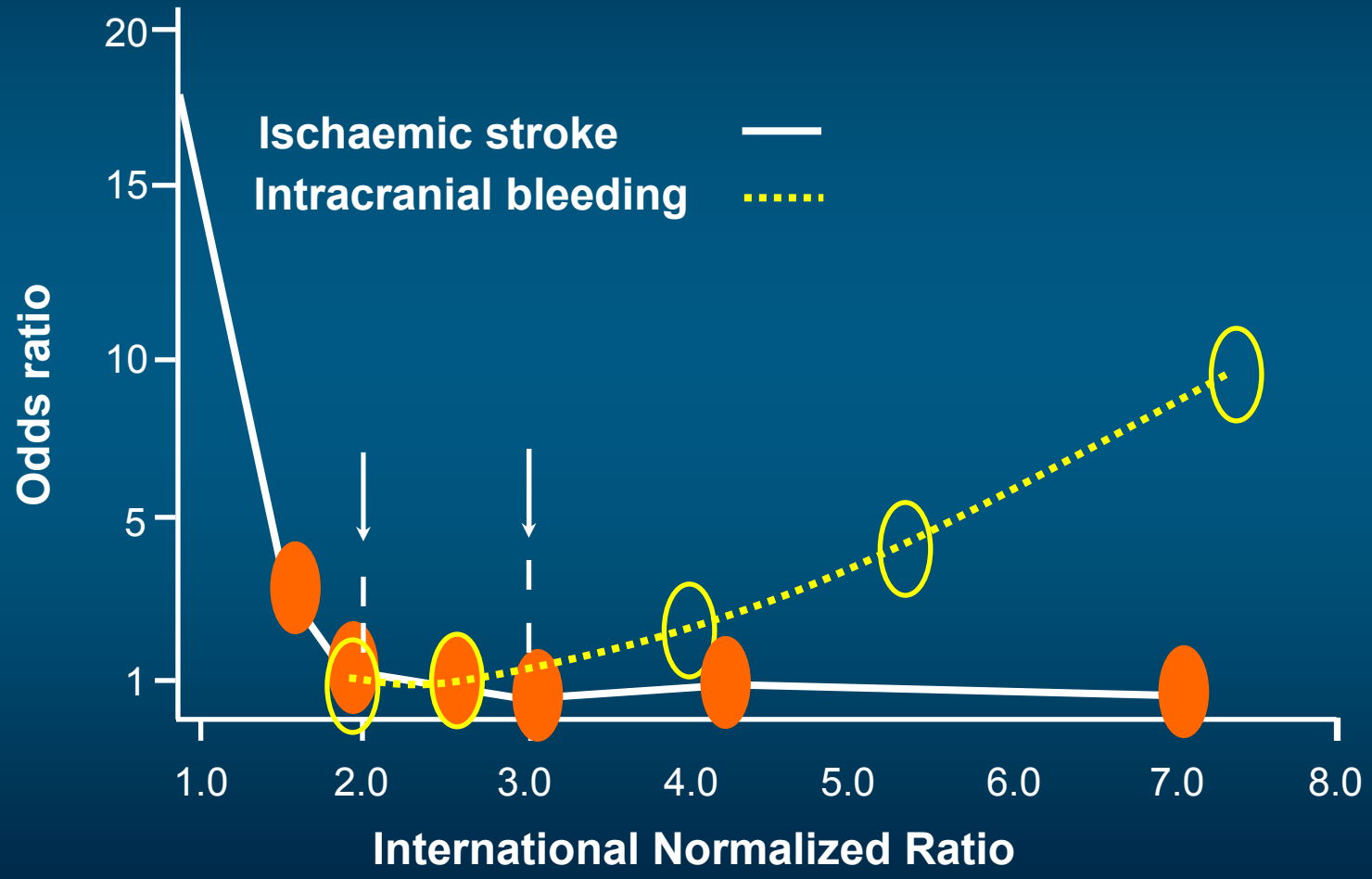
	Score	Bleeds per 100 patient-years
Low	0	1.13
Inter-mediate	1	1.02
	2	1.88
High	3	3.74
	4	8.70

Pisters R, et al. Chest 2010;138:1093-100

Limitations of Warfarin

- Requires partnership between physician and patient to manage the INR, life-long
  - Multiple interactions with food and drugs
    - PK/PD, metabolic, genetic
  - High variability within and between patients
    - Genetic, comorbidity, co-medication, compliance
  - Narrow therapeutic range
    - Frequent testing needed
  - Need with frequent dose adjustment

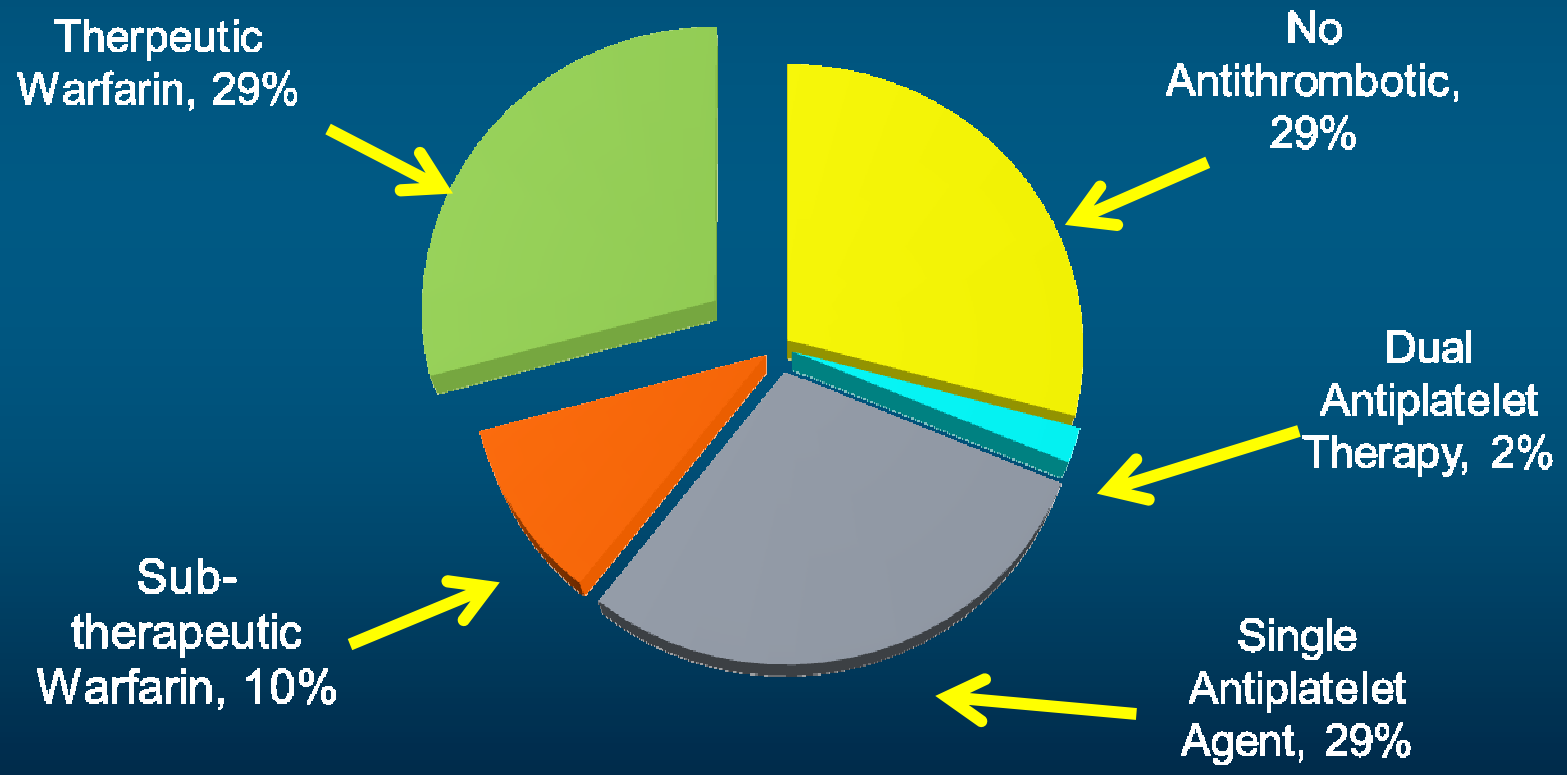
Adjusted Odds Ratios for Ischaemic Stroke and Intracranial Bleeding in Relation to Intensity of Anticoagulation



Fuster V, et al. Circulation 2006;114:e257-e354.

Missed Opportunities for Stroke Prevention in Atrial Fibrillation

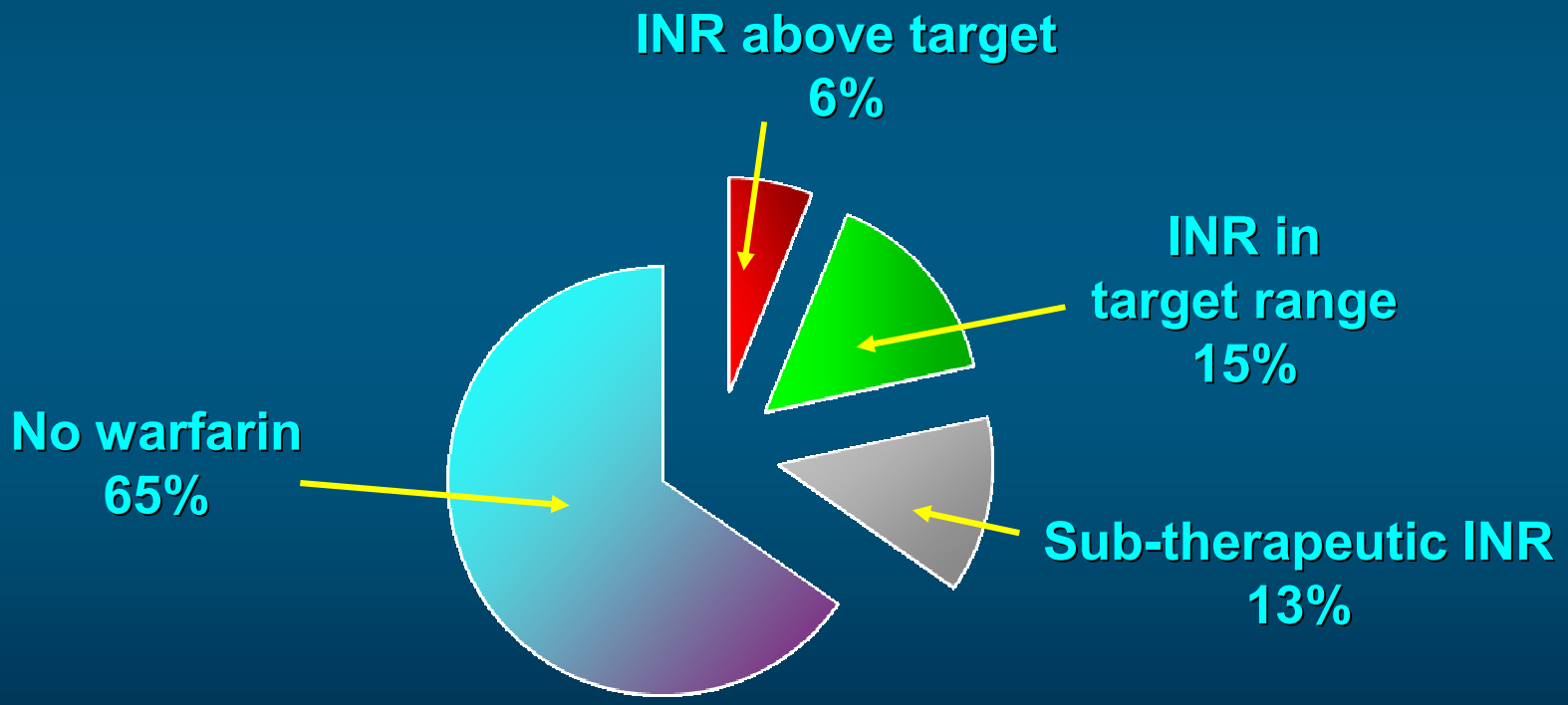
Preadmission medications in patients with known atrial fibrillation who were admitted with acute ischemic stroke (high-risk cohort, n=597)



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

Inadequate VKA Treatment for AF

Adequacy of Anticoagulation in Patients with AF in Primary Care Practice

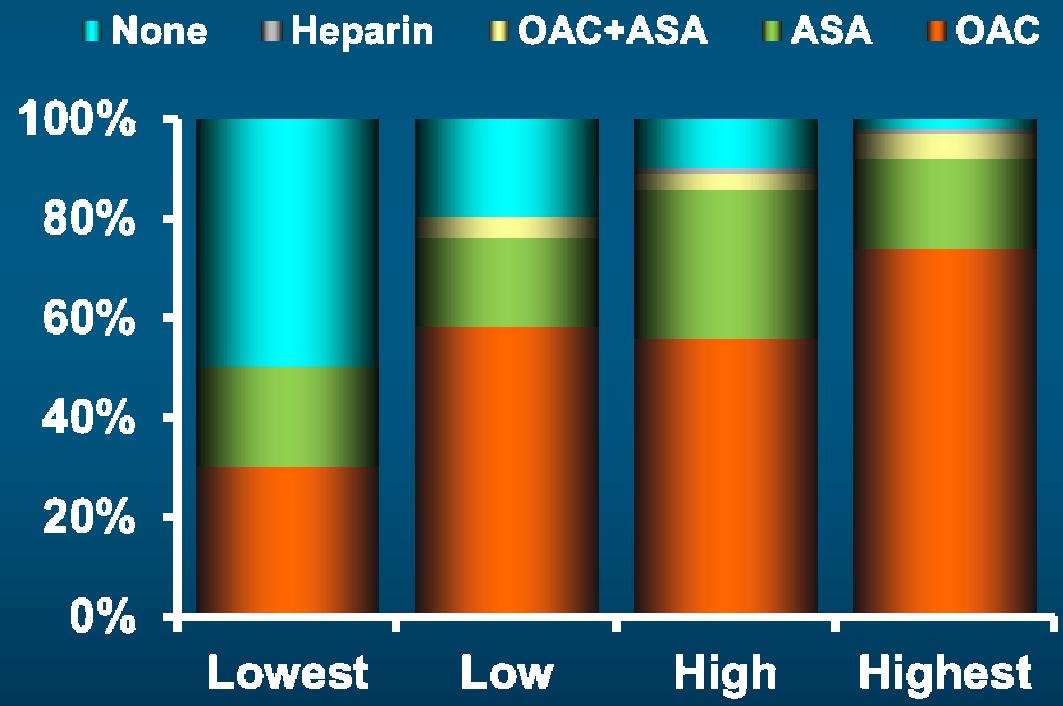


Samsa GP, et al. Arch Intern Med 2000;160:967.

Antithrombotic Treatment in AF

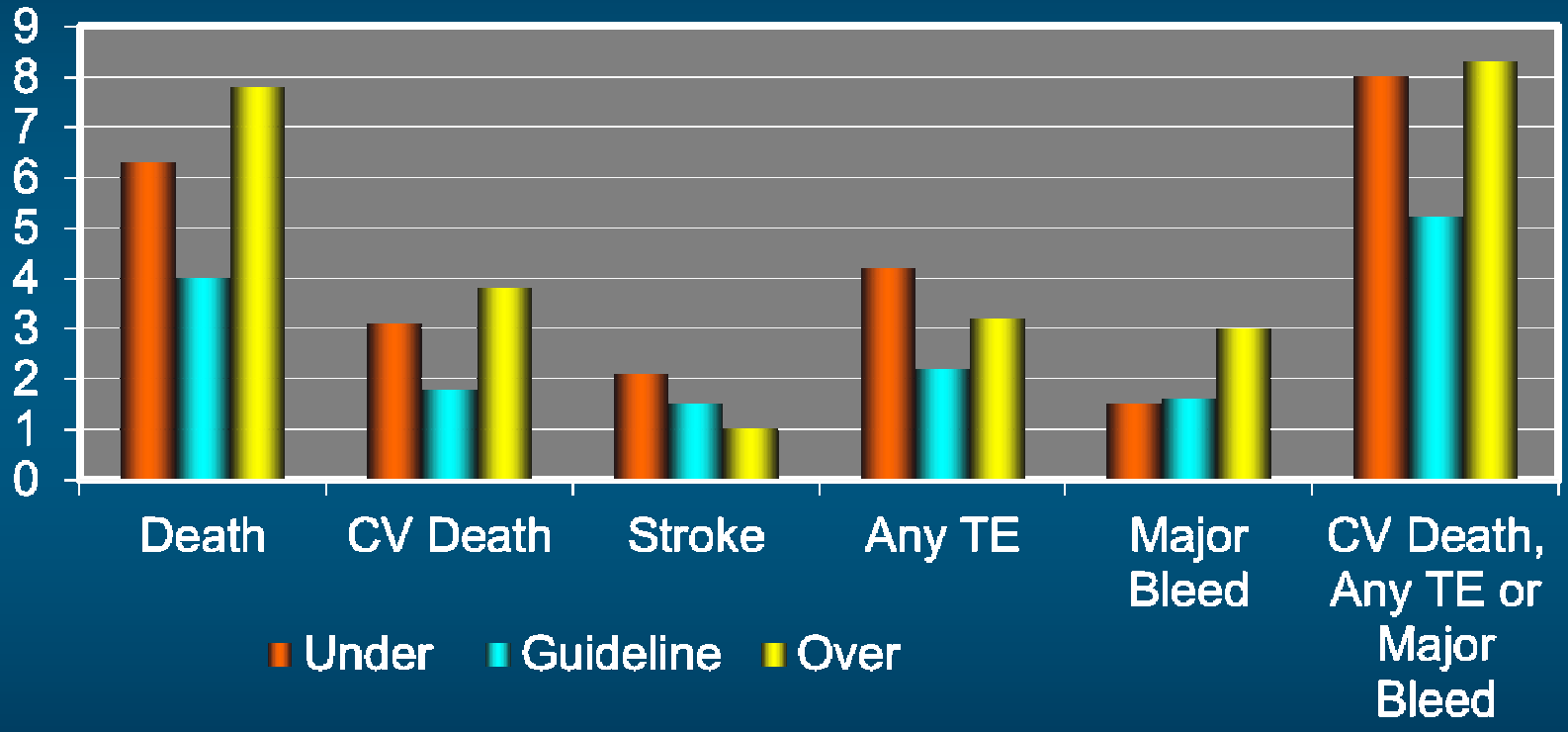
The Euro Heart Survey

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



Nieuwlaat R et al EHJ 2007

Consequences of Non-Adherence to AC Guidelines

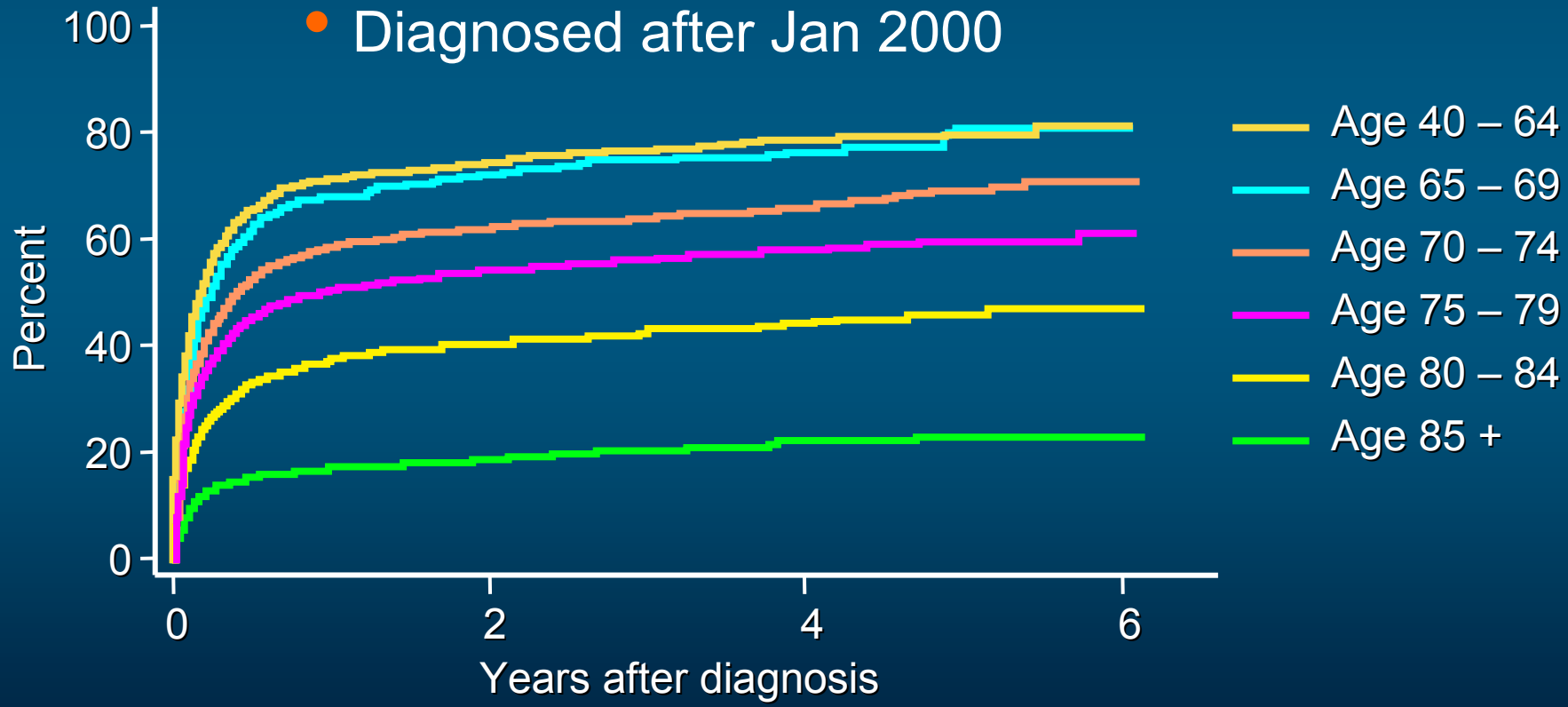


Nieuwlaat R et al EHJ 2007

Euro Heart Survey

Warfarin Use in General Practice in the UK: Initiation of VKA

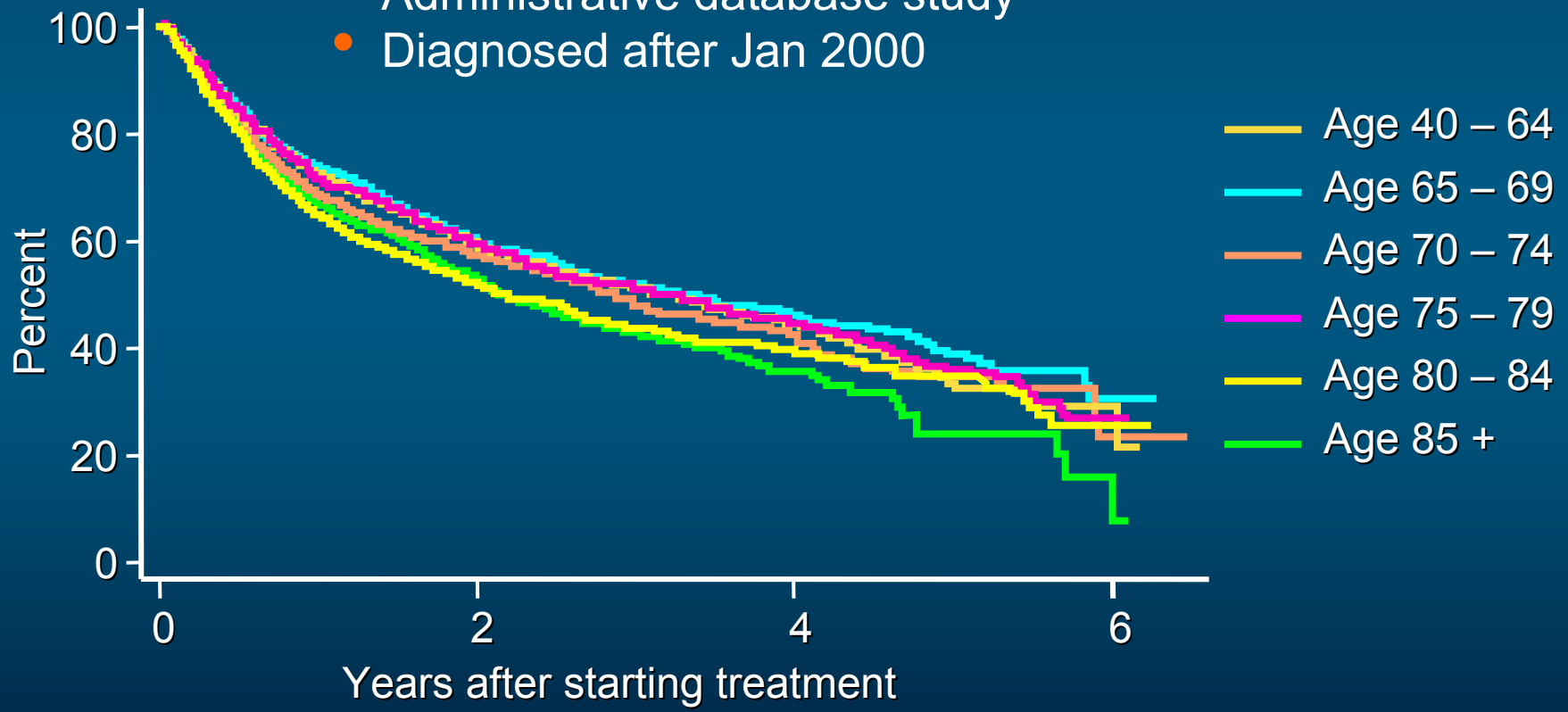
- 41,000 chronic AF treated by GPs in UK
- Administrative database study
- Diagnosed after Jan 2000



Gallagher AM, et al. *J Thromb Haemost*. 2008;6:1500-1506.

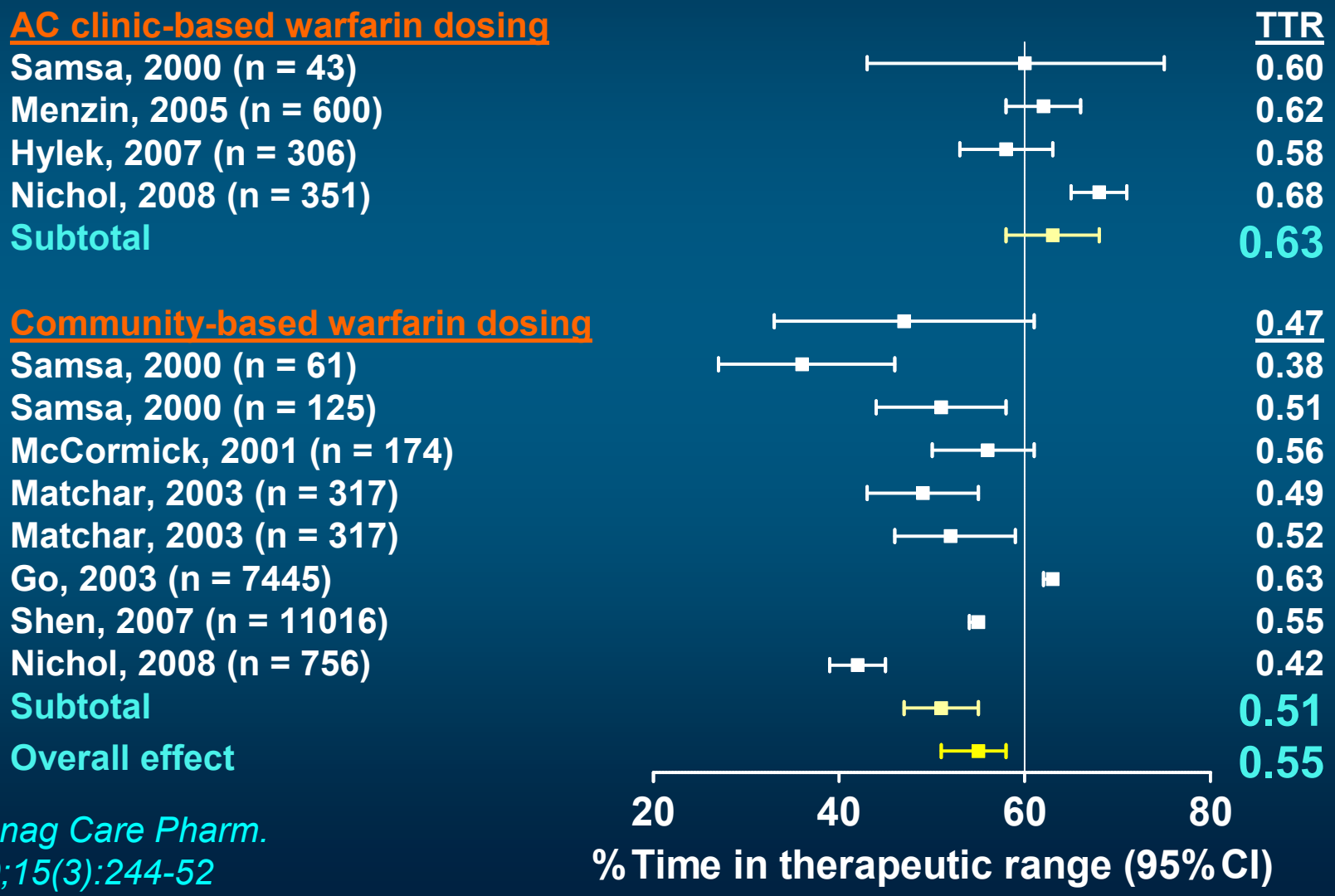
Warfarin Use in General Practice in the UK: Discontinuation of VKA

- 41,000 chronic AF treated by GPs in UK
- Administrative database study
- Diagnosed after Jan 2000



Gallagher AM, et al. *J Thromb Haemost*. 2008;6:1500-1506.

Time in Therapeutic Range (TTR) of Warfarin Treated AF Patients



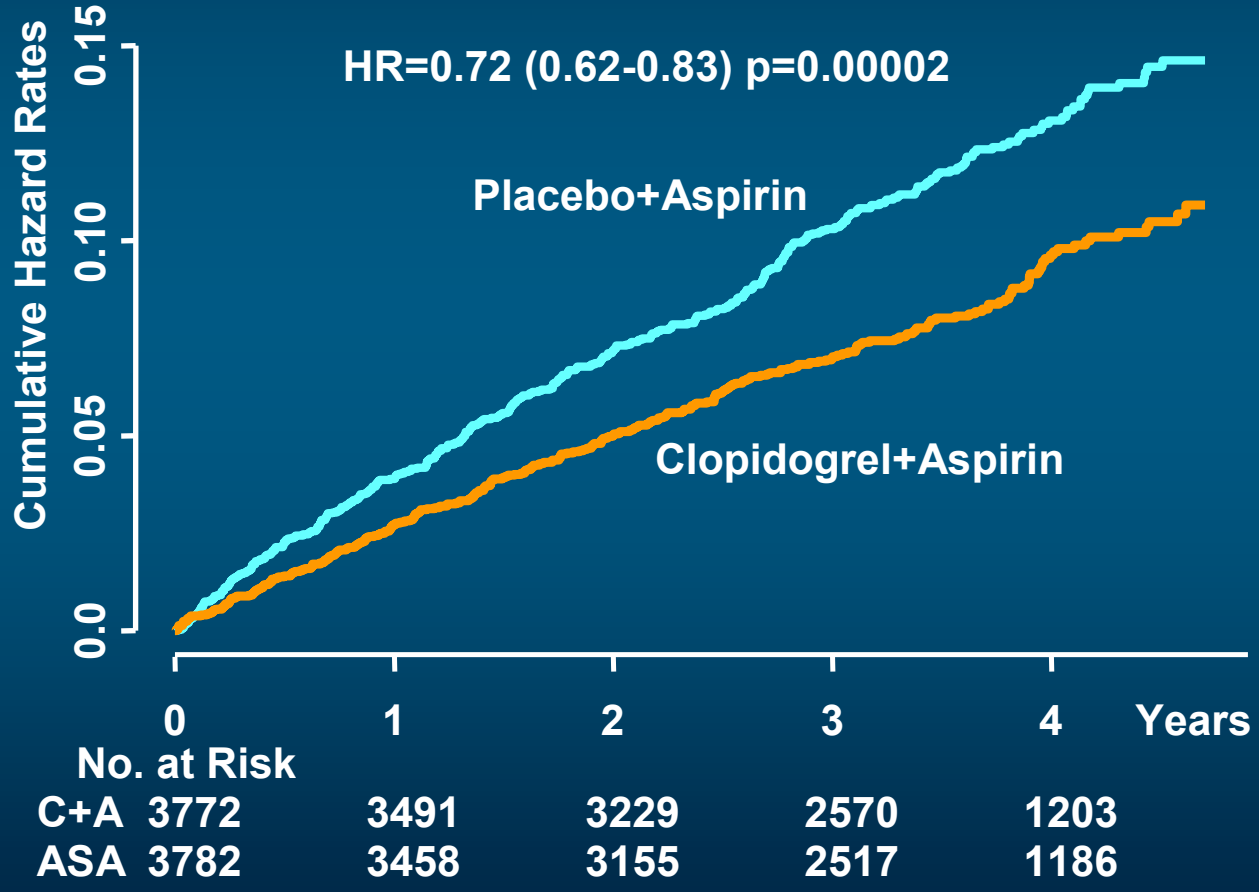
J Manag Care Pharm. 2009;15(3):244-52

Reasons Patients Enrolled in ACTIVE A rather than in ACTIVE W

	Overall	
	N	%
Inability to comply with INR monitoring	2069	27.4
Predisposition to falling or head trauma	732	9.7
Persistent BP >160/100	240	3.2
Previous serious bleeding on OAC	432	5.7
History of several alcohol abuse <2 yrs	83	1.1
Chronic renal insufficiency (Cr >2 mg/dL)	99	1.3
Documented peptic ulcer, between 6 months and 1 y r	51	0.7
Thrombocytopenia (<150 x 10^9/L)	169	2.2
Requirement for chronic NSAID (excl. COX-2 inhibitor)	117	1.5
Patient unwilling to take OAC	3682	48.7
Physician assessment OAC is inappropriate	3105	41.1
Other	367	4.9

Clopidogrel and Aspirin for Stroke Prevention in Patients Who Cannot Take Warfarin: The ACTIVE A Resuts

- 33 countries, 580 centers
- 7554 patients; 71±10 years; 64% permanent AF
- $CHADS_2$ 2 ± 1.1
- Median follow up 3.6 years

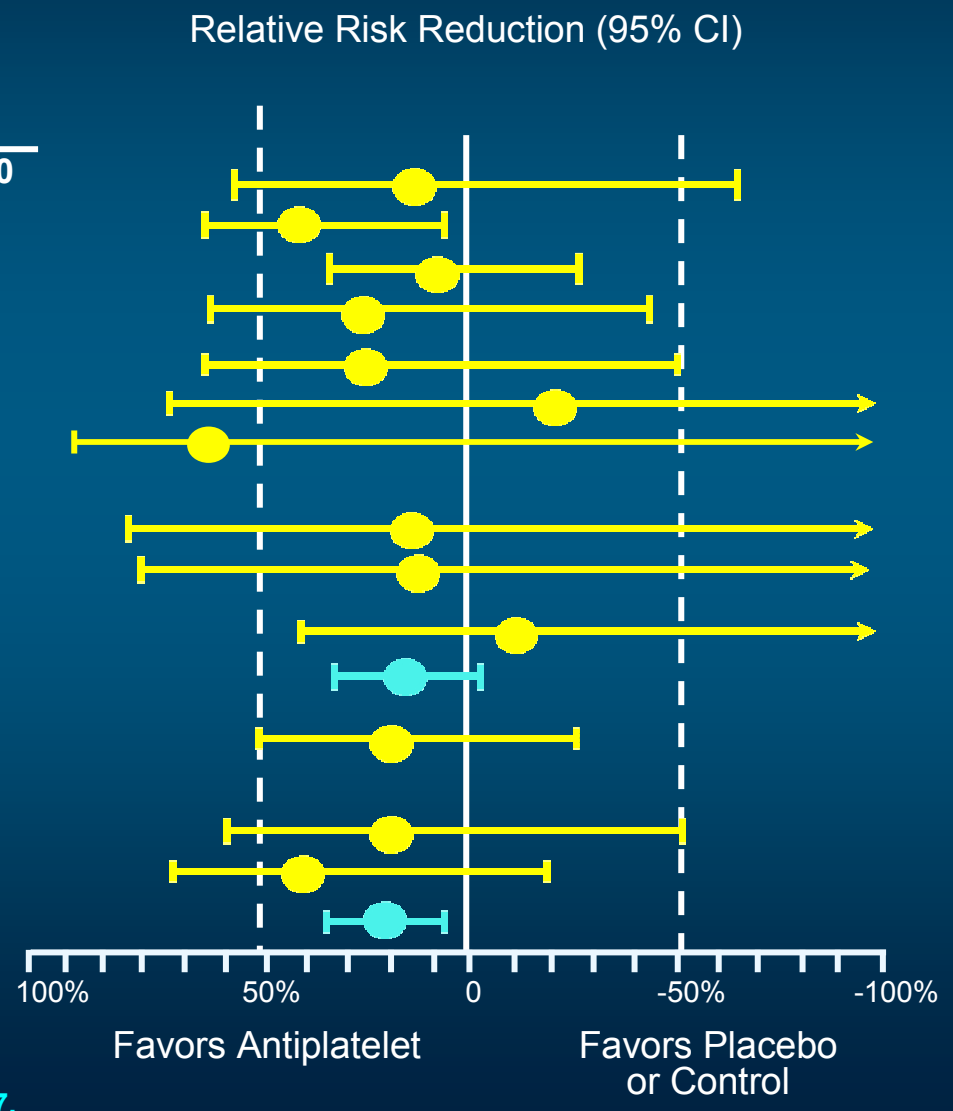


ACTIVE A Investigators. NEJM 2009 March

Efficacy of Anti-platelet Agents Compared With Placebo or Control in Eight Studies

Antiplatelet agents cf placebo/control

Study	Year
AFASAK I	**1989; 1990**
SPAF I	**1991**
EAFT	**1993**
ESPS II	**1997**
LASAF	**1997**
Daily	
Alternate day	
UK-TIA	**1999**
300 mg daily	
1200 mg daily	
JAST	**2006**
Aspirin trials *(n=7)*	
SAFT	**2003**
ESPS II	**1997**
Dipyridamole	
Combination	
All antiplatelet trials *(n=8)*	
N=4,876	



Hart RG et al. *Ann Intern Med*. 2007;146:857-867.

Clopidogrel and Aspirin for Stroke Prevention in Patients Who Cannot Take Warfarin: The ACTIVE A Results

Event	Clopidogrel + Aspirin		Aspirin alone		RR (95% CI)
	#	Rate / year	#	Rate/ year	
Ischemic or uncertain stroke	268	2.1%	388	3.2%	0.68 (0.59-0.80), p <0.001
Hemorrhagic stroke	30	0.2%	22	0.2%	1.37 (0.79-2.37), p=0.27
Major bleed	251	2.0%	162	1.3%	1.57 (1.29-1.92), p <0.001
Intracranial bleed	54	0.4%	29	0.2%	1.87 (1.19-1.94), p=0.006

ACTIVE A Investigators. NEJM 2009 March

Benefits and Risks: ACTIVE A Net Benefit

1000 patients treated for 3 years

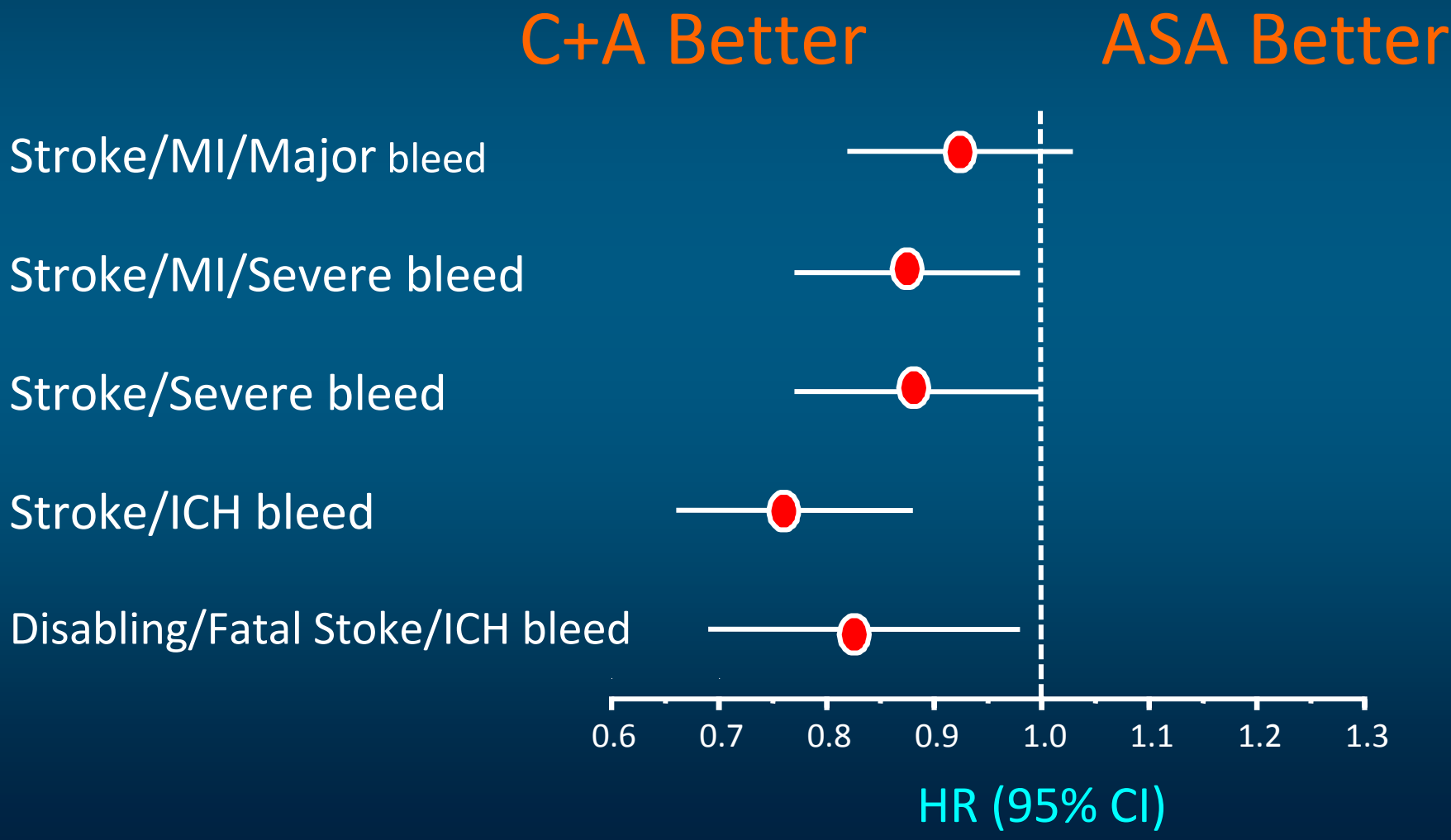
- Will prevent
  - 28 strokes (17 fatal or disabling)
  - 6 myocardial infarctions
- At a cost of 20 major bleeds (3 fatal)

Clinical Impact of Stroke and MI greater than that of Major Bleeding

	With Event	Without Event	Relative Effect of Event		
Event	Mortality (%)	Mortality (%)	Adjusted RR	95% CI	P value
Stroke	23%	4%	9.3	6.3-13.7	<0.001
MI	23%	5%	7.3	4.1-13.2	<0.001
Major Bleed	13%	5%	2.5	1.8-3.5	<0.001
Major, severe	16%	5%	5.7	3.6-9.1	<0.001
Major, not severe	7%	5%	1.7	0.5-4.7	0.28

DeCaterina et al. Eur Heart J 2010;31:2133–40.

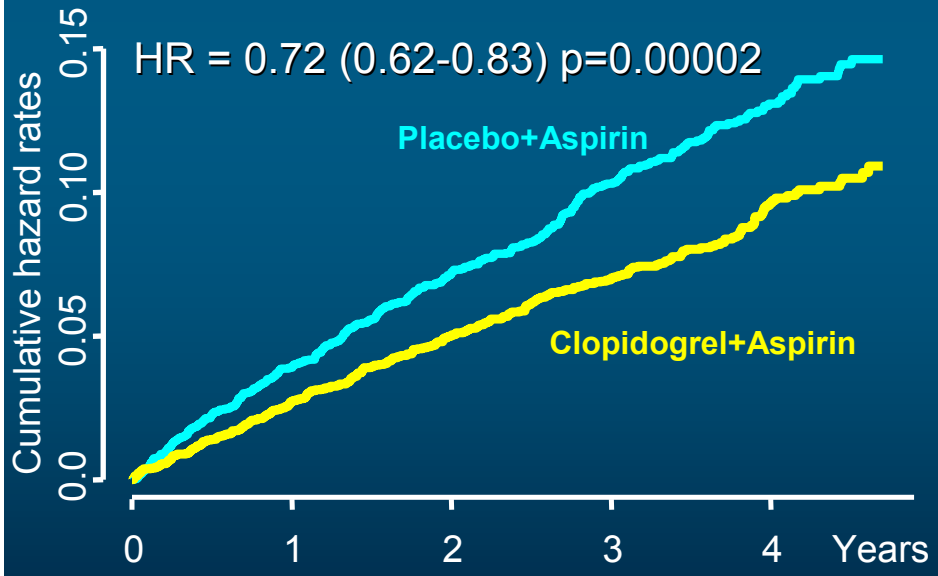
Net Clinical Benefit of Addition of Clopidogrel to ASA



Specific Recommendations for Anticoagulation: Dual Antiplatelet Therapy

ACTIVE A

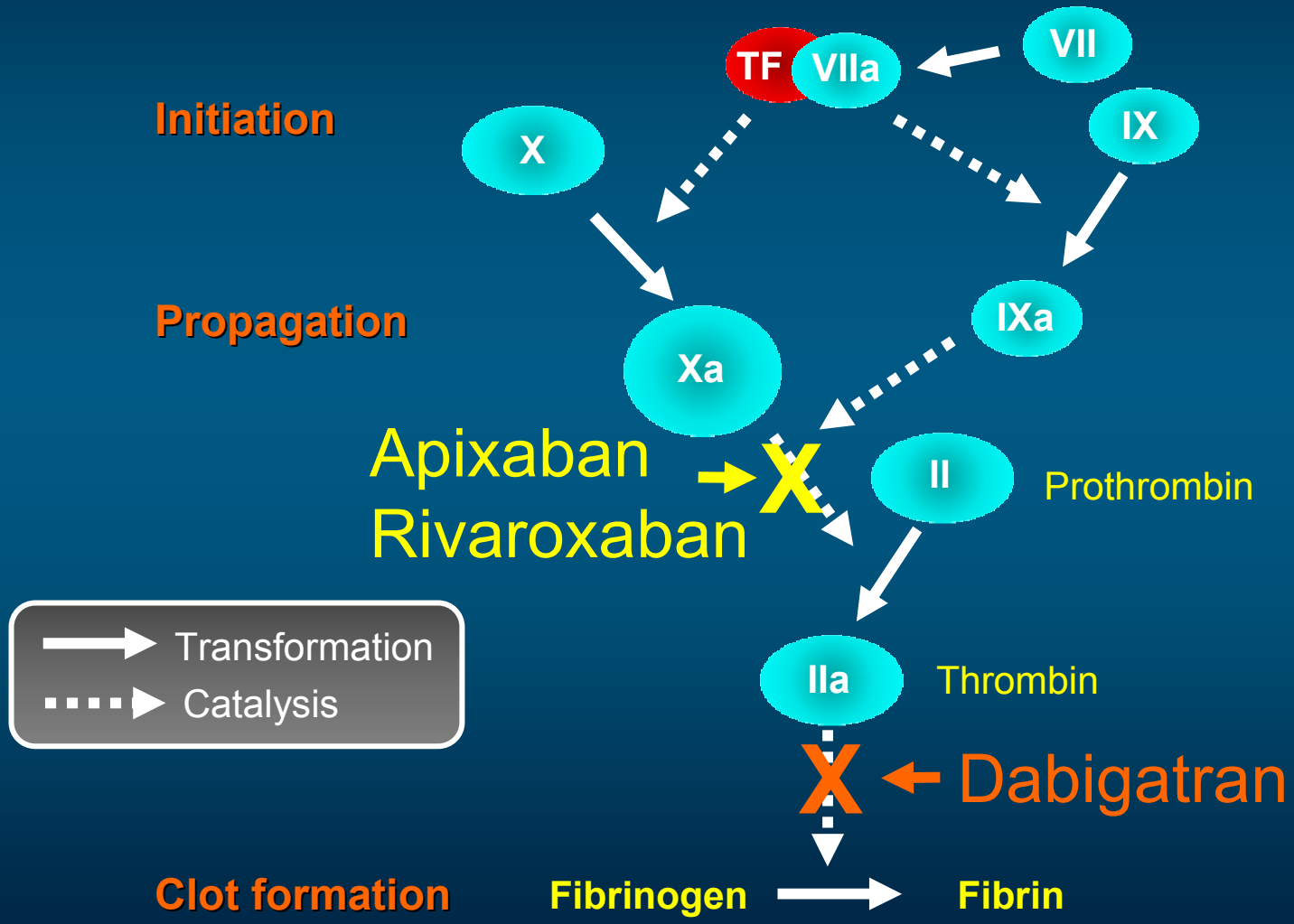
- 7554 patients; 71±10 years
- 64% permanent AF
- $CHADS_2$ 2±1.1
- Median follow up 3.6 years



ESC Recommendation	Class	Level
Combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily, should be considered for stroke prevention in patients for whom there is patient refusal to take OAC therapy or a clear contraindication to OAC therapy (e.g. inability to cope or continue with anticoagulation monitoring), where there is a low risk of bleeding	IIa	B

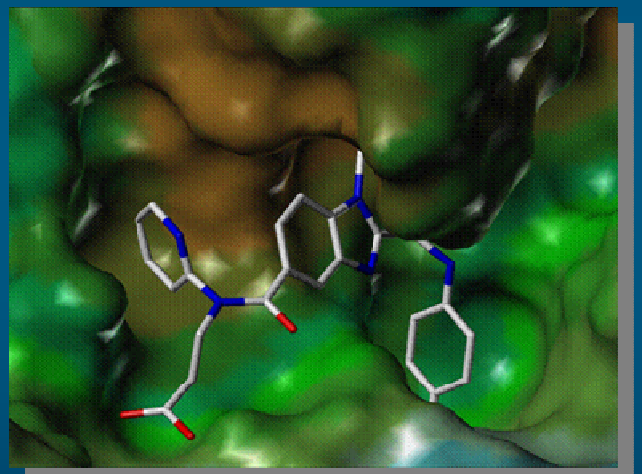
ACTIVE A Investigators. NEJM 2009;360:2066-78

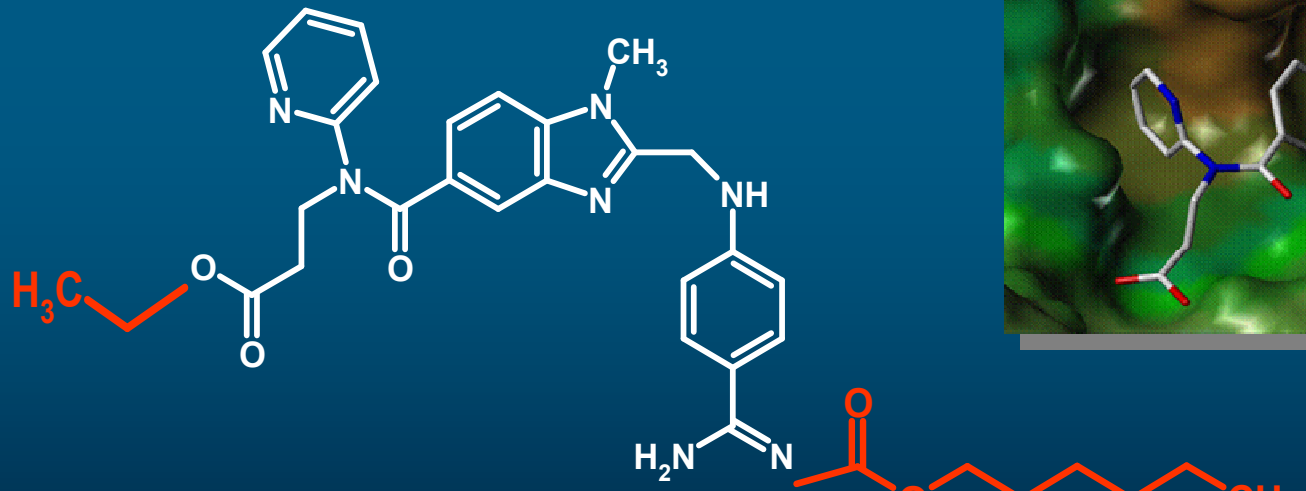
The Clotting Cascade



Dabigatran Etexilate

- Dabigatran etexilate is a novel, small molecule, reversible, direct thrombin inhibitor
- For oral administration the prodrug dabigatran etexilate was developed



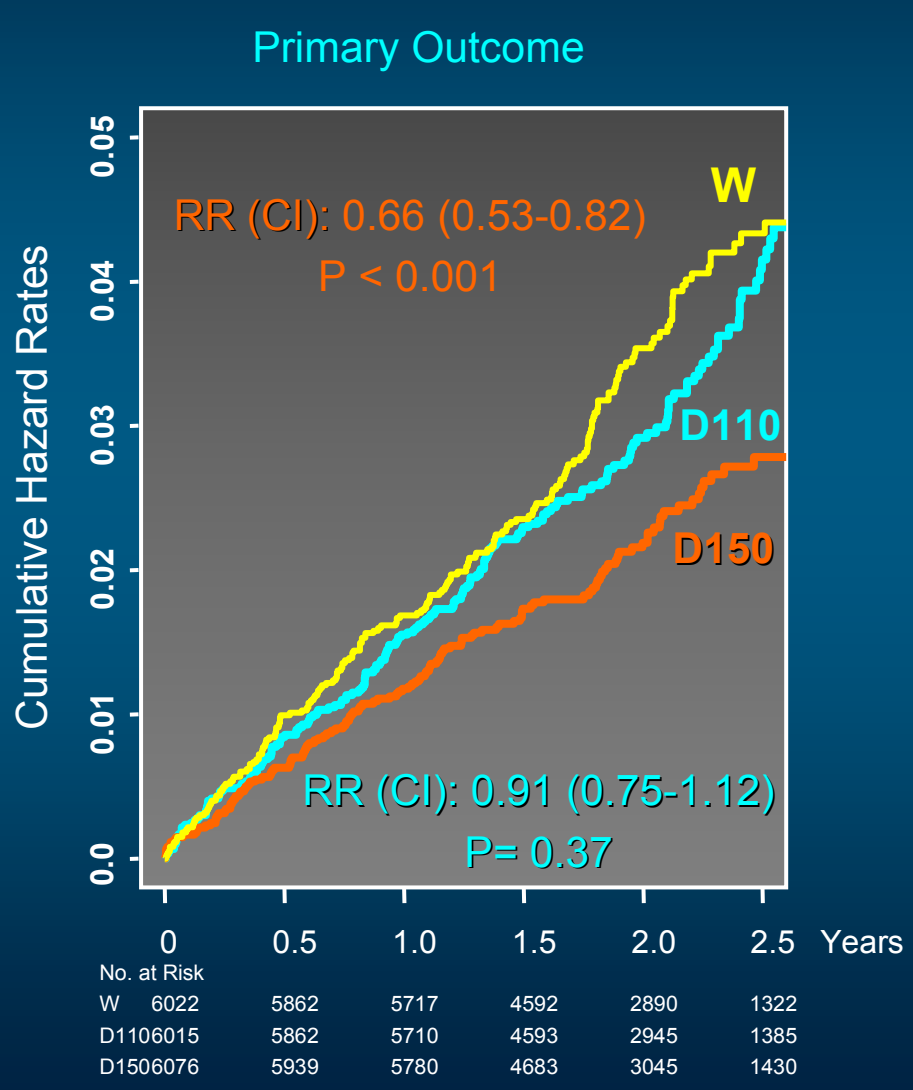


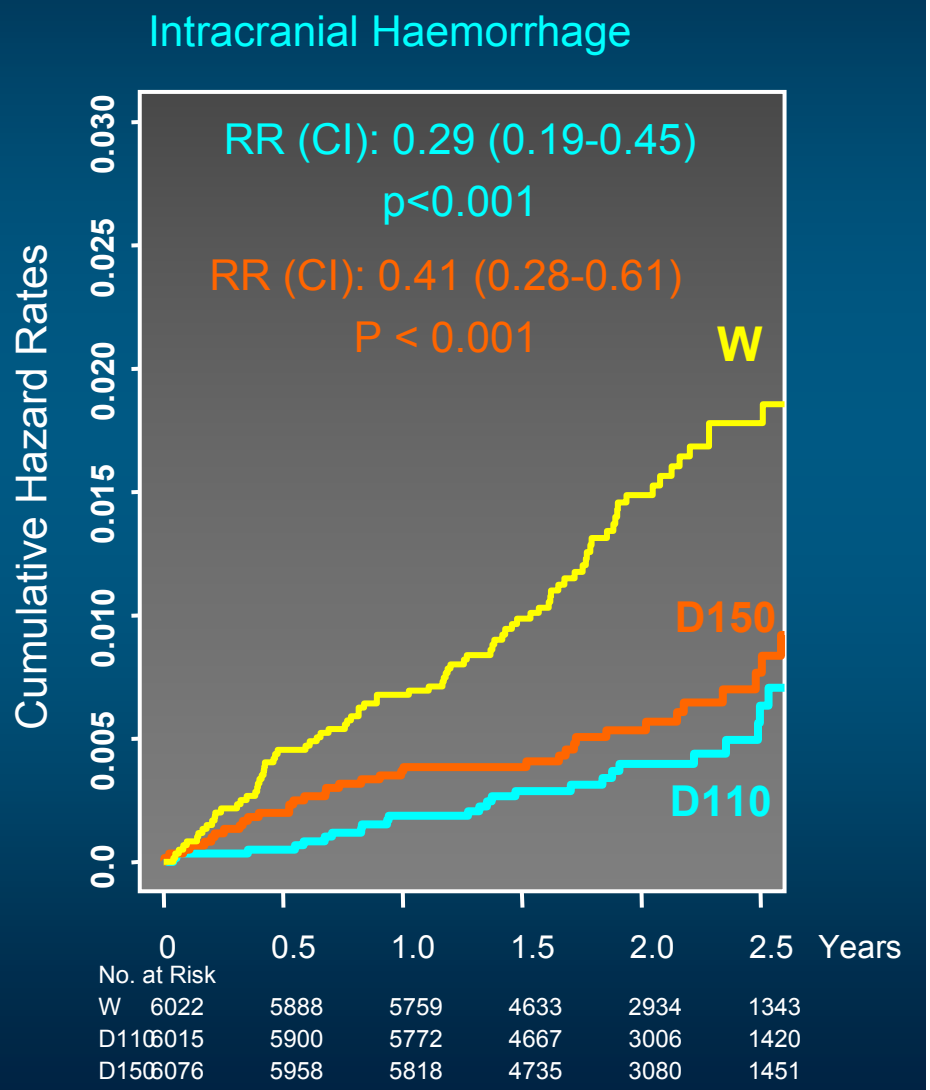
Dabigatran etexilate

Stangier J et al *British Journal of Clinical Pharmacology* 2007, DOI:10.1111/j.1365-2125.2007.02899. Sorbera LA et al Dabigatran/Dabigatran Etexilate Drugs of the Future 2005; 30 (9): 877-885. Belch S et al. *DMB* 2007; doi:10.1124/dmb.107.019083

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

The RE-LY Trial

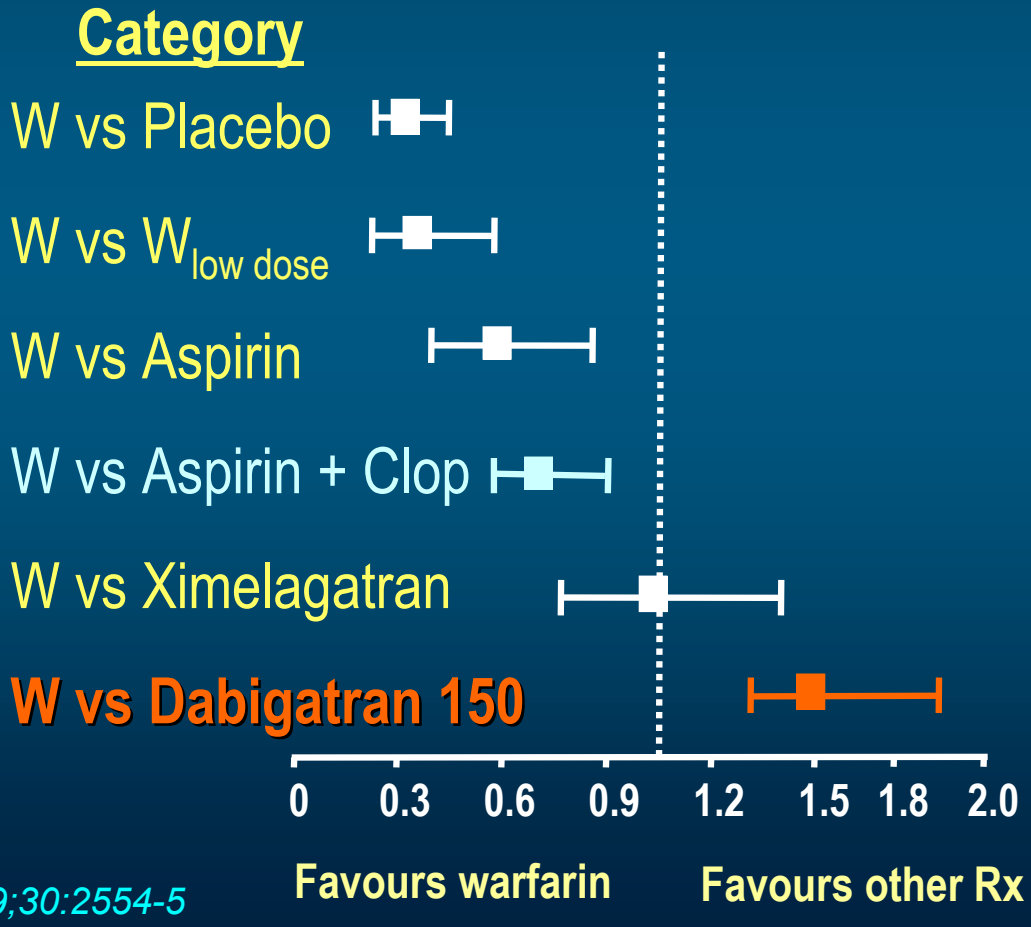




Connolly SJ, et al. NEJM 2009;361:12:1139-51

Stroke Prevention: *Dabigatran*

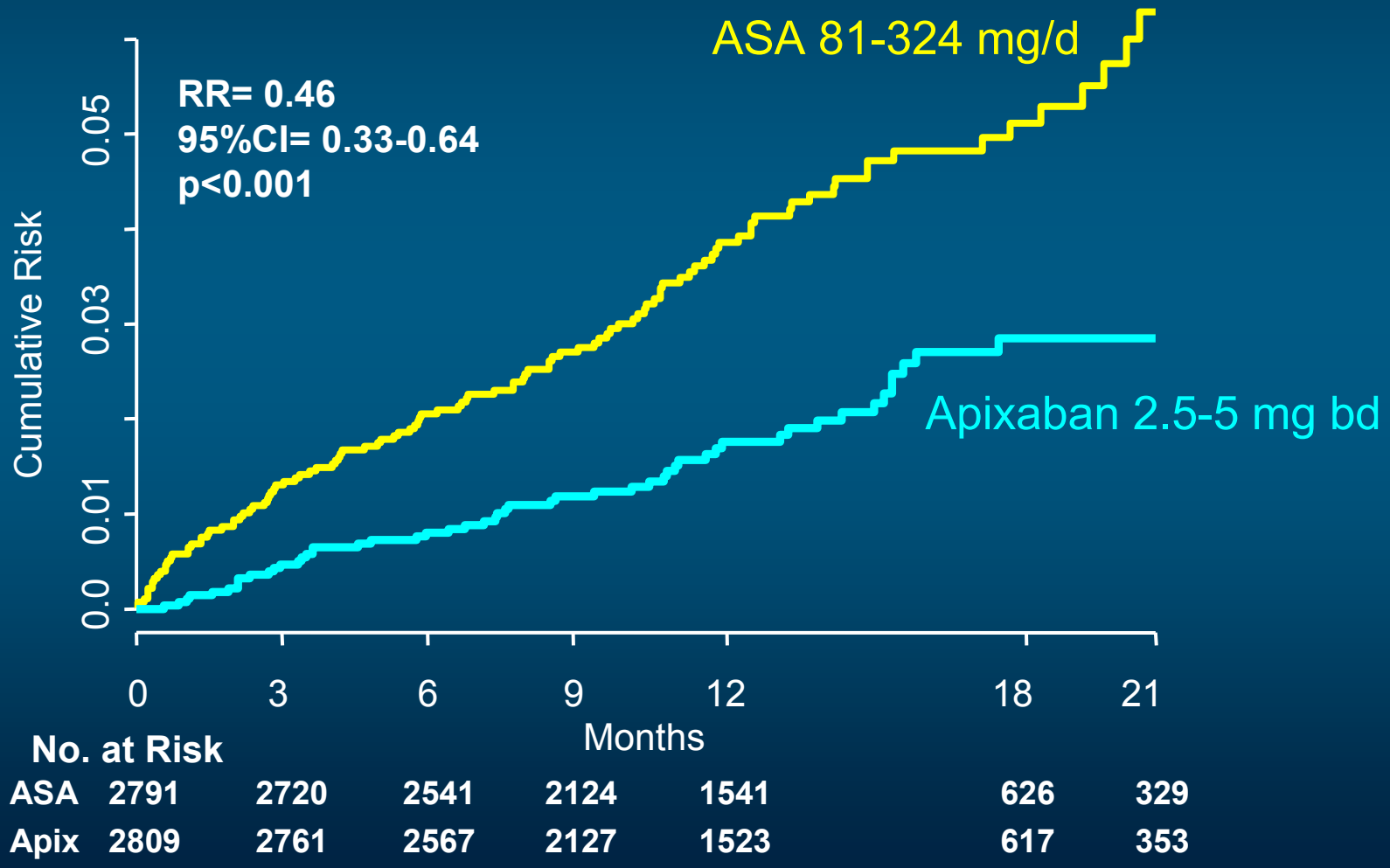
Meta-analysis of ischaemic stroke or systemic embolism



Camm AJ. EHJ 2009;30:2554-5

AVERROES: Stroke or SEE

5600 patients, 36 countries, 522 centres



Rocket AF
Study Design

Patel M, et al. AHA 2010
Late Breaking Trials

Risk factors
- CHF
- Hypertension
- Age ≥75
- Diabetes

At least 2 or 3 required*

OR
- Stroke, TIA or systemic embolus

Atrial Fibrillation

Randomized
Double Blind/
Double Dummy
(n ~14,000)

Rivaroxaban

20 mg daily
15 mg for Cr Cl 30–49 ml/min

Warfarin

INR target – 2.5
(2.0–3.0 inclusive)

Monthly monitoring
Adherence to standard of care guidelines

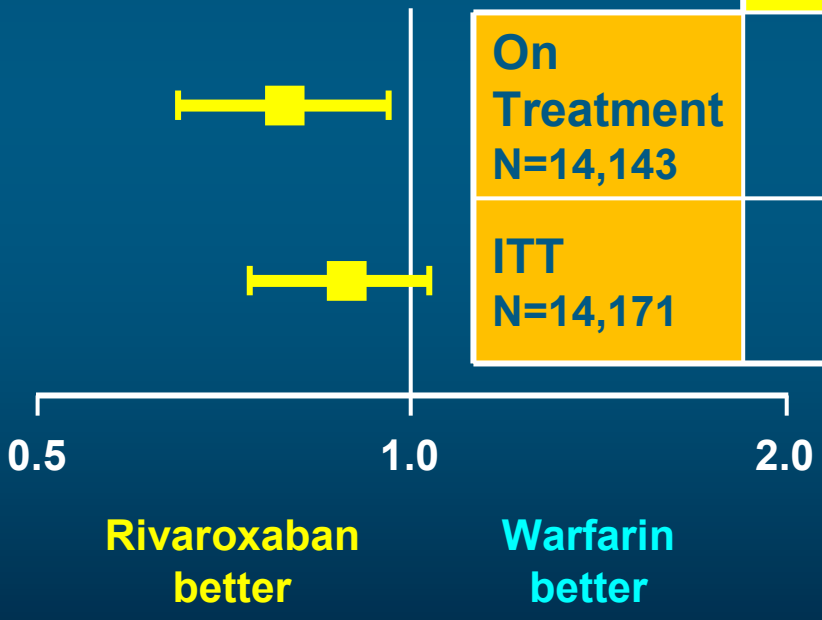
Primary Endpoint: Stroke or non-CNS systemic embolism

* Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%

Primary Efficacy Outcome

Stroke and non-CNS embolism

	Rivaroxaban	Warfarin		
	Event rate	Event rate	HR (95% CI)	*p*-value
On Treatment N=14,143	1.70	2.15	0.79 (0.65, 0.95)	0.015
ITT N=14,171	2.12	2.42	0.88 (0.74, 1.03)	0.117

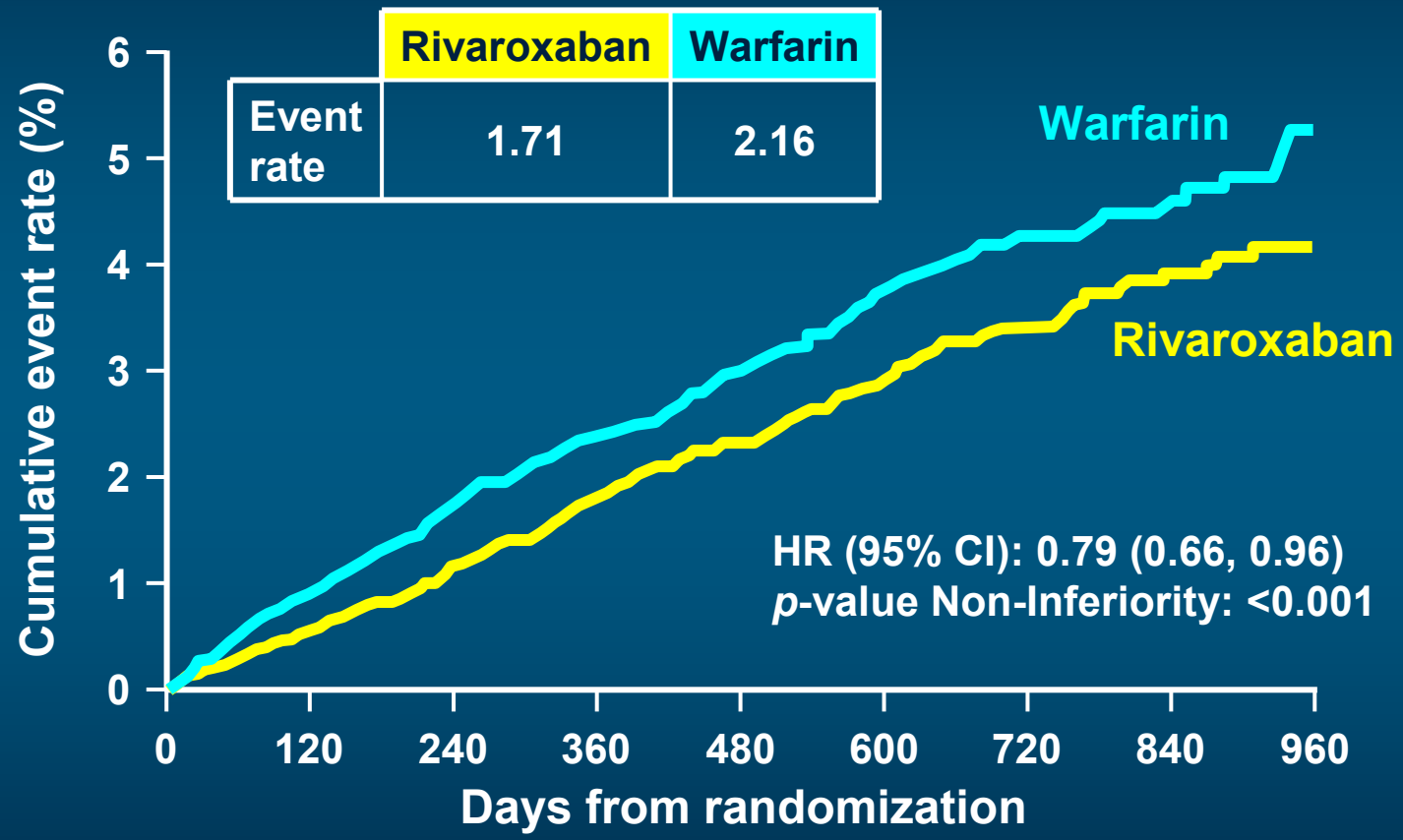


Patel M, et al. 2010 AHA Late Breaking Trials

Event rates are per 100 patient-years
Based on safety on treatment or intention-to-treat through site notification populations

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

Patel M, et al. 2010 AHA Late Breaking Trials

Key Secondary Efficacy Outcomes

	Rivaroxaban	Warfarin		
	Event rate	Event rate	HR (95% CI)	*p* value
Vascular death, stroke, embolism	3.11	3.63	0.86 (0.74, 0.99)	0.034
Stroke type				
Hemorrhagic	0.26	0.44	0.59 (0.37, 0.93)	0.024
Ischemic	1.34	1.42	0.94 (0.75, 1.17)	0.581
Unknown type	0.06	0.10	0.65 (0.25, 1.67)	0.366
Non-CNS embolism	0.04	0.19	0.23 (0.09, 0.61)	0.003
Myocardial infarction	0.91	1.12	0.81 (0.63, 1.06)	0.121
All cause mortality	1.87	2.21	0.85 (0.70, 1.02)	0.073
Vascular	1.53	1.71	0.89 (0.73, 1.10)	0.289
Non-vascular	0.19	0.30	0.63 (0.36, 1.08)	0.094
Unknown cause	0.15	0.20	0.75 (0.40, 1.41)	0.370

Event rates are per 100 patient-years
Based on Safety on Treatment Population

Patel M, et al. 2010 AHA Late Breaking Trials

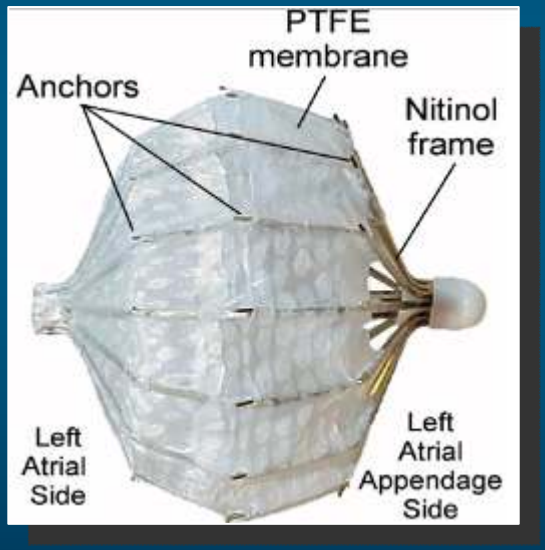
New Anticoagulants for AF: Potential Changes in Recommendations

Medication	Action	Phase III Trial	Comparator	Design	n
Dabigatran	**DTI**	**RE-LY**	**Warfarin**	**Non-inferiority**	**18 500**
Apixaban	Anti Xa	**AVERROES**	**Aspirin**	**Superiority**	**5 600**
		ARISTOLE	Warfarin	Non-inferiority	18 000
Rivaroxaban	**Anti Xa**	**ROCKET AF**	**Warfarin**	**Non-inferiority**	**14 269**
Edoxaban	Anti Xa	ENGAGE	Warfarin	Non-inferiority	16 500
Biotinylated Idraparinux	Anti Xa	BOREALIS-AF	Warfarin	Non-inferiority	9 600
Tecarfarin	VKA	EmbraceAC	Warfarin	Superiority	612

Others include: betrixaban (EXPLORE-Xa), YM 150 (OPAL-1)

Transcatheter Occlusion of the LAA

- Various types of occluding devices

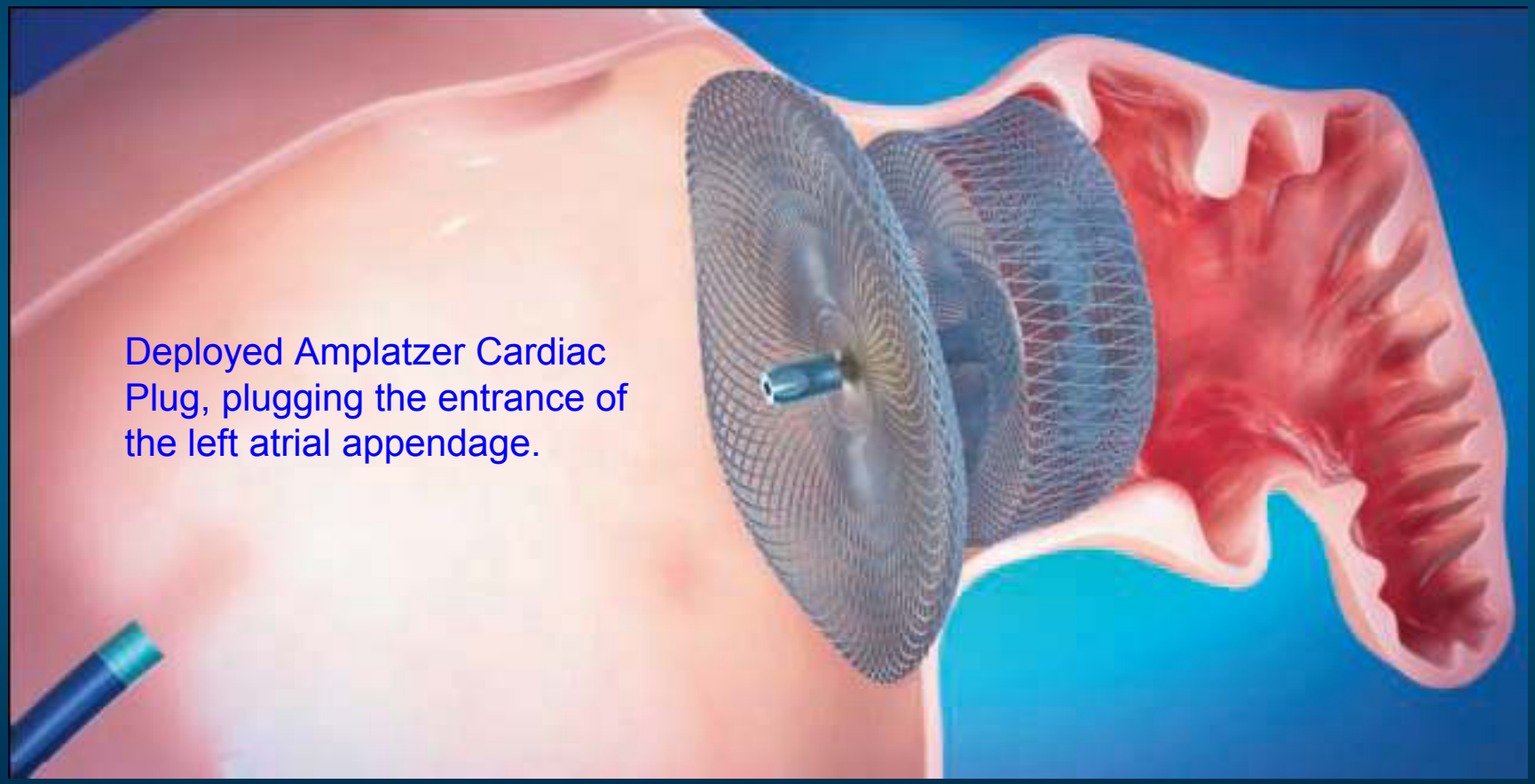


PLAATO®

WATCHMAN®

AMPLATZER® Cardiac Plug

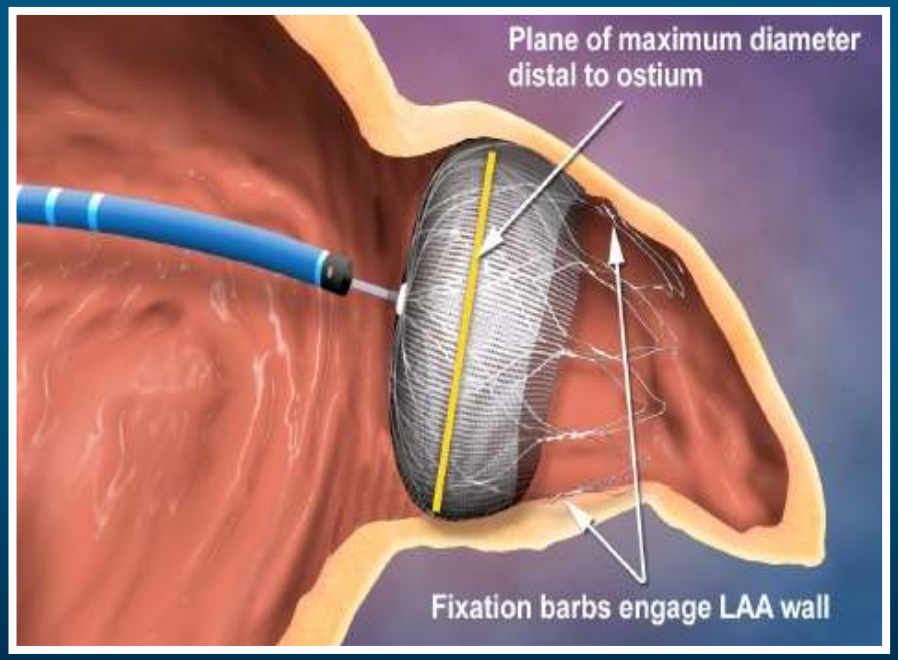
Principle of Trans-catheter Approach



Deployed Amplatzer Cardiac Plug, plugging the entrance of the left atrial appendage.

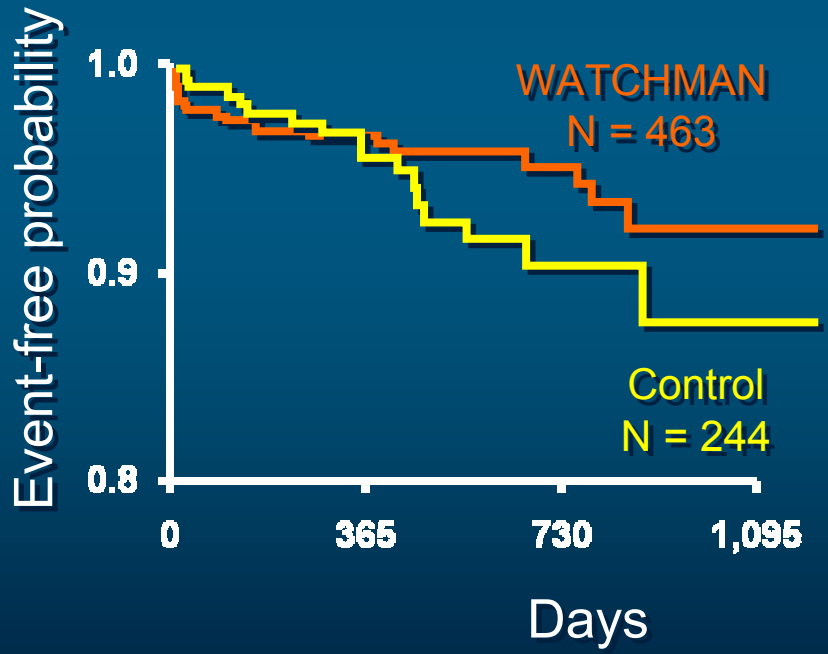
Watchman PROTECT-AF

WATCHMAN LAA Closure Device in situ



Primary Efficacy Results

Randomization allocation
(2 device : 1 control)



Holmes D et al, Lancet 2009; 374: 534–42 2009

Clinical Evidence: Proof of Concept

Protect-AF trial

PROTECT – AF: Updated **Data**

- Enrollment: 800 pts from 59 centers in the U.S, and Europe
- Randomized in device-to-control: 2:1
  - F/U with TEE at 45 days, 6 months, and 1 year
  - 87% were able to stop warfarin therapy
- Primary Efficacy End Point:
  - All stroke, CV or unexplained death, systemic embolization
- Primary Safety End Point:
  - Device embolization requiring retrieval
  - Pericardial effusion requiring intervention
  - Cranial, GI, or other significant bleed

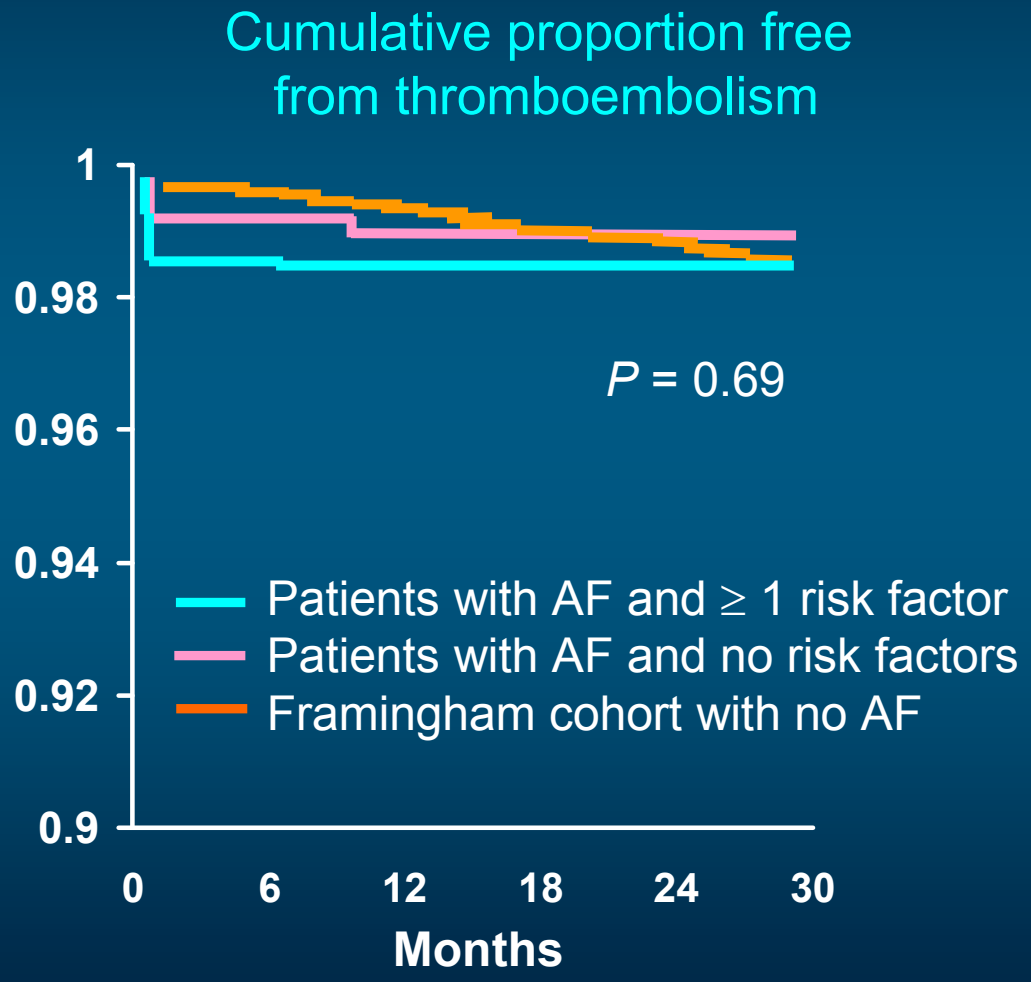
Holmes et al., Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with AF: a randomized non-inferiority trial, Lancet 2009; 374: 534–42

Stroke and Anticoagulation Post Ablation

Conclusions

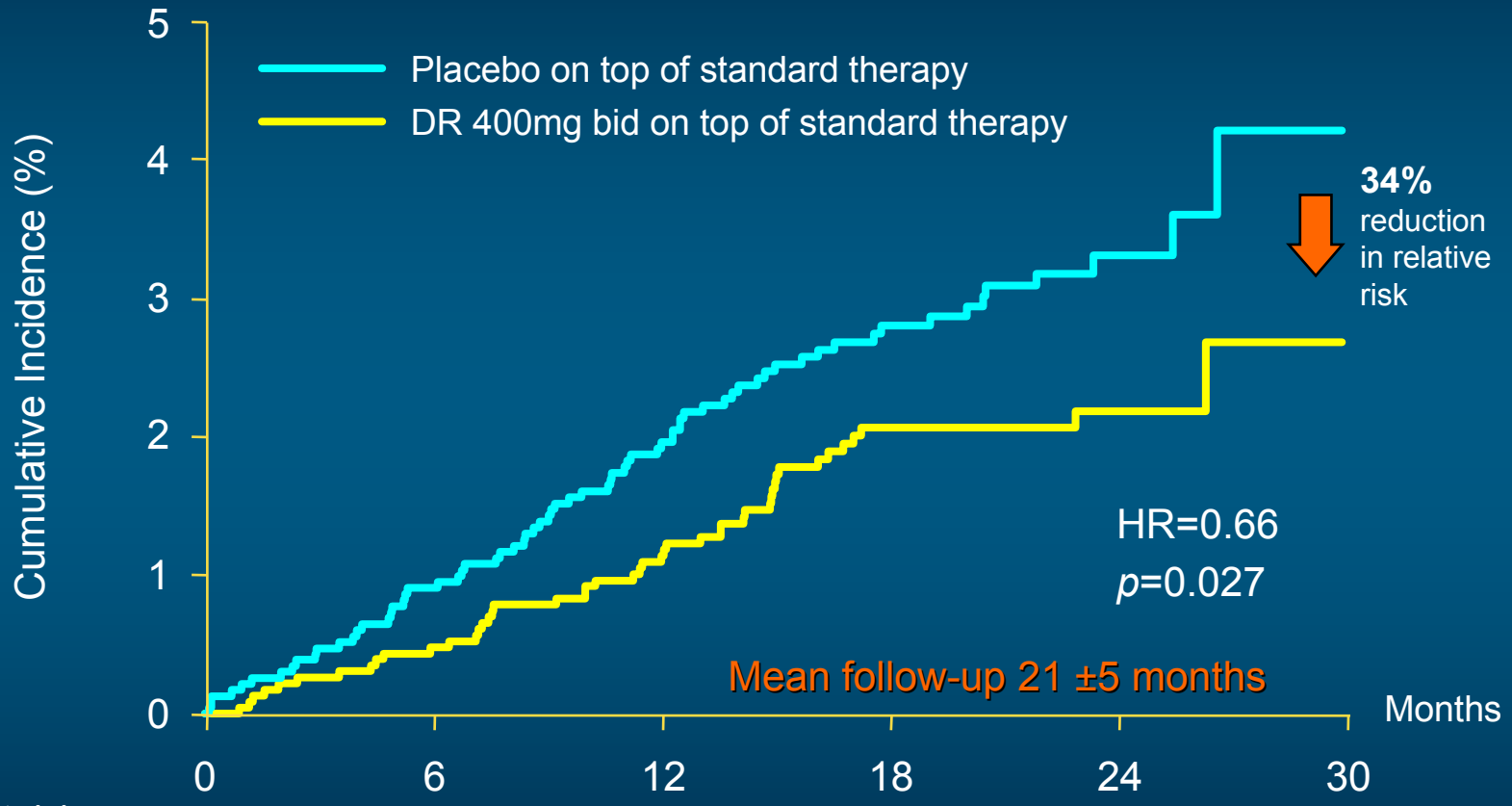
The risk of a TE after left atrial radiofrequency ablation (LARFA) is 1.1%, with most events occurring within 2 weeks

Discontinuation of anticoagulant therapy appears to be safe after successful LARFA



Oral H, et al. Circulation. 2006;114:759-765.

Dronedarone Reduced the Relative Risk of Stroke by 34%



Patients at risk:

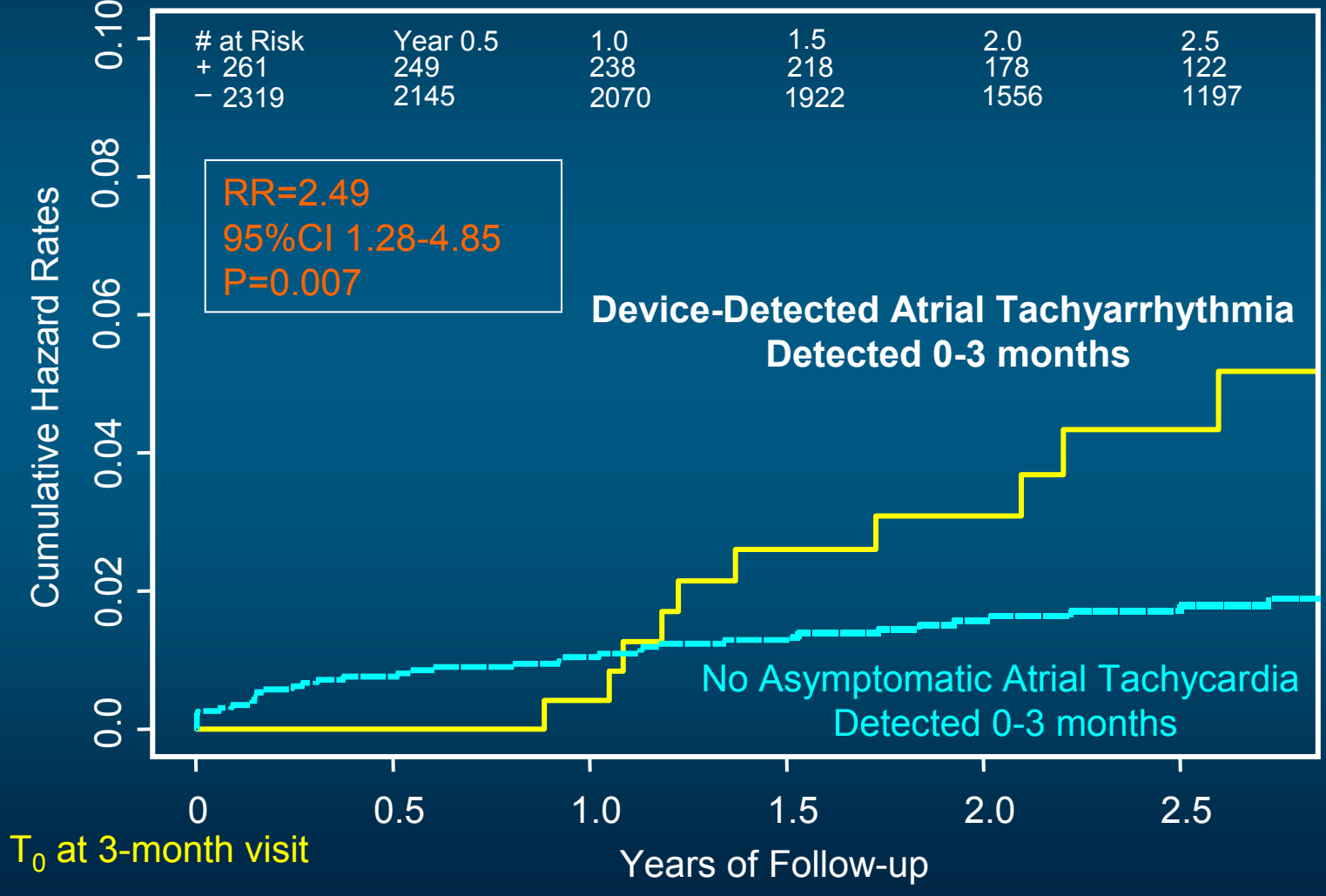
Placebo	2327	2275	2220	1598	618	6
DR 400mg bid	2301	2266	2223	1572	608	4

Connolly et al; Circulation. 2009;120:1174-1180

Monitoring of AF by Implantable Devices and Outcome: Clinical Trials and Registries

Study	TRENDS NCT00279981	ASSERT NCT00256152	IMPACT NCT00559988	RATE Registry NCT00837798
Sponsor	Medtronic	St Jude	Biotronik	St. Jude
# patients	2486	2580	2718	5000
Inclusion criteria	Class I/II indication for DDD PM, ICD or CRT; $CHADS_2$ ≥1 (age ≥65)	Class I/II indications for pacing; no previous AF; age ≥ 65 with hypertension	Class I/II ICD or CRT-D indications; $CHADS_2$ ≥1	Conventional indications for PM or ICD
Device and monitoring	Device interrogation every 3 mos; AHRE ≥20 s detected; AF burden in 30-day rolling window	Identity ADx DR or similar; device interrogation every 6 mos; AHRE > 190 bpm, > 6-min detected	Lumax HF-T or DR-T with home monitoring for AF > 48 h and active OAC upon detection	Victory, Atlas II, Frontier II, etc., with advanced AT/AF diagnostics
1° endpoint	Ischemic stroke, TIA, SE	Composite: ischemic stroke and SE	Composite: stroke, SE, major bleed	AT/AF burden and frequency; patterns of AF onset; CHF; stroke or SE; QoL; therapy; hospitalizations for AF and CHF; inappropriate shocks; mortality
2° endpoints	QoL; costs; VR; AF progression; impact of new onset AF	ECG-documented AF; composite of MI, vascular death, SE, CHF admission; AF burden; major bleed	ACM, stroke (any); major bleed; AF burden; QoL; HR	
Follow-up	Mean, 1.4 years Published in full 2010	Mean 2.8 years Results November 2010	Completion expected 2014	Completion expected 2014

ASSERT Study:
Ischemic Stroke or Systemic Embolism



Healey et al, AHA Late Breaking Trials, November 2010

ASSERT

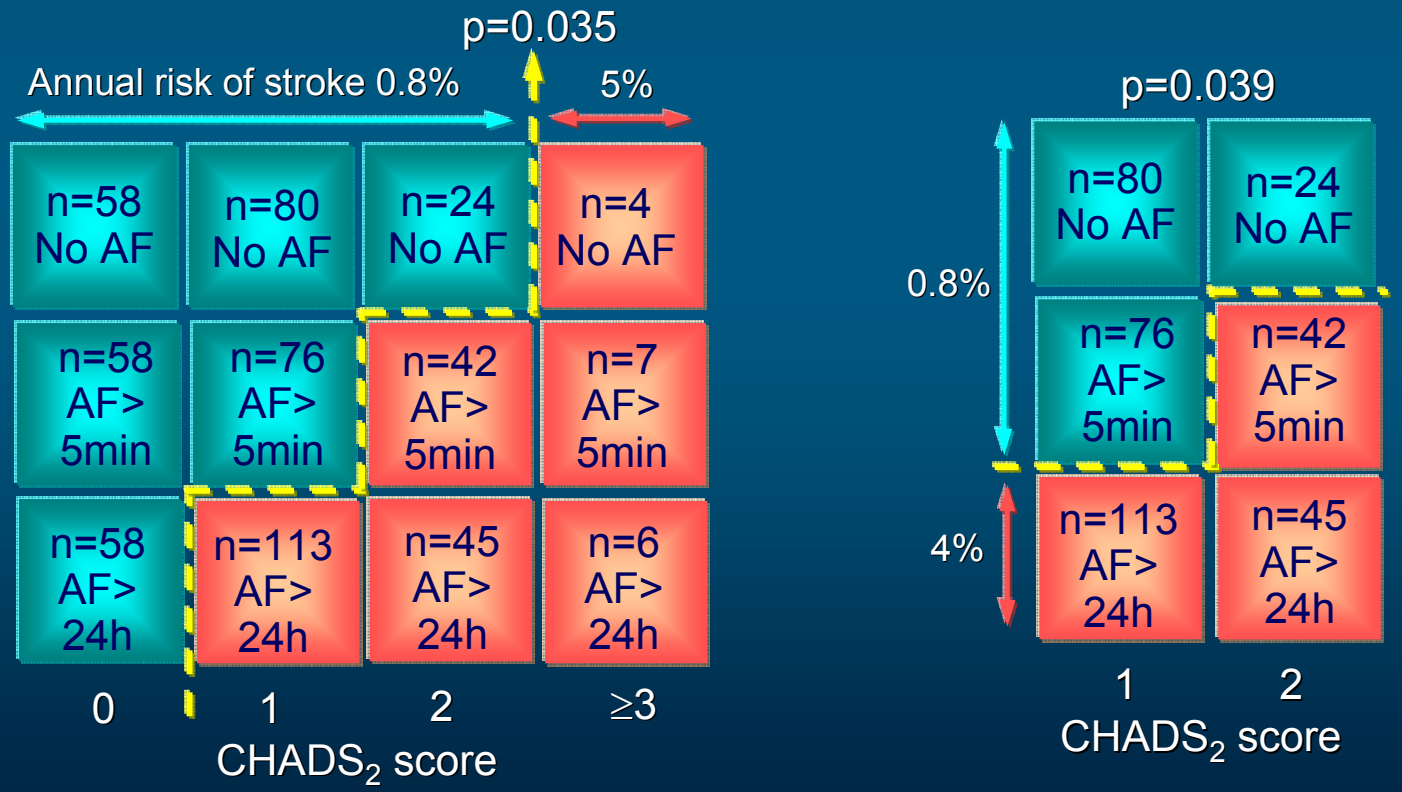
Clinical Outcomes Censored if Clinical Atrial Fibrillation/Flutter Occurs

Event	Device-Detected Atrial Tachyarrhythmia				Device-Detected Atrial Tachyarrhythmia Present vs. absent		
	Absent N= 2319		Present N= 261				
	events	%/ year	events	%/year	RR	95% CI	p
Ischemic Stroke or Systemic Embolism	40	0.70	10	1.67	2.41	1.21 – 4.83	0.01
Vascular Death	153	2.67	19	3.17	1.18	0.73 – 1.90	0.50
Stroke / MI / Vascular Death	206	3.59	29	4.84	1.32	0.90 – 1.95	0.16

Healey et al, AHA Late Breaking Trials, November 2010

Monitored AHRE / AF and $CHADS_2$ Score: Relation to Ischemic Stroke

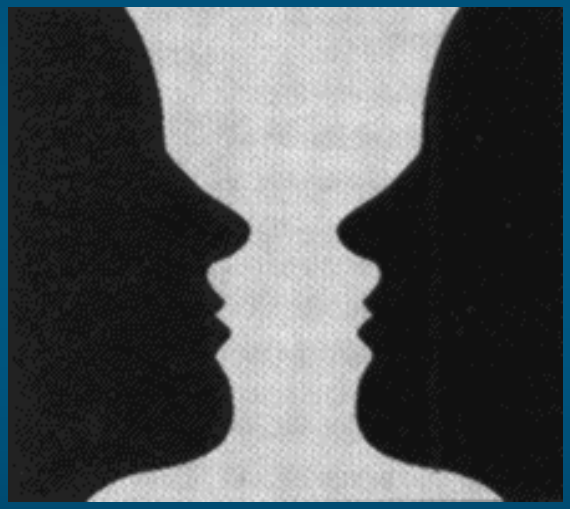
- 568 pts with AT500
- AHRE detection rate 174 ± 11 bpm
- Follow-up 1 year; 14 (2.5%) had TE



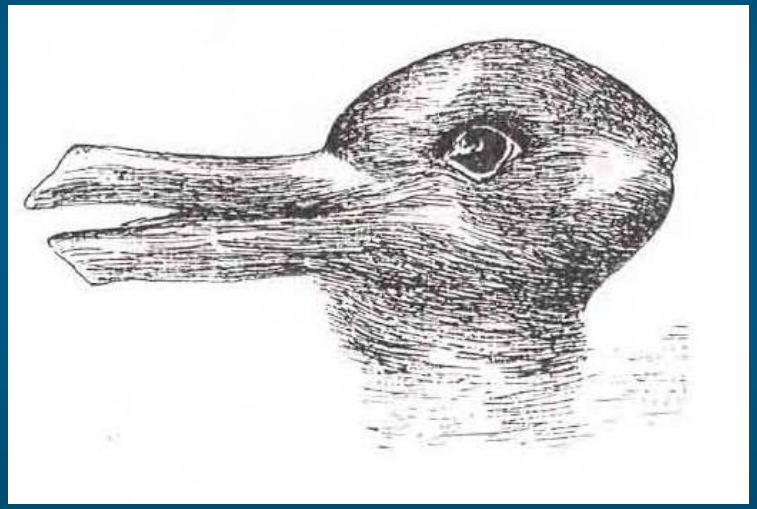
Botto GL et al. J Cardiovasc Electrophysiol. 2009;20(3):241-248.

“Paradigm Shift”

Thomas Kuhn in his influential book *“ The Structure of Scientific Revolutions”* to describe a change in basic assumptions within the ruling theory of science.



Vase versus Faces



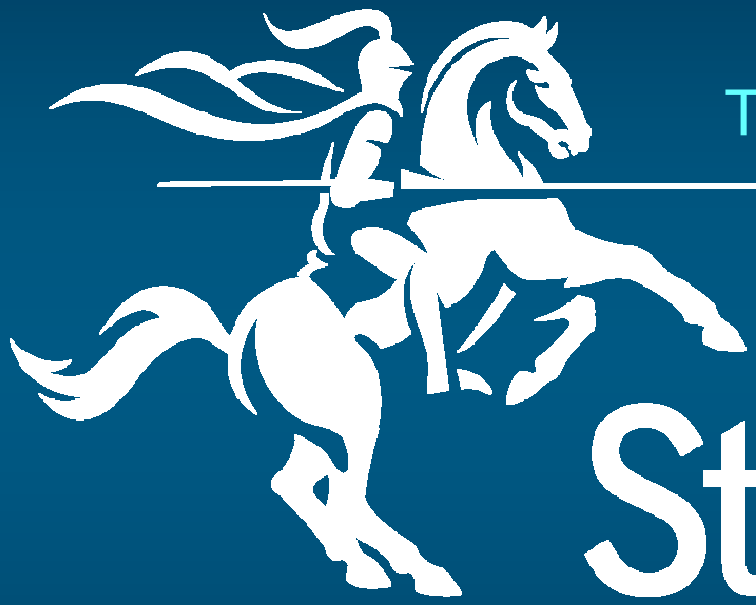
Duck versus Rabbit

Young lady v Old lady

A buzzword, popularized as marketing speak and appearing more frequently in print and publication. In his book, *Mind The Gaffe*, author Larry Trask advises readers to refrain from using it, because it is abused and overused to the point of becoming meaningless.

Conclusions

- Atrial fibrillation (AF) is common and ischemic stroke is a major complication
- Of the current anticoagulants Warfarin is much 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 hemorrhage
- Warfarin is badly and inconsistently used
- Something better is urgently needed and is just around the corner



Thank you for your attention

John Camm

St George's
University of London