Cardioembolic Stroke

WCN

TC 9B

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Disclosures

- Advisory Boards Boehringer Ingelheim, Sanofi Aventis, Pfizer
- Lectures Boehringer Ingelheim, Ever Neuropharma

Learning Objectives

- Understand the main causes of cardioembolic stroke
- Importance of atrial fibrillation as the leading cause of cardioembolic stroke
- Indications for anticoagulation – risks and benefits
- Warfarin and the New Oral Anticoagulants
- Advantages and challenges with the NOACs
- Current approaches to patent foramen ovale
- Aortic arch atheroma

Ischemic stroke classification 1 TOAST

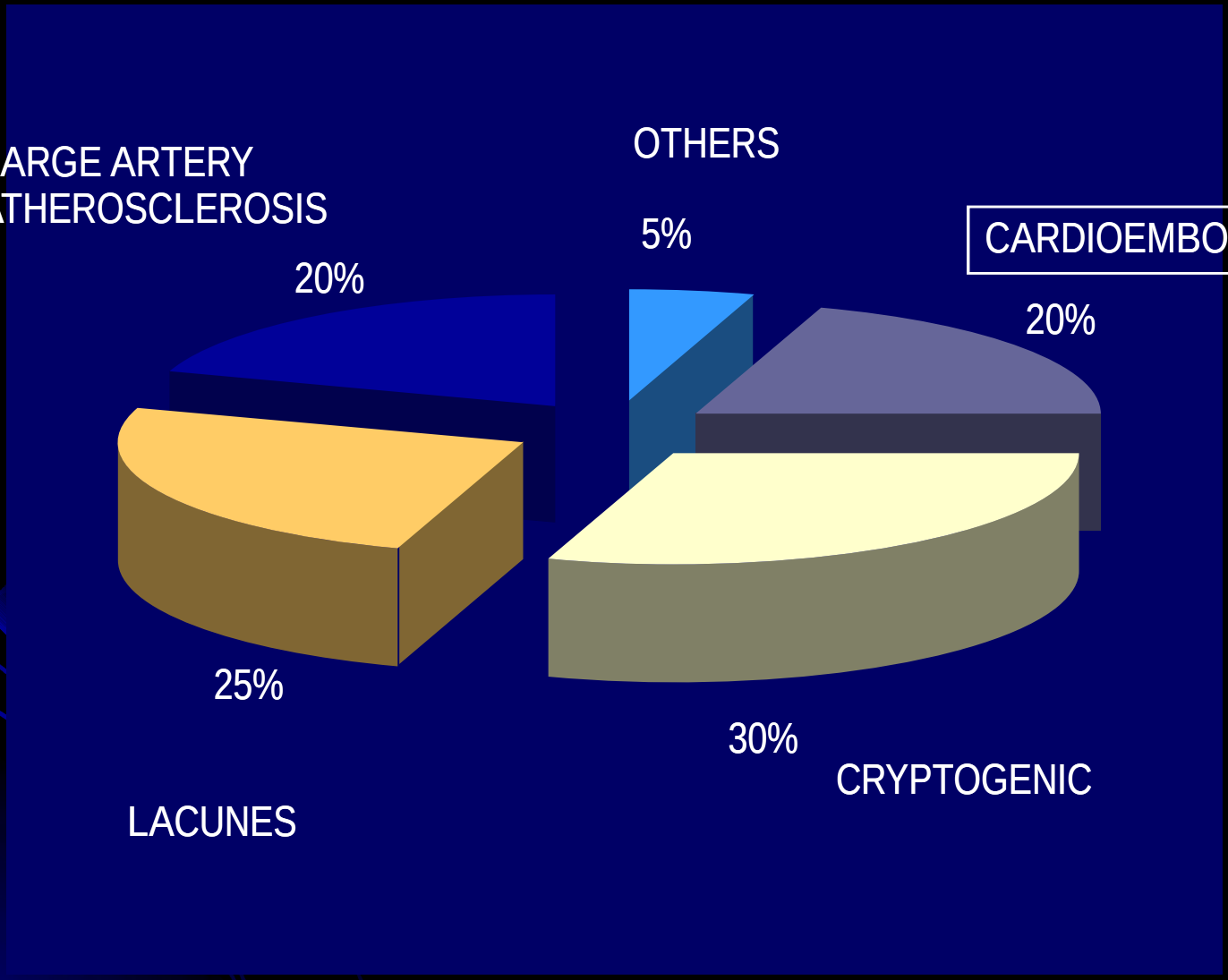
- Large artery thromboembolism
  - Cortical infarction, >50% relevant large artery stenosis, absence of cardiac source
- Cardiogenic embolism
  - Cortical infarction, cardiac source (most often Afib), absence of large artery disease
- Lacunar Infarction
  - Subcortical infarction, absence of large artery or cardiac source, clinical syndromes

Ischemic stroke classfication 2 TOAST

- Rare causes
  - eg arterial dissection, drugs, vasculitis, rarer arteriopathies such as Moyamoya disease
- Dual Pathology
  - Eg cardiac + large artery source
- Unclassified
  - Despite adequate investigation
  - Inadequate investigation

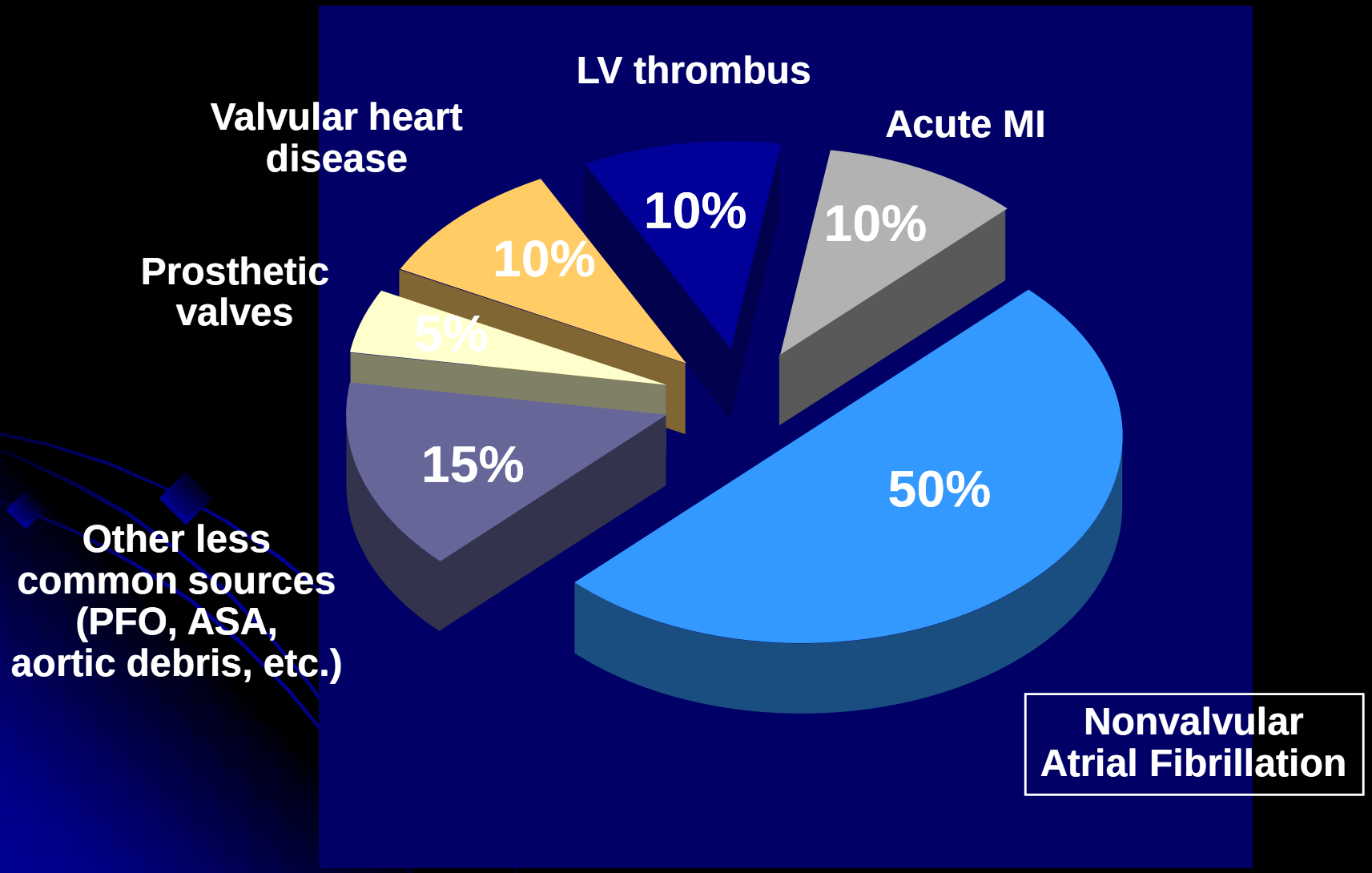
STROKE SUBTYPES

Pathogenesis

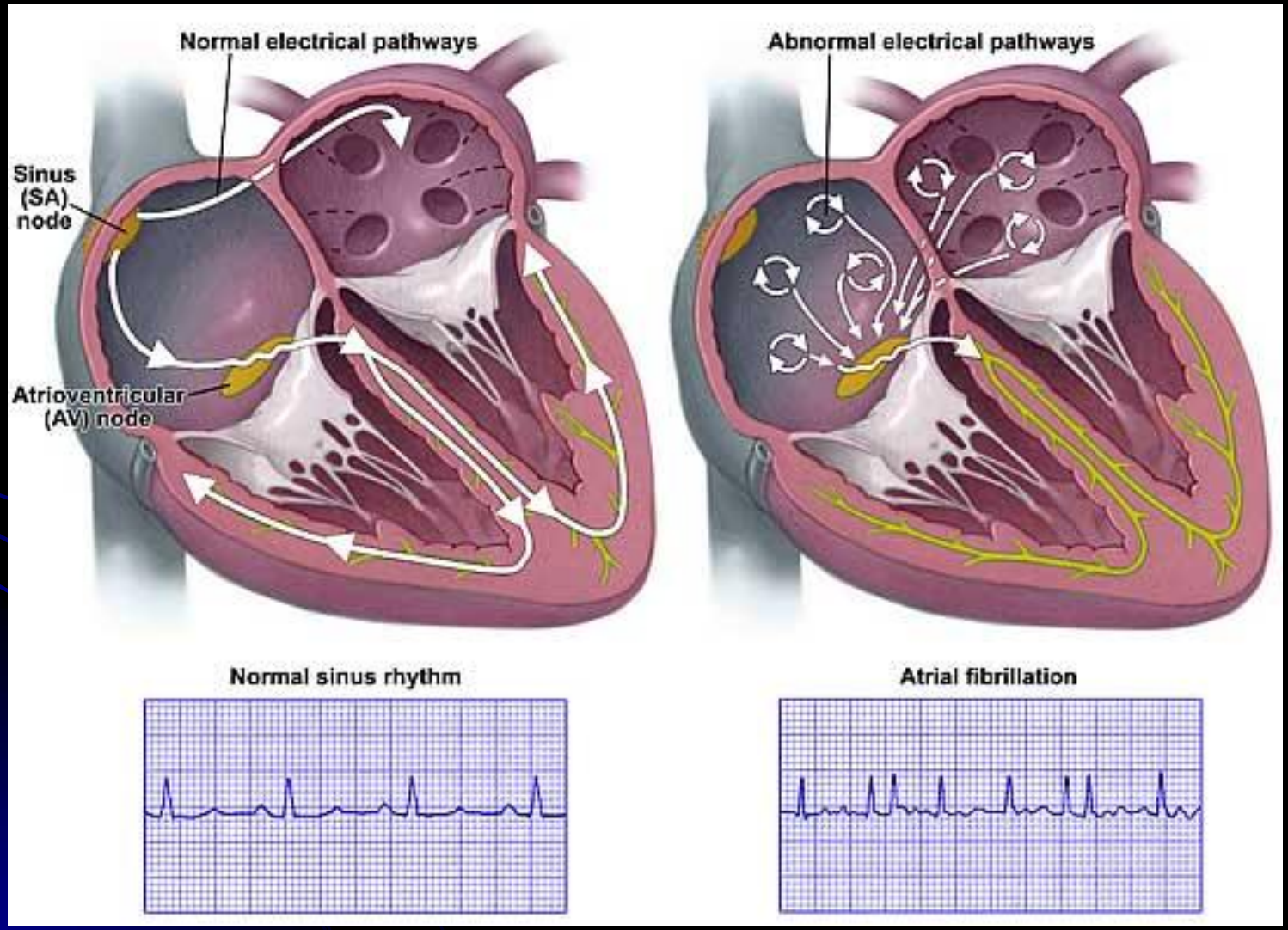


Albers GW et al. Antithrombotic and Thrombolytic Therapy for Ischemic Stroke; Chest 2001.

CARDIOEMBOLIC SOURCES



What is Atrial Fibrillation?

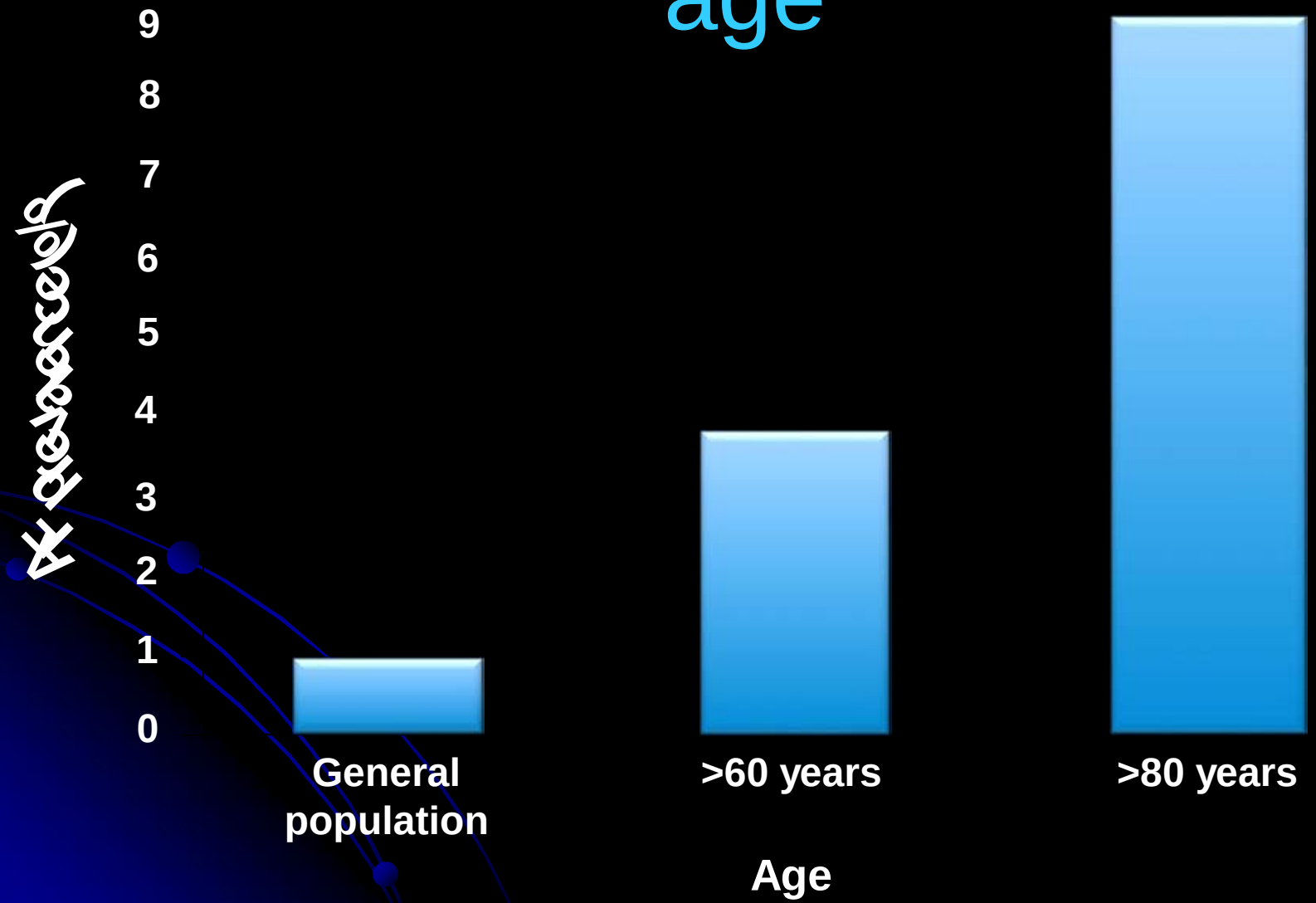


Atrial fibrillation (AF)

- AF is the most common heart rhythm disturbance[1]
- It is estimated 1 in 4 individuals aged 40 years will develop AF[1]
- In 2007, 6.3 million people in the US, Japan, Germany, Italy, Spain, France and UK were living with diagnosed AF[2]
- Due to the aging population, this number is expected to double within 30 years[3]

1. Lloyd-Jones DM, et al. *Circulation* 2004;110:1042-1046. 2. Decision Resources. *Atrial Fibrillation Report*. Dec 2008.
3. Go AS, et al. *JAMA* 2001;285:2370-2375.

AF prevalence increases with age



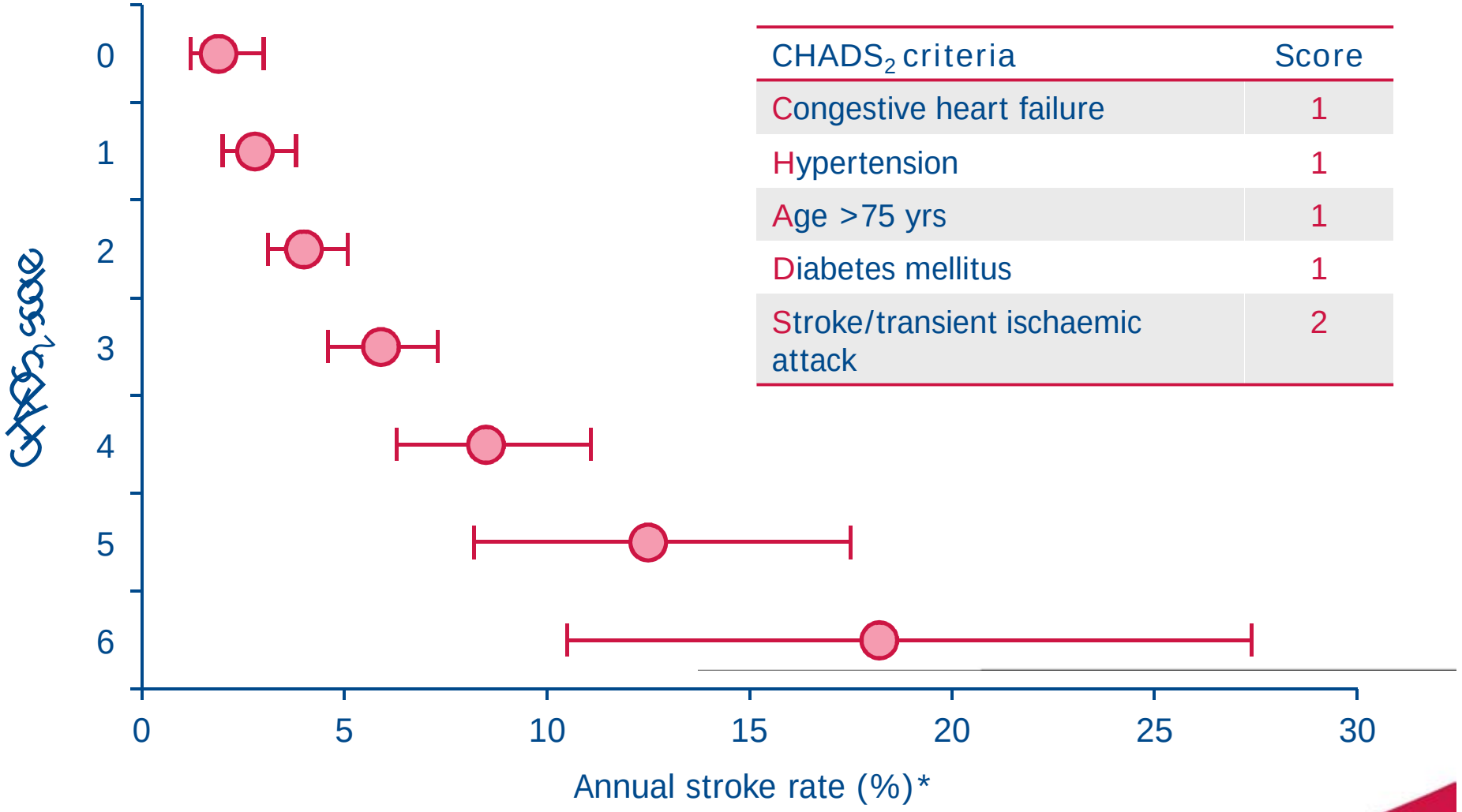
1. Go AS, et al. *JAMA* 2001;285:2370-2375.

AF increases the risk of stroke

- AF is associated with a prothrombotic state
  - ~5 fold increase in stroke risk[1]
- Risk of stroke is the same in AF patients regardless of whether they have paroxysmal or sustained AF[2,3]
- Probably 3 million Afib strokes/year worldwide
- AF-related stroke has a 1-year mortality of ~50%[5]

1. Wolf PA, et al. *Stroke* 1991;22:983-988; 2. Rosamond W et al. *Circulation.* 2008;117:e25–146; 3.Hart RG, et al. *J Am Coll Cardiol* 2000;35:183-187; 4. Lin H-J, et al. *Stroke* 1996; 27:1760-1764; 5. Marini C, et al. *Stroke* 2005;36:1115-1119.

Stroke risk assessment with $CHADS_2$



$CHADS_2$ criteria	Score
Congestive heart failure	1
Hypertension	1
Age >75 yrs	1
Diabetes mellitus	1
Stroke/transient ischaemic attack	2

Error bars = 95% CI; *Adjusted stroke rate = expected stroke rate per 100 patient-years based on exponential survival model, assuming Aspirin not taken

Gage BF et al. JAMA 2001;285:2864–70

KNOW YOUR STROKE RISK

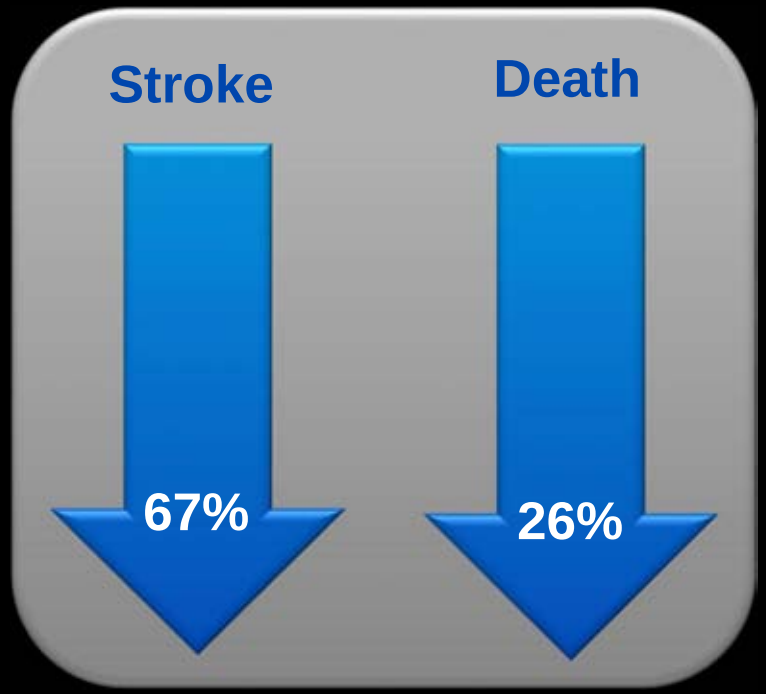
CHA2DS2-VASc Risk	Score	CHA2DS2-VASc Score	Adjusted stroke rate (% / year)
		0	0
CHF or LVEF <40%	1	1	1.3
Hypertension	1	2	2.2
Age > 75	2	3	3.2
Diabetes	1	4	4
Stroke / TIA / Thromboembolism	2	5	6.7
Vascular Disease	1	6	9.8
Age 65-74	1	7	9.6
Female	1	8	6.7
		9	15.2

CHF = congestive heart failure; TIA - transient ischemic attack;
LVEF = left ventricular ejection fraction.

AF-related stroke is preventable

- 2/3 of strokes due to AF are preventable with appropriate anticoagulant therapy with Warfarin (INR 2-3)[1]
- Anticoagulation with Warfarin is recommended for patients with more than 1 moderate risk factor[2]
- A meta-analysis of 29 trials in 28,044 patients showed that adjusted-dose warfarin results in a reduction in ischemic stroke and in all-cause mortality[1]

Warfarin vs placebo



1. Hart RG et al. *Ann Intern Med*. 2007;146:857-867 2. Fuster V, et al. *JACC*. 2006; 48: 854-906

Limitations of Warfarin

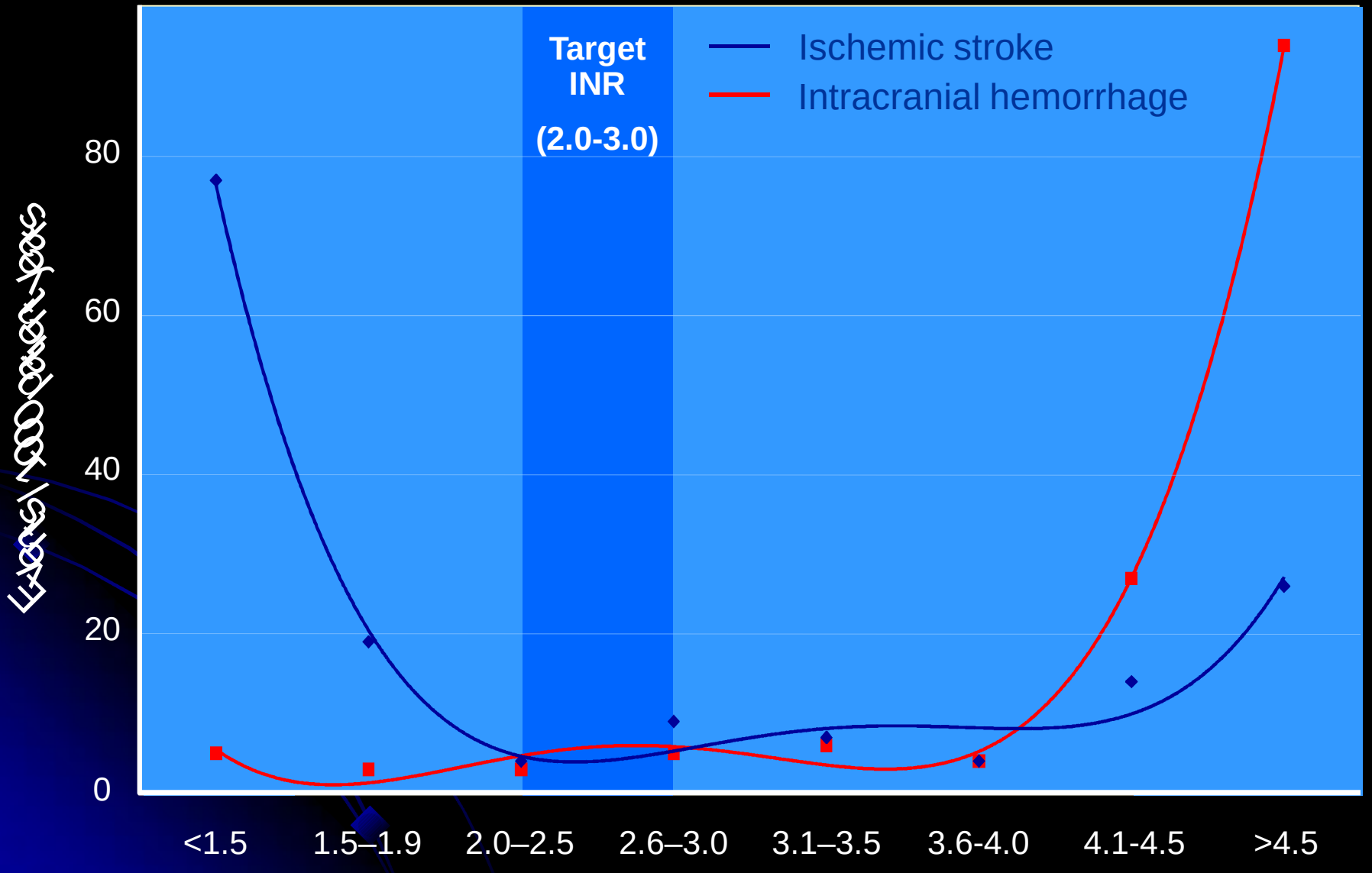
- Unpredictable response
- Narrow therapeutic window (INR range 2-3)
- Routine coagulation monitoring
- Slow onset/offset of action

Warfarin annual ICH rate ~ 1% in trials

- Frequent dose adjustments
- Numerous food-drug interactions
- Numerous drug-drug interactions
- Warfarin resistance

1. Ansell J, et al. *Chest* 2008;133;160S-198S; 2. Umer Ushman MH, et al. *J Interv Card Electrophysiol* 2008; 22:129-137; Nutescu EA, et al. *Cardiol Clin* 2008; 26:169-187.

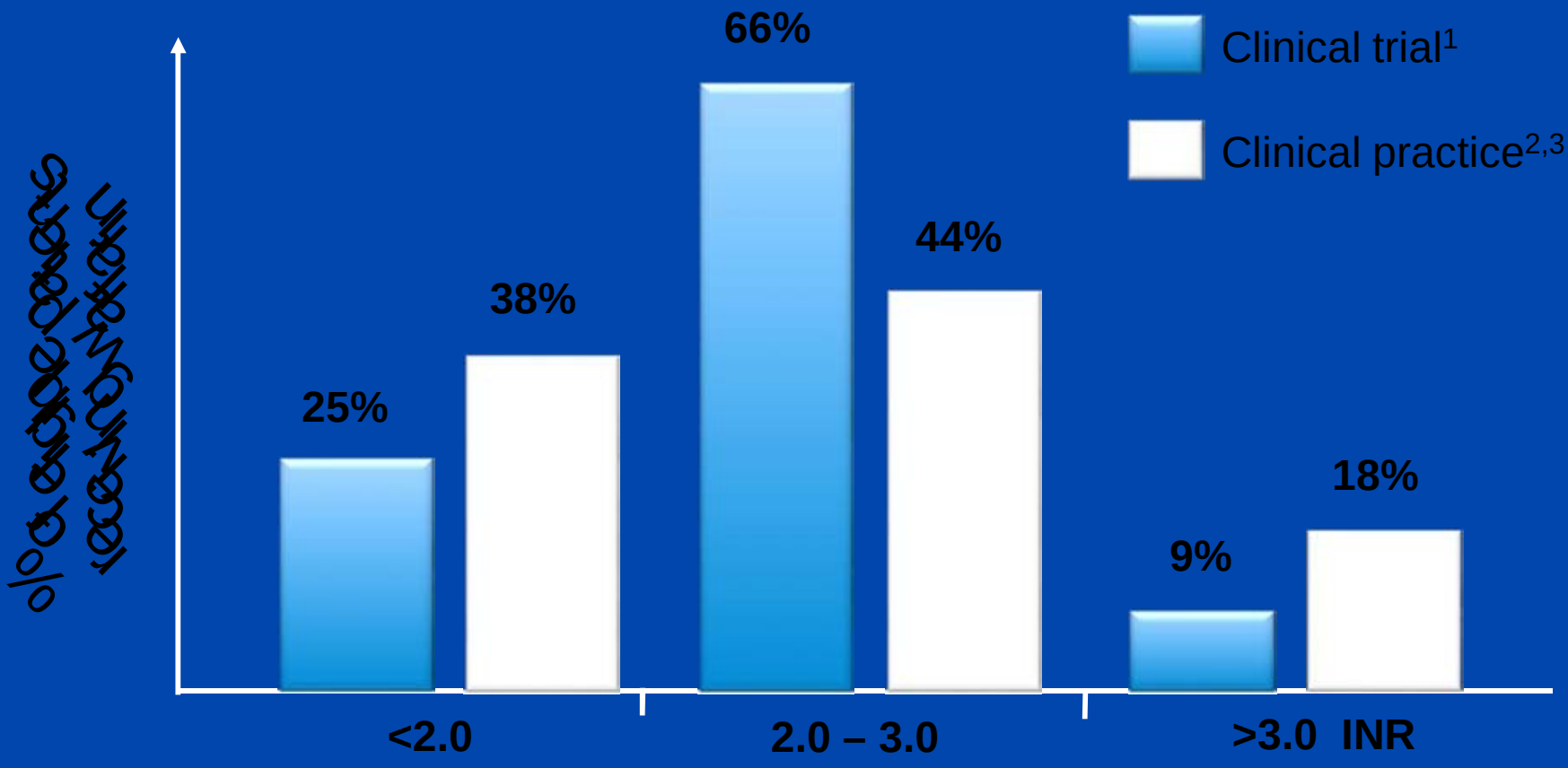
Narrow therapeutic range of Warfarin



1. Hylek EM, et al. *N Eng J Med* 2003; 349:1019-1026.

INR control: clinical trials v. clinical practice

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



*INR = International normalized ratio

** 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. Samsa GP, et al. Arch Int Med 2000
3. Matchar DB, et al. *Am J Med* 2002; 113:42-51.

American Heart Association. American Stroke Association.
Learn and Live.

Recommendations for Patients With Cardioembolic Stroke Types

Risk Factor – Cardiomyopathy	Class/Level of Evidence
In patients with prior stroke or transient cerebral ischemic attack in sinus rhythm who have cardiomyopathy characterized by systolic dysfunction (LVEF ≤35%), the benefit of warfarin has not been established.	Class IIb; LOE B New recommendation
Warfarin (INR 2.0 to 3.0), aspirin (81 mg daily), clopidogrel (75 mg daily), or the combination of aspirin (25 mg twice daily) plus extended-release dipyridamole (200 mg twice daily) may be considered to prevent recurrent ischemic events in patients with previous ischemic stroke or TIA and cardiomyopathy.	Class IIb; LOE B

Recommendations for Patients With Cardioembolic Stroke Types

Risk Factor – Native Valvular Heart Disease	Class/Level of Evidence
For patients with ischemic stroke or TIA who have rheumatic mitral valve disease, whether or not AF is present, long-term warfarin therapy is reasonable with an INR target range of 2.5 (range, 2.0 to 3.0).	Class IIa; LOE C
To avoid additional bleeding risk, antiplatelet agents should not be routinely added to warfarin.	Class III; LOE C
For patients with ischemic stroke or TIA and native aortic or nonrheumatic mitral valve disease who do not have AF, antiplatelet therapy may be reasonable.	Class IIb; LOE C
For patients with ischemic stroke or TIA and mitral annular calcification, antiplatelet therapy may be considered.	Class IIb; LOE C
For patients with MVP who have ischemic stroke or TIA, long-term antiplatelet therapy may be considered.	Class IIb; LOE C

Recommendations for Patients With Cardioembolic Stroke Types

Risk Factor – Prosthetic Heart Valves	Class/Level of Evidence
For patients with ischemic stroke or TIA who have mechanical prosthetic heart valves, warfarin is recommended with an INR target of 3.0 (range, 2.5 to 3.5).	Class I; LOE B
For patients with mechanical prosthetic heart valves who have an ischemic stroke or systemic embolism despite adequate therapy with oral anticoagulants, aspirin 75 mg/d to 100 mg/d in addition to oral anticoagulants and maintenance of the INR at a target of 3.0 (range, 2.5 to 3.5) is reasonable if the patient is not at high bleeding risk (e.g., history of hemorrhage, varices, or other known vascular anomalies conveying increased risk of hemorrhage, coagulopathy).	Class IIa; LOE B
For patients with ischemic stroke or TIA who have bioprosthetic heart valves with no other source of thromboembolism, anticoagulation with warfarin (INR 2.0 to 3.0) may be considered.	Class IIb; LOE C

AF indicates atrial fibrillation; INR, international normalized ratio; LMWH, low-molecular-weight heparin; LV, left ventricular; LVEF, left ventricular ejection fraction; MVP, mitral valve prolapse; and TIA, transient ischemic attack.
*See Tables 1 and 2 for explanation of class and level of evidence

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

John W. Eikelboom, M.D., Stuart J. Connolly, M.D., Martina Brueckmann, M.D., Christopher B. Granger, M.D., Arie P. Kappetein, M.D., Ph.D., Michael J. Mack, M.D., Jon Blatchford, C.Stat., Kevin Devenny, B.Sc., Jeffrey Friedman, M.D., Kelly Guiver, M.Sc., Ruth Harper, Ph.D., Yasser Khder, M.D., Maximilian T. Lobmeyer, Ph.D., Hugo Maas, Ph.D., Jens-Uwe Voigt, M.D., Maarten L. Simoons, M.D., and Frans Van de Werf, M.D., Ph.D., for the RE-ALIGN Investigators*

N Engl J Med 2013.
DOI: 10.1056/NEJMoa1300615

BACKGROUND

Dabigatran is an oral direct thrombin inhibitor that has been shown to be an effective alternative to warfarin in patients with atrial fibrillation. We evaluated the use of dabigatran in patients with mechanical heart valves.

METHODS

In this phase 2 dose-validation study, we studied two populations of patients: those who had undergone aortic- or mitral-valve replacement within the past 7 days and those who had undergone such replacement at least 3 months earlier. Patients were randomly assigned in a 2:1 ratio to receive either dabigatran or warfarin. The selection of the initial dabigatran dose (150, 220, or 300 mg twice daily) was based on kidney function. Doses were adjusted to obtain a trough plasma level of at least 50 ng per milliliter. The warfarin dose was adjusted to obtain an international normalized ratio of 2 to 3 or 2.5 to 3.5 on the basis of thromboembolic risk. The primary end point was the trough plasma level of dabigatran.

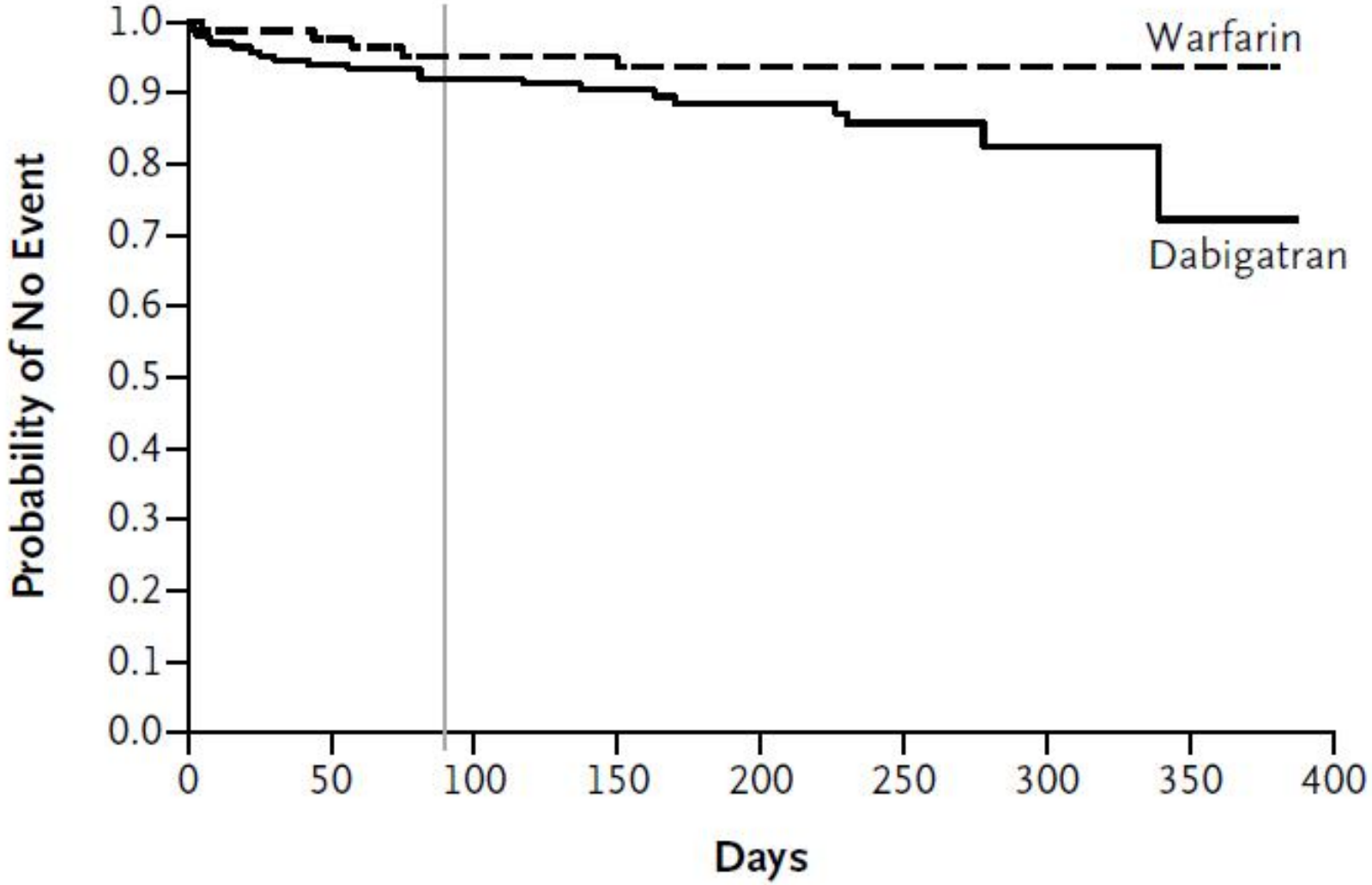
RESULTS

The trial was terminated prematurely after the enrollment of 252 patients because of an excess of thromboembolic and bleeding events among patients in the dabigatran group. In the as-treated analysis, dose adjustment or discontinuation of dabigatran was required in 52 of 162 patients (32%). Ischemic or unspecified stroke occurred in 9 patients (5%) in the dabigatran group and in no patients in the warfarin group; major bleeding occurred in 7 patients (4%) and 2 patients (2%), respectively. All patients with major bleeding had pericardial bleeding.

CONCLUSIONS

The use of dabigatran in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin, thus showing no benefit and an excess risk. (Funded by Boehringer Ingelheim; ClinicalTrials.gov numbers, NCT01452347 and NCT01505881.)

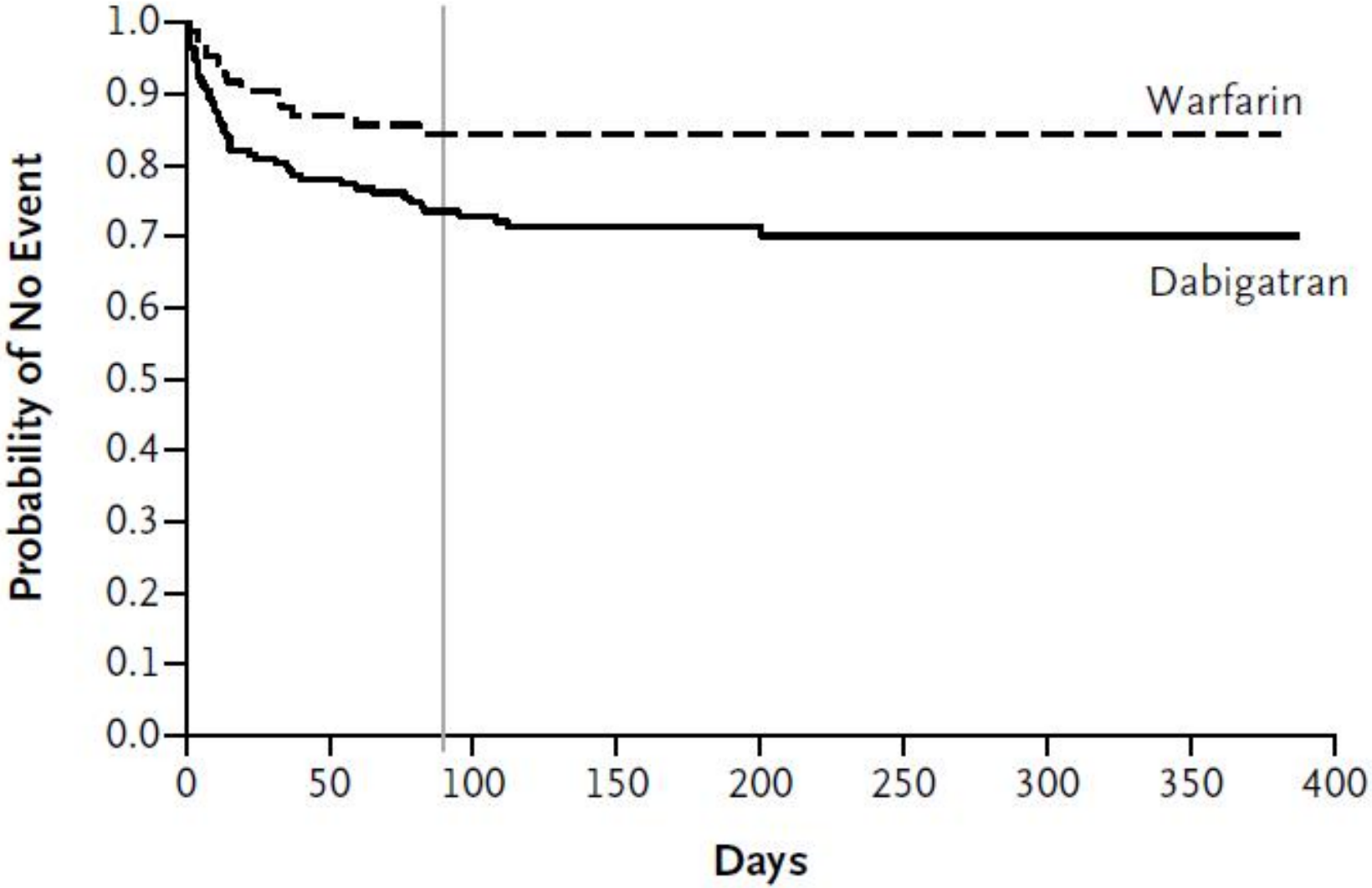
A First Thromboembolic Event



No. at Risk

Dabigatran	168	156	126	108	73	44	15	7
Warfarin	84	82	66	55	40	22	9	4

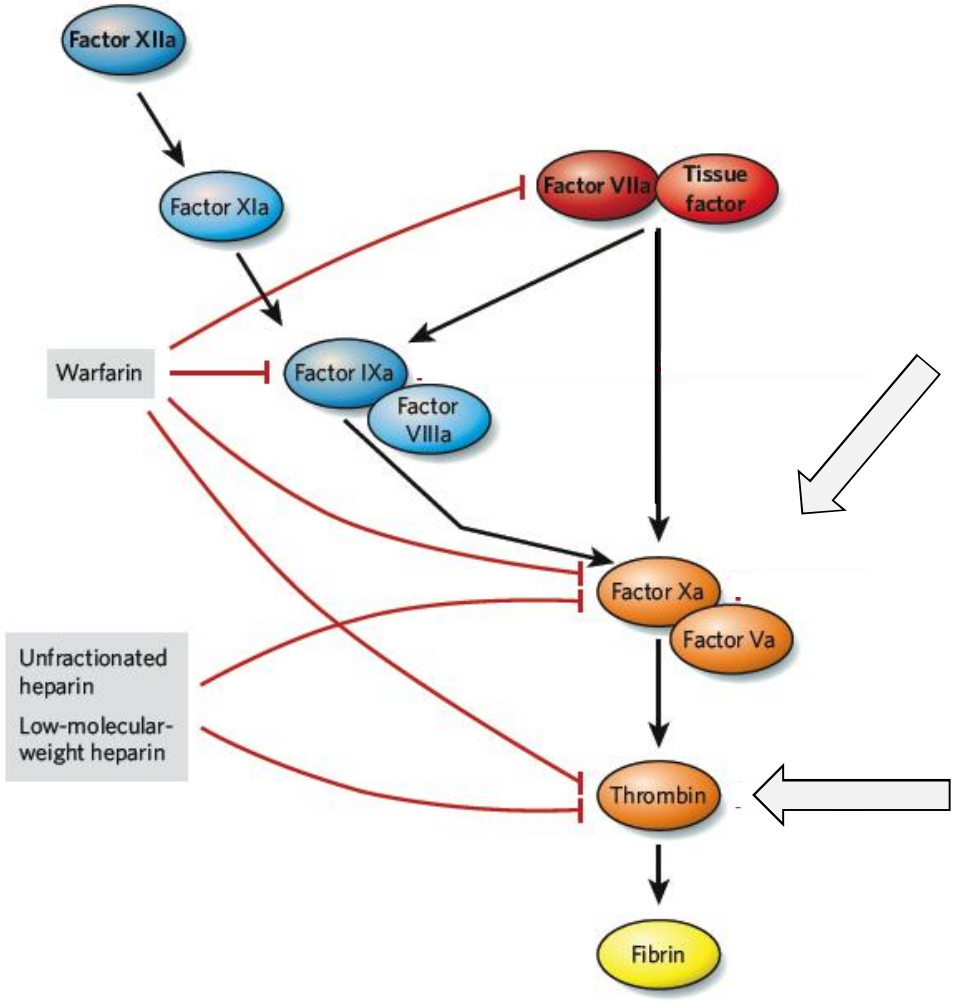
First Bleeding Event



No. at Risk

Dabigatran	168	129	103	86	58	32	11	6
Warfarin	84	73	56	50	38	22	11	4

NEW ANTICOAGULANTS



Apixaban (ARISTOTLE)

Edoxaban (ENGAGE-AF)

Rivaroxaban (ROCKET)

Dabigatran (RE-LY)

Ximelagatran (SPORTIF)

Advantages new anticoagulants

- More effective and safer than warfarin
- Fixed dose
- No monitoring
- No need for dietary restrictions
- Rapid onset, offset
- Few drug, food interactions

Warfarin and ICH

- ICH is the most feared complication of anticoagulation with warfarin
- At least doubles the risk
- At least 1% per year
- Larger volumes and more growth of ICH
- High mortality (at least 50%)

Hart RG et al. Stroke 2005;36:1588–93; Fang MC et al. Stroke 2012;43:1795–9

Disadvantages new anticoagulants

- Rapid onset, offset
- No ready blood test to indicate if patient is ON treatment and anticoagulant effect
- No effective reversal
- Issues with tPA for ischemic stroke
- Cost

Novel anticoagulants for stroke prevention in atrial fibrillation

- Dabigatran versus Warfarin in Patients with Atrial Fibrillation (RE-LY)
  NEJM 2009;361:1139-51
- Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET AF)
  NEJM 2011;365:883-91
- Apixaban in patients with Atrial Fibrillation (AVERROES)
  NEJM 2011;364:806-17
- Apixaban versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE)
  NEJM 2011;365:981-92

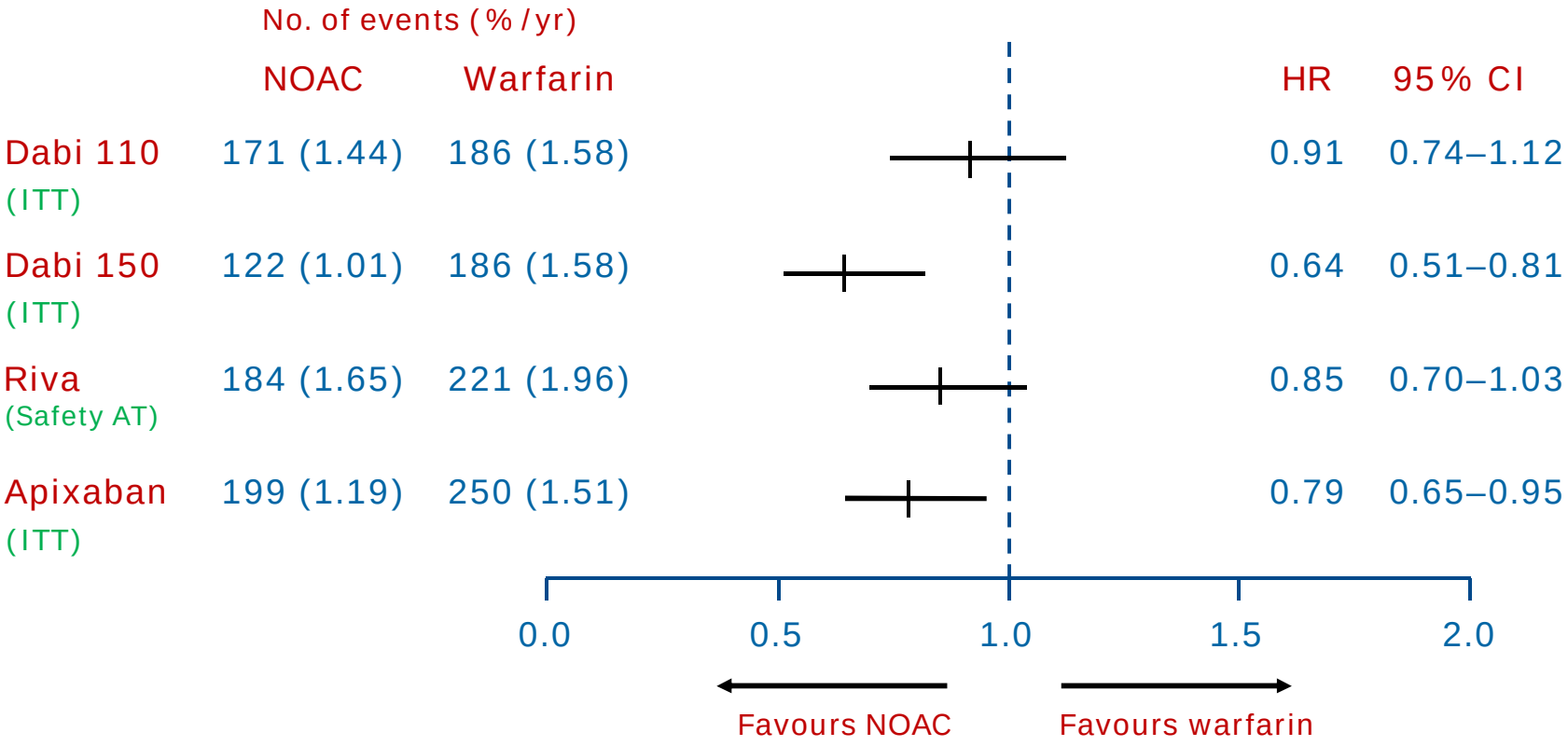
MAIN PHARMACOLOGICAL FEATURES OF NEW ANTICOAGULANTS*

	Dabigatran	Riavaroxaban	Apixaban
Time to peak concentration	1.5 – 3h	2 – 4 h	1 – 3 h
Half-life	12 – 14h	9 – 13 h	9 – 14h
Metabolism	Conjugation	Liver CYP3A4 and CYP2J2	Partially through CYP3A4
Elimination	80% renal 20% faecal	66% faecal 33% renal	75% Faecal 25% renal
Drug interactions	PPIs decrease absorption and potent P-gp inhibitors	Potent CYP 3A4 inhibitors and P-gp inhibitors	Potent CYP 3A4 inhibitors

* Phillips KW, Ansell J. Thromb Haemost 2010

Stroke

Courtesy HC Diener 2013



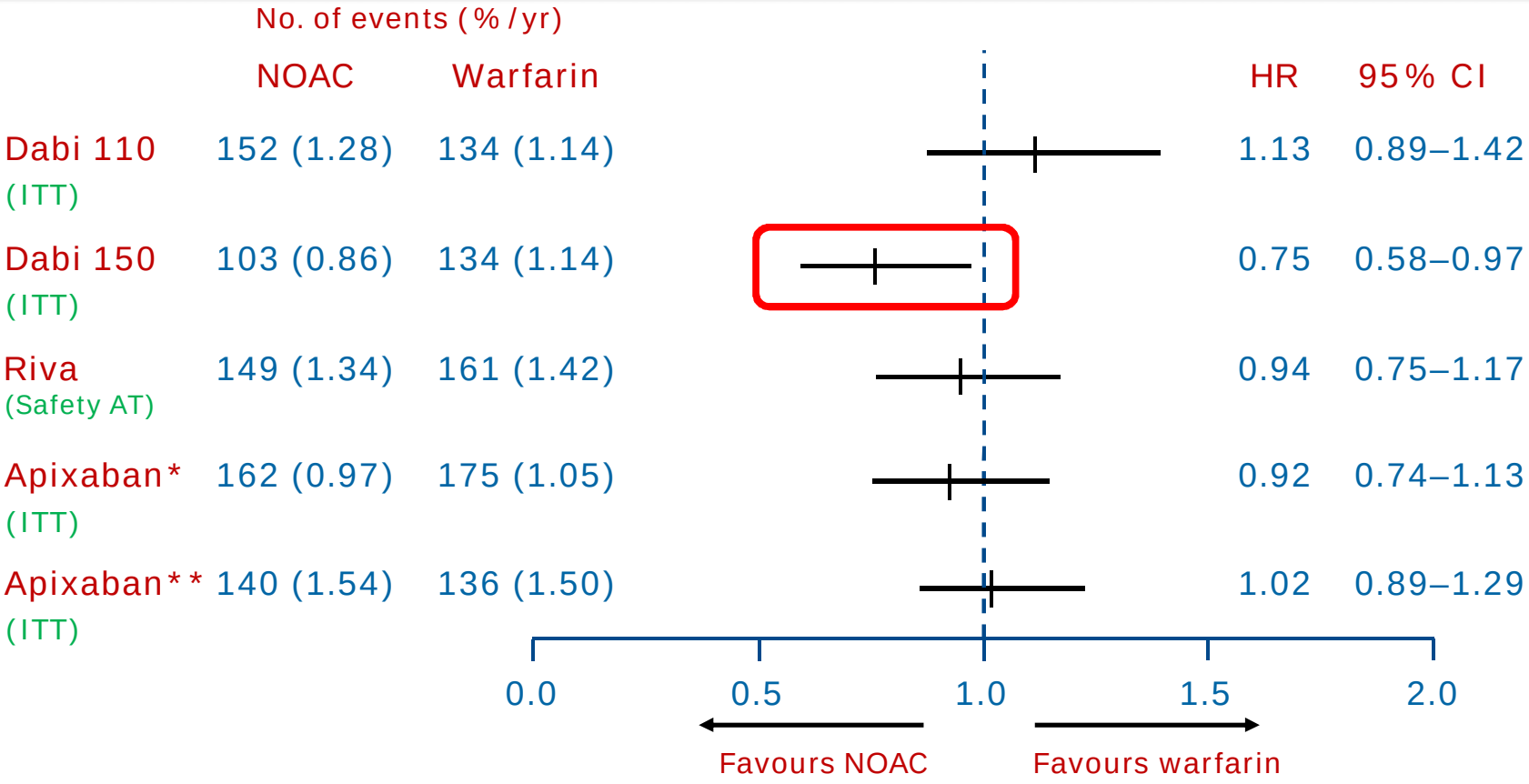
Clinical Trial Data for information only - no clinical conclusions should be drawn. Please refer to individual product SPCs for further information.

AT = as treated; CI = confidence interval; Dabi 110/150 = dabigatran 110 mg/150 mg twice daily; HR = hazard ratio; ITT = intention-to-treat; NOAC = novel oral anticoagulant; Riva = rivaroxaban

1. Connolly SJ et al. N Engl J Med 2009;361:1139–51; 2. Connolly SJ et al. N Engl J Med 2010;363:1875–6;
3. Patel MR et al. N Engl J Med 2011;365:883–91; 4. Granger C et al. N Engl J Med 2011;365:981–92

Courtesy HC Diener 2013

Ischaemic stroke



Clinical Trial Data for information only - no clinical conclusions should be drawn. Please refer to individual product SPCs for further information.

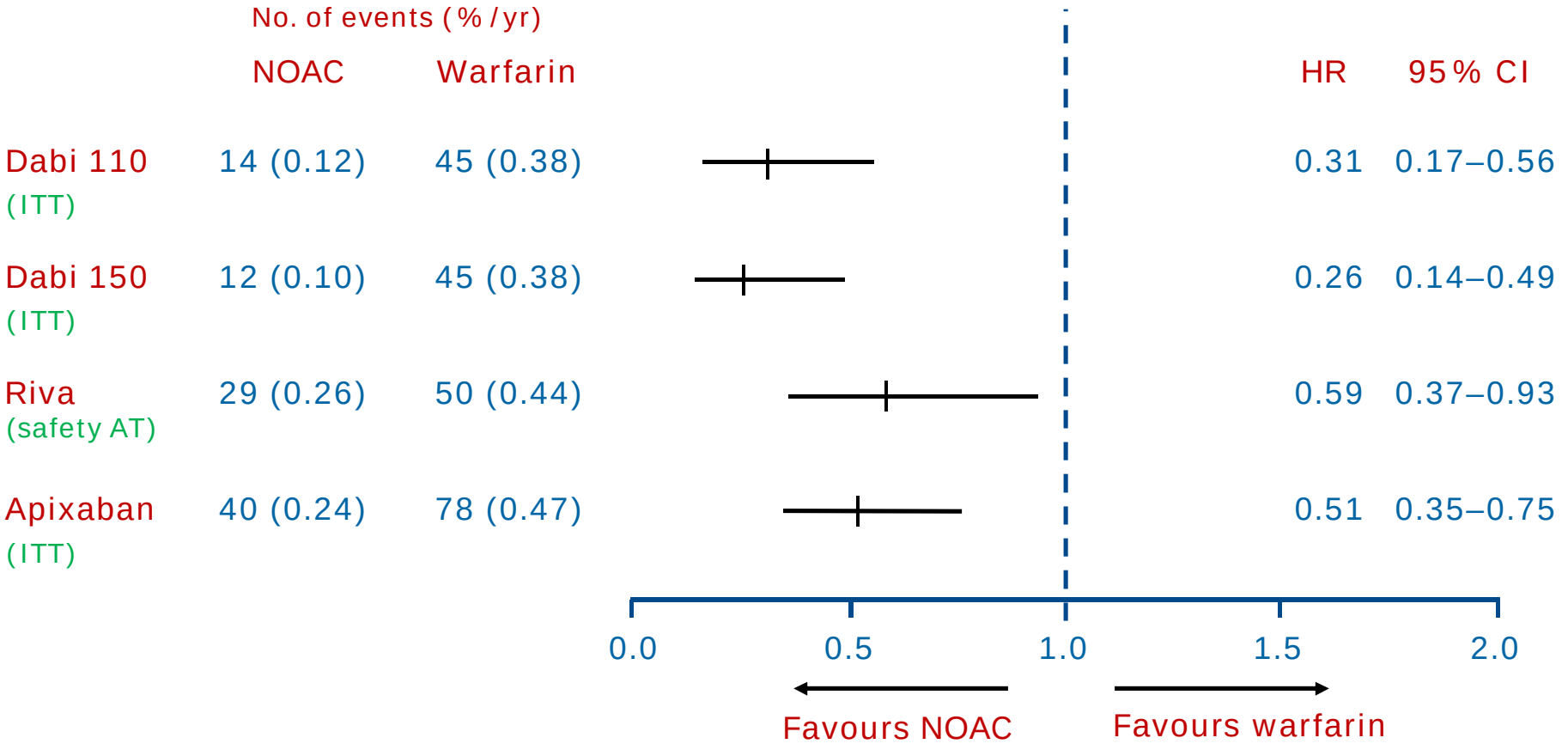
*Unknown type of stroke occurred in 14 patients in the apixaban group and 21 patients in the warfarin group. Among the patients with ischaemic strokes, haemorrhagic transformation occurred in 12 patients with apixaban and 20 patients with warfarin

** Revised data; re-categorized following original publication

1. Connolly SJ et al. N Engl J Med 2009;361:1139–51; 2.Pradaxa®: EU SmPC, 2013;
3. Patel MR et al. N Engl J Med 2011;365:883–91; 4. Granger C et al. N Engl J Med 2011;365:981–92;
5. Lopes R et al. Lancet 2012; 380:1749–58

Courtesy HC Diener 2013

Haemorrhagic stroke



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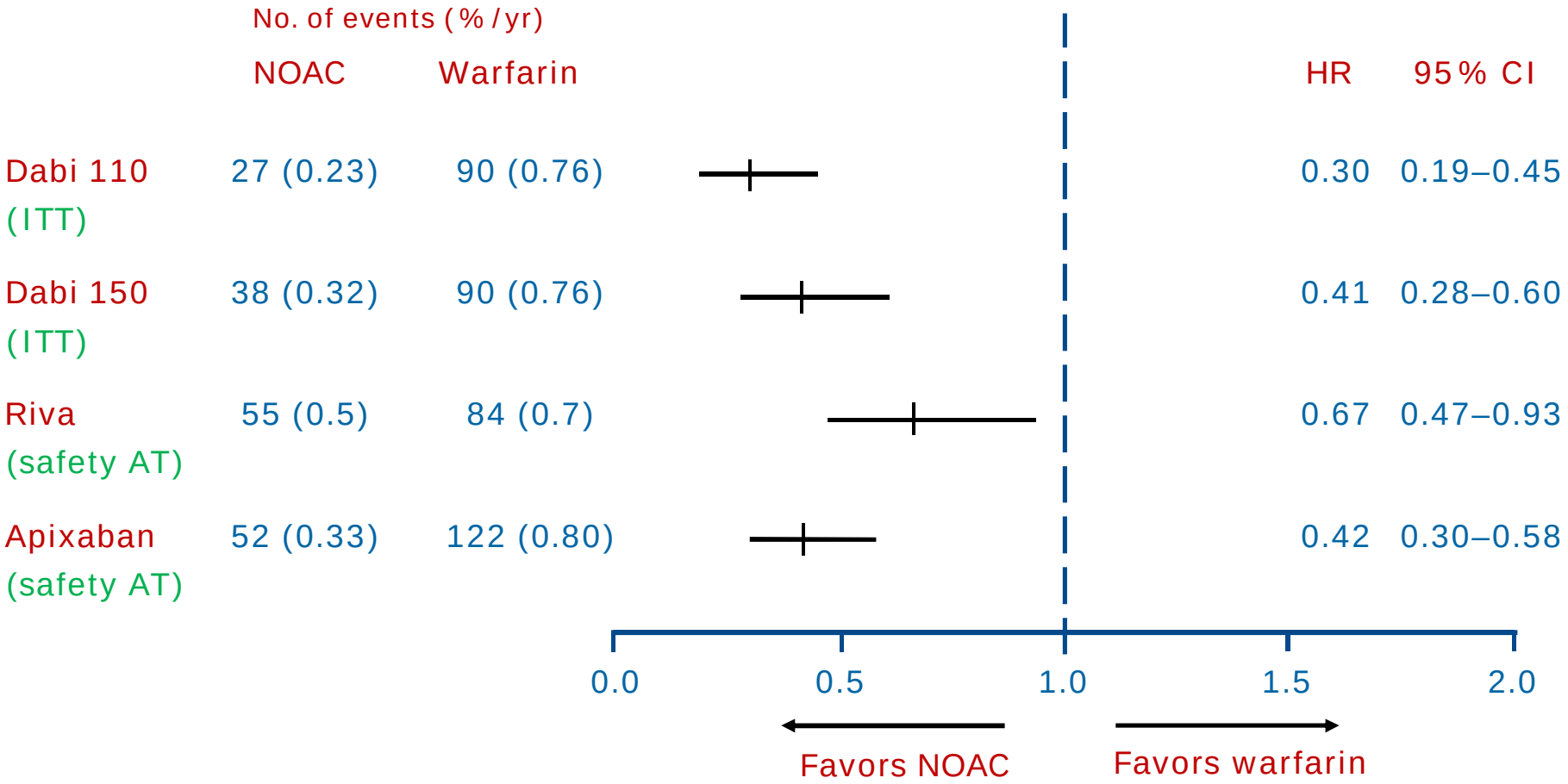
1. Connolly SJ et al. N Engl J Med 2009;361:1139–51; 2. Connolly SJ et al. N Engl J Med 2010;363:1875–6;
3. Patel MR et al. N Engl J Med 2011;365:883–91; 4. Granger C et al. N Engl J Med 2011;365:981–92

Courtesy HC Diener 2013

Intracranial bleeding



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1. Connolly SJ et al. N Engl J Med 2009;361:1139–51; 2. Connolly SJ et al. N Engl J Med 2010;363:1875–6;
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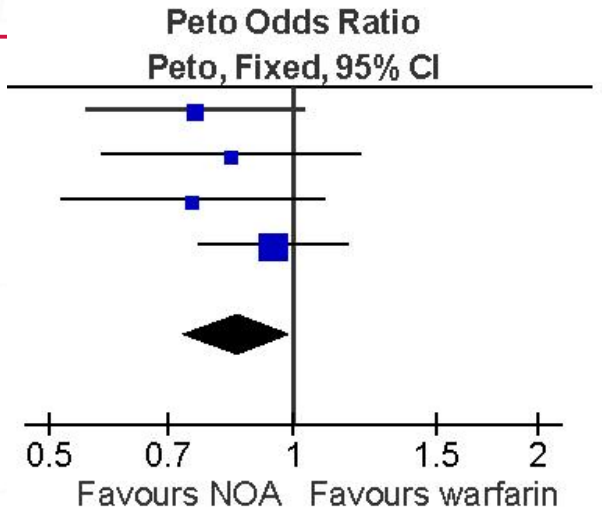
Effects of NOACs vs warfarin on stroke or systemic embolism in patients with AF and previous stroke or TIA (1) Courtesy HC Diener 2013

Stroke or systemic embolism	NOACs		Warfarin			Peto odds ratio
Study or subgroup	Events	Total	Events	Total	Weight	Peto, fixed (95% CI)
ARISTOTLE	73	1694	98	1742	22.1%	0.76 (0.56–1.03)
RE-LY 110	55	1195	65	1195	15.5%	0.84 (0.58–1.21)
RE-LY 150	51	1233	65	1195	15.0%	0.75 (0.52–1.09)
ROCKET AF	179	3754	187	3714	47.4%	0.94 (0.77–1.17)
Total (95% CI)		7876		7846	100%	0.85 (0.74–0.99)
Total events	358		415			

Heterogeneity: χ^2=1.93, df=3 (P=0.59); I^2=0%
Test for overall effect: Z=2.15 (P=0.03)



This study was not designed to compare NOACs against one another. Comparison between NOACs is not valid because of population differences among the studies. No head-to-head data are available

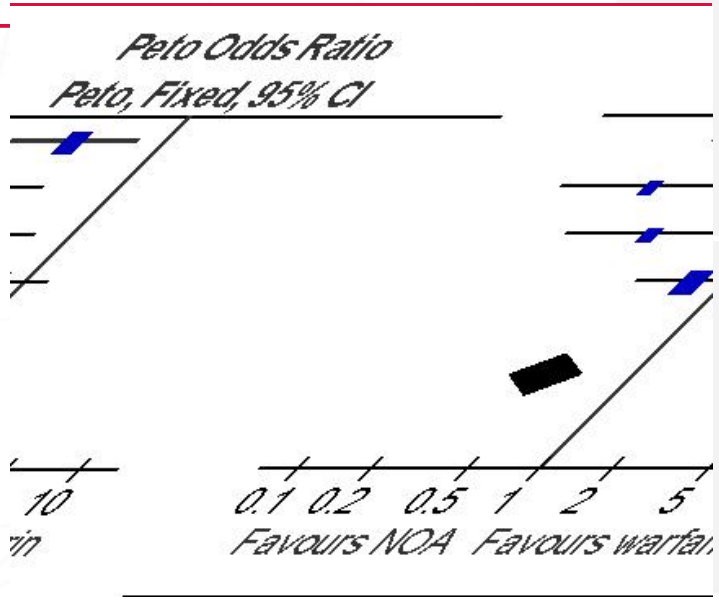
Ntaios G et al. Stroke 2012;42:3298–304

Effects of NOACs vs warfarin on haemorrhagic stroke in patients with AF and previous stroke or TIA (2)

Courtesy HC Diener 2013

Haemorrhagic stroke	NOACs		Warfarin			Peto odds ratio
Study or subgroup	Events	Total	Events	Total	Weight	Peto, fixed (95% CI)
ARISTOTLE	12	1694	31	1742	31.1%	0.42 (0.23–0.77)
RE-LY 110	2	1195	18	1195	14.5%	0.20 (0.08–0.48)
RE-LY 150	5	1233	18	1195	16.7%	0.31 (0.14–0.70)
ROCKET AF	22	3754	30	3714	37.8%	0.73 (0.42–1.25)
Total (95% CI)		7876		7846	100%	0.44 (0.32–0.62)
Total events	41		97			

Heterogeneity: χ^2=7.07, df=3 (P=0.07); I^2=58%
Test for overall effect: Z=4.79 (P<0.00001)



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Ntaios G et al. Stroke 2012;42:3298–304

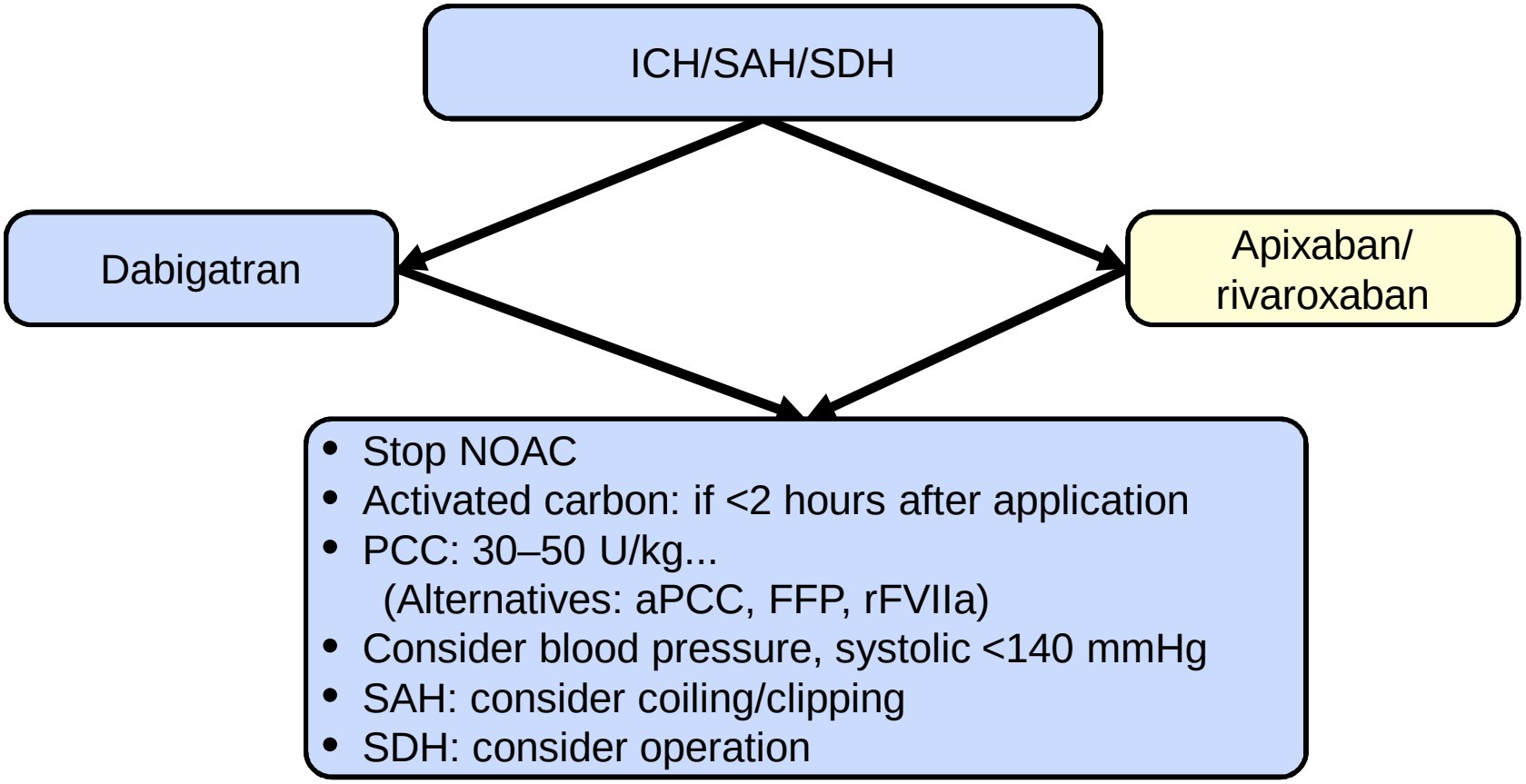
A new era of anticoagulation?

Diener HC et al. Int J Stroke 2012;7:139–41

Issues

- De Novo treatment easy – NOAC
- When to commence OAC after stroke?
- Most continue warfarin in well-stabilized patient, good INR levels
- Can tPA be used in a patient on a NOAC?
- ICH or symptomatic hemorrhagic transformation – can and when NOAC be recommenced?
- When to cease pre-op
- How to manage ICH or other major hemorrhage?

ICH and NOACs – recommendation

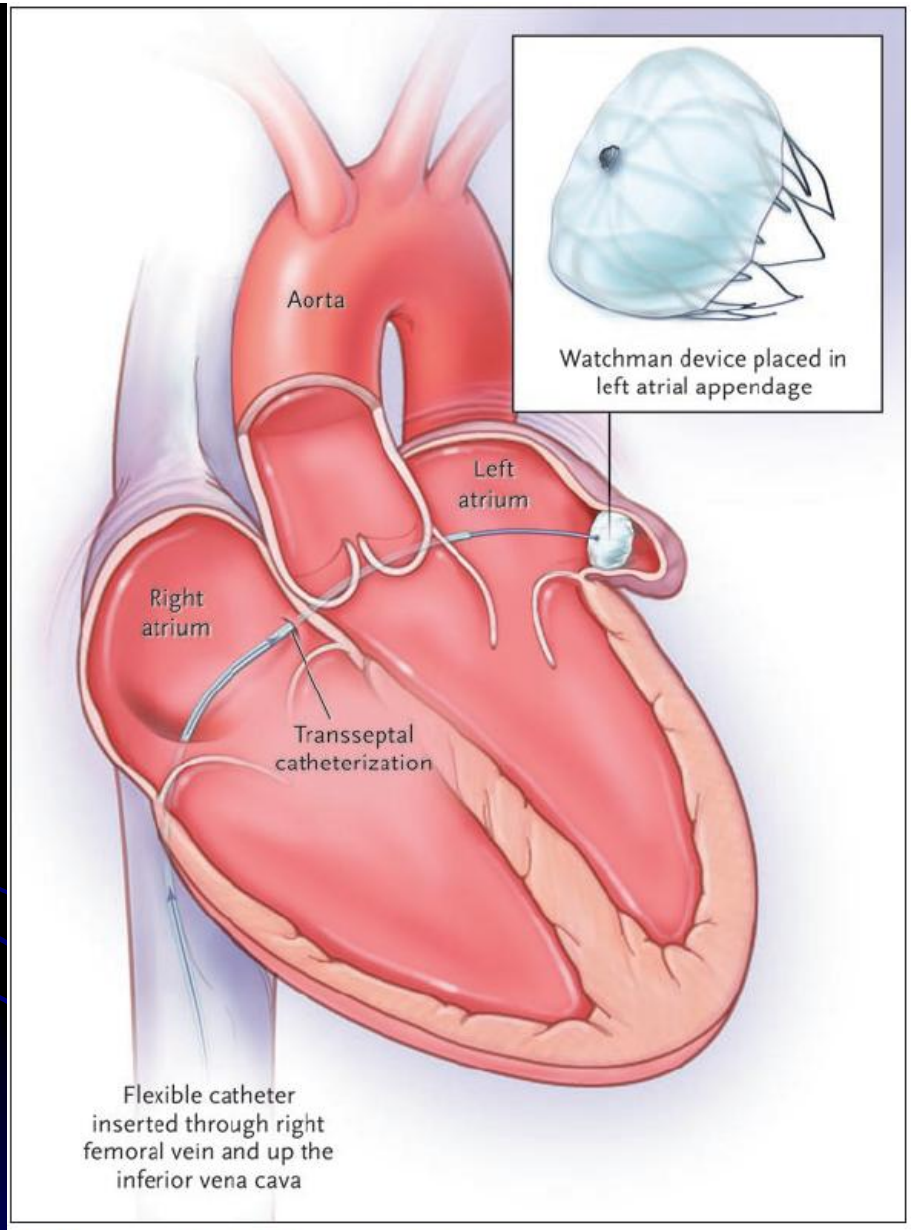


aPCC = activated prothrombin complex concentrate; FFP = fresh frozen plasma; rFVIIa = recombinant activated Factor VII; SAH = subarachnoid haemorrhage; SDH = subdural haematoma

Steiner T et al. Clin Res Cardiol 2013;102:399-412

Current state Afib

- Atrial fibrillation a common cause of stroke
- Highly preventable
- Warfarin has been the gold standard
- Newer anticoagulants appear generally better and safer, easier to use than warfarin
- Still issues re monitoring, reversal, cost
- Paradigm shift in stroke management



The Watchman Left Atrial Appendage Closure Device.

The device is a self-expanding nitinol structure that is delivered percutaneously with femoral venous access and transseptal technique to the left atrial appendage. The device is positioned with the use of angiography and transesophageal echocardiography, and implantation is performed in either a cardiac catheterization or electrophysiology laboratory with the patient under general anesthesia or conscious sedation.

	Intervention group (n=463)	Control group (n=244)
Characteristics		
Age (years)	71·7(8·8;46·0–95·0)	72·7(9·2;41·0–95·0)
Male	326 (70·4%)	171 (70·1%)
Race/ethnicity		
Asian	4 (0·9%)	1 (0·4%)
Black/African-American	6 (1·3%)	5 (2·0%)
White	425 (91·8%)	222 (91·0%)
Hispanic/Latin American	25 (5·4%)	15 (6·1%)
Hawaiian/Pacific Islander	1 (0·2%)	1 (0·4%)
Other	2 (0·4%)	0
Risk factors		
CHADS2 score*		
1	157 (33·9%)	66 (27·0%)
2	158 (34·1%)	88 (36·1%)
3	88 (19·0%)	51 (20·9%)
4	37 (8·0%)	24 (9·8%)
5	19 (4·1%)	10 (4·1%)
6	4 (0·9%)	5 (2·0%)
Congestive heart failure	124 (26·8%)	66 (27·0%)
History of hypertension	413 (89·2%)	220 (90·2%)
Age 75 years or more	190 (41·0%)	115 (47·1%)
Diabetes	113 (24·4%)	72 (29·5%)
Previous transient ischaemic attack/ischaemic stroke	82 (17·7%)	49 (20·1%)
Previous warfarin use		
Less than 1 year	254 (54·9%)	145 (59·4%)
1 year or more	203 (43·8%)	96 (39·3%)
No estimate	6 (1·3%)	3 (1·2%)
Atrial fibrillation pattern		
Paroxysmal	200 (43·2%)	99 (40·6%)
Persistent	97 (21·0%)	50 (20·5%)
Permanent	160 (34·6%)	93 (38·1%)
Unknown	6 (1·3%)	2 (0·8%)
Atrial fibrillation onset		
Less than 1 year	69 (14·9%)	50 (20·5%)
1 year or more	360 (77·8%)	182 (74·6%)
No estimate	34 (7·3%)	12 (4·9%)
Left ventricular ejection fraction (%)	57·3% (9·7; 30·0–82·0)	56·7% (10·1; 30·0–86·0)

Data are mean (SD; range) or n (%). *At least one of the following: previous stroke or transient ischaemic attack, congestive heart failure, diabetes mellitus, hypertension, or were 75 years or older.

Table 1: **Baseline characteristics and risk factors of study participants**

PROTECT AF Summary

- Randomized trial comparing LAA closure to warfarin (n=800, 449 in closure arm)
  - General anaesthesia required for closure
  - Perioperative warfarin + clopidogrel for 6 months + aspirin indefinitely
- 90.9% successful placement
- 93% warfarin cessation at 12 months
- Non-inferior primary endpoint
  - 3.4% vs 5% RR 0.68 (0.37-1.41)
- Warfarin higher rate Intracerebral hemorrhage
  - 0.2% vs 1.9% RR 0.09 (0.0-0.45)
- Primary safety endpoint
  - 8.7% vs 4.2% RR 2.08 (1.18-4.13)
  - Pericardial effusion 4.8%, major bleeding 3.5%, perioperative stroke 1.1%, device migration 0.6%

1. Maisel NEJM 2009;360:2601-3. 2. Holmes et al. Lancet 2009;374:534-42.

Patent Foramen Ovale

Observational studies:

- PFO ~25% general population,
  ~50% cryptogenic stroke
- Population-based recurrent stroke no difference between PFO and no PFO
- Suggestion that atrial septal aneurysm is a higher risk group (Mas NEJM, 2001)

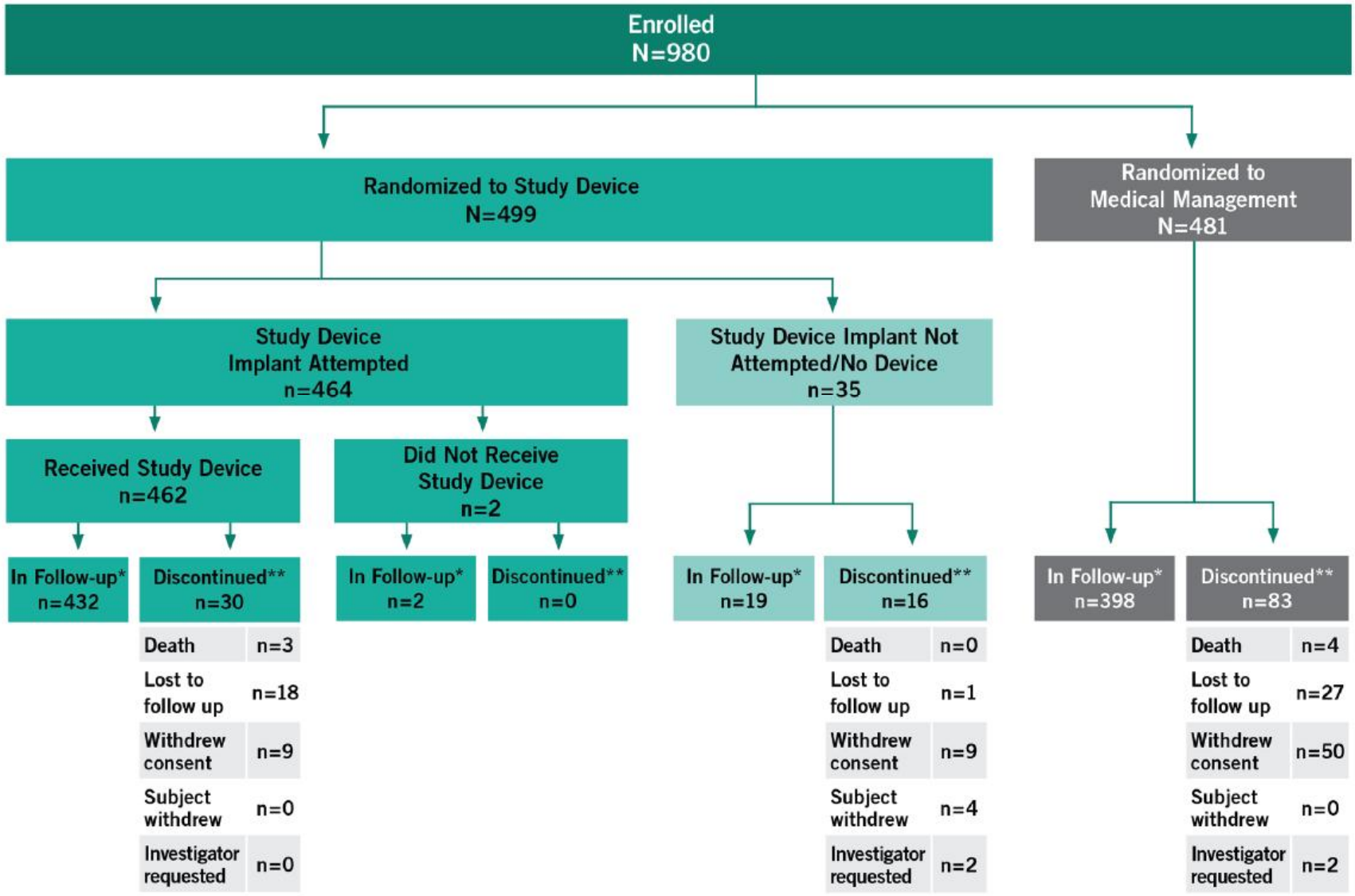
RESPECT AF Summary

- 69 sites Nth America, n=980, 8yr, Ampla
- Event-driven sample size
  Age 18-60 with cryptogenic stroke <270d
- 1 ° = stroke (+ any death within 45d randomization)
- Randomization stratified by site and ASA
- Closure group had 1/12 clopidogrel, 6/12 aspirin then at site discretion
- TOE at 6/12
- Median 2yr follow-up

Medical treatment specified pre-randomization by site neurologist	
Aspirin only	46.5%
Warfarin only	25.2%
Clopidogrel only	14.0%
Aspirin + dipyridamole	8.1%
Aspirin + clopidogrel[1]	6.2%

Removed 2006

Patient Disposition:
Randomization and Follow-Up

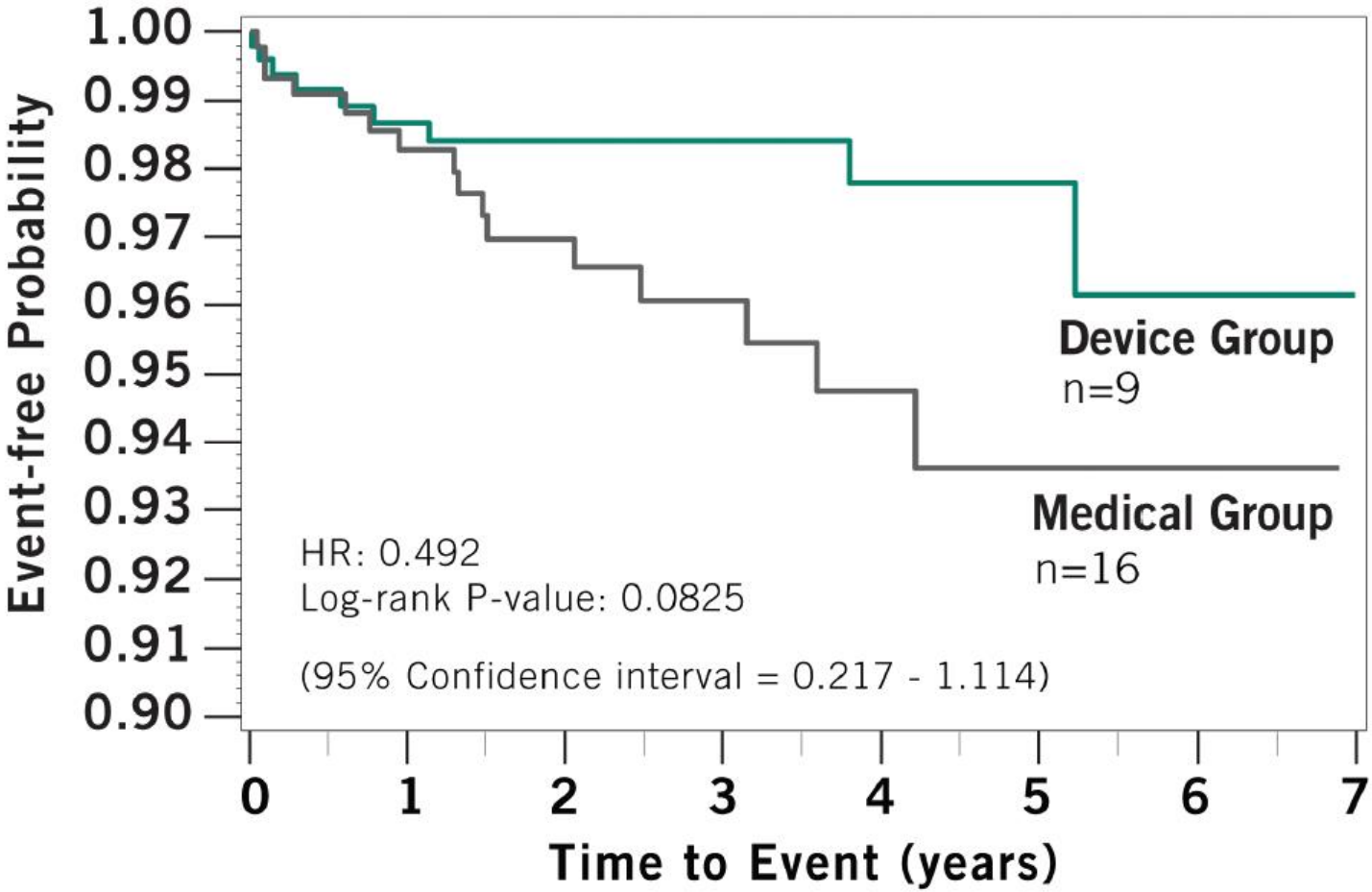


* Completed primary endpoint follow-up
** Discontinued prior to primary endpoint

Primary Endpoint Analysis – ITT Cohort

50.8% risk reduction of stroke in favor of device

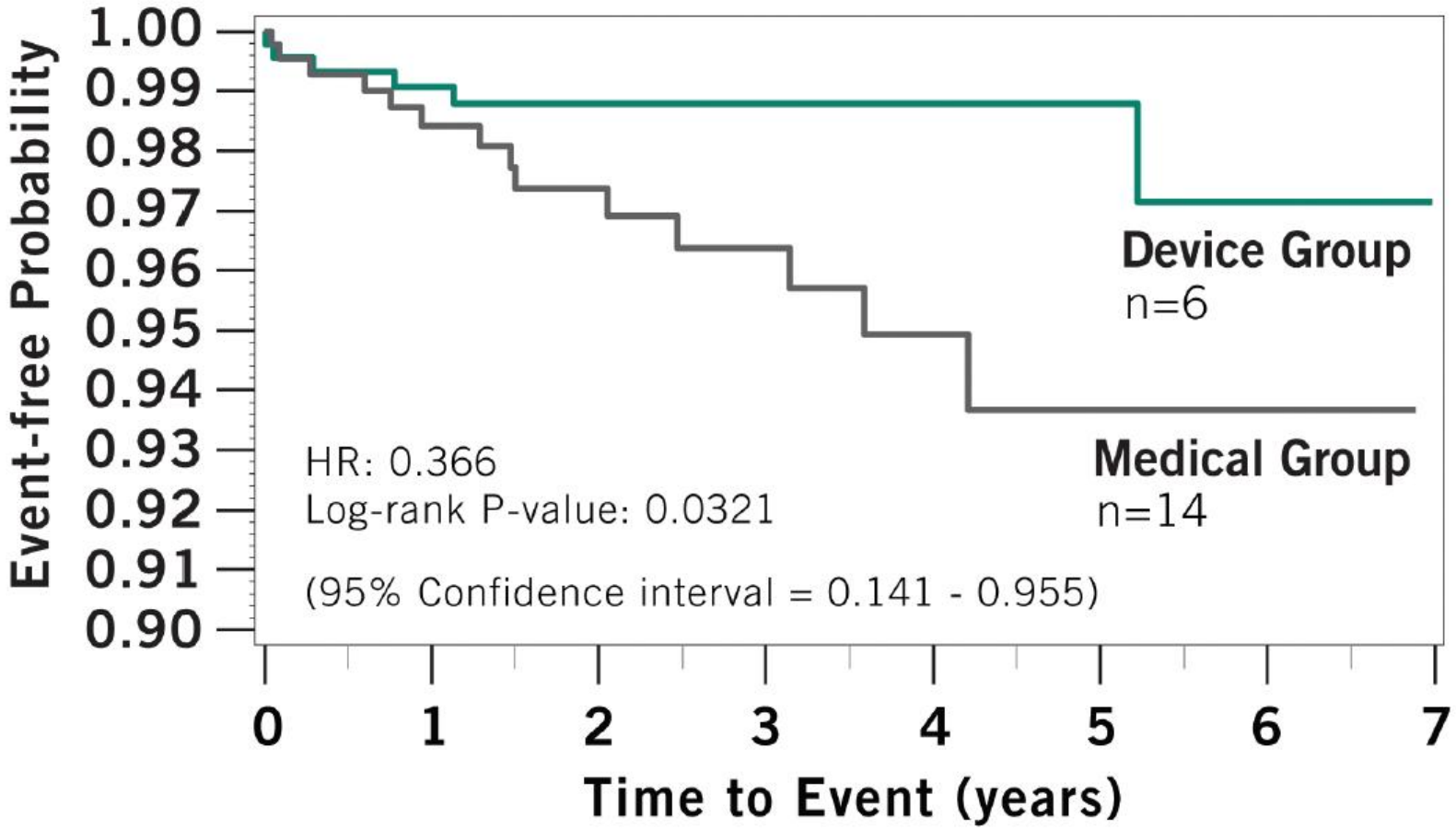
RESPECT CLINICAL TRIAL



- **3/9** device group patients did not have a device at time of endpoint stroke

1. Cox model used for analysis

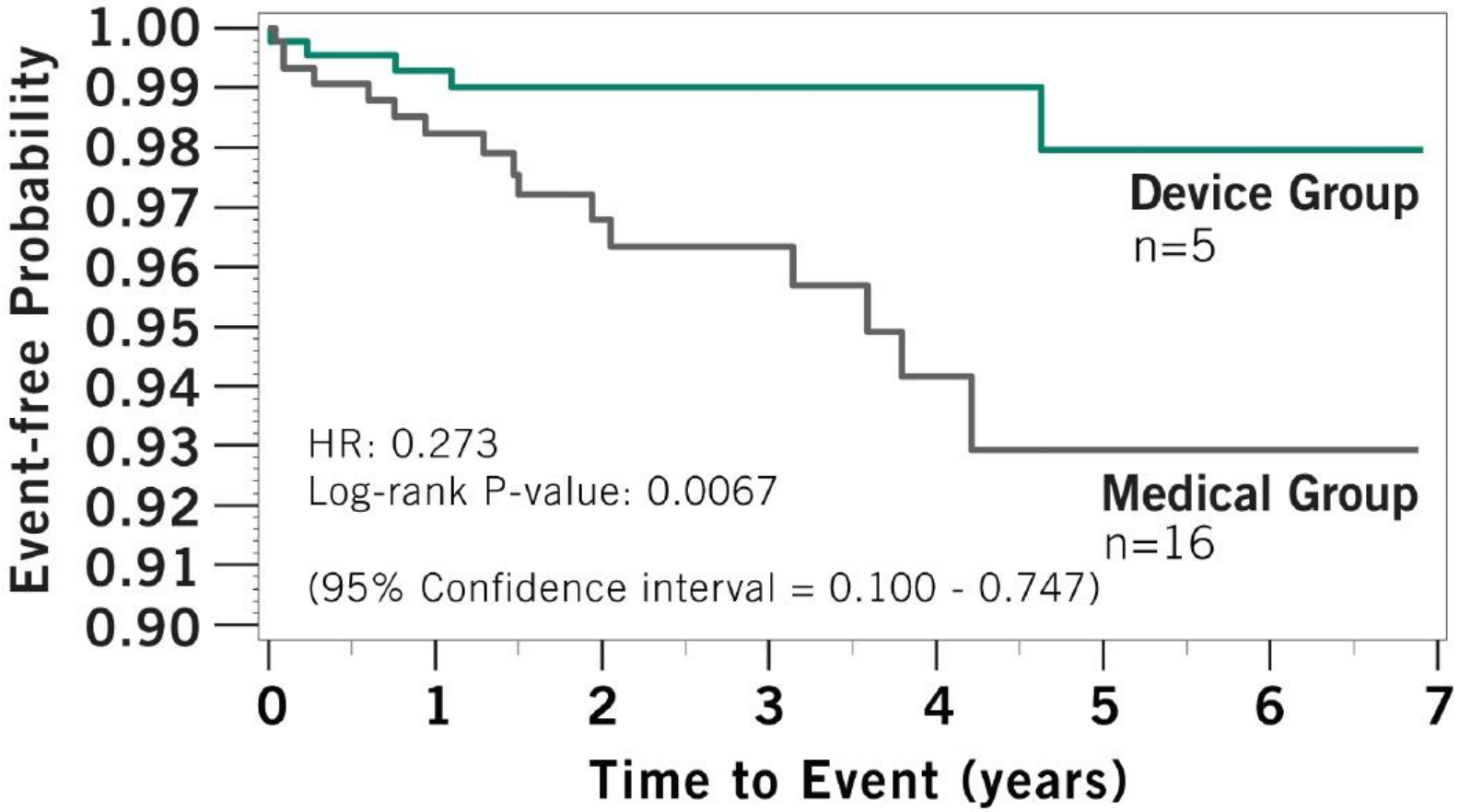
Primary Endpoint Analysis – Per Protocol Cohort
63.4% risk reduction of stroke in favor of device



- The Per Protocol (PP) cohort includes patients who adhered to the requirements of the study protocol

1. Cox model used for analysis

Primary Endpoint Analysis – As Treated Cohort
72.7% risk reduction of stroke in favor of device



- The As Treated (AT) cohort demonstrates the treatment effect by classifying subjects into treatment groups according to the treatment actually received, regardless of the randomization assignment

1. Cox model used for analysis

Totality of Evidence and NNT

46.6%-72.7% risk reduction of stroke in favor of device

RESPECT CLINICAL TRIAL

Totality of Evidence

Analysis	Risk Reduction	P-Value[1]
Intent to Treat Raw Count	46.6%	0.157
Intent to Treat KM	50.8%	0.083
Per Protocol KM	63.4%	0.032
As Treated KM	72.7%	0.007

Number Needed to Treat (NNT)

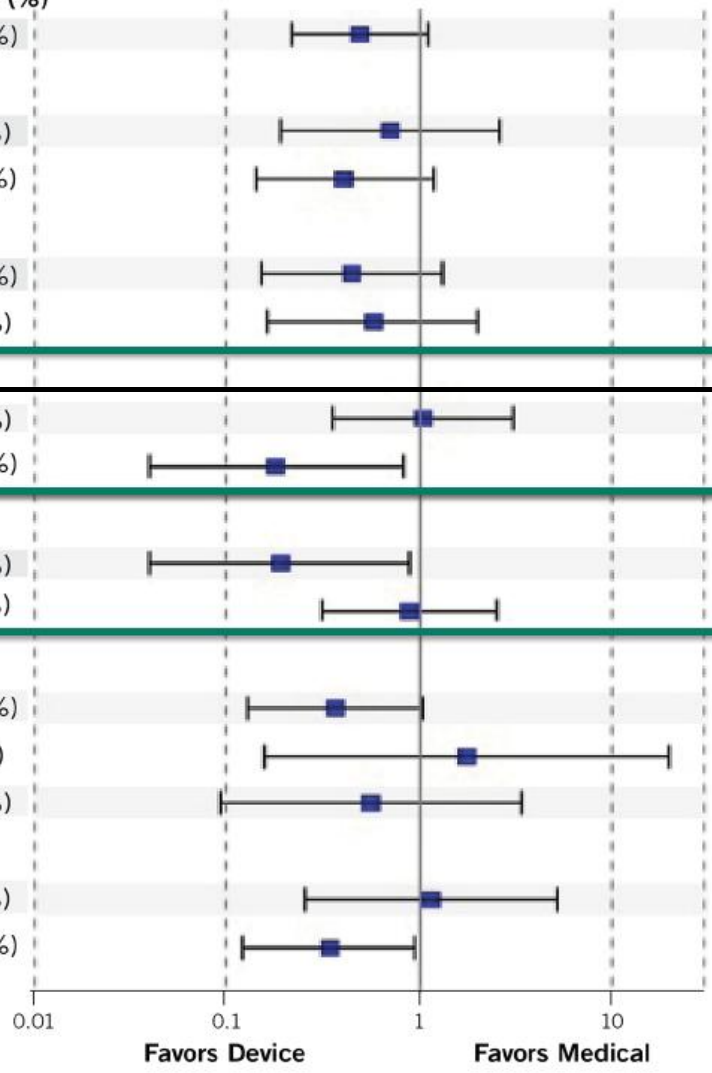
	NNT[2]	Device Group Event Rate[3]	Medical Group Event Rate[3]
1 Year	250	1.33%	1.73%
2 Year	70.4	1.60%	3.02%
5 Year	23.9	2.21%	6.40%

1. P-values: ITT Raw Count is calculated using Fisher's Exact test; all other P-values are calculated using log-rank test
2. The NNT is the average number of subjects that need to be treated with the AMPLATZER™ PFO Occluder in order to prevent one stroke in the respective time intervals. The NNT is calculated as the reciprocal of the difference between the control arm and device arm event rates
3. Calculated using the Kaplan-Meier estimated event rates for each treatment group

Subpopulation Differential Treatment Effect

RESPECT CLINICAL TRIAL

Subgroup	Device Group	Medical Group	Hazard Ratio and 95% CI		Pvalue (Log Rank)	Interaction Pvalue
	no. of patients/total number (%)					
Overall	9/499 (1.8%)	16/481 (3.3%)		0.492 (0.217, 1.114)	0.0825	
Age						0.5156
- 18-45	4/230 (1.7%)	5/210 (2.4%)		0.698 (0.187, 2.601)	0.5901	
- 46-60	5/262 (1.9%)	11/266 (4.1%)		0.405 (0.140, 1.165)	0.0828	
Sex						0.7312
- Male	5/268 (1.9%)	10/268 (3.7%)		0.448 (0.153, 1.311)	0.1321	
- Female	4/231 (1.7%)	6/213 (2.8%)		0.571 (0.161, 2.024)	0.3789	
Shunt Size						0.0667
- None, trace or moderate	7/247 (2.8%)	6/244 (2.5%)		1.034 (0.347, 3.081)	0.9527	
- Substantial	2/247 (0.8%)	10/231 (4.3%)		0.178 (0.039, 0.813)	0.0119	
Atrial septal aneurysm						0.1016
- Present	2/180 (1.1%)	9/169 (5.3%)		0.187 (0.040, 0.867)	0.0163	
- Absent	7/319 (2.2%)	7/312 (2.2%)		0.889 (0.312, 2.535)	0.8259	
Index infarct topography						0.3916
- Superficial	5/280 (1.8%)	12/269 (4.5%)		0.366 (0.129, 1.038)	0.0487	
- Small Deep	2/57 (3.5%)	1/70 (1.4%)		1.762 (0.156, 19.93)	0.6429	
- Other	2/157 (1.3%)	3/139 (2.2%)		0.558 (0.093, 3.340)	0.5167	
Planned medical regimen						0.1966
- Anticoagulant	4/132 (3.0%)	3/121 (2.5%)		1.141 (0.255, 5.098)	0.8628	
- Antiplatelet	5/367 (1.4%)	13/359 (3.6%)		0.336 (0.120, 0.944)	0.0299	



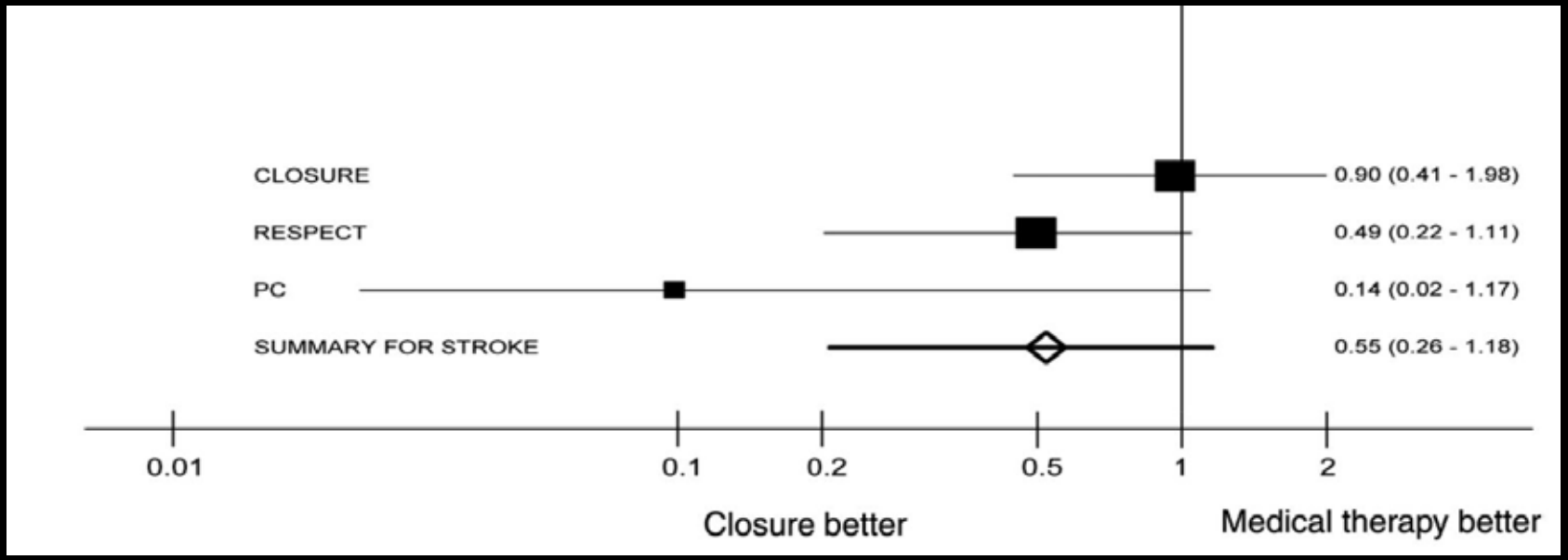


Table. Meta-Analysis Results for the Hazard Ratio of Stroke and Additional Outcomes

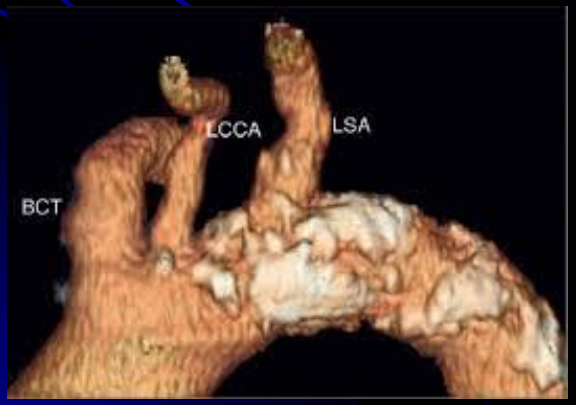
	All Devices (No. of Studies)	Amplatzer Only RCTs (n=2)	
Outcome	Random Effects Model	Random Effects Model	Fixed Effects Model
Stroke (ITT)	0.55 (0.26–1.18), n=3	0.38 (0.14–1.02)	**0.41 (0.19–0.88)**
Stroke/TIA (ITT)	0.69 (0.43–1.13), n=2*	NA	NA
Composite primary outcome† (ITT)	**0.67 (0.44–1.00)**, n=3	0.54 (0.29–1.01)	0.54 (0.29–1.01)
Composite primary outcome† (PP‡)	0.57 (0.32–1.02), n=3	0.44 (0.17–1.12)	**0.44 (0.22–0.89)**
Stroke (PP‡)	0.52 (0.16–1.70), n=2§	NA	NA

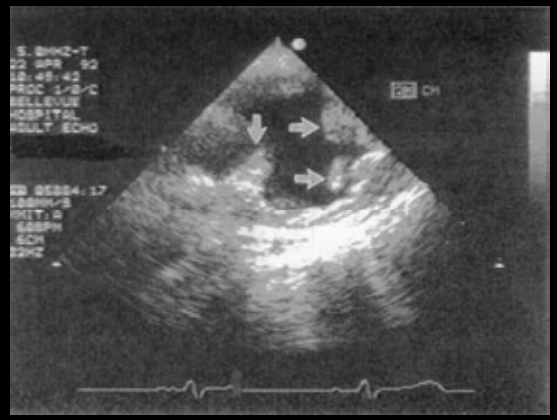
Kitsios et al Stroke 2013

Aortic Arch Atheroma

Amarenco P et al, NEJM 1994;331:1474-9; McLeod M et al. Lancet Neurol 2004; 3:408-14

- Important source cerebral embolism, particularly > 4 mm, mobile plaques
- Risk recurrent stroke 3-4 fold higher compared with prior stroke, no AAA
- Up to 26% per year





ARCH Trial

Amarenco P, Davis S, Donnan GA, Kaste M, Mentre F, McLeod M
ESC 2013

- Tested whether aspirin + clopidogrel was superior to warfarin
- 349 patients; 8 years
- Primary endpoint composite stroke, MI, vascular death
- NS reduction on A+C vs Warfarin
- Reduced vascular death on A+C
- Treatment of choice

Conclusions

- At least 20% of acute ischemic stroke
- Atrial fibrillation epidemic
- Warfarin being replace by the NOAC’s
- New data to assist decision making in patent foramen ovale
- New data re aortic arch atheroma and preferred approach