Malattie Cardiovascolari:

Dalla Fase Acuta alla Prevenzione, l'Accesso alle Terapie nell'Era del Risanamento Economico

Roma, 4 ottobre 2011
Camera dei Deputati
Palazzo Marini – Sala delle Colonne

Sessione 3 – Fibrillazione Atriale
ore 12:30-13:30

Strategie terapeutiche nella prevenzione di eventi cerebrovascolari nel paziente con fibrillazione atriale

Raffaele De Caterina

Università "G. d'Annunzio" – Chieti e
Fondazione "G. Monasterio" – Pisa, Italia

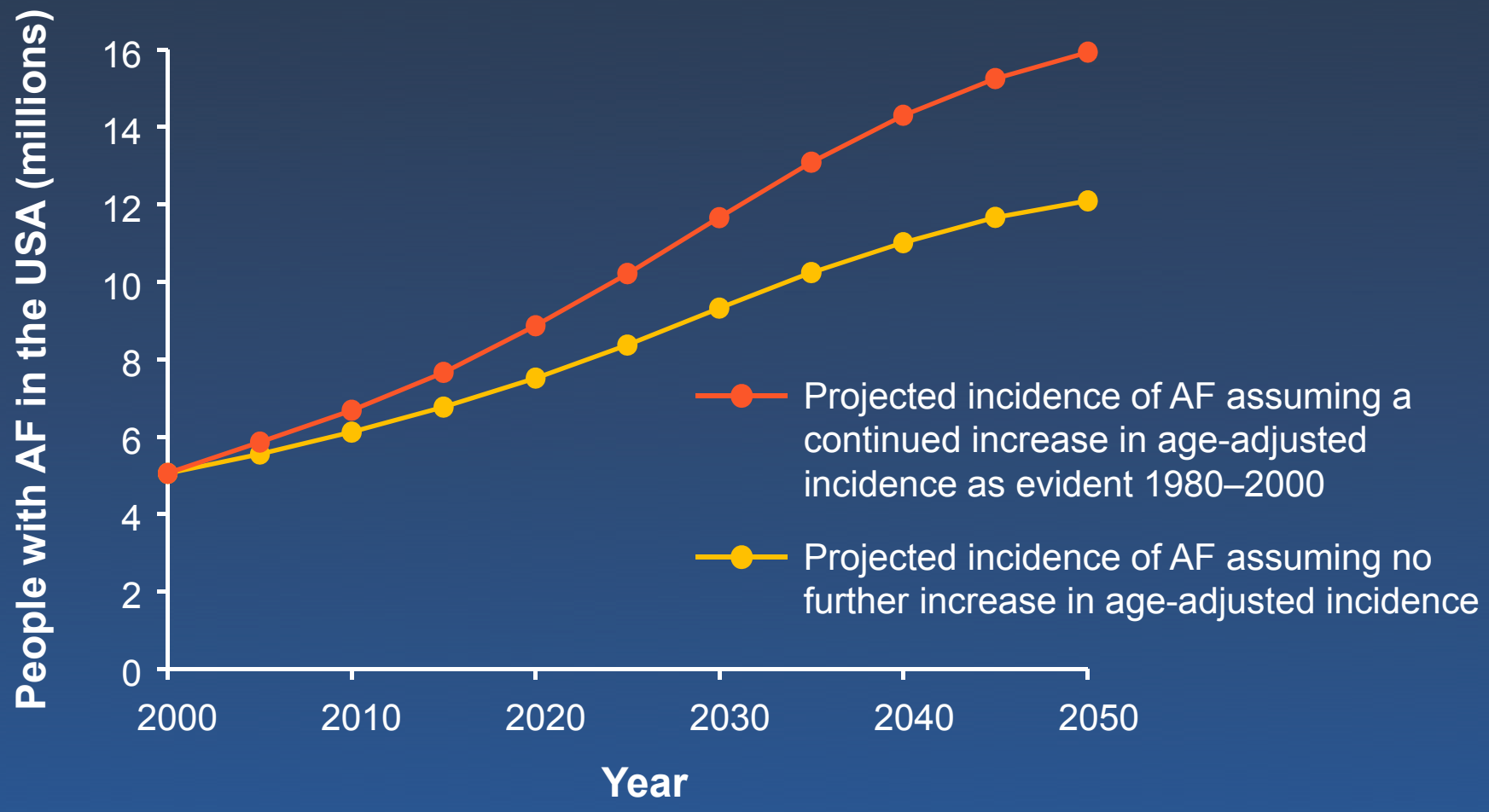
4 ottobre 2011, 12:45-13:00 + disc.

Raffaele De Caterina, MD, PhD Disclosures

- Co-author of 2010 ESC Guidelines on Atrial Fibrillation
- Steering Committee Member and/or Participant in main current trials in Atrial Fibrillation (ACTIVE, BOREALIS-AF, RE-LY, ARISTOTLE, AVERROES, ROCKET-AF, ENGAGE-AF)
- Consulting fees and honoraria from Boehringer Ingelheim, Bayer, Bristol Myers-Squibb, Merck Sharp & Dohme, Pfizer, Daiichi-Sankyo, Sanofi-Aventis
- Grant support from Bristol Myers-Squibb, Boehringer Ingelheim, Sanofi-Aventis

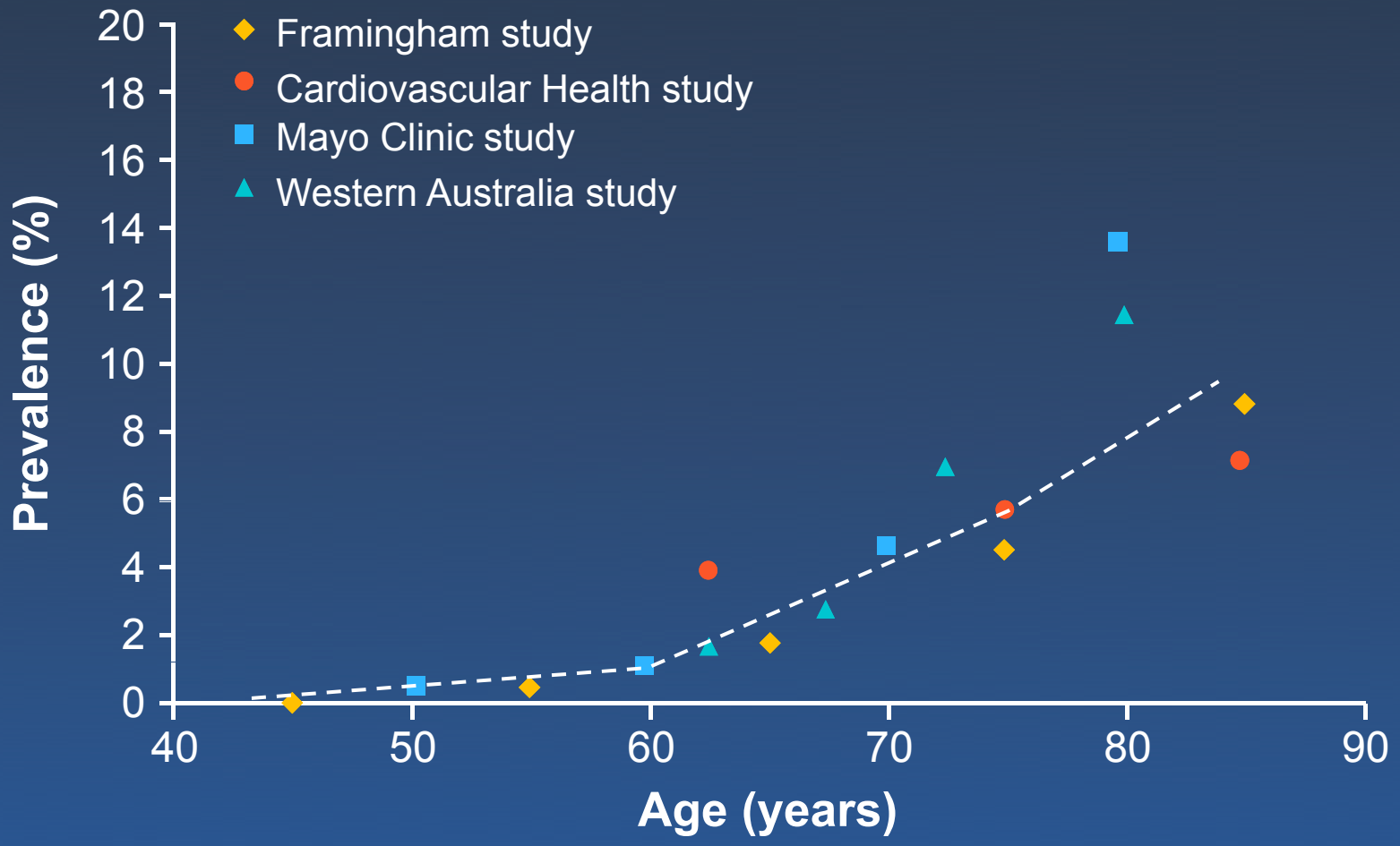


Projected number of persons with AF in the USA, 2000–2050



Miyasaka Y et al. Circulation 2006;114:119–25

Prevalence of AF by age



Feinberg WM. Arch Intern Med 1995;155:469–73

The epidemic of atrial fibrillation

Increasing prevalence of risk factors for AF:

- Older age
- Hypertension
- Heart failure
- Myocardial infarction
- Valvular heart disease
- Diabetes mellitus/metabolic syndrome
- Obesity/obstructive sleep apnoea
- Cigarette smoking

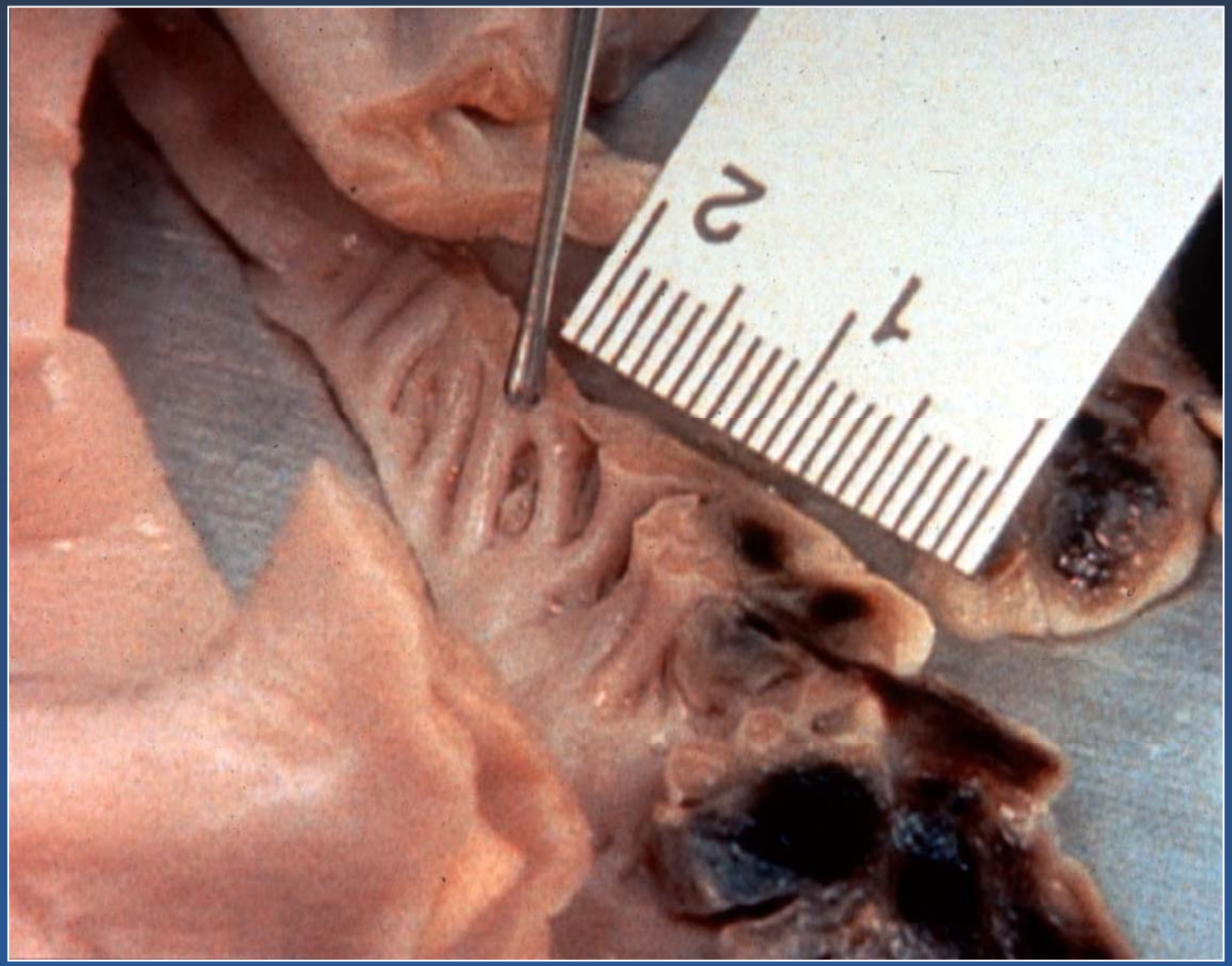
Sawin CT et al. N Engl J Med 1994;331:1249–52; Kannel WB & Benjamin EF. Med Clin North Am 2008;92:17–40; AHA/ACC/ESC Guidelines. Circulation 2006;114:e257–354

Atrial fibrillation: morbidity and mortality

- 4- to 5-fold increased risk of stroke
- Doubling of the risk of dementia
- Tripling of risk of heart failure
- 40–90% increased risk for overall mortality
- Risk of stroke in AF patients by age group:
  - 1.5% in 50–59 years age group
  - 23.5% in 80–89 years age group

Benjamin EJ et al. Circulation 2009;119:606–18; Albers GW et al. Chest 2001;119;194S–206S

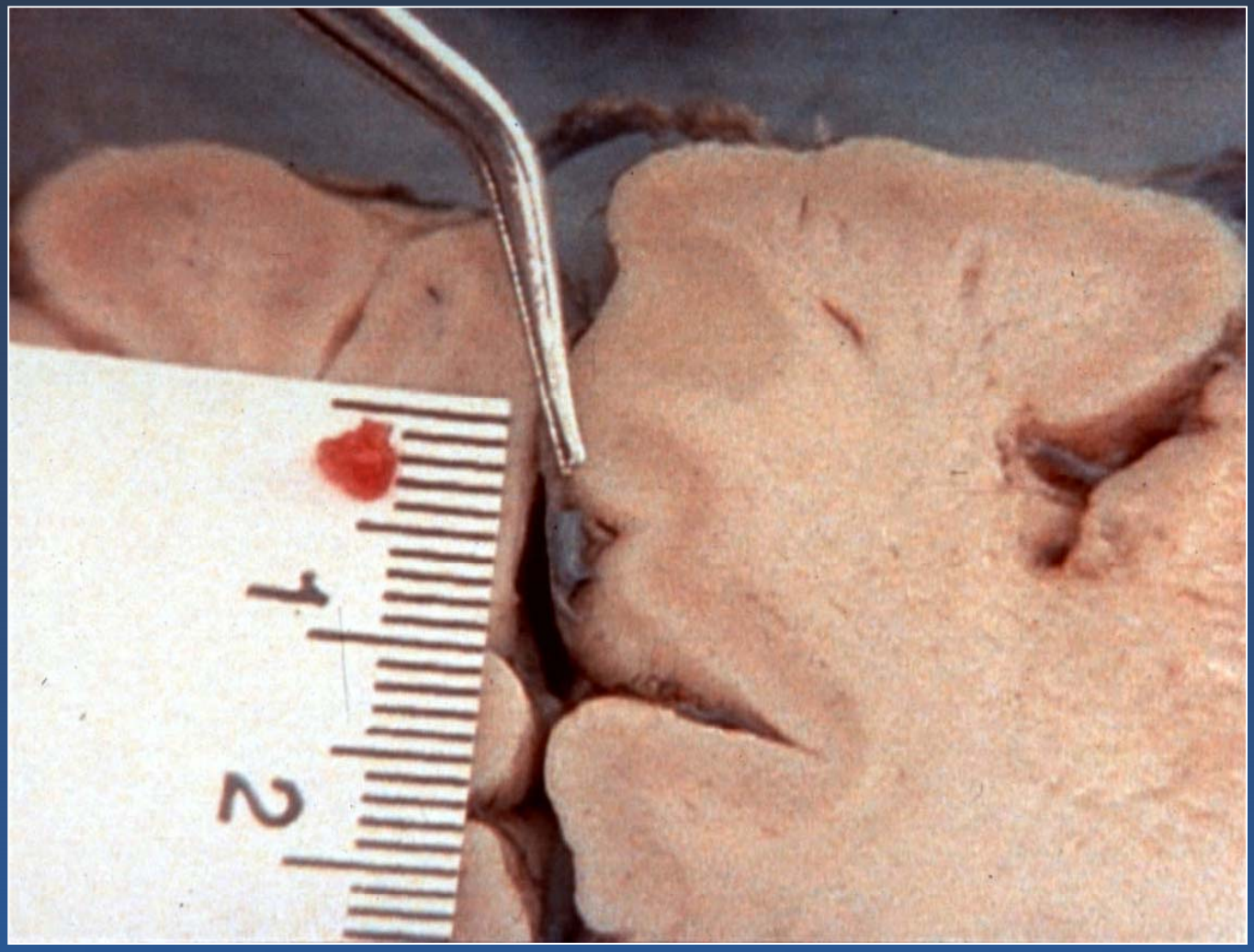
LAA thrombus



LAA = left atrial appendage

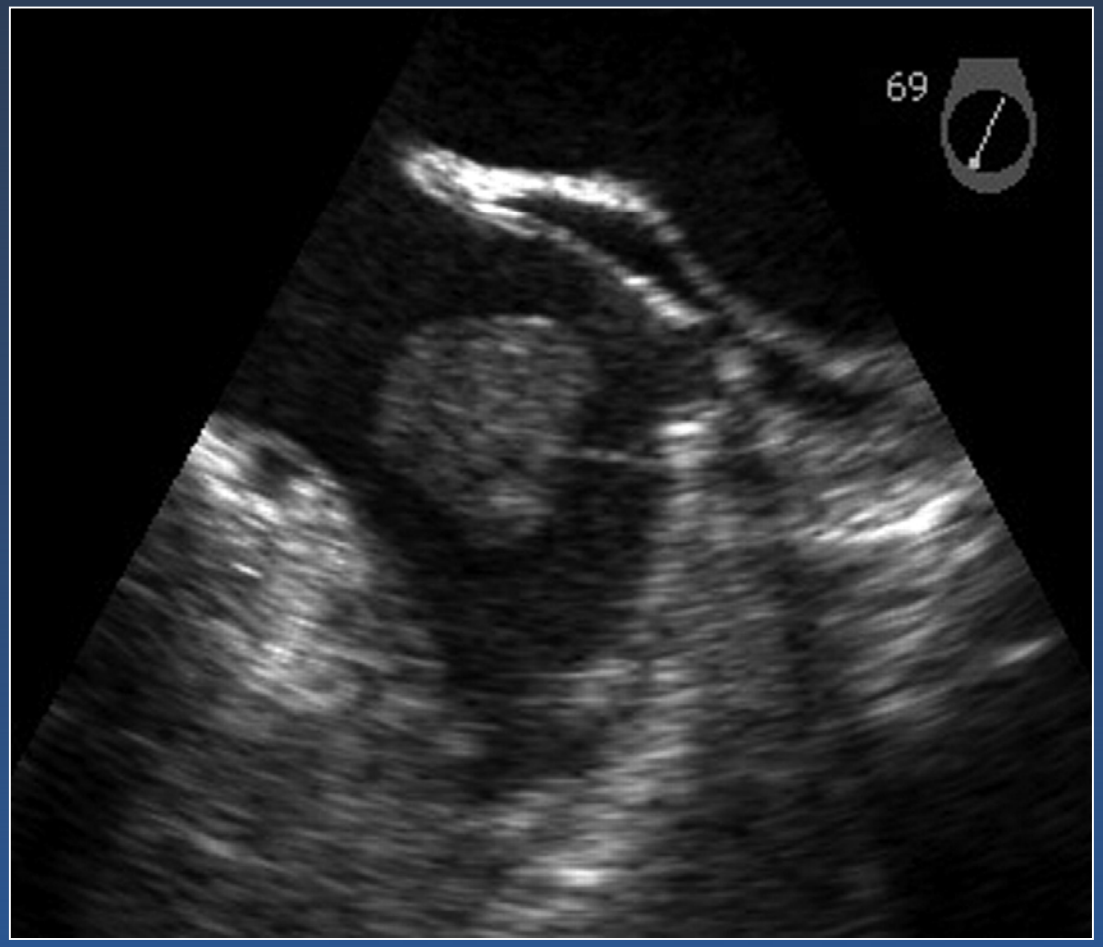
Stanford Stroke Center, Albers G

Cardiac embolism to cerebral artery



Stanford Stroke Center, Albers G

TEE depicting a large LAA thrombus attached to the lateral wall



LAA = left atrial appendage; TEE = transoesophageal echocardiogram

Hesse B et al. Circulation 2006;113:e456–7

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Efficacy of warfarin in atrial fibrillation

Five randomized trials in non-rheumatic AF

Study	Warfarin (n)	Cont. (n)	INR	RR	P value
AFASAK	335	336	2.8–4.2	**60%**	0.027
SPAF	210	211	2.0–4.5	**67%**	0.01
BAATAF	212	208	1.5–2.7	**86%**	<0.05
CAFA*	187	191	2.0–3.0	**45%**	0.25
SPINAF	260	265	1.4–2.8	**79%**	0.001

68% overall risk reduction for stroke

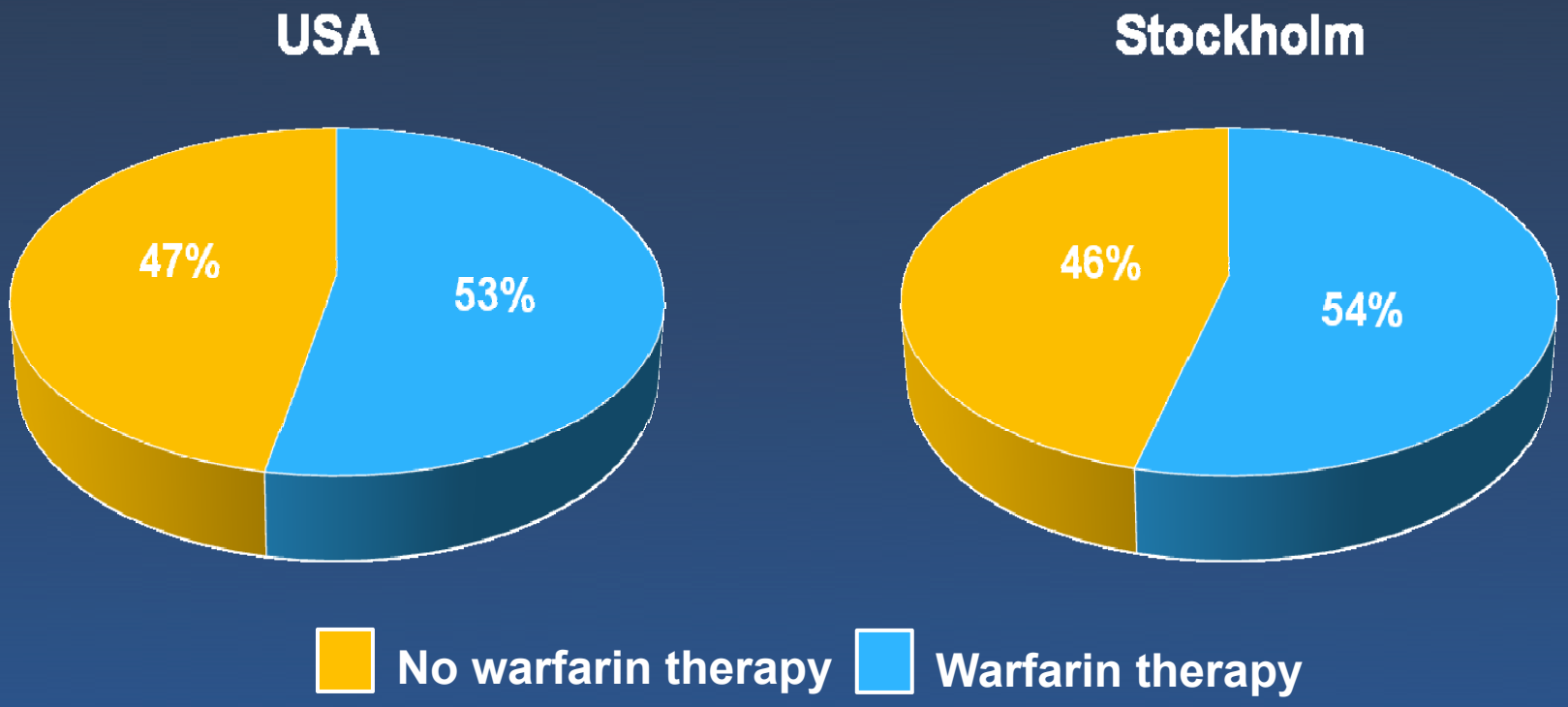
*Stopped early due to published positive results

INR = international normalized ratio; RR = relative risk

Atrial Fibrillation Investigators. Arch Intern Med 1994;154:1449–57

Underuse of anticoagulation therapy in AF

Approximately half of high-risk patients with AF receive warfarin therapy



Age >80 years and perceived bleeding risk were negative predictors of warfarin use

Waldo et al. JACC 2005;46:1729–36; Friberg L et al. Eur Heart J 2006;27:1954–64

European Heart Survey: 5333 patients with AF in 35 countries (2003–2004)

Oral anticoagulant therapy by $CHADS_2$ score

1	→	**58%**
2	→	**59%**
3	→	**64%**
4	→	**61%**

Nieuwlaat R et al. Eur Heart J 2006;27:3018–26

Hazards of anticoagulant medications

- Number 1 in 2003 and 2004 in the number of mentions of “deaths for drugs causing adverse effects in therapeutic use”[1]
- Warfarin: 6% of 702,000 ADEs treated in EDs per year[1]
  - 17% require hospitalization
- 21 million warfarin prescriptions in 1998 >>>31 million in 2004[2]
- The incidence of OAC-related intracranial haemorrhage quintupled during this time period[2]

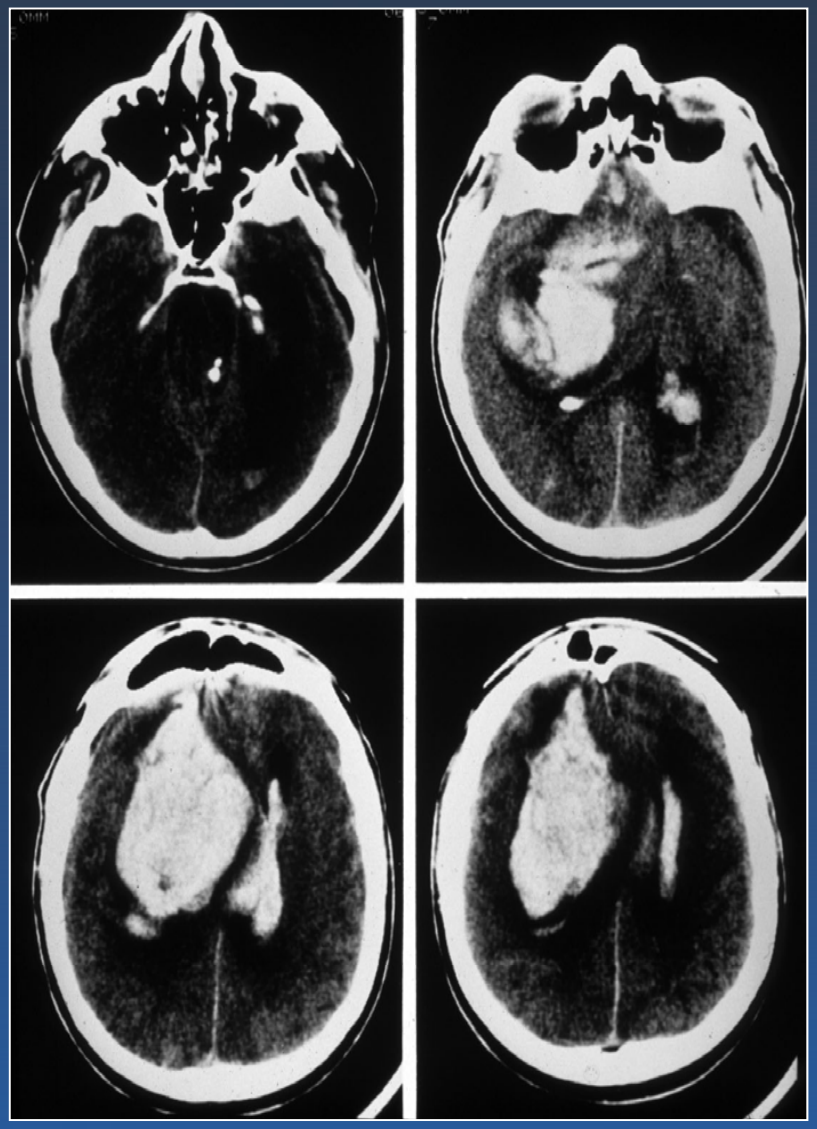
FDA BOXED WARNING ISSUED OCTOBER 2006

ADEs = adverse events; EDs = emergency departments; OAC = oral anticoagulant

1. Wysowski DK et al. Arch Intern Med 2007;167:1414–9; **2.** Flaherty ML et al. Neurology 2007;68 68:116-121

Intracerebral haemorrhage: the most feared complication of antithrombotic therapy

- 46% mortality
- 17% major deficit
- 2/3 occur with an INR in 2.0–3.0 range
- Age ≥80 years is a significant risk factor
  - OR = 2.8 (1.3 to 5.8); P<0.001



INR = international normalized ratio; OR = odds ratio

Hylek EM & Singer DE. Ann Intern Med 1994;120:897–902

Optimizing benefit and reducing risk

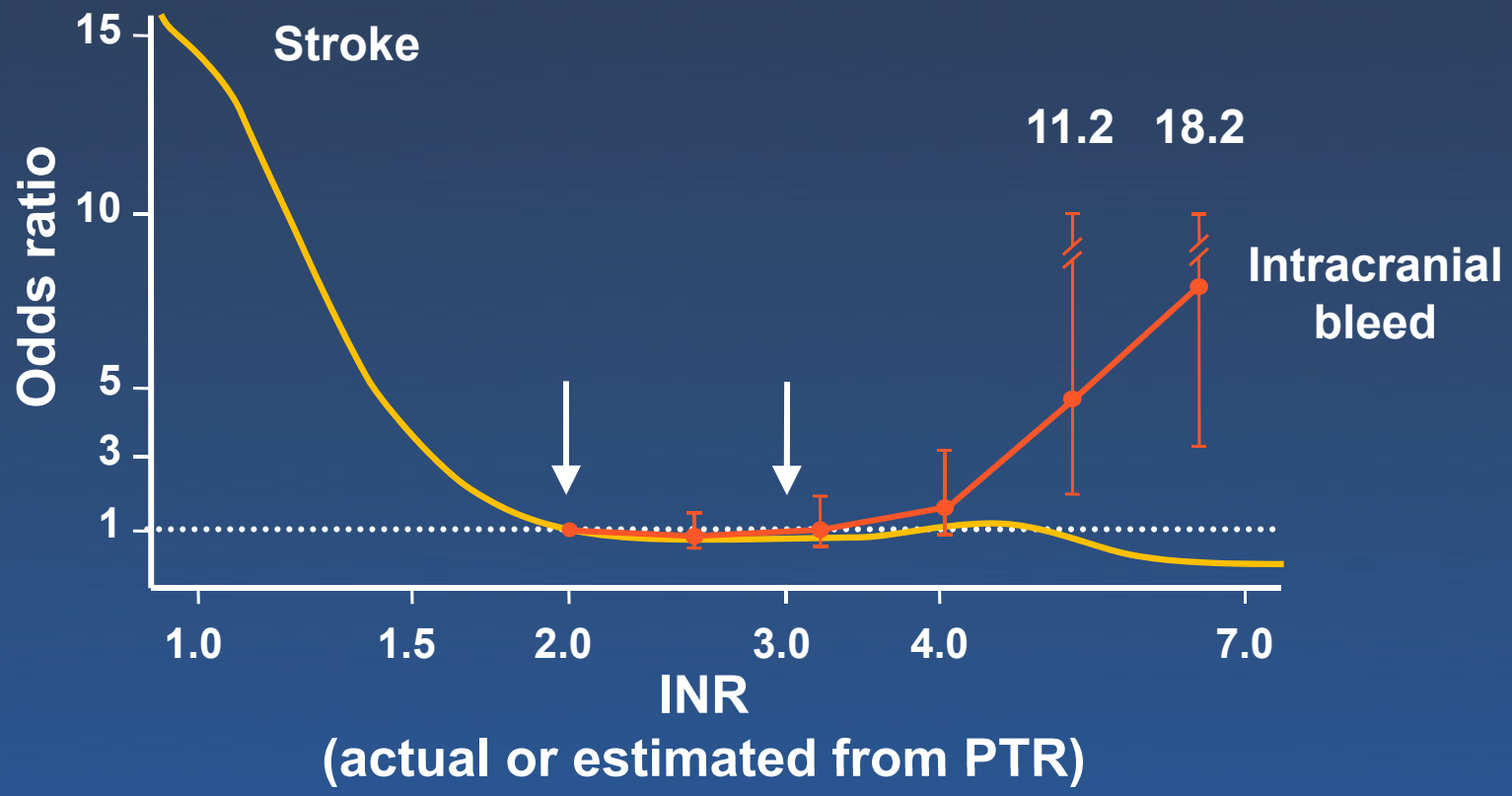


AF-related stroke is associated with
a 30-day mortality of 24%

Hylek EM et al. N Engl J Med 2003;349:1019–26

Warfarin has a narrow therapeutic window

Relationship between clinical events and INR intensity

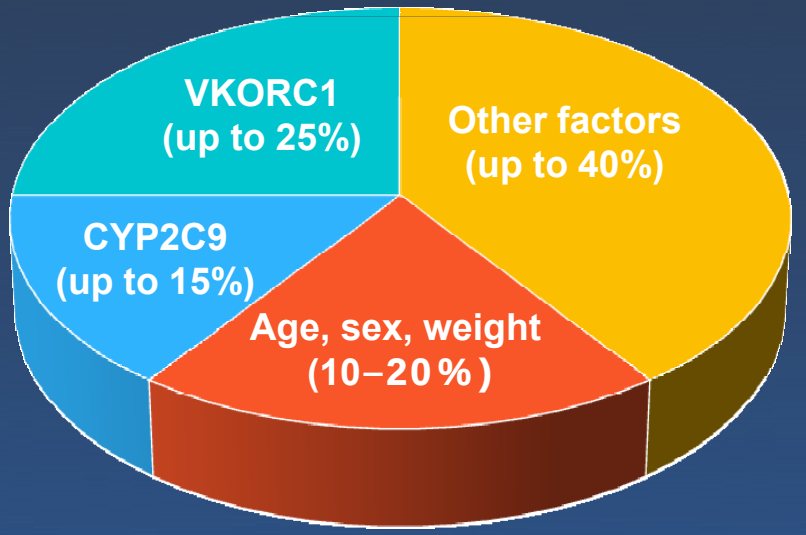


INR = international normalized ratio; PTR = prothrombin ratio

Hylek EM & Singer DE. Ann Intern Med 1994;120:897–902; Hylek EM et al. N Engl J Med 1996;335:540–6

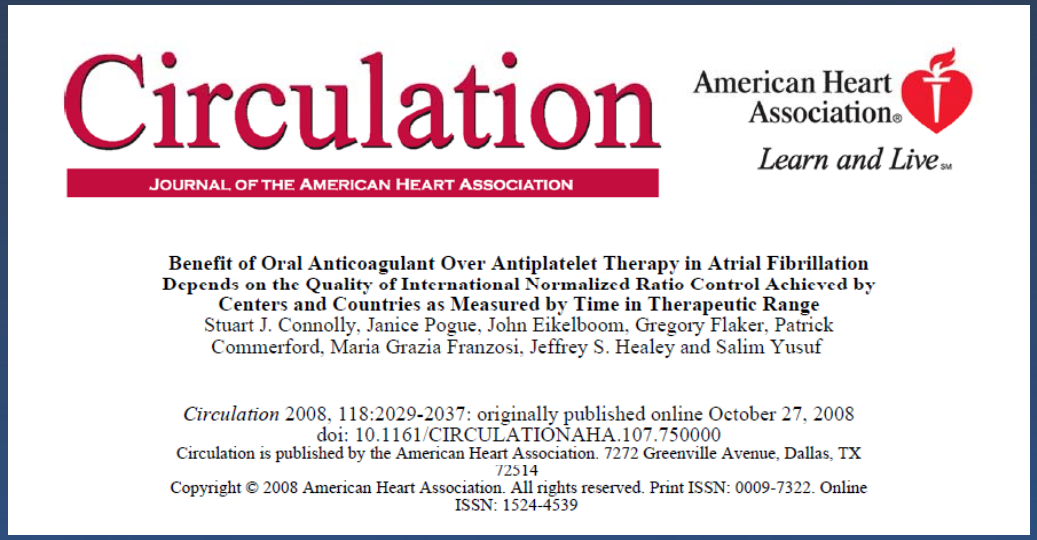
Warfarin dosing is complex
Factors that correlate with warfarin dose

- Age
- Body surface area or weight
- Amiodarone
- Other drugs (e.g. acetaminophen)
- Target INR
- Race
- Sex
- Plasma vitamin K level
- Decompensated CHF
- Malignancy
- Genetic status



CHF = congestive heart failure; CYP2C9 = cytochrome P450 2C9; INR = international normalized ratio; VKORC1 = vitamin K epoxide reductase complex subunit 1

ACTIVE W Trial: VKA vs. dual antiplatelet therapy



Circulation

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Benefit of Oral Anticoagulant Over Antiplatelet Therapy in Atrial Fibrillation Depends on the Quality of International Normalized Ratio Control Achieved by Centers and Countries as Measured by Time in Therapeutic Range

Stuart J. Connolly, Janice Pogue, John Eikelboom, Gregory Flaker, Patrick Commerford, Maria Grazia Franzosi, Jeffrey S. Healey and Salim Yusuf

Circulation 2008, 118:2029-2037: originally published online October 27, 2008
doi: 10.1161/CIRCULATIONAHA.107.750000
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
Copyright © 2008 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

Minimum threshold TTR necessary to realize benefit of warfarin:

≥58–65%

TTR = time in therapeutic range; VKA = vitamin K antagonist

Connolly SJ for Active W Investigators. Circulation 2008;118:2029–37

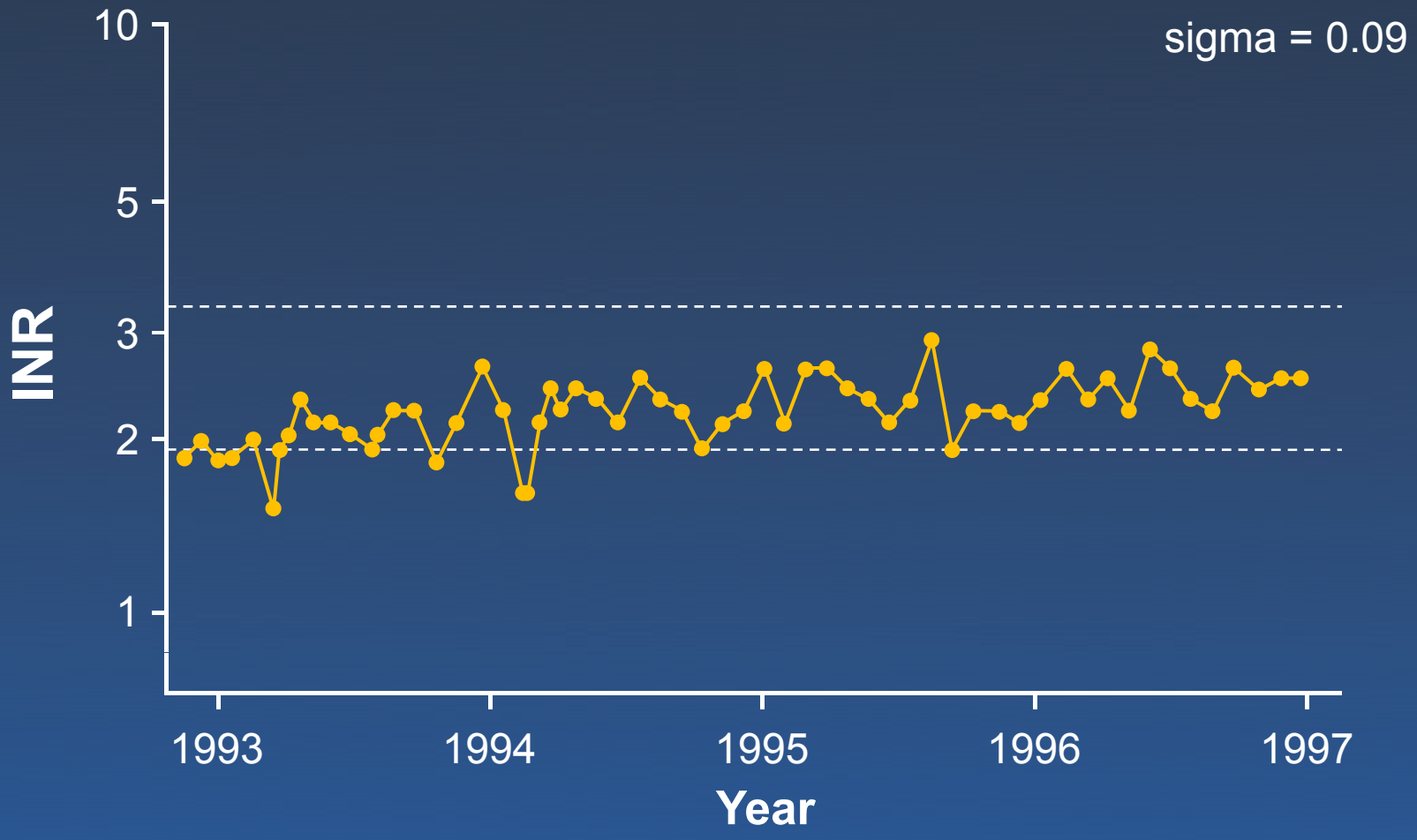
Comparison of outcomes among patients randomized to warfarin according to anticoagulant control results from SPORTIF III and V

	TTR <60%	TTR 60–75%	TTR >75%
Mortality, %	4.2	1.84	1.69
Major bleed, %	3.85	1.96	1.58
Stroke/SEE, %	2.10	1.34	1.07

SSE = systemic embolism event; TTR = time in therapeutic range

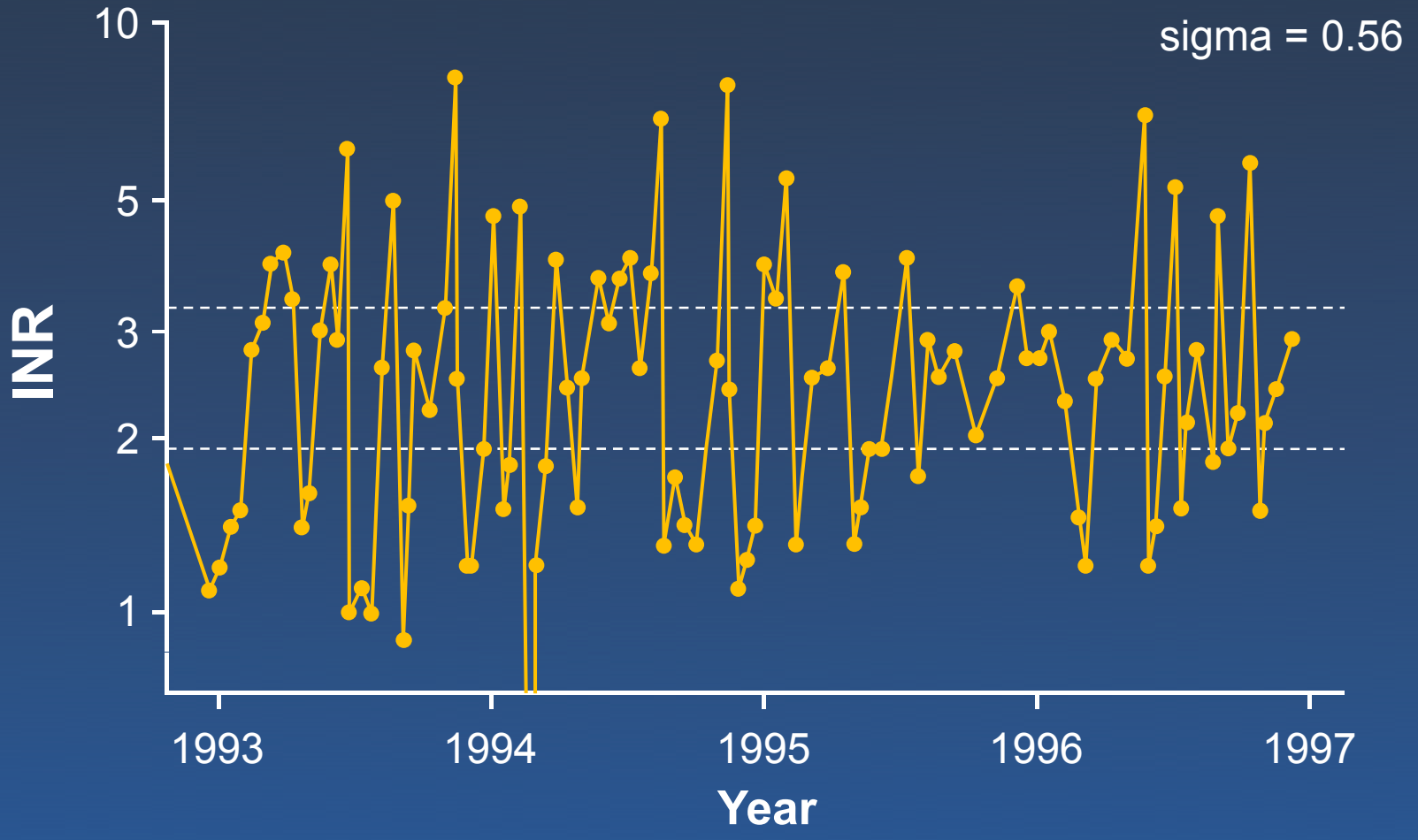
White HD et al. Arch Intern Med 2007;167:239–45

Patient with low INR variability



Hylek EM. J Cardiovasc Med 2009;10:605–9

Patient with high variability



Hylek EM. J Cardiovasc Med 2009;10:605–9

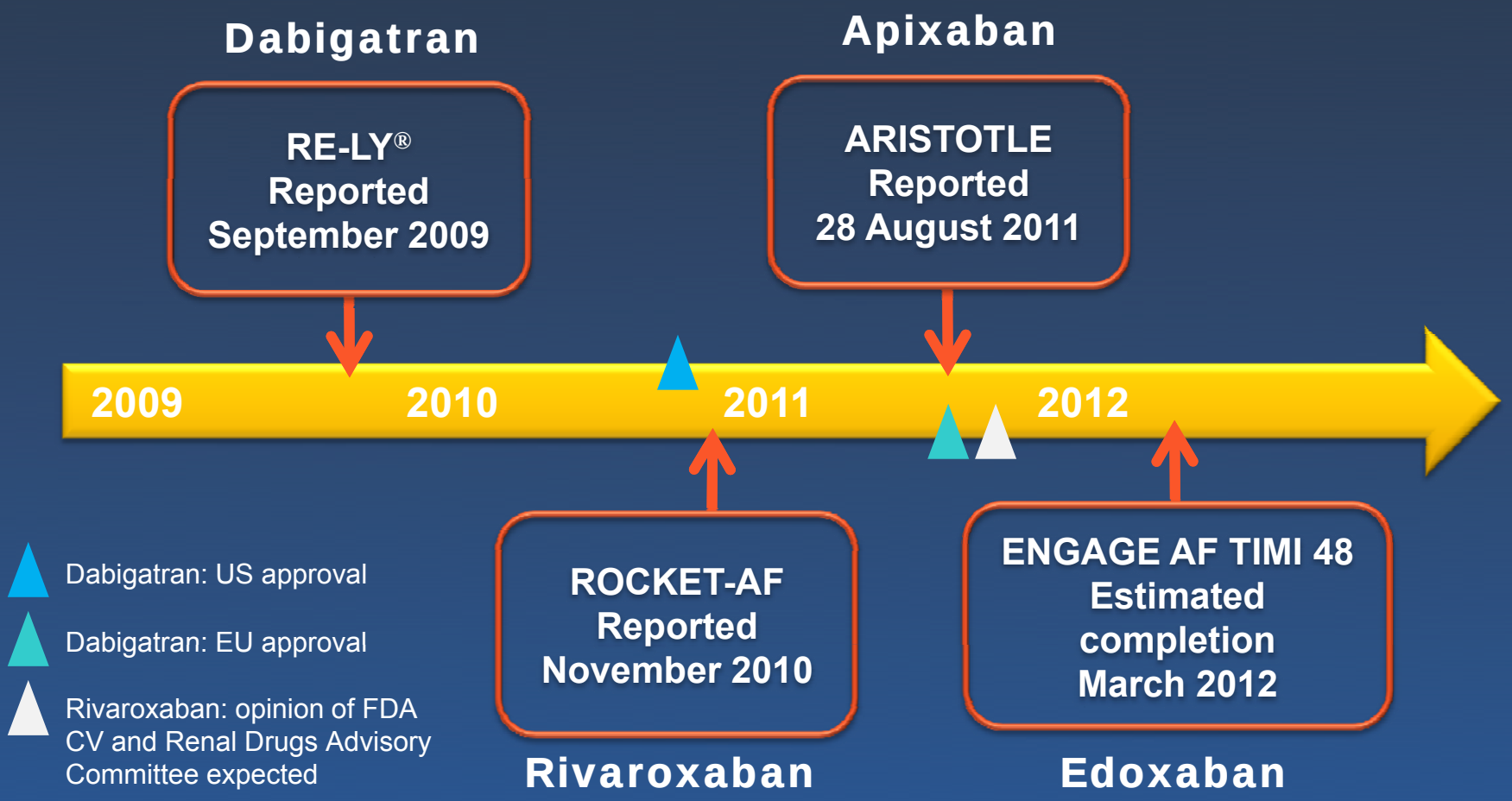
New oral anticoagulants: summary

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

Atrial fibrillation Phase III study timelines



CV = cardiovascular; FDA = Food and Drug Administration

http://www.clinicaltrials.gov

A new era in anticoagulation has begun!