DILEMMAS IN THE INTERVENTIONAL TREATMENT OF CORONARY ARTERY DISEASE

Patients with Atrial Fibrillation and anticoagulation treatment

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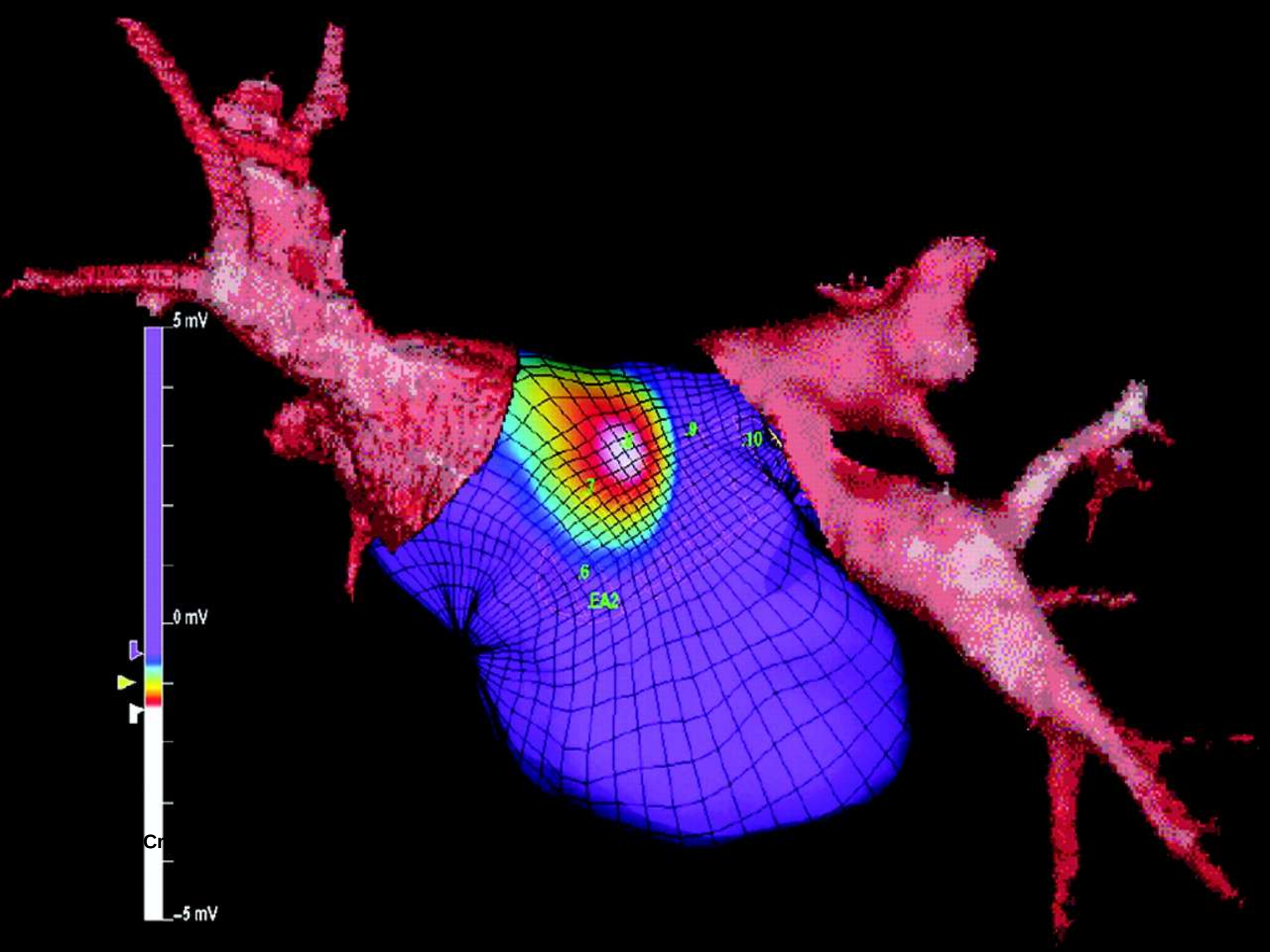
ΑΙΜΟΔΥΝΑΜΙΚΟ ΕΡΓΑΣΤΗΡΙΟ
Γ.Ν.Θ. «Γ.ΠΑΠΑΝΙΚΟΛΑΟΥ» ΘΕΣΣΑΛΟΝΙΚΗ


5 mV
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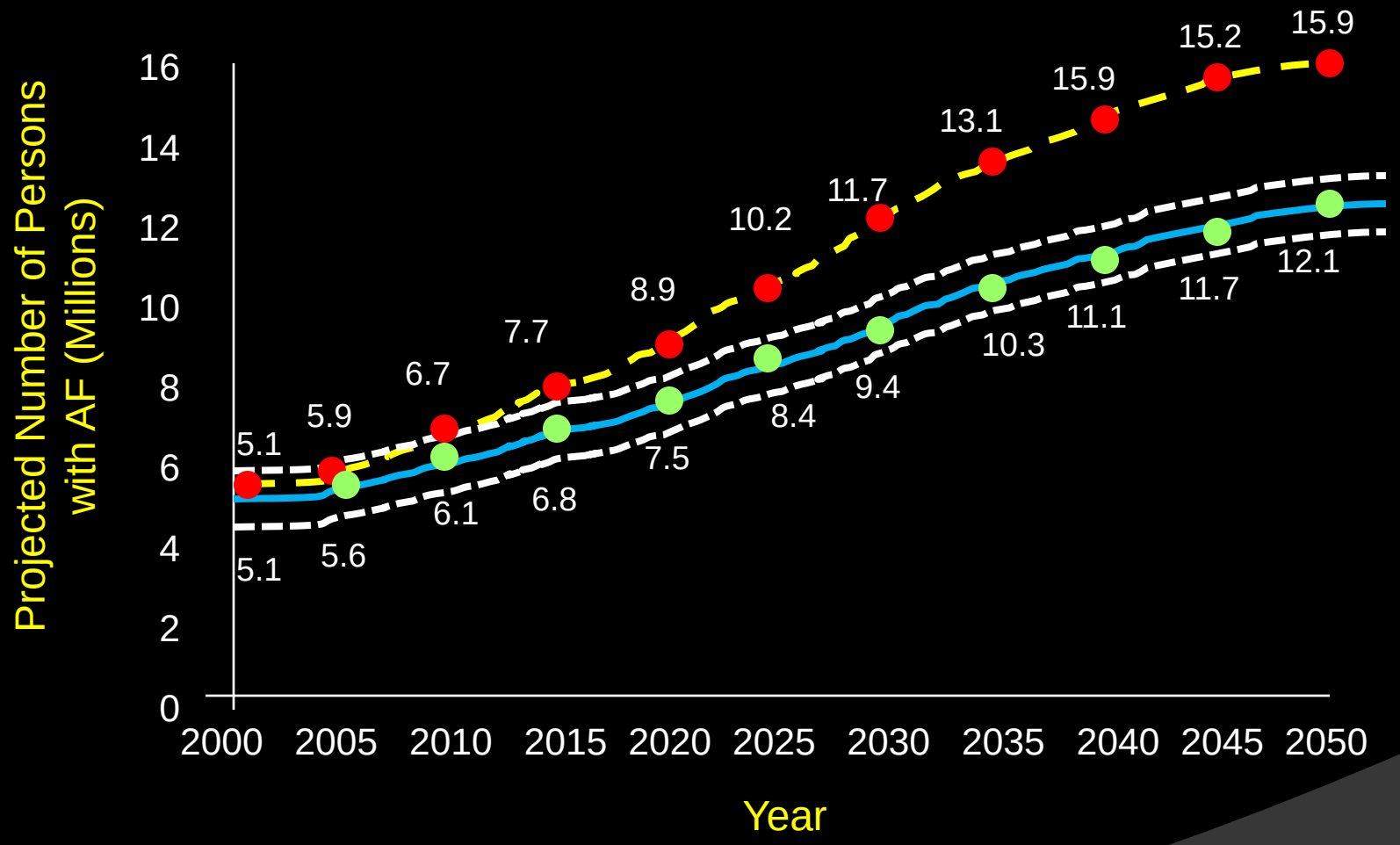
AFIB: MAGNITUDE OF THE PROBLEM

Projected Number of Persons with AF in the U.S. Between 2000 and 2050

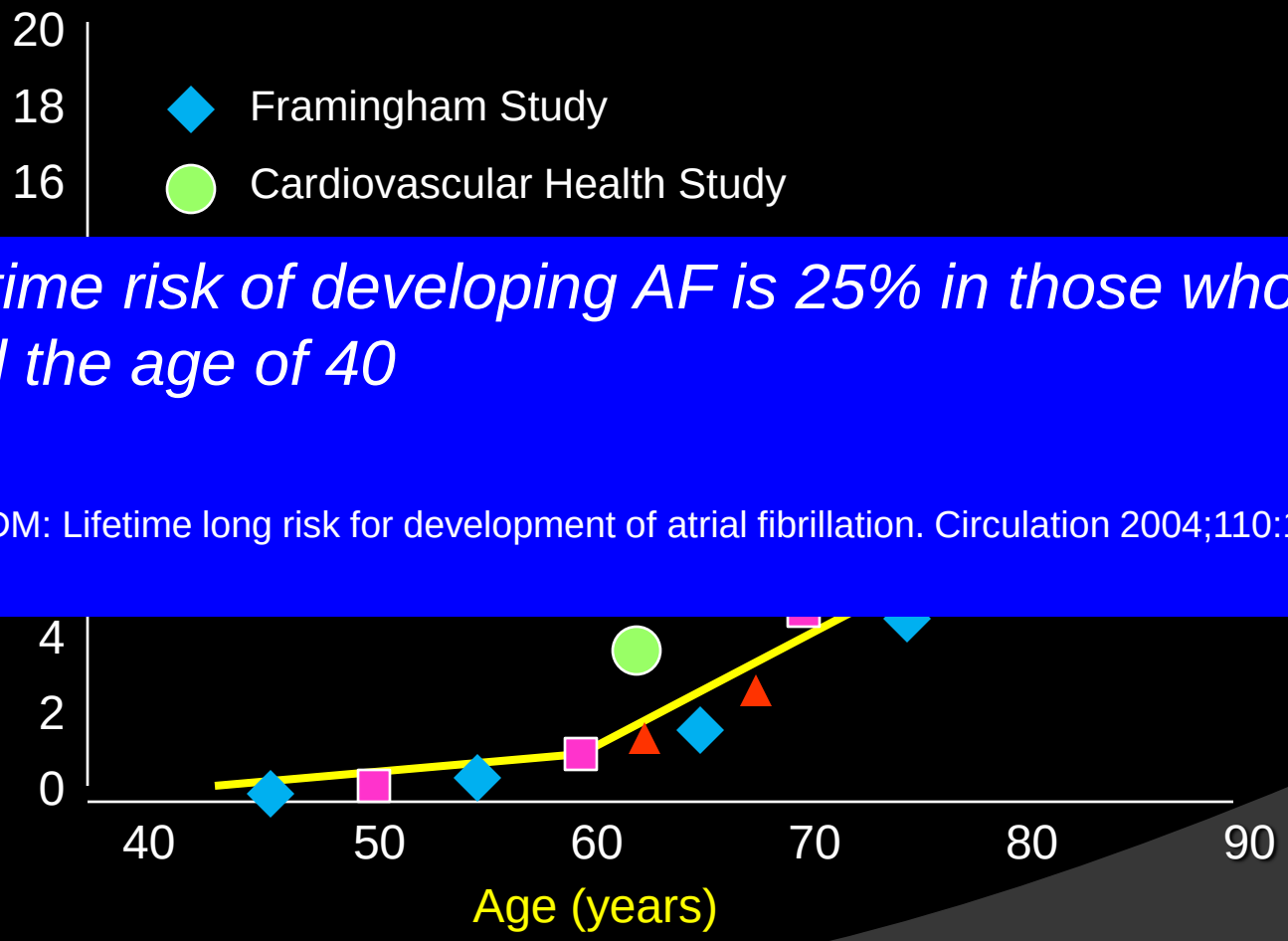


Assumes no further increase in age-adjusted AF incidence (blue curve) and assumes a continued increase in incidence rate as evident in 1980 to 2000 (yellow curve)

Miyasaka Y. Secular Trends in Incidence of Atrial Fibrillation in Olmsted County, Minnesota, 1980 to 2000, and Implications on the Projections for Future Prevalence. Circulation 2006;114:119-125

AFIB: MAGNITUDE OF THE PROBLEM

Prevalence of AF by Age



The lifetime risk of developing AF is 25% in those who have reached the age of 40

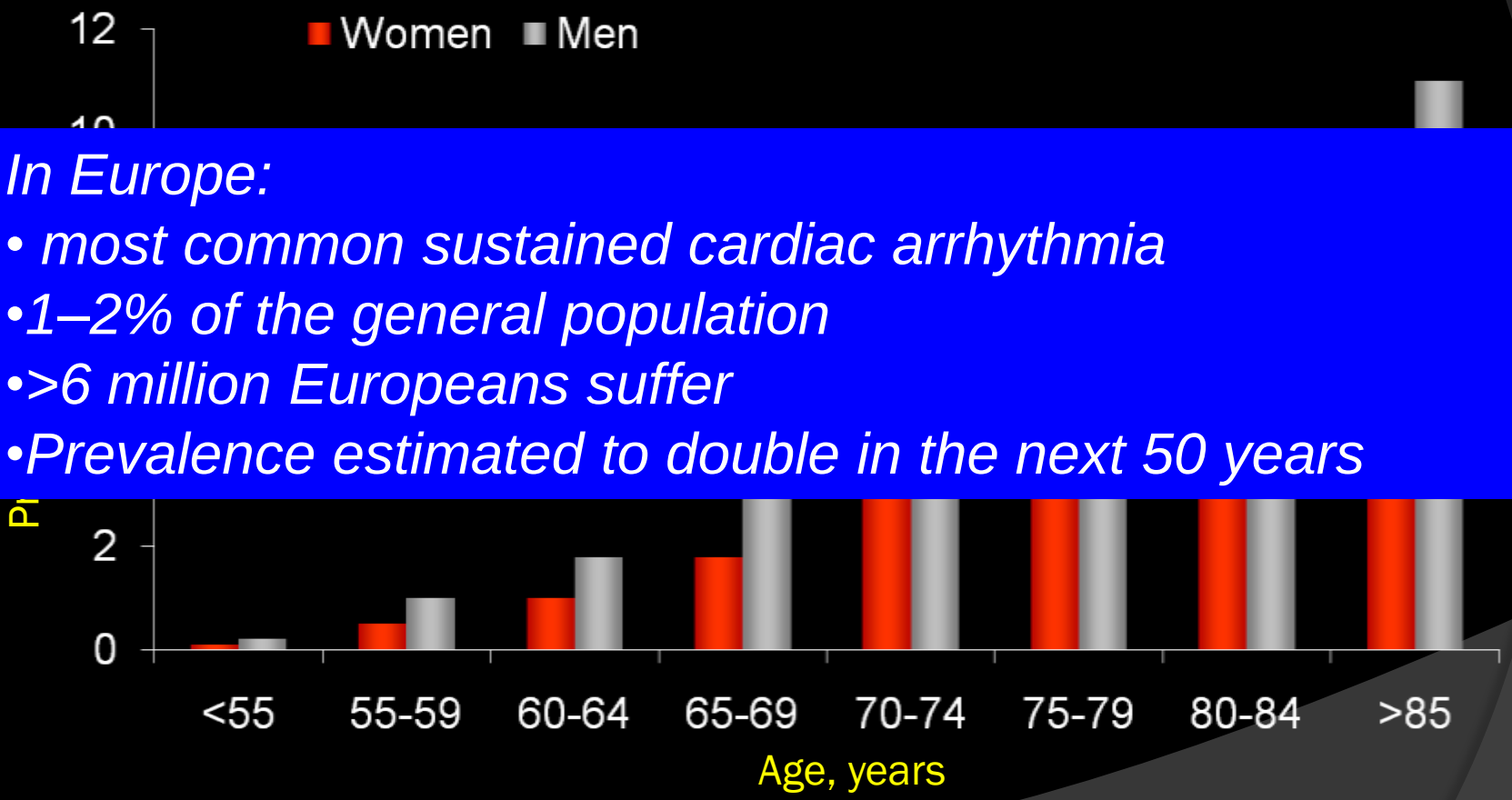
Lloyd Jones DM: Lifetime long risk for development of atrial fibrillation. Circulation 2004;110:1042-1046

Feinberg WM. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications Arch Intern Med. 1995;155(5):469–473

AFIB MAGNITUDE OF THE PROBLEM

AF Prevalence: Age and Gender

Prevalence of atrial fibrillation with age



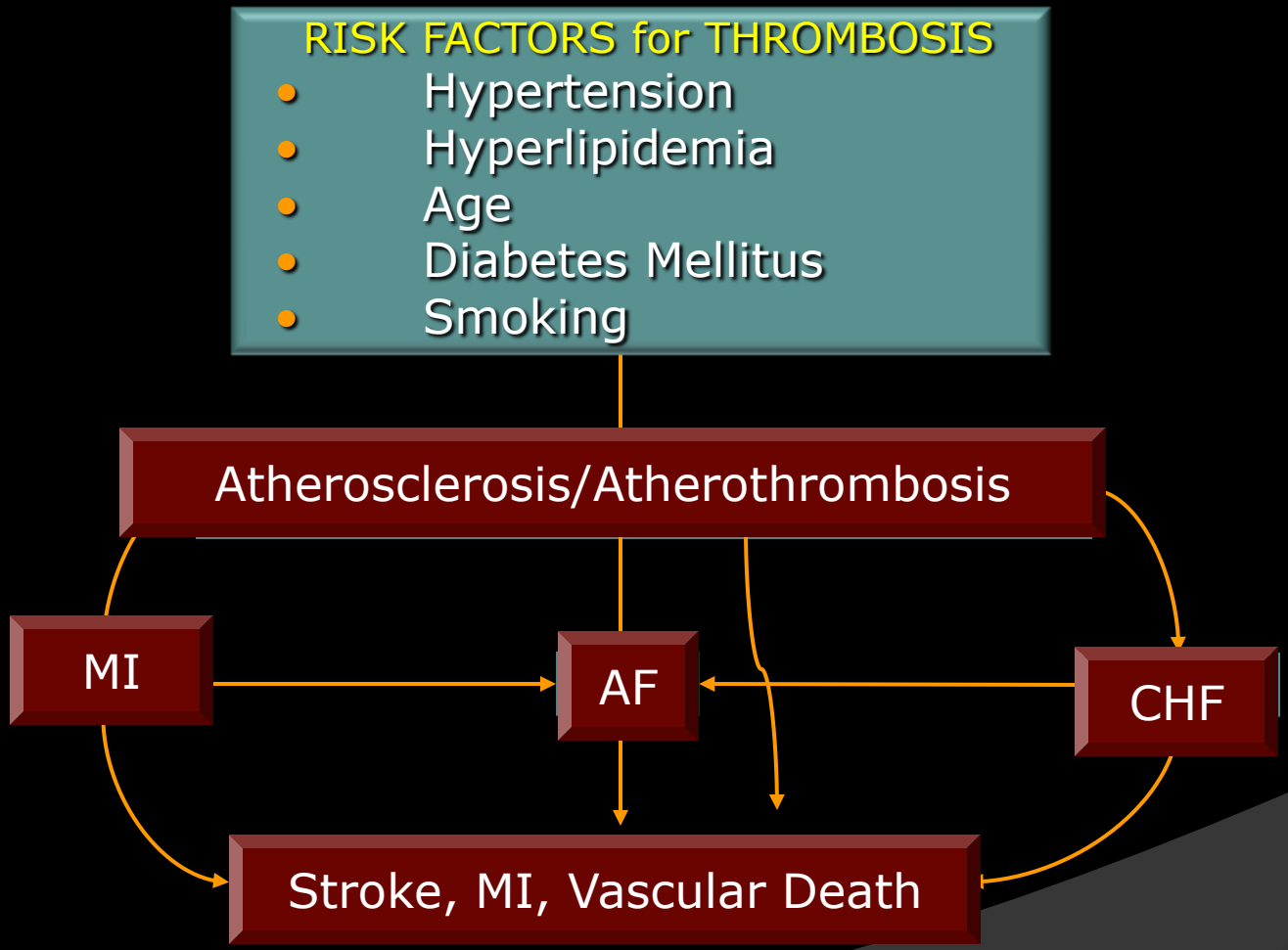
In Europe:

- *most common sustained cardiac arrhythmia*
- *1–2% of the general population*
- *>6 million Europeans suffer*
- *Prevalence estimated to double in the next 50 years*

Go AS. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001 May 9;285(18):2370-5

AFIB: RELATED CV EVENTS

Atrial Fibrillation: A Risk Factor for Vascular Events

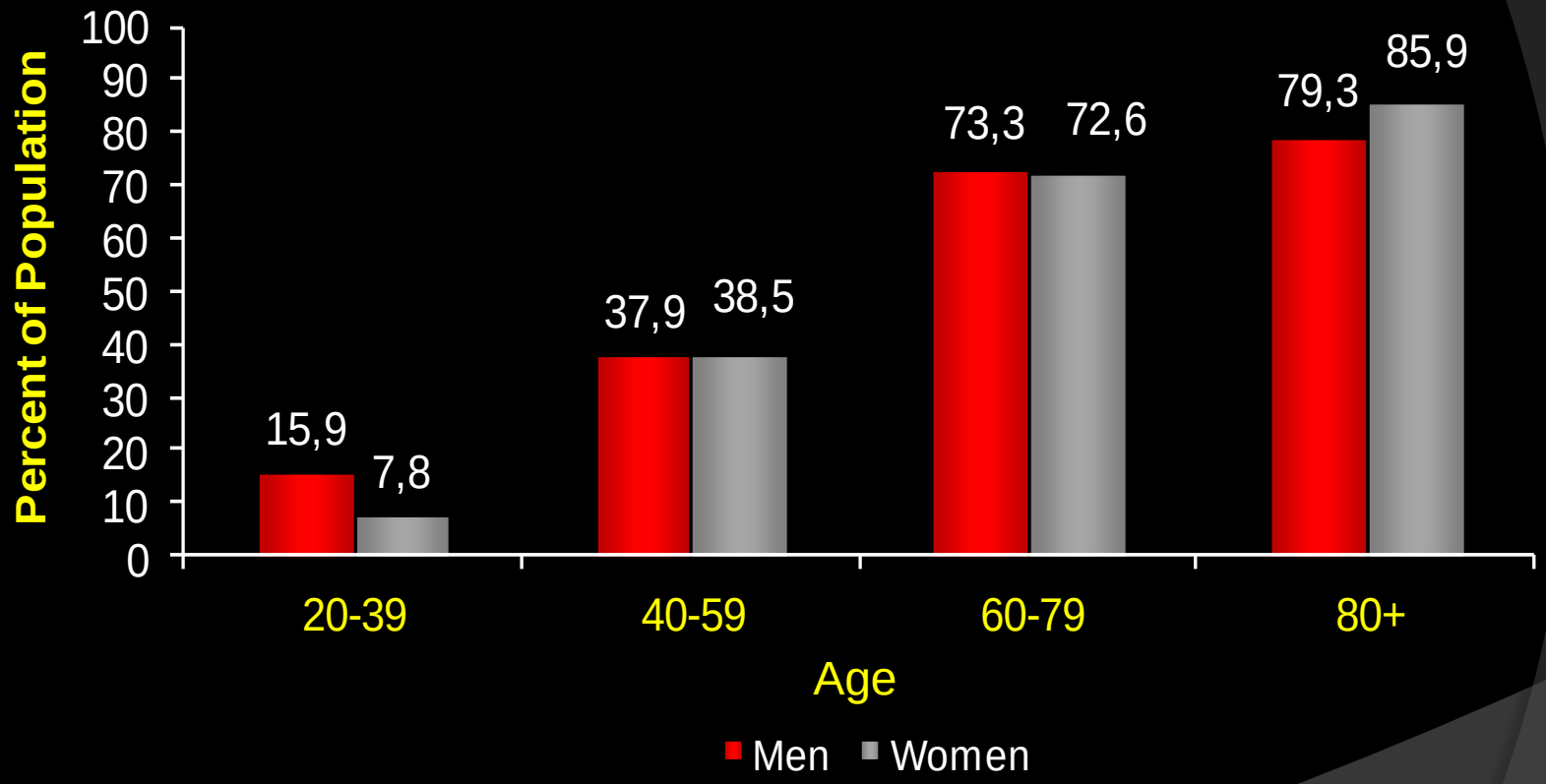


Wolf PA. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. Arc. Int. Med1987 Sep;147(9):1561-4

Leckey R. Atrial fibrillation and the use of warfarin in patients admitted to an acute stroke unit. Can J Cardiol 2000; 16: 481-485

AFIB RELATED CV EVENTS

Prevalence of CVD* in Adults by Age and Sex (NHANES: 2005-2006)



*Coronary heart disease, heart failure, stroke and hypertension

Source: NCHS and NHLBI

Clinical Events (outcomes) affected by AF

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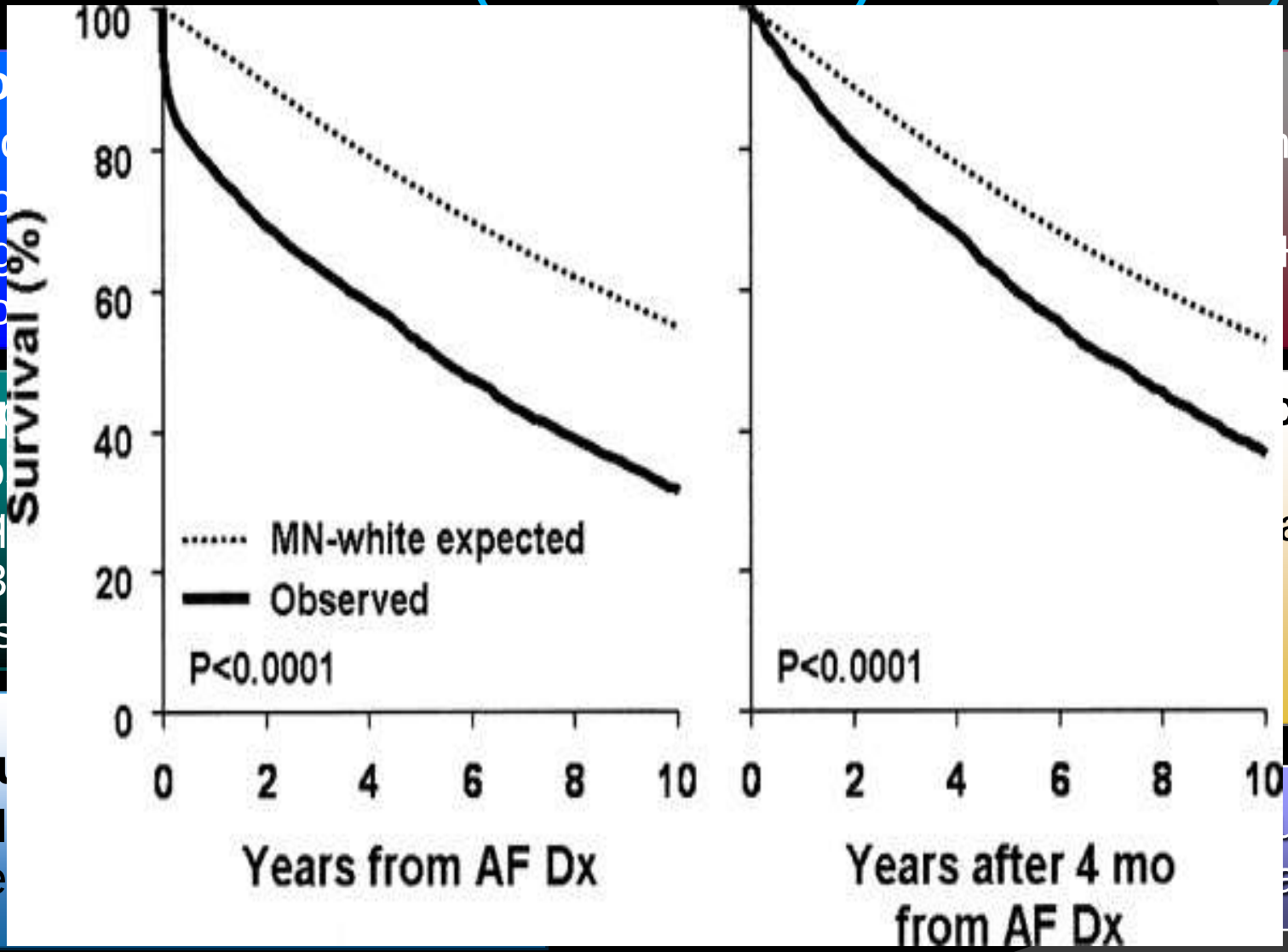
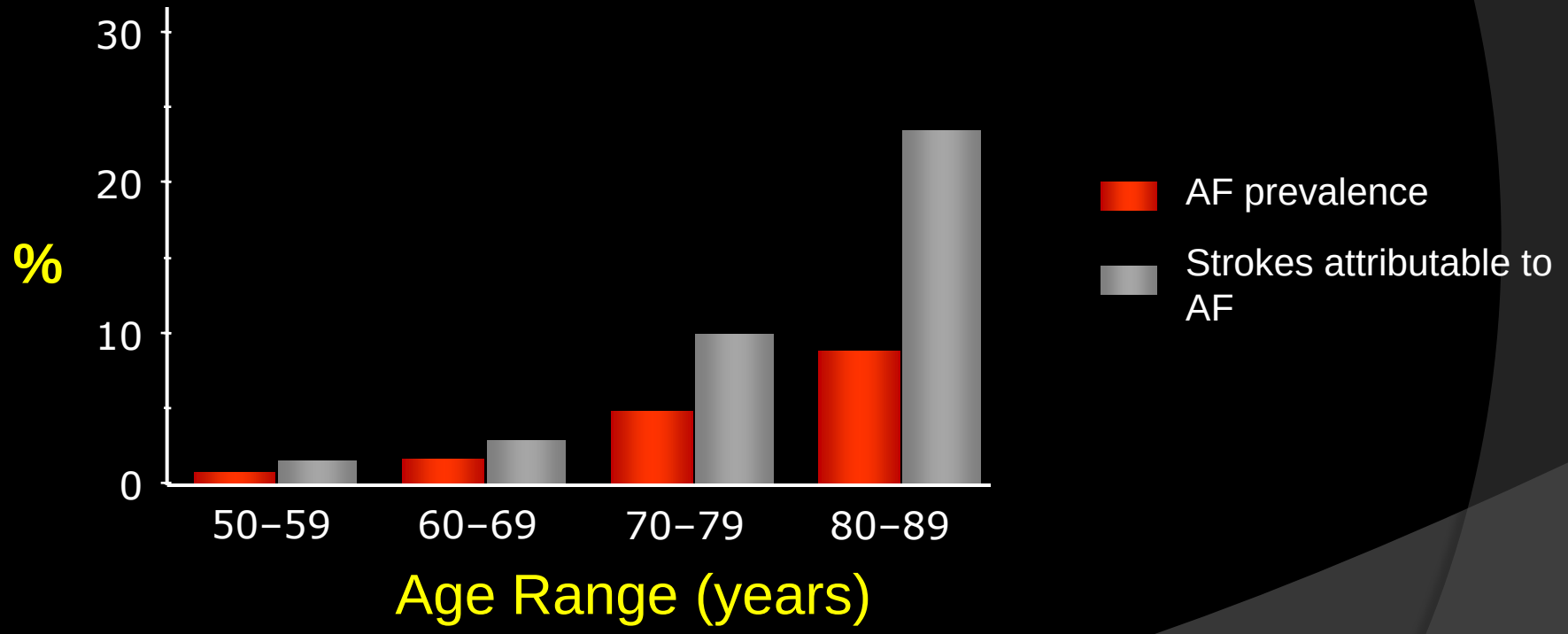


•Van Gelder IC. The progressive nature of atrial fibrillation: a rationale for early restoration and maintenance of sinus rhythm.Europace. 2006;8:943-949
•Narayan SM. Atral Fibrilation. Lancet. 1997;350:943-950.
•Wattigney WA, et al. Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: implications for primary prevention.Circulation. 2003;108:711-716
•Wyse DG. Atrial fibrillation: a perspective: thinking inside and outside the box.Circulation.2004;109:3089-95
•Favale S, et al. Sudden death due to atrial fibrillation in hypertrophic cardiomyopathy: a predictable event in a young patient. PACE. 2003;26:637-639.

One Sixth of all Strokes Attributable to AF

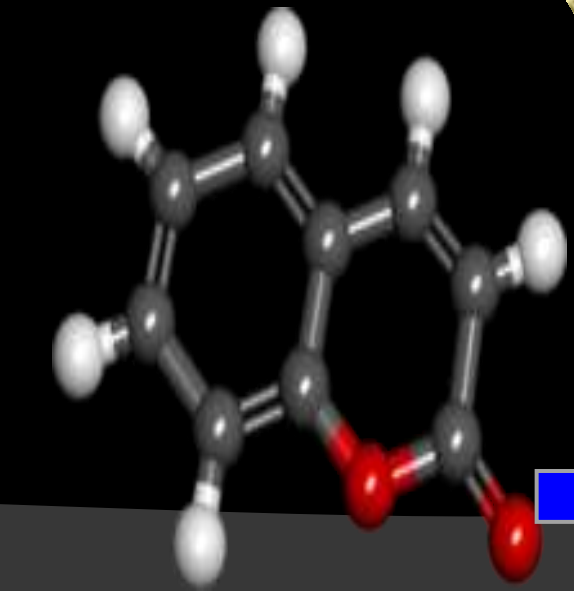
Framingham Study



Wolf et al. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991; 22: 983-988

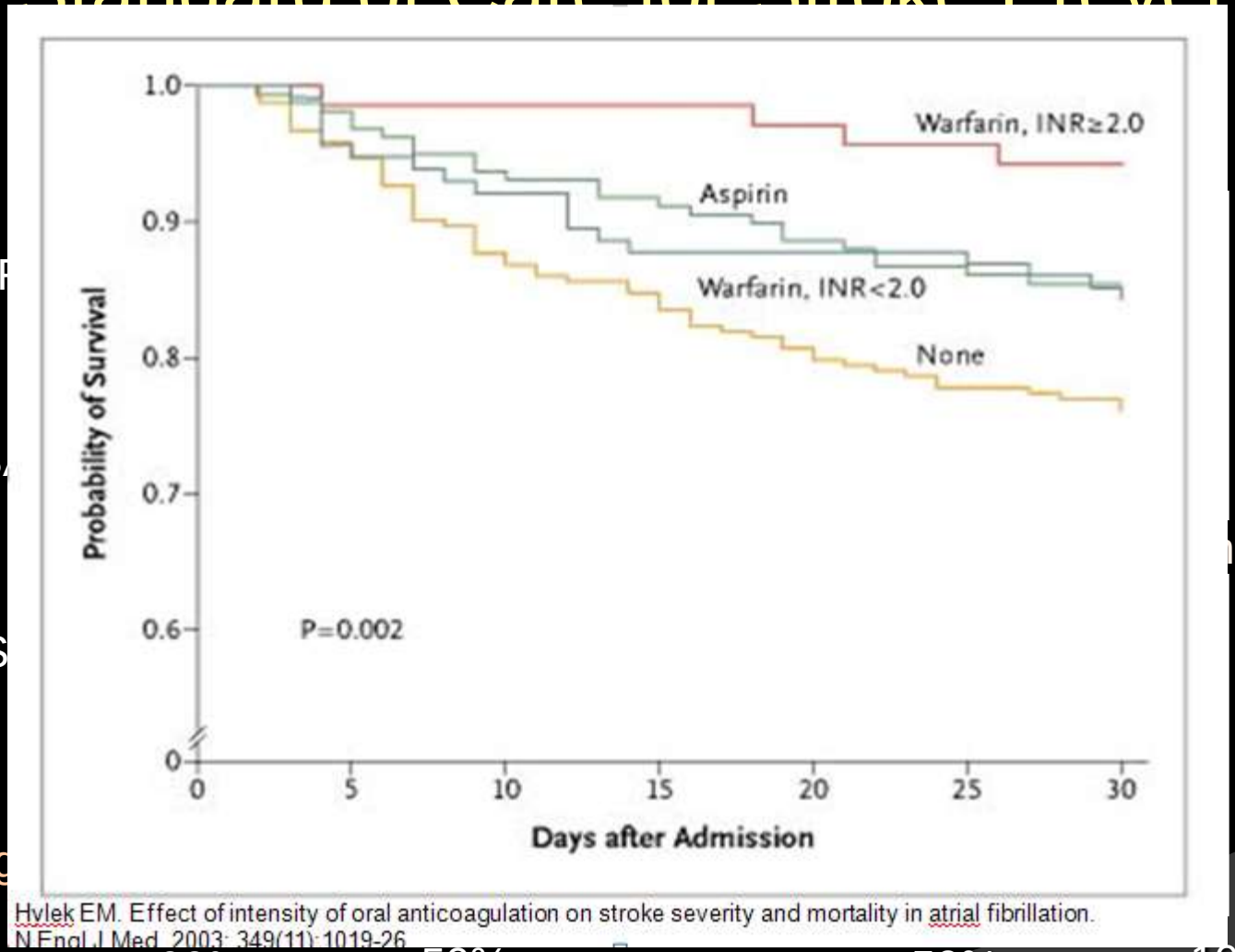
"What was good for a war hero and the President of the United States must be good for all, despite being a rat poison!"

Duxbury BM, Poller L. The oral anticoagulant saga: past, present, and future.
Clin Appl Thromb Hemost. 2001 Oct;7(4):269-75



ANTICOAGULATION IN ATRIAL FIBRILLATION

The Standard of Care for Stroke Prevention



Hvlek EM. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med. 2003; 349(11):1019-26

AF

BA

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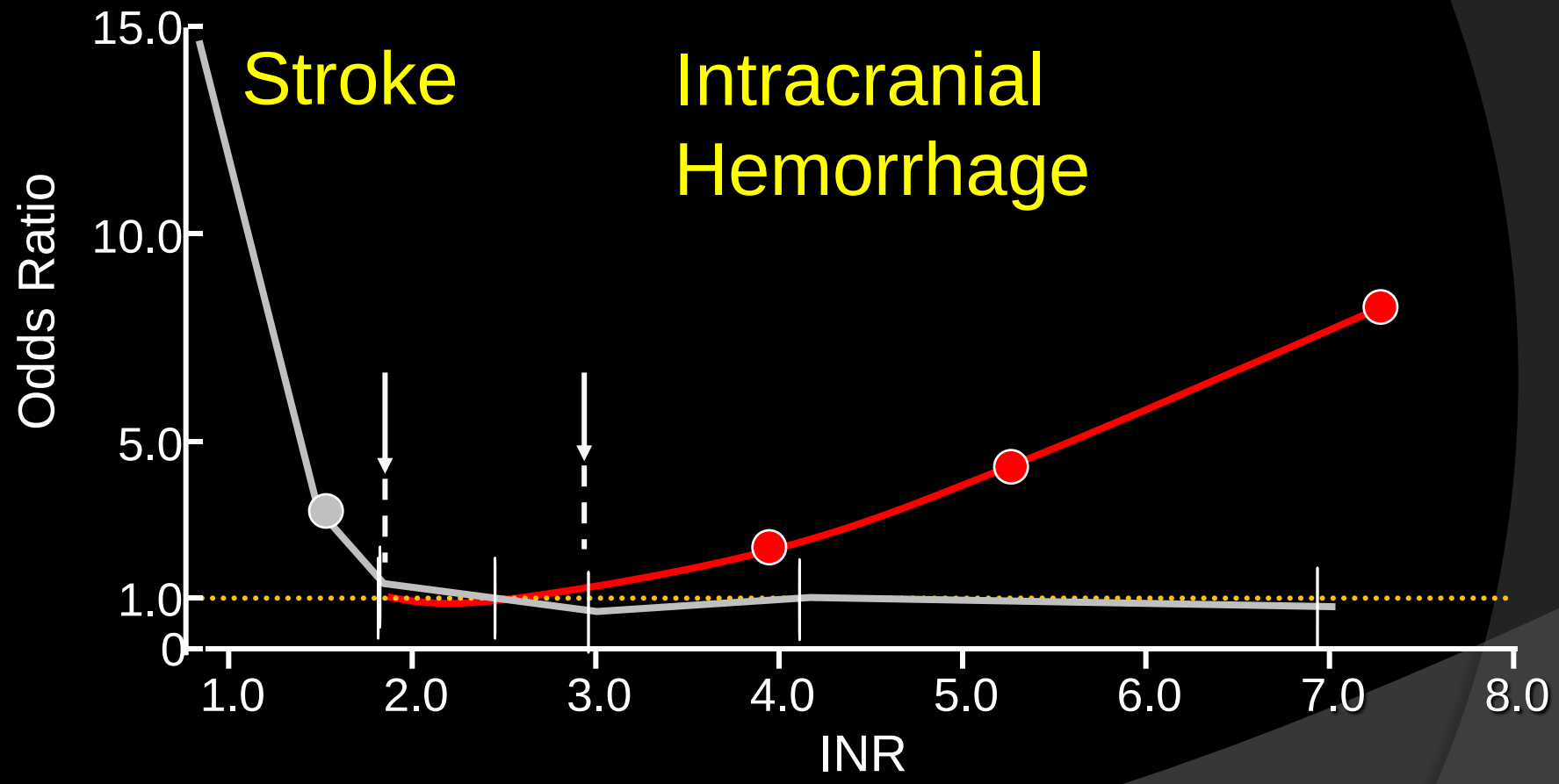
100% 50% 0 -50% -100%

Hart R. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation Ann.Intern Med 2007;146:857.

THERAPEUTIC RANGE FOR WARFARIN

INR Values at Stroke or ICH



Fuster et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary. A Report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation): developed in Collaboration With the North American Society of Pacing and Electrophysiology.

J Am Coll Cardiol. 2001;38:1231-1266

Table 5. Incidence Rates of Ischemic Stroke and Intracranial Hemorrhage among Patients with Nonvalvular Atrial Fibrillation Who Were Taking Warfarin, According to the International Normalized Ratio (INR) at the Time of the Stroke.*

INR	Person-yr†	Stroke (95% CI) (N=152)	Person-yr†	Intracranial Hemorrhage (95% CI) (N=58)
		rate/100 person-yr		*rate/100 person-yr*
<1.5	556	7.7 (5.7–10.4)	561	0.5 (0.2–1.7)
1.5–1.9	2847	1.9 (1.4–2.4)	2867	0.3 (0.1–0.6)
2.0–2.5	5357	0.4 (0.3–0.7)	5400	0.3 (0.2–0.4)
2.6–3.0	2388	0.9 (0.6–1.4)	2409	0.5 (0.3–0.9)
3.1–3.5	834	0.7 (0.3–1.6)	843	0.6 (0.3–1.4)
3.6–3.9	243	0.4 (0.1–2.9)	247	0.4 (0.1–2.9)
4.0–4.5	144	1.4 (0.4–5.5)	147	2.7 (1.0–7.3)
>4.5	115	2.6 (0.8–8.1)	118	9.4 (5.2–16.9)

Hylek EM. Effect of Intensity of Oral Anticoagulation on Stroke Severity and Mortality in Atrial Fibrillation N Engl J Med. 2003;349:1019-2614

"Most intracranial hemorrhages (62%) occur at INRs < 3.0"

Characteristic	Case-Patients (n = 170)	Controls (n = 1020)
Median age (interquartile range), *y*	78 (72–84)	75 (69–81)
Median international normalized ratio (interquartile range)†	2.7 (2.1–3.6)	2.3 (1.9–2.8)
Men, %	57	59
White, %‡	93	96
Comorbid conditions, %§		
Hypertension	69	61
Cerebrovascular disease	37	20
Diabetes mellitus	19	21
Congestive heart failure	27	36
Coronary artery disease	41	40
Cancer	20	21
Aspirin use, %	20	19

Fang MC. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. Ann Intern Med. 2004;141:745-52

Risk Factors for Stroke

Risk Factor	Relative Risk
Old Stroke/TIA	2.5
Hypertension	1.6
CHF	1.4
Increased age	1.4/10 years
DM	1.7
CAD	1.5

Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials.
[No authors listed] Arch Intern Med 1994; 154: 1449-1457

The $CHADS_2$ Index

Score (points)	Risk of Stroke (%/year)	
0	1.9	
1	2.8	
Approximate Risk threshold for Anticoagulation		3%/year
2	4.0	
3	5.9	
4	8.5	
5	12.5	
6	18.2	

•Van Walraven C. A clinical prediction rule to identify patients with atrial fibrillation and a low risk for stroke while taking aspirin. Arch Intern Med 2003; 163:936.

•Go A. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? JAMA 2003; 290: 2685.

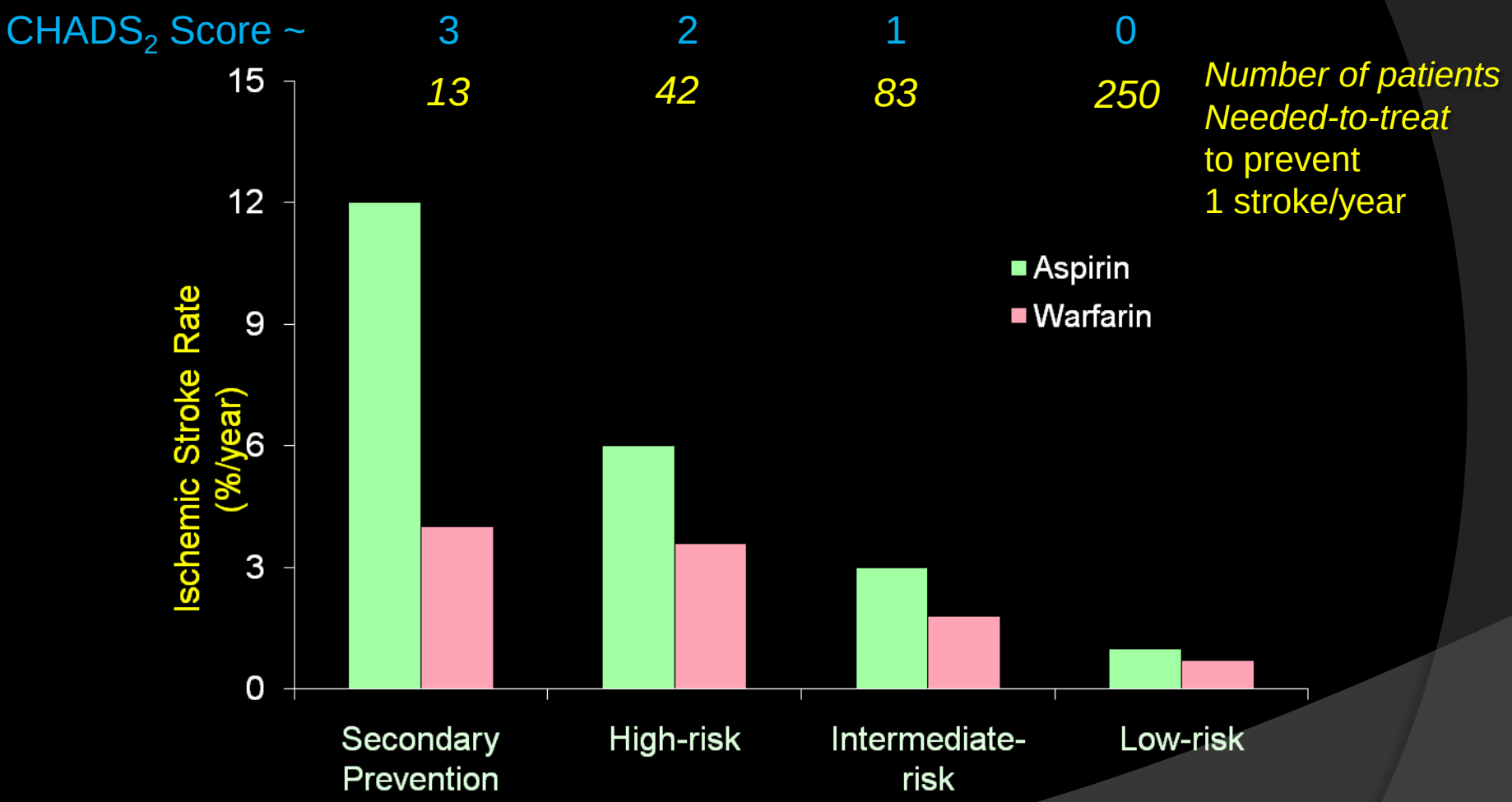
•Gage BF. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. Circulation 2004; 110: 2287.

taking aspirin. Arch Intern Med 2003; 163:936-43

• Nieuwlaat R. Antithrombotic treatment in real-life atrial fibrillation patients: a report from the Euro Heart Survey on Atrial Fibrillation Eur Heart J 2006 Dec;27(24):3018-26

RISK STRATIFICATION AND ANTICOAGULATION

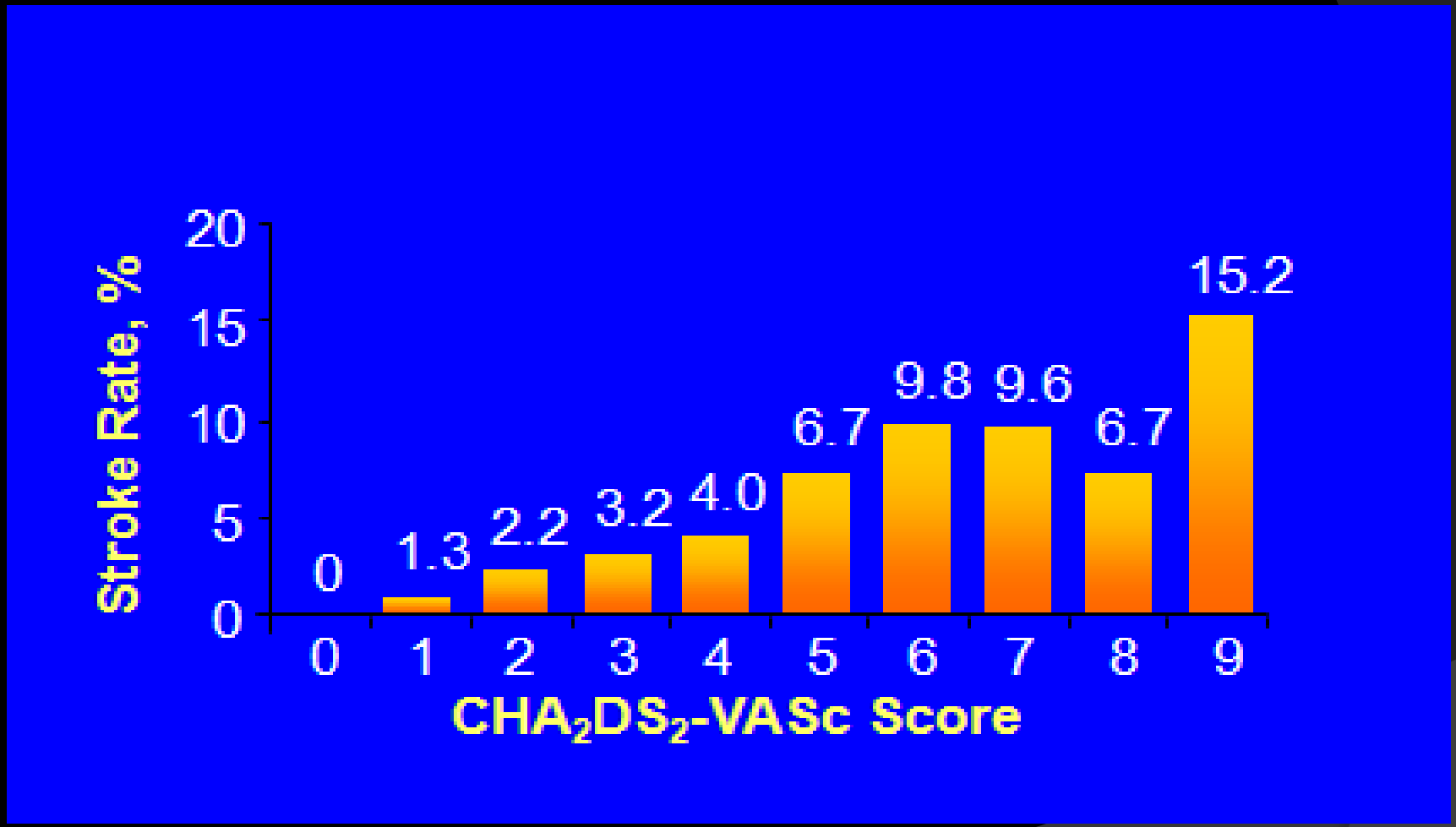
Stroke Reduction with Warfarin Instead of Aspirin



•EAFT Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke Lancet 1993; 342:1255-1262

•Zabalgoitia M. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. Stroke Prevention in Atrial Fibrillation III Investigators. JAm Coll Cardiol 1998; 31:1622.

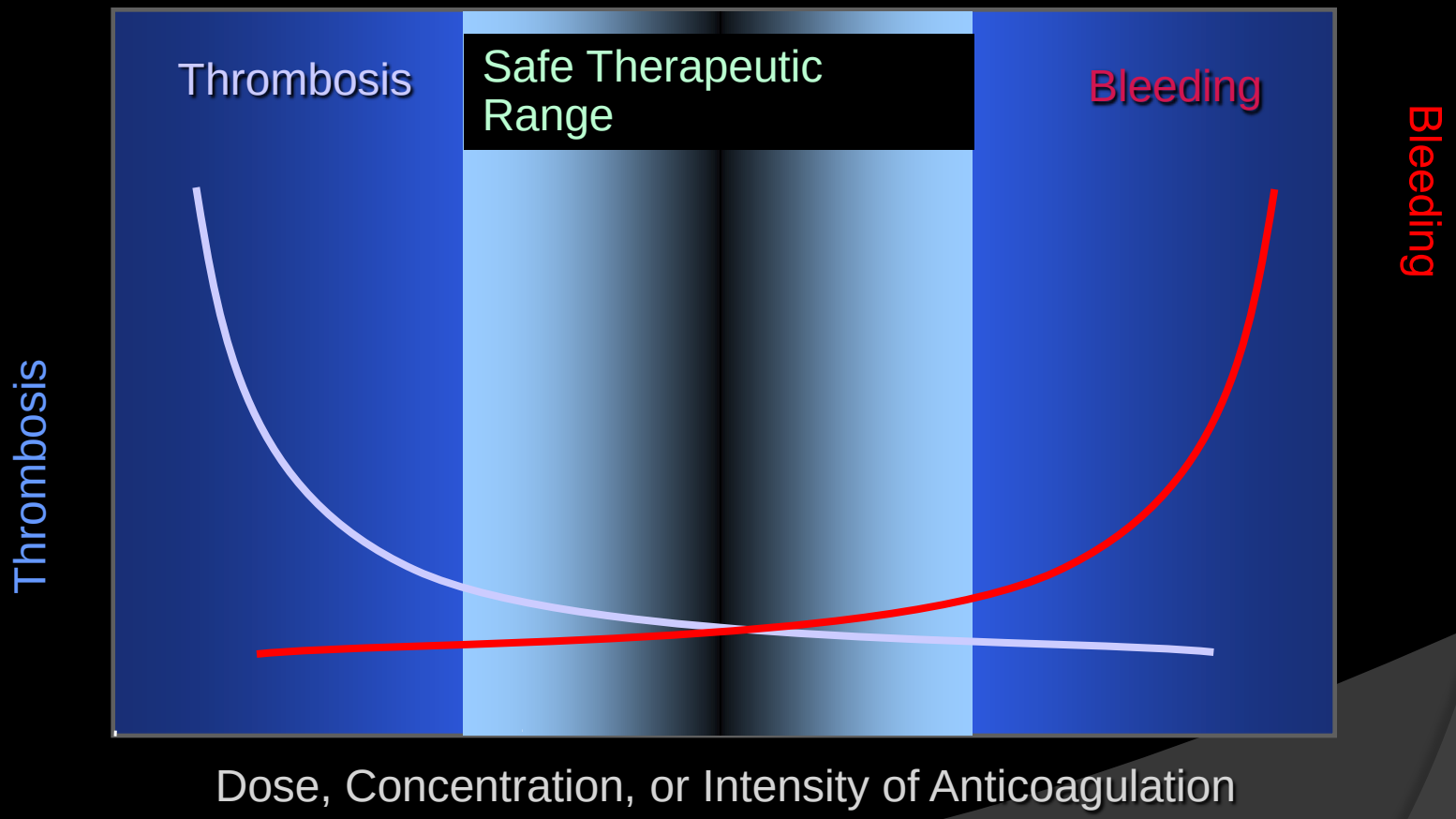
Risk factor-based point-based scoring system - CHA_2DS_2-VASc



Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur H J 2010; 31(19):2369-2429

THE IDEAL ANTICOAGULANT

Wide Therapeutic Margin



Th…ore

Risk factors for thromboembolism	Bleeding risk factors
Previous stroke, transient ischaemic attack, or embolism	Cerebrovascular disease
Age ≥75 years (Age 65 to 74 years)	Advanced age (>75 years)
Heart failure or moderate-severe left ventricular dysfunction on echocardiography [e.g. Ejection fraction ≤40%] (Vascular disease)	History of myocardial infarction or ischaemic heart disease
Hypertension	Uncontrolled hypertension
Diabetes mellitus	?
(Female gender)	?
Mitral stenosis Prosthetic heart valve	
	Anaemia
(Renal dysfunction (stage III-V)	(Renal dysfunction [stage III-V])
	History of bleeding
	Concomitant use of other antithrombotic substances such as antiplatelet agents

Thrombosis and Haemostasis 103.1/2010

*Hype…

INR =

Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur H J 2010; 31(19):2369-2429

AF and CAD:

"*The graying population will slowly, radically transform society.*" Richard Suzman, NIA .

- *70–80% of pts. in AF have an indication for continuous OAC*, and *CAD co-exists in 20–30%* of these pts.

- estimated *prevalence of AF is 1–2%* of the population:

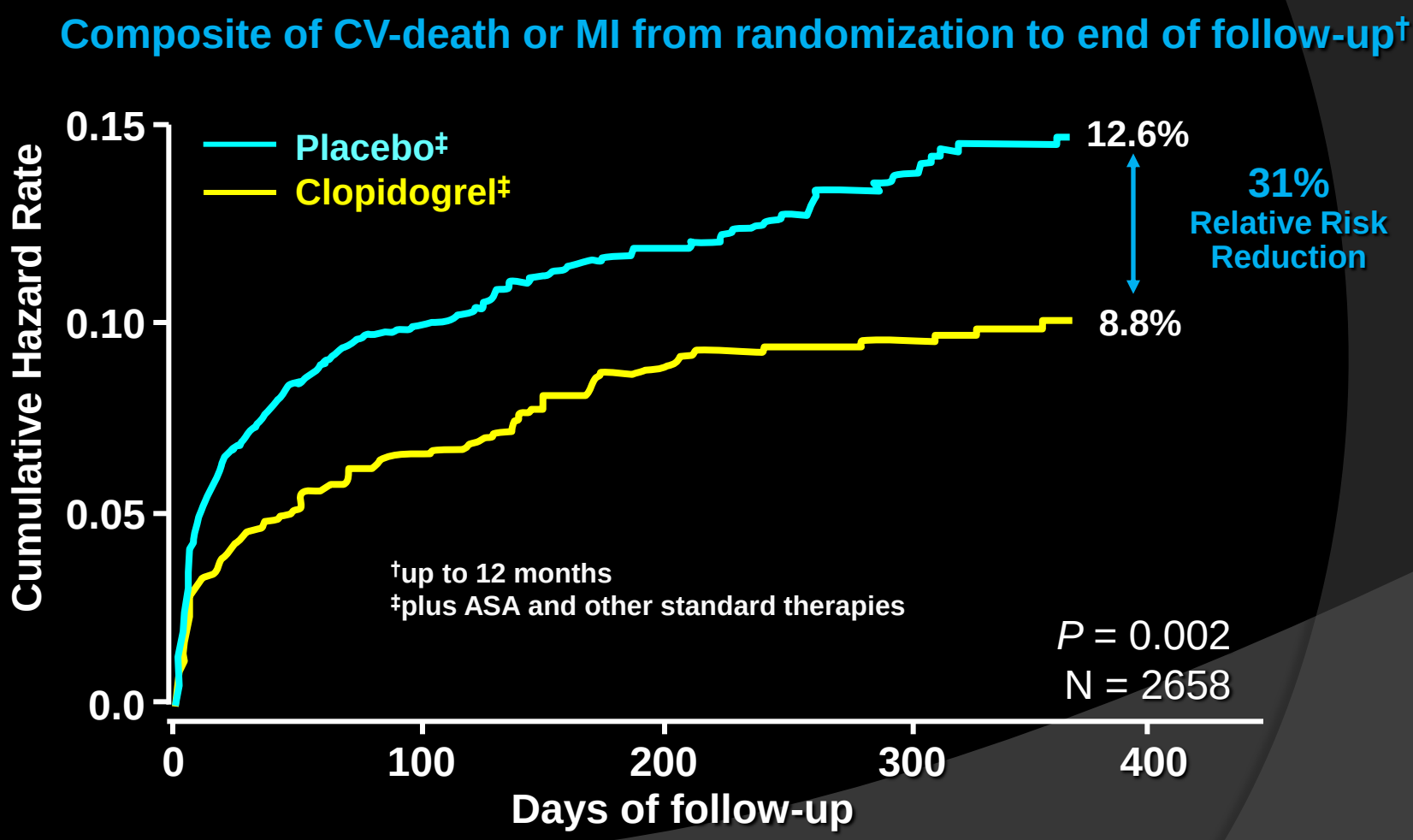
  1- 2 million anticoagulated pts. in Europe are candidates for cor. revasc. often in the form of PCI usually including stents.

- U.S: *5–7% of pts. undergoing PCI have AF* or other indications for *chronic oral anticoagulant therapy*

•Faxon D. Consensus document: Antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting. Thromb Haemost 2011 106: 571–584

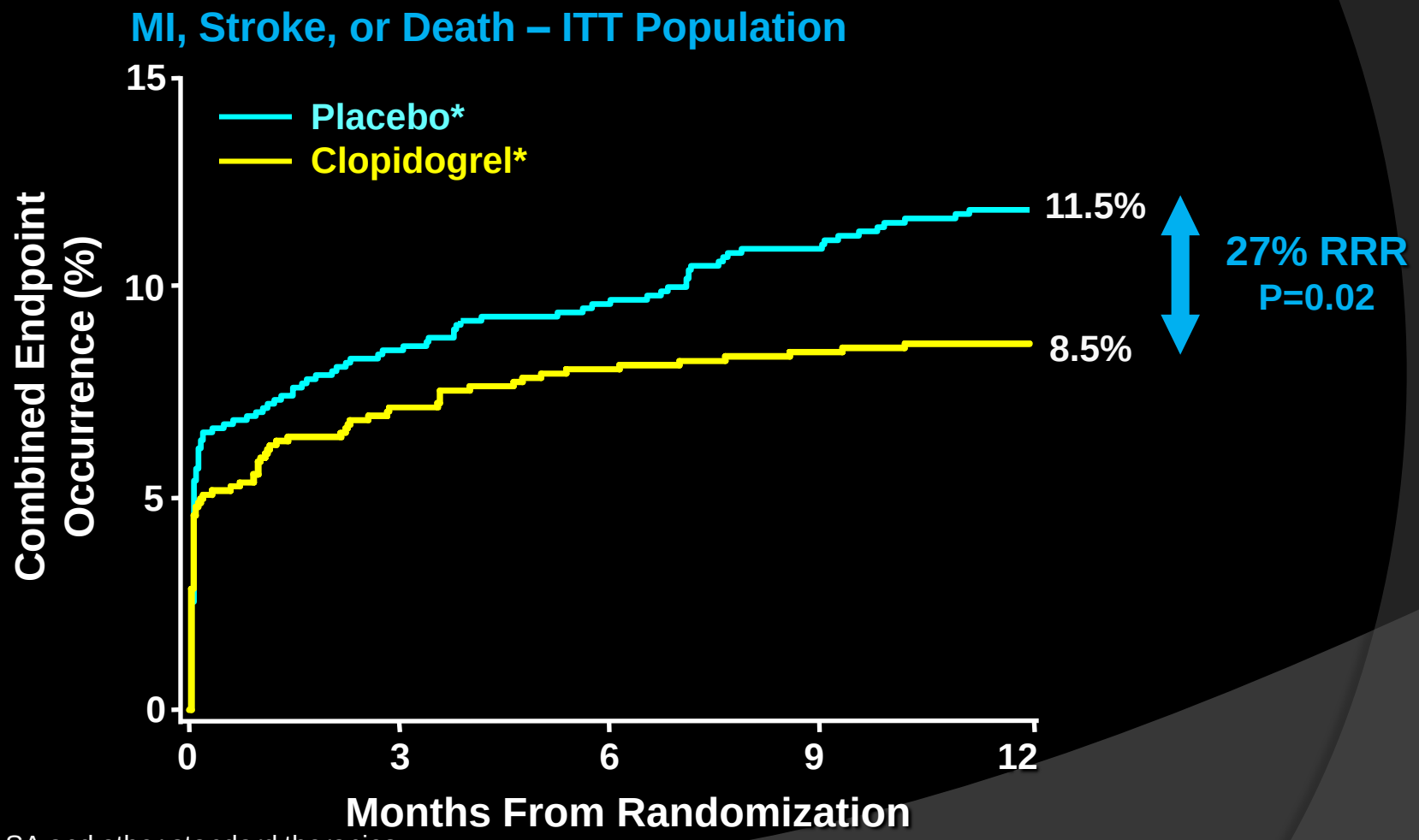
•Lip GY. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary intervention/ stenting. Thromb Haemost 2010; 103:13-28

PCI-CURE
Long-Term Efficacy of Clopidogrel



Mehta et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001;358 (9281): 527-533.

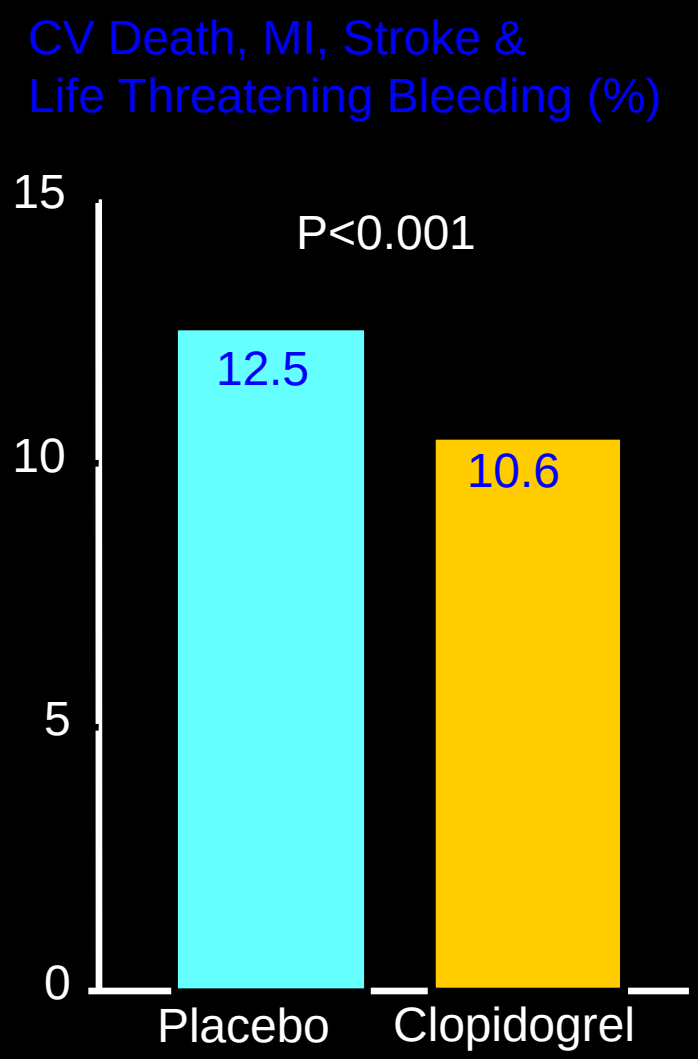
Long-Term (1 Year) Benefits of Clopidogrel in PCI Patients

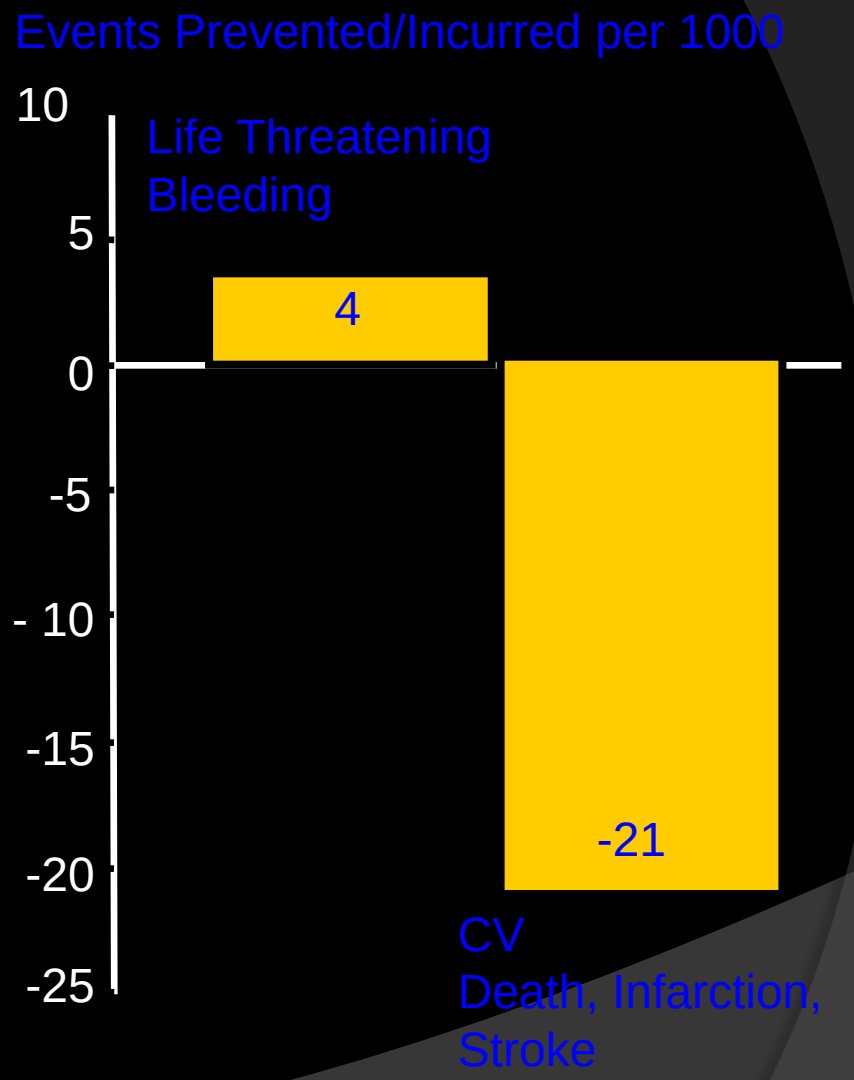


* Plus ASA and other standard therapies

Steinhubl S et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA. 2002;Vol 288 (19): 2411-2420.

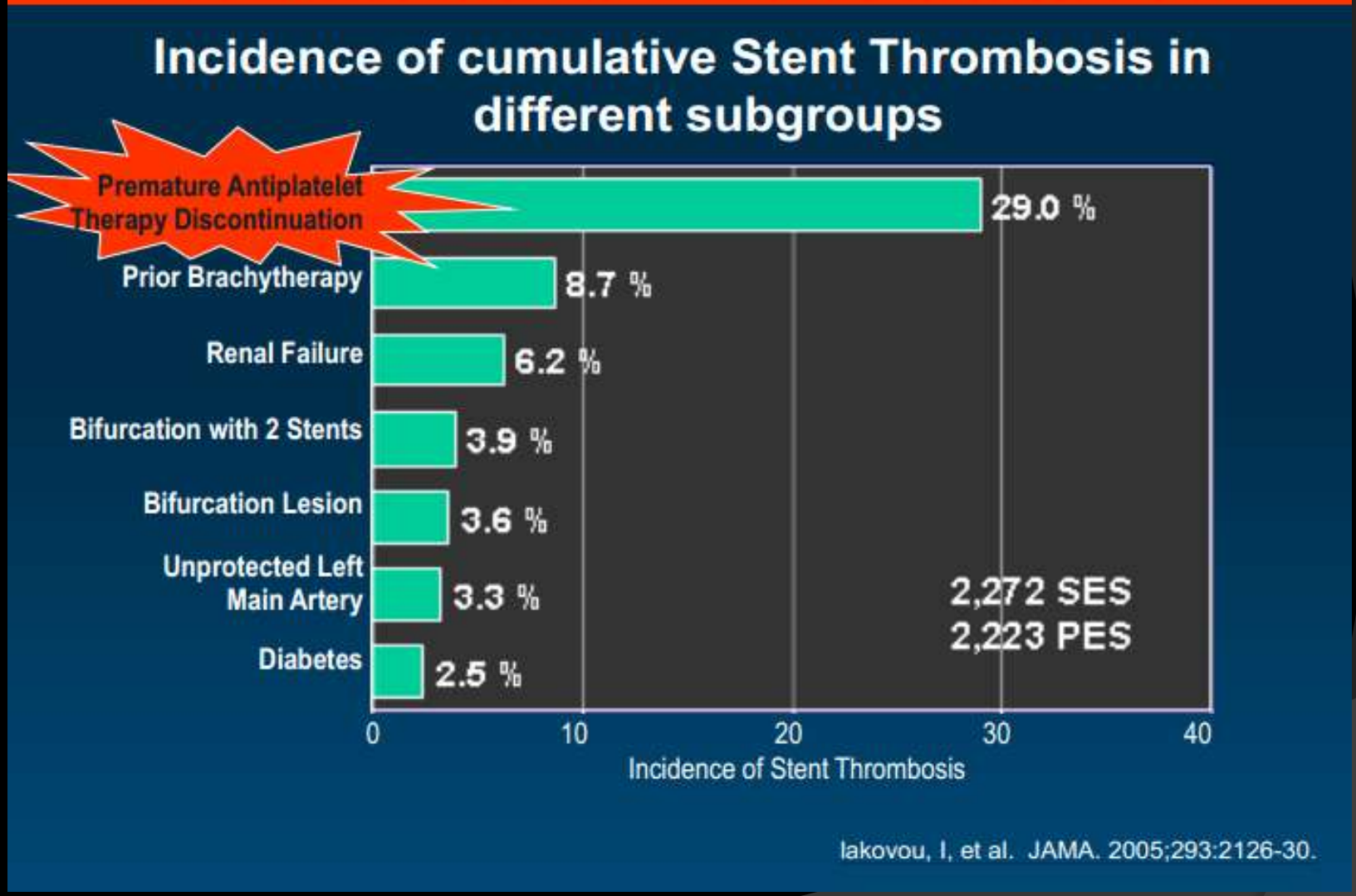
Risk/Benefit Ratio of Clopidogrel in CURE





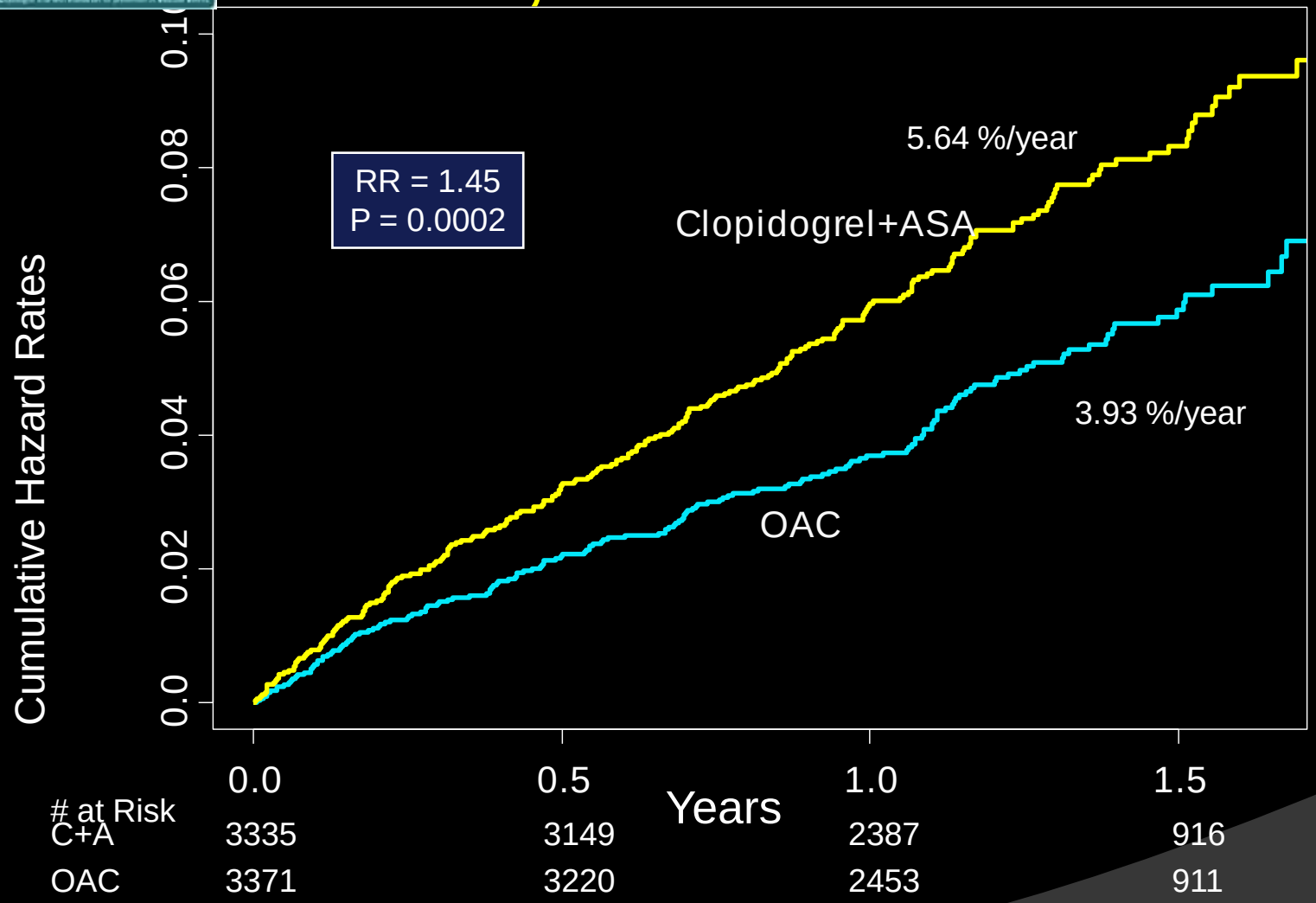
Fox KA . Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. Circulation 2004 ;110(10):1202-8.

Premature DAPT Discontinuation



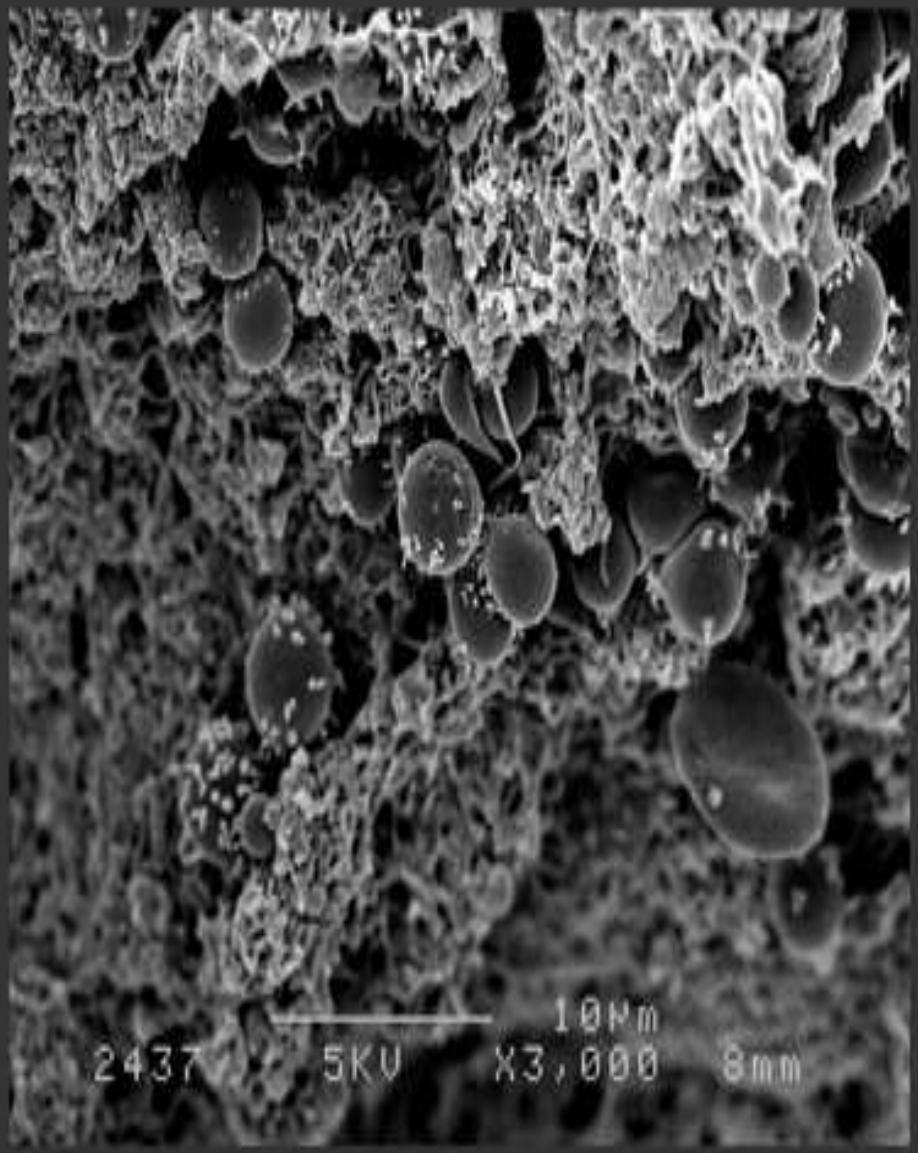
Sammy Elmariah. Acute Stent Thrombosis: Technical Complication or Inadequate Antithrombotic Therapy?: An Optical Coherence Tomography Study J Am Coll Cardiol Intv. 2012;5(2):e3-e4

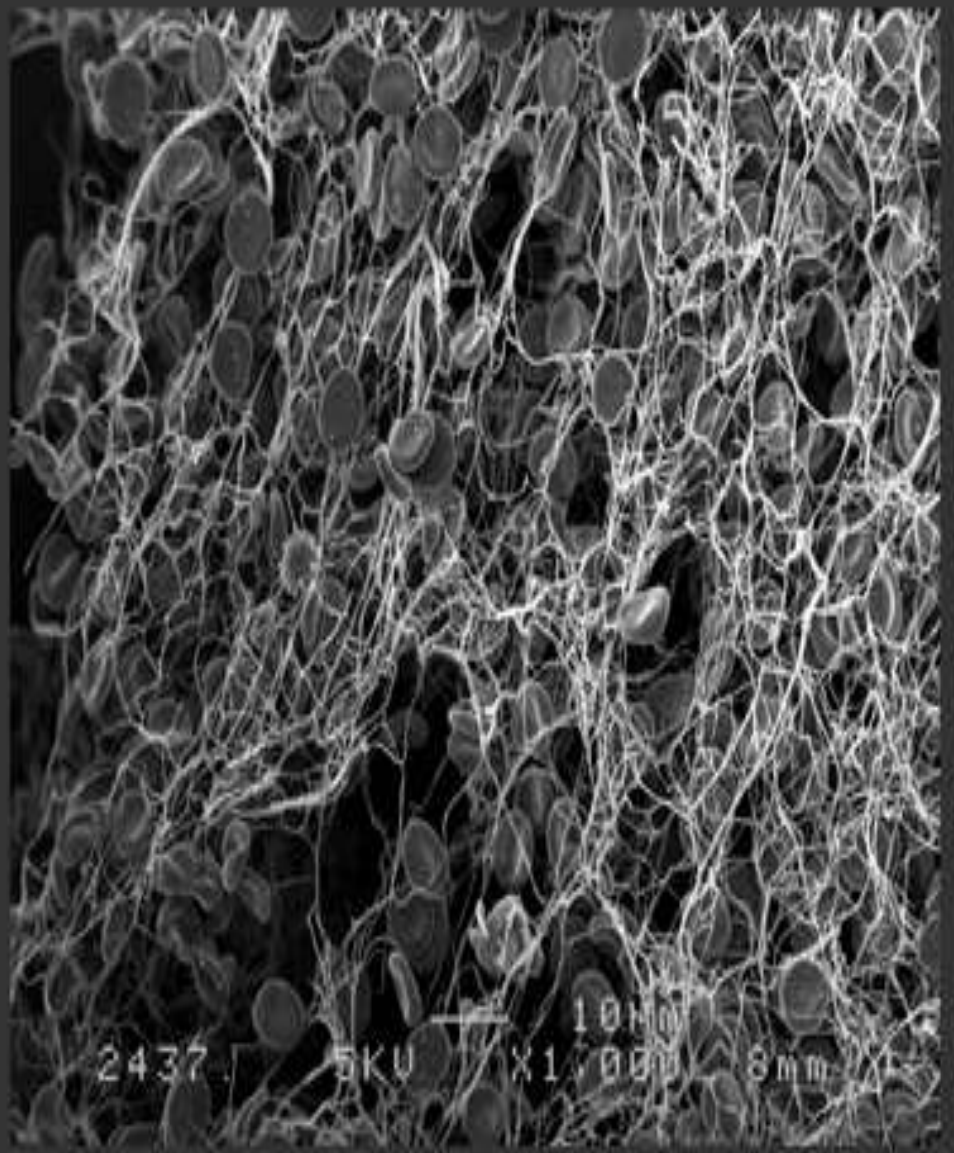
Stroke, Non-CNS Systemic Embolism, MI & Vascular Death



ACTIVE Writing Group of the ACTIVE Investigators, Connolly S. et al.
Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006 Jun 10;367(9526):1903-12

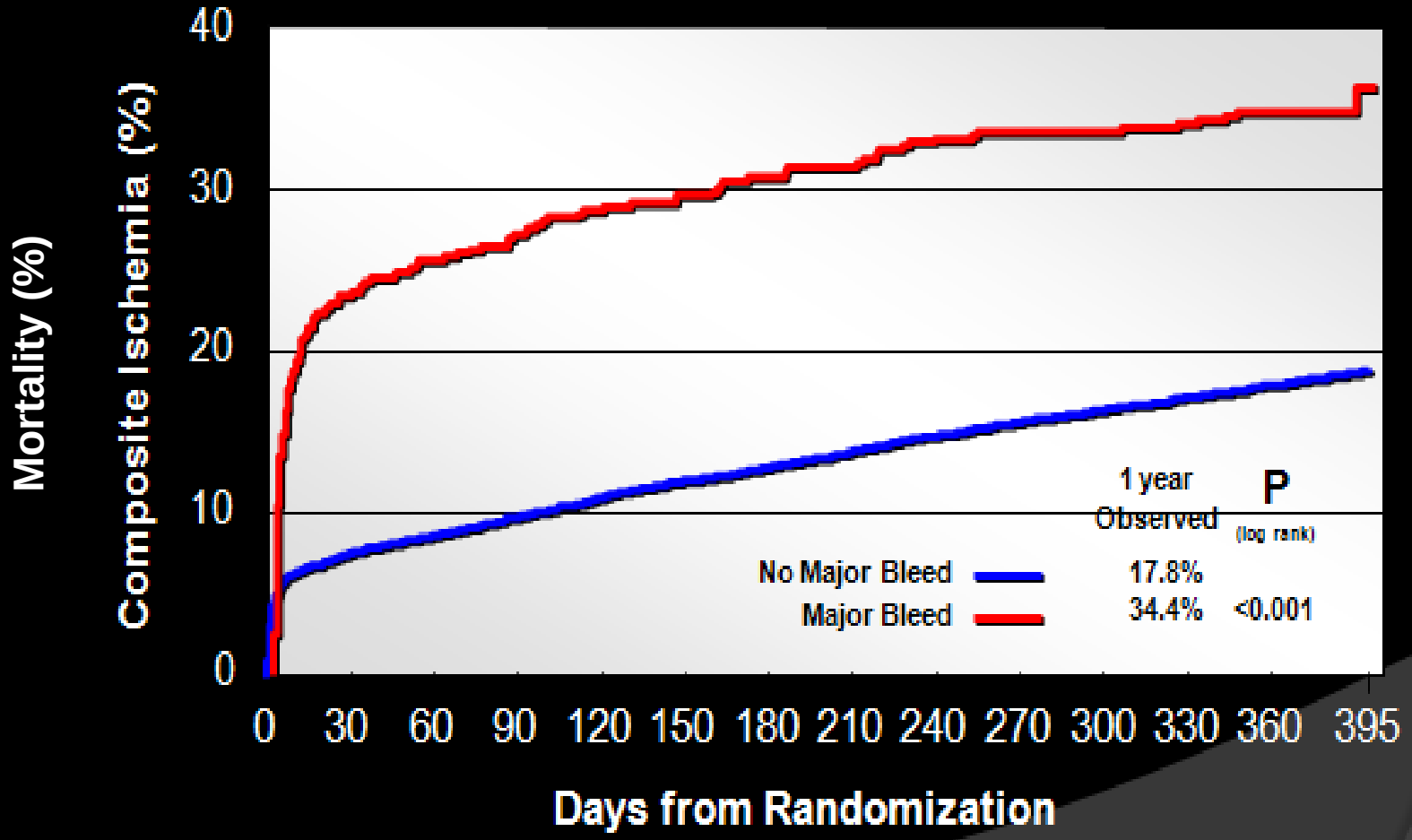
WHITE THROMBUS VS RED THROMUS





ACUITY PCI

Major Bleeding Long-Term (1-Year) Mortality
Landmark Analysis



Manoukian SV et al. TCT 2007

TRIPLE THERAPY: OAC + DAPT

Optin Risk

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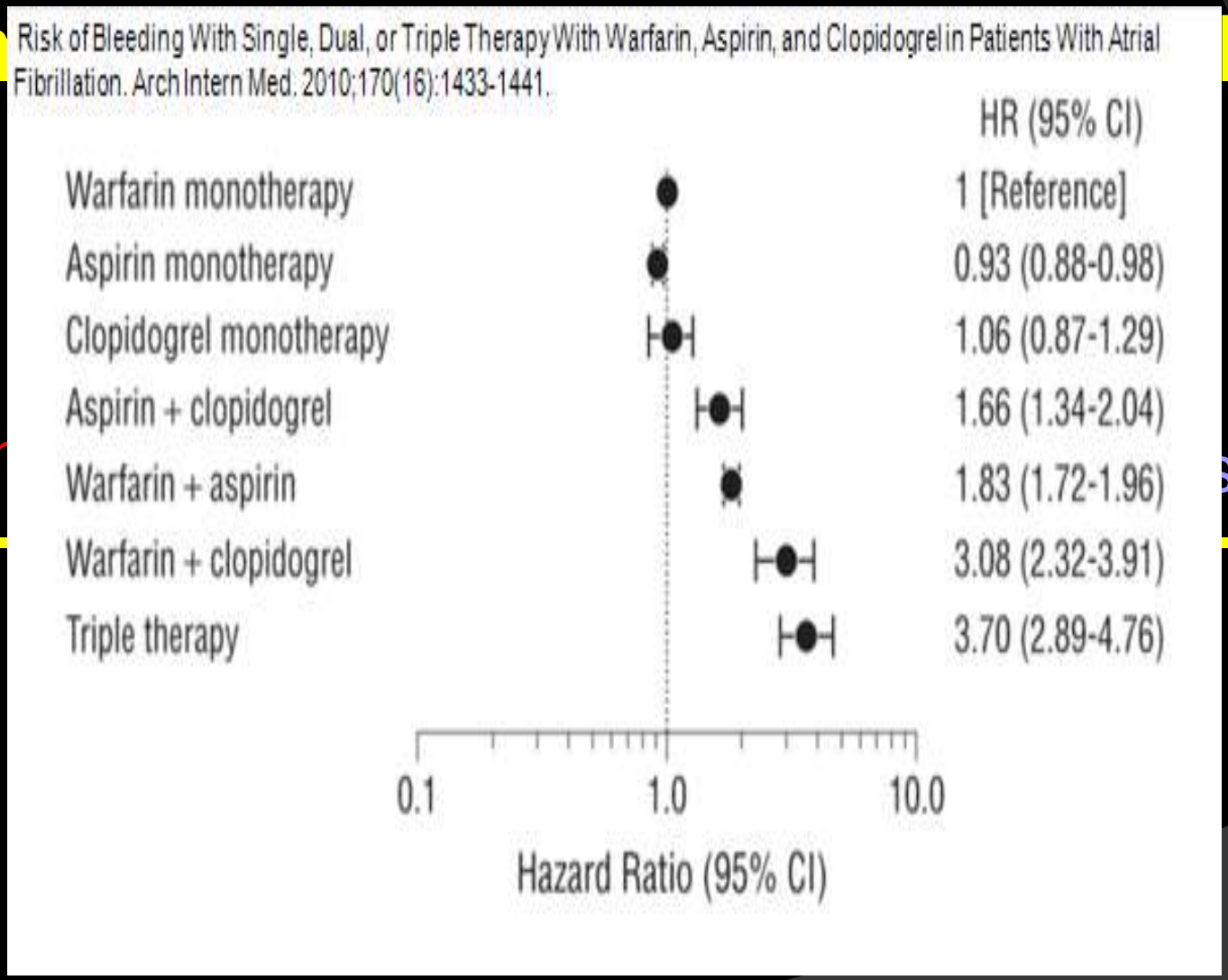


AF and PCI:

Table 1: SCAI survey (168 respondents, conducted on 2/21/2011).

1.How often do you use a drug eluting stent in patients with AF on warfarin?

a. Never 1.8%
b. Rarely 32.9%
c. Sometimes 35.3%
d. Often 30.6%

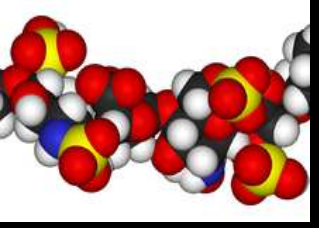
2.What is your preferred regimen in a patient with chronic AF on warfarin and requiring a DES?

a. ASA, clopidogrel and warfarin for one month then ASA + warfarin 5.3%
b. ASA, clopidogrel and warfarin for one month then clopidogrel + warfarin 19.3%
c. ASA, clopidogrel and warfarin for 6 months or more 47.5%
d. ASA and clopidogrel for 6 months or more 8.8%
e. Clopidiogrel and warfarin for 6 months or more 9.6%

3.What is your preferred regimen in a patient with chronic AF on warfarin and requiring a BMS?

a. ASA, clopidogrel and warfarin for one month then ASA + warfarin 86.5%
b. ASA, clopidogrel and warfarin for one month then clopidogrel + warfarin 7.6%
c. ASA, clopidogrel and warfarin for 6 months or more 3.2%
d. ASA and clopidogrel for 6 months or more 1.3%
e. Clopidogrel and warfarin for 6 months or more 0.6%

Thrombosis and Haemostasis 106.4/2011



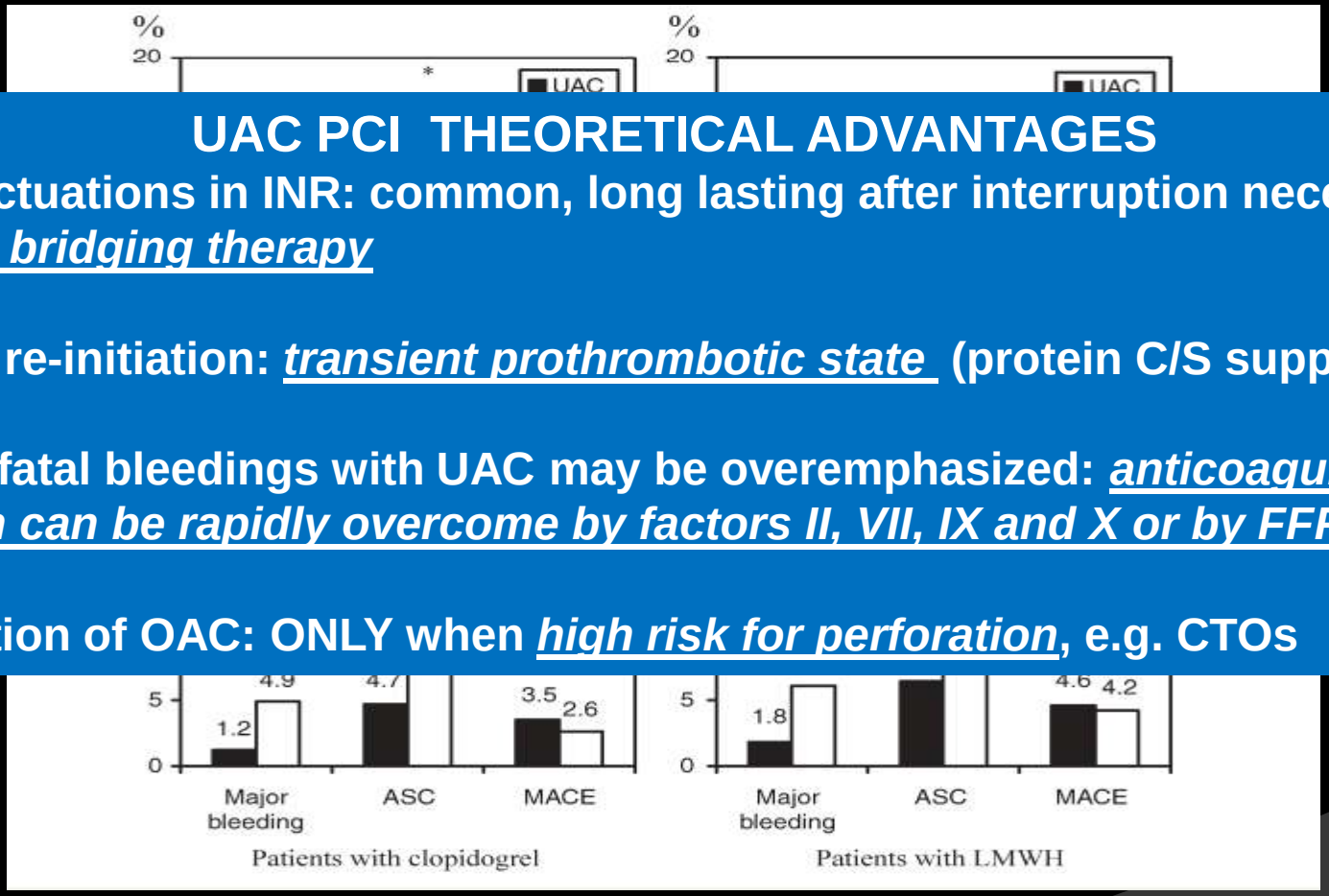
PERIPROCEDURAL ISSUES
to bridge or not to bridge?

- patients with ACS and on home warfarin: significantly less likely to undergo Cor. Angio – PCI
- General perception: OAC discontinuation prior to PCI until periprocedural INR level < 1.5–1.8
- strategy of temporary replacement of warfarin by DAPT: *NOT* a good option
- *Current guidelines*: bridging therapy with UFH or LMWH if high risk for TE
- Recommendations based on circumstantial evidence: no RCTs
- *Spyropoulos et al*.:major bleeding of 3.3% UFH vs 5.5% LMWH in 901pts
- *MacDonald et al*.: 4.2% of 119 pts. enoxaparin-associated access site complications during LMWH bridging therapy after cardiac catheterisation
- *UFH BETTER THAN LMWH FOR BRIDGING TO MANAGE OAC FOR PCI?*

•Spyropoulos A. Perioperative bridging interruption with heparin for the patient receiving long-term anticoagulation.
Curr Opin Pulm Med 2005; 11: 373–379.
•Spyropoulos A. Clinical outcomes with unfractionated heparin or low molecular weight heparin as bridging therapy in patients on long term oral anticoagulants: the REGIMEN registry.
J Tromb Haemost 2006; 4: 1246 – 1252
•Mc Donald L.Post cardiac cathetirization access site complications and low molecular weight heparin following cardiac cathetirization
J Invasive Cardiol 2003; 15: 60 -62

PERIPROCEDURAL ISSUES

to bridge or not to bridge?



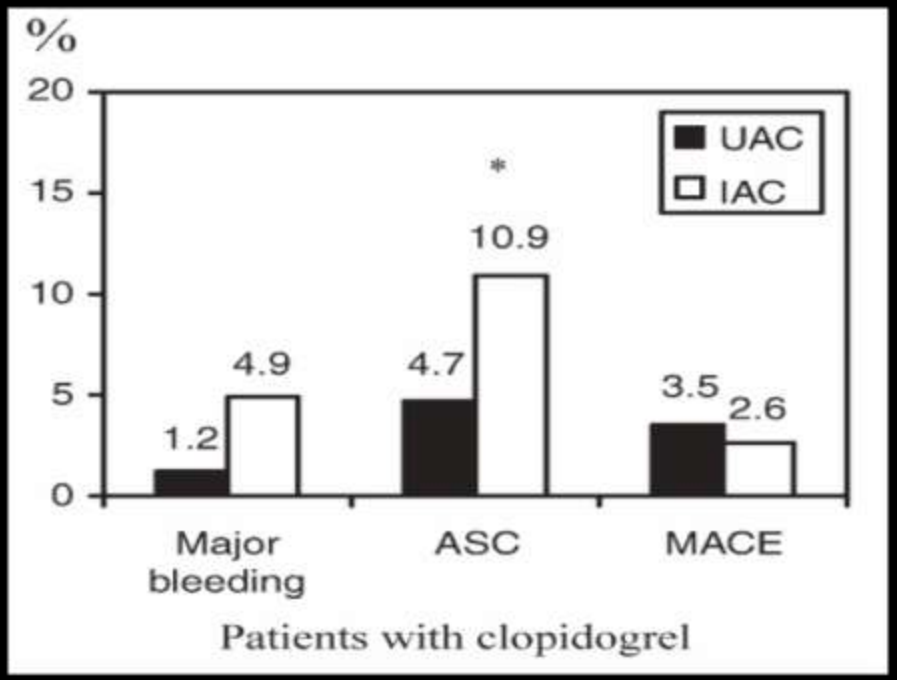
UAC PCI THEORETICAL ADVANTAGES

- **Wide fluctuations in INR: common, long lasting after interruption necessitating *prolonged bridging therapy***
- **warfarin re-initiation: *transient prothrombotic state* (protein C/S suppression)**
- **fear for fatal bleedings with UAC may be overemphasized: *anticoagulant effect of warfarin can be rapidly overcome by factors II, VII, IX and X or by FFP***
- **Interruption of OAC: ONLY when *high risk for perforation*, e.g. CTOs**

Karjalainen P et al. Safety of percutaneous coronary intervention during uninterrupted oral anticoagulant treatment. Eur Heart J 2008; 29: 1001–1010.

PERIPROCEDURAL ISSUES
aspirin and clopidogrel

- ASA: in all patients prior to any PCI procedures
- Clopidogrel: pretreatment whenever it can be accomplished



Karjalainen P et al. Safety of percutaneous coronary intervention during uninterrupted oral anticoagulant treatment. Eur Heart J 2008; 29: 1001–1010.

Rubboli A et al. Antithrombotic therapy in patients treated with oral anticoagulation undergoing coronary artery stenting. An expert consensus document with focus on atrial fibrillation. Ann Med 2008; 40: 428–436.

WOEST

ESC, Hotline III, Munchen, August 28th, 2012

The WOEST Trial: First randomised trial comparing two regimens with and without aspirin in patients on oral anticoagulant therapy undergoing coronary stenting

Willem Dewilde, Tom Oirbans, Freek Verheugt, Johannes Kelder, Bart De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius Heestermans, Marije Vis, Saman Rasoul, Kaioum Sheikjoesoef, Tom Vandendriessche, Carlos Van Mieghem, Kristoff Cornelis, Jeroen Vos, Guus Brueren, Nicolien Breet and Jurriën ten Berg

The **WOEST** Trial= **W**hat is the **O**ptimal antiplat**E**let and anticoagulant therapy in patients with oral anticoagulation and coronary **S**ten**T**ing

(clinicaltrials.gov NCT00769938)

WOEST

Study Design

1:1 Randomisation:

Double therapy group:

OAC + 75mg Clopidogrel qd

1 month minimum after BMS

1 year after DES

Triple therapy group

OAC + 75mg Clopidogrel qd + 80mg Aspirin qd

1 month minimum after BMS

1 year after DES

Follow up: **1 year**

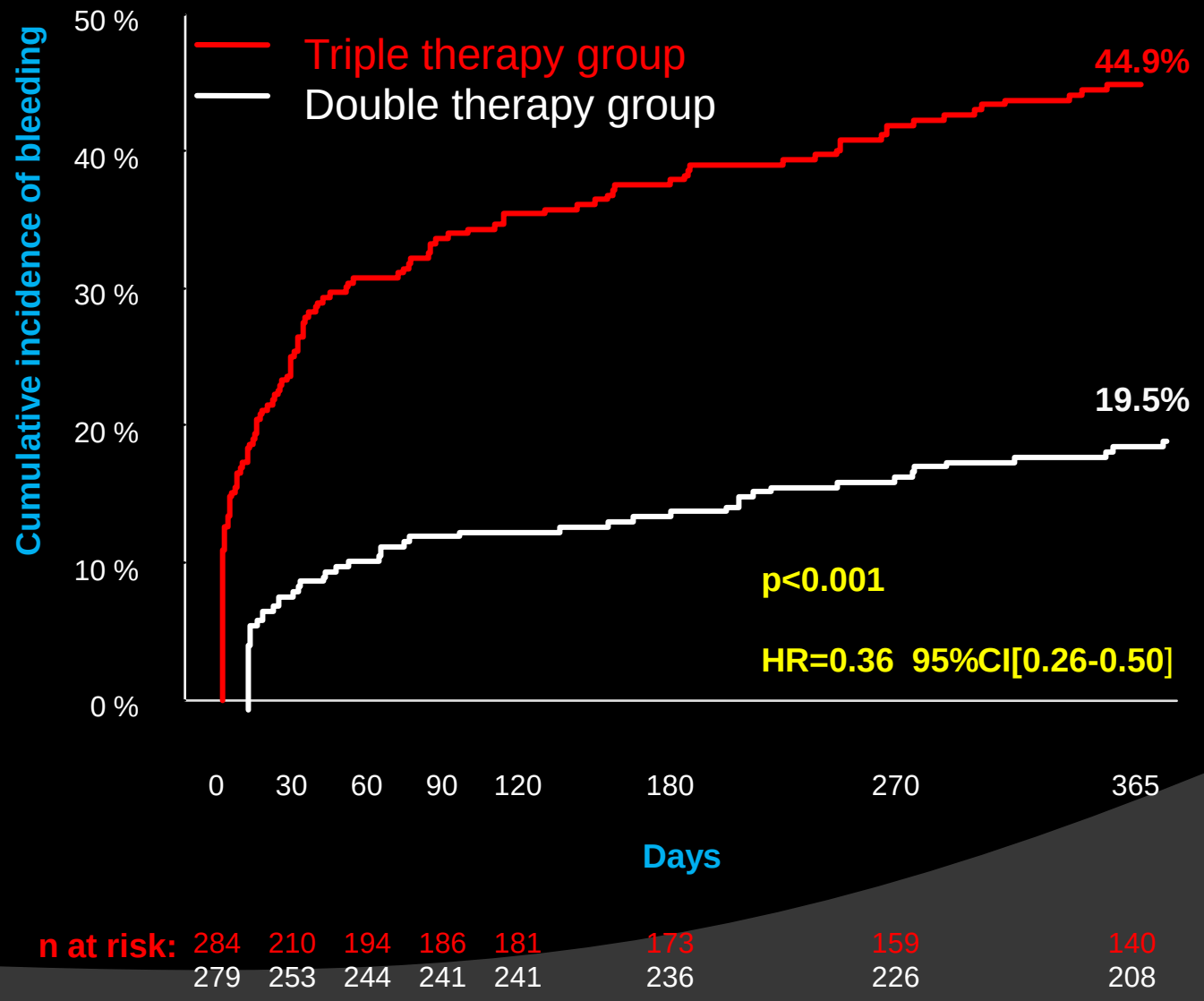
Primary Endpoint: **The occurence of all bleeding events (TIMI criteria)**

Secondary Endpoints:

- **Combination of stroke, death, myocardial infarction, stent thrombosis and target vessel revascularisation**
- **All individual components of primary and secondary endpoints**

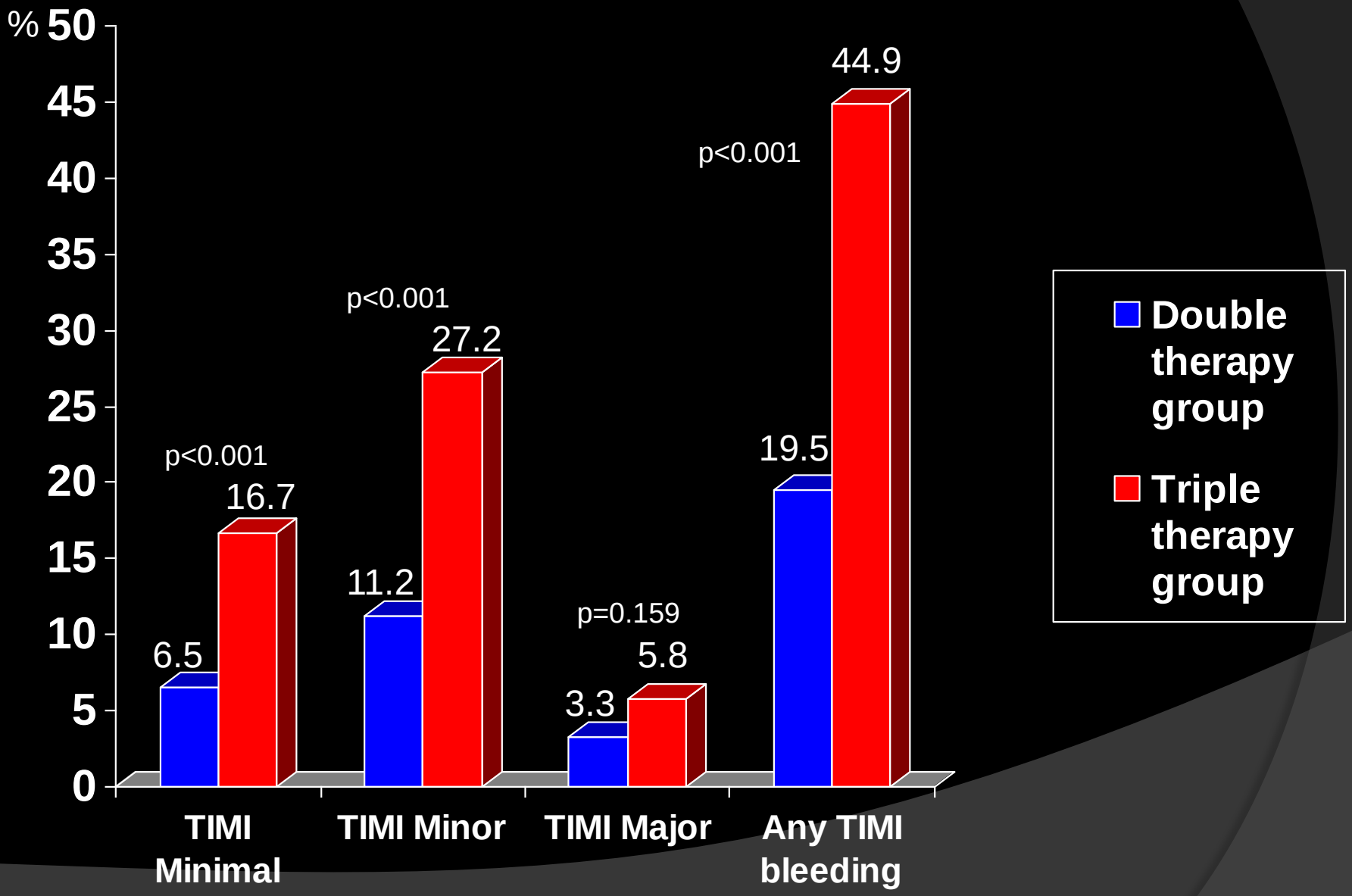
WOEST

Primary Endpoint: Total number of TIMI bleeding events



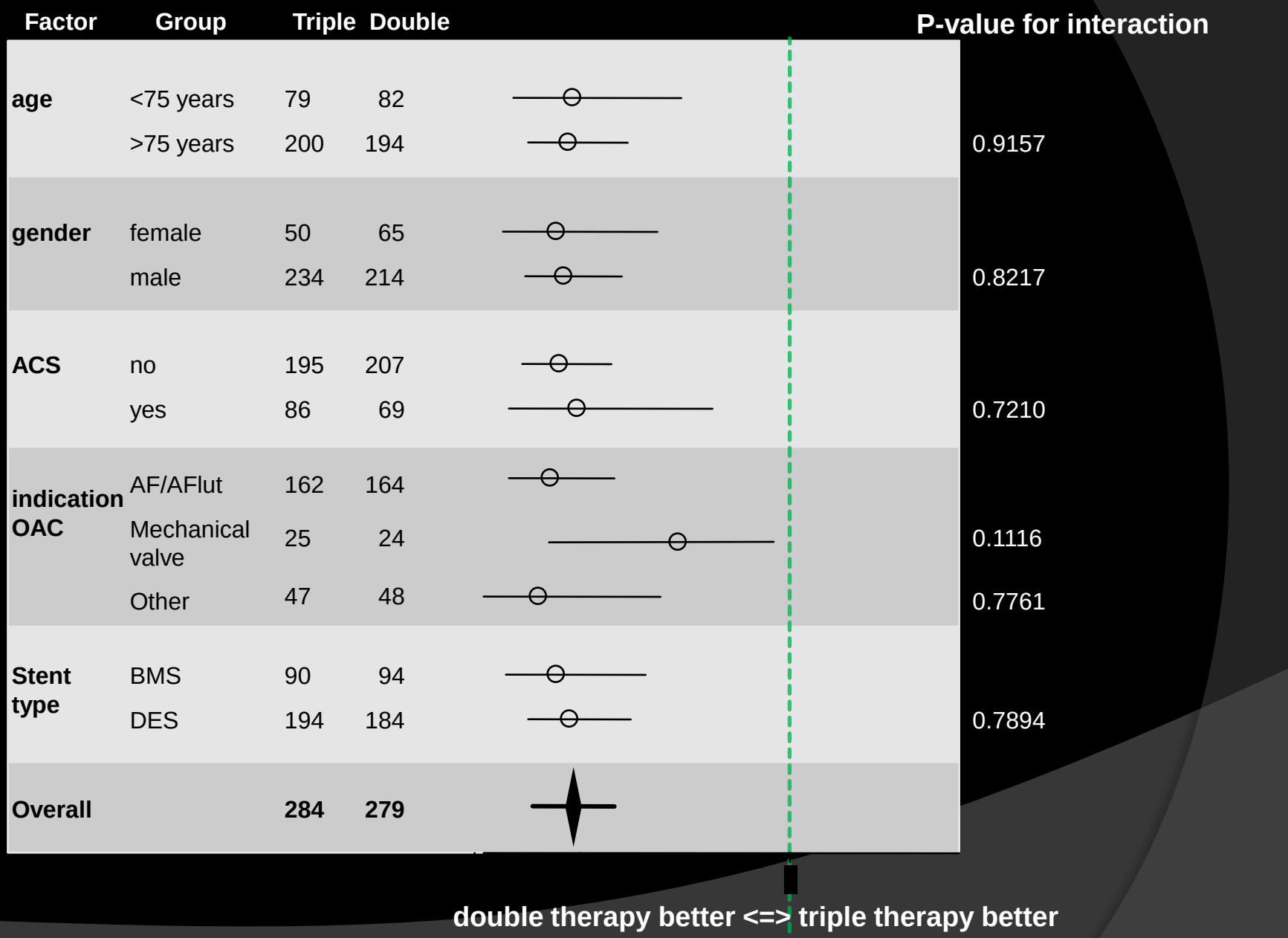
WOEST

Primary Endpoint: Bleeding events TIMI classification



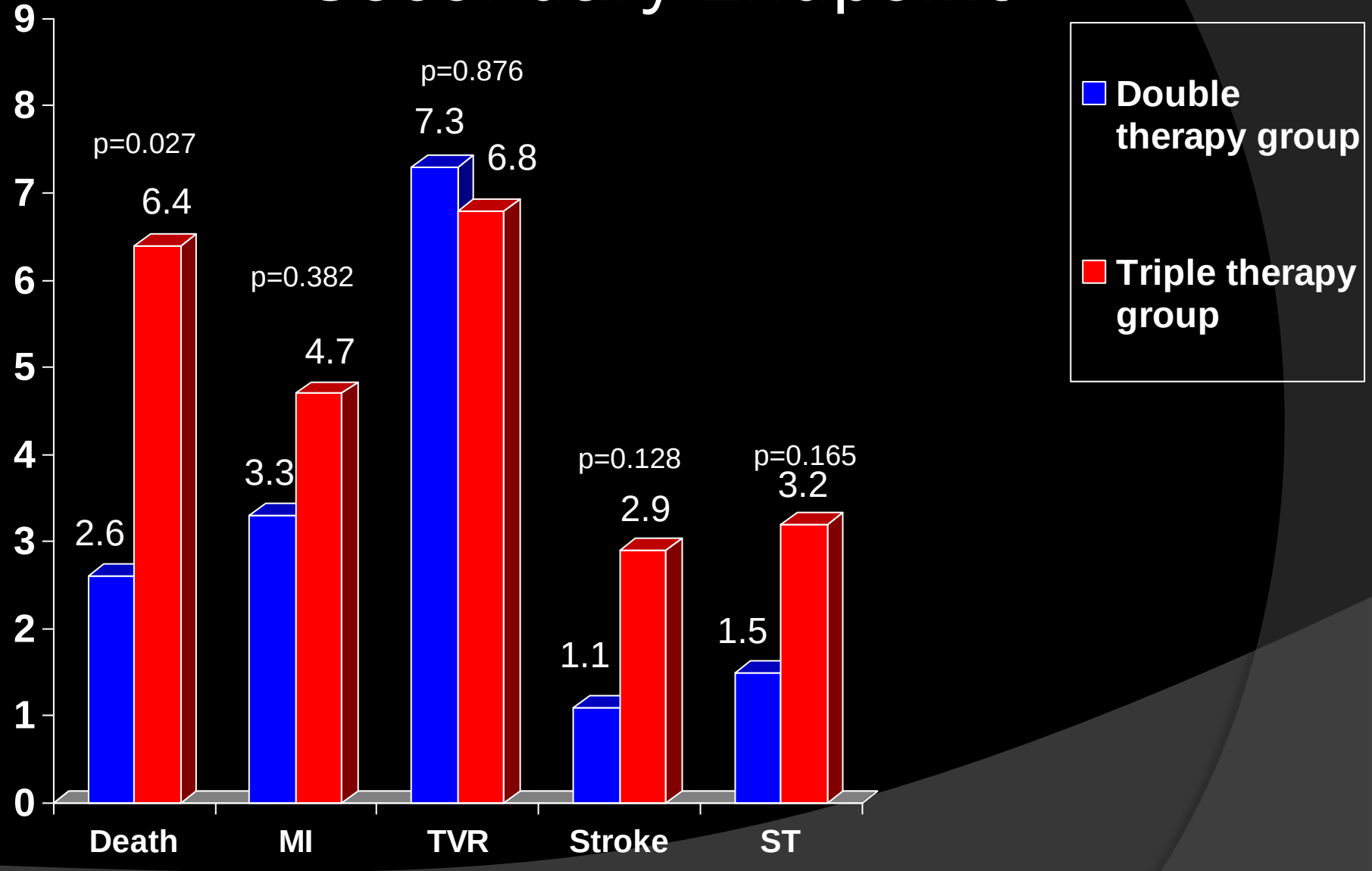
WOEST

Forest plot of primary endpoint Hazard Ratios



WOEST

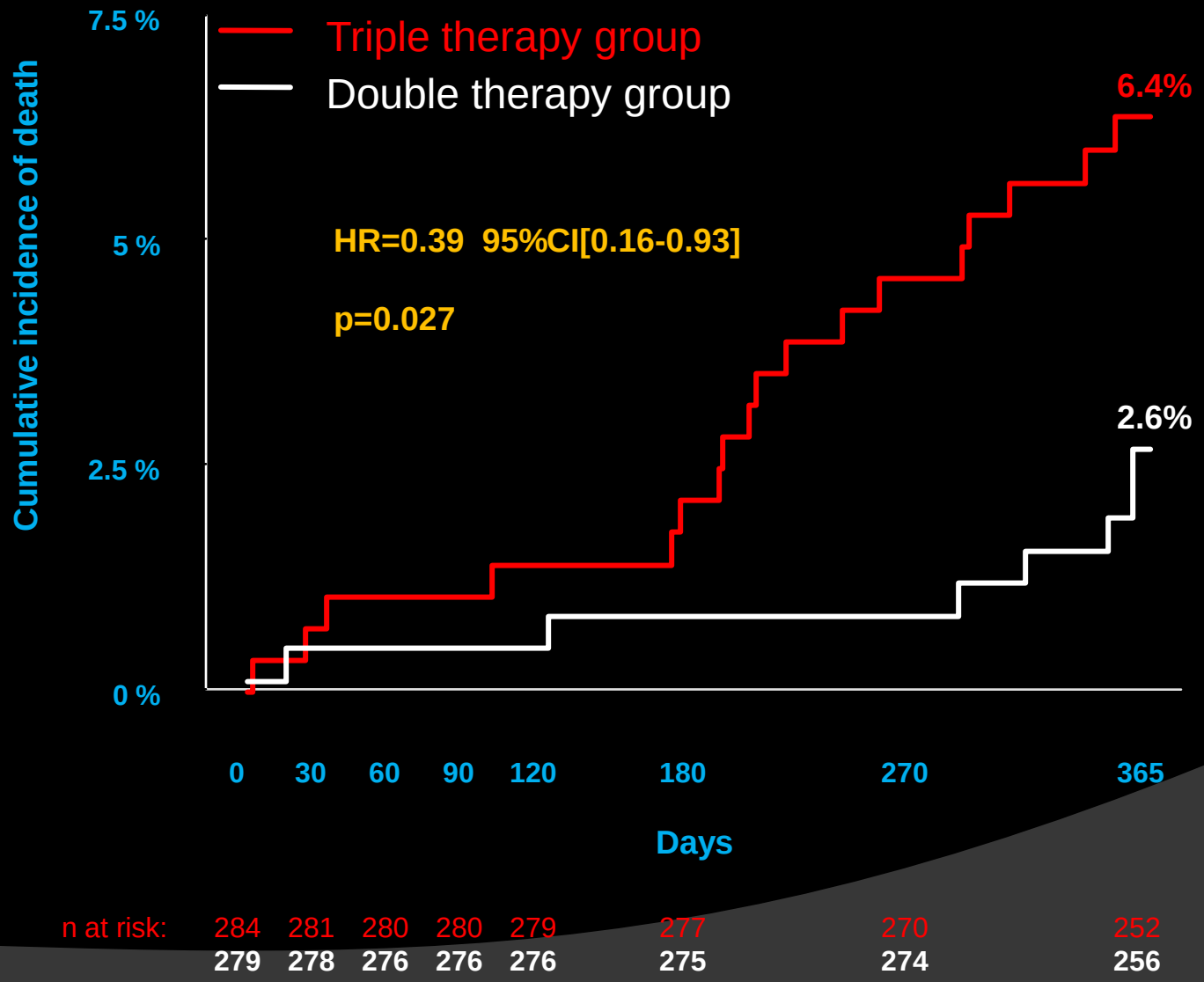
Secondary Endpoint



MI=any myocardial infarction; TVR= target vessel revascularisation (PCI + CABG); ST= stent thrombosis

WOEST

All-Cause Mortality



PERIPROCEDURAL ISSUES
Glycoprotein IIb/ IIIa inhibitors (GPI)

- no safety data: on warfarin-treated pts. have been excluded from all GPIIb/IIIa RCTs
- CRUSADE Registry: GPI use was associated with increased in-hospital risk of major bleeding (13.8% vs 9.0%) and transfusions (10.8% vs 9.1%) in pts on OAC
- use of GPIs in the cath lab varies between 3% -71% on OAC pts.
- 10 clinical trials assessing the efficacy and safety of various antithrombotic medications in ACS: new AF in 7% of the randomised pts. x four-fold increase in moderate or severe bleeding in NSTEMI pts randomised to GPI
- AVOID if use is not indicated: *ONLY massive intraluminal thrombi*

•Lopes R et al. Short- and long-term outcomes following atrial fibrillation in patients with acute coronary syndromes with or without ST-segment elevation. Heart 2008; 94: 867–873.

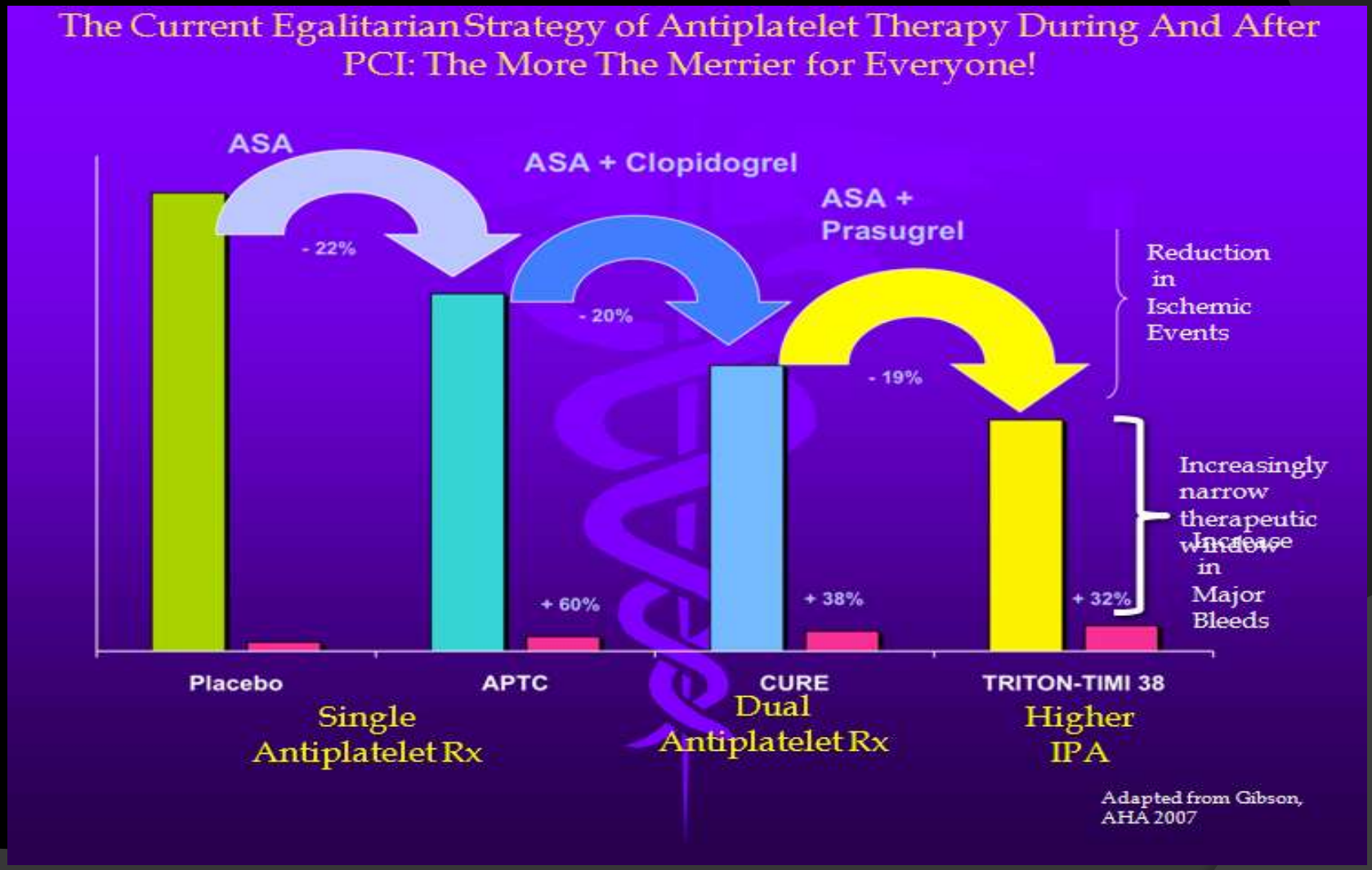
•Kastrati A et al.Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment Study Investigators. A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel.
N Engl J Med 2004; 350: 232–238.

•Kastrati A et al.Intracoronary Stenting and Antithrombotic: Regimen Rapid Early Action for Coronary Treatment 2 (ISAR-REACT 2) Trial Investigators. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. J Am Med Assoc 2006; 295: 1531–1538.

PERIPROCEDURAL ISSUES

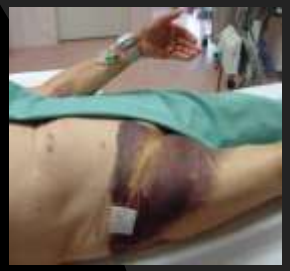
new P2Y12 antagonists:

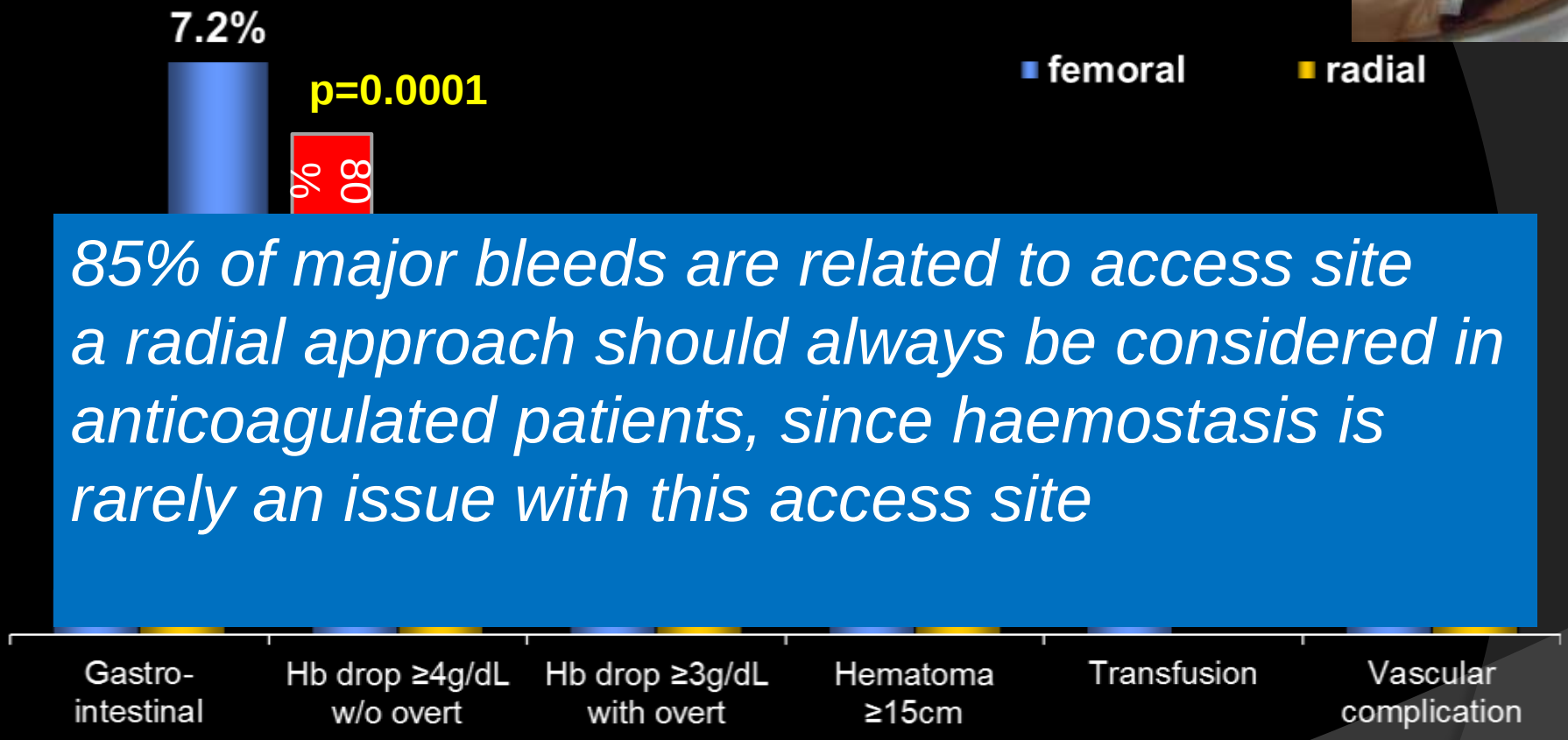
"*a lawsuit waiting to happen*"



PERIPROCEDURAL ISSUES

ACCESS SITE



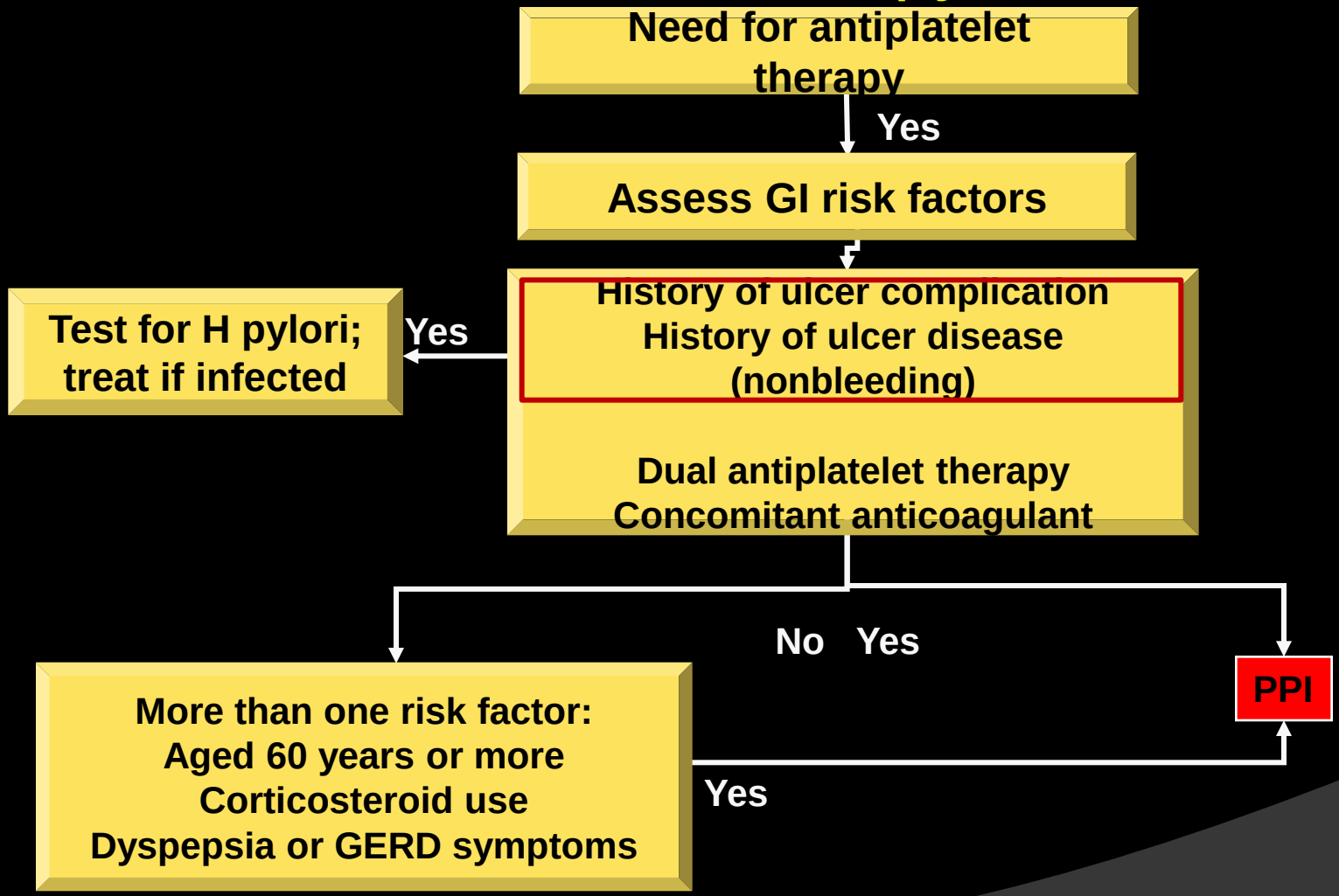


85% of major bleeds are related to access site
a radial approach should always be considered in anticoagulated patients, since haemostasis is rarely an issue with this access site

TCT 2012

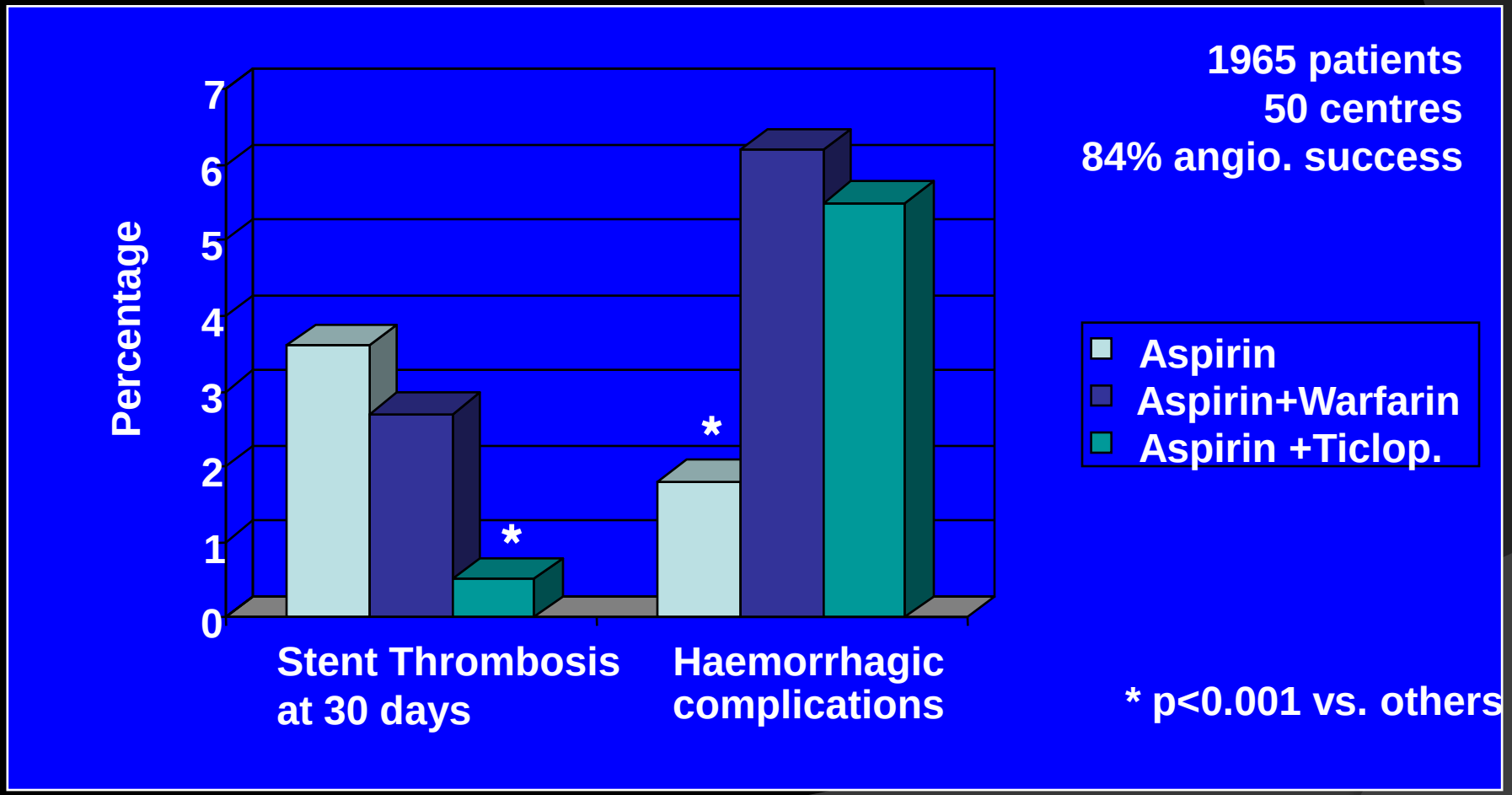
PERIPROCEDURAL ISSUES

Algorithm to Assess GI Risk With Antiplatelet Therapy



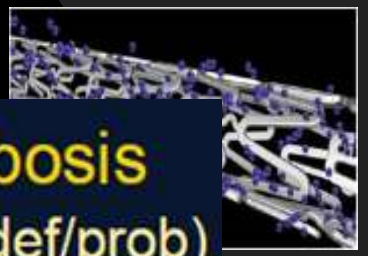
Bhatt D.ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol.2008 Oct 28;52(18):1502-17

STENT SELECTION
The STARS Trial



Leon MB et al.Coronary-artery stents--gauging, gorging, and gouging. NEJM 1998;339:1702-4

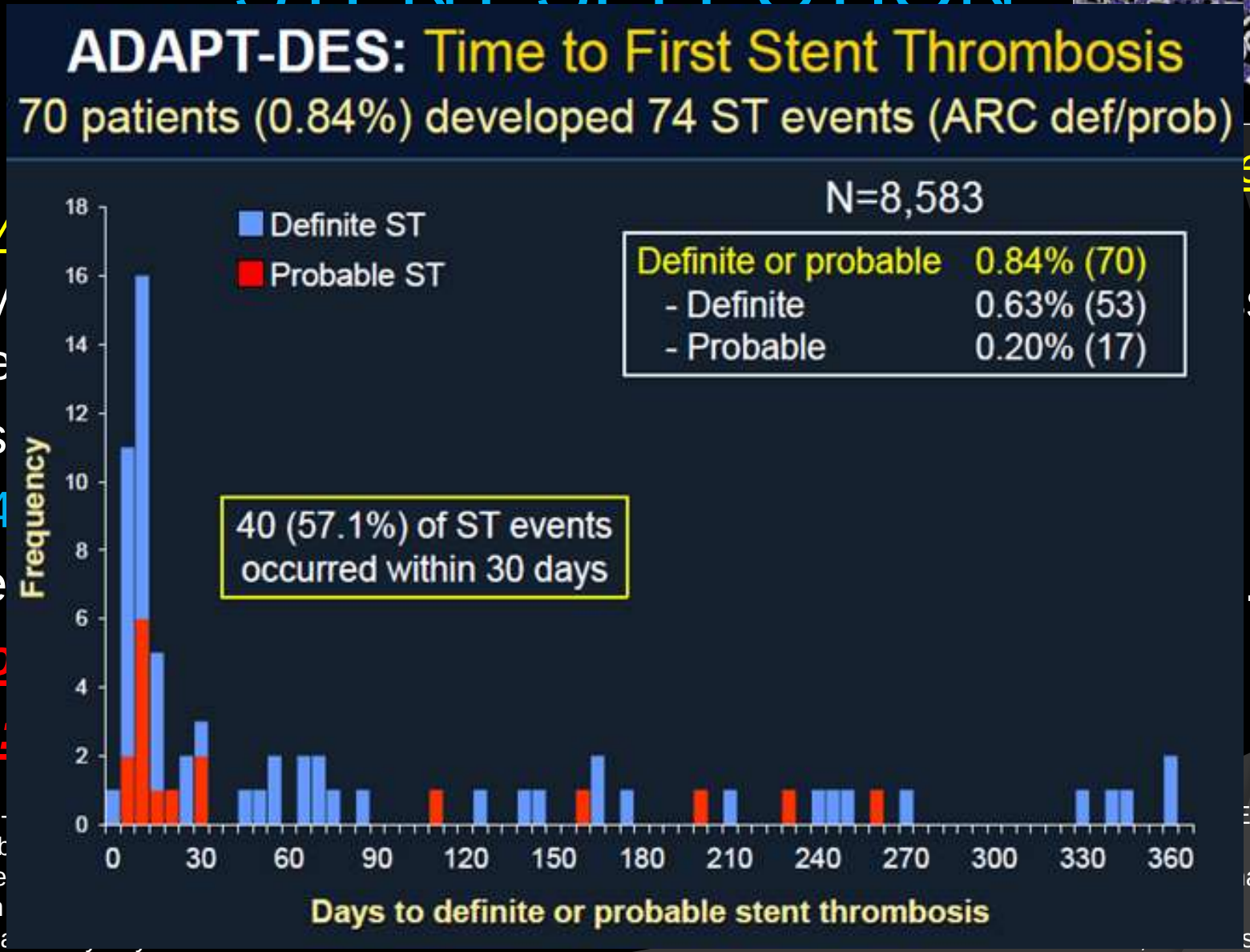
STENT SELECTION



- 1st
- BM
- BM
- les
- 0.4
- Re
- Mo
- MI

ADAPT-DES: Time to First Stent Thrombosis

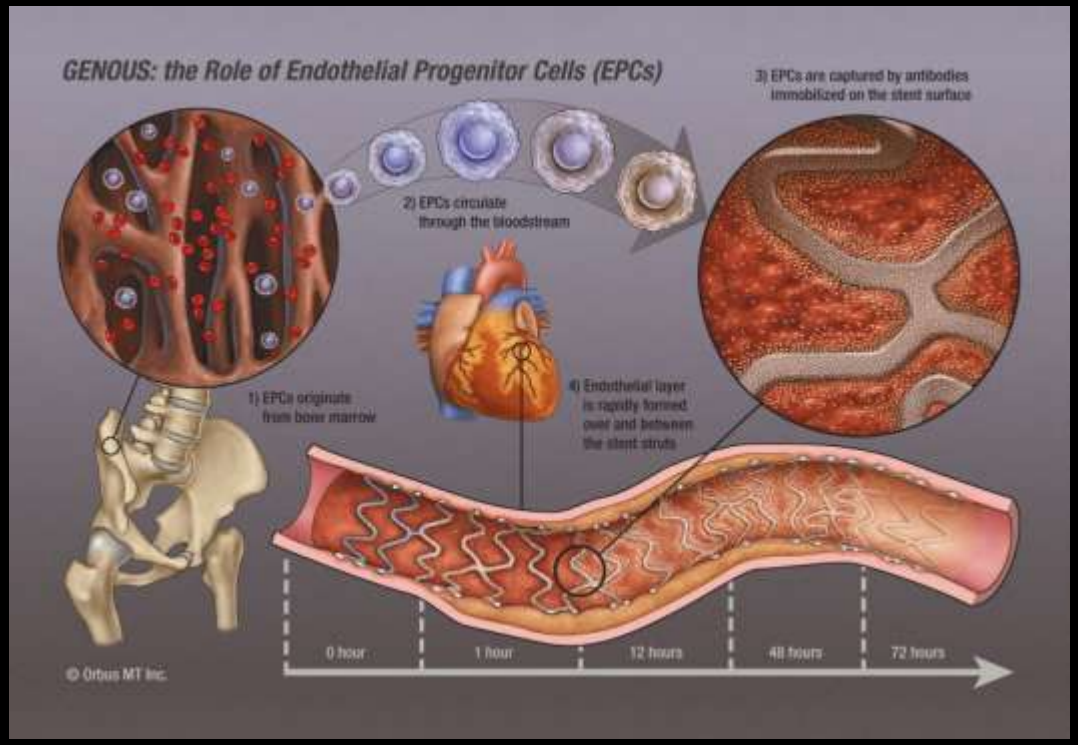
70 patients (0.84%) developed 74 ST events (ARC def/prob)



•de la Torre- Estudio Espanol sob
•Wenawese ary intervention
•Ong AT et a s, or paclitaxel stent implantation. J Am Coll Cardiol 2005; 45: 947–953.
•Roukoz H et al. Comprehensive meta-analysis on drugelutingstents versus bare-metal stents during extended follow-up. Am J Med 2009; 122: 581 e1–10.

STENT SELECTION

- BMS STENT OF CHOICE



- avoid DES: use only in high risk pt. (ie. DM)
- If DES mandatory: 3nd GEN

Crude estimates of risk for each adverse outcome (low and high)

- ***Stroke risk*** (CHADS2 ≥1) on warfarin average 1.5%(1.0% for CHADS2=1 to 7% for CHADS2=5–6) per year (or adjusted stroke rates from 1.95 %/year to >12.5%/year)

- ***Stent thrombosis*** (first year) on DAPT = 1.5% (1 to 5%) but five- to 36-fold higher for premature discontinuation within the first month, and 2.5– to five-fold if between one and six months. On DAPT the risk is greatest in the first month.

- ***Major bleeding*** requiring hospitalisation on triple therapy= 6 to 15%/year; warfarin and one antiplatelet agent = 6–12%/year; and on either DAPT or warfarin alone 2.5– 4%/year. The rate is highest within the first 30 days after the procedure.

Faxon D. Consensus document: Antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting.
Thromb Haemost 2011 106: 571–584

Consensus Document of the ESC Working Group on Thrombosis

Recommended antithrombotic strategies following coronary artery stenting in patients with atrial fibrillation at moderate-to-high thromboembolic risk (in whom oral anticoagulation therapy is required). Thrombosis and Haemostasis 103.1/2010

Haemorrhagic risk	Clinical setting	Stent implanted	Recommendations
Low or intermediate	Elective	Bare metal	***1 month:*** triple therapy of warfarin (INR 2.0–2.5) + aspirin ≥100 mg/day + clopidogrel 75 mg/day + gastric protection
			lifelong: warfarin (INR 2.0–3.0) alone.
	Elective	Drug eluting	***3 (-olimus group) to 6 (paclitaxel) months:*** triple therapy of warfarin (INR 2.0–2.5) + aspirin ≥100 mg/day + clopidogrel 75 mg/day;
			up to 12th month: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day* (or aspirin 100 mg/day);
			lifelong: warfarin (INR 2.0–3.0) alone.
	ACS	Bare metal/drug eluting	***6 months:*** triple therapy of warfarin (INR 2.0–2.5) + aspirin ≥100 mg/day + clopidogrel 75 mg/day;
			up to 12th month: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day* (or aspirin 100 mg/day);
			lifelong: warfarin (INR 2.0–3.0) alone.
High	Elective	Bare metal#	***2 to 4 weeks:*** triple therapy of warfarin (INR 2.0–2.5) + aspirin ≥100 mg/day + clopidogrel 75 mg/day;
			lifelong: warfarin (INR 2.0–3.0) alone.
	ACS	Bare metal#	***4 weeks:*** triple therapy of warfarin (INR 2.0–2.5) + aspirin ≥100 mg/day + clopidogrel 75 mg/day ;
			up to 12th month: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day*(or aspirin 100 mg/day); mg/day);
			lifelong: warfarin (INR 2.0–3.0) alone.

* combination of warfarin (INR 2.0–3.0) + aspirin = 100 mg/day (with PPI, if indicated) may be considered as an alternative. # drug eluting stents should be avoided. INR = international normalized ratio; PPI = proton pump inhibitors; ACS = acute coronary syndrome

Expert consensus recommendations of a practical, pragmatic approach to management of patients with AF who need anticoagulation with Vitamin K antagonists

1.Elective

- BMS — stents of choice in patients with AF and stable coronary artery
- DES — should be avoided or strictly limited to those clinical and/or anatomical situations, such as long lesions, small vessels, diabetes, etc. where a significant benefit is expected
- If BMS: *TT for 4 weeks*
  lifelong: VKA alone
- If DES: *TT for 3 months (-olimus group)/ 6 months (paclitaxel)*
  combination of warfarin +clop. 75mg day/or ASA ≥100mg day up to 12th month
  lifelong: VKA alone
- If TT/AP+ W: gastric protection with either PPIs, H2-receptor antagonists or antacids depending on the bleeding and thrombotic risks of the individual patient

- Where OAC patients are at moderate-high risk of thromboembolism,an uninterrupted anticoagulation strategy can be the preferred strategy and radial access used as the first choice even during therapeutic anticoagulation (INR 2–3).
- When the procedures require interruption of OAC for longer than 48 hours in high-risk patients, UFH may be administered. LMWH (enoxaparin, dalteparin) is an alternative, although the efficacy of this strategy in this situation is uncertain. There may actually be an excess bleeding risk associated with such “bridging“ therapies.
- *OAC in combination with clopidogrel and/or low-dose aspirin: target INR of 2.0–2.5*

Expert consensus recommendations of a practical, pragmatic approach to management of patients with AF who need anticoagulation with Vitamin K antagonists

2. NSTEACS-ACS

- NSTE ACS ± PC in pts. with AF: DAPT but in an AF patient at moderate-high risk of stroke, anticoagulation therapy should also be given/continued (Class IIa, Level of Evidence: B)

- Acute setting: pts. are often given ASA + clop.+heparin (whether UFH or LMWH) or bivalirudin and/or a GPI. Given the risk of bleeding with such combination antithrombotic therapies, it may be prudent to stop OAC therapy, and administer antithrombins or GPIs only if INR ≤2.

- DES should be avoided

- anticoagulated pts. at very high risk of thromboembolism: uninterrupted strategy of OAC can be the preferred strategy and radial access used as the first choice even during therapeutic anticoagulation (INR 2–3)

- *For medium to chronic management:*

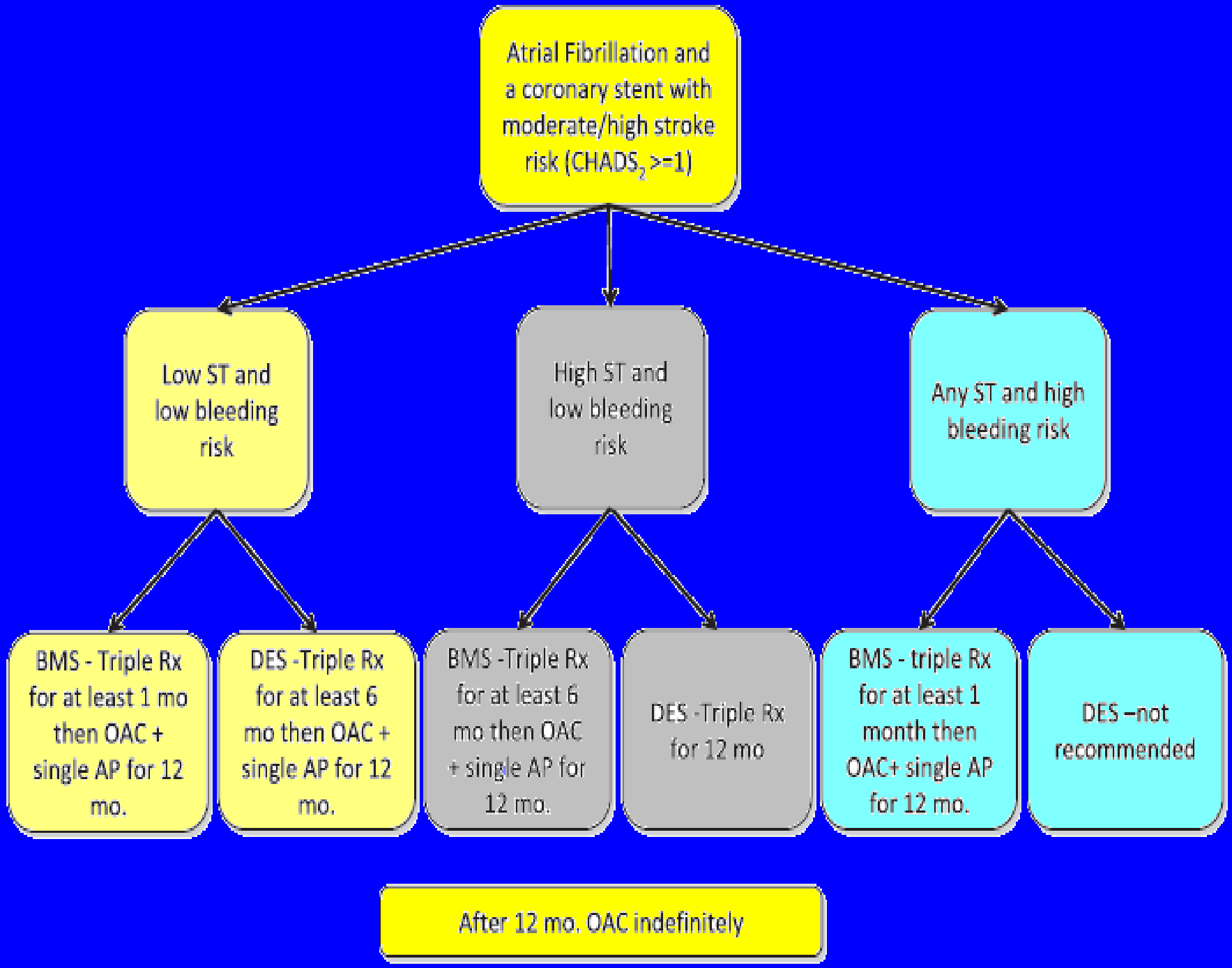
  TT in the short term (3–6 months)
  longer in selected patients at low bleeding risk
  high risk pts.: combination of warfarin +clop/ASA up to 12th month

- *OAC in combination with clopidogrel and/or low-dose aspirin: target INR of 2.0–2.*

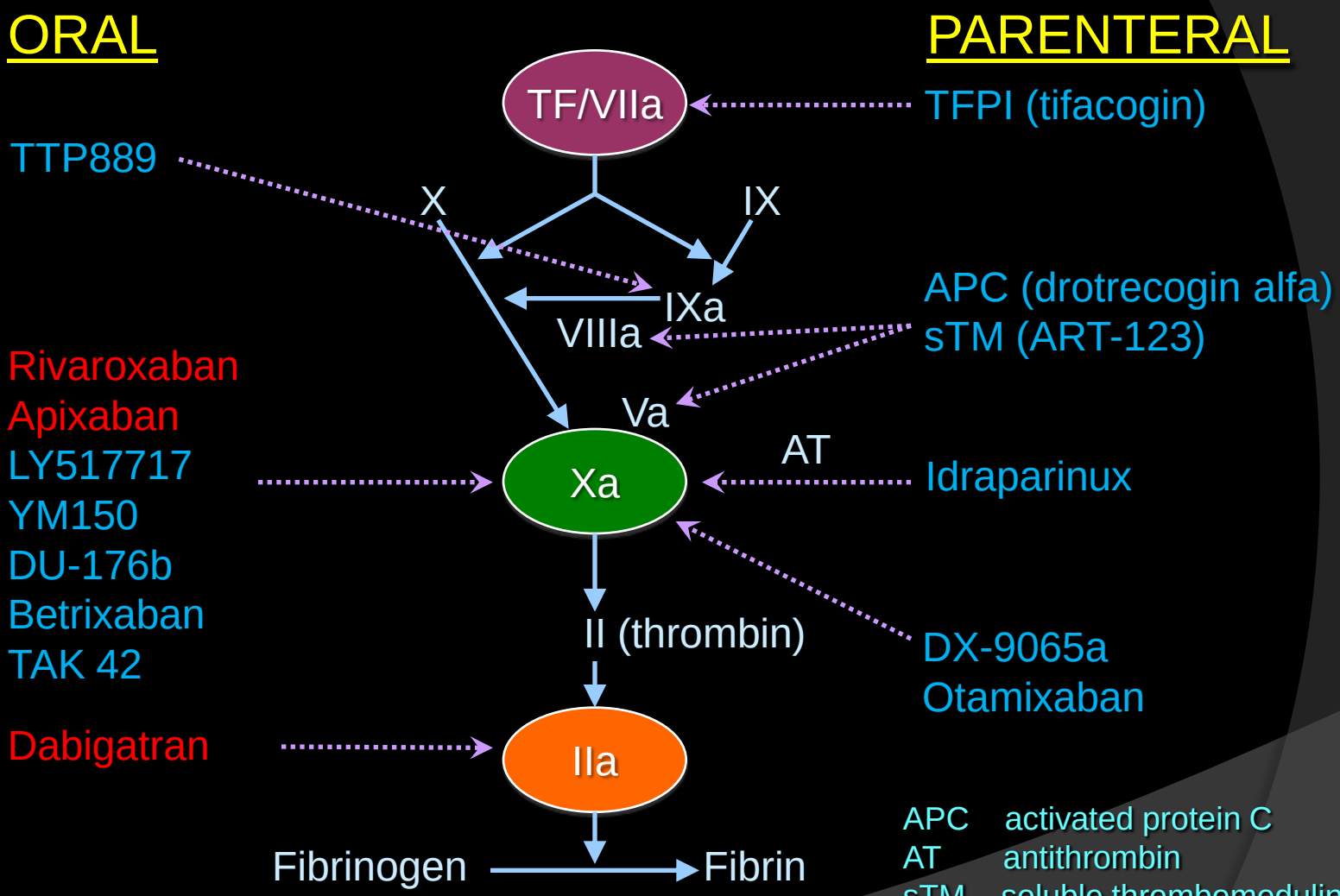
Expert consensus recommendations of a practical, pragmatic approach to management of patients with AF who need anticoagulation with Vitamin K antagonists

3. primary PCI

- primary PCI pt. with AF: high thrombus load, bivalirudin or GPIs (preferably abciximab) as a 'bail out' option.
- bivalirudin can be used as an alternative to heparin + GPI
- Mechanical thrombus removal (e.g. thrombus aspiration) is encouraged.
- *risk of bleeding with such combination antithrombotic therapies: prudent to stop OAC therapy.*
- GPIs/ bivalirudin, not considered if INR is >2, except in a 'bail out' option
- heparin: 200–250 seconds in patients receiving a GPI
  250–300 seconds in patients not receiving a GPI
- Radial access
- *For medium to chronic management:* *TT in the short term (3–6 months)*
  longer in selected patients at low bleeding risk
  high risk pts.: combination of warfarin +clop/ASA up to 12th month


Atrial Fibrillation and a coronary stent with moderate/high stroke risk ($CHADS_2$ >=1)
Low ST and low bleeding risk
High ST and low bleeding risk
Any ST and high bleeding risk
BMS - Triple Rx for at least 1 mo then OAC + single AP for 12 mo.
DES -Triple Rx for at least 6 mo then OAC + single AP for 12 mo.
BMS -Triple Rx for at least 6 mo then OAC + single AP for 12 mo.
DES -Triple Rx for 12 mo
BMS - triple Rx for at least 1 month then OAC+ single AP for 12 mo.
DES –not recommended
After 12 mo. OAC indefinitely

Investigational Anticoagulant Targets



APC activated protein C
AT antithrombin
sTM soluble thrombomodulin
TF tissue factor
FPI tissue factor pathway inhibitor

Weitz JI. Factor Xa or thrombin: is thrombin a better target? Thromb Haemost 2007; 5 Suppl 1:65-67.

Comparison of Features of New Anticoagulants With Those of Warfarin

Features	Warfarin	New Agents
Onset	Slow	Rapid
Dosing	Variable	Fixed
Food effect	Yes	No
Drug interactions	Many	Few
Monitoring	Yes	No
Half-life	Long	Short
Antidote	Yes	No

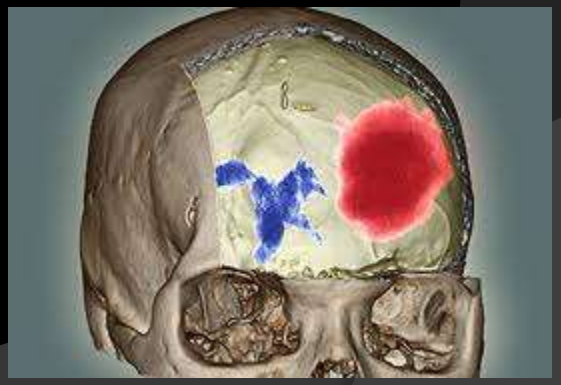
Comparison of Features of New Oral Anticoagulants in Advanced Stages of Development

Features	Rivaroxaban	Apixaban	Dabigatran Etexilate
Target	Xa	Xa	IIa
Molecular Weight	436	460	628
Prodrug	No	No	Yes
Bioavailability (%)	80	50	6
Time to peak (h)	3	3	2
Half-life (h)	9	9-14	12-17
Renal excretion (%)	65	25	80
Antidote	None	None	None

Intracerebral Hemorrhage

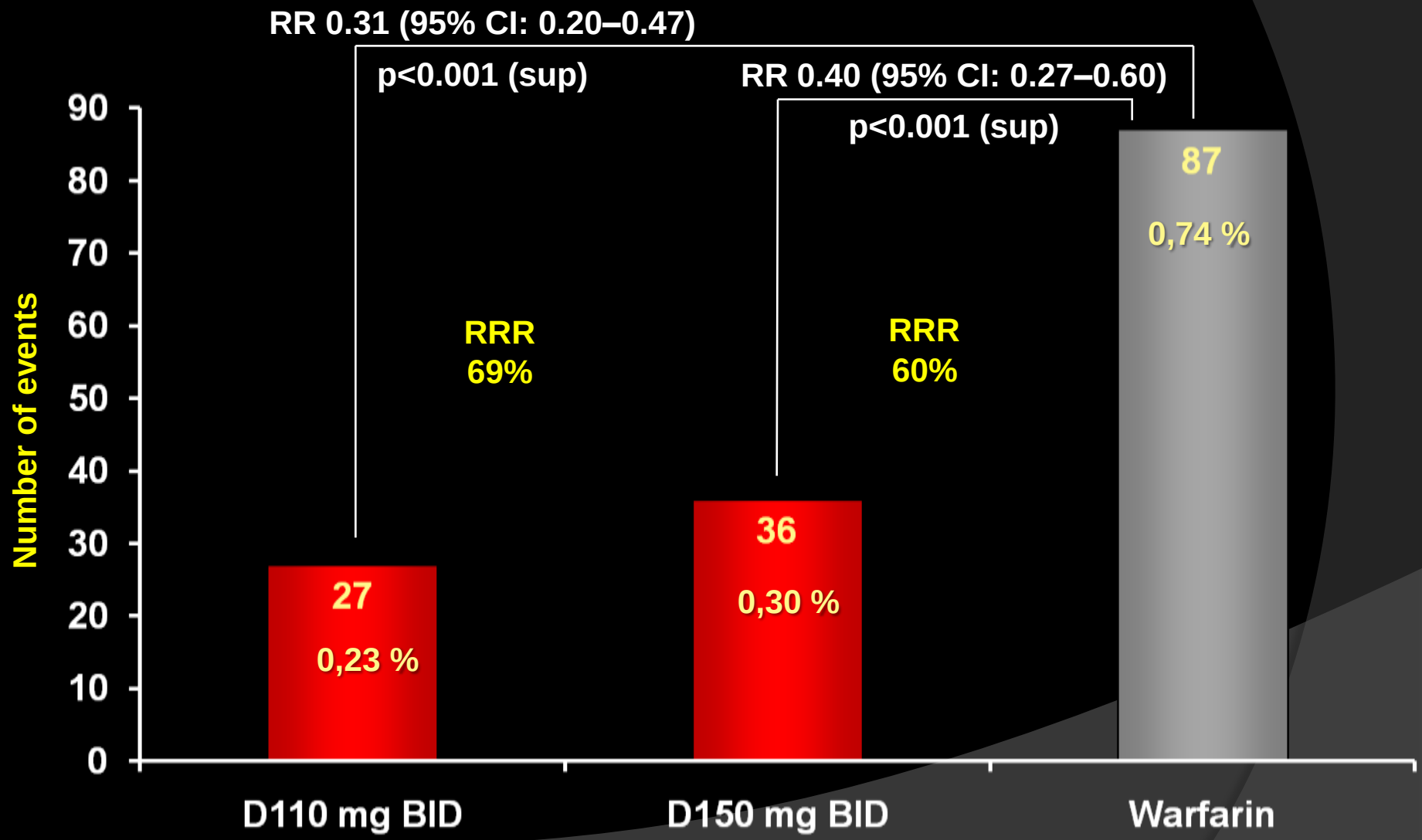
The Most Feared Complication of Antithrombotic Therapy

- >10% of intracerebral hemorrhages (ICH) occur in patients on antithrombotic therapy
- Aspirin increases the by ~ 40%
- Warfarin (INR 2–3) doubles the risk to 0.3–0.6%/year
- ICH during anticoagulation is catastrophic

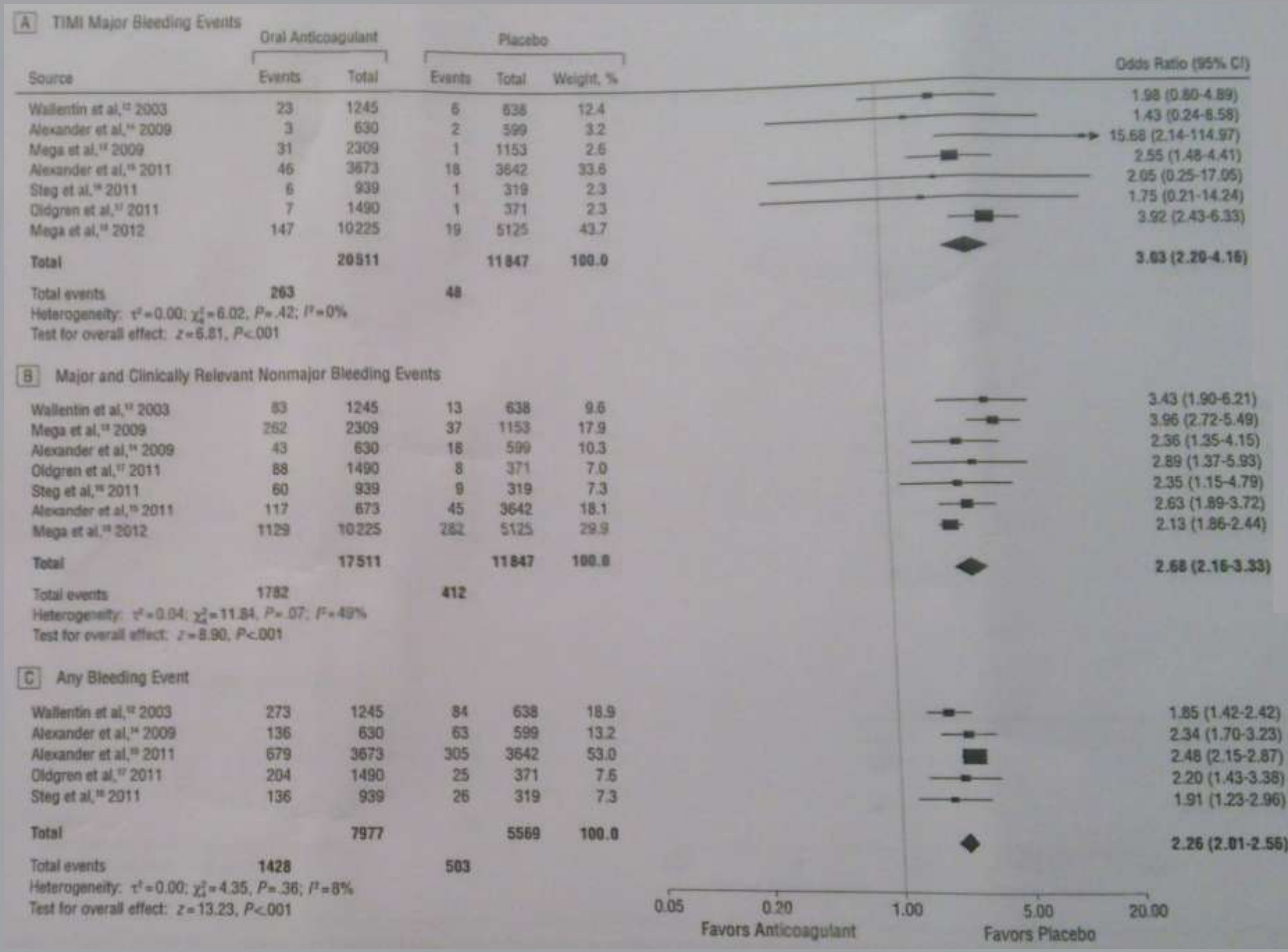


Hart RG. Avoiding central nervous system bleeding during antithrombotic therapy: recent data and ideas. Stroke 2005;36:1588

RE-LY: Intra-cranial Bleeding Rates



Connolly et al. Dabigatran versus warfarin in patients with atrial fibrillation. NEJM 2009, Sep 17;361(12):1139-1151


A TIMI Major Bleeding Events
Oral Anticoagulant
Placebo
Source
Events
Total
Events
Total
Weight, %
Odds Ratio (95% CI)
Wallentin et al,[12] 2003 23 1245 6 638 12.4 1.98 (0.80-4.89)
Alexander et al,[14] 2009 3 630 2 599 3.2 1.43 (0.24-8.58)
Mega et al,[13] 2009 31 2309 1 1153 2.6 15.68 (2.14-114.97)
Alexander et al,[15] 2011 46 3673 18 3642 33.6 2.55 (1.48-4.41)
Steg et al,[16] 2011 6 939 1 319 2.3 2.05 (0.25-17.05)
Oldgren et al,[17] 2011 7 1490 1 371 2.3 1.75 (0.21-14.24)
Mega et al,[18] 2012 147 10225 19 5125 43.7 3.92 (2.43-6.33)
Total 20511 11847 100.0 3.03 (2.20-4.16)
Total events 263 48
Heterogeneity: $\tau^2=0.00$; $\chi^2_6=6.02$, $P=.42$; $I^2=0\%$
Test for overall effect: $z=6.81$, $P<.001$
B Major and Clinically Relevant Nonmajor Bleeding Events
Wallentin et al,[12] 2003 83 1245 13 638 9.6 3.43 (1.90-6.21)
Mega et al,[13] 2009 262 2309 37 1153 17.9 3.96 (2.72-5.49)
Alexander et al,[14] 2009 43 630 16 599 10.3 2.36 (1.35-4.15)
Oldgren et al,[17] 2011 88 1490 8 371 7.0 2.89 (1.37-5.93)
Steg et al,[16] 2011 60 939 9 319 7.3 2.35 (1.15-4.79)
Alexander et al,[15] 2011 117 673 45 3642 18.1 2.63 (1.89-3.72)
Mega et al,[18] 2012 1129 10225 282 5125 29.9 2.13 (1.86-2.44)
Total 17511 11847 100.0 2.68 (2.16-3.33)
Total events 1782 412
Heterogeneity: $\tau^2=0.04$; $\chi^2_6=11.84$, $P=.07$; $I^2=49\%$
Test for overall effect: $z=8.90$, $P<.001$
C Any Bleeding Event
Wallentin et al,[12] 2003 273 1245 84 638 18.9 1.85 (1.42-2.42)
Alexander et al,[14] 2009 136 630 63 599 13.2 2.34 (1.70-3.23)
Alexander et al,[15] 2011 679 3673 305 3642 53.0 2.48 (2.15-2.87)
Oldgren et al,[17] 2011 204 1490 25 371 7.6 2.20 (1.43-3.38)
Steg et al,[16] 2011 136 939 26 319 7.3 1.91 (1.23-2.96)
Total 7977 5569 100.0 2.26 (2.01-2.56)
Total events 1428 503
Heterogeneity: $\tau^2=0.00$; $\chi^2_4=4.35$, $P=.36$; $I^2=8\%$
Test for overall effect: $z=13.23$, $P<.001$
0.05
0.20
1.00
5.00
20.00
Favors Anticoagulant
Favors Placebo

Alternatives to Anticoagulation

Atrial Fibrillation

CURRENT APPROACHES

Restoration and maintenance of sinus rhythm

- Antiarrhythmic drug therapy
- Catheter ablation
- Maze operation

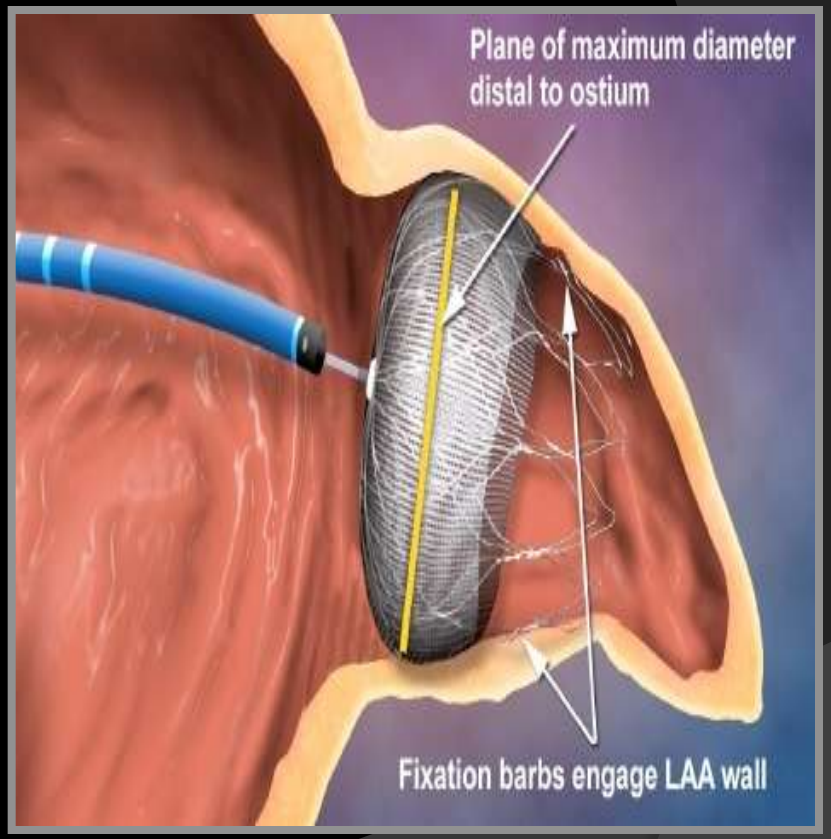
EMERGING APPROACHES

Obliteration of the LAA

- Trans-catheter occluding devices
- Thoracoscopic epicardial plication
- Amputation

LAA Device for AF
PROTECT-AF Study

- 707 patients with nonvalvular AF randomized to LAA device + 45 days of warfarin vs warfarin vs warfarin alone
- Primary efficacy end point of stroke, CV death, or systemic embolism was 3.0% (1.9-4.5) with device and 4.9% (2.8-7.1) with warfarin; [RR 0.62, 95% CI (0.35-1.25)]
- Primary safety end point of excessive bleeding, serious pericardial effusion, device embolization, or procedure-related stroke was 7.4% with device and 4.4% with warfarin; [RR 1.69, 95% CI (1.01-3.19)]



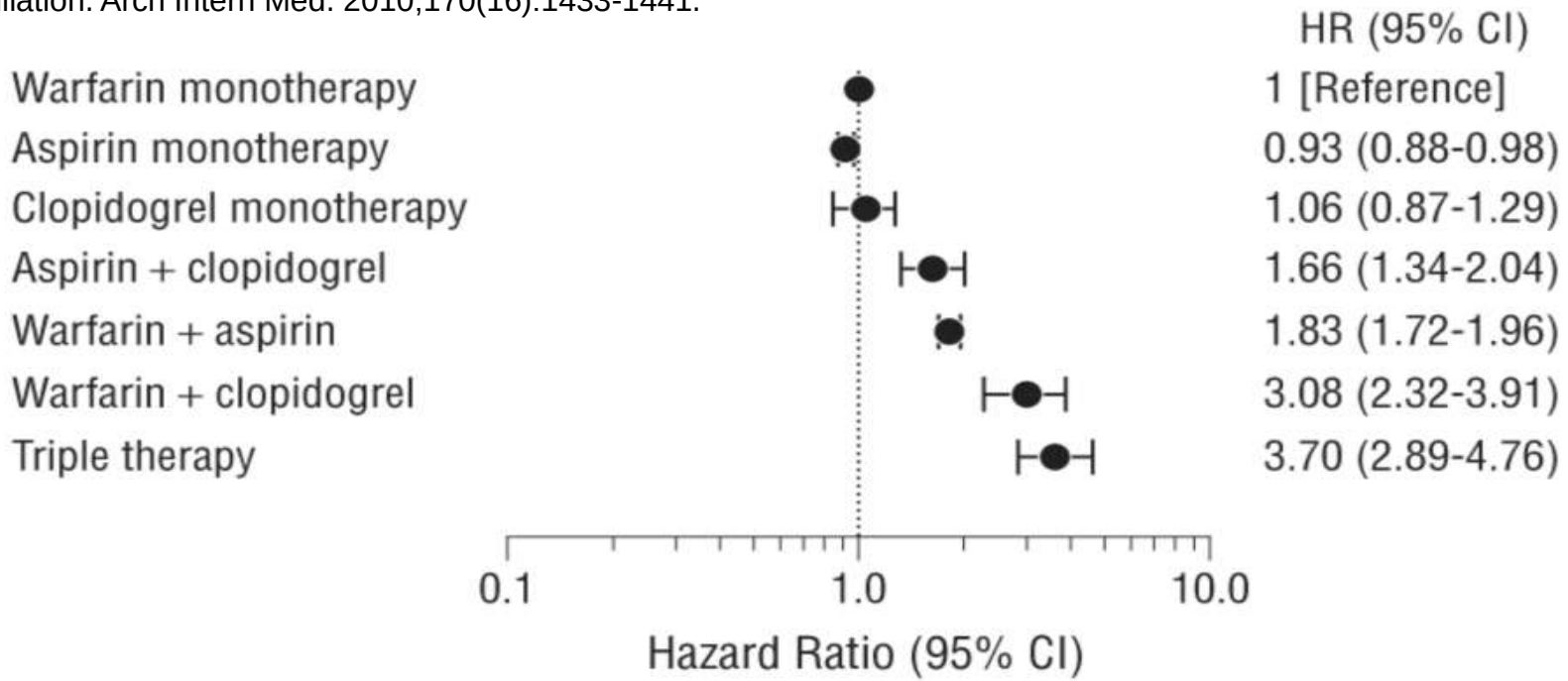
Holmes DR, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet. 2009;374:534-542.

MORE DATA NEEDED

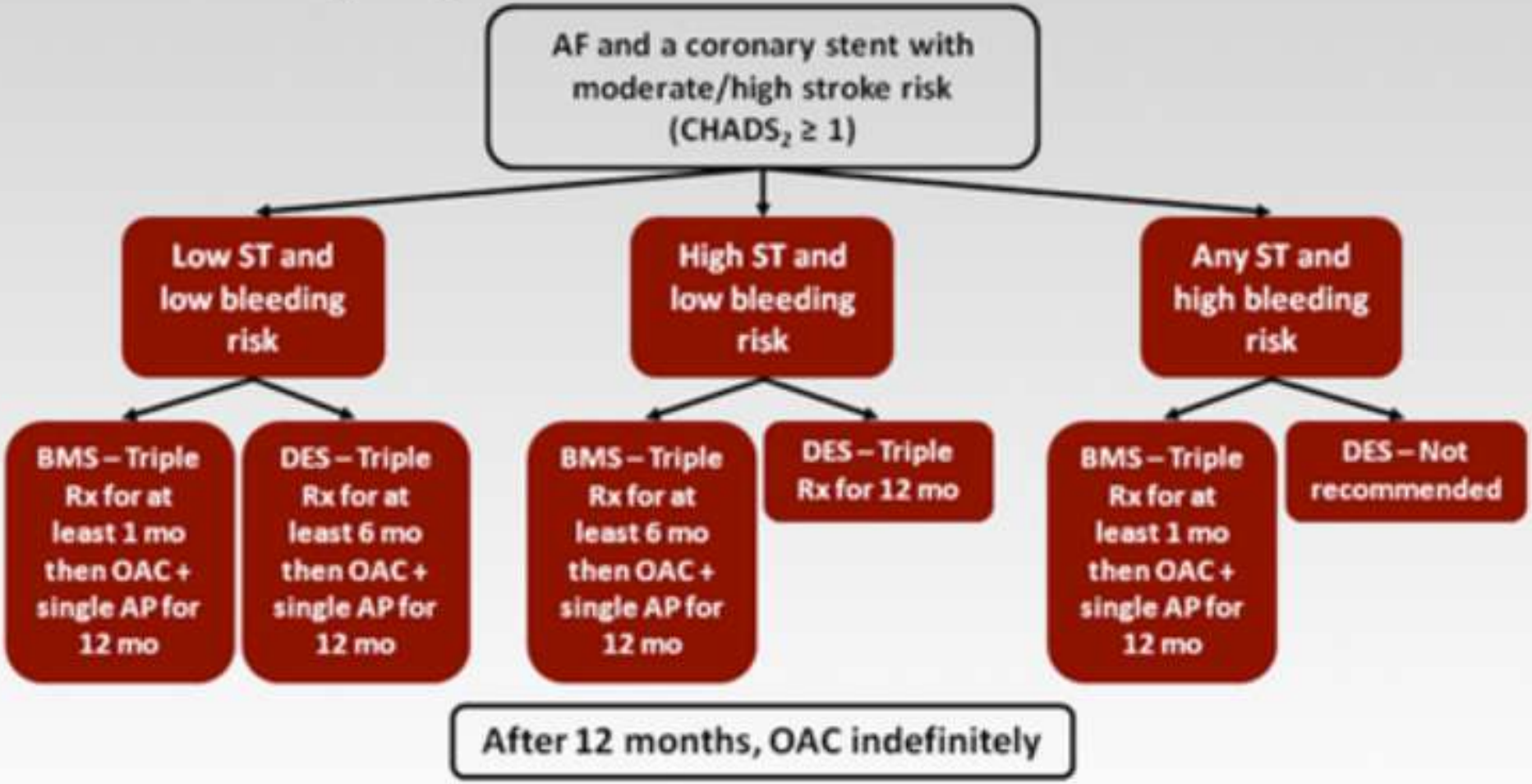
- *ISAR TRIPLE* (NCT00776633)
- *MUSICA-2* (NCT01141153)
- *DAPT* (NCT01459627)
- *ABSORB II* (NCT01425281)

doi:10.1001/archinternmed.2010.271

Risk of Bleeding With Single, Dual, or Triple Therapy With Warfarin, Aspirin, and Clopidogrel in Patients With Atrial Fibrillation. Arch Intern Med. 2010;170(16):1433-1441.



Recommendations for Triple Therapy in Patients With AF and Coronary Stent With Moderate/High Stroke Risk



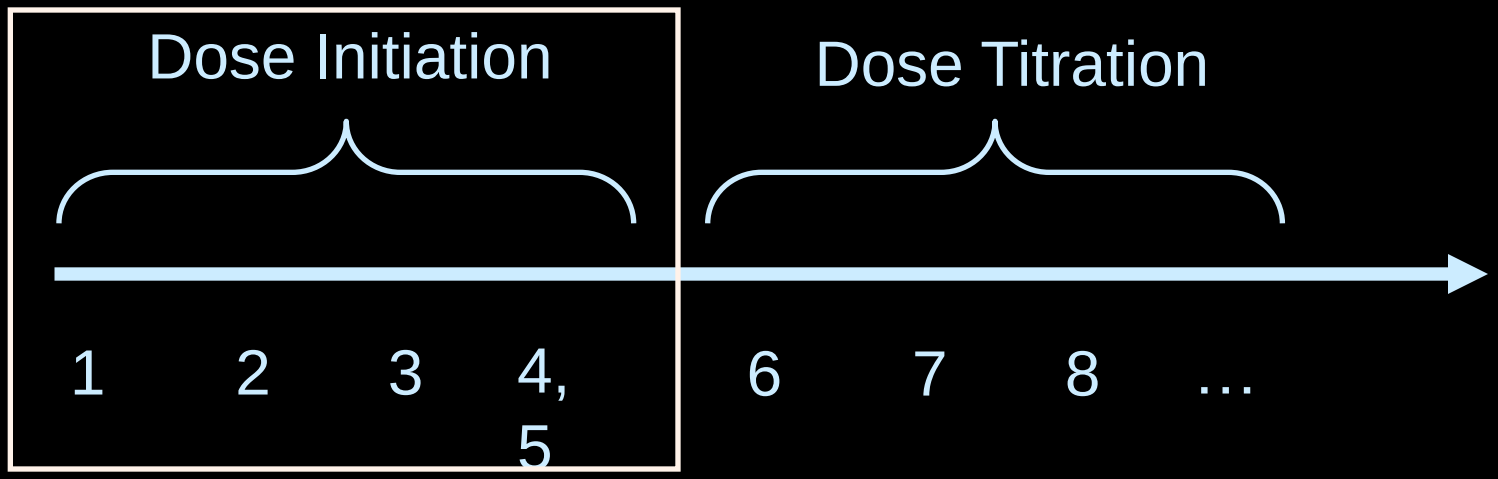
AP = antiplatelet agent; BMS = bare metal stent; ST = stent thrombosis; triple therapy = aspirin, clopidogrel, and warfarin

From Faxon DP, Eikelboom JW, Berger PB, et al. Consensus Document: Antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting. A North-American perspective. *Thromb Haemost.* 2011;106:572-584. Republished with permission.

C O A G Clarification of Optimal Anticoagulation Through Genetics

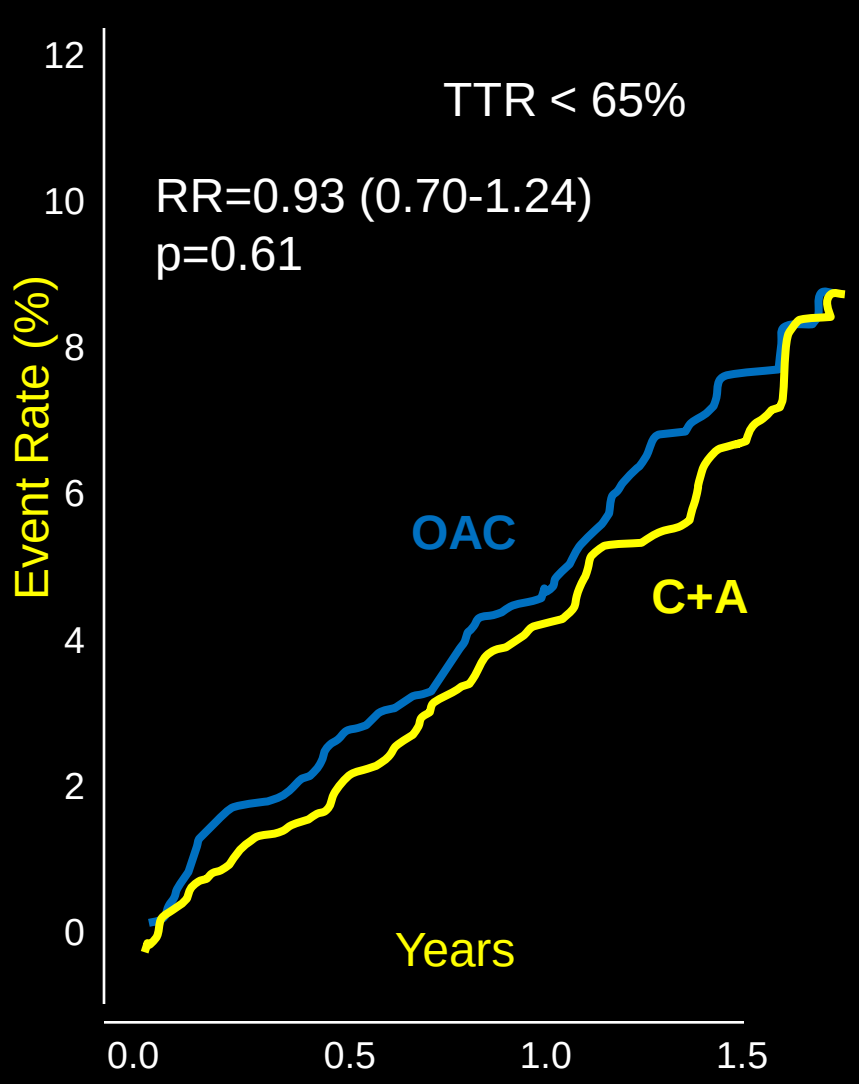
Intervention Period:

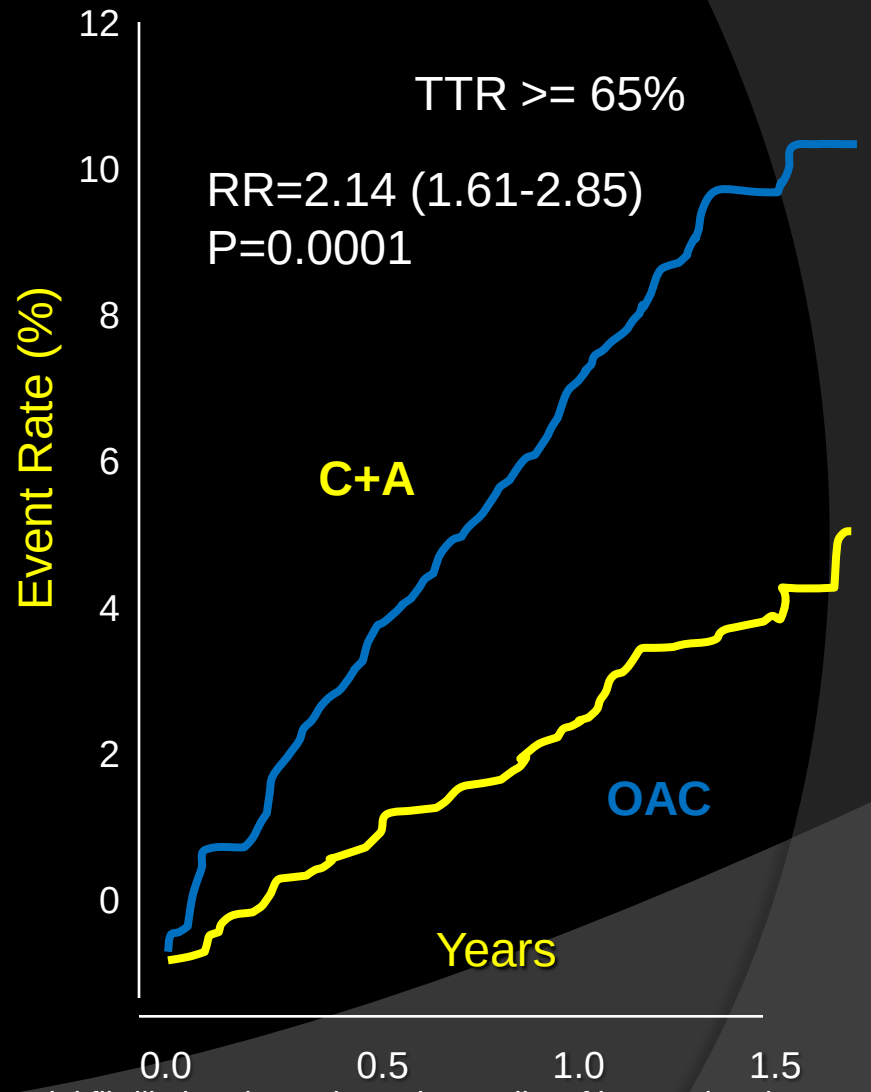
Informed by genetic/clinical information



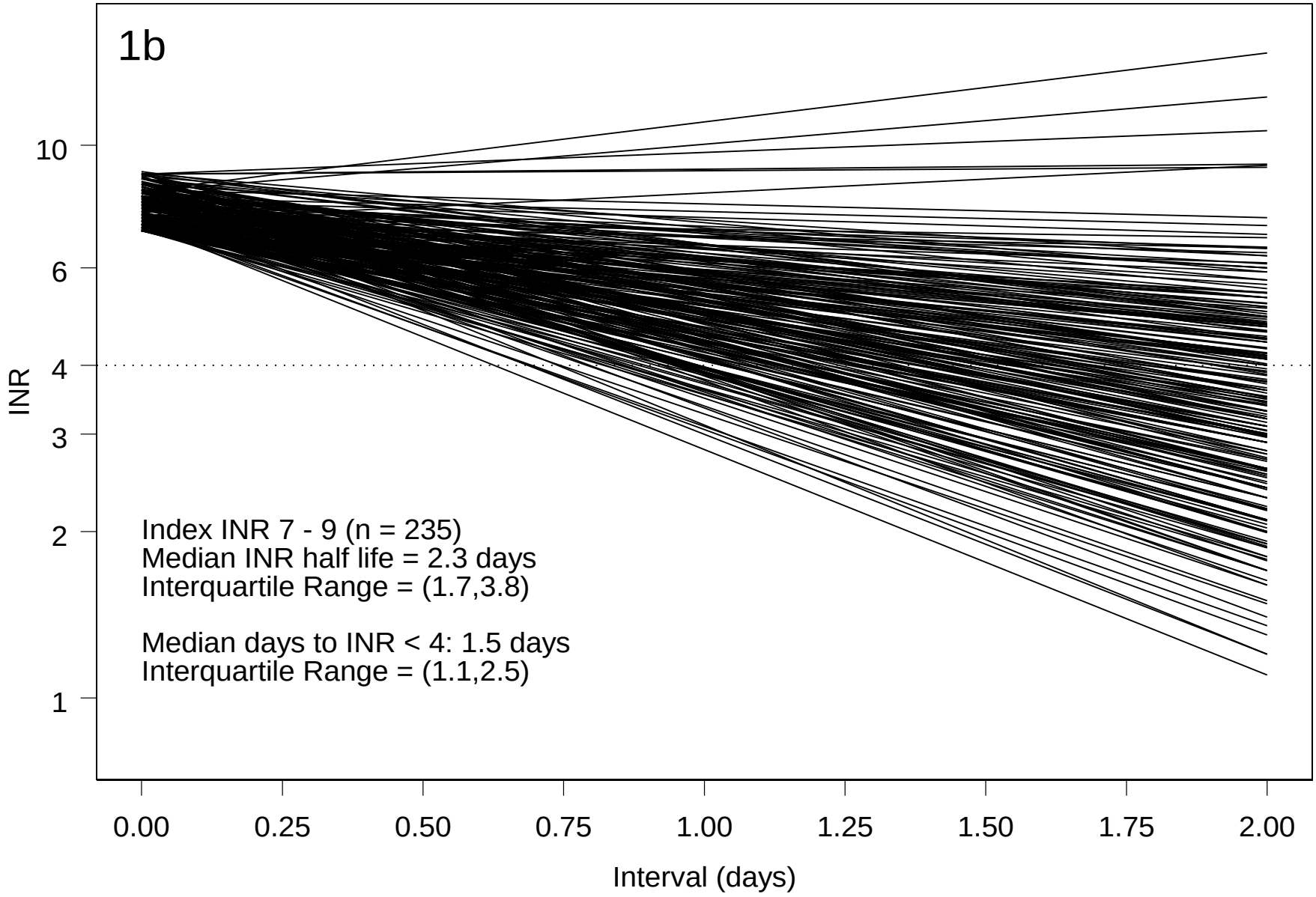
Objective: To compare the effect of pharmacogenetic & clinical warfarin dosing algorithms on initial proportion of time in therapeutic range of anticoagulation intensity

Cumulative risk of stroke, myocardial infarction, systemic embolism, or vascular death for patients treated at centers with a TTR below or above the study median (65%)





Connolly S. 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. Circulation 2008;118:2029-2037


1b
10
6
4
3
2
1
INR
Index INR 7 - 9 (n = 235)
Median INR half life = 2.3 days
Interquartile Range = (1.7,3.8)
Median days to INR < 4: 1.5 days
Interquartile Range = (1.1,2.5)
0.00
0.25
0.50
0.75
1.00
1.25
1.50
1.75
2.00
Interval (days)