

Prevention of thrombo- embolic complications



Felicita Andreotti

Dept of Cardiovascular Science

Catholic University, Rome, IT

Consultant or speaker in past 2 years for Amgen,

Bayer, BMS-Pfizer, Daiichi-Sankyo, Eli-Lilly

Background

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graph TD; A([Background]) --> B[AF is dangerous ~5%/yr stroke, if untreated]; A --> C[AF is common up to 70 M worldwide]; A --> D[Rx for stroke prevention is effective];
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AF is
dangerous
*~5%/yr stroke,
if untreated*

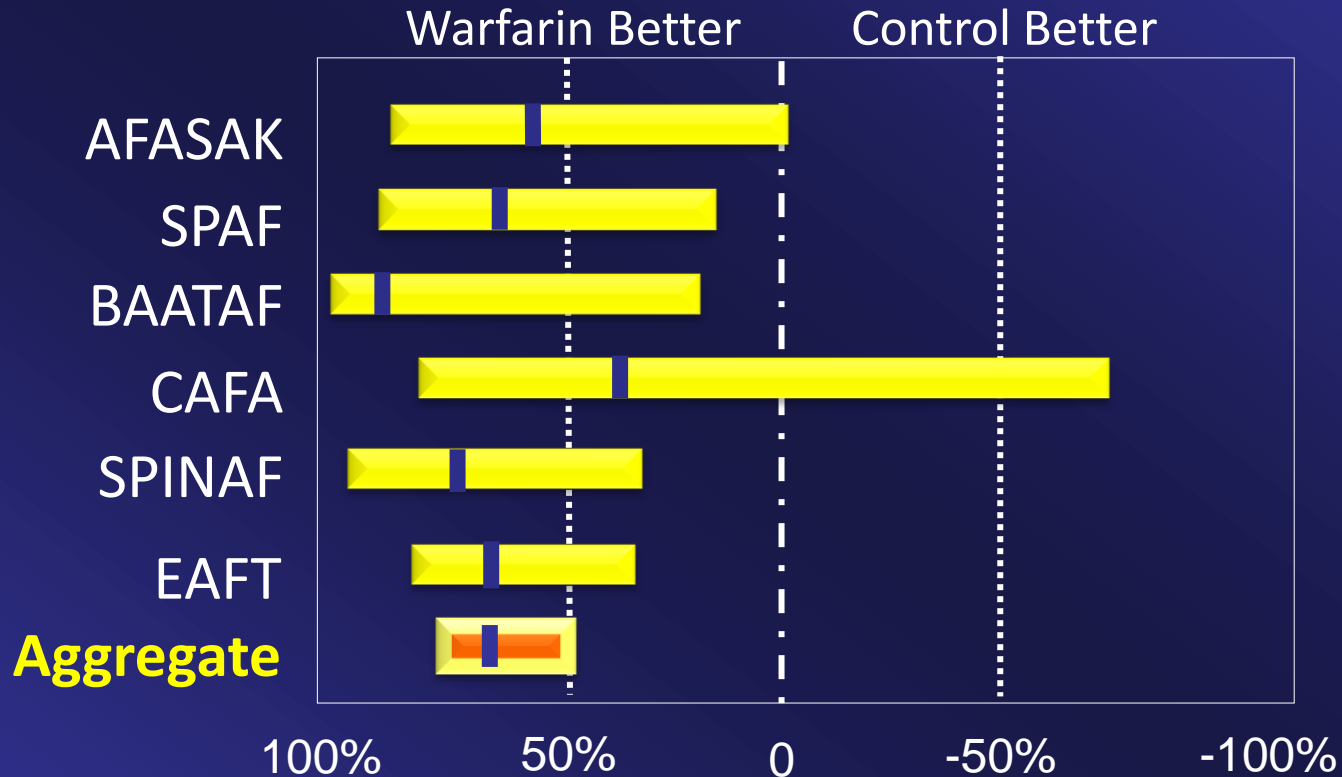
AF is
common
*up to 70 M
worldwide*

*Rx for stroke
prevention
is
effective*

Camm et al. ESC AF Guidelines. EHJ 2010;31:2369-429 - en.wikipedia.org/wiki/World_population

Bernhardt P et al. JACC 2005;45:1807-12 - 2011 Canadian AF Guidelines

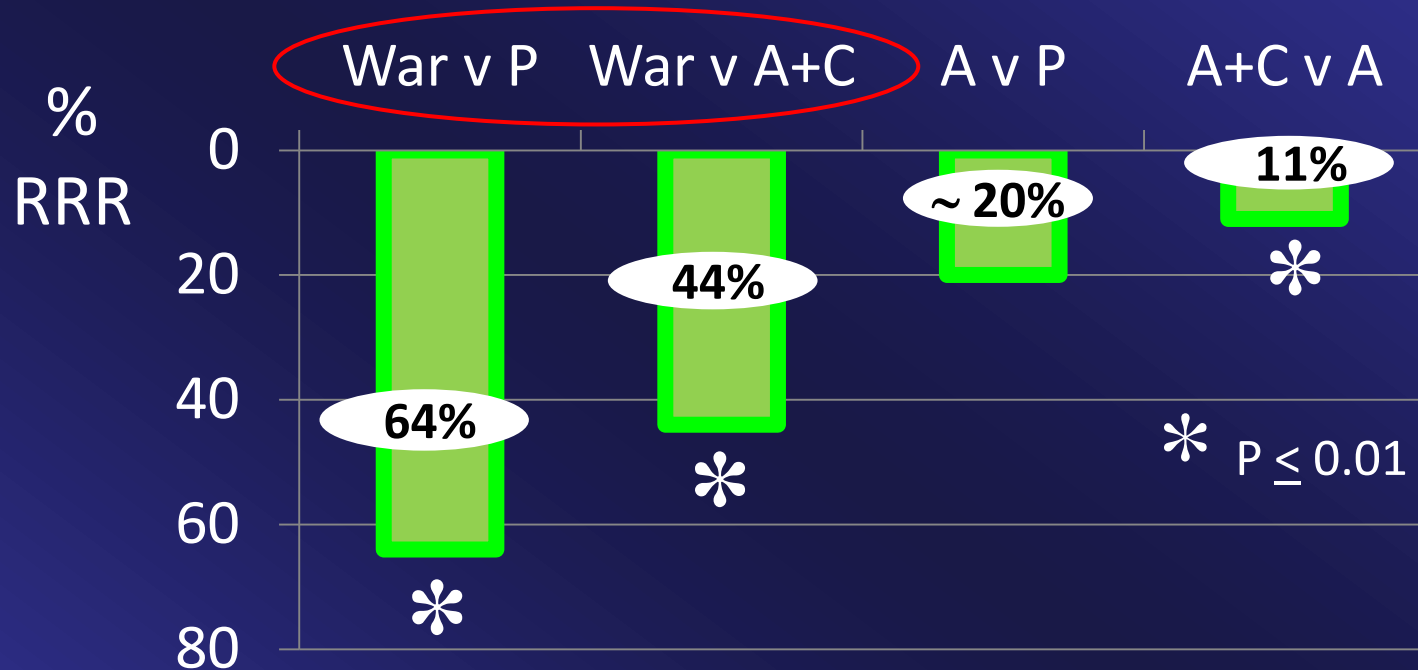
Stroke Risk Reduction by Warfarin in nonvalvular atrial fibrillation (NVAF)



AFASAK, Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation Study; EAFT, European Atrial Fibrillation Trial; SPAF Stroke Prevention in Atrial Fibrillation Study; SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation

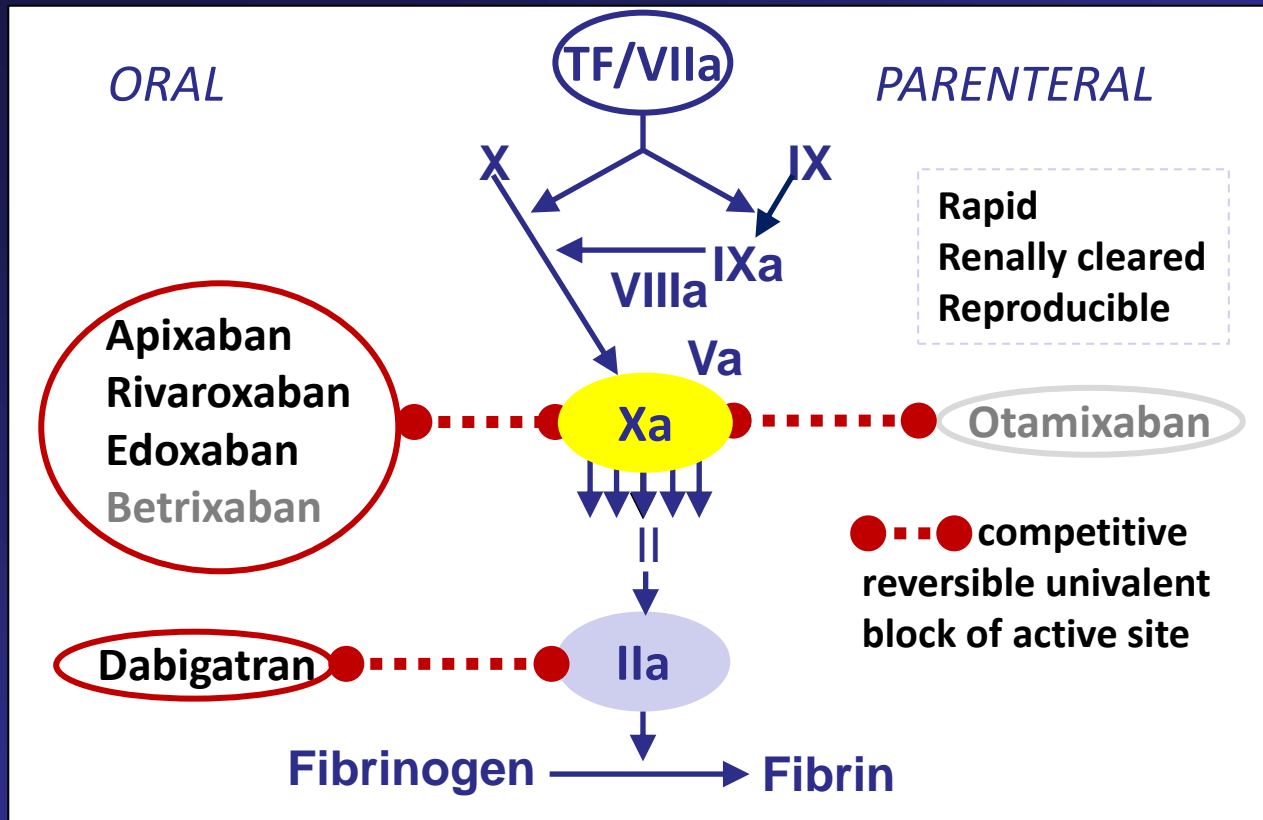
Antithrombotic strategies in NVAF

% Relative risk reduction of Stroke or MACE



A, aspirin. A+C, aspirin + clopidogrel. MACE, major adverse cardiovascular events. NVAF, nonvalvular atrial fibrillation. P, placebo. RRR, relative risk reduction. War, warfarin.

Novel Direct Oral AntiCoagulants (NOACs)



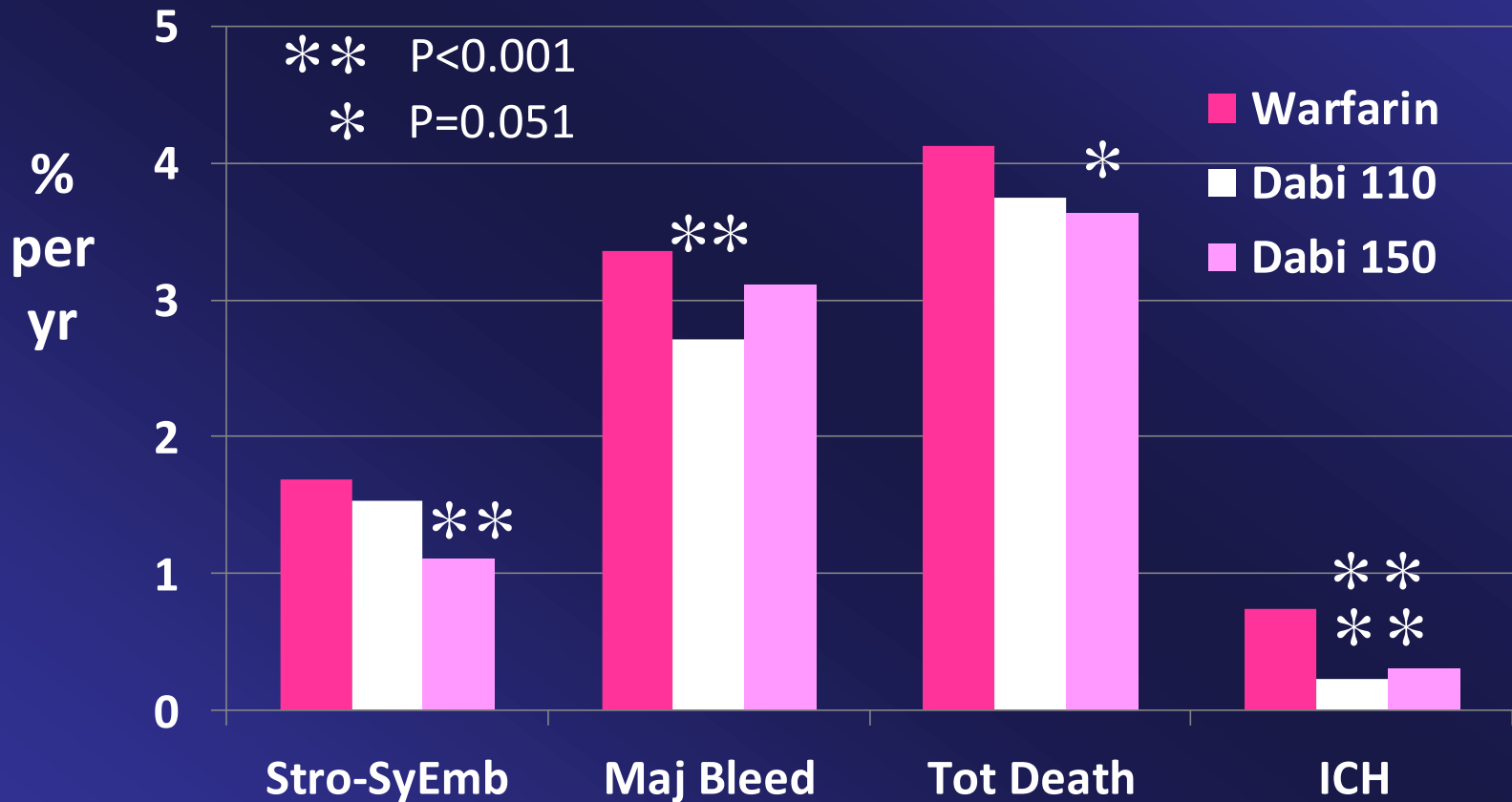
Five published phase III trials with NOACs in NVAF

	Dabigatran Pradaxa®	Rivaroxaban Xarelto®	Apixaban Eliquis®	Edoxaban Lixiana®*
VTE prev Orthop	RE-MODEL RE-NOVATE RE-MOBILIZE	RECORD 1 RECORD 2 RECORD 3 RECORD 4	ADVANCE I ADVANCE 2 ADVANCE 3	STARS E3
VTE prev Med III	RE-SOLVE	MAGELLAN	ADOPT	—
VTE tx	RE-COVER RE-MEDY RE-SONATE	EINSTEIN-DVT EINSTEIN-PE EINSTEIN-EXT	AMPLIFY AMPLIFY-EXT	HOKUSAI
SPAF	RE-LY	ROCKET-AF	ARISTOTLE AVERROES	ENGAGE- TIMI48
ACS Secondary prevention	—	ATLAS 2	APPRAISE 2	

* Savayasa® proposed in USA

RE-LY: main outcomes

N=18000, open v War, mn CHADS=2.1, BID, 2 yr FU, no dose adj, mn TTR 64%



Update 1 in NVAF

Dabigatran (all NOACs ?) vs Warfarin

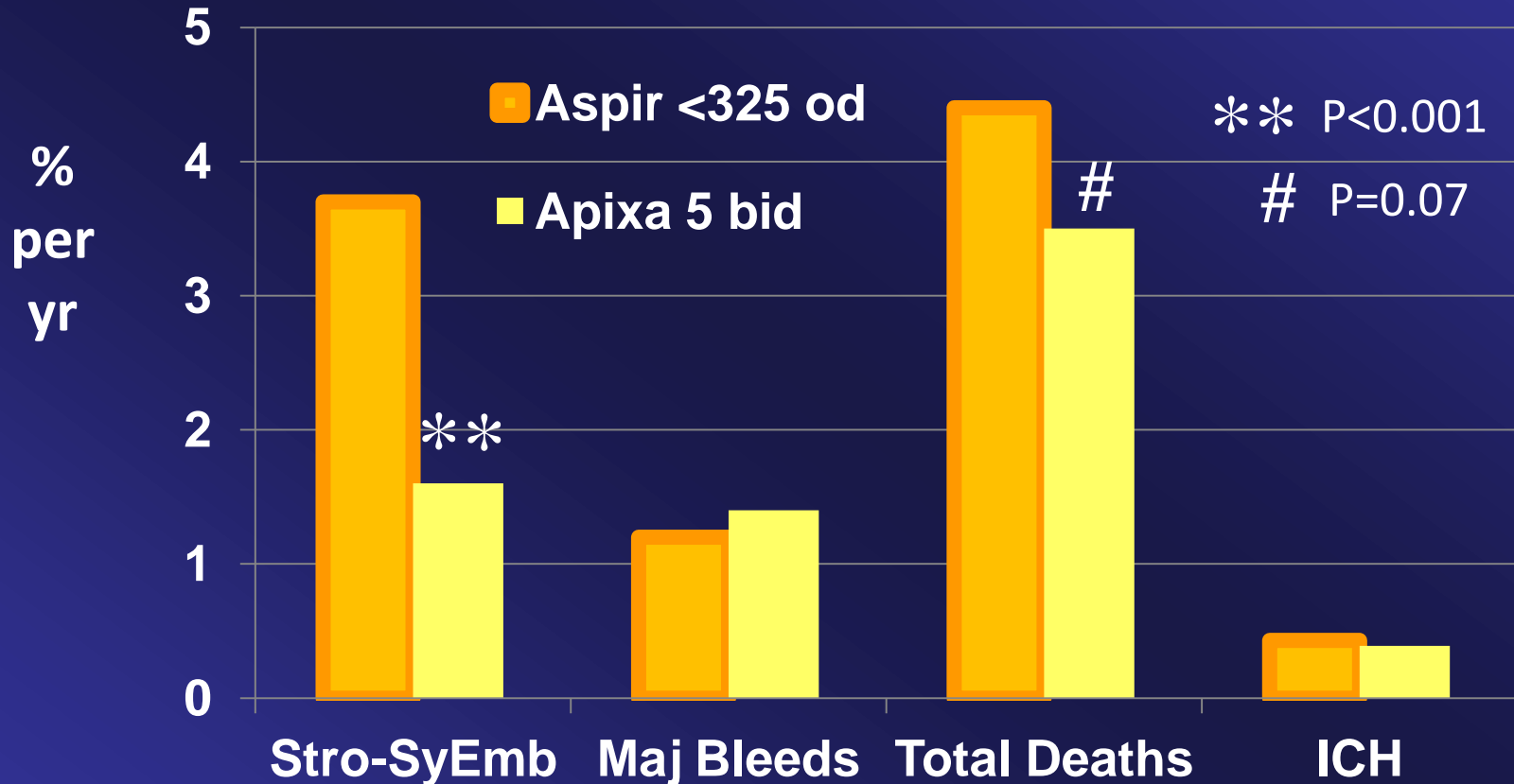
1a. effective

1b. fewer ICH

1c. fewer major bleeds (according to dose) and deaths (trend)

AVERRROES: main outcomes

N=5599, blinded, War unsuitable, mn CHADS=2, BID, 1.1 yr FU, dose adj ¥



¥ 2.5 mg if ≥ 2 of age ≥ 80 y, wgt ≤ 60 kg, serum creat ≥ 1.5 mg/dl

Update 2 in NVAF

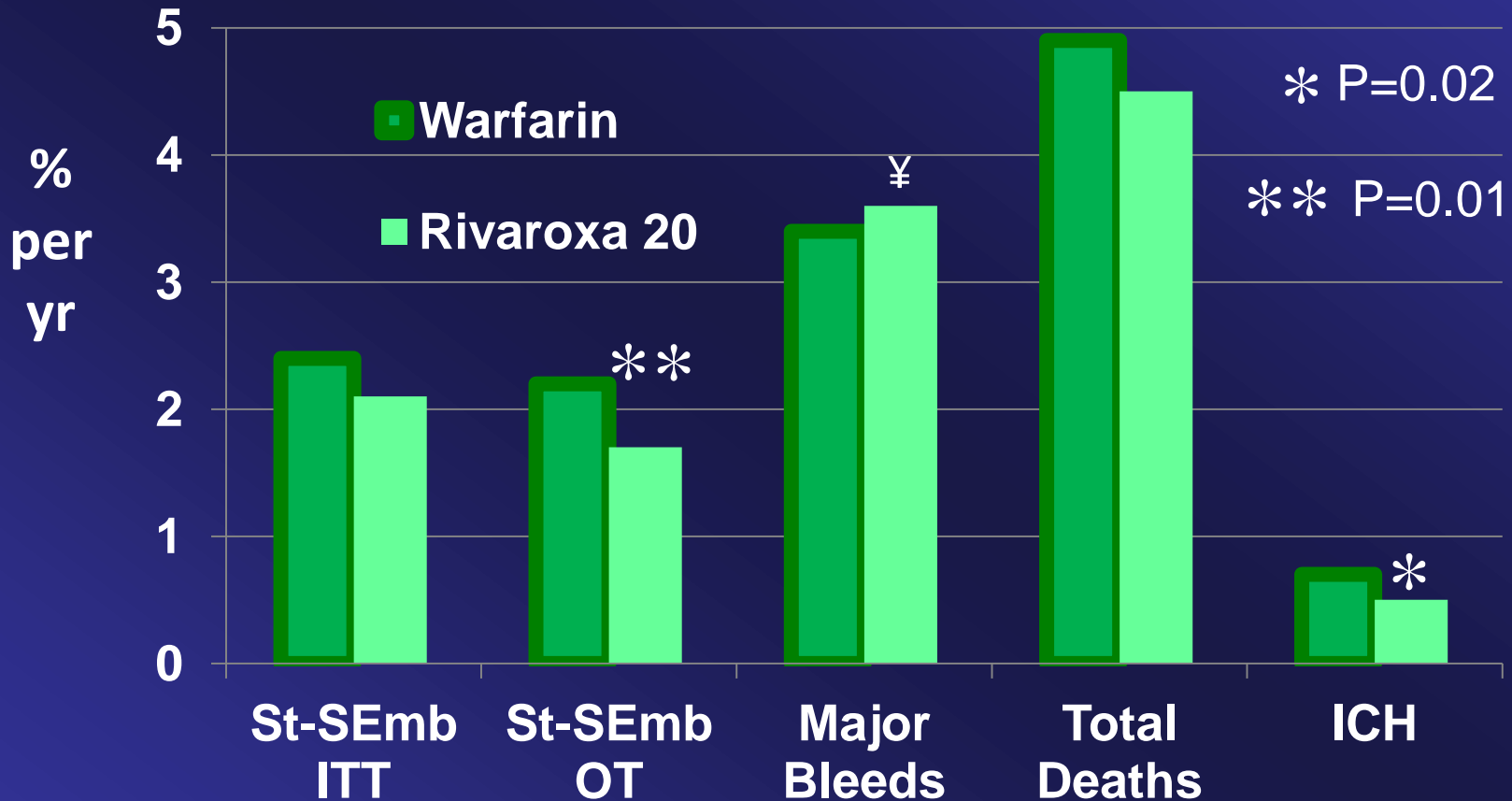
Apixaban (all NOACs ?) vs Aspirin

2a. definitely more effective

*2b. equally safe in warfarin
unsuitable patients*

ROCKET AF: main outcomes

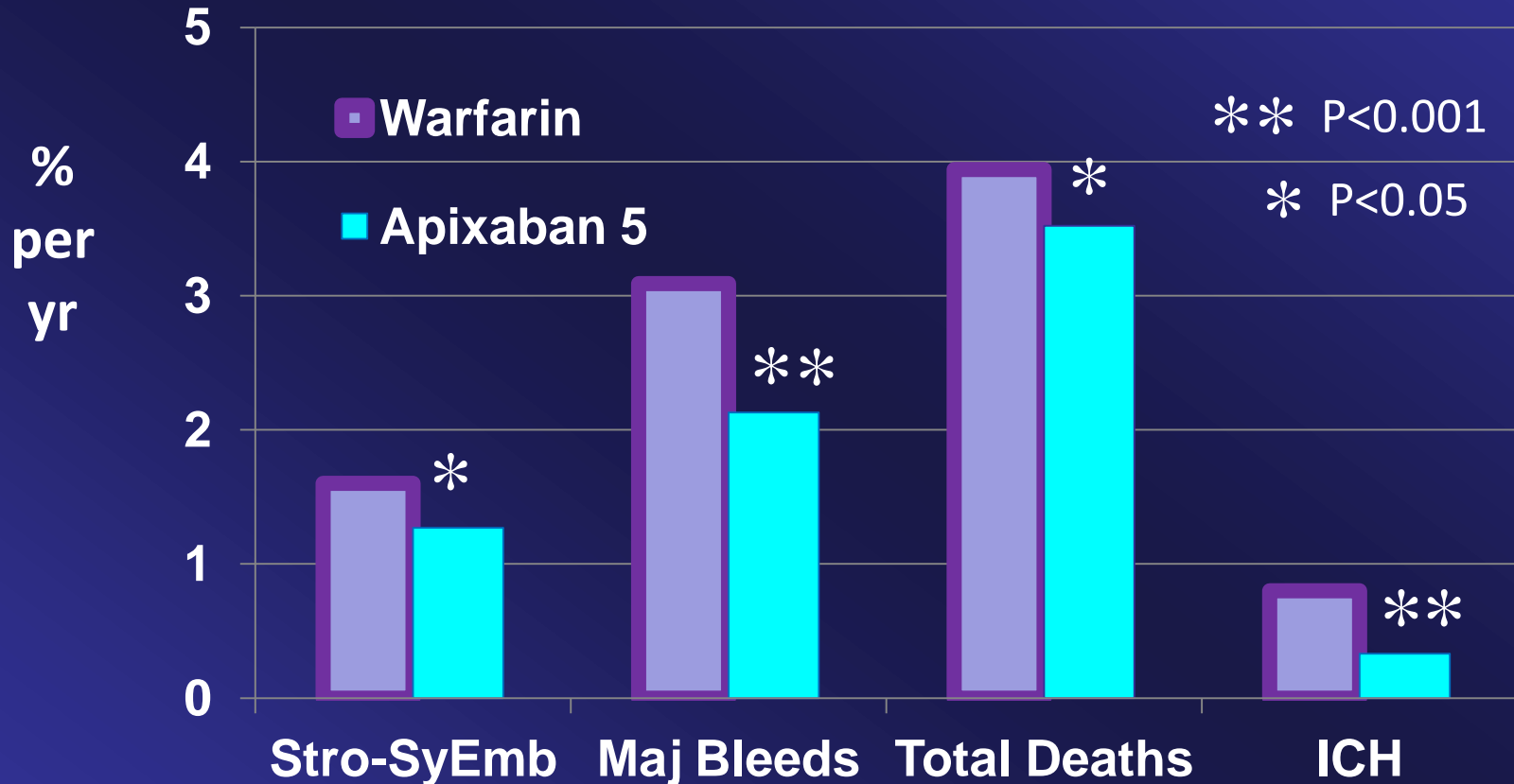
N=14000, blinded, mn CHADS=3.5, 0D, 2 yr FU, renal dose adj #, mn TTR 55%



15 mg if Cr Cl 30-49 ml/min; ITT = intention to treat analysis; OT = on treatment prespecified analysis
¥ fewer fatal bleeds with rivaroxaban v warfarin, P=0.003

ARISTOTLE: main outcomes

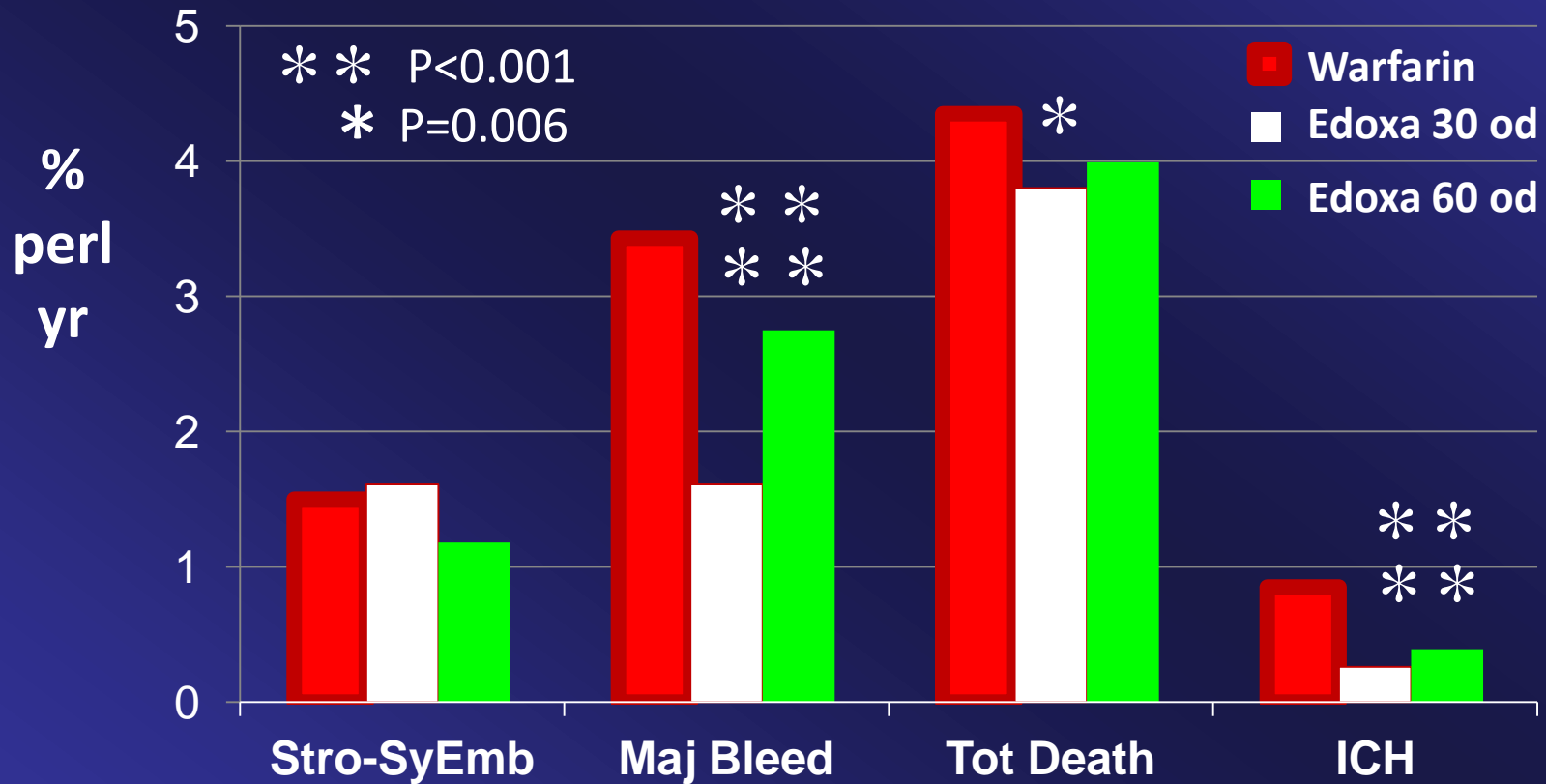
N=18000, blinded, mn CHADS=2.1, BID, 1.8 yr FU, dose adj #, mn TTR 62%



2.5 mg if ≥ 2 of age ≥ 80 y, wgt ≤ 60 kg, serum creat ≥ 1.5 mg/dl

ENGAGE: main outcomes

N=21105, blinded, mn CHADS=2.8, OD, 2.8 yr FU, dynamic dosing #, mn TTR 65%



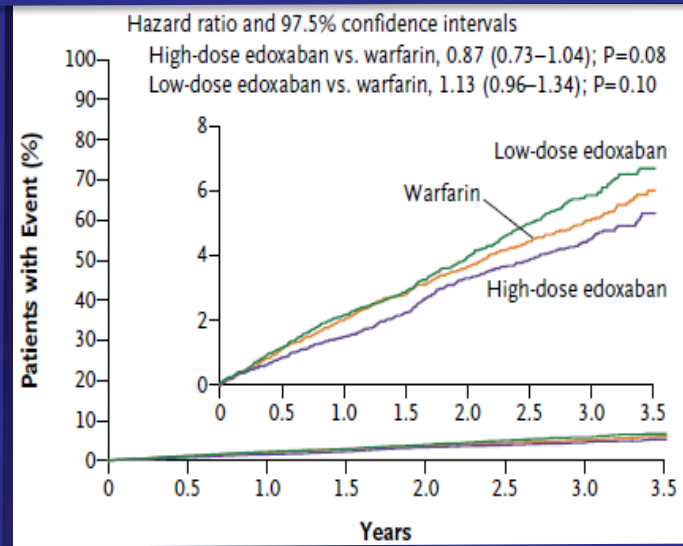
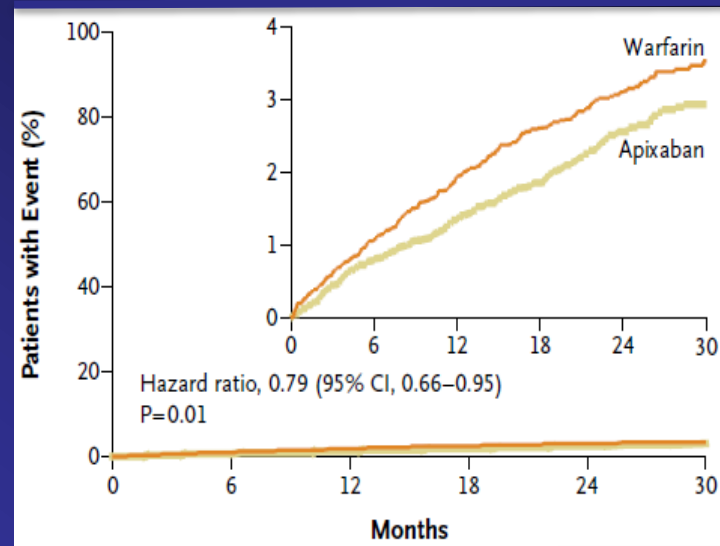
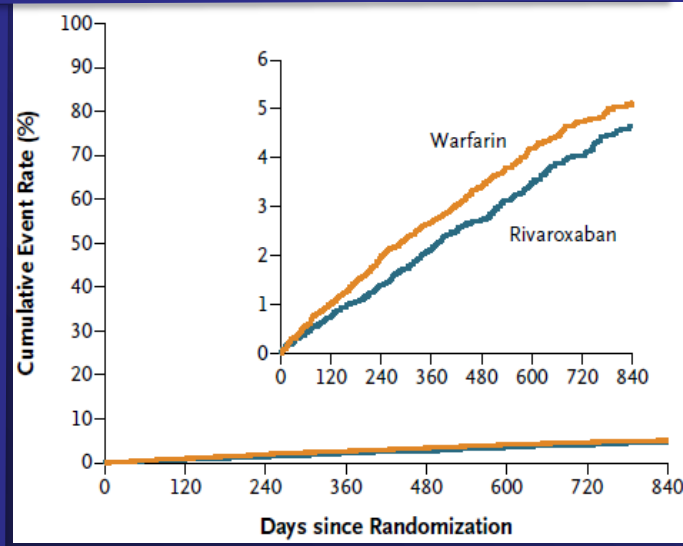
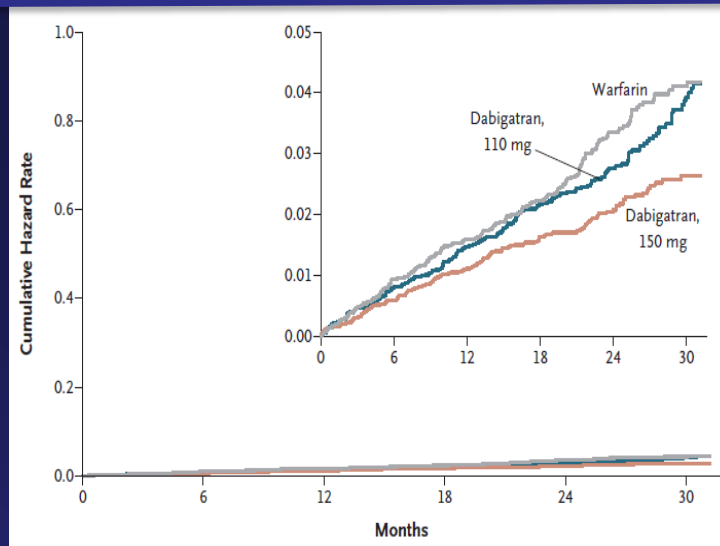
half dose if ≥ 1 of Cr Cl 30-50 ml/min; wgt ≤ 60 kg; verapamil, dronedarone, quinidine

Update 3 in NVAF

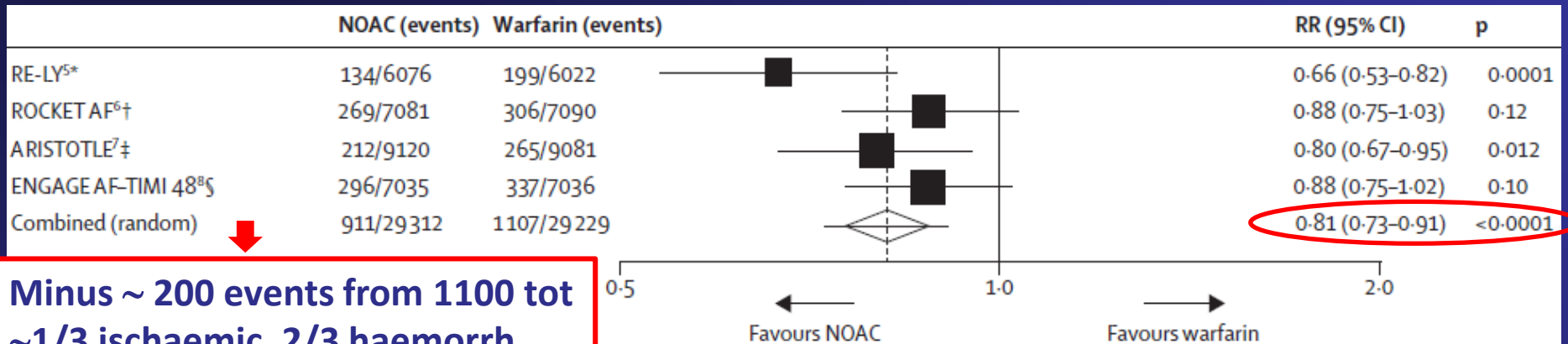
Compared to warfarin all NOACs

- 3a. reduce the rates of ICH and haemorrhagic stroke*
- 3b. show consistent reductions in rates of stroke-SyEmb (at higher doses), major or fatal bleeds, and death*

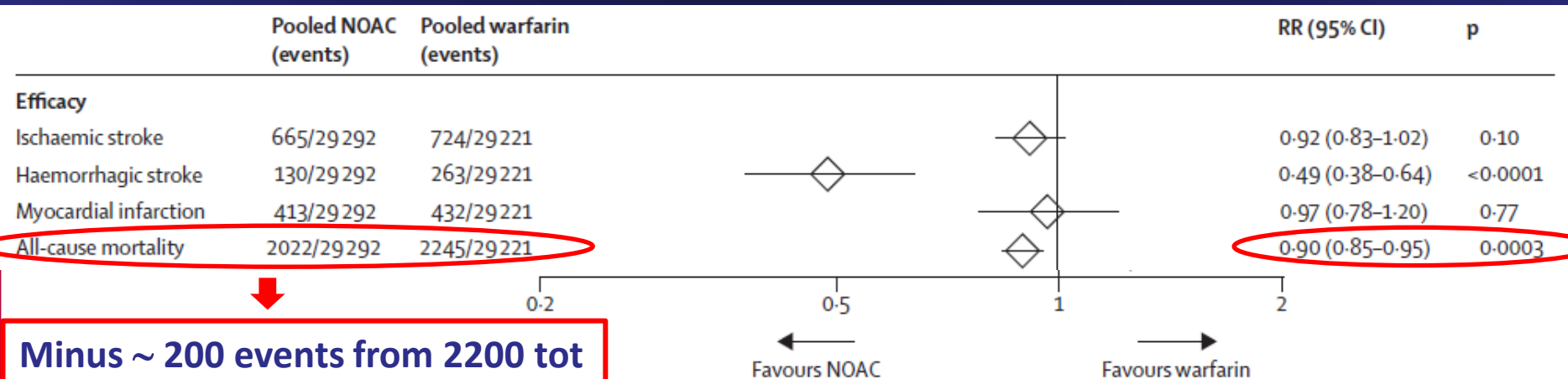
K-M curves for Stroke or Systemic Embolism



Stroke or Systemic Embolism



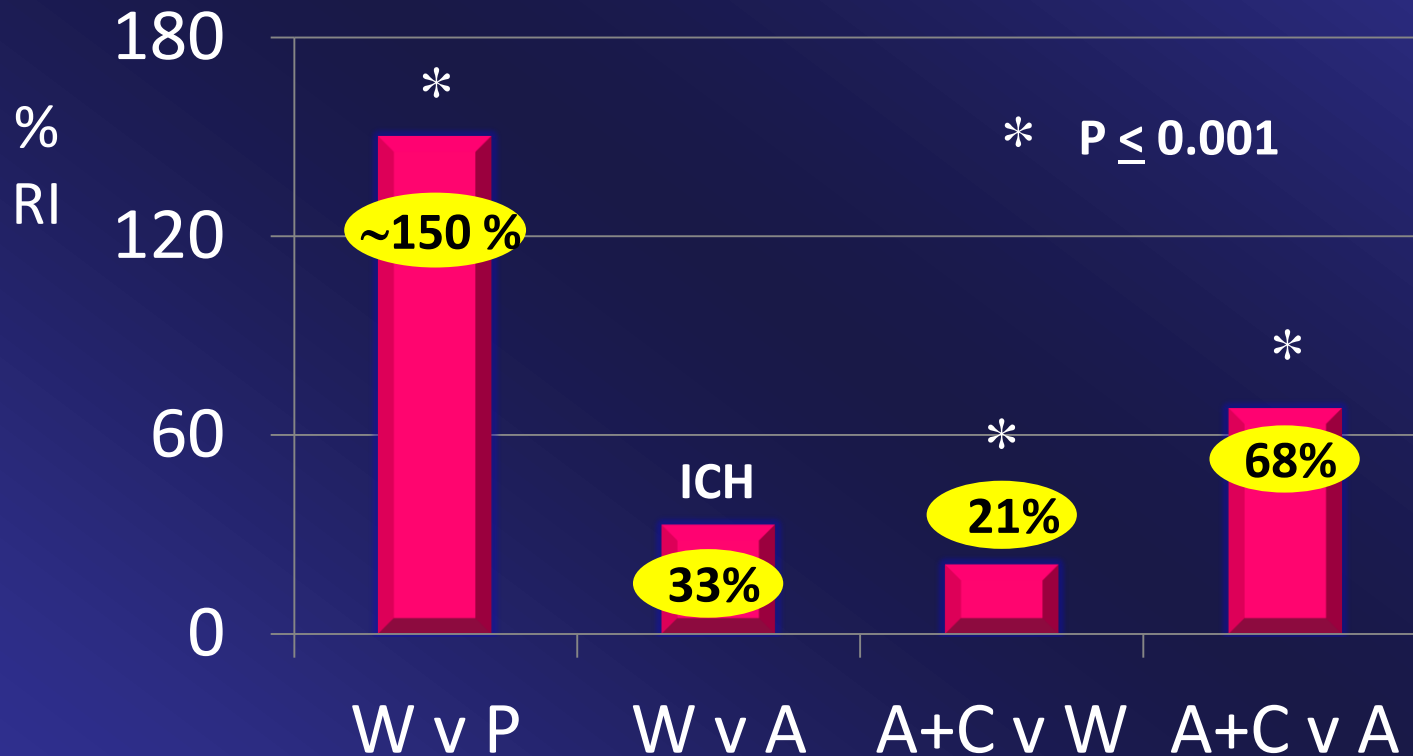
Secondary outcomes



Safety of antithrombotic regimens tested in NVAF

% Relative increase of any bleeds or ICH

A, aspirin. A+C, aspirin + clopidogrel. ICH, intracranial haemorrhage. NVAF, nonvalvular atrial fibrillation. P, placebo. RI, relative risk increase. W, warfarin.

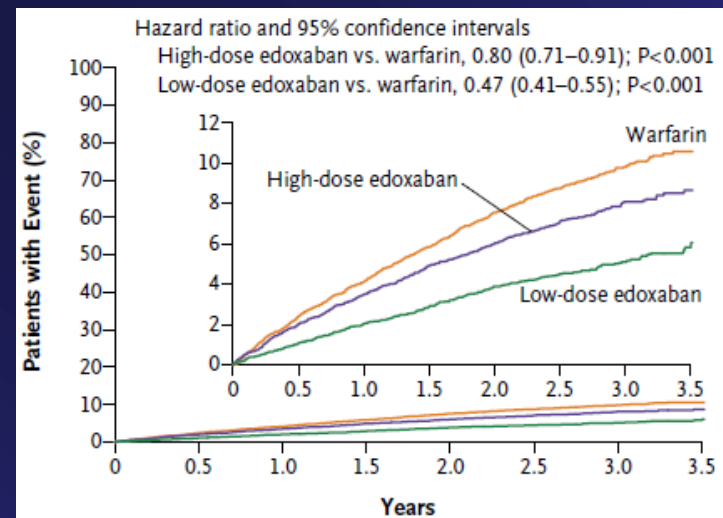
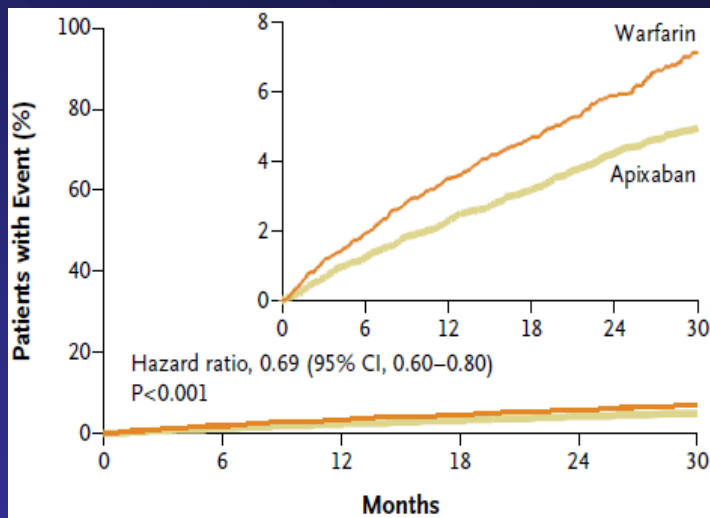
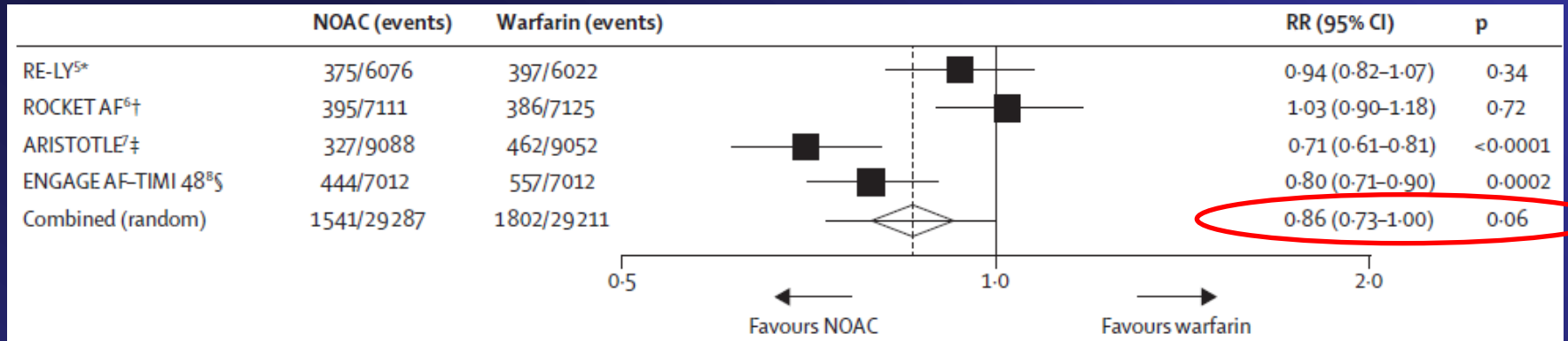


Update 4 in NVAF

4a. Warfarin increases bleeding risk vs placebo ~ 2.5 x

4b. Aspirin or dual antiplatelet therapy are not significantly safer than warfarin

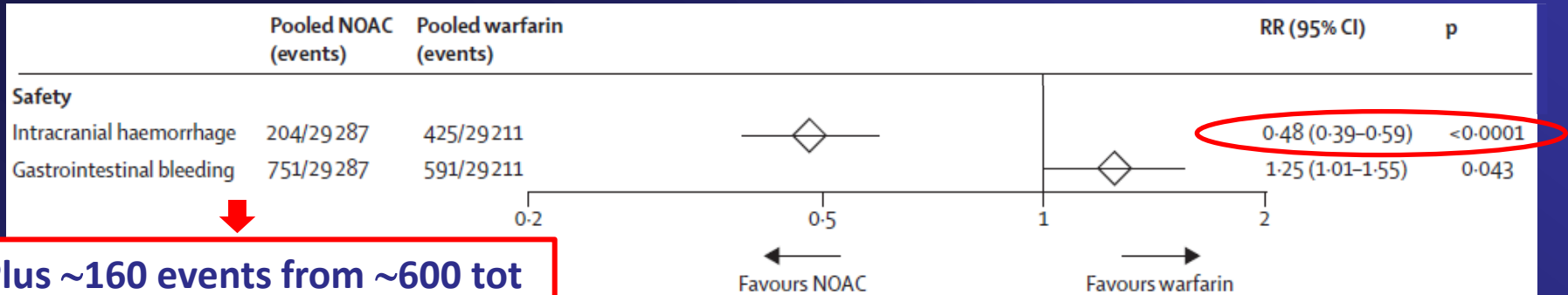
Major Bleeding with NOACs v Warfarin



Ruff et al. Lancet 2013 Dec 3 [Epub ahead of print]

Granger et al. N Engl J Med 2011;365:981-92 - Giugliano et al. N Engl J Med 2013;369:2093-5104

Intracranial and GI Bleeds



Ruff et al. Lancet 2013 Dec 3 [Epub ahead of print]

GI bleeds, % per yr

	RE-LY	AVERROES	ROCKET	ARISTOTLE	ENGAGE
WARFARIN	1.1	0.4	2.2	0.86	1.2
FULL DOSE NOAC	1.5	0.4	3.2	0.76	1.5

Connolly et al. N Engl J Med 2009;361:1139-51 -

Connolly et al. N Engl J Med 2011;364: 806-17 Patel et al. N Engl J Med 2011;365:883-91
 Granger et al. N Engl J Med 2011;365:981-92 - Giugliano et al. N Engl J Med 2013;369:2093-5104



For NVAF, NOACs vs warfarin in aggregate are

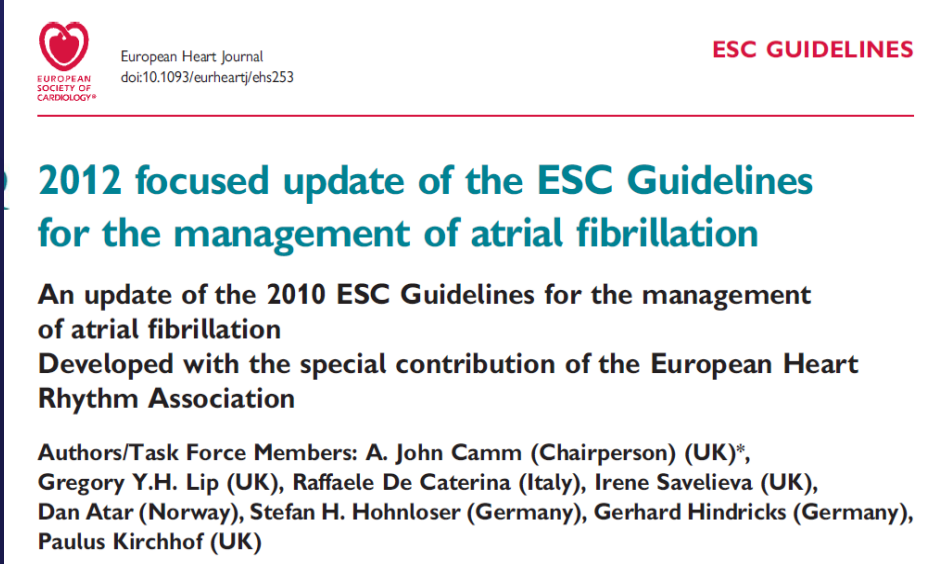
- LIFE-SAVING
- MORE EFFECTIVE for stroke prevention
- SAFE in terms of major bleeds
- SAFER in terms of haemorrhagic stroke and intracranial bleeds



Michelangelo ~1510

2012 Updates - ESC

- ESC Guidelines
 - NOACs are the first-choice anticoagulants
 - Consider for CHADS 1→6 and CHADS-VASC ≥ 1
 - Consider for permanent, persistent and parosysmal AF
 - Efficacy of aspirin weak, with same potential harm as OAC



European Heart Journal
doi:10.1093/eurheartj/ehs253

ESC GUIDELINES

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

An update of the 2010 ESC Guidelines for the management of atrial fibrillation
Developed with the special contribution of the European Heart Rhythm Association

Authors/Task Force Members: A. John Camm (Chairperson) (UK)*, Gregory Y.H. Lip (UK), Raffaele De Caterina (Italy), Irene Savelieva (UK), Dan Atar (Norway), Stefan H. Hohnloser (Germany), Gerhard Hindricks (Germany), Paulus Kirchhof (UK)

ESC, European Society of Cardiology; (N)OAC, (novel) oral anticoagulant; OAC, oral anticoagulant