Séminaire
Winter Arrhythmia
School
Annual Cardiac Arrhythmia Meeting
Division of Cardiology, University of Toronto

Update on Management of Atrial Fibrillation Patients with CAD

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Disclosures

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Grants/Research Support: AstraZeneca

Speakers Bureau/Honoraria: Amgen, AstraZeneca, Bayer, Pfizer/BMS, Sanofi,

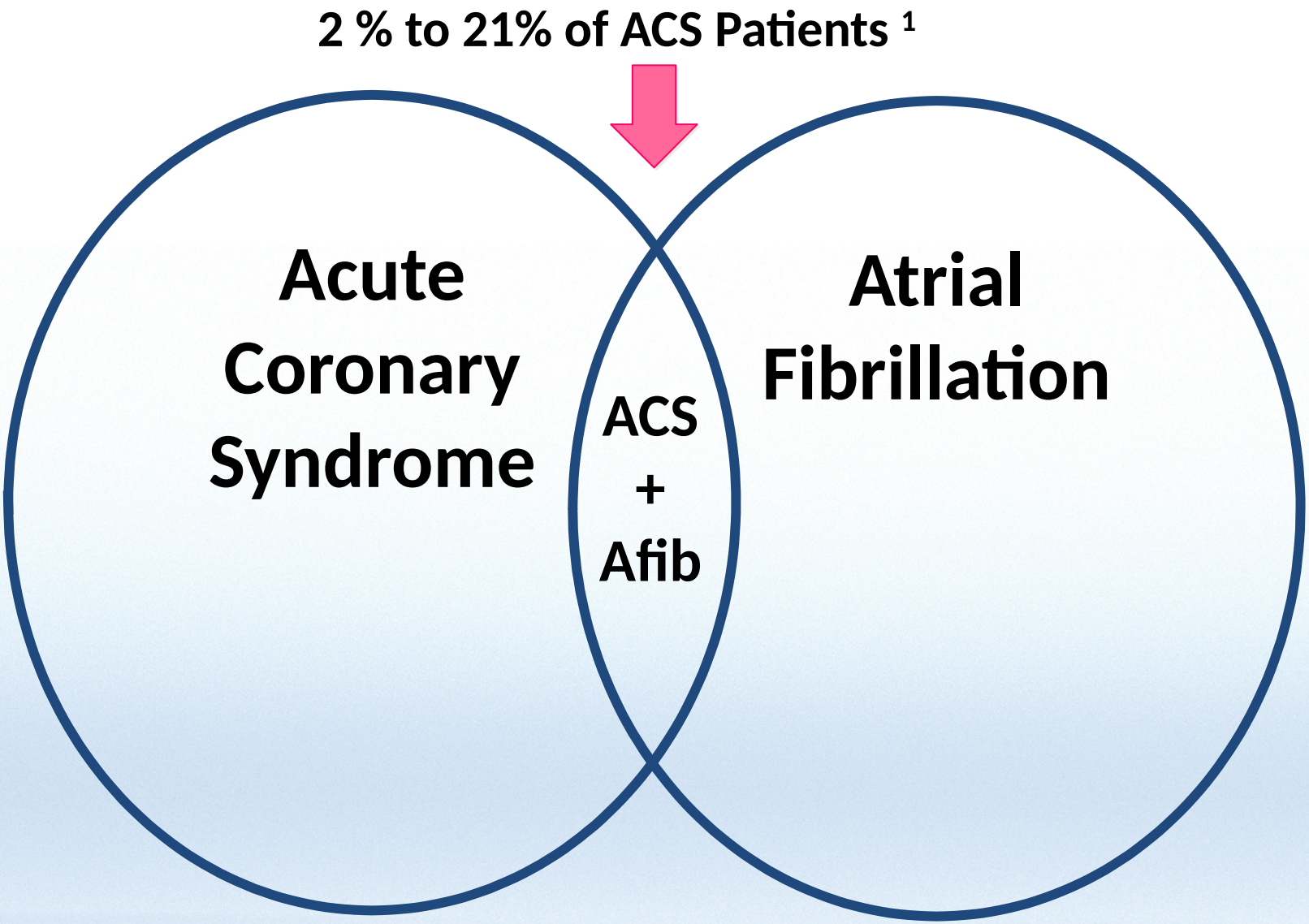
Consulting Fees: Amgen, AstraZeneca, Bayer, Pfizer/BMS, Sanofi,

Other: None

Objectives

1. Review background data on management of atrial fibrillation patients with CAD.
2. 2016 Update of the Canadian AF Guidelines recommendations on management of atrial fibrillation patients with CAD.
3. Discuss PIONEER-AF trial results and implications.
4. Future trials and expectations on the management of atrial fibrillation patients with CAD.

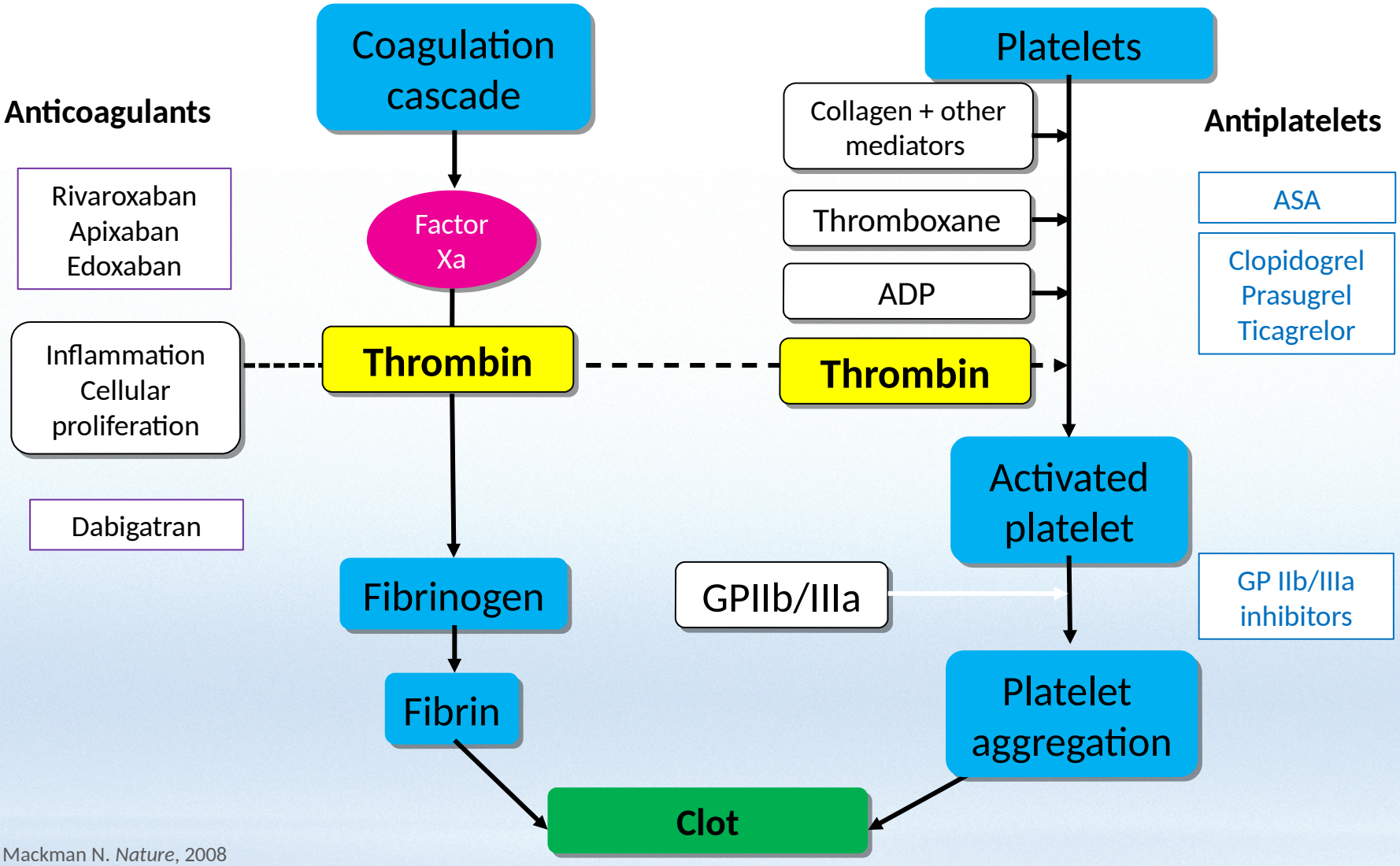
Incidence of Atrial Fibrillation in ACS Patients



1. Schmitt J *et al.*, Atrial fibrillation in acute myocardial infarction: a systematic review of the incidence, clinical features and prognostic implications. *Eur Heart J* 2009;30:1038–1045.

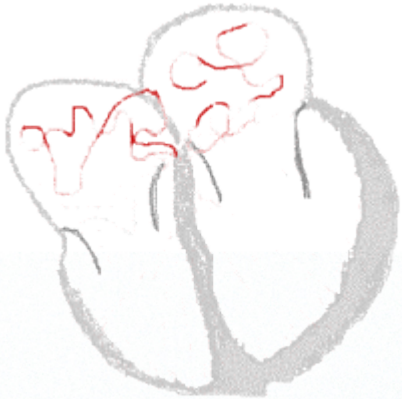
Pathophysiological Basis for Dual Pathway Strategies

Thrombus formation involves both platelet activation and blood coagulation



Mackman N. *Nature*, 2008

The Optimal Management of Atrial Fibrillation and ACS Differ



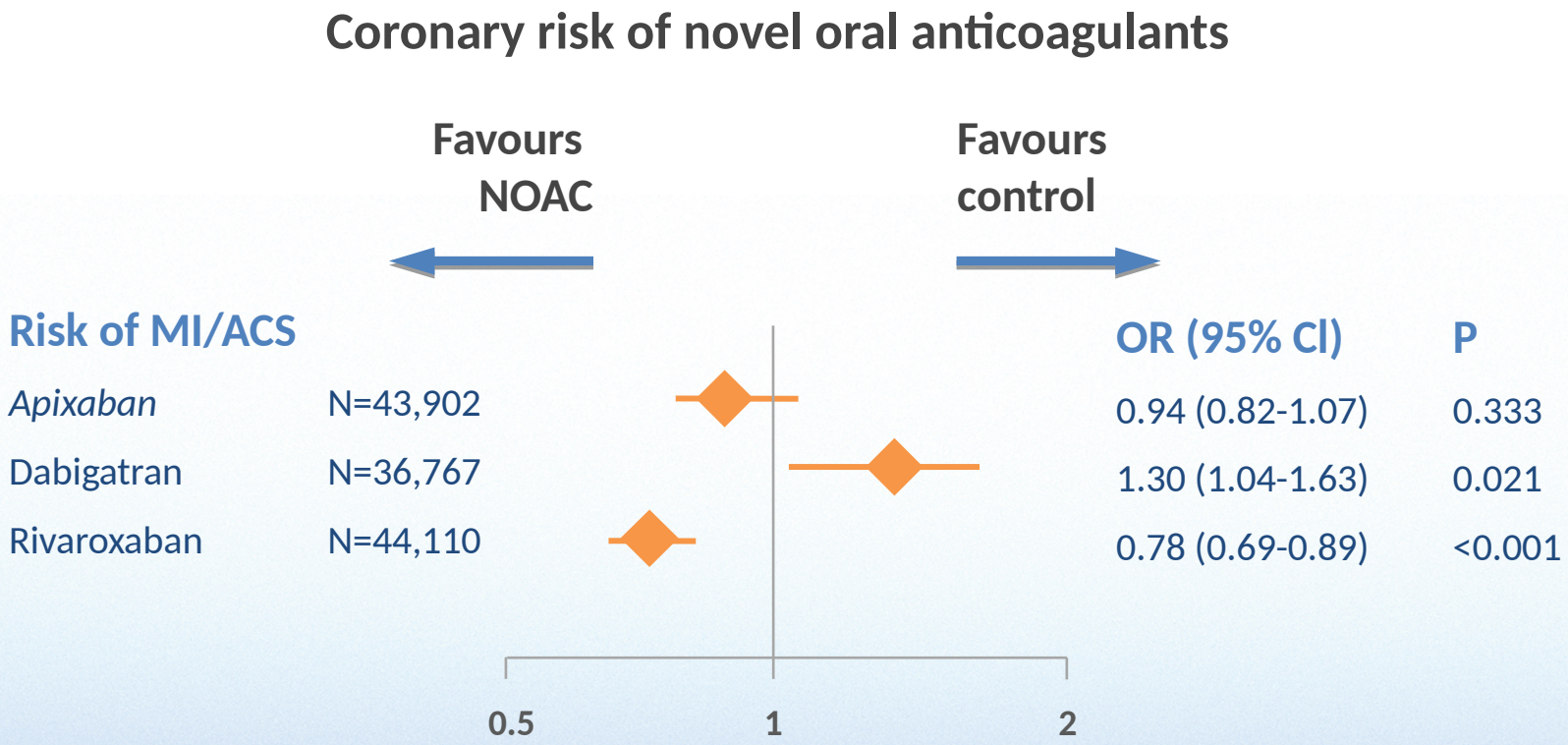
Atrial Fibrillation (ACTIVE W)[1]: The combination of aspirin and clopidogrel is not as effective as *warfarin* in patients with AF[1]

However

Stenting (STARS)[2]: The combination of *aspirin and a thienopyridine* is more effective than warfarin in patients with coronary stents [2]

1. Lancet 2006 Jun 10;367(9526):1903-12. 2. N Eng J Med 1998 Dec 3;339(23):1665-71.

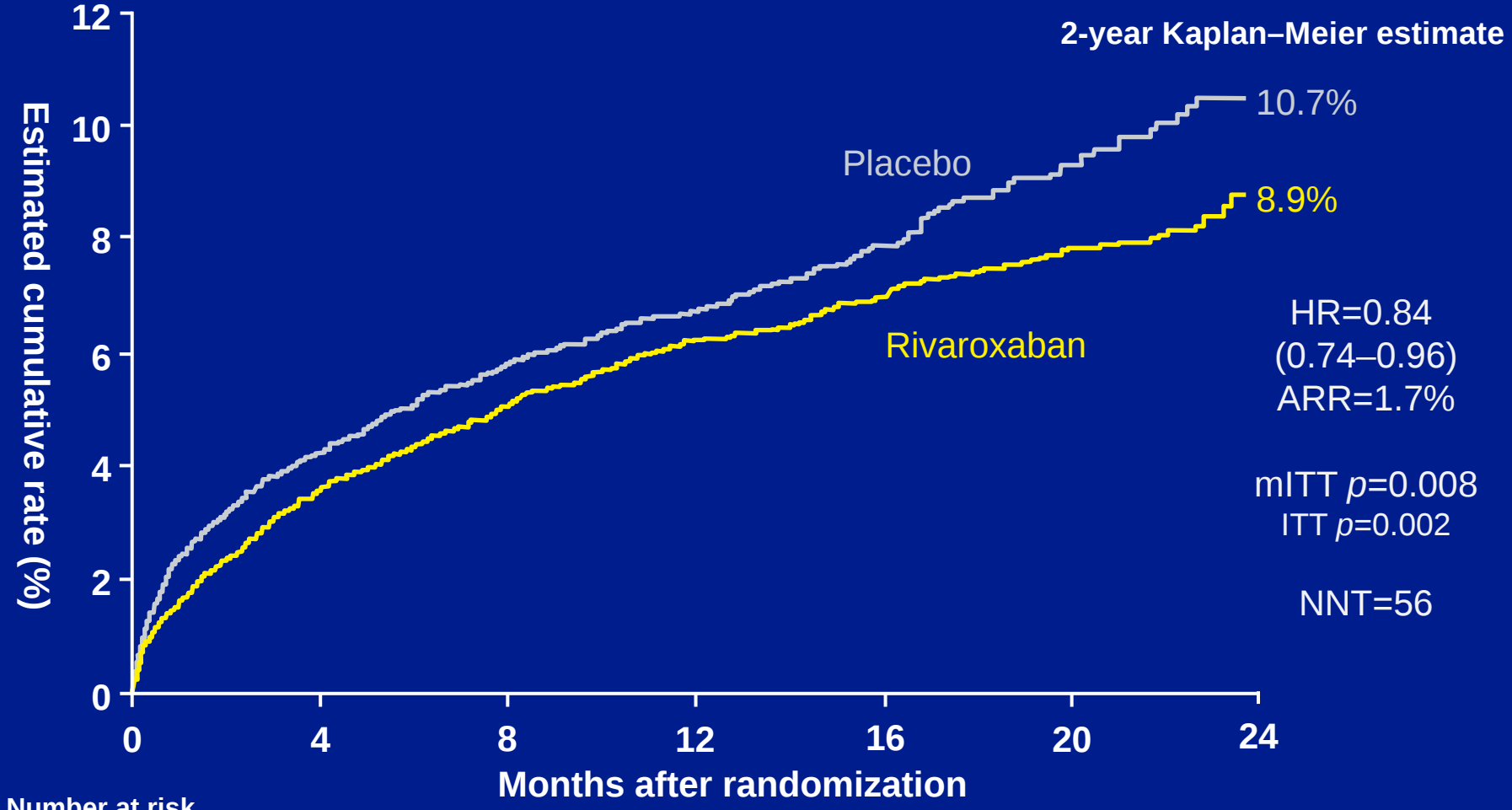
What if My Atrial Fibrillation Patient Had a Recent ACS?



Mak K-H. *BMJ* Open 2012;2:e001592.

ATLAS ACS 2 TIMI 51

Primary efficacy endpoint (CV death/MI/stroke)



Number at risk

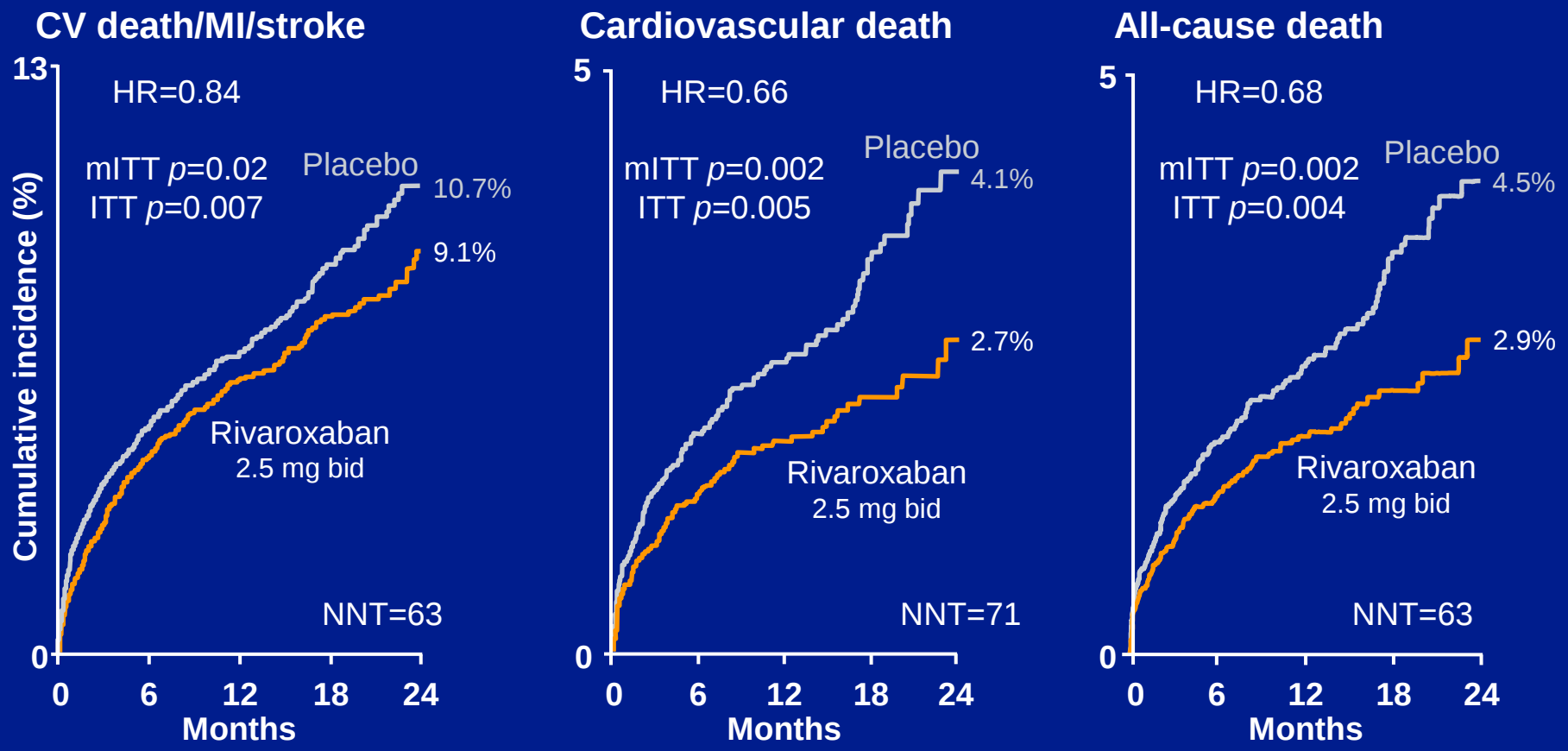
Placebo	5113	4307	3470	2664	1831	1079	421
Rivaroxaban	10,229	8502	6753	5137	3554	2084	831

Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches

Gibson *et al*, 2011; Mega *et al*, 2011.

ATLAS ACS 2 TIMI 51

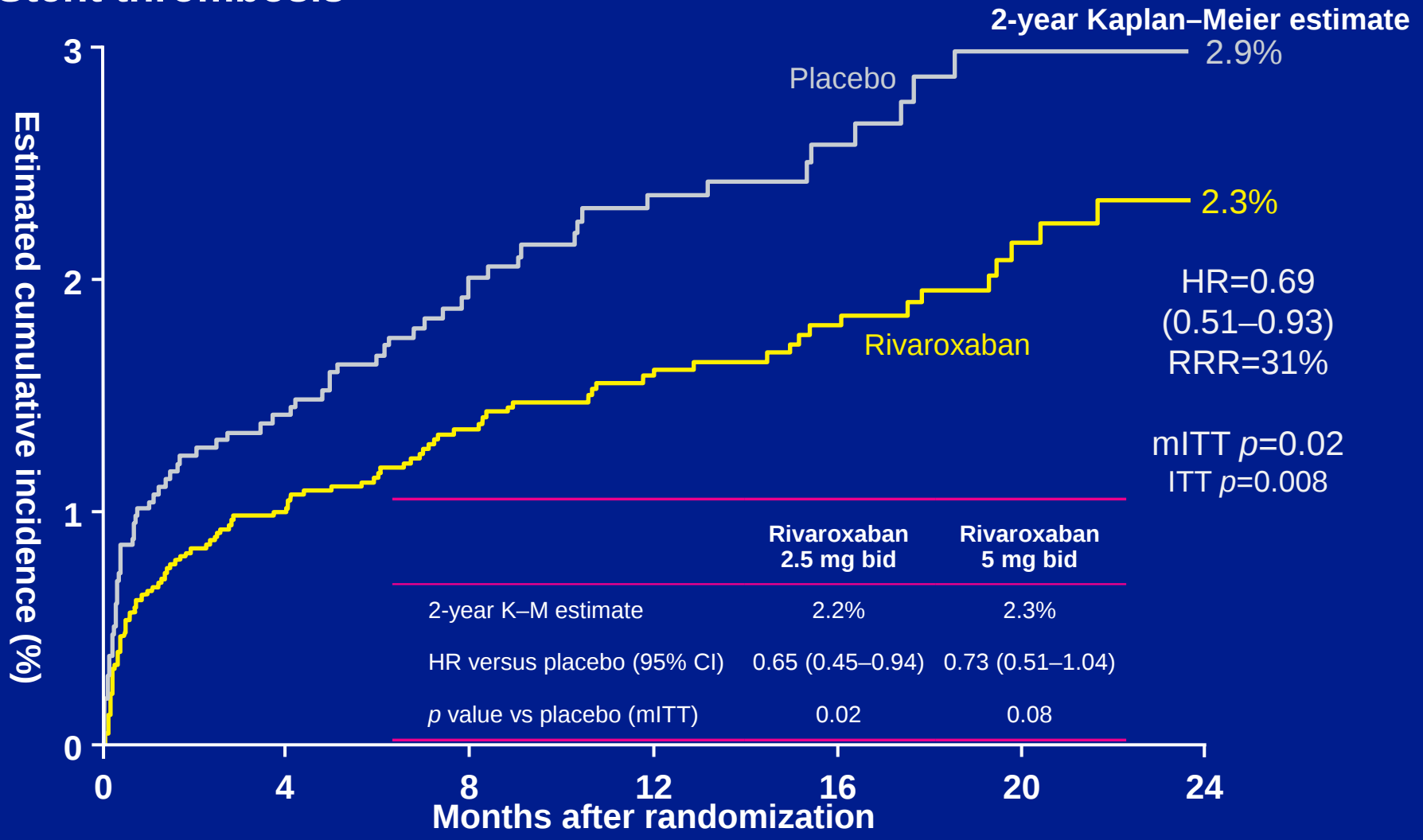
Components of primary endpoint, Rivaroxaban 2.5 mg bid



Mega *et al*, 2011; Gibson *et al*, 2011

ATLAS ACS 2 TIMI 51

Stent thrombosis



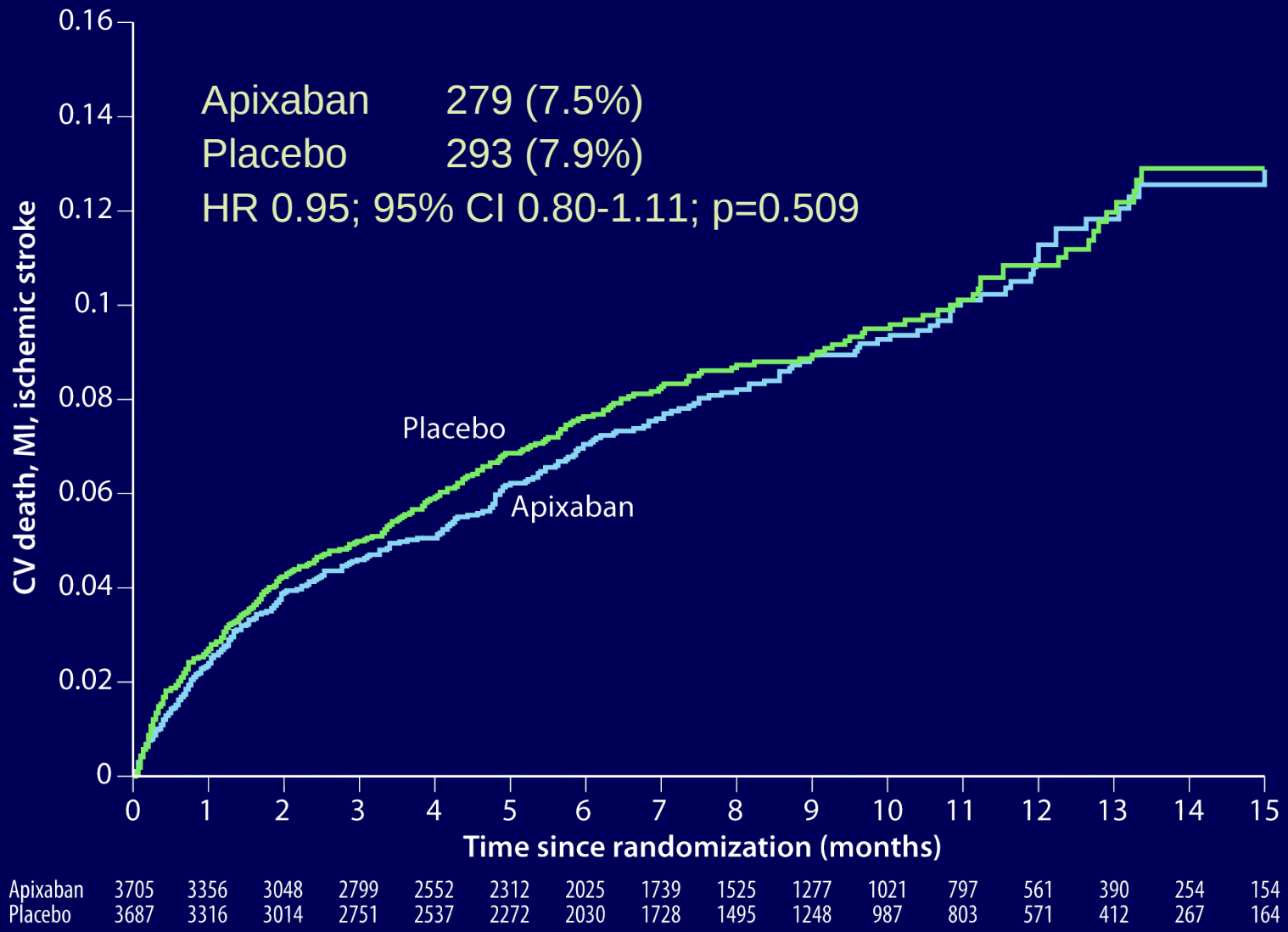
	Rivaroxaban 2.5 mg bid	Rivaroxaban 5 mg bid
2-year K–M estimate	2.2%	2.3%
HR versus placebo (95% CI)	0.65 (0.45–0.94)	0.73 (0.51–1.04)
p value vs placebo (mITT)	0.02	0.08

*Stent thrombosis events: definite, probable or possible (Academic Research Consortium definitions)

Gibson *et al*, 2011; Mega *et al*, 2011

Primary Outcome

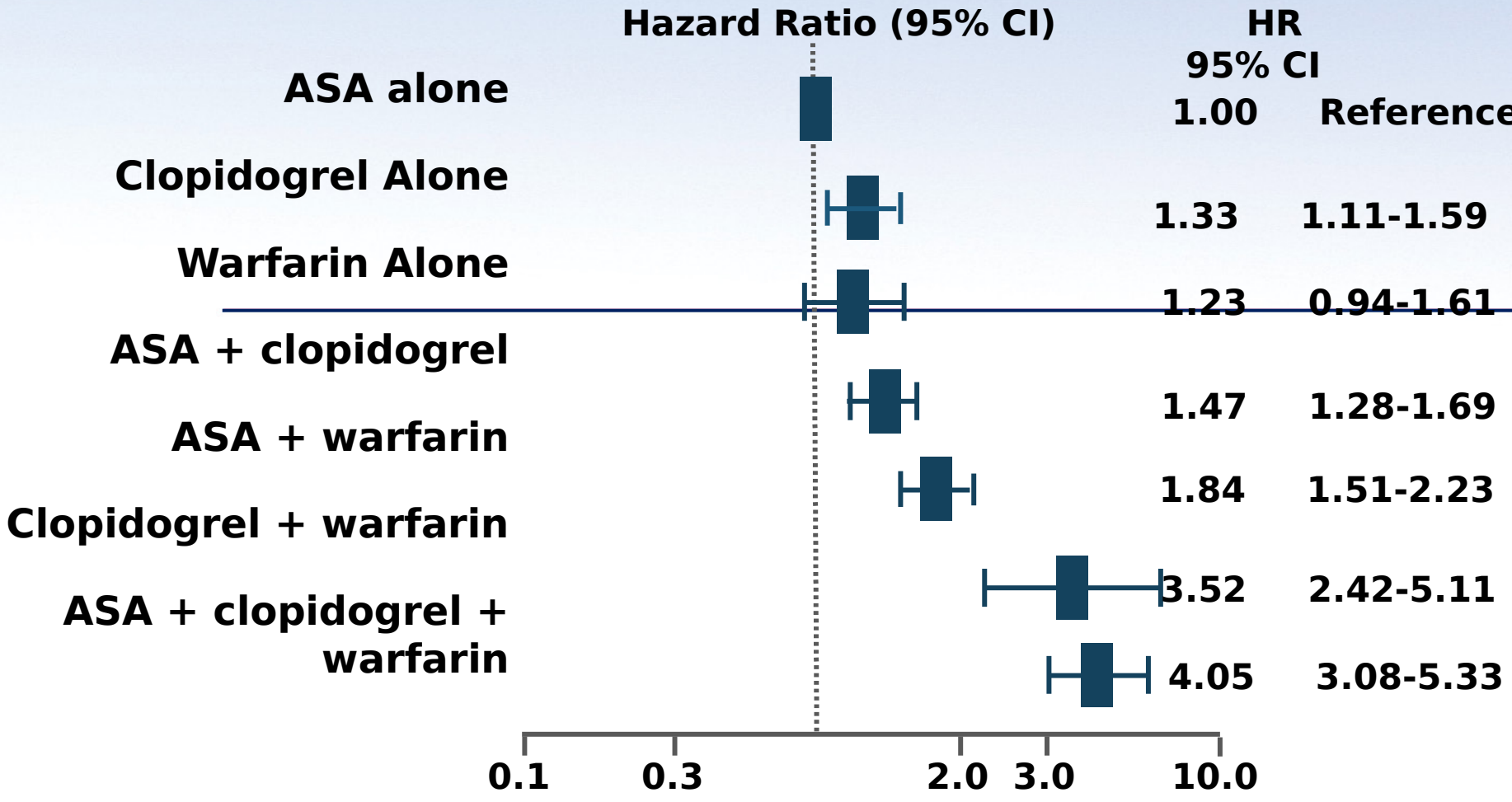
CV Death, MI, Ischemic Stroke



Duke Clinical Research Institute

UCR
UPPSALA CLINICAL
RESEARCH CENTER

Bleeding Risk with Combination Antithrombotic Therapy



CI = Confidence Interval

Lancet 2009; 374: 1967-74.

Triple antithrombotic therapy in cardiac patients: more questions than answers

Moser et al *Eur Heart J* 2014;35:216-23

Difficult decision making in the management of patients with atrial fibrillation and acute coronary syndrome or invasive cardiovascular interventions: new recommendations for daily practice

Boriani et al *Europace* 2015;17:1319-22

Triple therapy for percutaneous coronary intervention in atrial fibrillation: a nightmare

Verheugt *Eur Heart J* 2015;37:326-27

Number of Strategies in the ACS Patient with Atrial Fibrillation

- ASA Dose: None Low High 3
- ASA Duration (months): 1 3 6 12 4
- ADPri: None Clopidogrel Prasugrel Ticagrelor 4
- ADPri Duration (months): 1 3 6 12 4
- OAC: None Warfarin Dabigatran Rivaroxaban Apixaban Edoxaban 5
- OAC INR/Dose: Low High 2

1+8 = 9

ASA

1+12 = 13

ADPri

1+10 = 11

OAC

Permutations of Single, Dual, or Triple Therapy as *Early Initial Therapy (0,1,3,6 months)* following ACS: 9 x 13 x 11 = 1,287

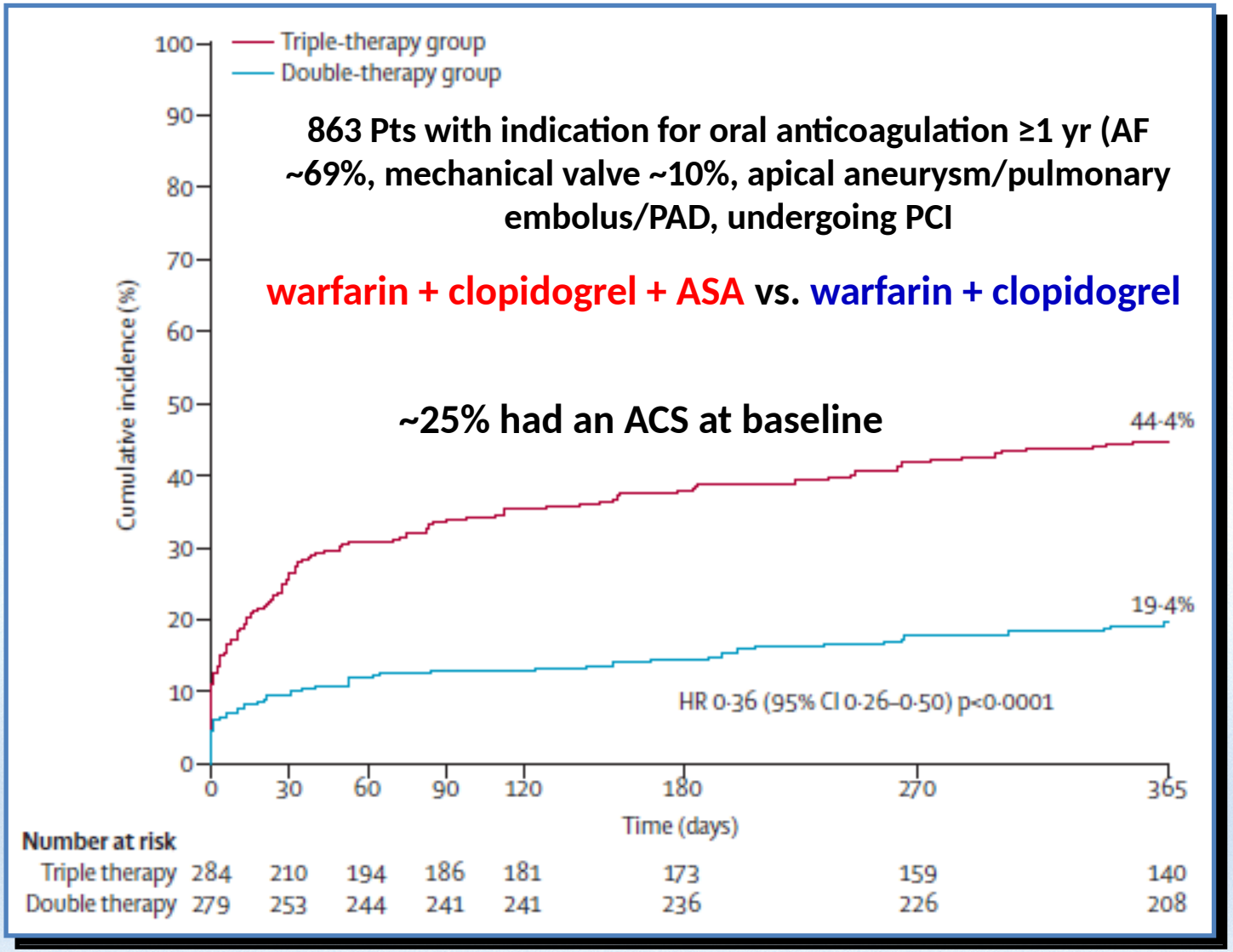
Permutations of Single or Dual Therapy *Late After Early (0,1,3,6 months)* following ACS: 1,287

Total Permutations *throughout 1 year:* 1,656,369

Adapted from C. Michael Gibson

Primary Endpoint: Any Bleeding

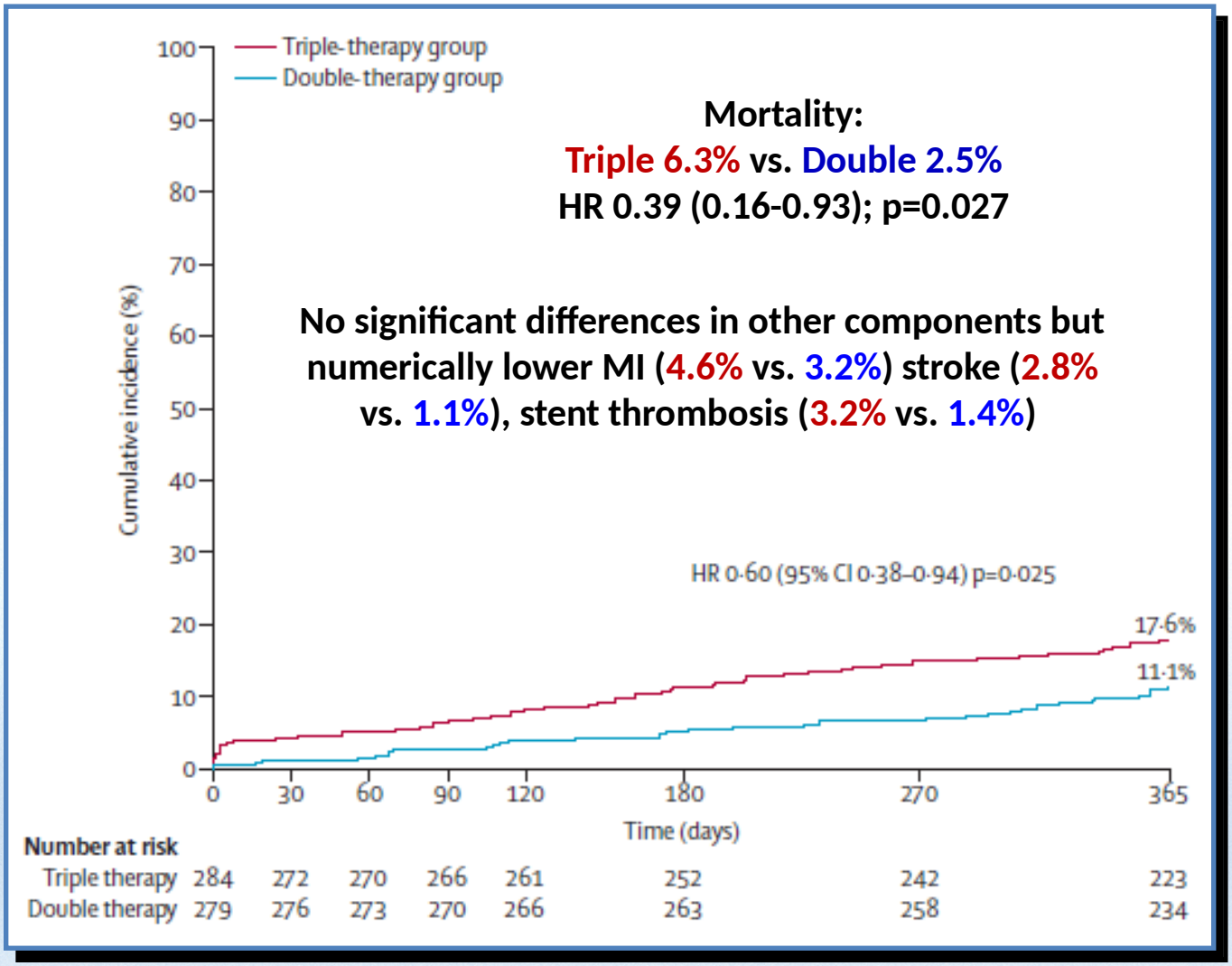
WOEST



Dewilde *et al*., *Lancet* 2013;381:1107-15

Secondary Endpoint: Death/MI/Stroke/Target Vessel Revascularization/Stent Thrombosis

WOEST



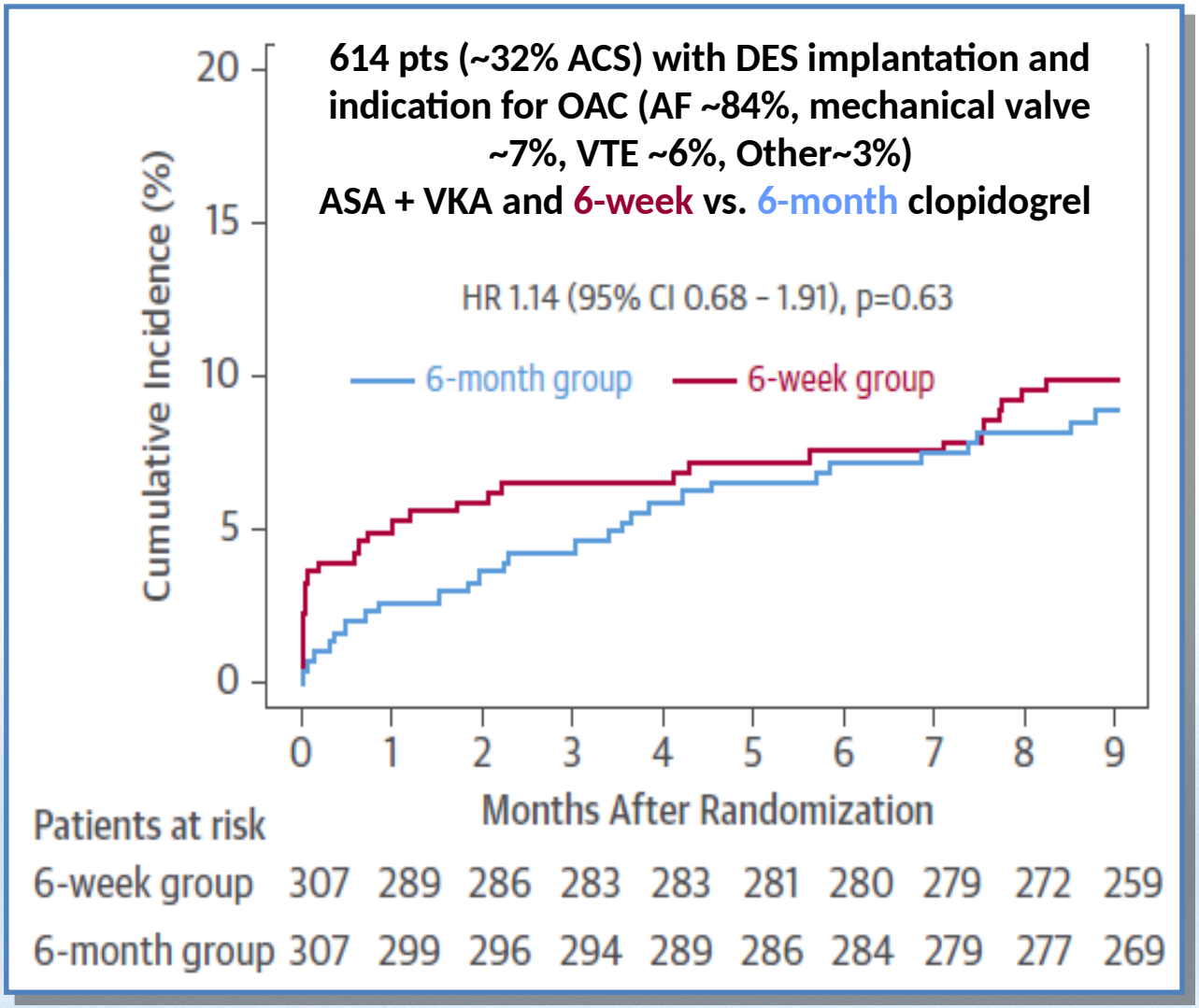
Mortality:
Triple 6.3% vs. Double 2.5%
HR 0.39 (0.16-0.93); p=0.027

No significant differences in other components but numerically lower MI (4.6% vs. 3.2%) stroke (2.8% vs. 1.1%), stent thrombosis (3.2% vs. 1.4%)

Dewilde *et al* ., *Lancet* 2013;381:1107-15

Primary Endpoint: Death, MI, Stent Thrombosis, Stroke, or TIMI Major Bleeding

ISAR-TRIPLE

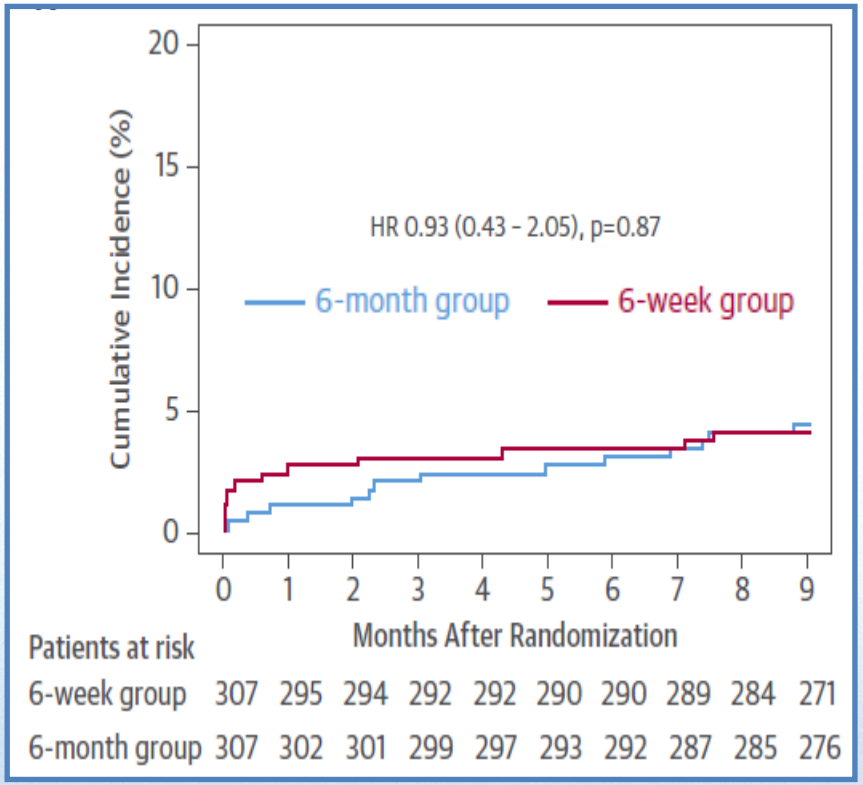


Fiedler *et al.*, *J Am Coll Cardiol* 2015;65:1619-29

Secondary Endpoints

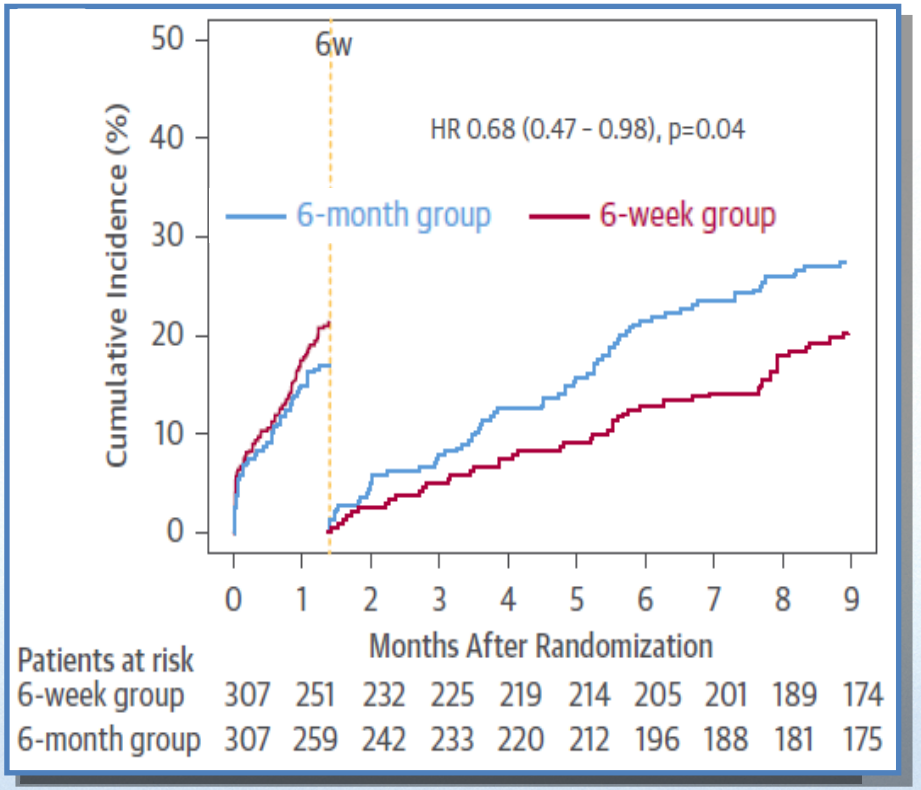
ISAR-TRIPLE

Cardiac Death, MI, Stent Thrombosis or Stroke



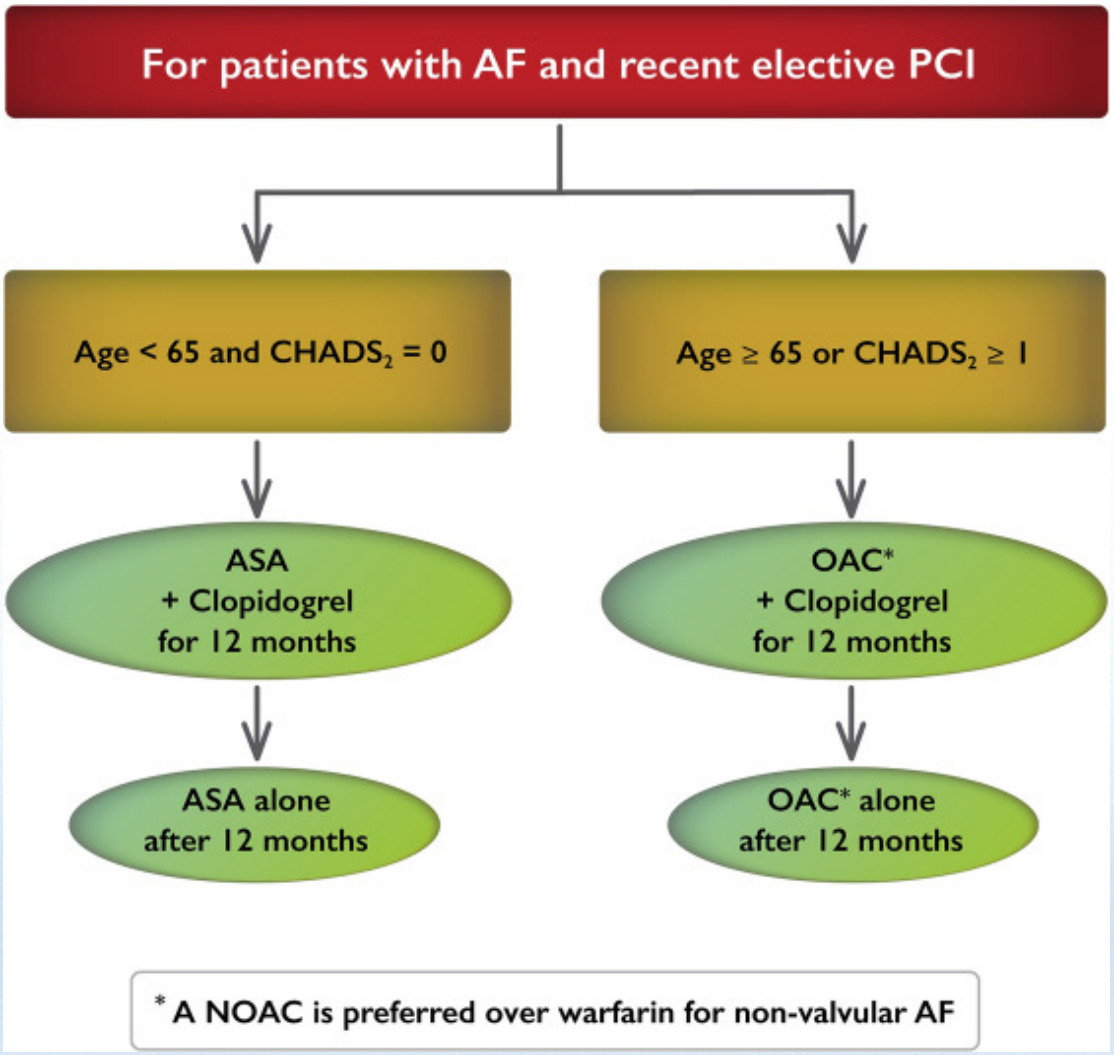
BARC Bleeding (Landmark Analysis)

TIMI Major Bleeding



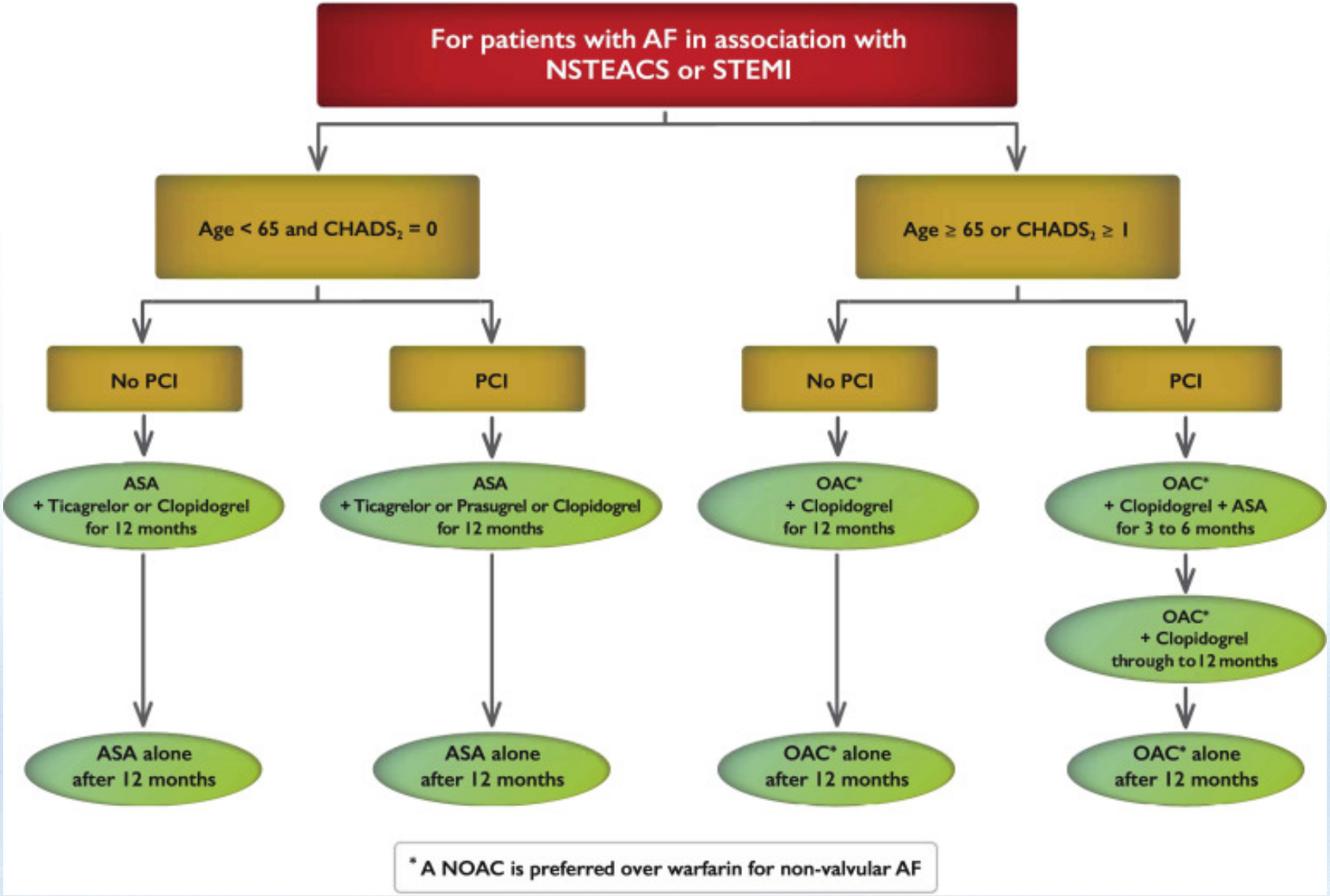
Fiedler *et al .*, *J Am Coll Cardiol* 2015;65:1619-29

2016 CCS Atrial Fibrillation Guidelines: Patients with AF/ elective PCI



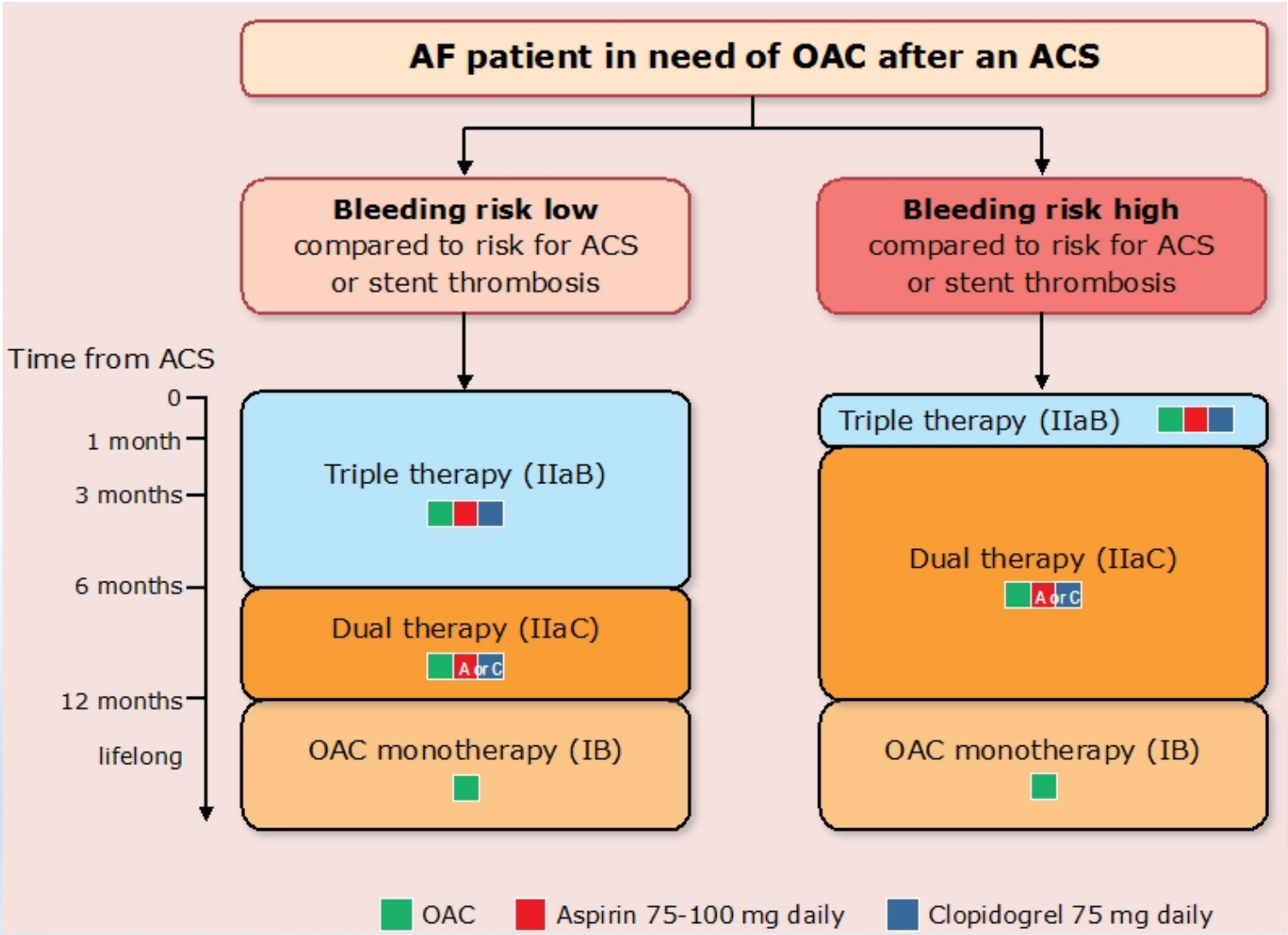
Canadian Journal of Cardiology DOI: (10.1016/j.cjca.2016.07.591)

2016 CCS Atrial Fibrillation Guidelines: Patients with AF/ ACS



Canadian Journal of Cardiology DOI: (10.1016/j.cjca.2016.07.591)

2016 ESC Atrial Fibrillation Guidelines: Patients with AF/ACS

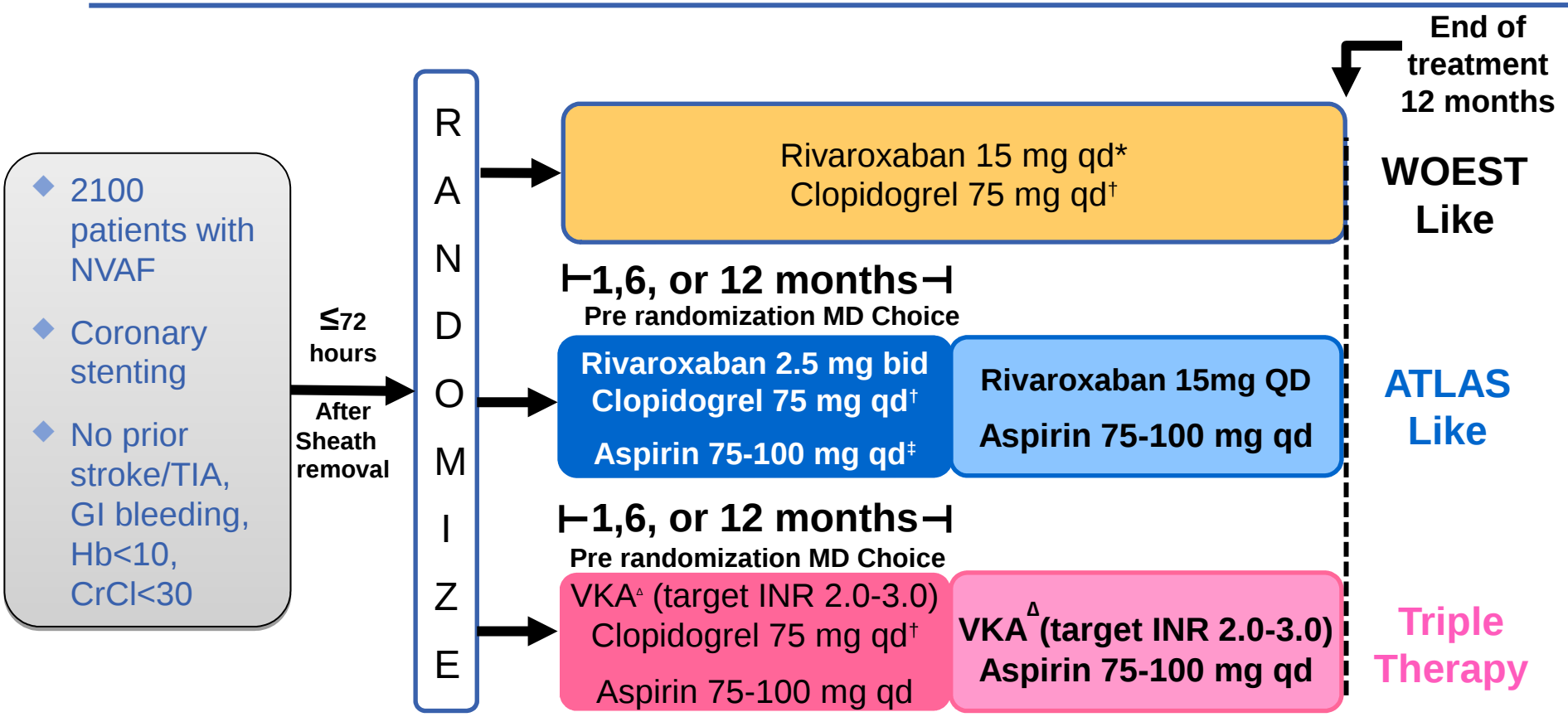


DOI: http://dx.doi.org/10.1093/eurheartj/ehw210 ehw210 First published online: 27 August 2016 www.escardio.org/guidelines

PIONEER AF-PCI: First Prospective Study in Patients with AF Undergoing PCI Taking a NOAC

In an area of limited evidence,
rivaroxaban is the first and currently only NOAC
(versus VKA) to provide data from a dedicated
RCT for patients with AF undergoing PCI

Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI



- Primary endpoint: TIMI major + minor + bleeding requiring medical attention
- Secondary endpoint: CV death, MI, and stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

*Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.

†Alternative $P2Y_{12}$ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.

‡Low-dose aspirin (75-100 mg/d). Δ Open label VKA

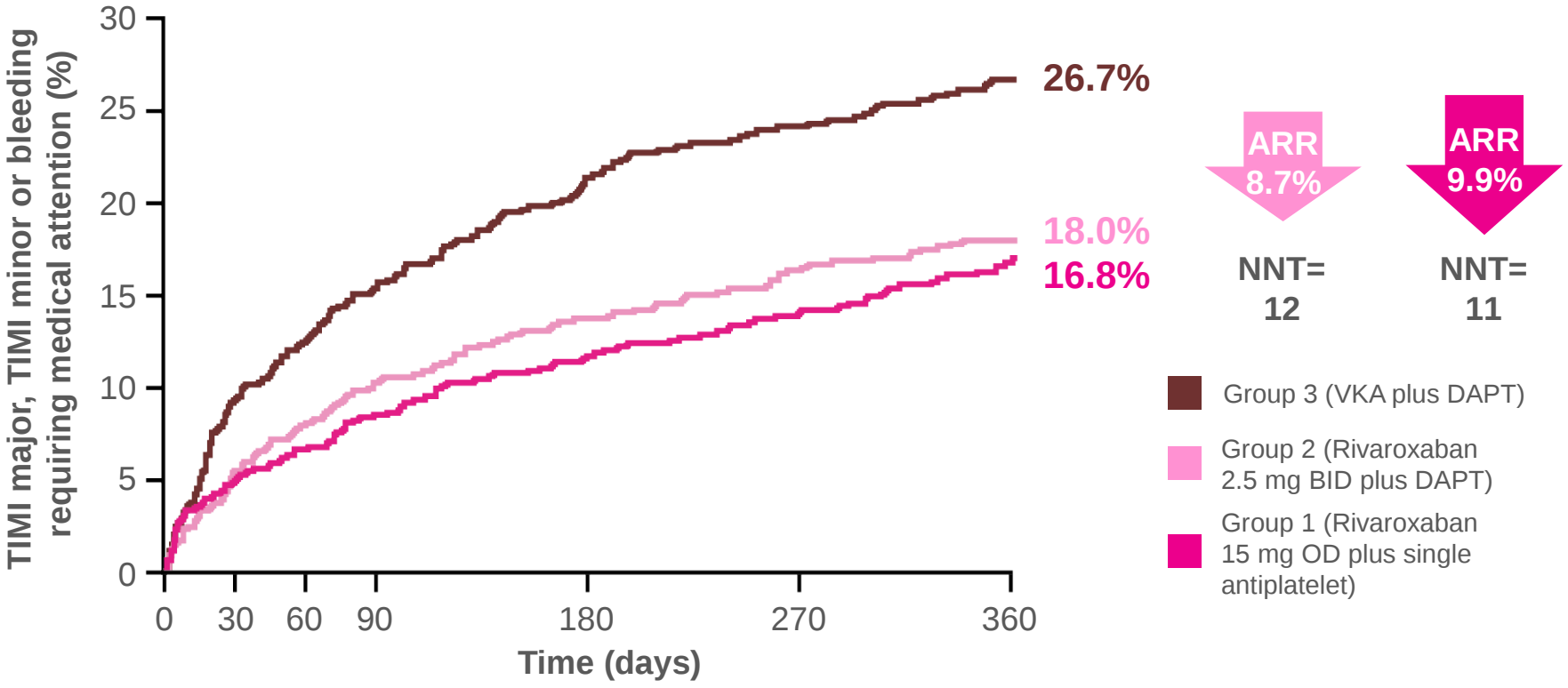
. Janssen Scientific Affairs, LLC. 2016. https://clinicaltrials.gov/ct2/show/NCT01830543 [accessed 10 Oct 2016];
2. Gibson CM *et al*, *Am Heart J* 2015;169:472–478e5; 3. Gibson CM et al, *New Engl J Med* 2016; doi: 10.1056/NEJMoa1611594

Gibson et al. AHA 2016

Both Rivaroxaban Strategies were Associated With Significantly Improved Safety

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=0.59; (95% CI 0.47–0.76); *p*<0.001

Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.63 (95% CI 0.50–0.80); *p*<0.001



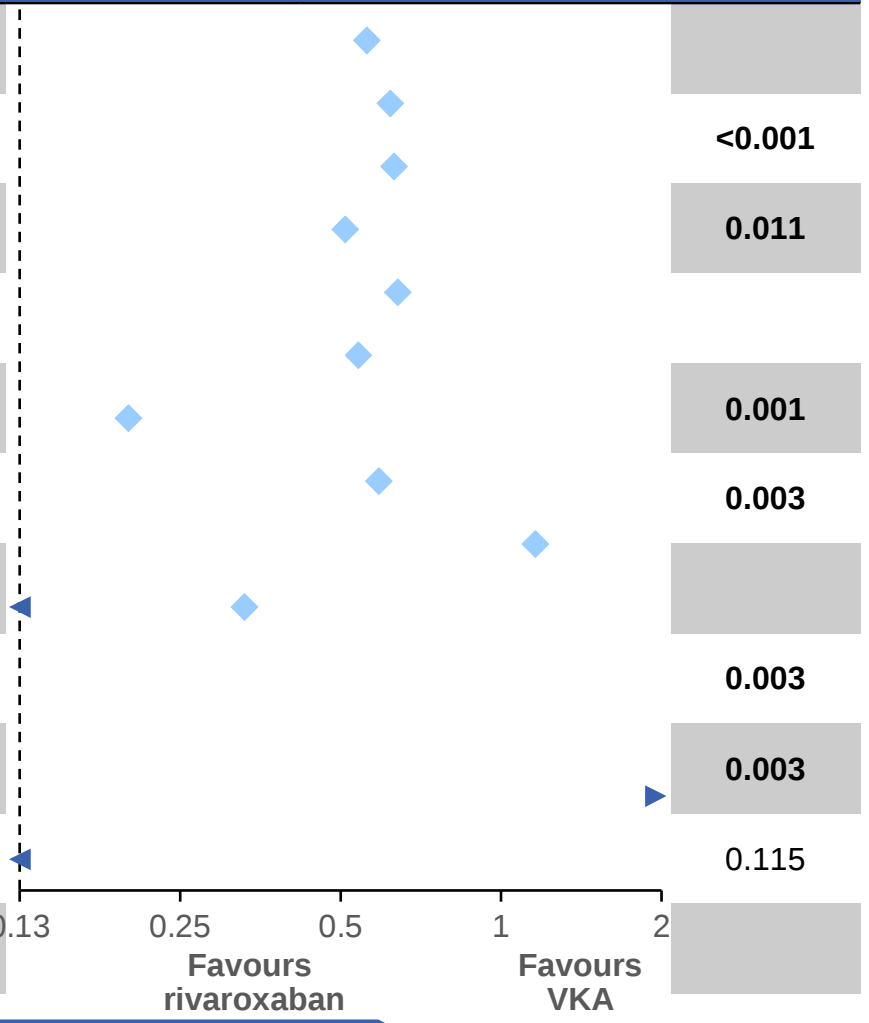
All subgroups analyzed were consistent with overall results

Gibson CM et al, *New Engl J Med* 2016; doi: 10.1056/NEJMoa1611594]

PIONEER AF-PCI

Significantly Reduced Bleeding* with Rivaroxaban 15 mg Strategy Across Subgroups vs VKA plus DAPT

Subgroup	HR	95% CI	*p*-value
Age			
<75 years	0.56	0.41–0.77	**<0.001**
≥75 years	0.62	0.42–0.90	**0.011**
Sex			
Male	0.63	0.47–0.84	**0.001**
Female	0.51	0.32–0.80	**0.003**
Type of stent			
Drug-eluting	0.64	0.47–0.86	**0.003**
Bare metal	0.54	0.36–0.82	**0.003**
Both	0.20	0.02–1.82	0.115
Type of P2Y$_{12}$ inhibitor			
Clopidogrel			**<0.001**



*Composite of TIMI major bleeding, TIMI minor bleeding and bleeding requiring medical attention

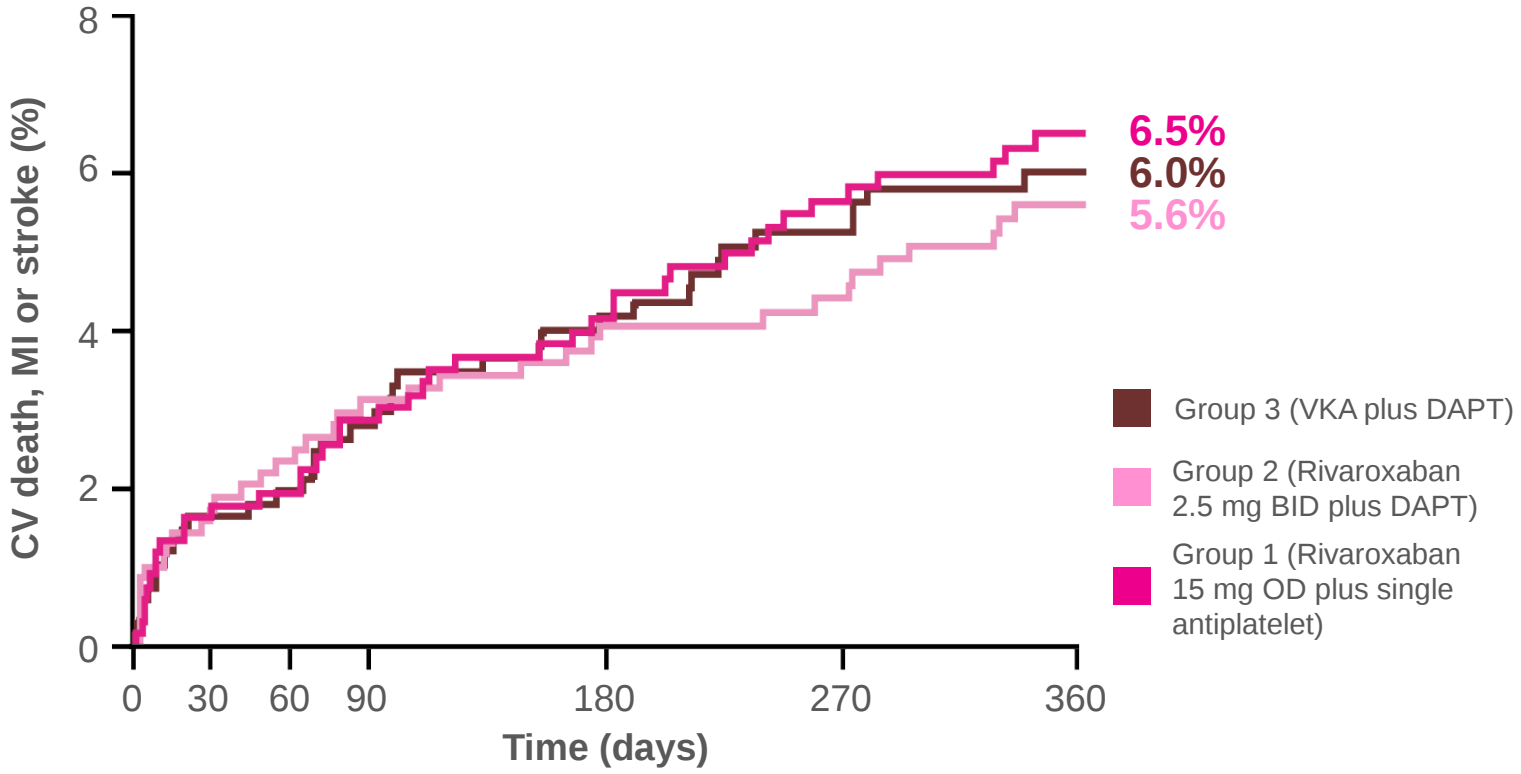
Gibson CM et al, *New Engl J Med* 2016; doi: 10.1056/NEJMoa1611594]

No significant p-value for interaction

Efficacy (CV Death, MI, Stroke) was Comparable Between All Three Treatment Strategies*

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=1.08; (95% CI 0.69–1.68); *p*=0.750

Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.93 (95% CI 0.59–1.48); *p*=0.765



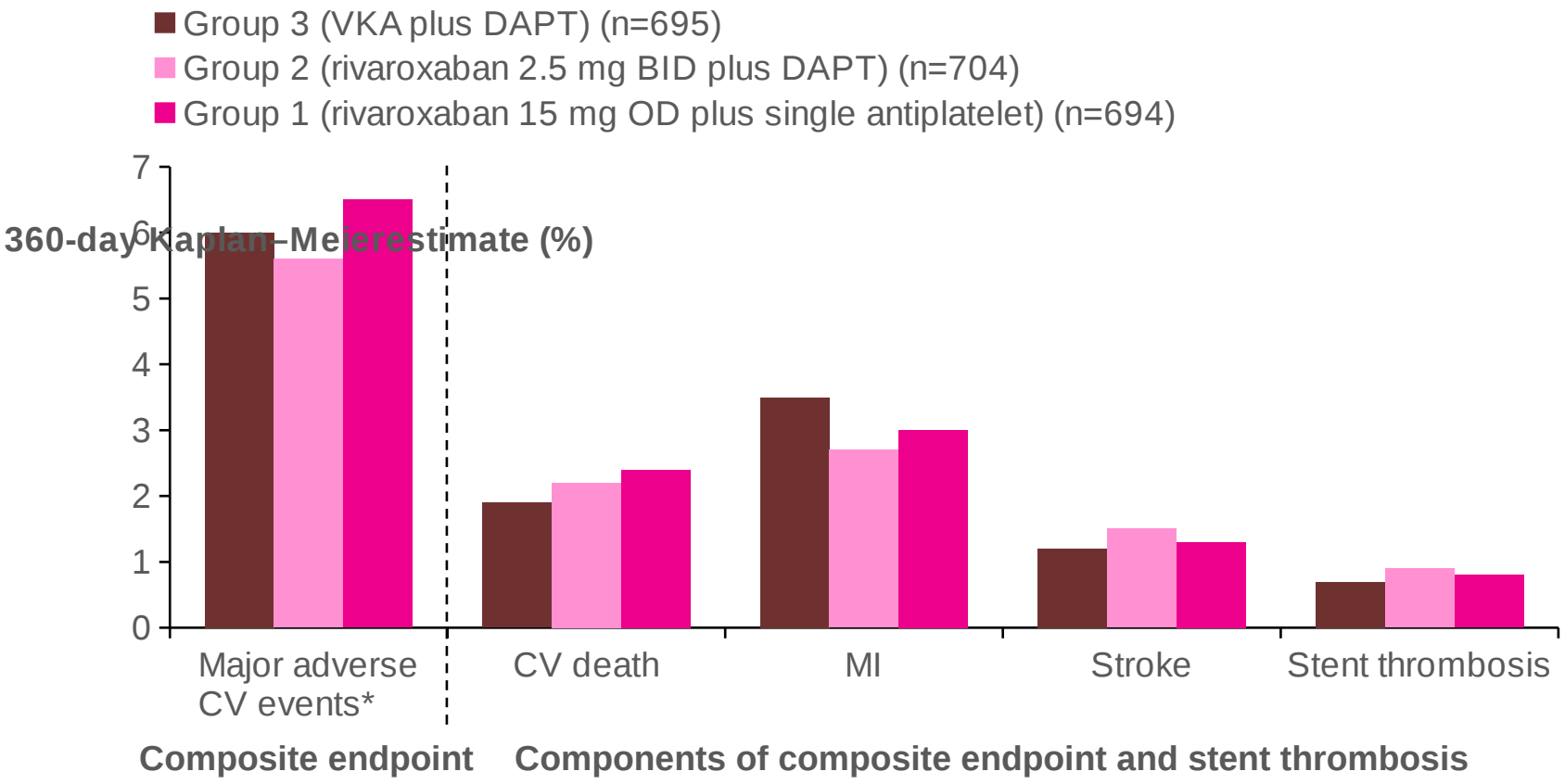
All subgroups analyzed were consistent with overall results

*Trial not powered to definitively demonstrate either superiority or non-inferiority for efficacy endpoints

Gibson CM et al, *New Engl J Med* 2016; doi: 10.1056/NEJMoa1611594

PIONEER AF-PCI

Comparable Efficacy with Rivaroxaban Strategies vs VKA plus DAPT

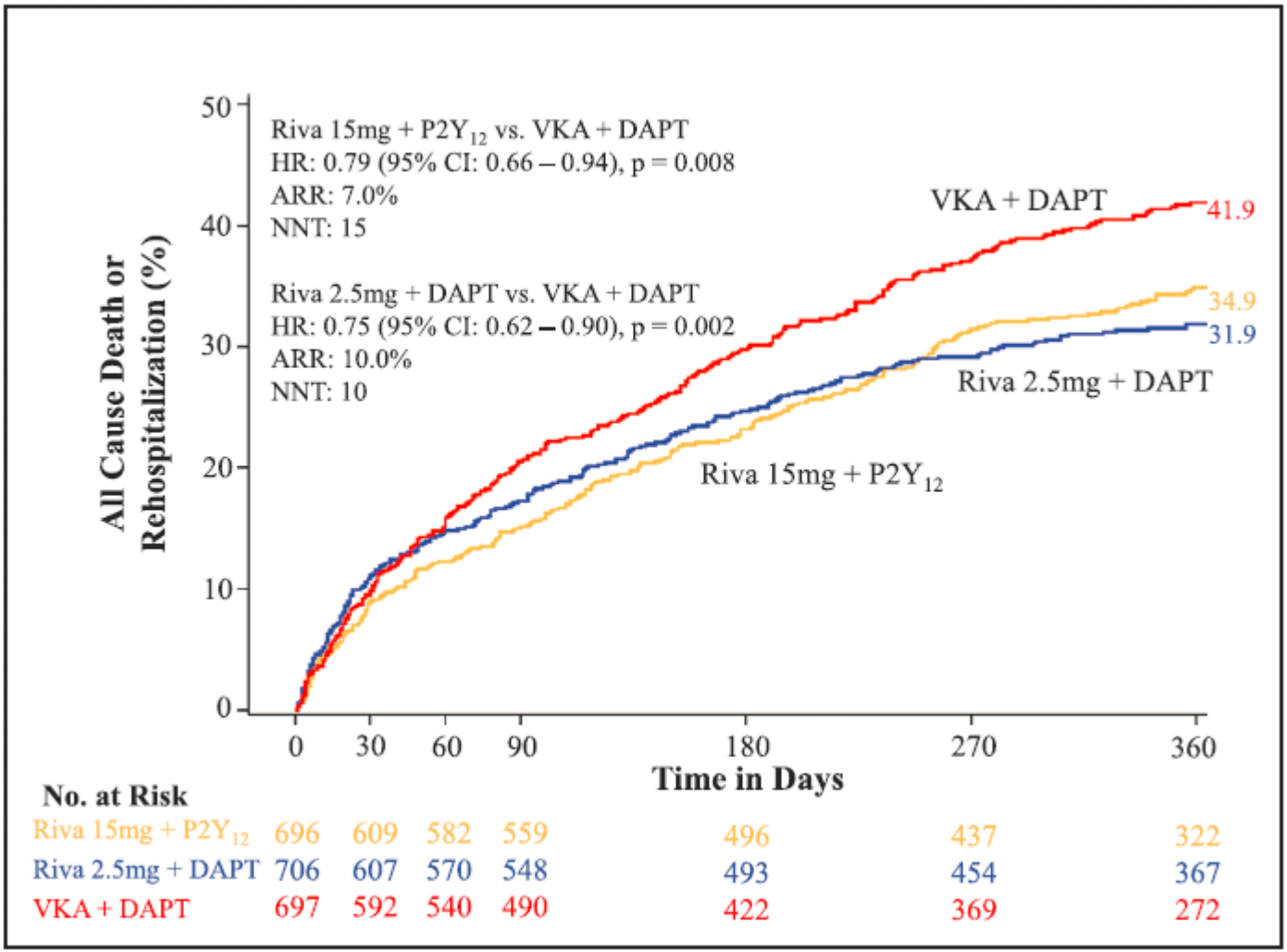


Incidence of major adverse CV events was comparable between all three treatment strategies; however, the trial was not powered for efficacy

*Composite of CV death, MI and stroke

Gibson CM et al, *New Engl J Med* 2016; doi: 10.1056/NEJMoa1611594]

Time to All Cause Death or First Rehospitalization is Reduced in Both Rivaroxaban Treatment Arms



Gibson CM *et al*, *Circulation* 2016; doi:10.1161/CIRCULATIONAHA.116.025783

Summary

1. A strategy of either rivaroxaban plus a $P2Y_{12}$ was associated with a reduction in clinically significant bleeding compared with conventional triple therapy of warfarin + DAPT (NNT = 11 or 12).

2. CV death / MI / stroke were comparable among the groups.

3. Rates of all cause death or hospitalization were reduced in the rivaroxaban arms (NNT = 10-15).

Clinical Implications of PIONEER AF-PCI Trial

In Patients with Atrial Fib who undergo PCI;

- Drop the ASA in all patients except for those with highest coronary ischemic risk.
- Maintain the patient on rivaroxaban 15 g daily plus clopidogrel or ticagrelor for up to 12 months.
- Subsequently drop the clopidogrel or ticagrelor and increase the rivaroxaban to 20mg daily (or one of other NOACS at recommended dose)

Management of Atrial Fib Patients with CAD

- Its going to be difficult to create a universal rule to apply to the wide spectrum of patients with CAD and atrial fibrillation.
- Need to consider;
  I. **Coronary ischemic risk** – chronic CAD vs NSTEMI vs STEMI, extent of CAD, number of stents, other technical interventional factors
  II. **Stroke risk** – CHADS2 score
  III. **Bleeding risk**
- There is not going to be a simple risk score to integrate all these continuous variables; we will have guiding principles.
- We will need to work as a team to determine the optimal combination of anticoagulant and anti-platelet agents for the individual patient and reassess the plan over time.

HCRI
Harvard Clinical Research Institute

RE-DUAL PCI™

Study in NVAF patients undergoing PCI

Worldwide Event Driven Trial

Paroxysmal, persistent or permanent AF
(PCI with stenting [BMS or DES] elective or ACS)

Run in period*

Dabigatran 150mg BID + P2Y12 inhibitor¥

‡ 1° EP
Bleeding, death, MI, and stroke

ibitor¥ + ASA ‡

5M∏ 18/24/30M or EOT∏

0-3 days post-PCI

Complex patient with Dabigatran inhibitor¥ + ASA vs 3.0) + P2

Non-Complex pat Dabigatran 15 inhibitor¥ (with d/c of ASA) vs. TAT with Warfarin (INR 2.0-3.0) + P2Y12 inhibitor¥ + ASA

r arm nts)

Maintenance of DAT regimen in D110/D150 arms

TAT: triple antithrombotic therapy
DAT: dual antithrombotic therapy

RE-DUAL PCI stopped in November 2016 after recruiting 2727 patients and results expected for ESC 2017. It is no longer powered for efficacy endpoints (similar to PIONEER-AF)

*Run in: pre-assessment of the patient high-risk vs. non-high risk characteristics (bridging therapy during the procedure [LMWH, Bivalirudin , UFH, etc.] at the discretion of practicing physician)

**Randomization can be done immediately after PCI and up to 72 hours post-PCI; study drug can be started between 6 hours after sheath removal and hemostasis is assured and up to 72 hours post-PCI

†Complex criteria: patient's clinical presentation (ACS vs. non-ACS) and lesion/procedure characteristics (e.g. left main, etc.) → DAPT Study Complexity Criteria

Δ Initiation of DAT or TAT in Complex patients randomized to receive dabigatran is left at the discretion of the practicing physician

‡ ASA will be discontinued in the warfarin arm. BMS: Discontinuation of ASA at month 1 ; DES: discontinuation of ASA at month 3

∏ Follow up visits at month 1, 3, 6, 9, 12, 15 and 18, 24 and 30 post-randomization

¥ P2Y12 inhibitor (either Clopidogrel or Ticagrelor). The P2Y12 inhibitor can be discontinued after month 12 of follow up at the discretion of the physician

Apixaban Versus Warfarin in Patients with AF and ACS or PCI: The AUGUSTUS Trial

AF (prior, persistent, or >6 hrs duration)
- Physician decision that oral anticoag is indicated
- ACS or PCI with planned P2Y12 inhibitor for 6 months

Randomize
n=4,600
Patients

Exclusion
- Contraindication to DAPT
- Other reason for VKA (prosthetic valve, mod/severe MS)

Apixaban 5mg BID

Warfarin

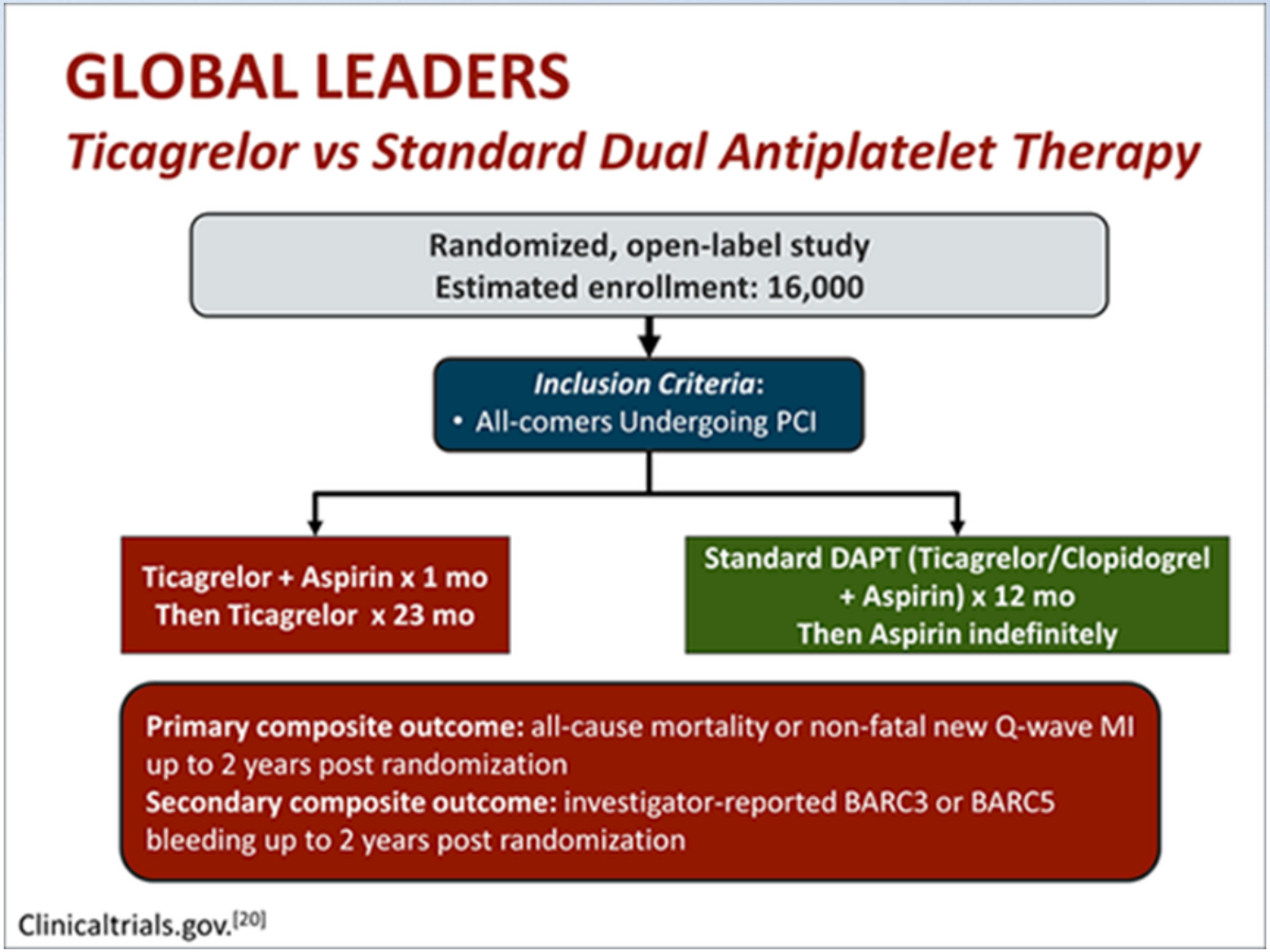
P2Y12 inhibitor for all patients x 6 months
ASA for all on the day of ACS or PCI
ASA versus placebo after randomization

ASA | **placebo** | **ASA** | **placebo**

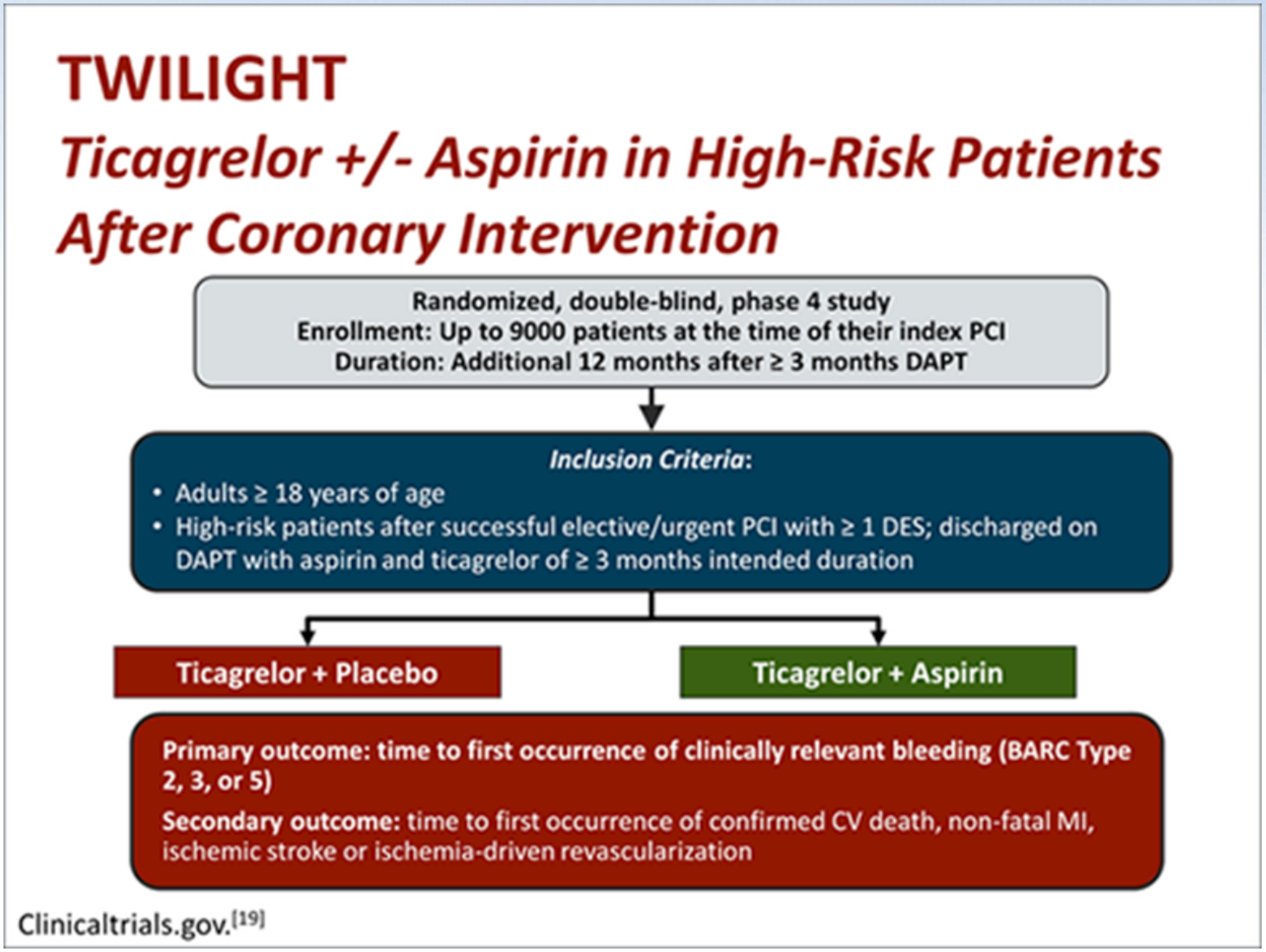
Primary outcome: major/clinically relevant bleeding (through 6 months)

Secondary objective: Death, MI, stroke, stent thrombosis

What is the Future of ASA in CAD



What is the Future of ASA in CAD



What is the Future of ASA in CAD - COMPASS Trial

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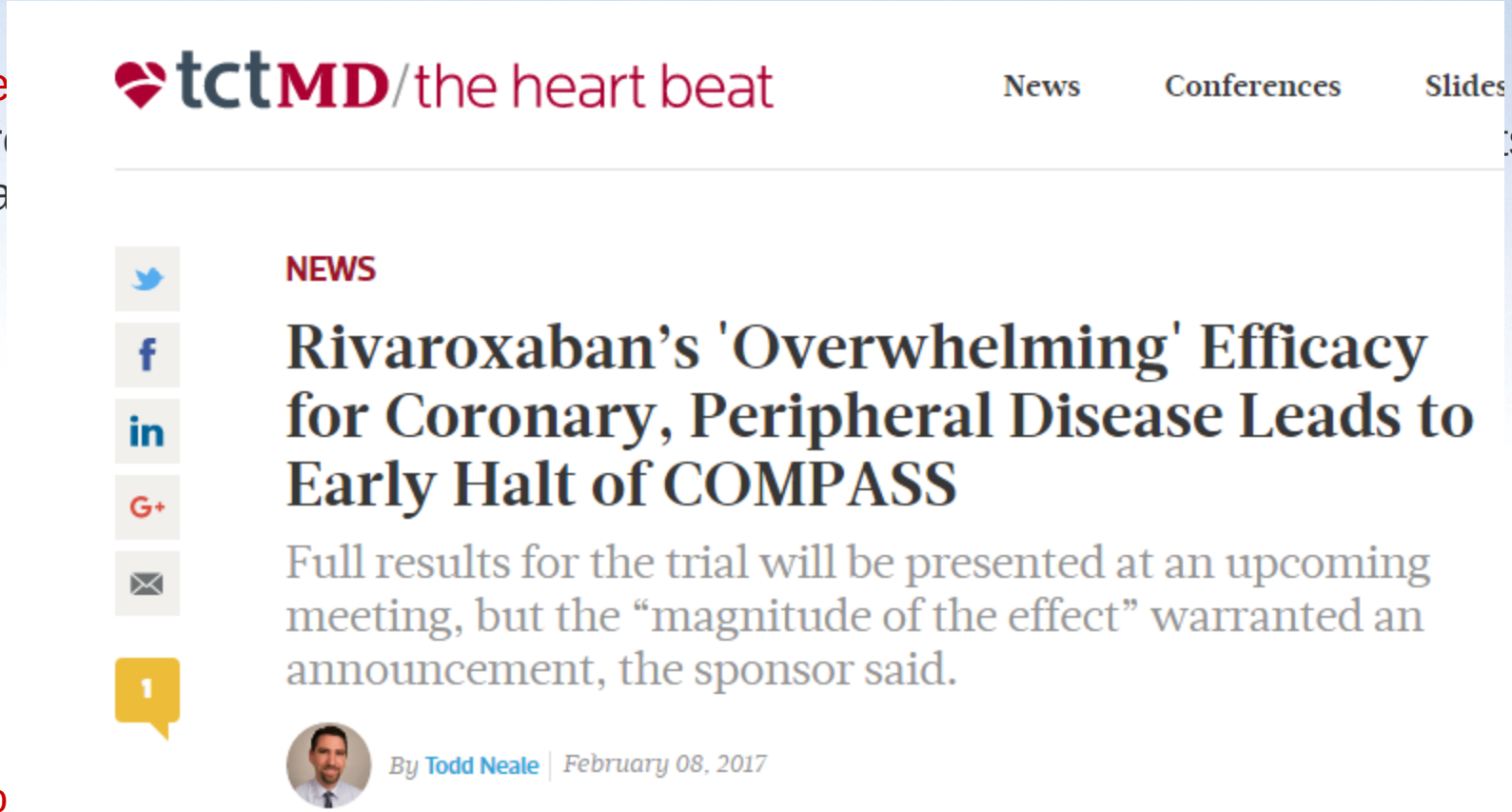

tctMD/the heart beat

News Conferences Slides

NEWS

Rivaroxaban's 'Overwhelming' Efficacy for Coronary, Peripheral Disease Leads to Early Halt of COMPASS

Full results for the trial will be presented at an upcoming meeting, but the "magnitude of the effect" warranted an announcement, the sponsor said.

By Todd Neale | February 08, 2017

Endpo

Primary efficacy endpoint: composite of CV death, MI and stroke
Primary safety endpoint: major bleeding
Secondary outcome measures: composite of MI, stroke, CV death, venous thromboembolism and CV hospitalization, all-cause mortality