Which drug do you prefer for stable CAD?

- P2Y12 inhibitor

Jung Rae Cho, MD, PhD

Cardiovascular Division, Department of Internal Medicine

Kangnam Sacred Heart Hospital, Hallym University Medical Center, Seoul, Korea

HALLYM UNIVERSITY MEDICAL CENTER
KANGNAM SACRED HEART HOSPITAL

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Mechanism of platelet activation & thrombosis

Binding sites of antiplatelet agents

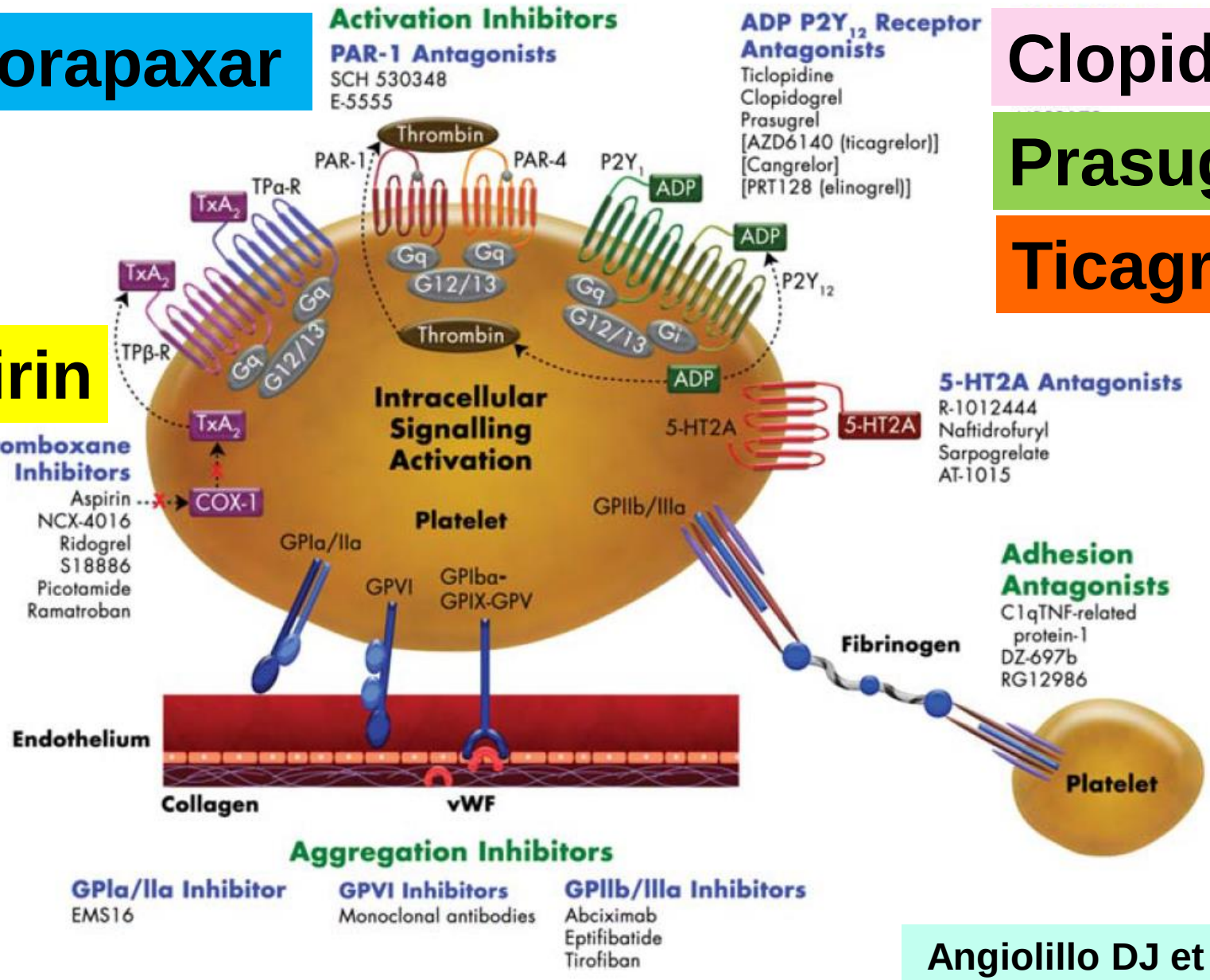
Vorapaxar

Aspirin

Clopidogrel

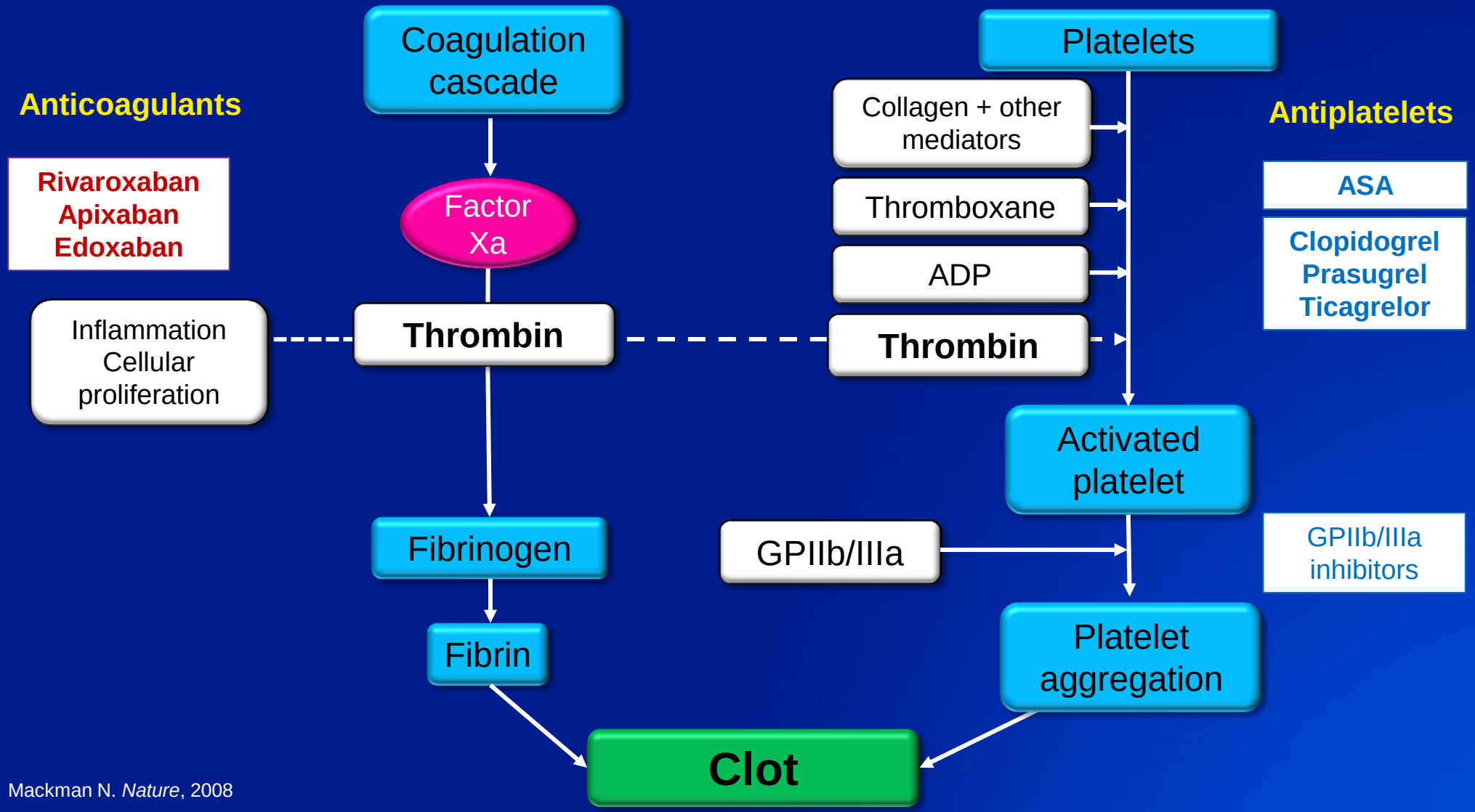
Prasugrel

Ticagrelor



Angiolillo DJ et al. EHJ 2010

Thrombus formation involves both platelet activation and blood coagulation



Mackman N. *Nature*, 2008

Standard of care for stable CAD undergoing PCI

Antithrombotic Therapy in Patients with SCAD undergoing PCI

Recommendations for PCI	Class[a]	Level[b]	Ref[c]
Pretreatment with antiplatelet therapy			
Treatment with 600 mg clopidogrel is recommended in elective PCI patients once anatomy is known and decision to proceed with PCI preferably 2 hours or more before the procedure.	I	A	789–792
Pretreatment with clopidogrel may be considered in patients with high probability for significant CAD.	IIb	C	
In patients on a maintenance dose of 75 mg clopidogrel, a new loading dose of 600 mg or more may be considered once the indication for PCI is confirmed.	IIb	C	
Antiplatelet therapy during PCI			
ASA is indicated before elective stenting.	I	B	776,793,794
ASA oral loading dose of 150–300 mg (or 80-150 mg i.v.) is recommended if not pre-treated.	I	C	
Clopidogrel (600 mg loading dose or more, 75 mg daily maintenance dose) is recommended for elective stenting.	I	A	795–798
GP IIb/IIIa antagonists should be considered only for bail-out.	IIa	C	
Antiplatelet therapy after stenting			
DAPT is indicated for at least 1 month after BMS implantation.	I	A	791,799–801
DAPT is indicated for 6 months after DES implantation.	I	B	799,802,803
Shorter DAPT duration (<6 months) may be considered after DES implantation in patients at high bleeding risk.	IIb	A	804,805
Life-long single antiplatelet therapy, usually ASA, is recommended.	I	A	776,794
Instruction of patients about the importance of complying with antiplatelet therapy is recommended.	I	C	-
DAPT may be used for more than 6 months in patients at high ischaemic risk and low bleeding risk.	IIb	C	-
Anticoagulant therapy			
Unfractionated heparin 70–100 U/kg.	I	B	806
Bivalirudin (0.75 mg/kg bolus, followed by 1.75 mg/kg/hour for up to 4 hours after the procedure) in case of heparin-induced thrombocytopenia.	I	C	-
Bivalirudin (0.75 mg/kg bolus, followed by 1.75 mg/kg/hour during the procedure) in patients at high bleeding risk.	IIa	A	783–785
Enoxaparin i.v. 0.5 mg/kg.	IIa	B	786,788,807

2014 ESC Guideline for Myocardial Revascularization

Co-primary Endpoints : MACCE

DAPT STUDY

Major Adverse Cardiovascular and Cerebrovascular Events	
12–30 mo	Thienopyridine vs. placebo, 4.3% vs. 5.9%; hazard ratio, 0.71; P<0.001
12–33 mo	Thienopyridine vs. placebo, 5.6% vs. 6.5%; hazard ratio, 0.82; P=0.02

For patients with highly-perceived ischemic risk treated using DES (EES 47%, PES 27%), prolonged DAPT (clopidogrel 65%, prasugrel 35%) might reduce ischemic events, with increase of bleeding events

Months since Enrollment

No. at Risk								
Thienopyridine	5020	4917	4840	4778	4702	4611	4554	3029
Placebo	4941	4799	4715	4635	4542	4476	4412	2997

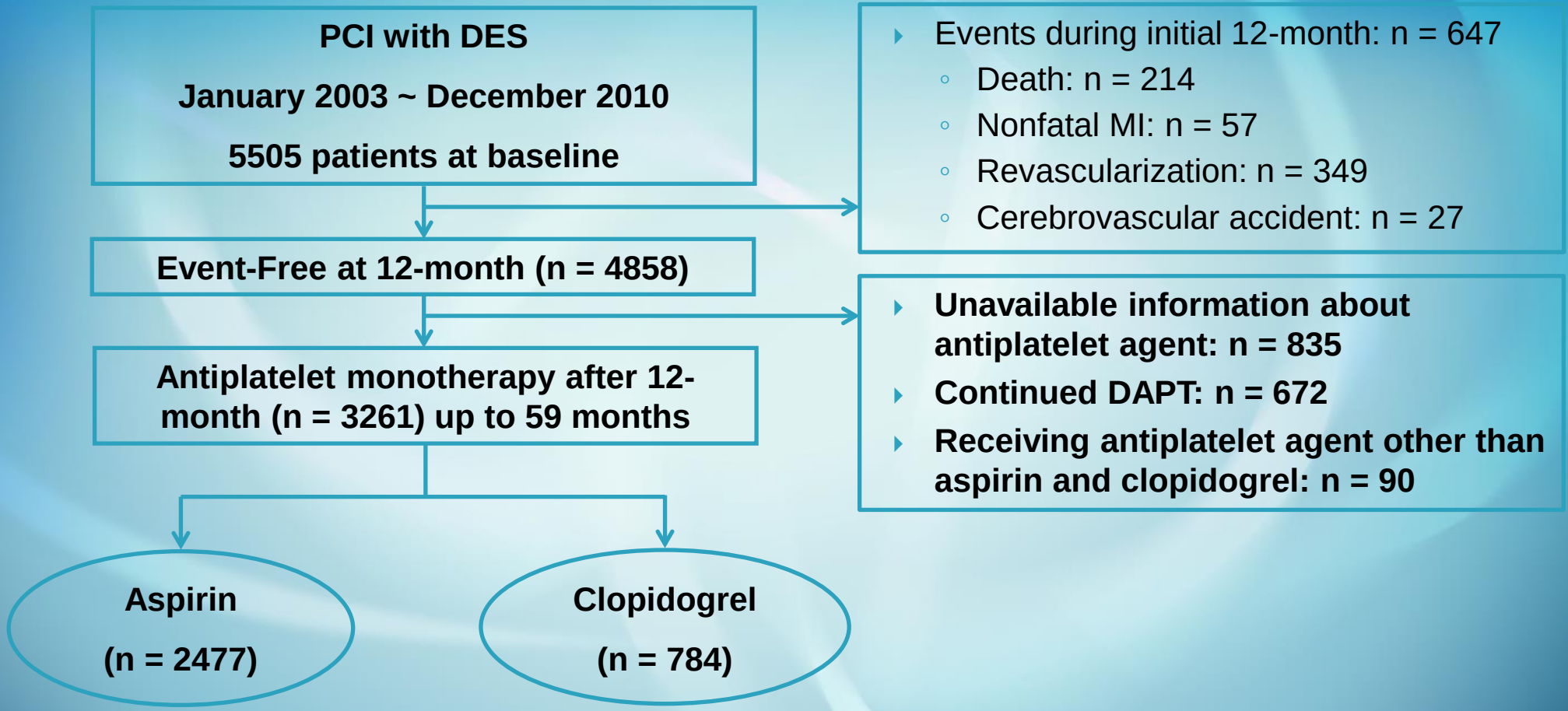
The group that continued thienopyridine, as compared with the group that received placebo, had a significantly lower cumulative incidence of major adverse cardiovascular and cerebrovacular events.

Mauri L, et al. *NEJM. 2014. Published Online http://www.nejm.org/doi/pdf/10.1056/NEJMoa1409312*

Aspirin vs. Clopidogrel after DAPT

Single center, observational study (Samsung Medical Center in) Korea

Choice of antiplatelet agent → the operator's discretion



SANOFI

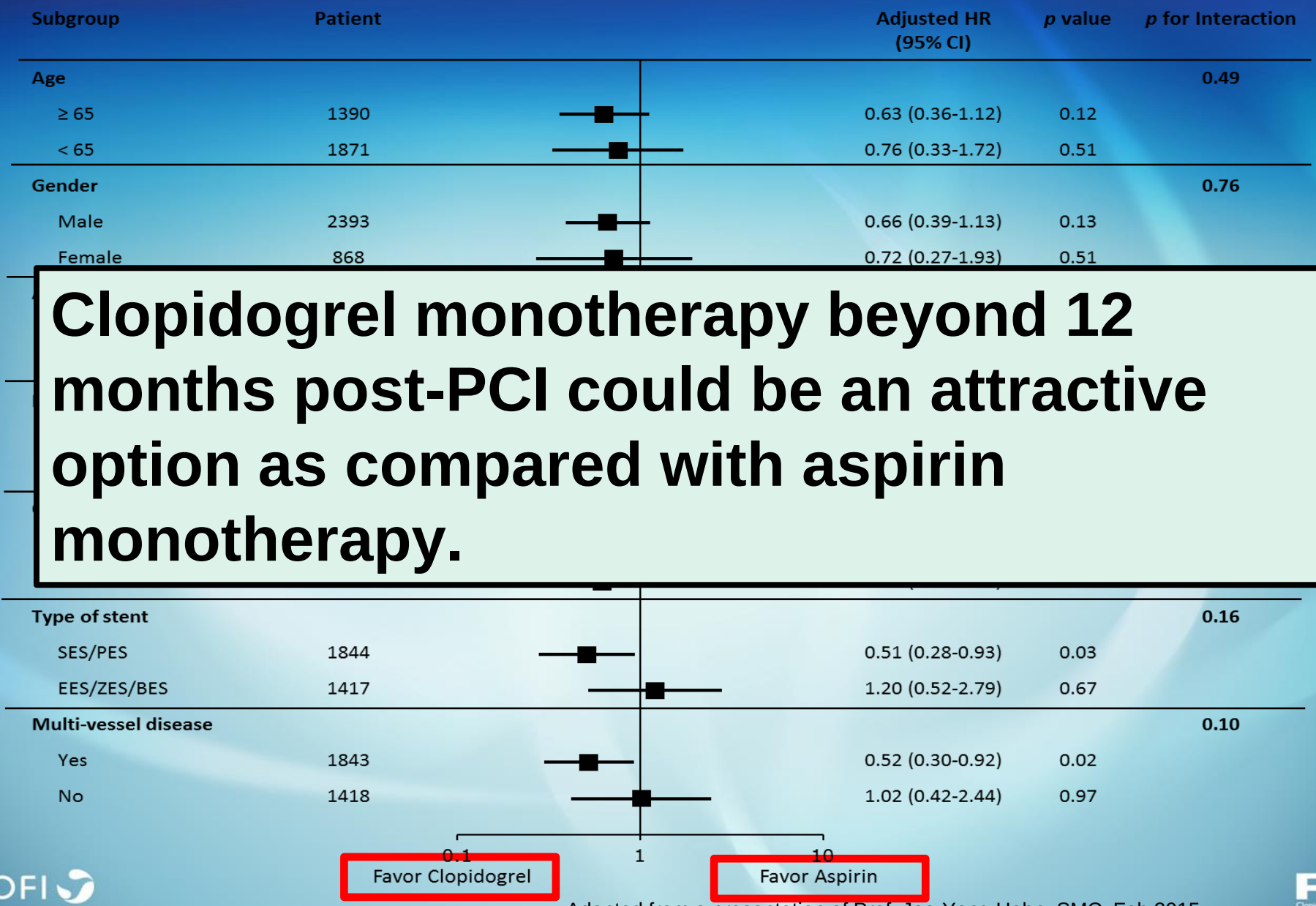
Park TK, Song YB et al. ACC 2014

Clinical outcomes

	Aspirin (n=2477)	Clopidogrel (n=784)	Before weighting HR* (95% CI)	Before weighting P value	After IPTW weighting HR* (95% CI)	After IPTW weighting P value
Total death	131 (5.3)	26 (3.3)	0.85 (0.55-1.33)	0.48	0.89 (0.61-1.31)	0.56
Cardiac death	50 (2.0)	7 (0.9)	0.51 (0.22-1.16)	0.11	0.54 (0.25-1.15)	0.11
MI	51 (2.1)	7 (0.9)	0.68 (0.30-1.54)	0.36	0.42 (0.17-1.04)	0.06
Stent thrombosis	18 (0.7)	1 (0.1)	0.29 (0.04-2.29)	0.24	0.12 (0.01-2.19)	0.15
TLR	109 (4.4)	14 (1.8)	0.71 (0.40-1.26)	0.24	0.63 (0.37-1.08)	0.09
TVR	184 (7.4)	23 (2.9)	0.64 (0.41-0.99)	0.05	0.53 (0.34-0.82)	0.004
CVA	60 (2.4)	11 (1.4)	0.73 (0.37-1.42)	0.36	0.62 (0.32-1.20)	0.16
Cardiac death or MI	93 (3.8)	13 (1.7)	0.61 (0.33-1.11)	0.11	0.51 (0.28-0.93)	0.03
Cardiac death, MI, or CVA	144 (5.8)	22 (2.8)	0.65 (0.41-1.04)	0.07	0.51 (0.32-0.83)	0.006

Values are expressed as number of patients (%).
IPTW indicates inverse probability of treatment weighting; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; CVA, cerebrovascular accident.
*Adjusted covariates included age, sex, clinical presentation, diabetes mellitus, hypertension, dyslipidemia, current smoker, chronic renal failure, previous MI, previous percutaneous coronary intervention, previous bypass surgery, previous CVA, angiographic disease extent, number of treated lesion, number of stent used, stent diameter, total stent length, left main or left anterior descending artery as a treated vessel, and type of drug-eluting stent.

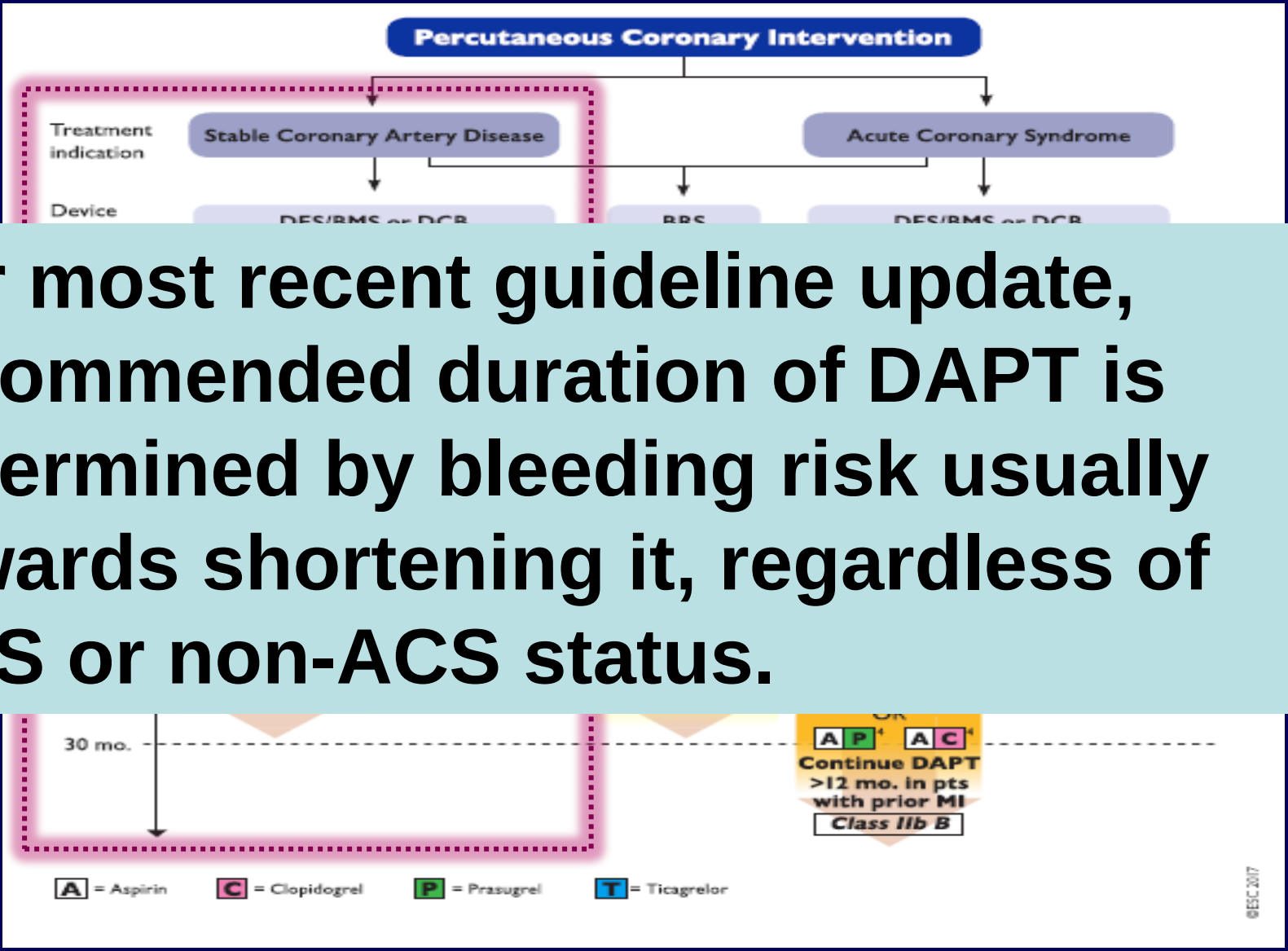
Subgroup analysis



Clopidogrel monotherapy beyond 12 months post-PCI could be an attractive option as compared with aspirin monotherapy.

Adapted from a presentation of Prof. Joo-Yong Hahn, SMC, Feb 2015

Updated ESC guideline in acute and long term therapy



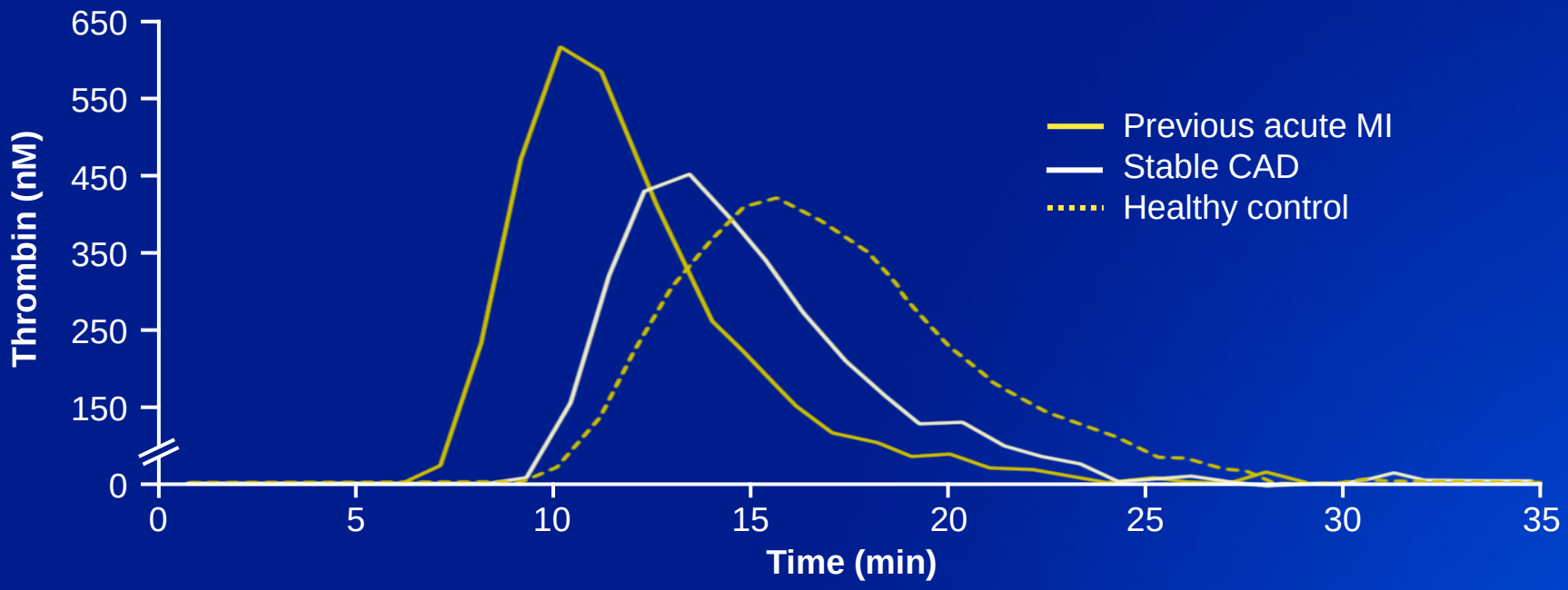
Per most recent guideline update, recommended duration of DAPT is determined by bleeding risk usually towards shortening it, regardless of ACS or non-ACS status.

European Heart Journal (2017) 0, 1–48. doi:10.1093/eurheartj/ehx419

Alternative therapeutic efforts

Faster and greater thrombin response in ACS persists long-term

- Study in patients with ACS (acute MI; n=60), stable CAD (n=35) or healthy controls (n=15)
- Thrombin generation assessed by fluorogenic assay, 3–11 months (mean 6 months) after initial diagnosis



ACS, acute coronary syndrome; CAD, coronary artery disease; MI, myocardial infarction.

Orbe *et al. Thromb Haemost* 2008;99:382–7.

Trial Design

Morrow et al. N Engl J Med 2012
ClinicalTrials.gov NCT00526474

Prior MI, CVA, or PAD
N=26,449

Prior MI Inclusion:
Type 1 MI >2 wks and <12 months before randomization

Standard care including oral antiplt rx

RANDOMIZE 1:1 DOUBLE BLIND

Stratified by:
1) Qualifying Disease State
2) Use of thienopyridine

Vorapaxar 2.5 mg/d

Placebo

Median F/U 30 Months

Follow up Visits
Day 30, Mo 4, Mo 8, Mo 12
Q6 months

Final Visit

Primary Efficacy Analysis:
1. CVD/MI/Stroke
2. CVD/MI/Stroke/Urgent Coronary Revasc

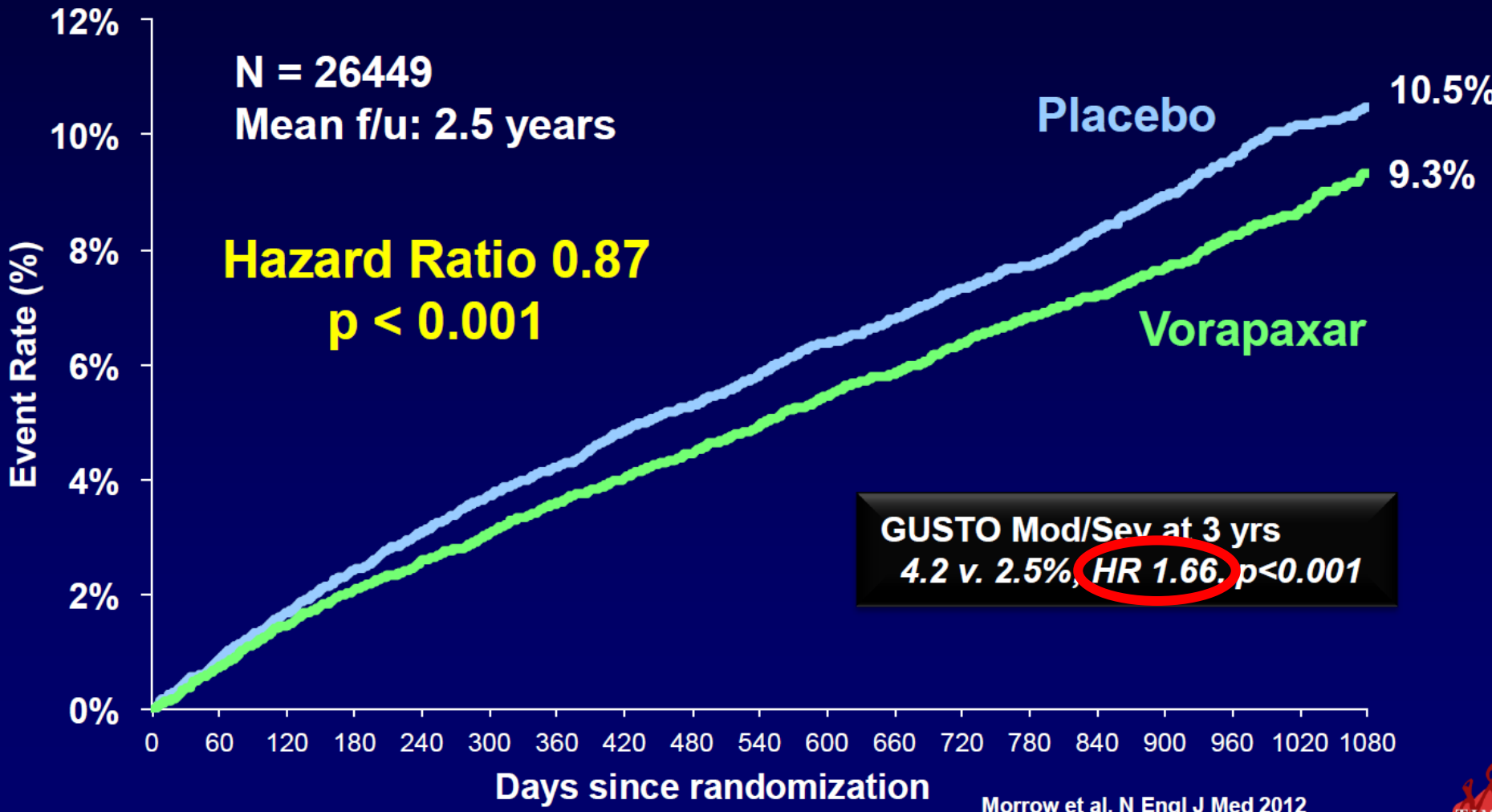
Principal Safety EP:
- GUSTO Mod/Sev bleeding

TRA 2°P TIMI 50

Background – 1° Efficacy Evaluation

Overall Population

CV Death, MI, or Stroke



Morrow et al. N Engl J Med 2012
ClinicalTrials.gov NCT00526474c

TIMI

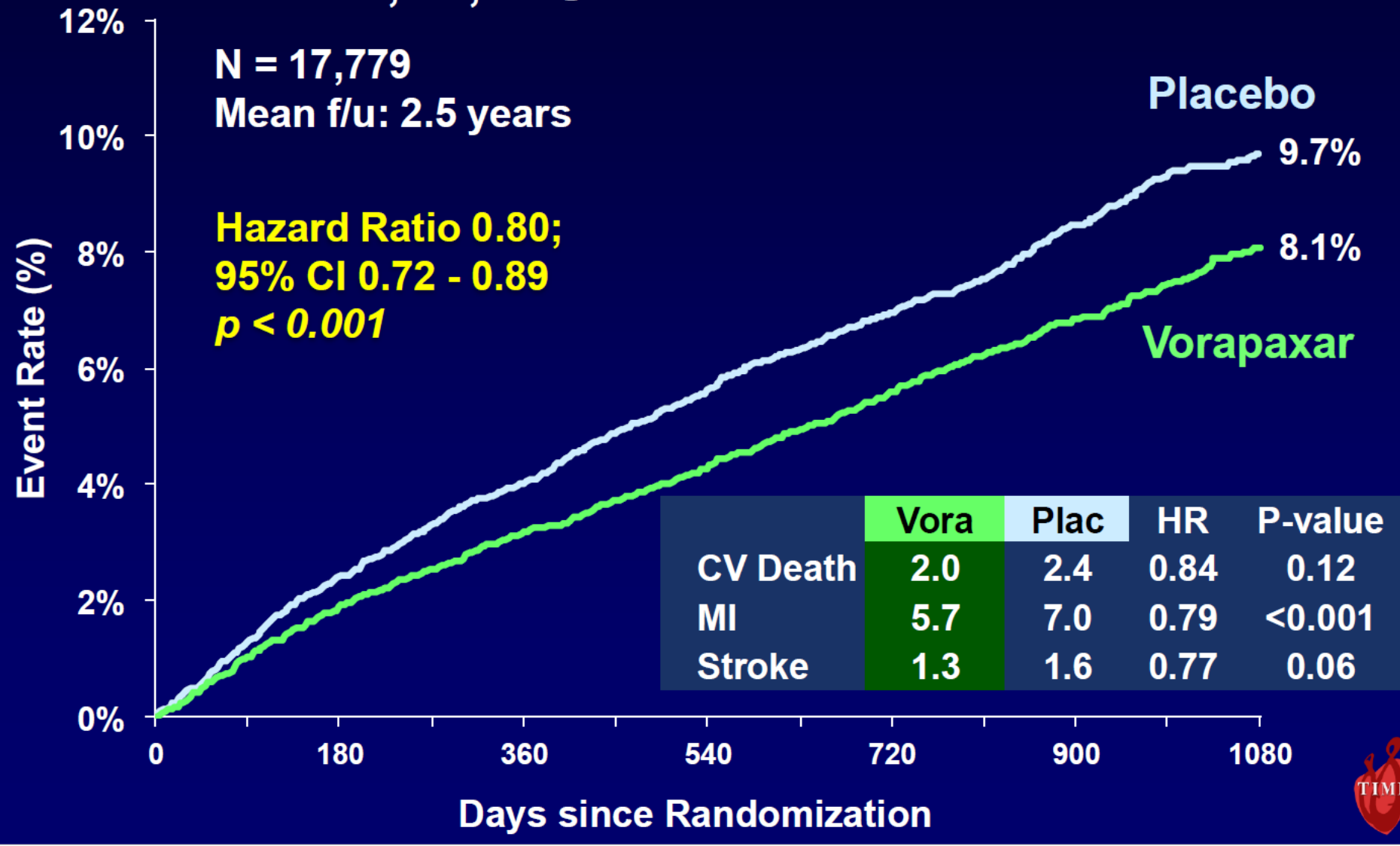
MI Cohort

TRA 2°P TIMI 50

Primary Efficacy Evaluation

Prior MI Cohort

CV Death, MI, or Stroke



	Vora	Plac	HR	P-value
CV Death	2.0	2.4	0.84	0.12
MI	5.7	7.0	0.79	<0.001
Stroke	1.3	1.6	0.77	0.06

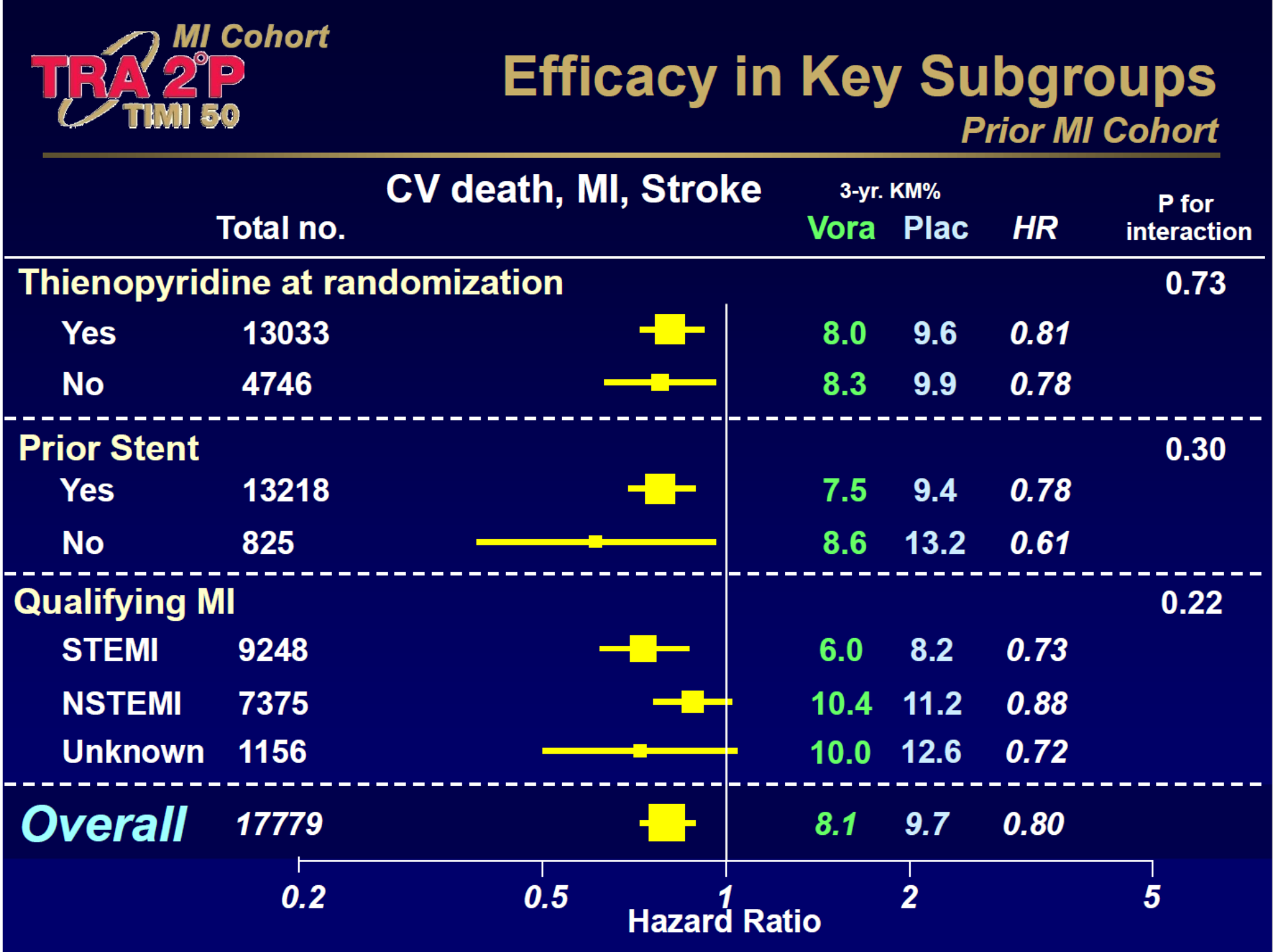
TIMI

MI Cohort

TRA 2°P TIMI 50

Efficacy in Key Subgroups

Prior MI Cohort

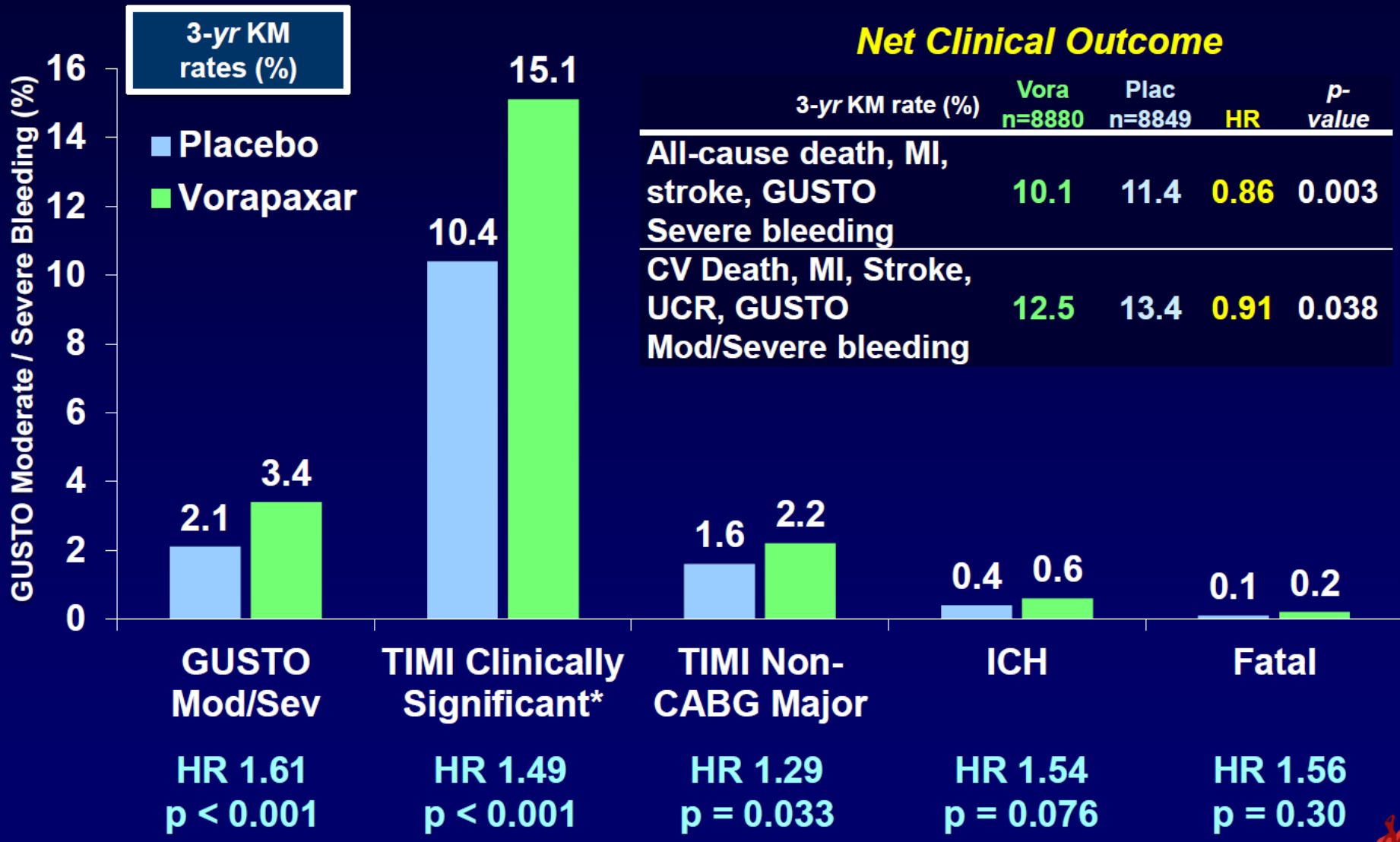


MI Cohort

TRA 2°P TIMI 50

Bleeding Endpoints

Prior MI Cohort



Net Clinical Outcome

3-yr KM rate (%)	Vora n=8880	Plac n=8849	HR	p-value
All-cause death, MI, stroke, GUSTO Severe bleeding	10.1	11.4	0.86	0.003
CV Death, MI, Stroke, UCR, GUSTO Mod/Severe bleeding	12.5	13.4	0.91	0.038

* TIMI Major/Minor/Requiring medical attention

Prescription Information of Vorapaxar

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZONTIVITY safely and effectively. See full prescribing information for ZONTIVITY.

ZONTIVITY® (vorapaxar) Tablets 2.08 mg*, for oral use
***Equivalent to 2.5 mg vorapaxar sulfate**
Initial U.S. Approval: 2014

WARNING: BLEEDING RISK
See full prescribing information for complete boxed warning.
- **Do not use ZONTIVITY in patients with a history of stroke, transient ischemic attack (TIA), or intracranial hemorrhage (ICH); or active pathological bleeding. (4.1, 4.2)**
- **Antiplatelet agents, including ZONTIVITY, increase the risk of bleeding, including ICH and fatal bleeding. (5.1)**

----------INDICATIONS AND USAGE----------
ZONTIVITY is a protease-activated receptor-1 (PAR-1) antagonist indicated for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD). ZONTIVITY has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization. (1.1)

---------- DOSAGE AND ADMINISTRATION ----------
- One tablet of ZONTIVITY orally once daily. (2.1)
- Use with aspirin and/or clopidogrel according to their indications or standard of care. There is limited clinical experience with other antiplatelet drugs and none with ZONTIVITY as the only antiplatelet agent. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------
Tablets: 2.08 mg vorapaxar. (3)

----------CONTRAINDICATIONS----------
- History of stroke, TIA, or ICH. (4.1)
- Active pathologic bleeding. (4.2)

---------- WARNINGS AND PRECAUTIONS ----------
- Like other antiplatelet agents, ZONTIVITY increases the risk of bleeding. (5.1)
- Avoid use with strong CYP3A inhibitors or inducers. (5.2)

---------- ADVERSE REACTIONS ----------
- Bleeding, including life-threatening and fatal bleeding, is the most commonly reported adverse reaction. (6.1)

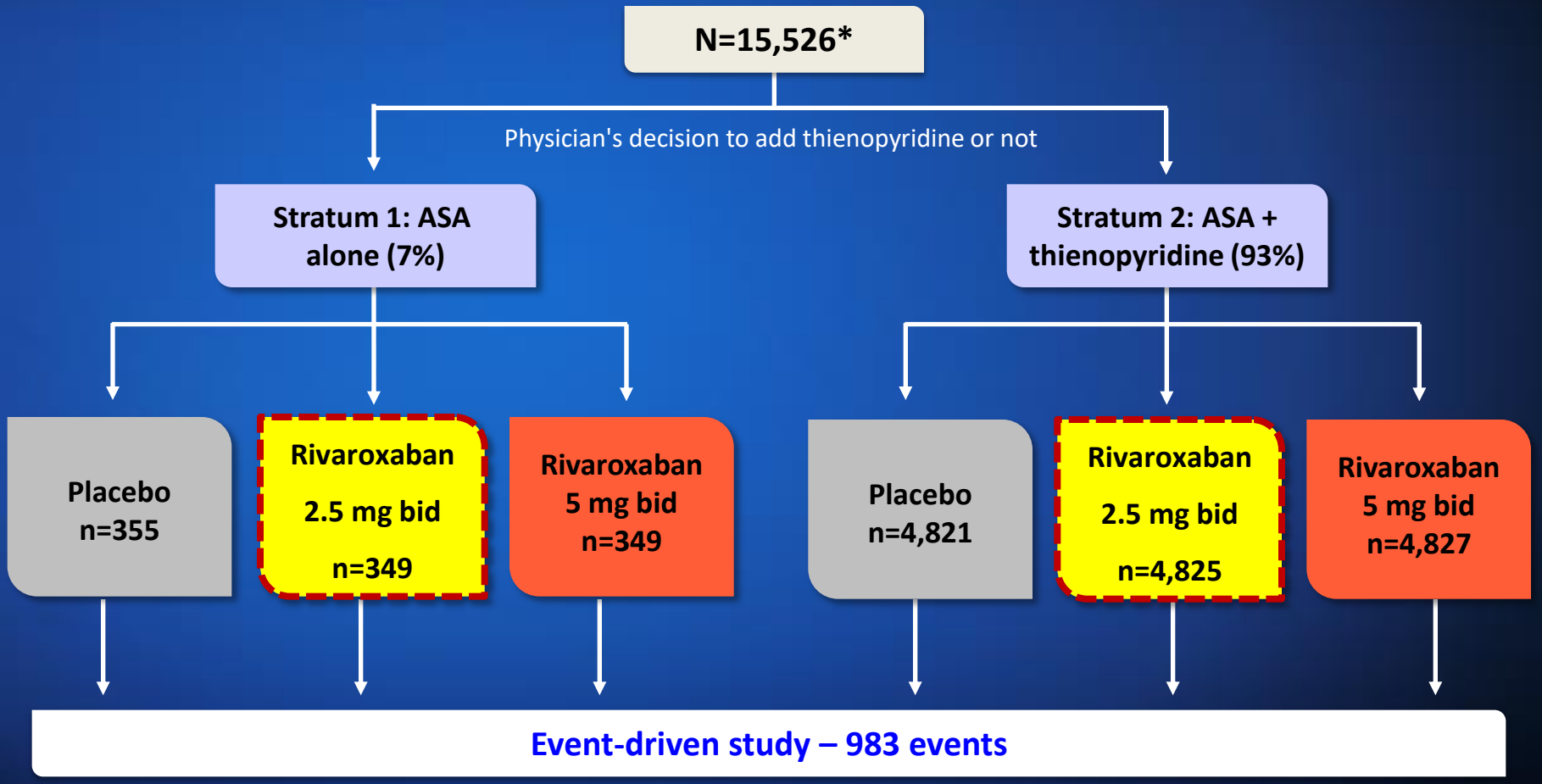
To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2015

Package Insert of Vorapaxar by Merck, Inc.

ATLAS ACS 2-TIMI 51:
Study design (2)



ASA dose= 75–100 mg/day

*184 patients were excluded from the efficacy analyses prior to unblinding because of trial misconduct at three sites

ATLAS ACS, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome; bid, twice daily; ASA, acetylsalicylic acid.

Mega JL *et al*. *N Engl J Med* 2012;366:9-19

ATLAS ACS 2 TIMI 51:
Main inclusion & exclusion criteria

Inclusion criteria

- Diagnosis of STEMI, NSTEMI, or UA with at least one of the following:
  - ✓ ≥ 0.1 mV ST-segment deviation
  - ✓ TIMI risk score ≥4
- Patients aged 18-55 years only with either:
  - ✓ Diabetes mellitus or
  - ✓ Prior MI
- Patients received ASA 75-100 mg/day alone or ASA + thienopyridine
  - ✓ Based on national/local dosing guidelines

Exclusion criteria

- Increased bleeding risk, e.g.
  - ✓ Low platelet count
  - ✓ History of intracranial haemorrhage
  - ✓ Active internal bleeding
- Prior stroke or TIA in stratum 2 patients
- AF
  - ✓ Except single episodes >2 years previously in patients aged <60 years with no evidence of cardiopulmonary disease

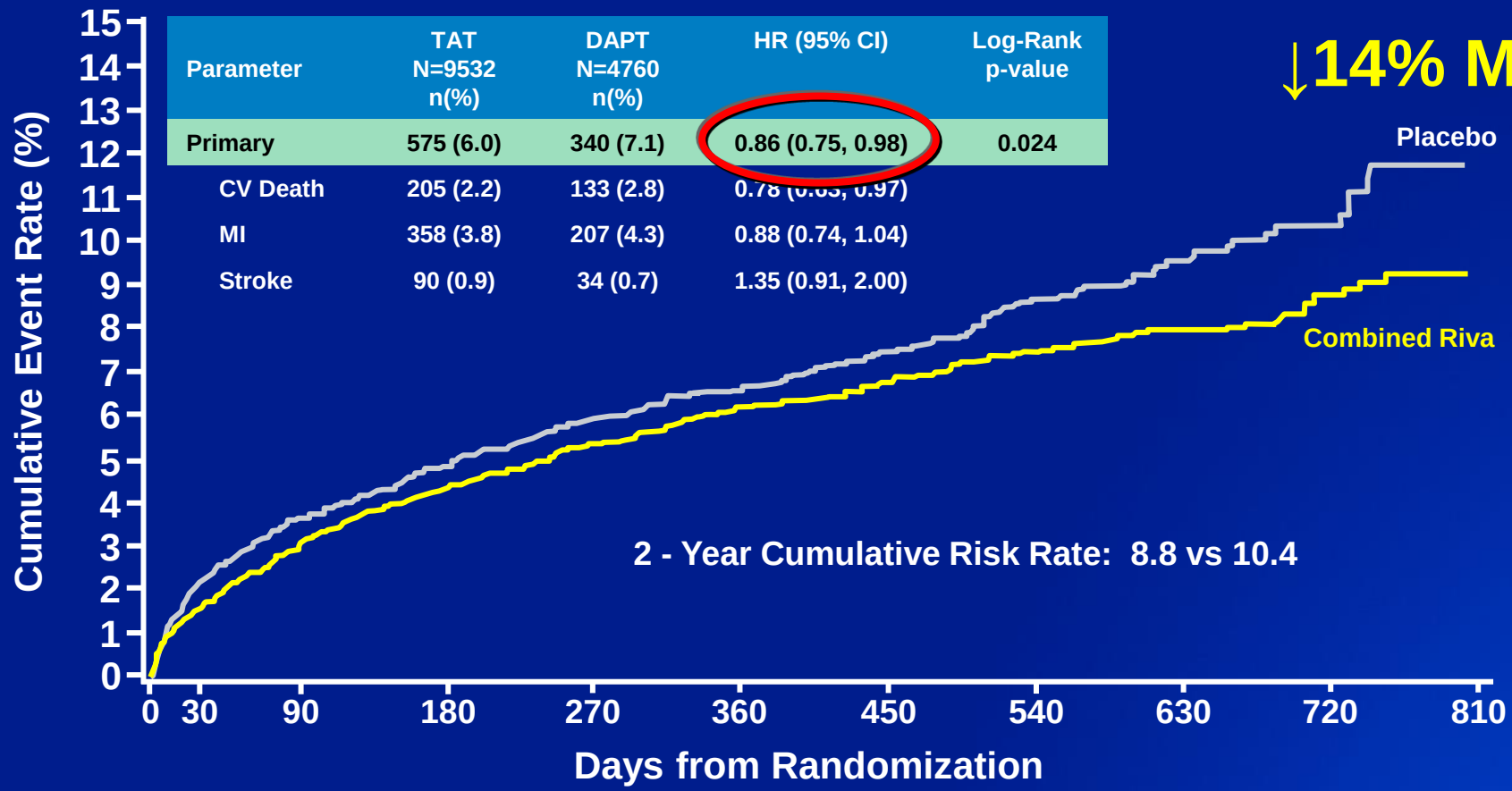
ATLAS ACS, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome; STEMI, ST-Elevation Myocardial Infarction; NSTEMI, non- ST-Elevation Myocardial Infarction; UA, unstable angina; AF, atrial fibrillation; MI, myocardial infarction; CABG, Coronary artery bypass graft surgery; TIMI, thrombolysis in myocardial infarction; ASA, acetylsalicylic acid.

Mega JL *et al*. *N Engl J Med* 2012;366:9-19

ATLAS ACS 2 TIMI 51: Primary efficacy endpoint in TAT(combined rivaroxaban doses, ASA and thienopyridine) vs. DAPT

Parameter	TAT N=9532 n(%)	DAPT N=4760 n(%)	HR (95% CI)	Log-Rank p-value
Primary	575 (6.0)	340 (7.1)	0.86 (0.75, 0.98)	0.024
CV Death	205 (2.2)	133 (2.8)	0.78 (0.63, 0.97)	
MI	358 (3.8)	207 (4.3)	0.88 (0.74, 1.04)	
Stroke	90 (0.9)	34 (0.7)	1.35 (0.91, 2.00)	

↓14% MACE



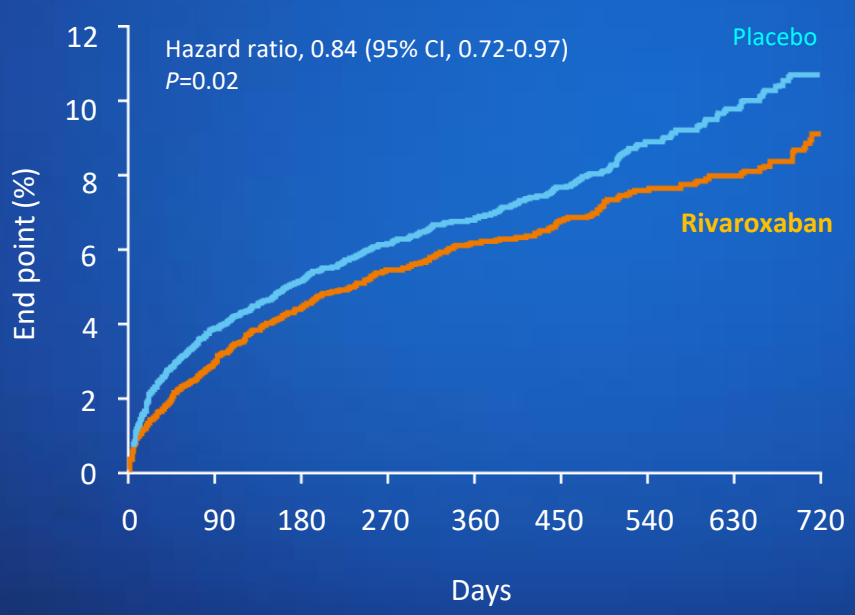
Subjects at risk										
TAT	9532	8225	7277	5915	4811	3717	2641	1638	779	159
DAPT	4760	4152	3720	3056	2503	1935	1369	830	397	82

ATLAS ACS 2 TIMI 51 trial

ATLAS ACS 2-TIMI 51:
Primary efficacy endpoint

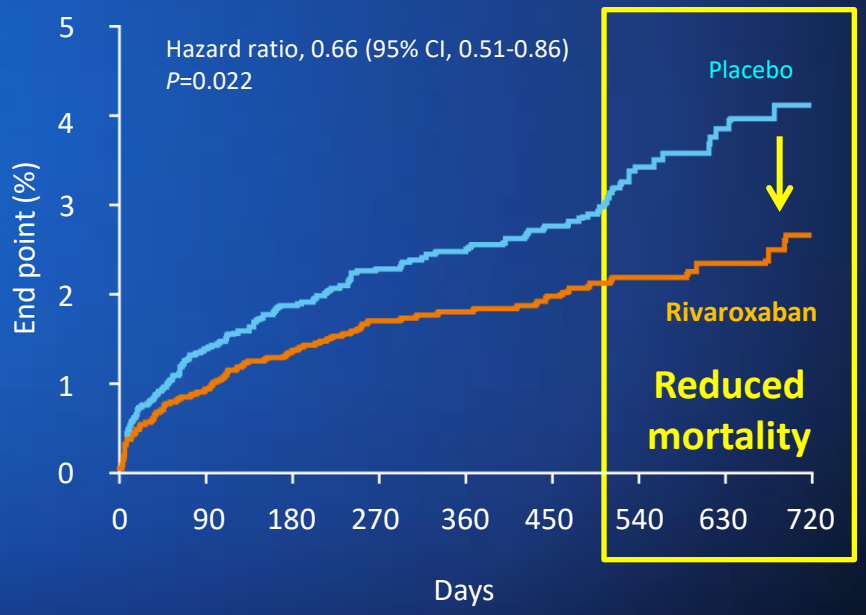
- **in Rivaroxaban 2.5 mg bid**

Primary efficacy endpoint, 2.5mg BID



↓16% MACE

Death from cardiovascular causes, 2.5mg BID



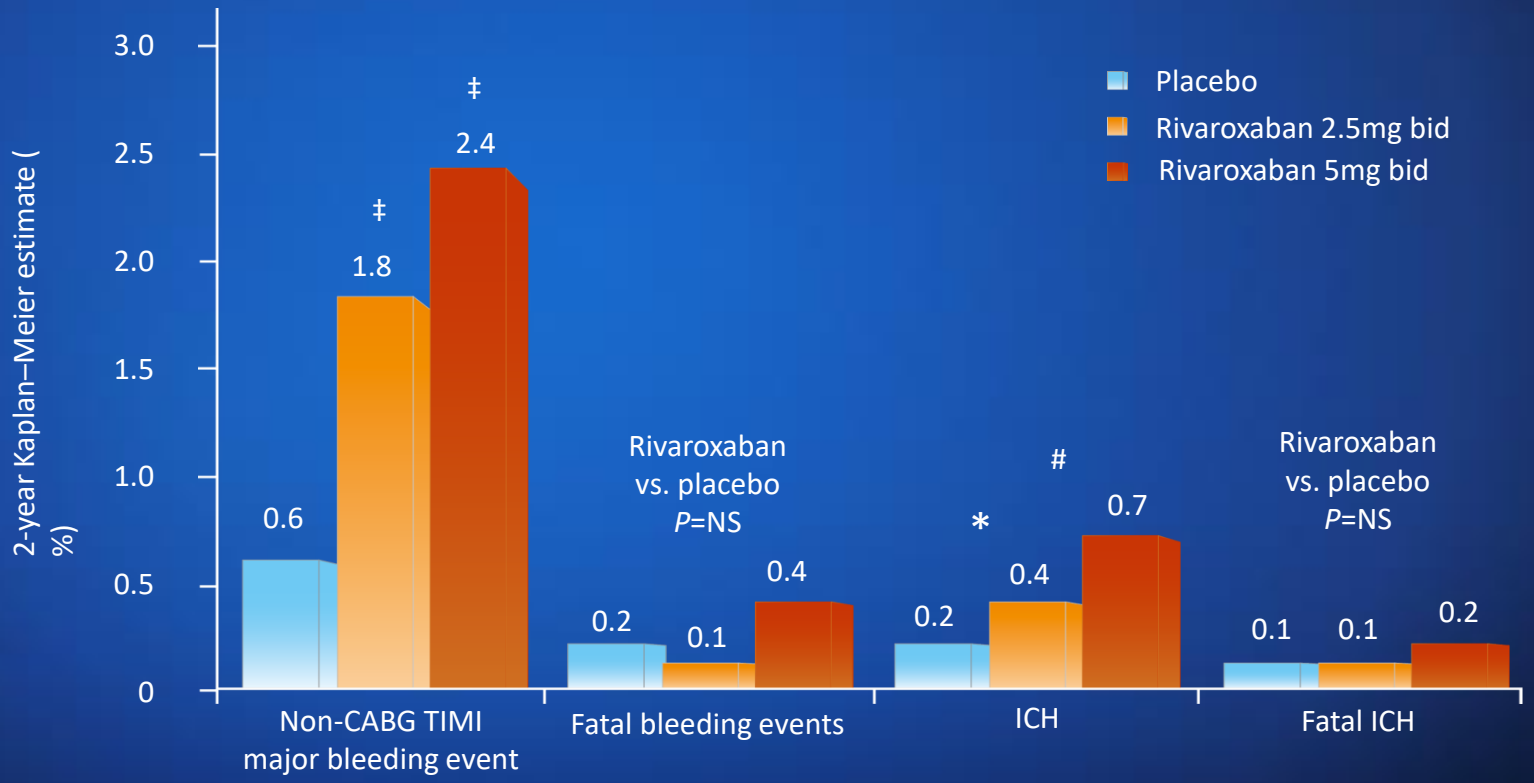
↓34% Cardiac death

ATLAS ACS, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome.

Mega JL et al. N Engl J Med 2012;366:9-19

ATLAS ACS 2 TIMI 51:
Fatal bleeding or fatal ICH

- **No increase in fatal bleeding or fatal ICH rates in rivaroxaban vs. antiplatelet therapy alone**



(principal safety outcome)

*P=0.04 vs. placebo; #P=0.005 vs. placebo; ‡P<0.001 vs. placebo.

ATLAS ACS, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome; bid, twice daily; CABG, coronary artery bypass graft; ICH, intracranial haemorrhage; NS, not significant.

1. Mega *et al. N Engl J Med* 2012;366:9–19; 2. Gibson *et al.* AHA 2011 (www.clinicaltrialresults.org).

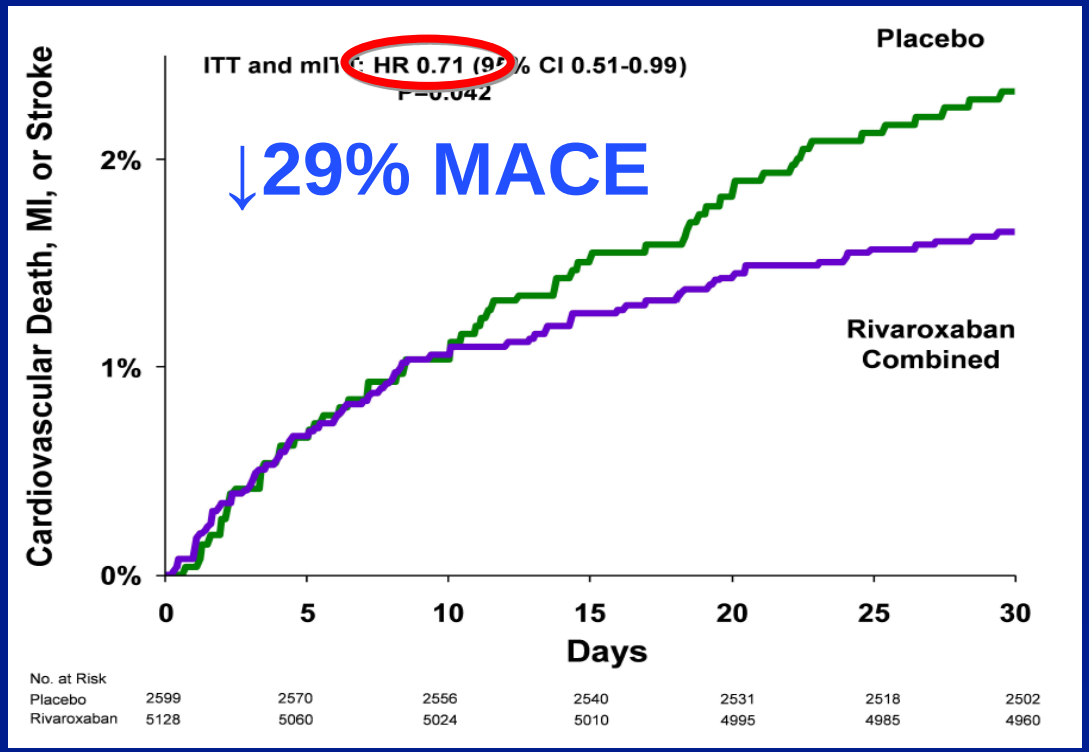
ATLAS ACS 2 TIMI 51:
Rivaroxaban 2.5 mg bid

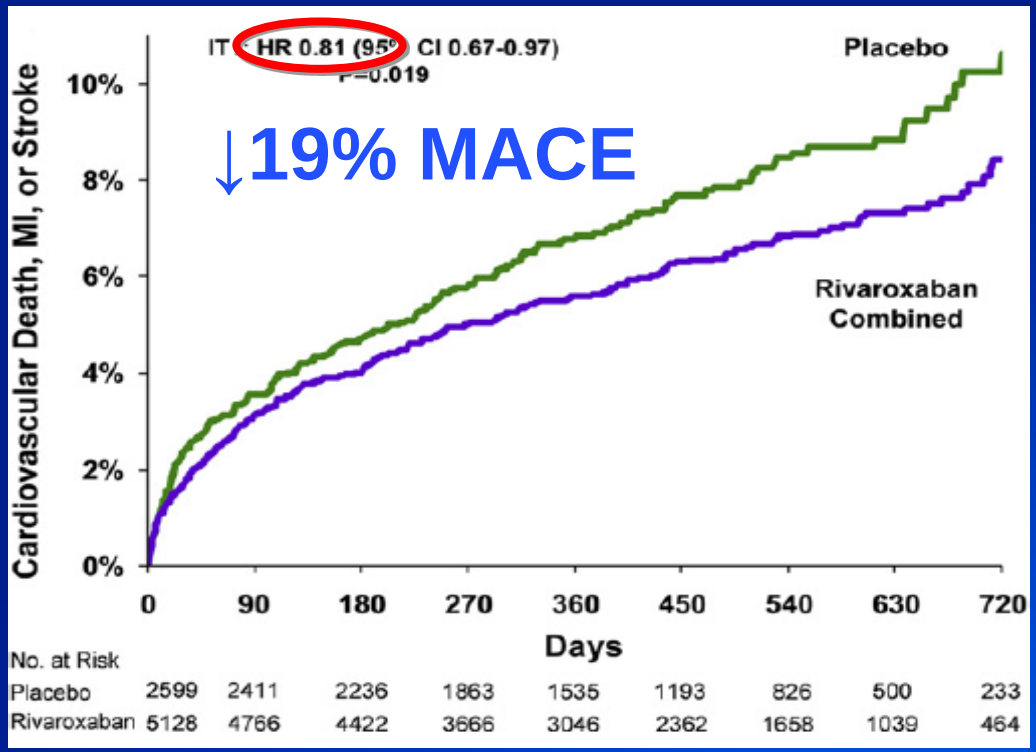
- Compared with placebo, **rivaroxaban 2.5 mg bid on top of ASA or ASA plus clopidogrel** showed:
  - ✓ A significant **16% RRR** in the risk of the composite of **CV death, MI or stroke** (*p*=0.02)
  - ✓ A significant **34% RRR** in the risk of **CV mortality**
  - ✓ A significant **32% RRR** in the risk of **all-cause mortality**
  - ✓ **A significant increase in non-CABG-related TIMI major bleeding (1.8% vs 0.6%; *p*<0.001)**
  - ✓ **Similar increase in fatal bleeding or fatal ICH**

ATLAS ACS, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome; ASA, acetylsalicylic acid; CV, cardiovascular; MI, myocardial infarction; RRR, relative risk ratio; CABG, Coronary artery bypass graft surgery; TIMI, thrombolysis in myocardial infarction; ICH, intracranial hemorrhage; ACS, acute coronary syndrome.

Mega JL et al. N Engl J Med 2012;366:9-19

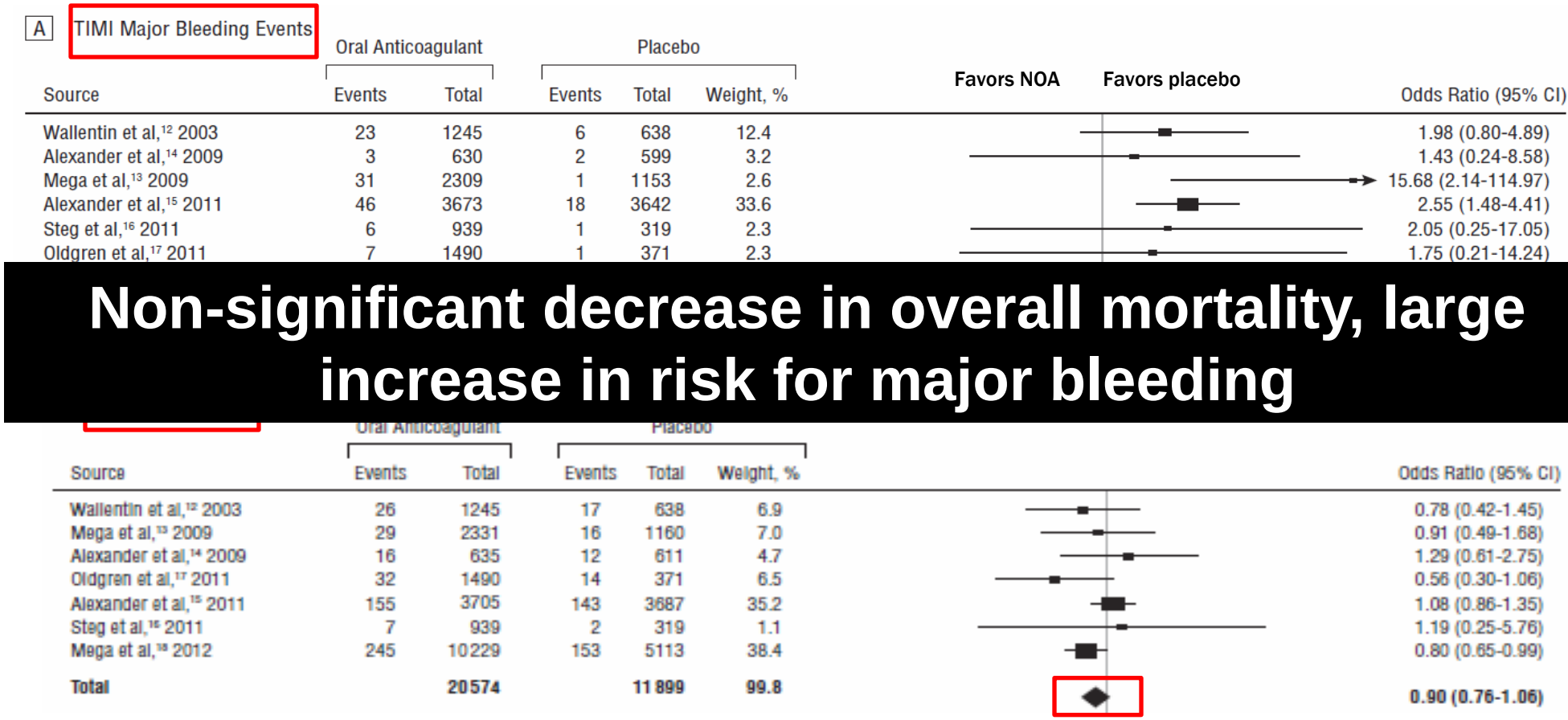
ATLAS ACS 2 TIMI 51 – Recent STEMI cohort: Primary efficacy endpoint in TAT vs. DAPT (up to 30 days and 2-years)





Mega JL *et al. JACC* 2013 Published online March 2013

NOACs plus antiplatelet therapy in ACS: meta-analysis

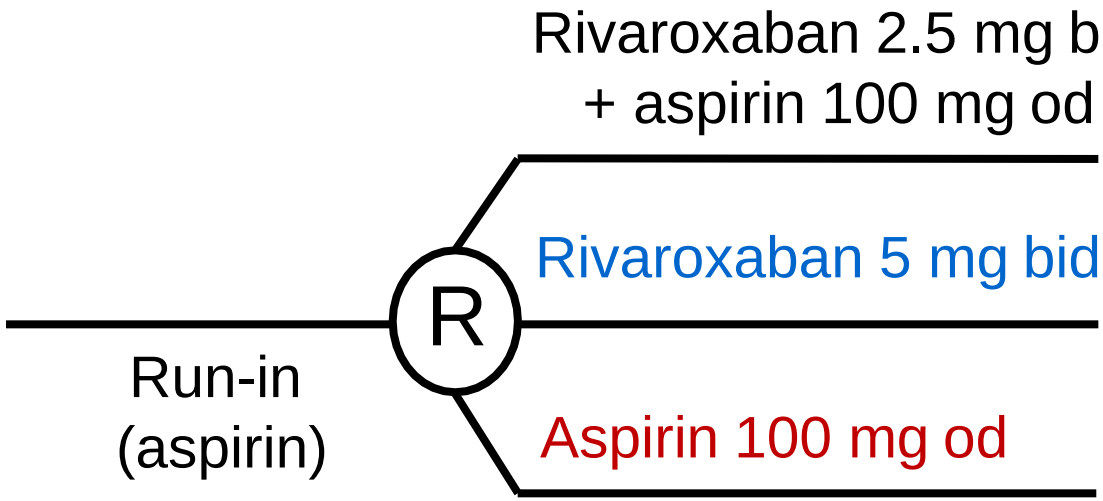


Non-significant decrease in overall mortality, large increase in risk for major bleeding

Arch Intern Med 2012; 172:1537

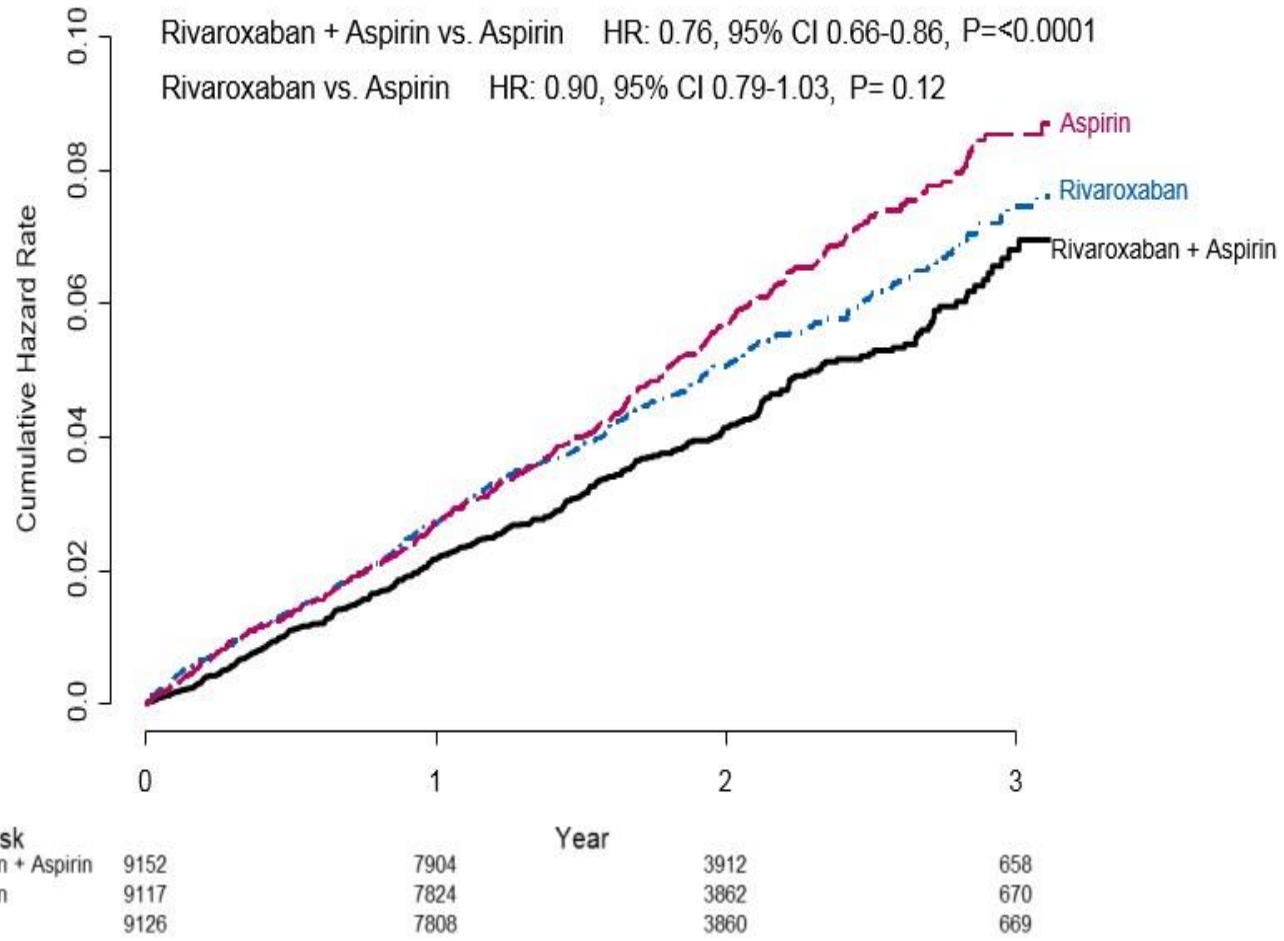
COMPASS design

Stable CAD or PAD
2,200 with a primary outcome event



Expected follow up
3-4 years

Primary: CV death, stroke,



Major bleeding

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Outcome	R + A N=9,152	R N=9,117	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin		Rivaroxaban vs. Aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P	HR (95% CI)	P
Major bleeding	288 (3.1%)	255 (2.8%)	170 (1.9%)	1.70 (1.40-2.05)	<0.0001	1.51 (1.25-1.84)	**<0.0001**
Fatal	15 (0.2%)	14 (0.2%)	10 (0.1%)	1.49 (0.67-3.33)	0.32	1.40 (0.62-3.15)	0.41
Non fatal ICH*	21 (0.2%)	32 (0.4%)	19 (0.2%)	1.10 (0.59-2.04)	0.77	1.69 (0.96-2.98)	0.07
Non-fatal other critical organ*	42 (0.5%)	45 (0.5%)	29 (0.3%)	1.43 (0.89-2.29)	0.14	1.57 (0.98-2.50)	0.06

* symptomatic

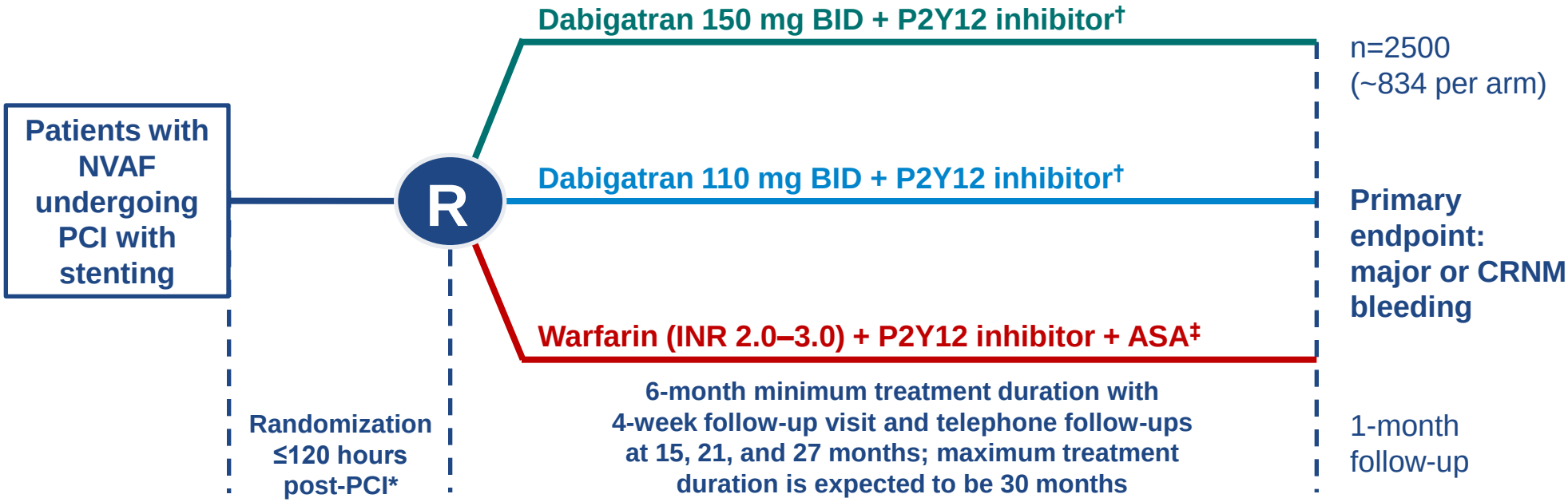
Conclusion

Rivaroxaban 2.5 mg bid plus aspirin 100 mg od:

- Reduces CV death, stroke, MI
- Increases major bleeding without a significant increase in fatal, intracranial or critical organ bleeding
- Provides a net clinical benefit

No significant benefit of rivaroxaban alone

RE-DUAL PCI™ tests the hypothesis of non-inferiority in safety of dual antithrombotic therapy with dabigatran vs triple therapy with VKA



Estimated completion March 2017

Click here to see the RE-DUAL PCI key inclusion/exclusion criteria

***Study drug should be administered 6 hours after sheath removal and no later than ≤120 hrs post-PCI (≤72 hrs is preferable). †Dabigatran arms: ASA discontinued at randomization. ‡Warfarin arm: ASA discontinued 1 month after bare metal stent or 3 months after drug-eluting stent.**

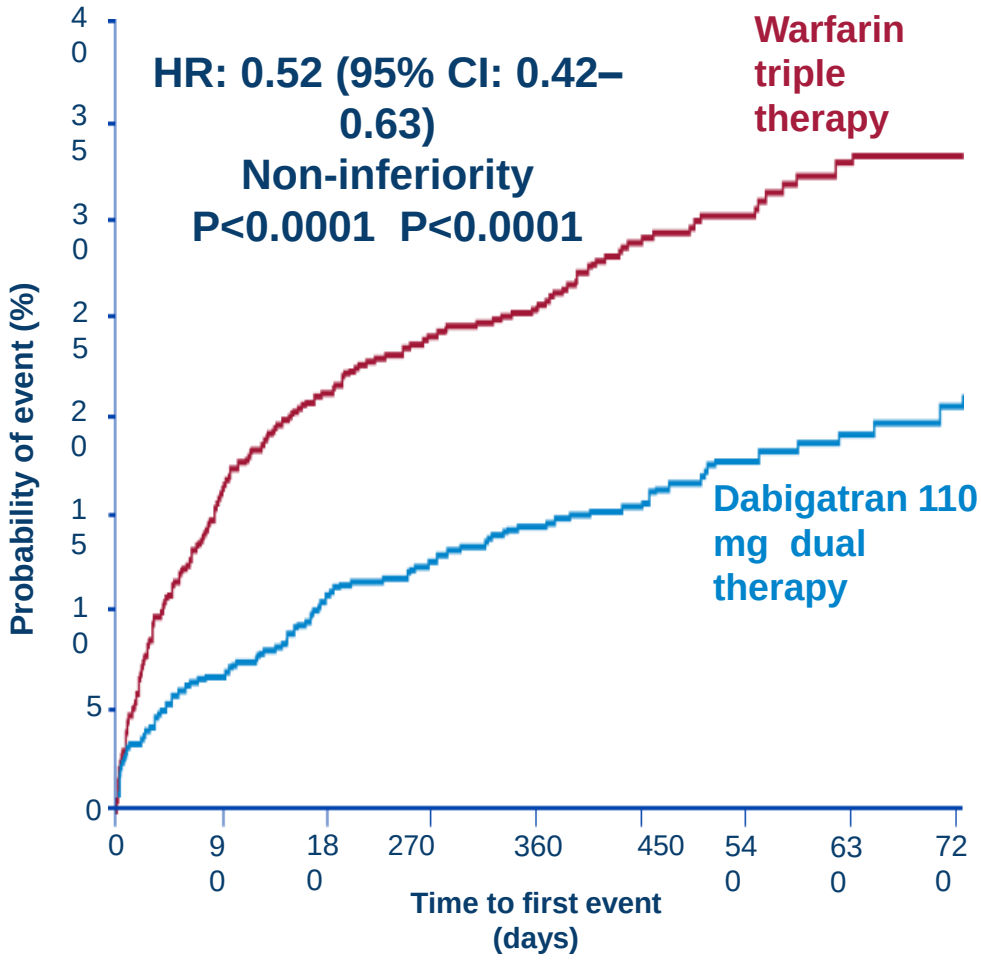
ASA, acetylsalicylic acid; CRNM, clinically-relevant non-major; PCI, percutaneous coronary intervention; R, randomization.

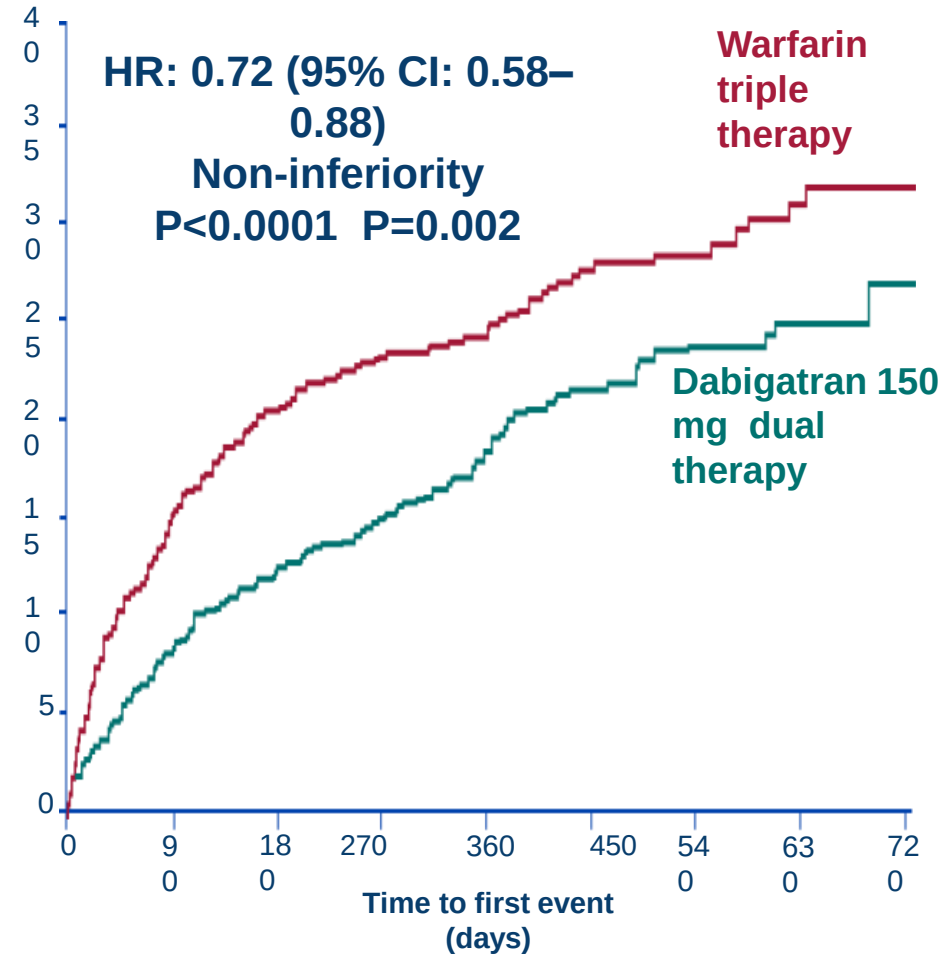
ClinicalTrials.gov: NCT02164864; Cannon C et al. Clin Cardiol 2016

RE-DUAL PCI™
Study in NVAF patients undergoing PCI

Primary Endpoint: Time to first ISTH major or clinically relevant non-major bleeding event

RE-DUAL PCI
Study in NVAF patients undergoing PCI

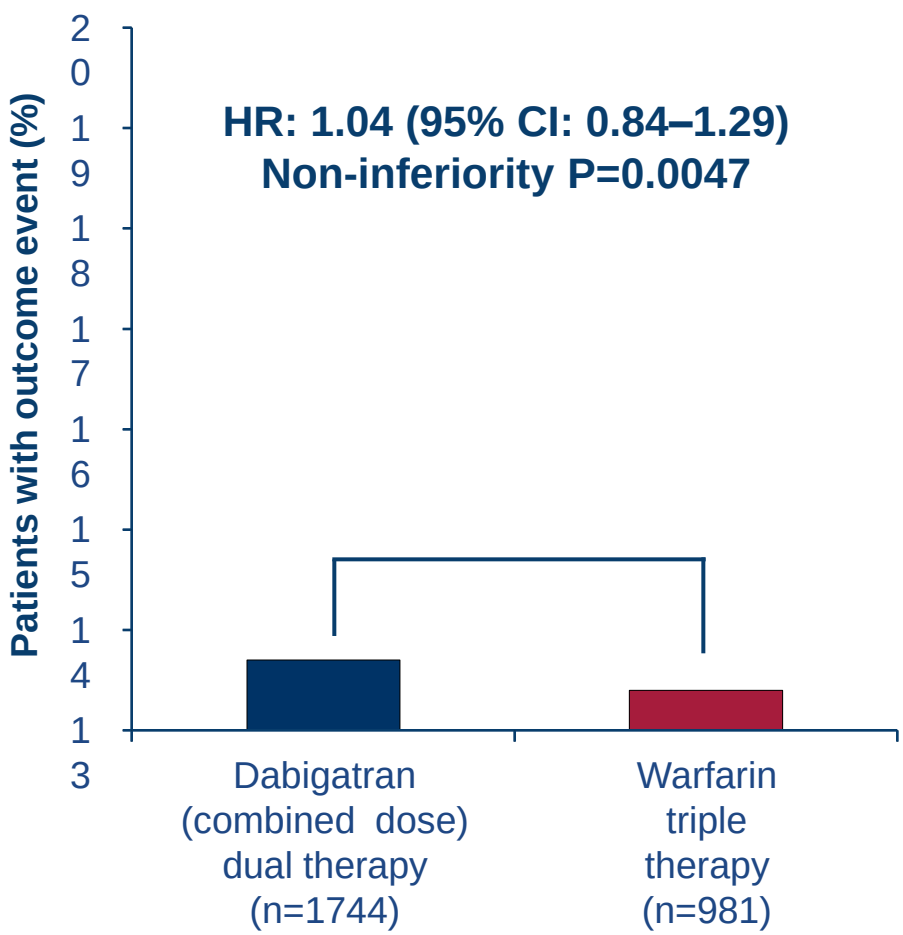


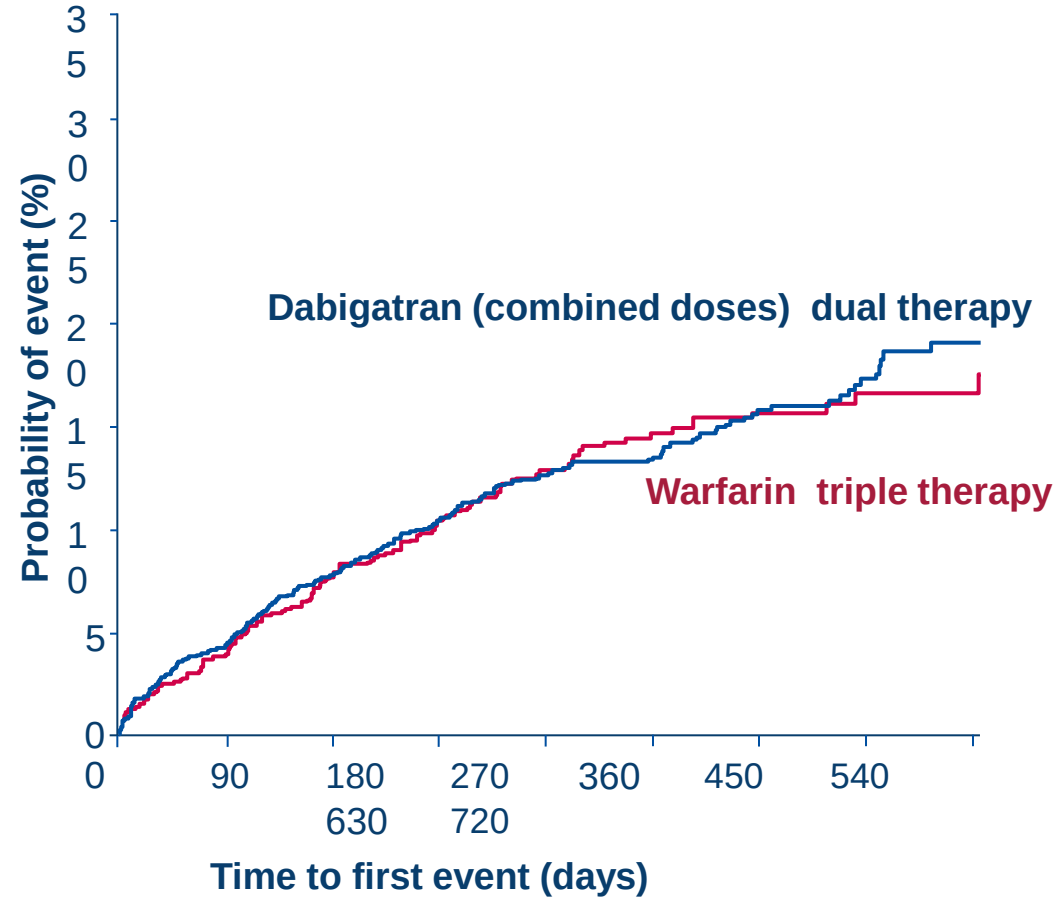


Full analysis set presented. HRs and Wald CIs from Cox proportional-hazard model. For the dabigatran 110 mg vs warfarin comparison, the model is stratified by age, non-elderly vs elderly (<70 or ≥70 in Japan and <80 or ≥80 years old elsewhere). For the dabigatran 150 mg vs warfarin comparison, an unstratified model is used, elderly patients outside the USA are excluded. Non-inferiority P value is one sided (alpha=0.025). Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05)

Time to death or thromboembolic event, or unplanned revascularization

RE-DUAL PCI
Study in NVAF patients undergoing PCI





Non-inferiority P value is one sided (alpha=0.025). Results presented are Step 3 of hierarchical testing procedure, testing non-inferiority of dabigatran dual therapy (combined doses) to warfarin triple therapy in death or thromboembolic event and unplanned revascularization

Summary

- From the mechanistic point of view, there are other receptors on the platelet surface than P2Y12, giving opportunities to develop drugs targeting these receptors to exert its antiplatelet action.
- The current guideline however generally recommends dual antiplatelet therapy with aspirin and P2Y12 inhibitor in patients undergoing PCI (including stable CAD) due to its vast evidence in the literature.
- Other alternative efforts using different agents, such as thrombin-receptor inhibitor and NOACs have been made, which turned out to be not fully satisfactory. In that sense, we need more, well-designed study.
- As of now, it is reasonable to regard DAPT with aspirin and P2Y12 inhibitor as default therapy for patients undergoing PCI.


Thank you for your attention !!