Duration of DAPT after ACS

Robert Storey

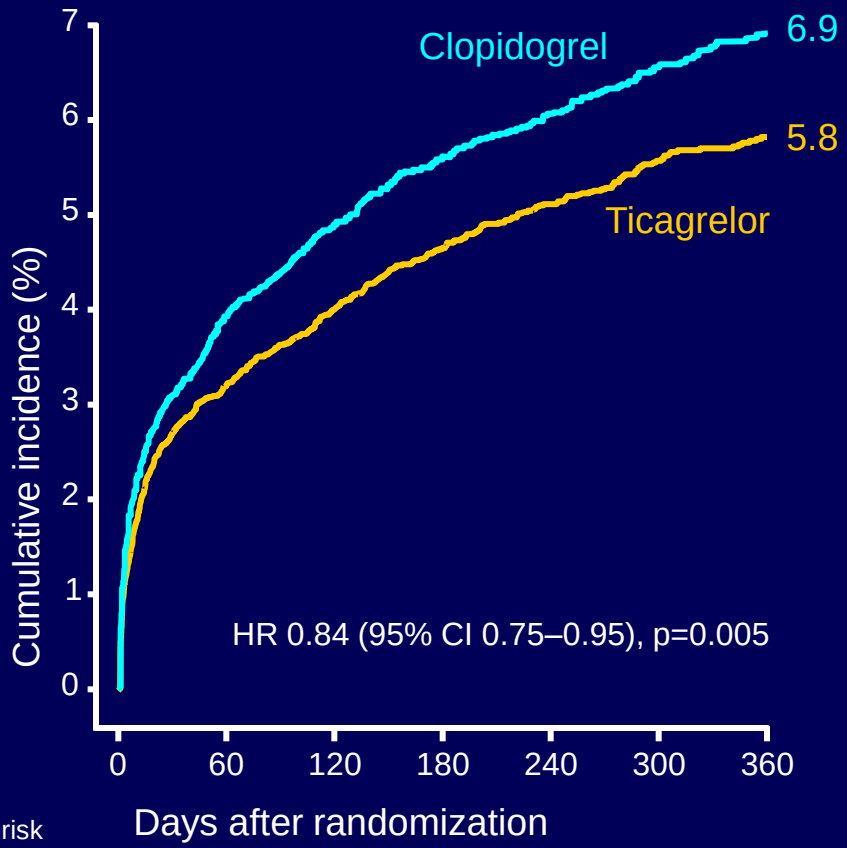
Professor of Cardiology, University of Sheffield
and
Academic Director and Honorary Consultant Cardiologist,
Cardiology and Cardiothoracic Surgery Directorate,
Sheffield Teaching Hospitals NHS Foundation Trust,
Sheffield, United Kingdom

Disclosures

Company name	Relationship
• AstraZeneca	Research grant, honoraria, consultant
• Avacta	Consultant
• Bayer	Consultant
• BMS/Pfizer	Consultant
• PlaqueTec	Research grant, consultant
• Aspen	Consultant
• ThermoFisher Scientific	Consultant
• The Medicines Company	Consultant

PLATO Secondary efficacy endpoints

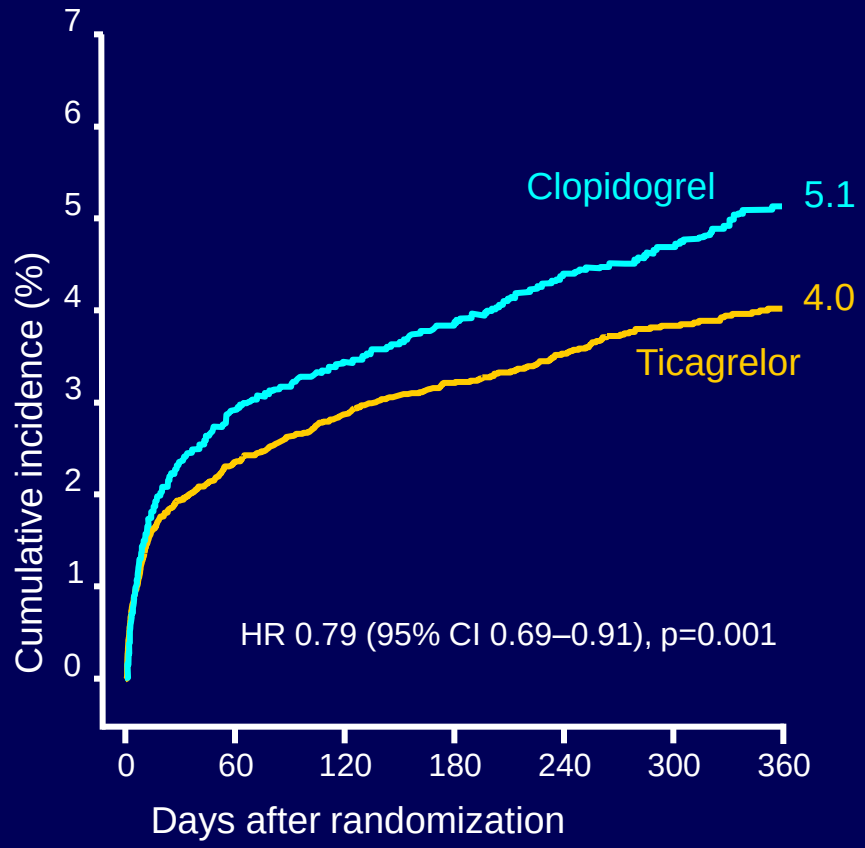
Myocardial infarction



No. at risk

Ticagrelor	9333	8678	8520	8279	6796	5210	4191
Clopidogrel	9291	8560	8405	8177	6703	5136	4109

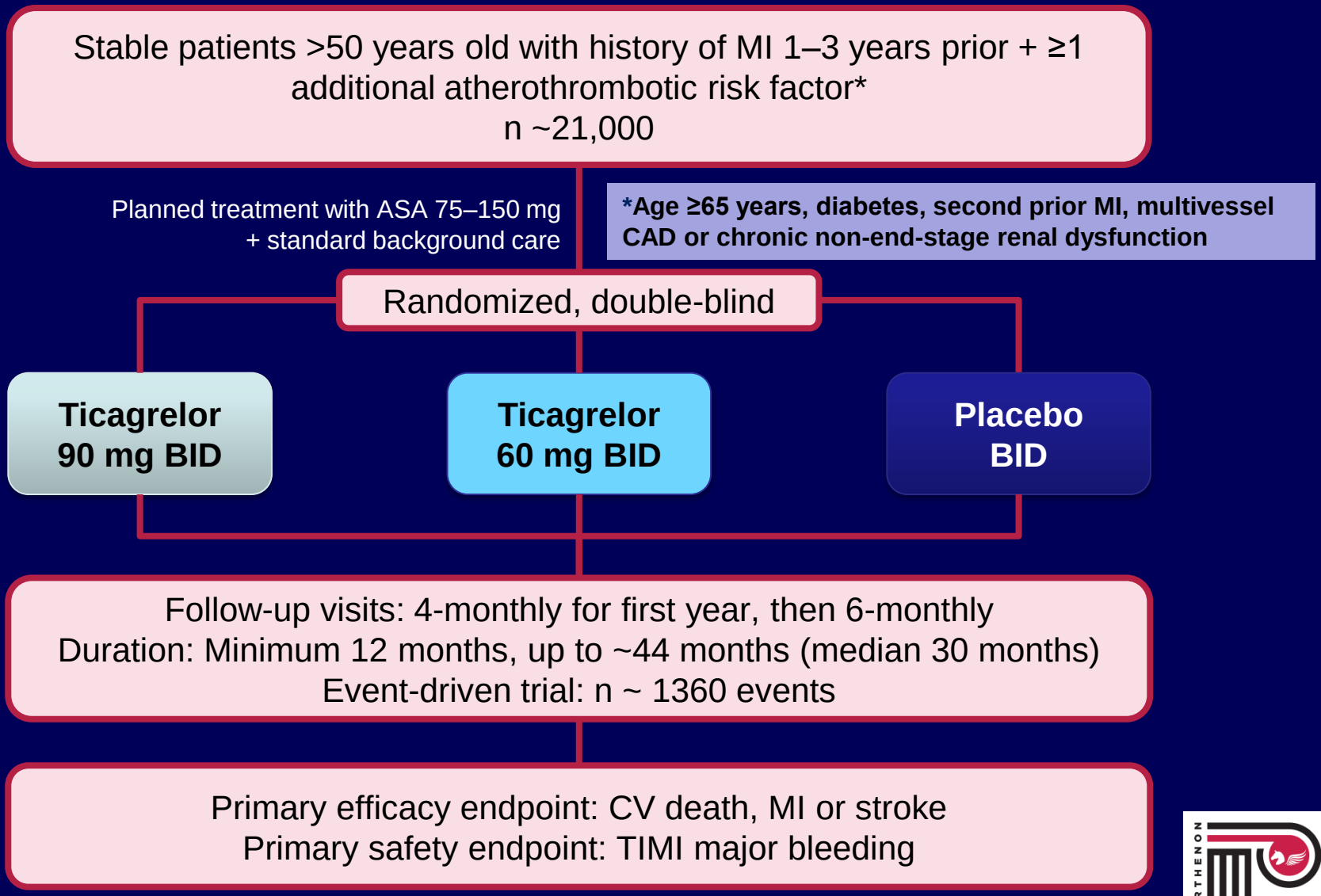
Cardiovascular death



	9333	8294	8822	8626	7119	5482	4419
	9291	8865	8780	8589	7079	5441	4364

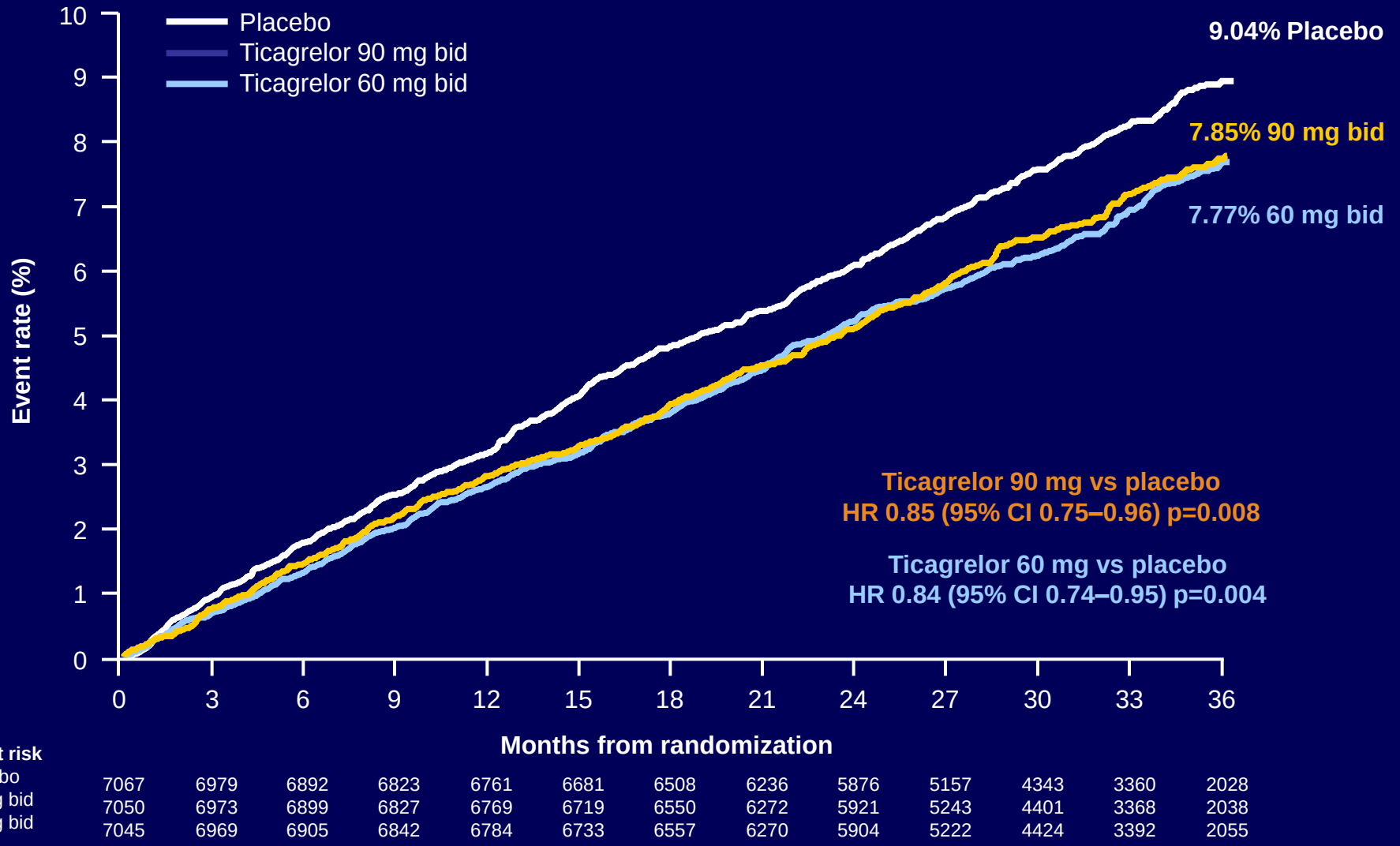
Wallentin L et al. *N Eng J Med.* 2009

PEGASUS-TIMI 54 study design



BID, twice daily; CAD, coronary artery disease; TIMI, thrombolysis in myocardial infarction

PEGASUS-TIMI 54: Primary endpoint

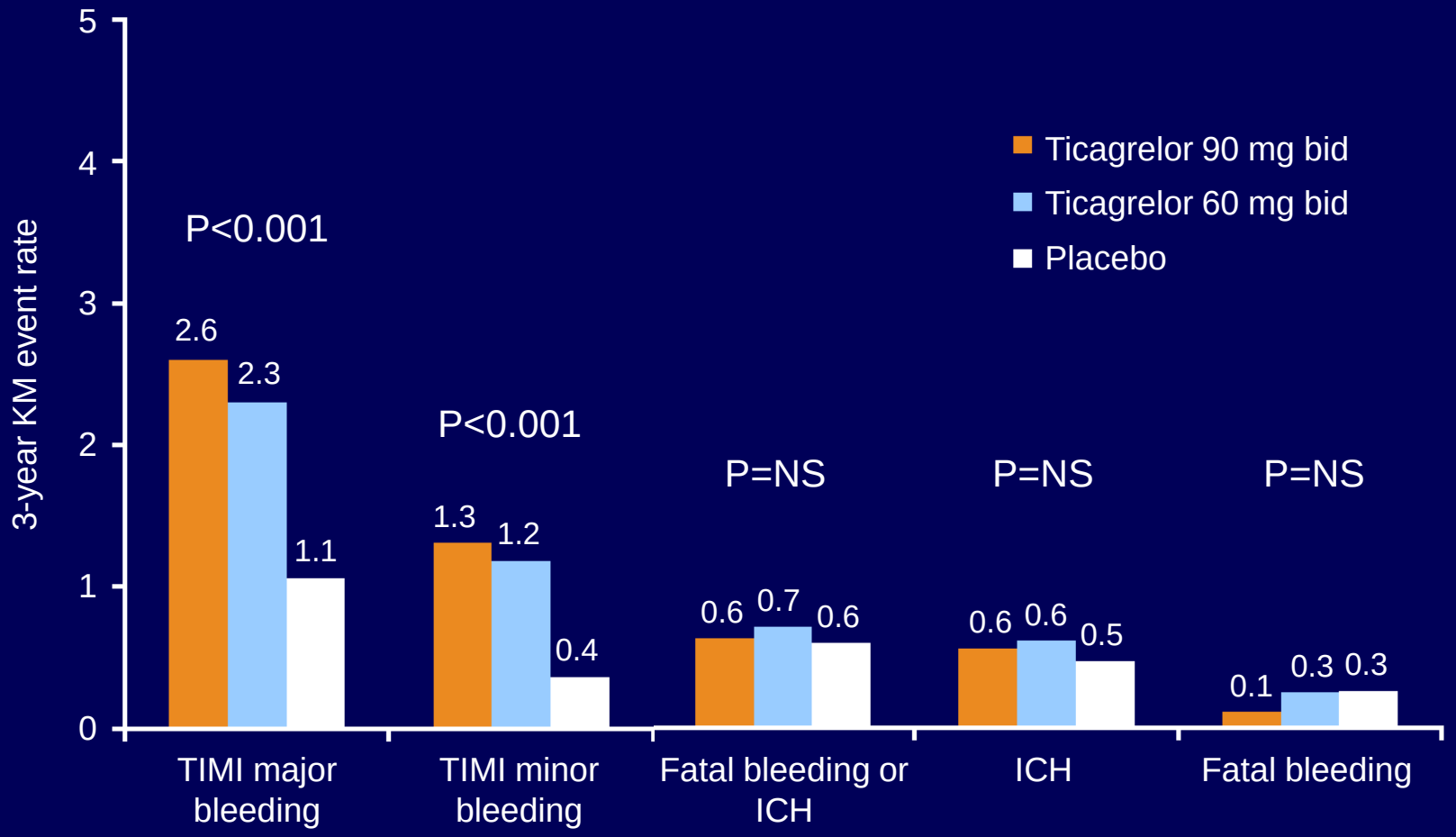


No. at risk													
Placebo	7067	6979	6892	6823	6761	6681	6508	6236	5876	5157	4343	3360	2028
90 mg bid	7050	6973	6899	6827	6769	6719	6550	6272	5921	5243	4401	3368	2038
60 mg bid	7045	6969	6905	6842	6784	6733	6557	6270	5904	5222	4424	3392	2055

p<0.026 indicates statistical significance; CI, confidence interval; HR, hazard ratio

Bonaca MP et al. *N Engl J Med.* 2015;372:1791–1800.

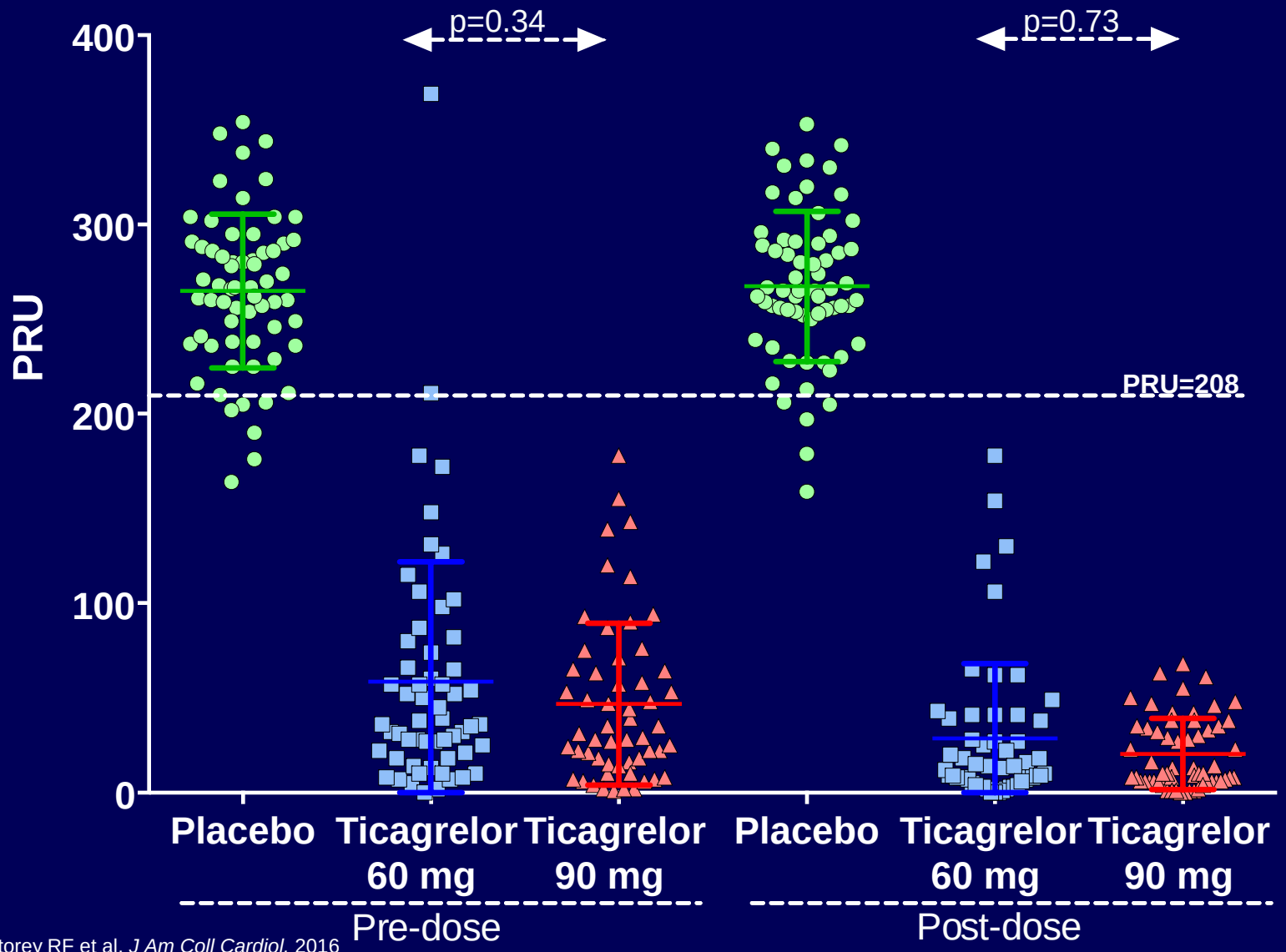
PEGASUS-TIMI 54: Bleeding



Rates are presented as 3-year Kaplan-Meier estimates

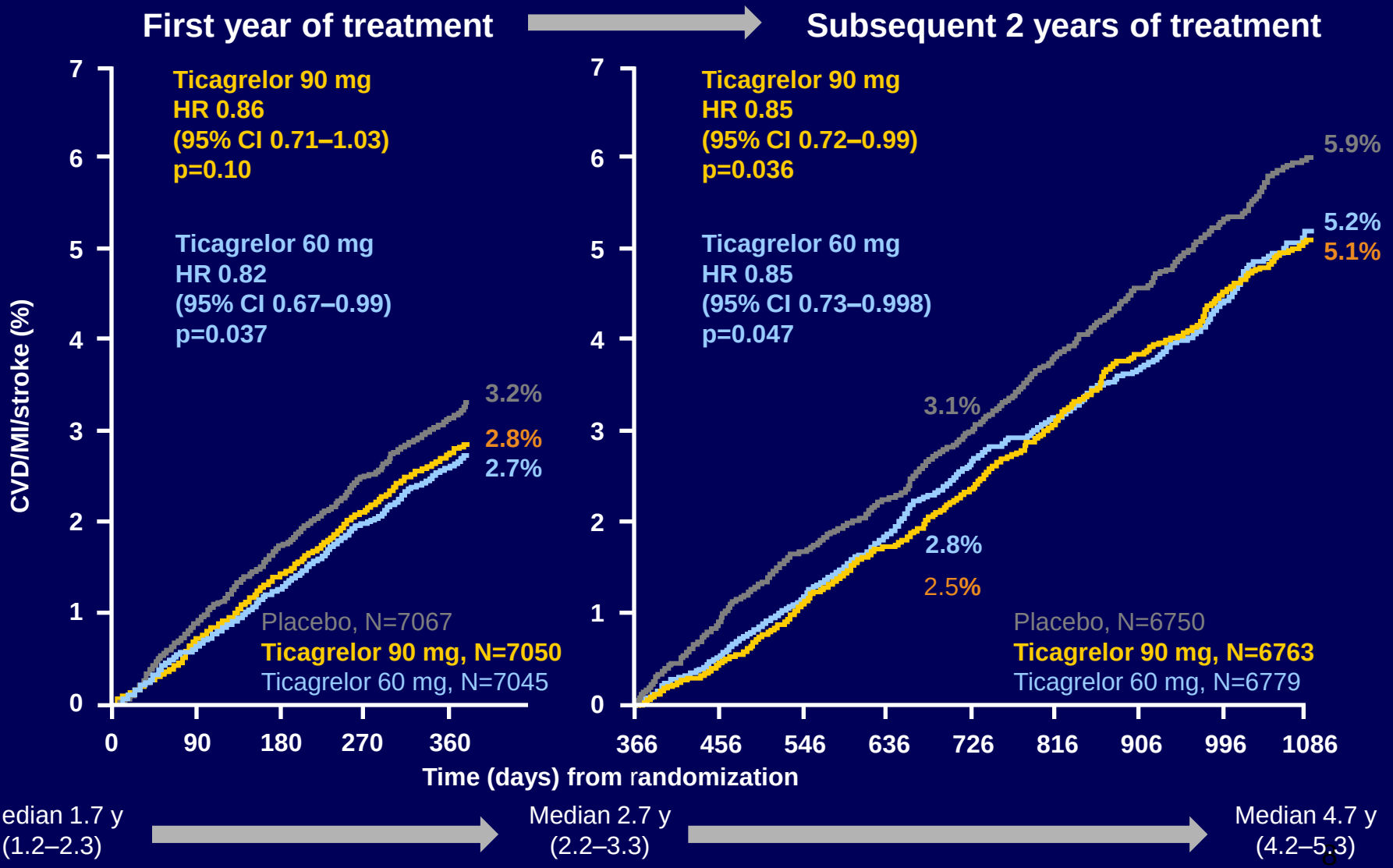
Bonaca MP *et al*. *N Engl J Med* 2015;372:1791–1800

PEGASUS-TIMI 54 platelet function substudy
VerifyNow PRU



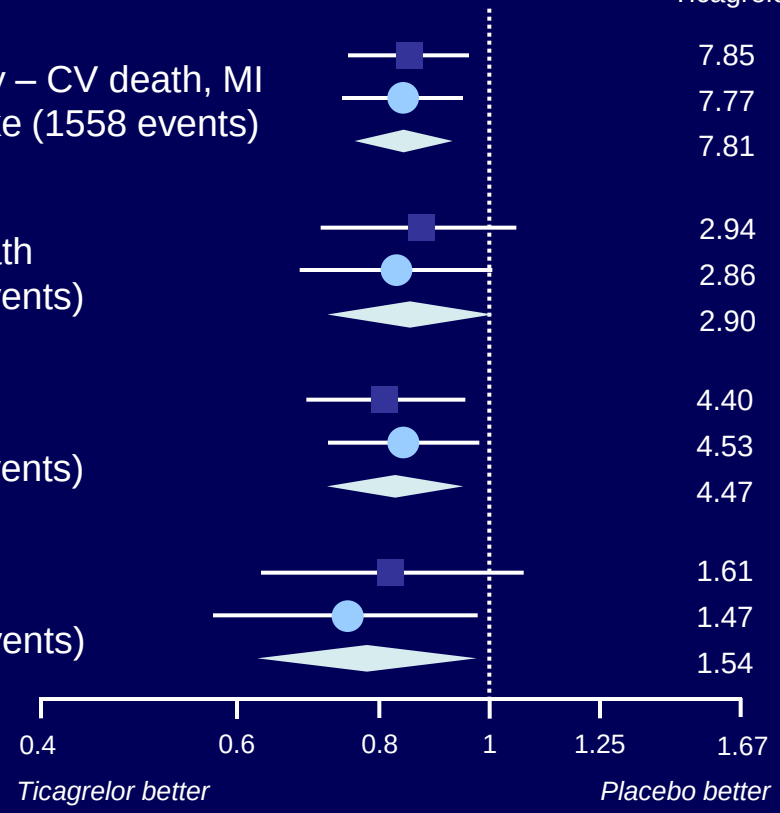
Storey RF et al. *J Am Coll Cardiol.* 2016

Primary endpoint – landmark (ITT)



Bonaca MP et al. Presented at AHA Congress 2015 (Abstract 383).

PEGASUS-TIMI 54: Efficacy endpoints



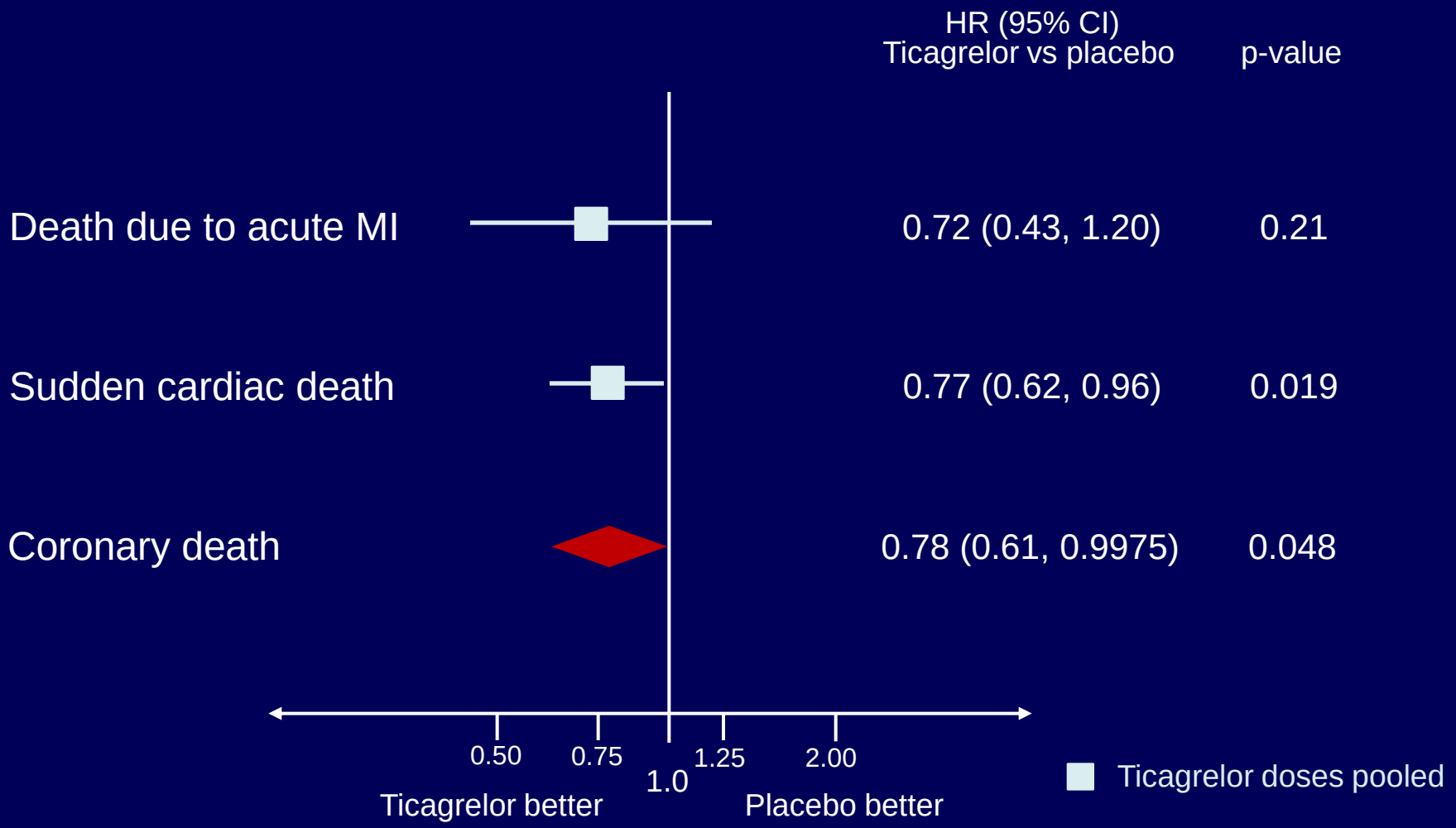
Endpoint	3-year KM event rates (%) Ticagrelor	Placebo	HR (95% CI)	P-value
Primary – CV death, MI or stroke (1558 events)	7.85	9.04	0.85 (0.75–0.96)	0.008
	7.77	9.04	0.84 (0.74–0.95)	0.004
	7.81	9.04	0.84 (0.76–0.94)	0.001
CV death (566 events)	2.94	3.39	0.87 (0.71–1.06)	0.15
	2.86	3.39	0.83 (0.68–1.01)	0.07
	2.90	3.39	0.85 (0.71–1.00)	0.06
MI (898 events)	4.40	5.25	0.81 (0.69–0.95)	0.01*
	4.53	5.25	0.84 (0.72–0.98)	0.03*
	4.47	5.25	0.83 (0.72–0.95)	0.005*
Stroke (313 events)	1.61	1.94	0.82 (0.63–1.07)	0.14*
	1.47	1.94	0.75 (0.57–0.98)	0.03*
	1.54	1.94	0.78 (0.62–0.98)	0.03*

Ticagrelor 90 mg bid
Ticagrelor 60 mg bid
Ticagrelor pooled

*Indicates nominal p-value; p<0.026 indicates statistical significance.

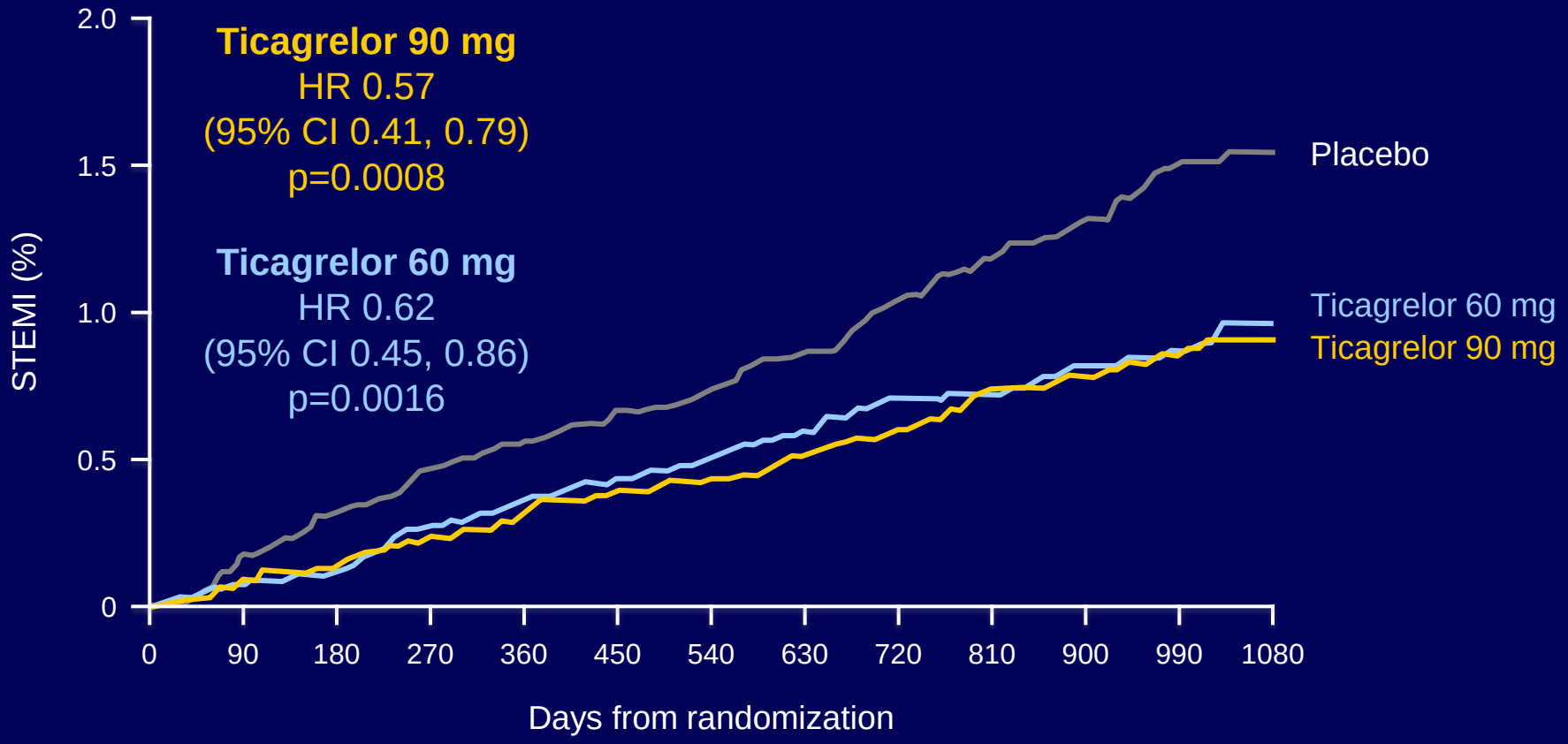
Bonaca MP et al. *N Engl J Med.* 2015;372:1791–1800.

Effect of ticagrelor on CAD-related death



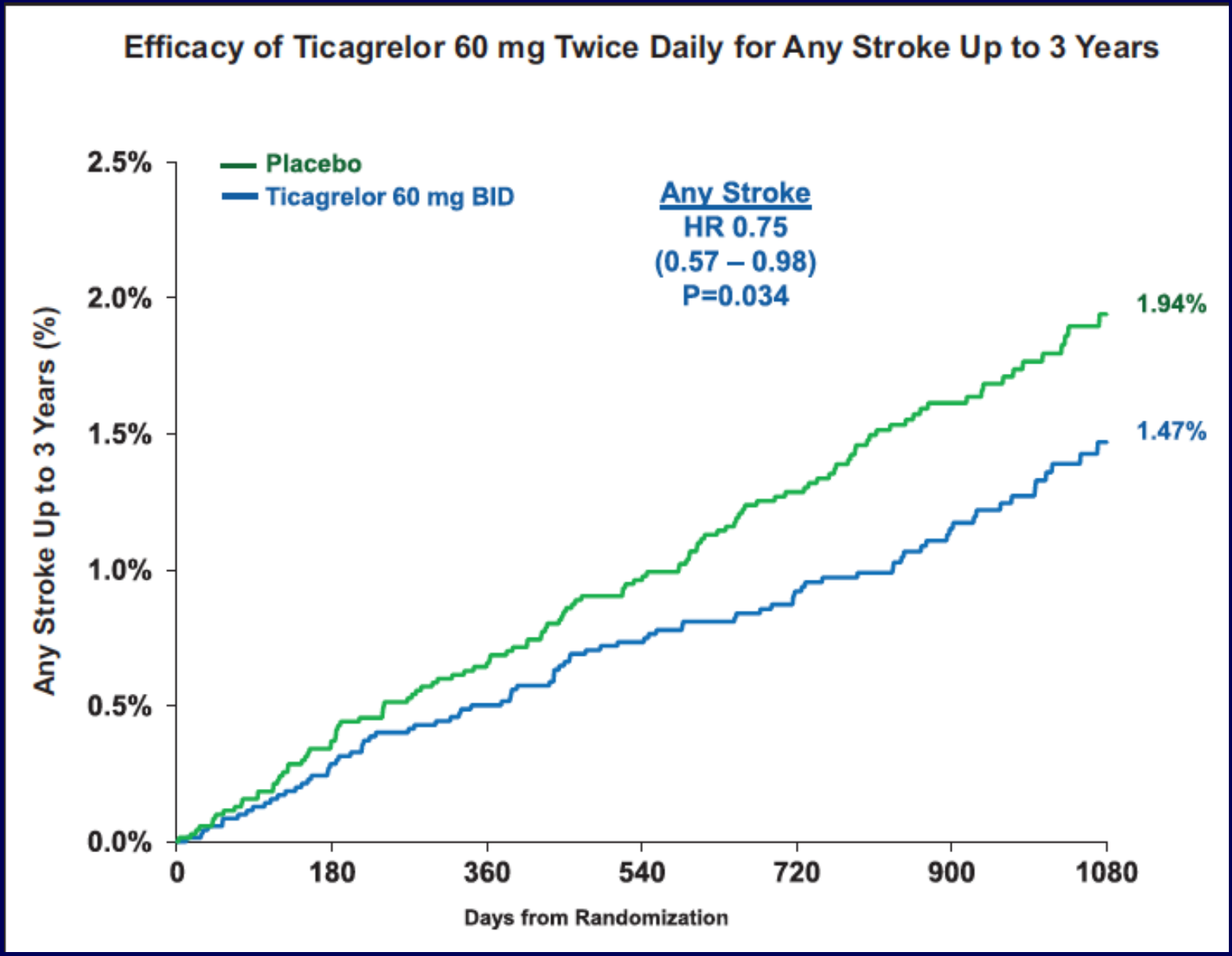
Bonaca MP et al. Presented at AHA Congress 2015 (Abstract 891).

Effect of ticagrelor on STEMI



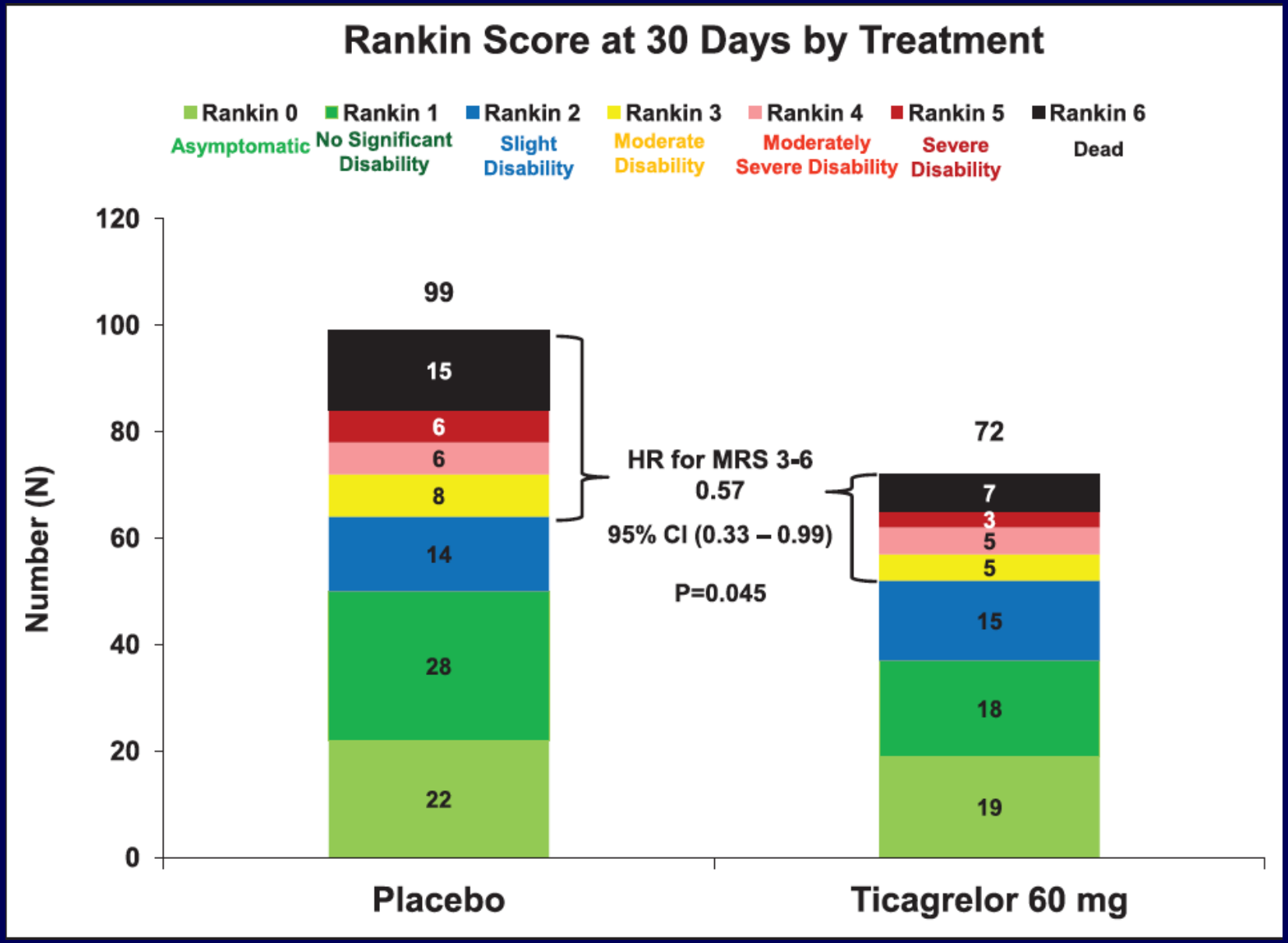
Bonaca MP et al. Presented at AHA Congress 2015 (Abstract 891).

Effect of ticagrelor 60mg on stroke



Bonaca MP et al. Circulation 2016

Effect of ticagrelor 60mg on stroke



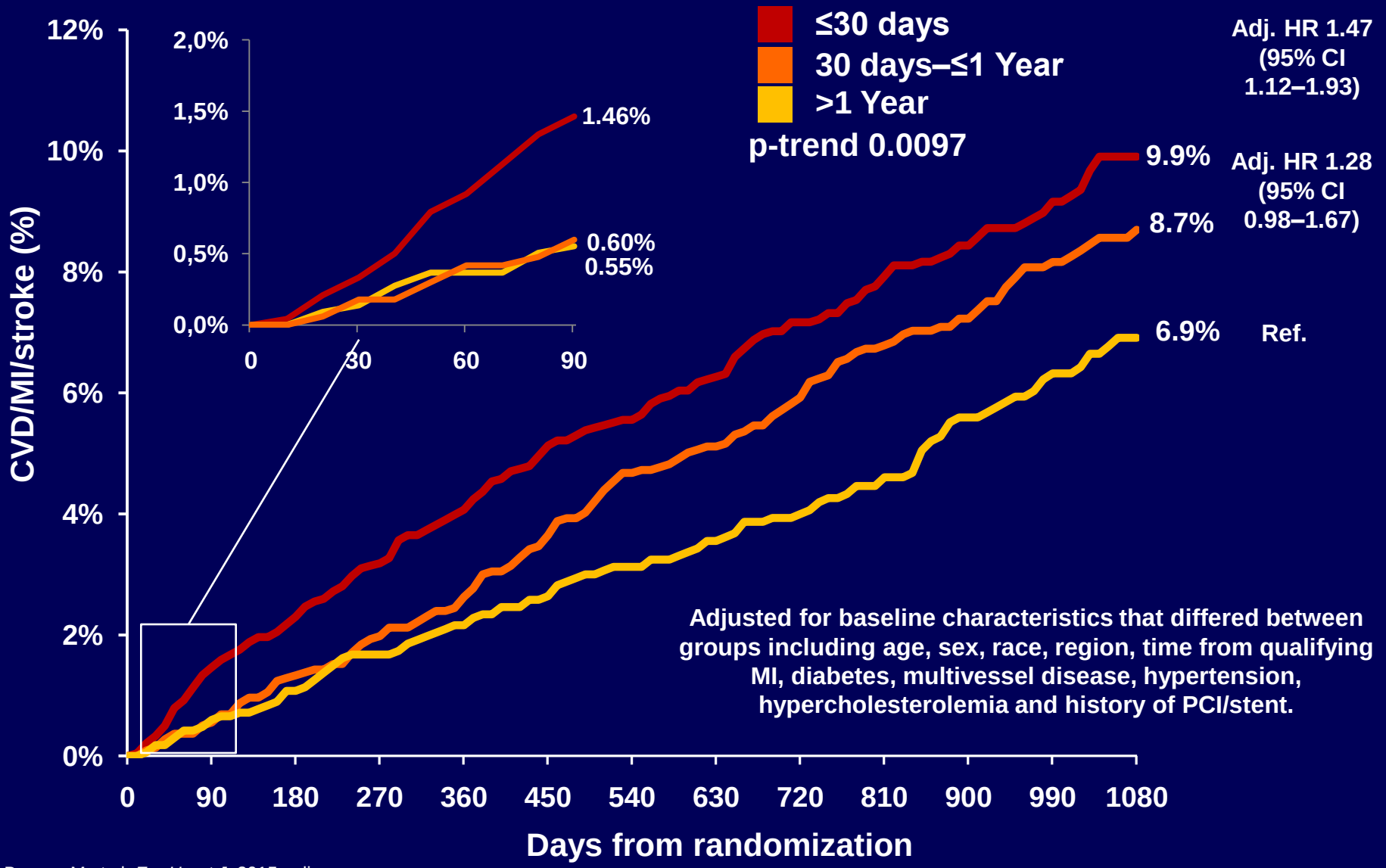
Bonaca MP et al. Circulation 2016

PEGASUS-TIMI 54: Non-CV deaths

Adverse event	Ticagrelor 90 mg bid N=7050; n (%)	Ticagrelor 60 mg bid N=7045; n (%)	Placebo N=7067; n (%)
All-cause death	336 (4.8)	299 (4.2)	336 (4.8)
Non-CV death	145 (2.1)	117 (1.7)	115 (1.6)
Accident/trauma	6 (0.09)	2 (0.03)	4 (0.06)
Infection/sepsis	31 (0.44)	25 (0.36)	24 (0.34)
Malignancy	77 (1.10)	64 (0.92)	53 (0.76)
Pulmonary failure	10 (0.14)	9 (0.13)	9 (0.13)
Renal failure	2 (0.03)	4 (0.06)	4 (0.06)
Other	19 (0.27)	13 (0.19)	21 (0.30)

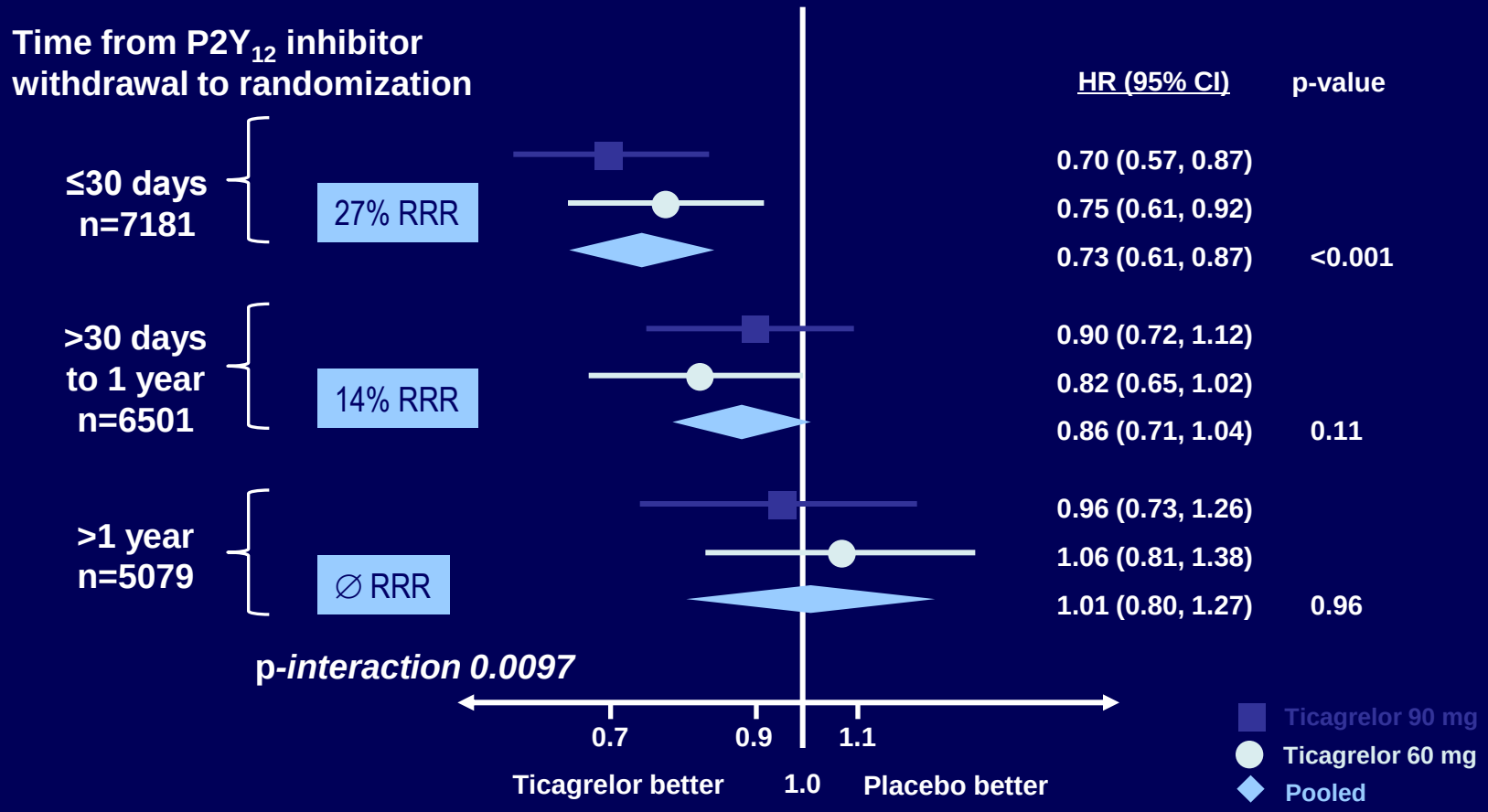
Includes deaths occurring after the common study end date (safety window).
Data presented as proportions.
n=number of patients with events, not the number of events.
Bonaca MP et al. *N Engl J Med.* 2015, Supplementary Appendix [Epub ahead of print].

PEGASUS TIMI 54: MACE in patients randomized to placebo by time from $P2Y_{12}$ inhibitor withdrawal



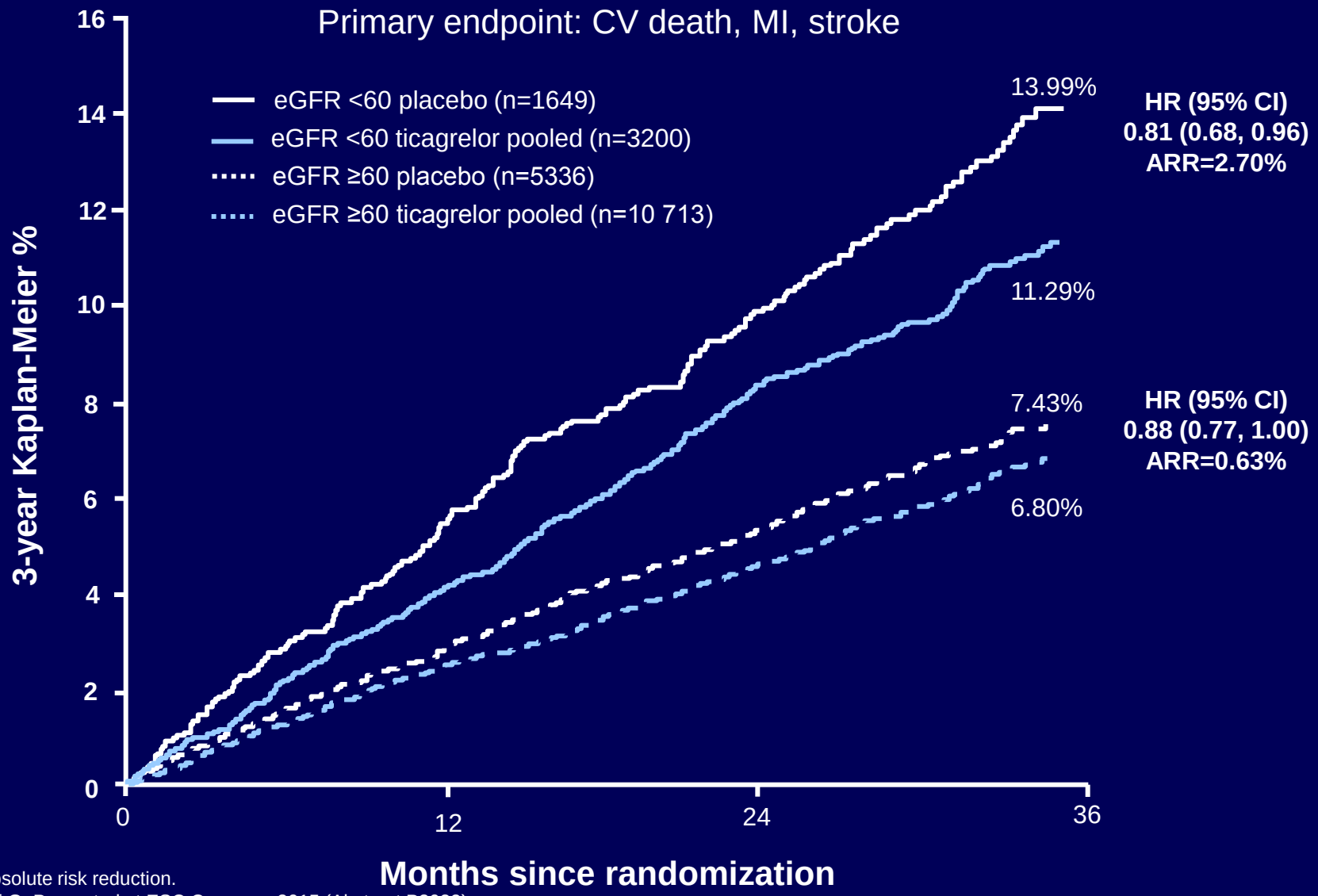
Bonaca M et al. *Eur Heart J.* 2015 online.

Reduction in CV death, MI or stroke with ticagrelor by time from $P2Y_{12}$ inhibitor withdrawal



Bonaca MP. Presented at ESC Congress 2015 (Abstract 3918).

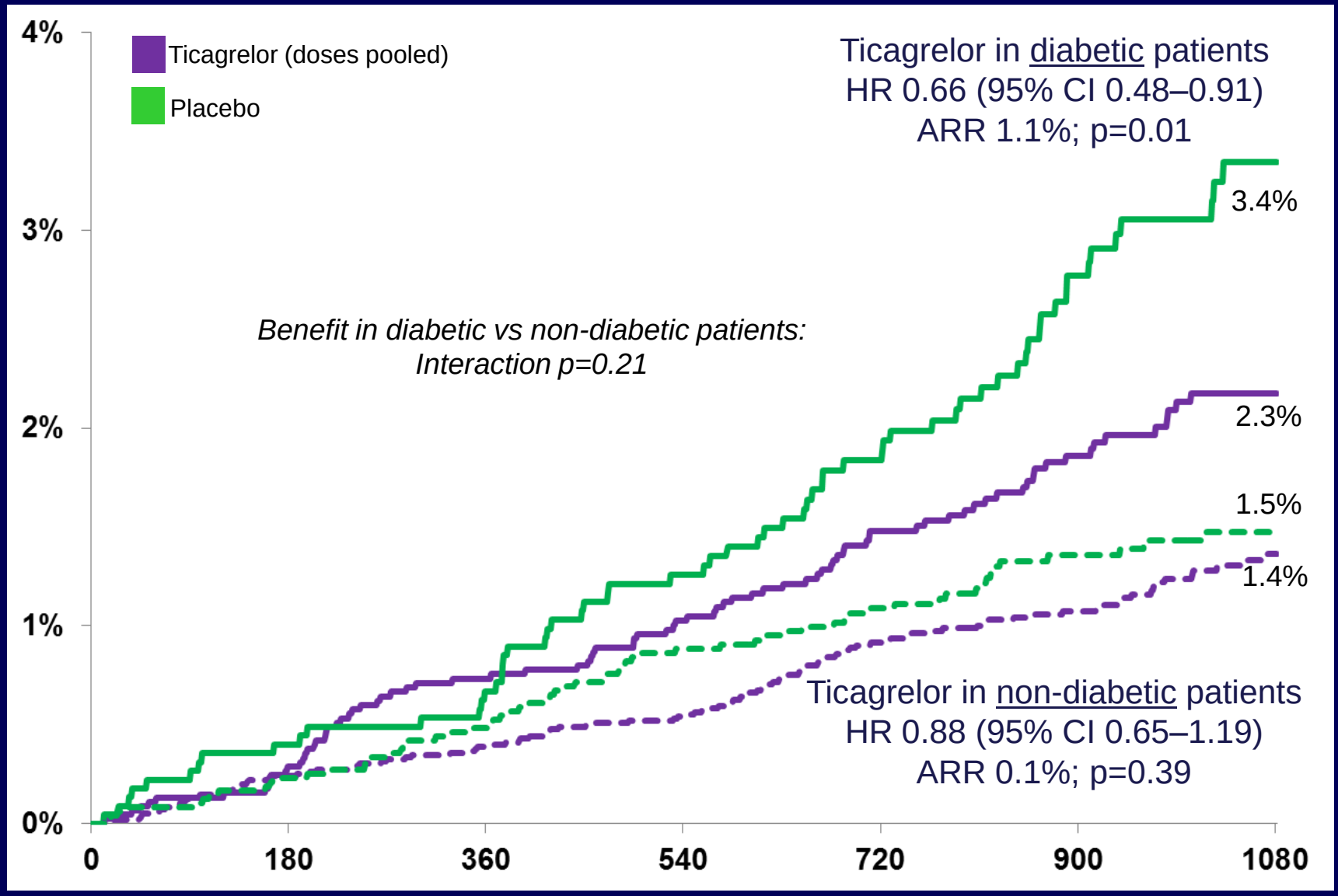
Efficacy of ticagrelor by eGFR



ARR, absolute risk reduction.

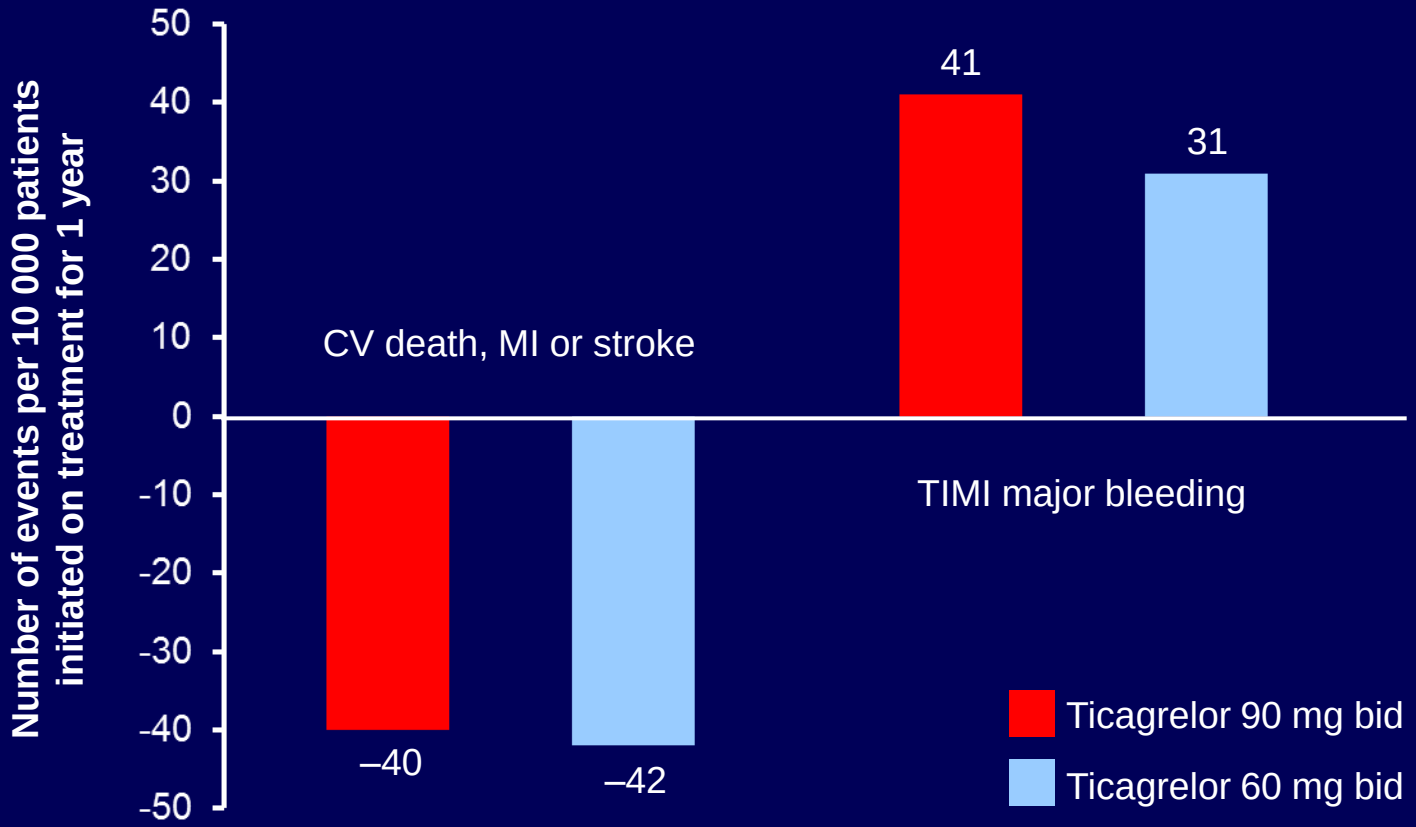
Magnani G. Presented at ESC Congress 2015 (Abstract P3032).

PEGASUS-TIMI 54 diabetes substudy: CAD-related death



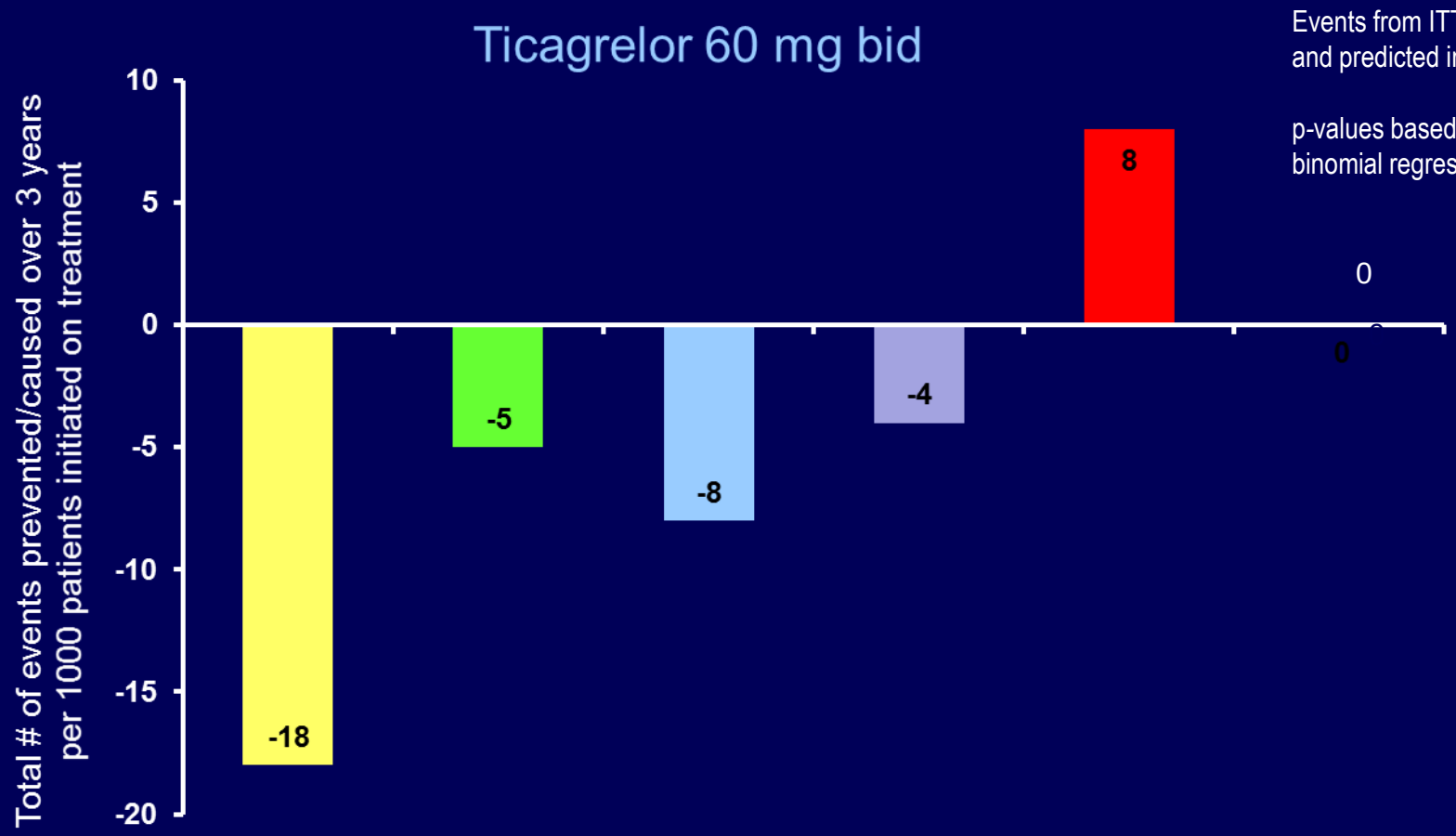
Bhatt DL et al. *J Am Coll Cardiol.* 2016.

PEGASUS-TIMI 54: Estimates of first efficacy and bleeding events prevented and caused



Rates are annualised from 3-year Kaplan-Meier event rates in the intention-to-treat population.
Bonaca MP et al. *N Engl J Med.* 2015, Supplementary Appendix [Epub ahead of print].

Total events: efficacy and safety

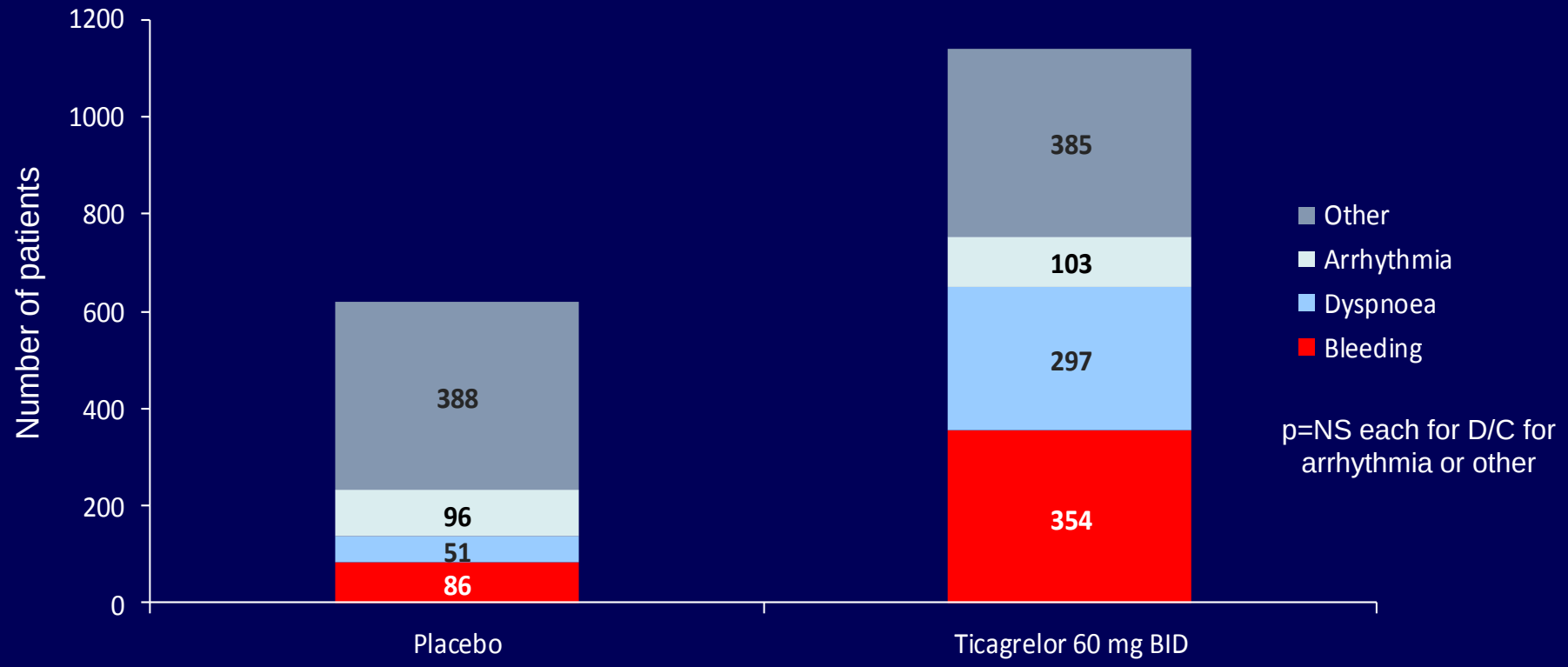


Murphy SA et al. Presented at AHA Congress 2015 (Abstract 742).

Adverse events leading to discontinuation

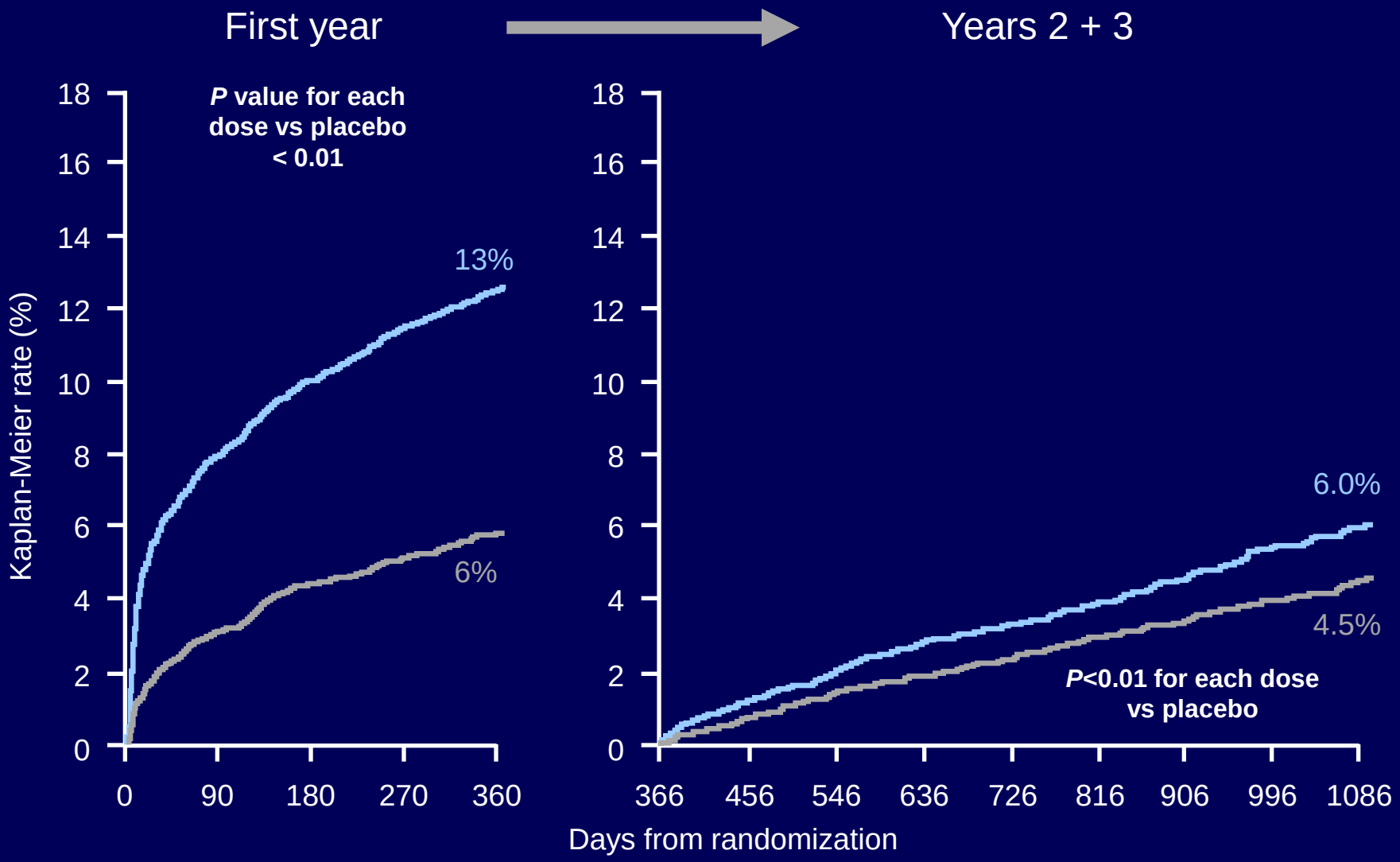
3 year KM rate (%) – p-value for 60 mg ticagrelor versus placebo <0.001

Treatment arm	Any AE	Bleeding	Dyspnoea
Ticagrelor 60 mg bid	16.4%	6.2%	4.6%
Placebo	8.9%	1.5%	0.8%



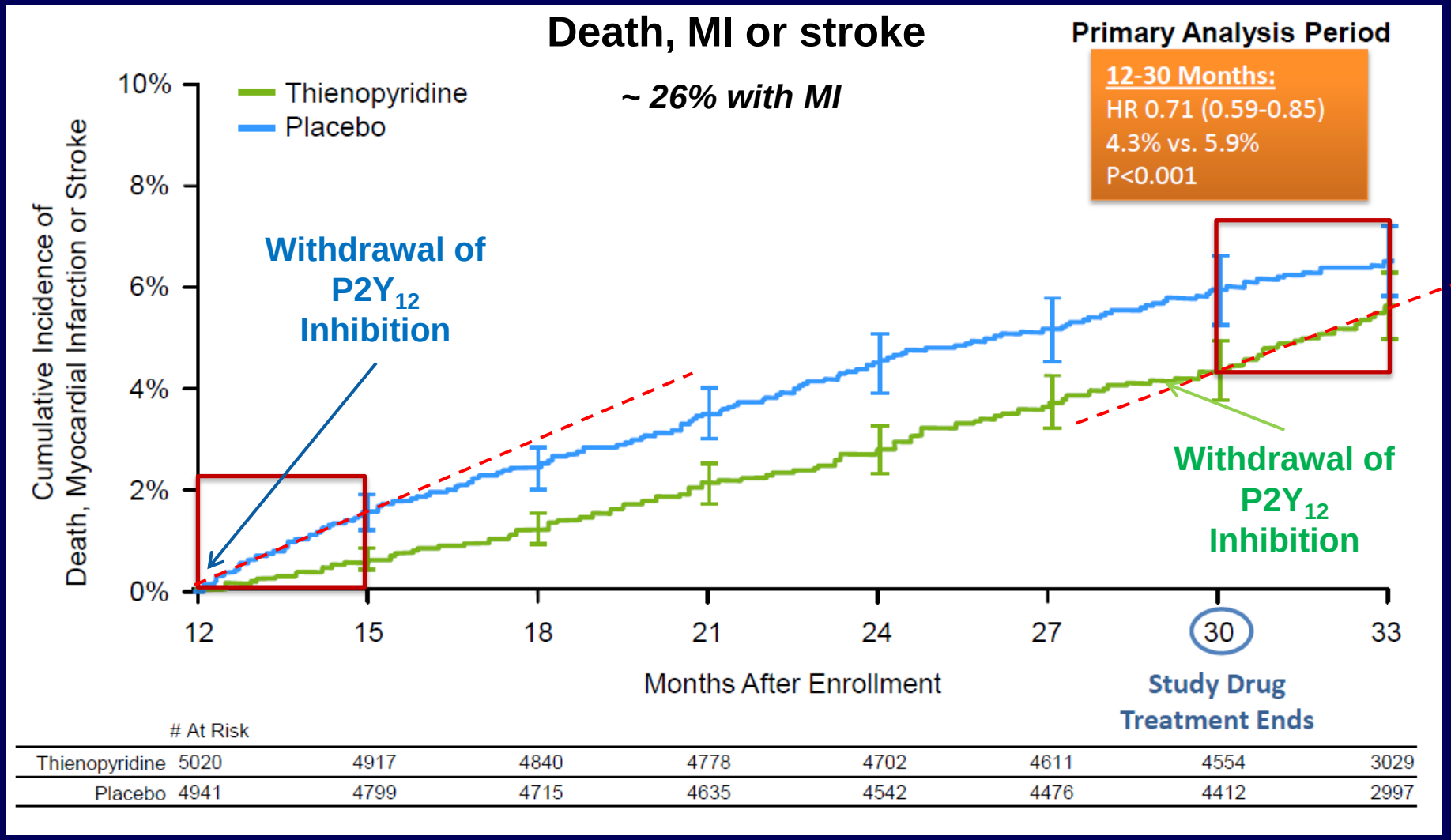
AE, adverse event; D/C, discontinuation; NS, not significant.
Bonaca MP et al. Presented at AHA Congress 2015 (Late Breaking Clinical Trial).

Drug discontinuation for AE by treatment arm



Bonaca MP *et al.* Presented at AHA Congress 2015 (Late Breaking Clinical Trial)

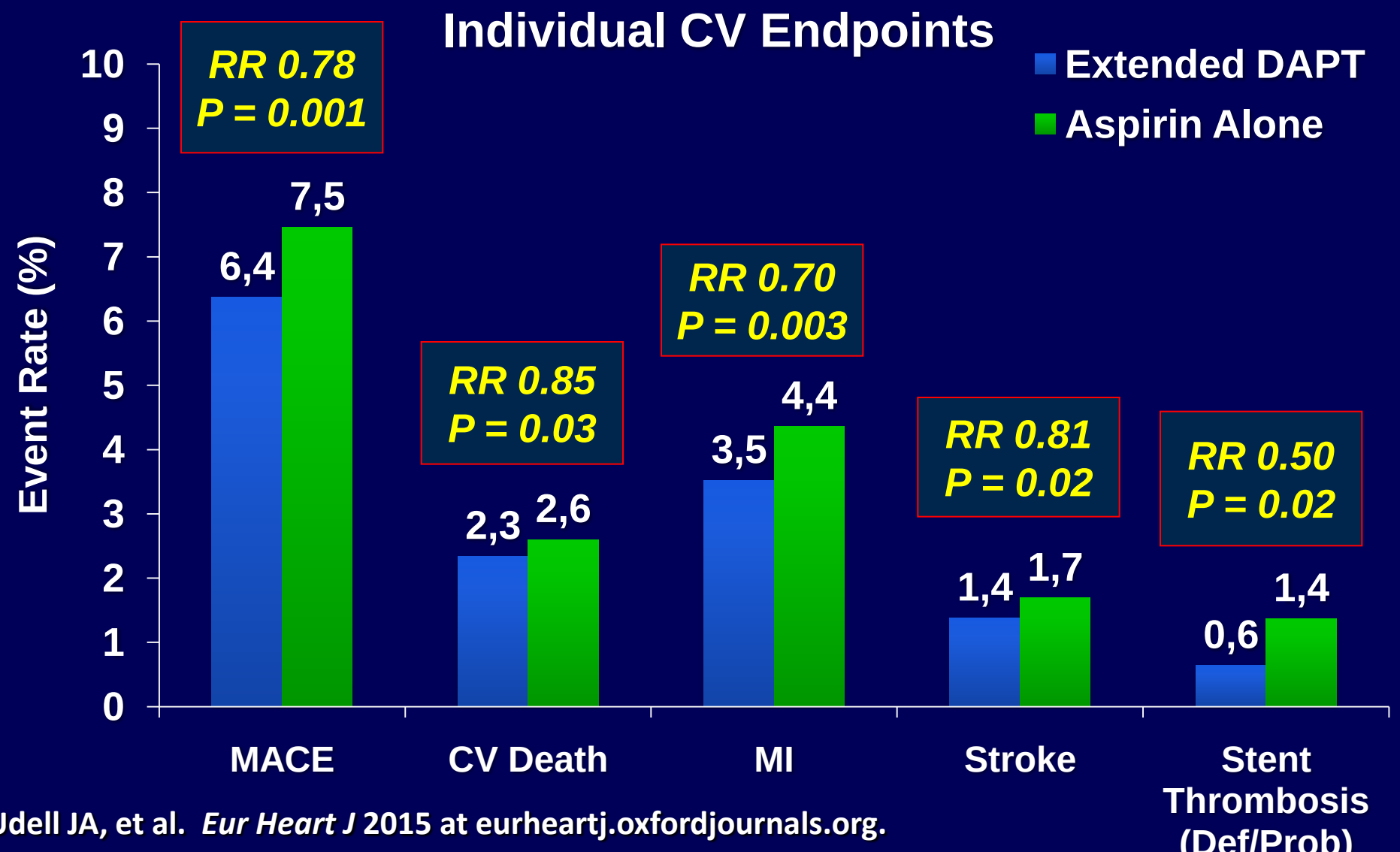
DAPT study: Continuation or withdrawal of thienopyridine 12 months after coronary stenting



# At Risk								
Thienopyridine	5020	4917	4840	4778	4702	4611	4554	3029
Placebo	4941	4799	4715	4635	4542	4476	4412	2997

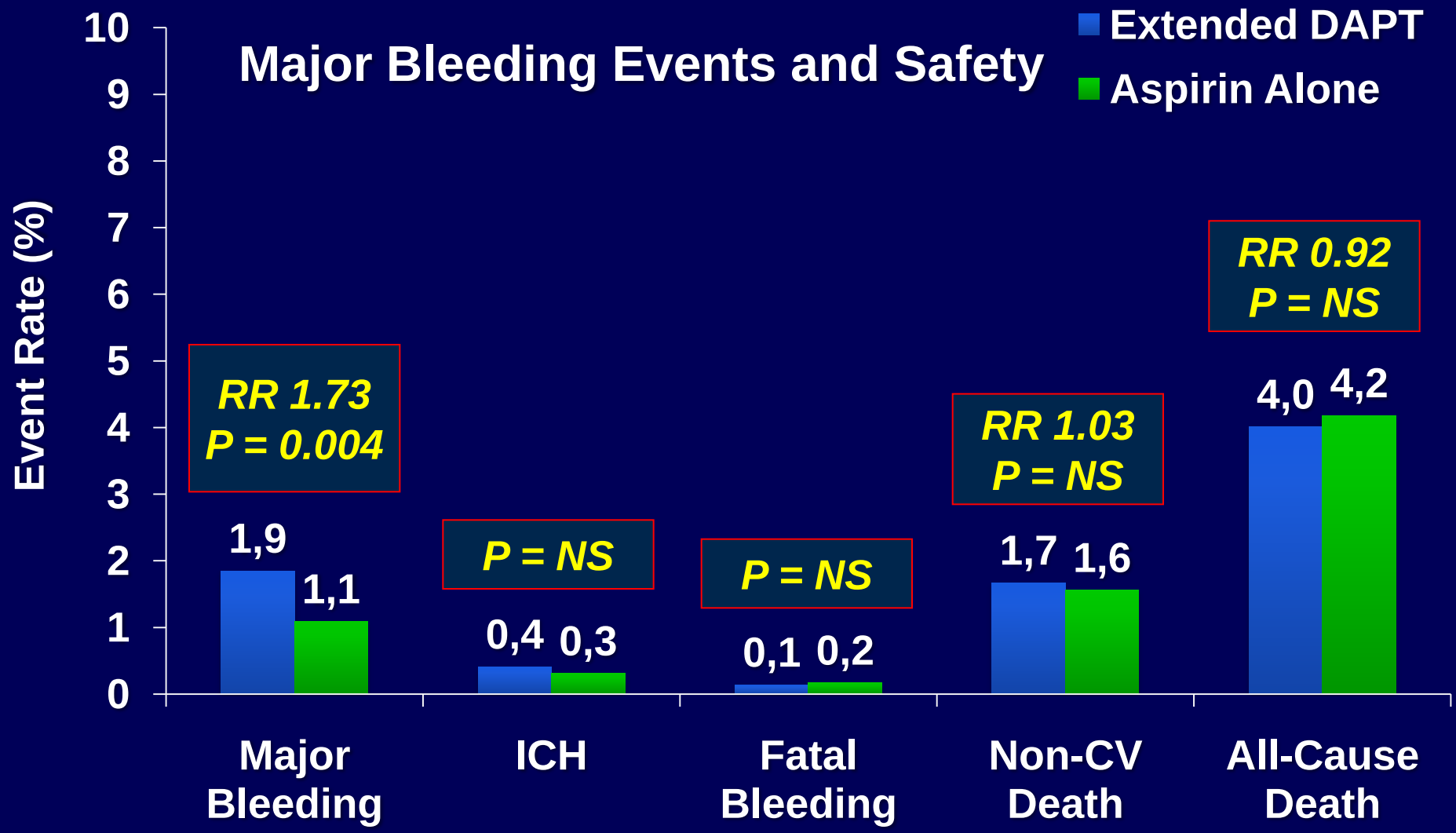
Mauri et al. NEJM 2014

Long-term DAPT post MI: meta-analysis (n=33,435)



Udell JA, et al. *Eur Heart J* 2015 at eurheartj.oxfordjournals.org.

Long-term DAPT post MI: meta-analysis (n=33,435)



Udell JA, et al. *Eur Heart J* 2015 at eurheartj.oxfordjournals.org.

Conclusions

- Extended DAPT post-MI reduces risks of stent thrombosis and ischaemic events at the expense of increased risk of non-fatal major bleeding
- The higher the ischaemic risk, the greater the absolute risk reduction with extended DAPT post MI e.g. CKD, DM, PAD
- Extended ticagrelor-based DAPT associated with numerically lower rates of all-cause death in the 60 mg bid group due to lower rates of CV death, particularly CAD-related death, and no excess of non-CV death
- Extended thienopyridine-based DAPT may be an alternative to ticagrelor-based DAPT but relative efficacy and safety of the regimens is uncertain
- Efficacy data for aspirin/NOAC combination awaited with interest

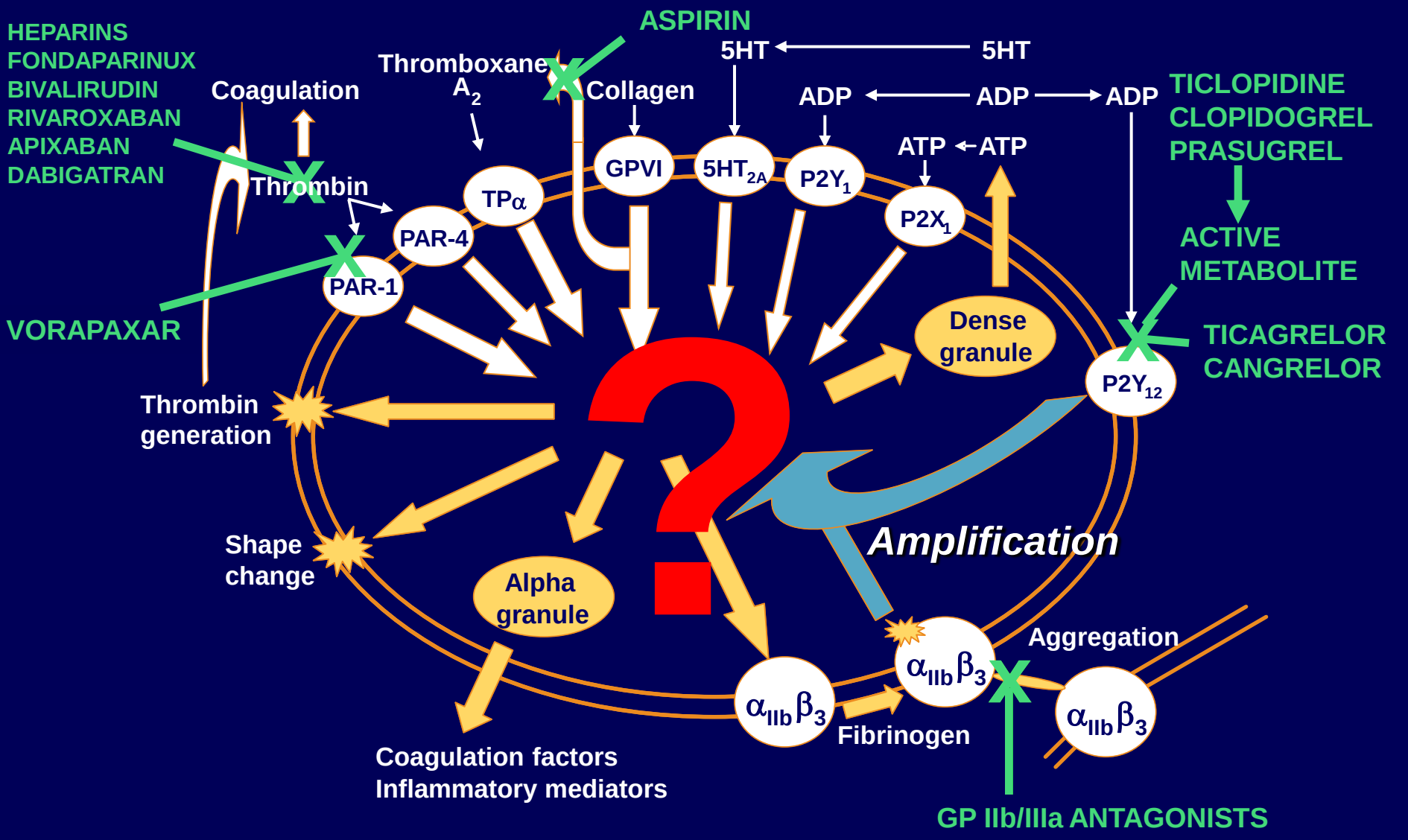
My personal opinion

- Long-term ticagrelor 60 mg bid and aspirin 75 mg od is recommended in post-MI patients at high risk of CAD-related death who do not have high risk of fatal bleeding
- Long-term thienopyridine-based DAPT may be considered in ticagrelor-intolerant patients at high risk of CAD-related death
- Coronary anatomy should be considered along with clinical variables when deciding on duration of DAPT post-MI in order to guide risk of CAD-related death
- Duration of DAPT can be recommended following the coronary angiography procedure but reviewed at any stage should complications arise

Example of discharge letter advice….

Follow-up by GP: Please continue ticagrelor 90 mg bd for 1 year and then downtitrate to 60 mg bd long term, if tolerated, in view of extent of coronary artery disease and clinical risk factors. Continue aspirin, statin and other secondary prevention medication long term.

Discussion



ADP, adenosine diphosphate; ATP, adenosine triphosphate; GP = glycoprotein; PAR = protease-activated receptor; TP, thromboxane A2/prostaglandin H2.
Storey RF. *Curr Pharm Des.* 2006.