

The Risk of CV Events for Patients Treated with Clopidogrel or Prasugrel in Combination with a Proton Pump Inhibitor

Results from the TRITON-TIMI 38 Trial

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Disclosures

- **M. O'Donoghue:** none
- **SD Wiviott:** Grants from Eli Lilly, Daiichi Sankyo, sanofi aventis, Schering Plough. Consulting or advisory board fees: Astra Zeneca, sanofi aventis. Honoraria from Eli Lilly, Daiichi Sankyo, Astra Zeneca, Schering Plough
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- **E. Braunwald:** Research grants and honoraria from Eli Lilly, Daiichi Sankyo.

Background

- PPIs are often administered with dual antiplatelet therapy for gastric protection
- *Ex vivo* studies have shown diminished platelet inhibition in response to clopidogrel in the presence of a PPI ^{1,2}
- Recent studies have raised concerns that PPIs may attenuate the clinical benefit of clopidogrel ^{3,4}

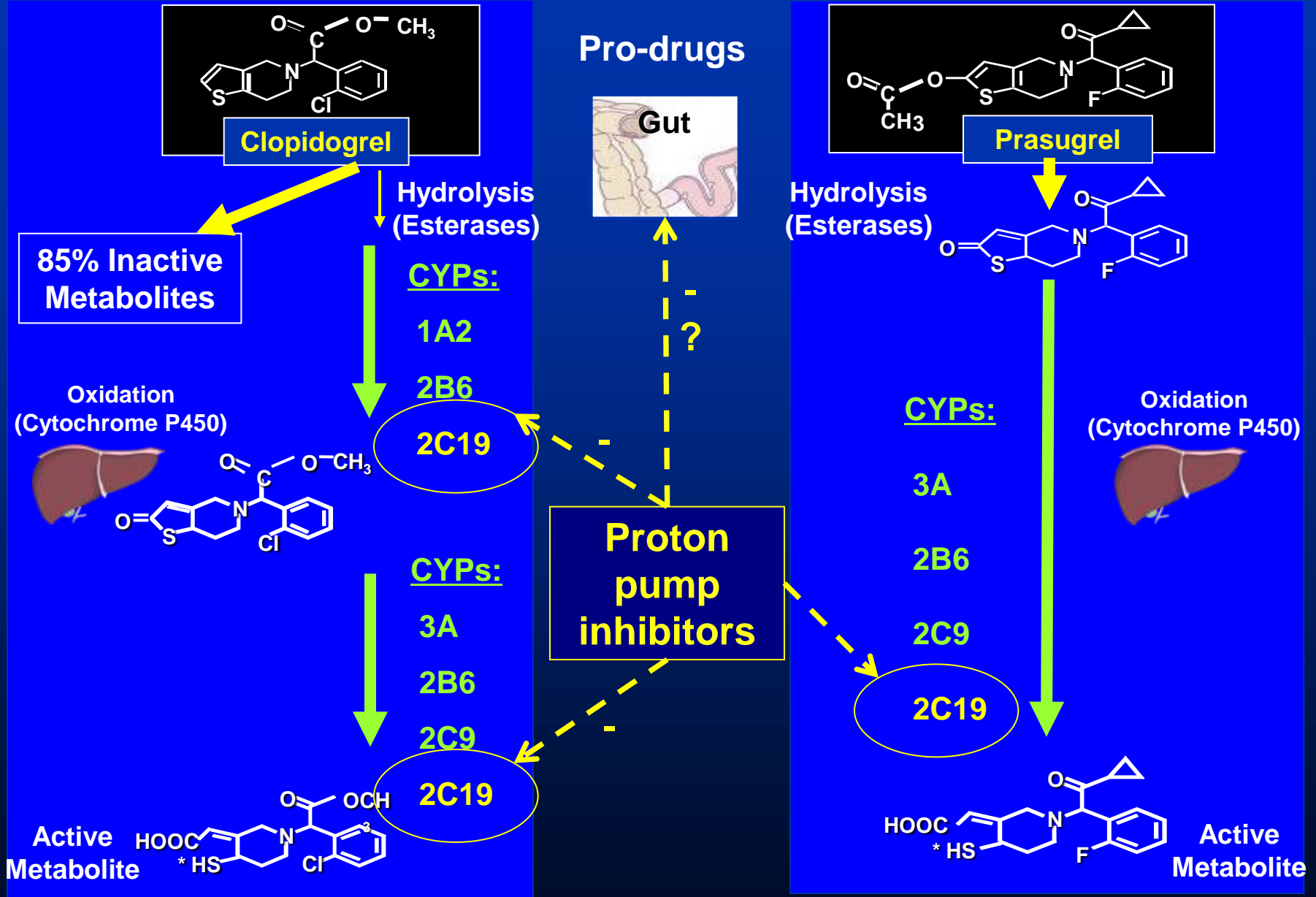
¹ Gilard et al., *J Am Coll Cardiol* 2008

² Sibbing et al., *Thromb Haemost* 2009

³ Juurlink et al., *CMAJ* 2009

⁴ Ho et al., *JAMA* 2009

Thienopyridines: Formation of Active Metabolite



Aims

- To examine the association between PPI use and the risk of CV events for patients on clopidogrel or prasugrel
- As an exploratory analysis, to examine this relationship in patients with a single reduced function *CYP2C19* allele

TRITON – TIMI 38

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA



N= 13,608

Double-blind



PRASUGREL

(60 mg LD, 10 mg QD)

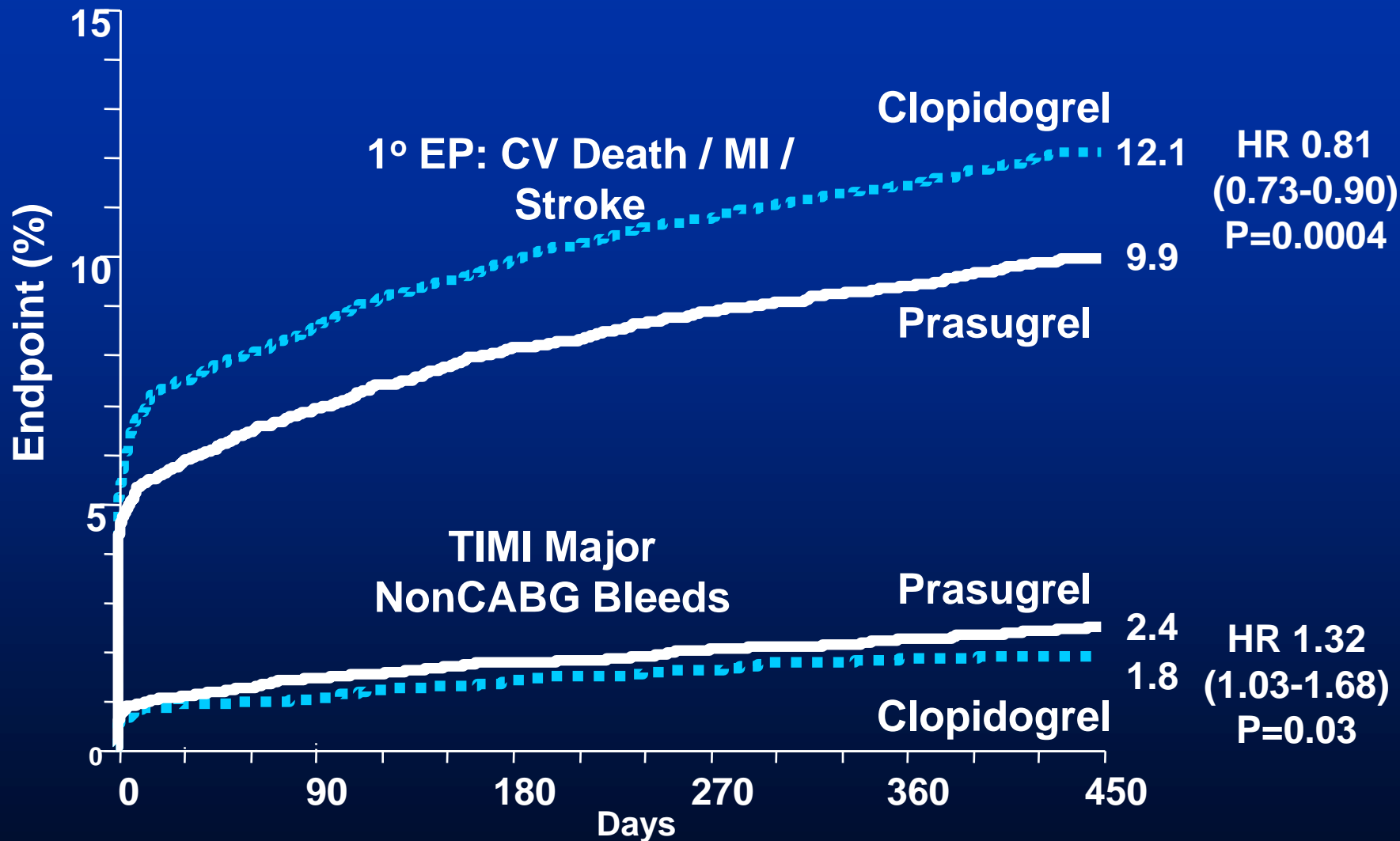
CLOPIDOGREL

(300mg LD, 75 mg QD)

Median duration of therapy – 14.5 months

1° endpoint: CV death, MI, Stroke

TRITON – TIMI 38



Methods

- PPI use was at the discretion of the treating physician and captured on the case-report forms
- Propensity scores were constructed using stepwise selection to predict PPI use at different timepoints
- Cox proportional hazards models included the propensity score and potential confounders

Methods

Primary analysis:

- PPI use at randomization through long-term f/u

Sensitivity analyses:

- Varying durations of follow-up
- Consistent PPI use throughout follow-up
- Individual PPI types
- Use of an H2 receptor antagonist
- Landmark analyses

PPI Use at Randomization

n=4529, 33% of study population

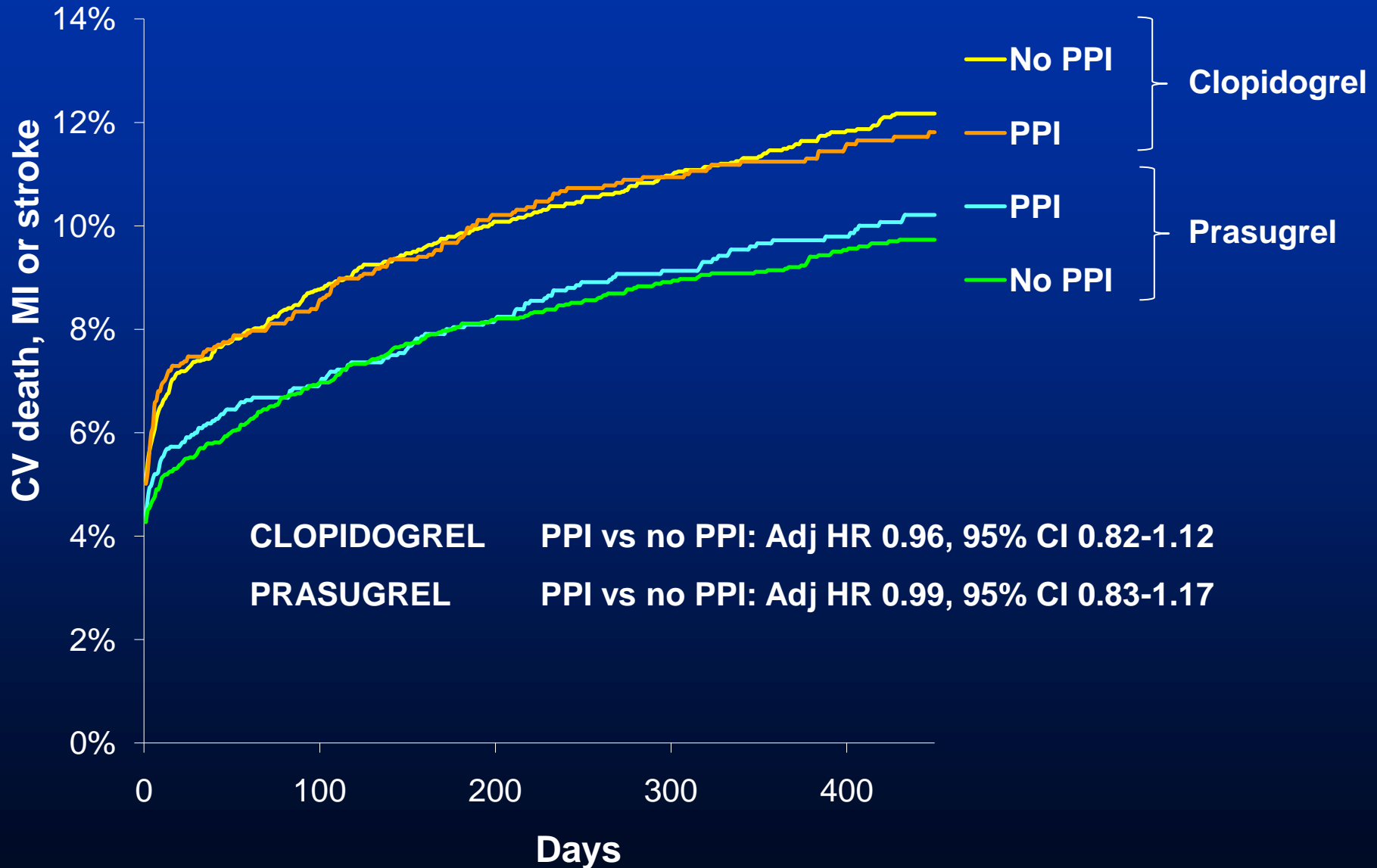
Type of PPI	Frequency
Pantoprazole	1844 (40%)
Omeprazole	1675 (37%)
Esomeprazole	613 (14%)
Lansoprazole	441 (9.7%)
Rabeprazole	66 (1.5%)

Baseline Characteristics

	PPI used (n=4529)	No PPI (n=9079)	P value
Age (median)	61 y	60 y	<0.001
Male	72%	75%	<0.001
Caucasian	94%	92%	<0.001
Western Europe or North America	66%	54%	<0.001
UA or NSTEMI	75%	73%	0.007
Diabetes mellitus	24%	23%	0.14
Hypertension	65%	64%	0.08
Hyperlipidemia	57%	55%	0.07
History peptic ulcer disease	9.7%	4.1%	<0.001
Hemoglobin (g/dl)	13.8	14.0	<0.001

Outcomes stratified by use of a PPI

PPI use at randomization (n= 4529)



	Clopidogrel Adj HR (95% CI)	Prasugrel Adj HR (95% CI)
CV death, MI or stroke	0.96 (0.82-1.12)	0.99 (0.83-1.17)
CV death	0.97 (0.82-1.14)	1.02 (0.85-1.22)
Myocardial infarction	1.00 (0.84-1.18)	0.98 (0.80-1.19)
Stent thrombosis (ARC def or prob)	1.12 (0.78-1.59)	1.01 (0.60-1.71)
Net clinical outcome *	1.00 (0.86-1.15)	1.00 (0.85-1.16)

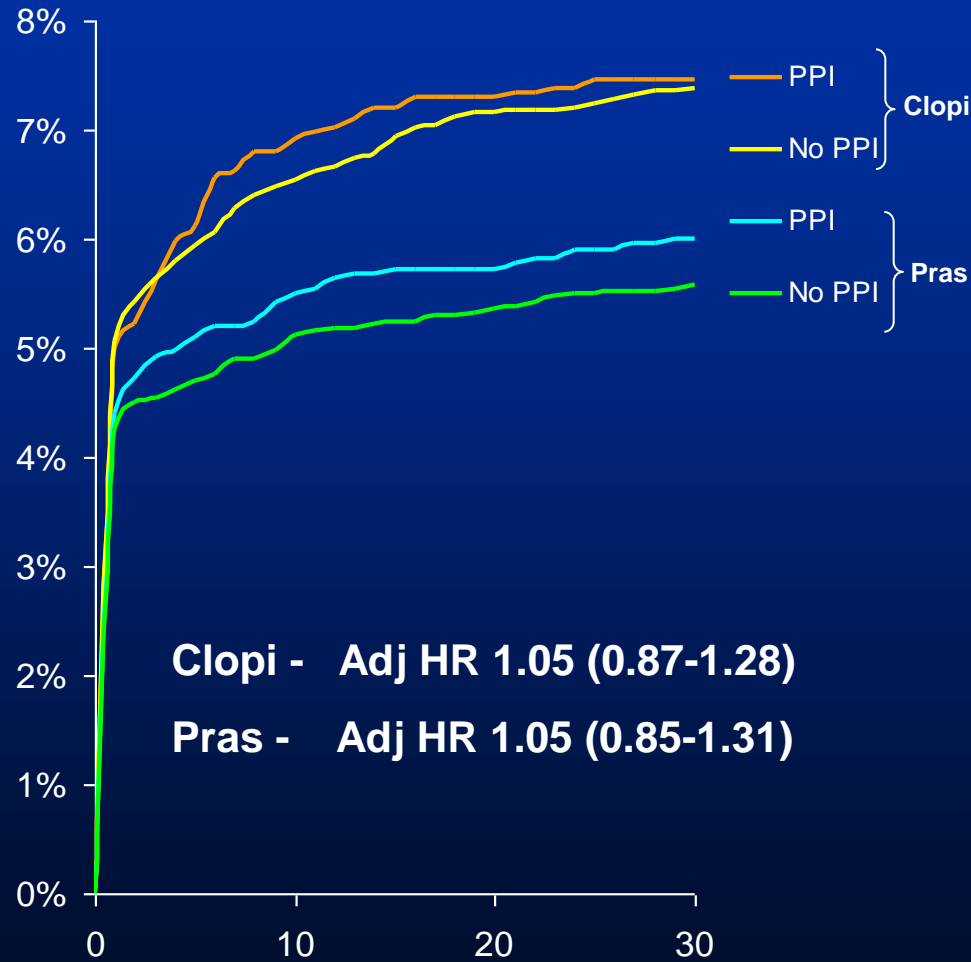
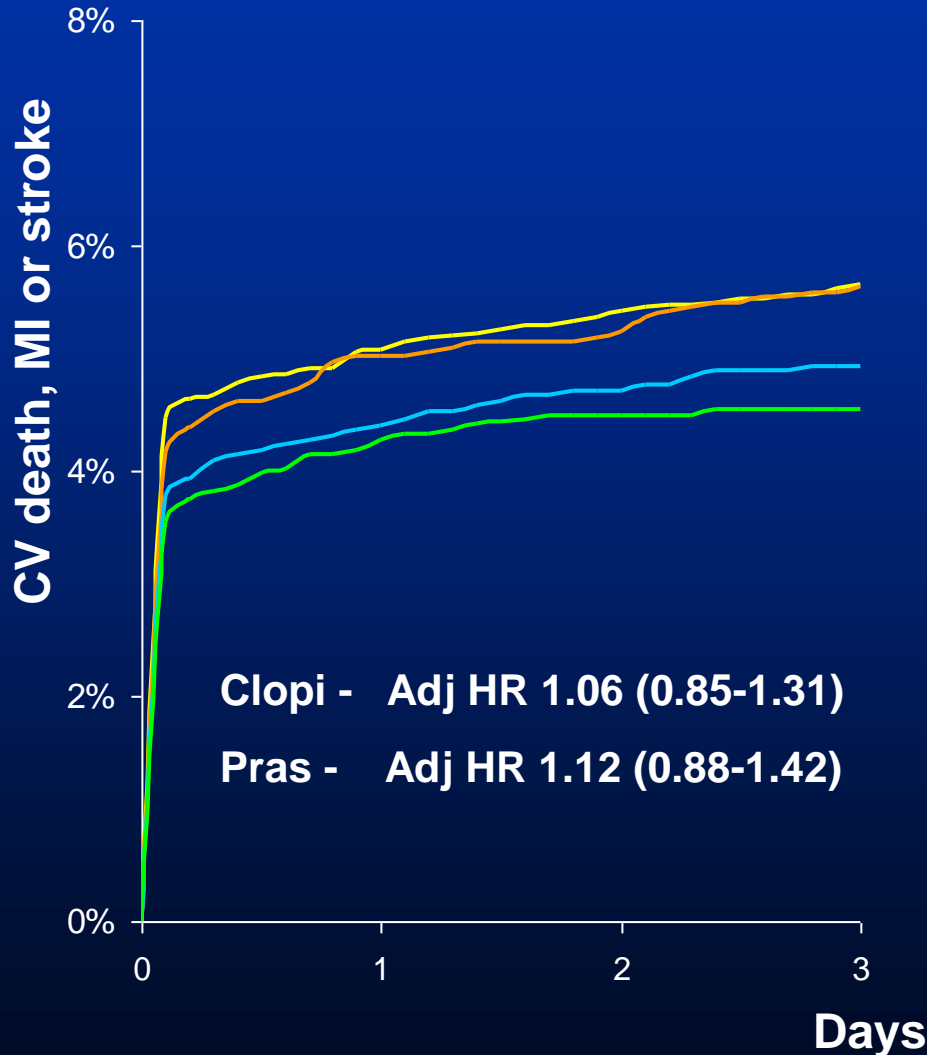
* Death, MI, stroke or TIMI major non-CABG bleeding

Outcomes stratified by use of a PPI

PPI use at randomization (n= 4529)

THROUGH 3 DAY FOLLOW-UP

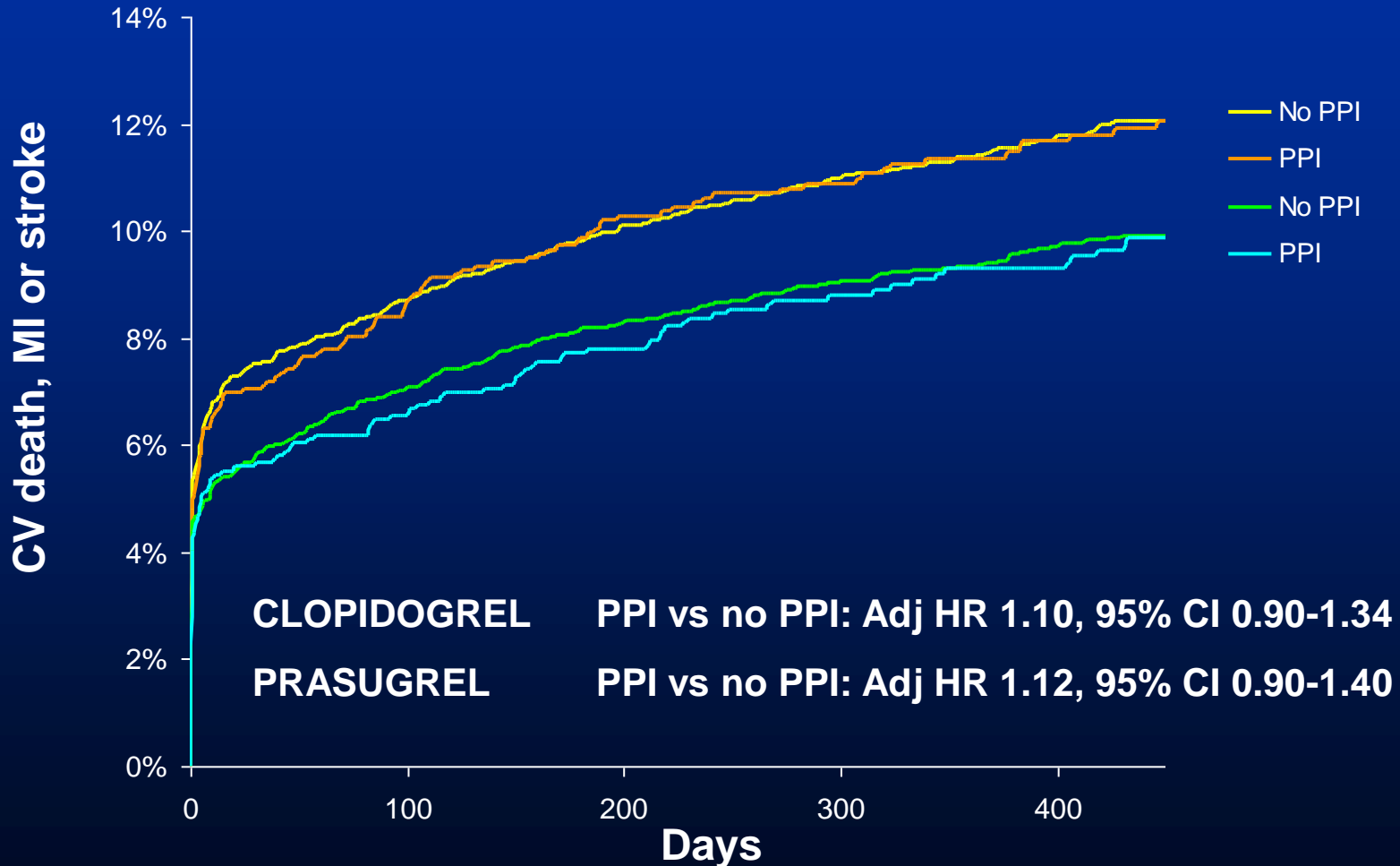
THROUGH 30 DAY FOLLOW-UP



“Consistent” PPI Use – Baseline and End of F/U

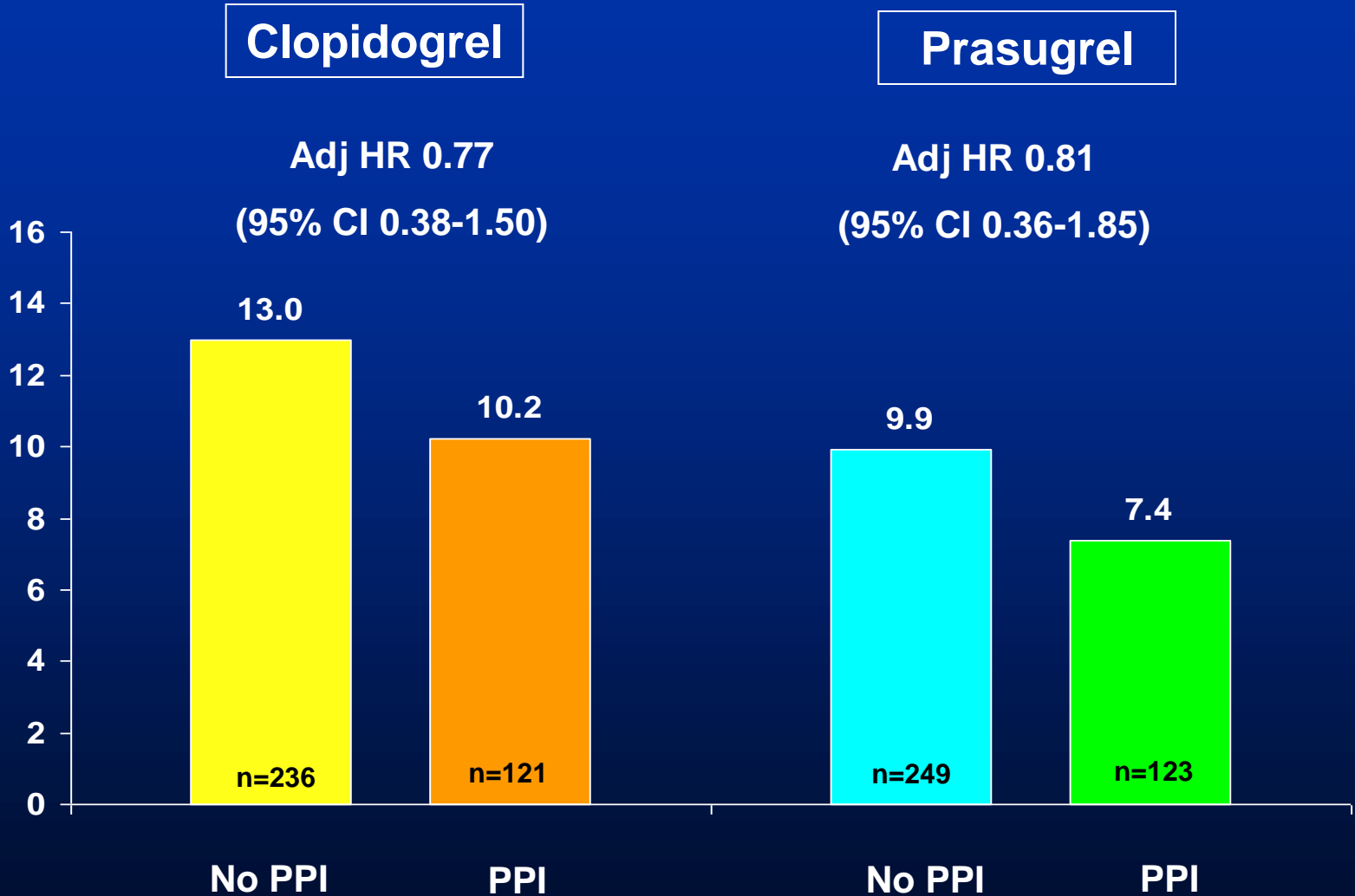
PPI use at randomization and end of f/u (n= 2814)

Patients exposed to PPI for shorter durations were censored (n=3882)



Reduced function *CYP2C19* allele

CVD, MI or stroke through long-term follow-up



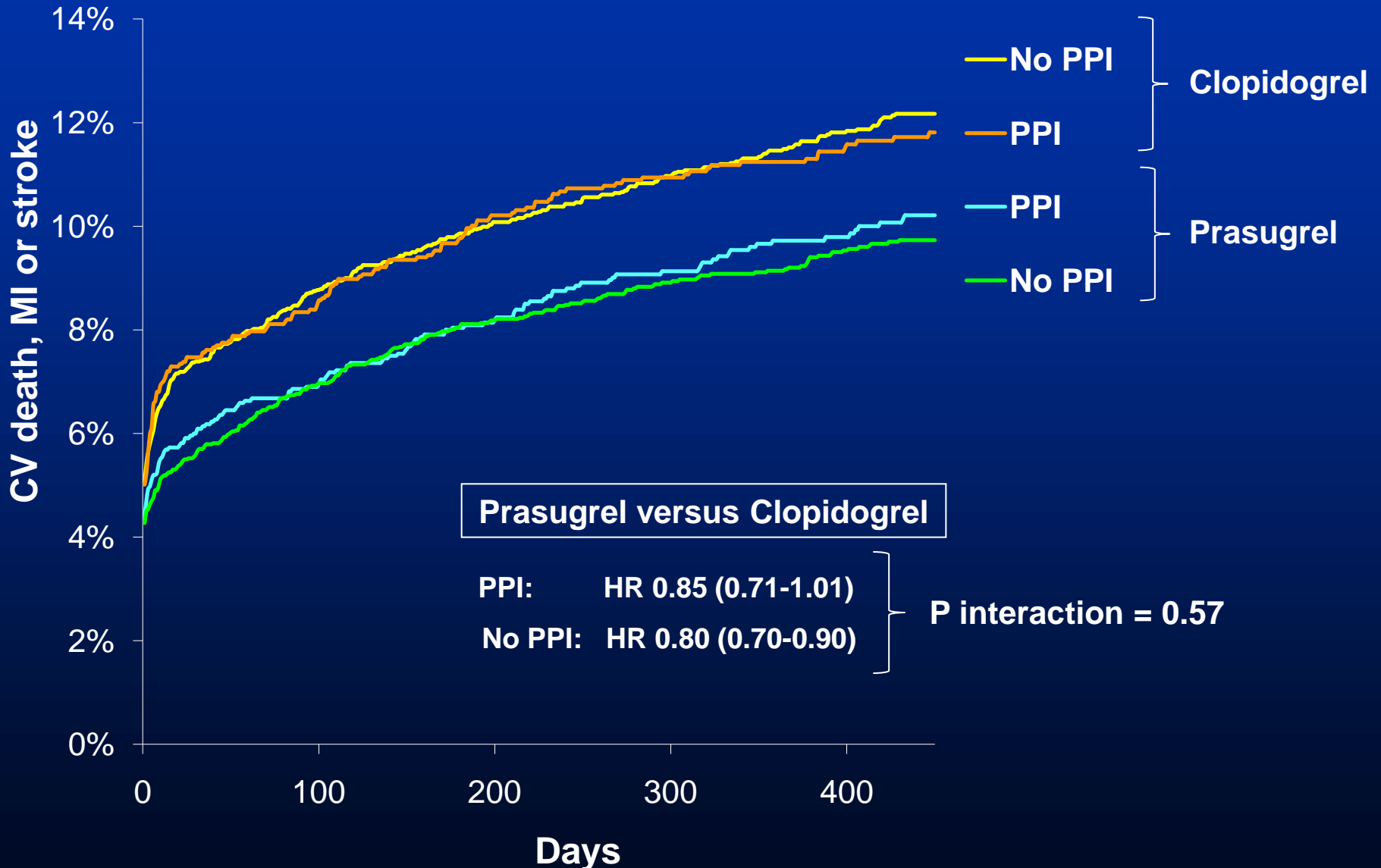
Additional Sensitivity Analyses

No association between PPI use and the risk of CV death, MI or stroke for:

- **Any individual types of PPI (including exclusion of patients on pantoprazole)**
- **Use of either PPI or H2 receptor antagonist**
- **Landmark analyses**

Efficacy of Prasugrel in Setting of PPI

PPI use at randomization (n= 4529)



Limitations

- **Use of a PPI was not randomized, thus there is the potential for residual confounding**
- **PPIs could be started or stopped during course of follow-up**
- **Limited power within individual subgroups to detect an association**

Conclusion

- In TRITON-TIMI 38, PPI use was not associated with an increased risk of CV events for patients on clopidogrel or prasugrel
- Only a randomized trial of PPI use can definitively establish the safety of PPIs in combination with thienopyridines

