Proton Pump Inhibitors increase cardiovascular risk in pt taking Clopidogrel???

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Introduction

- While antiplatelet therapy has clear efficacy in the reduction of cardiovascular events, it also has the well-known side effect of gastrointestinal (GI) bleeding.

- In a case-control study of 1443 subjects with serious UGIB compared with 57,720 age and sex matched controls, the use of both aspirin and clopidogrel was associated with about **7-fold** higher risk of UGIB (OR: 7.4; 95% CI 3.5–15) compared to the use of acetylsalicylic acid (ASA) alone

Helles et al.. Population based BMJ-2006:333;726 case control study

Immediate question?

- So should these patients be put on PPIs?

PPIs and the treatment and prevention of bleeding upper gastrointestinal ulcers

- PPIs are effective in both the treatment and prevention of upper gastrointestinal ulcers

- In recent systematic reviews of randomized control trial data, PPI treatment initiated after endoscopic diagnosis of peptic ulcer bleeding **significantly reduced re-bleeding** (OR: 0.49; 95% CI 0.37–0.65)

Leontiadis GI, Sreedharan A, Dorward S, et al. Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. Health Technol Assess. 2007; 11: iii-iv, 1-164.

NSAID and PPI- Evidence

- The risk of non-steroidal anti-inflammatory drug (NSAID)-induced endoscopic gastric and duodenal ulcers **was also reduced by PPI** (relative risk [RR]: 0.37; 95% CI 0.27–0.51 for gastric ulcers)

Rostom A, Wells G, Tugwell P, et al. The prevention of chronic NSAID induced upper gastrointestinal toxicity: a Cochrane collaboration metaanalysis of randomized controlled trials. J Rheumatol. 2000; 27: 2203- 2214.

Clopidogrel and PPI

- A case-control study of 2777 patients with UGIB and 5532 controls demonstrated that use of PPIs is associated **with decreased risk of bleeding OR: 0.19 (05% CI 0.07–0.49) in clopidogrel users**
- Recent studies indicate from 1 in 3

  patients discharged on antiplatelet therapy following acute coronary syndrome (ACS) are prescribed a PPI

Lanas A, Garcia-Rodriguez LA, Arroyo MT, et al. Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants. Am J Gastroenterol. 2007; 102: 507-515.

Whats the problem with the story?

- Despite the potential benefits of the combination of clopidogrel and a PPI to prevent UGIB, several papers have raised concerns about a potential pharmacological interaction between PPIs and clopidogrel

. Specifically, PPIs may attenuate clopidogrel's antiplatelet response which may then attenuate its cardioprotective effects.

PPIs and clopidogrel – how do they work?

- Cytochrome P450(CYP2C19 isoenzyme), in the liver, mediates clopidogrel's transformation to its active metabolite
- ADP activation results in dephosphorylation of intraplatelet vasodilator-stimulated phosphoprotein**(VASP)**
- Clopidogrel users should have **lower measures of VASP** compared to patients not taking clopidogrel.

PPI metabolism

- PPIs are also metabolized by the cytochrome P450 system with the main isoenzymes

  involved being CYP2C19.
- Therefore**, in theory**, the use of PPIs in combination with clopidogrel could decrease

  the conversion of clopidogrel to its active metabolite through competitive inhibition of CYP2C19 and thereby decrease clopidogrel's therapeutic effect.

Theory escapes few things

- PPIs and their active metabolites both have short half-lives (<1 hour).

- **Clopidogrel resistance:** polymorphisms causing loss of function of CYP2C19 retain more platelet aggregation compared with those without these polymorphisms

- PPI are usually taken in morning or at night while clopidogrel used in the lunch time and both agents have very short half life.

- So chances of interaction through metabolism is just a laboratory theory rather than clinical importance.

Is it safe to use a proton pump inhibitor with clopidogrel?

- Mechanistic studies suggest that PPIs may diminish clopidogrel's effect.
- Observational study, cohort (mostly retrospective), American and Canadian data base and many others in Europe showed theories and theories of VASP reduction and so PPI should be under gueillatin
- **The impact of this attenuation on clinical outcomes was not clear in any of the study**

Any hard core evidence- RCT or Meta-analysis

The COGENT Trial :

- To determine whether PPI versus placebo reduced important GI events in patients on dual antiplatelet therapy
- To determine if there was any cardiovascular interaction between clopidogrel and PPI

Methods

- Multicenter, international, randomized, double-blind, double-dummy, placebo-controlled, parallel group, phase 3 efficacy and safety study of CGT-2168, a fixed-dose combination of clopidogrel (75 mg) and omeprazole (20 mg), compared with clopidogrel.
- All patients were to receive enteric coated aspirin at a dose of 75 to 325 mg

Deepak L. Bhatt, M.D. et al. N Engl J Med 2010;363:1909-17.

Methods

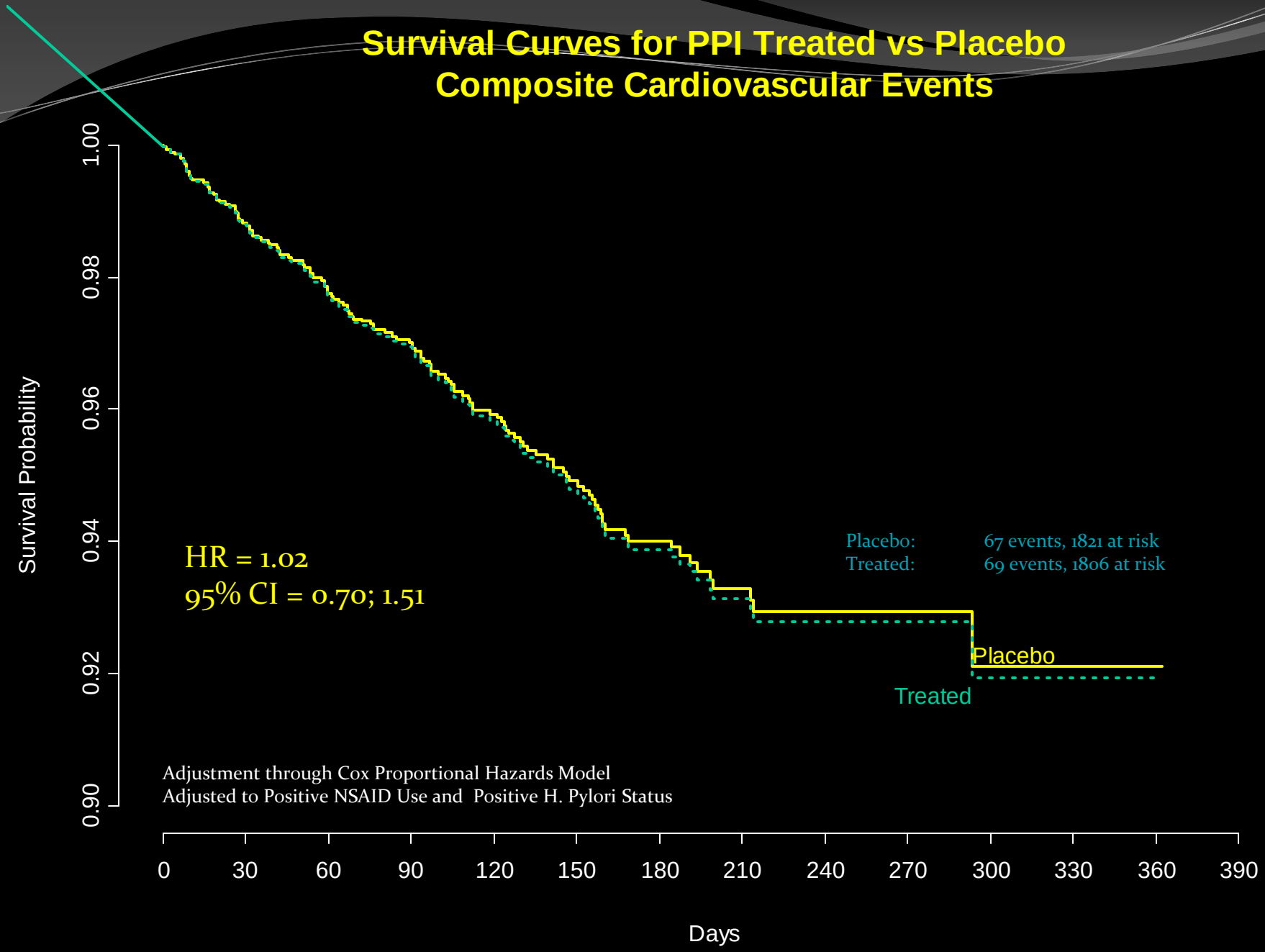
- The GI endpoint was upper GI bleeding, bleeding of presumed occult GI origin with decrease in hemoglobin of ≥ 2 g/dL or decrease in hematocrit ≥ 10%, symptomatic gastroduodenal ulcer confirmed by endoscopy or radiography, pain of presumed GI origin with underlying multiple erosive disease confirmed by endoscopy, obstruction, or perforation.

- The cardiovascular endpoint was the composite of cardiovascular death, non-fatal MI, CABG or PCI, or ischemic stroke.

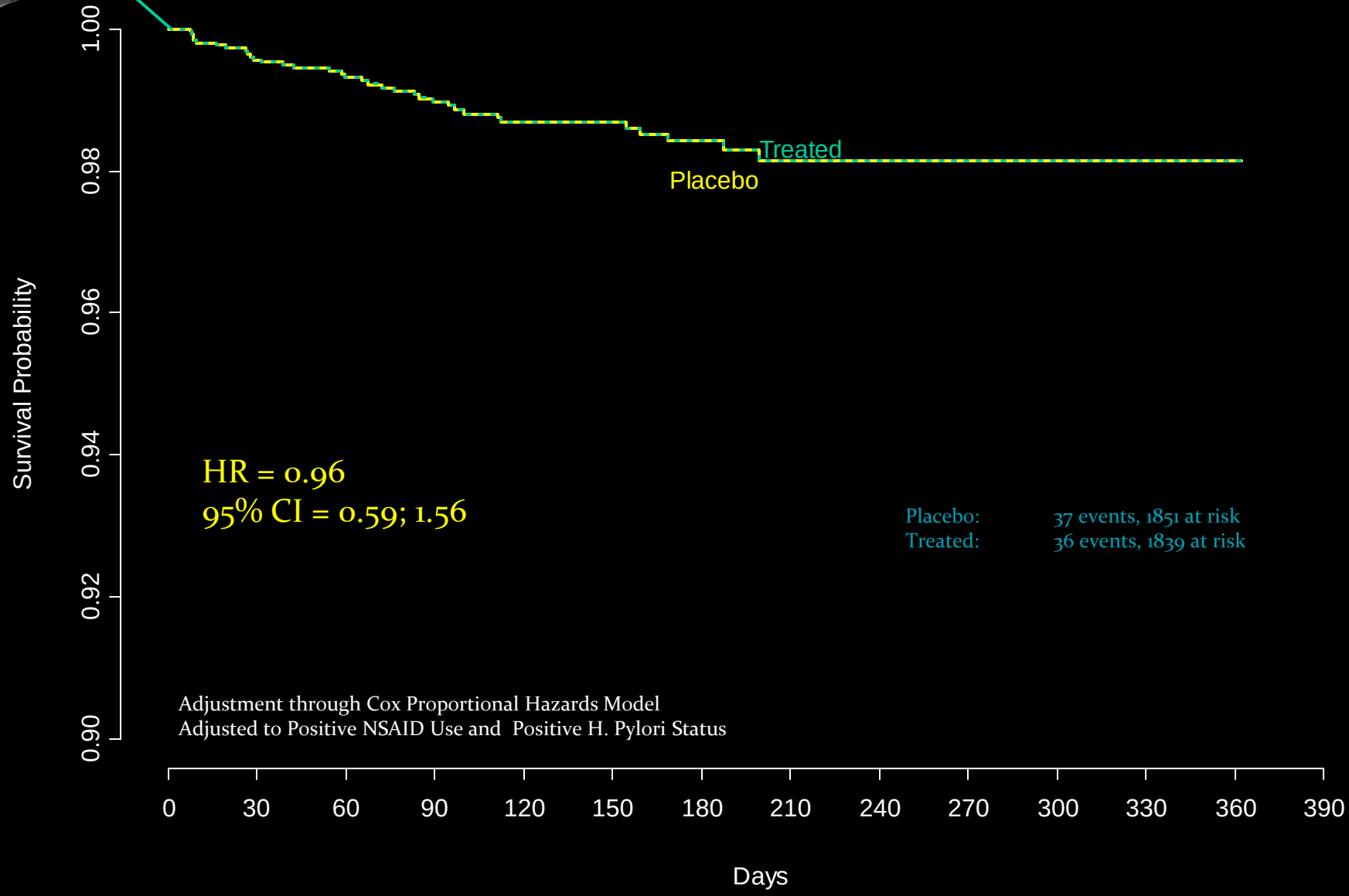
Results

- 3627 patients (above the initial target of 3200)
- 393 sites
- Median follow-up 133 days (maximum 362 days)
- 136 adjudicated cardiovascular events (*preliminary*)
- 105 adjudicated GI events (*preliminary*)
  - 143 had been planned

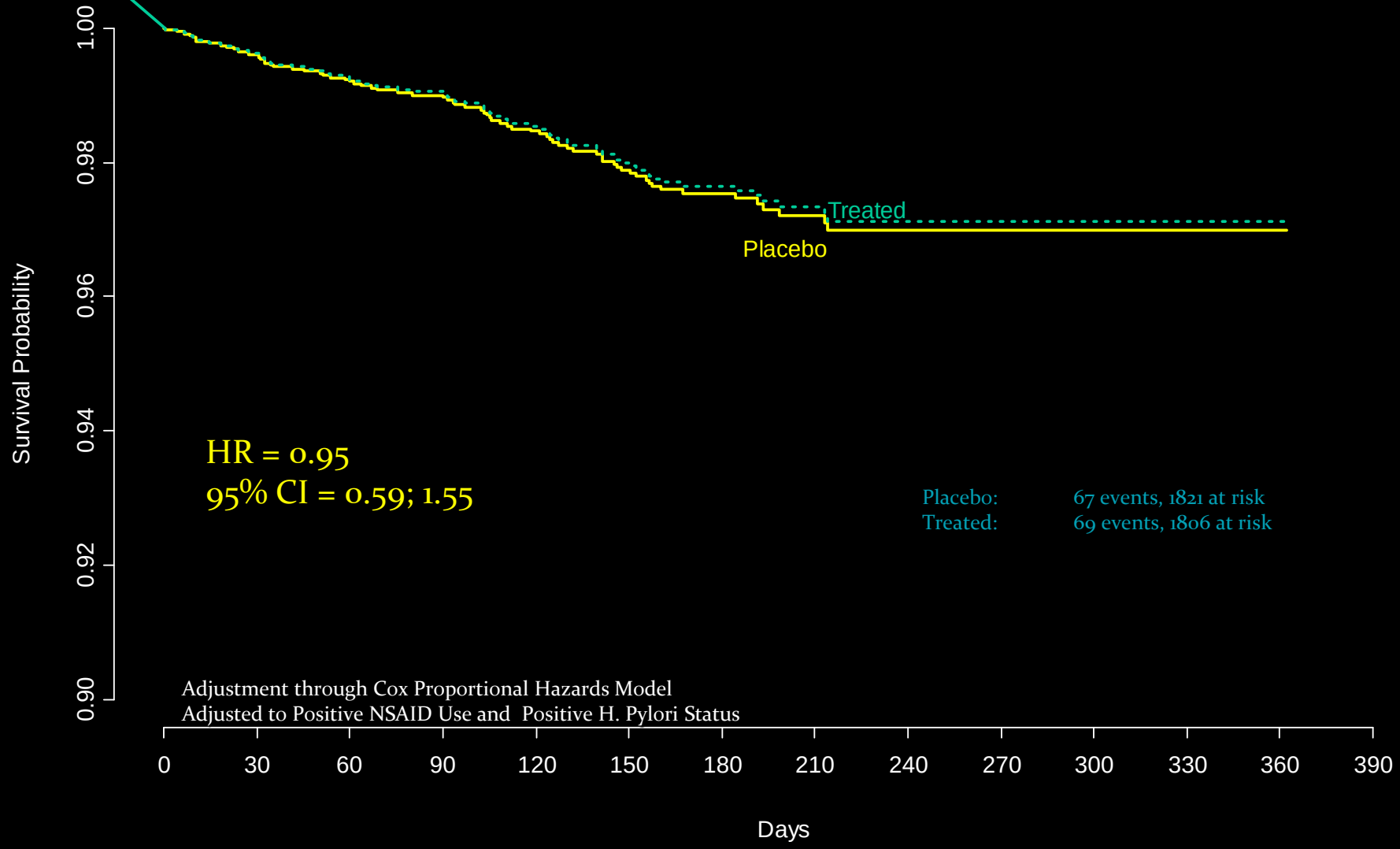
Survival Curves for PPI Treated vs Placebo
Composite Cardiovascular Events



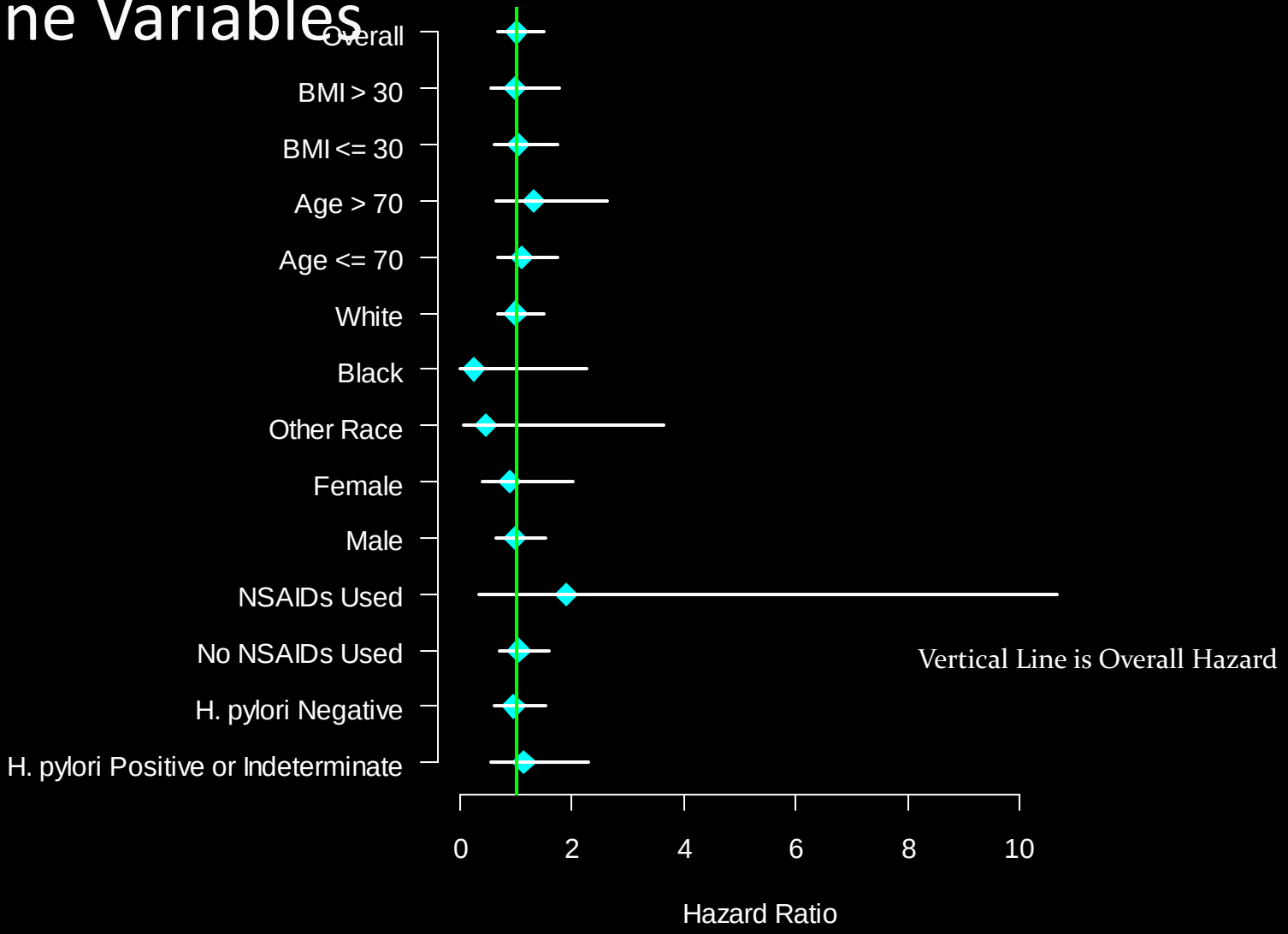
Survival Curves for PPI Treated vs Placebo
MI Events



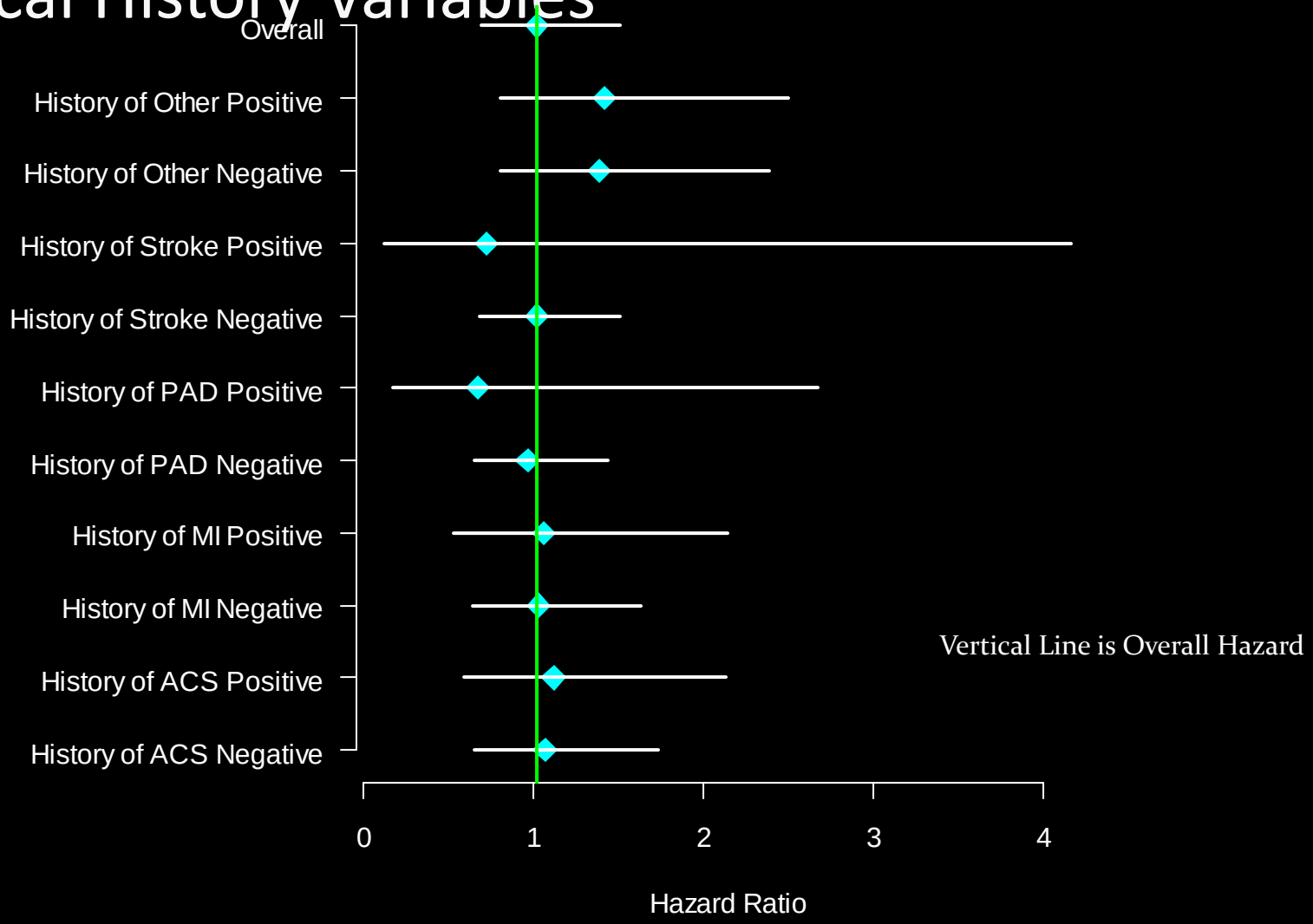
Survival Curves for PPI Treated vs Placebo Revascularization



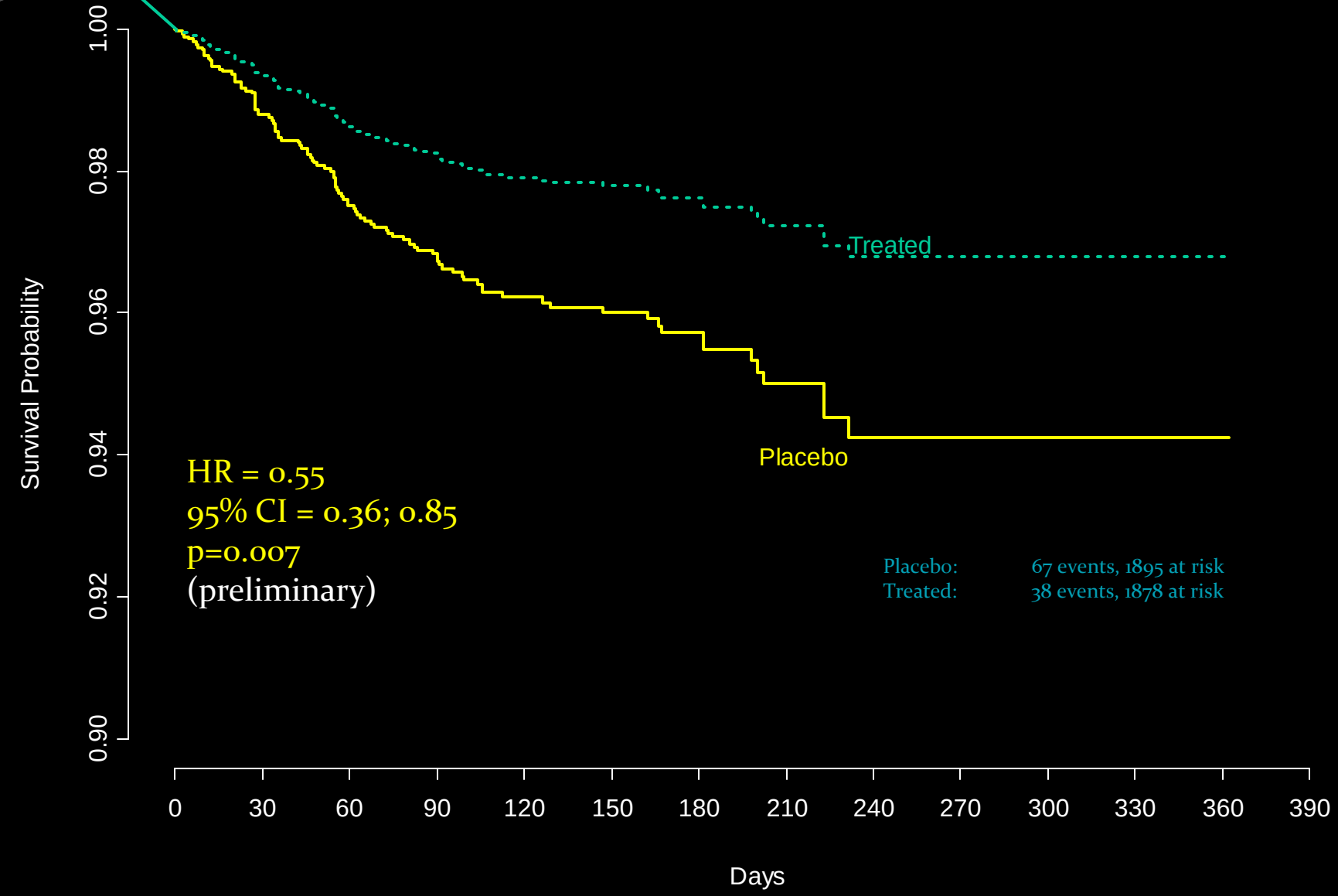
Composite Cardiovascular Event Hazard Ratios for Baseline Variables



Composite Cardiovascular Event Hazard Ratios for Medical History Variables



Survival Curves for PPI Treated vs Placebo
Composite GI Events



Conclusions

- COGENT is the first, randomized assessment of clopidogrel and PPIs on clinical events
- The data provide strong reassurance that there is no clinically relevant adverse cardiovascular interaction between clopidogrel and PPIs
- The results call into question the exact relationship between *ex vivo* platelet assays and clinical outcomes, especially with respect to assessing drug interactions
  - **Platelet assays and observational data are not a substitute for RCT data**

Meta-analysis

- 23 studies (1 RCT) and 22 observational
- Huge heterogeneity(70%)
- Conflicting and inconsistent data
- 93,278 patients
- Many confounding elements
- Many limitation in even review process

Meta-analysis: the effects of proton pump inhibitors on cardiovascular events and mortality in patients receiving Clopidogrel, C. S. KWOK & Y. K. LOKE, Aliment Pharmacol Ther , 2010, 31, 810–823

Results and conclusion of Meta-analysis

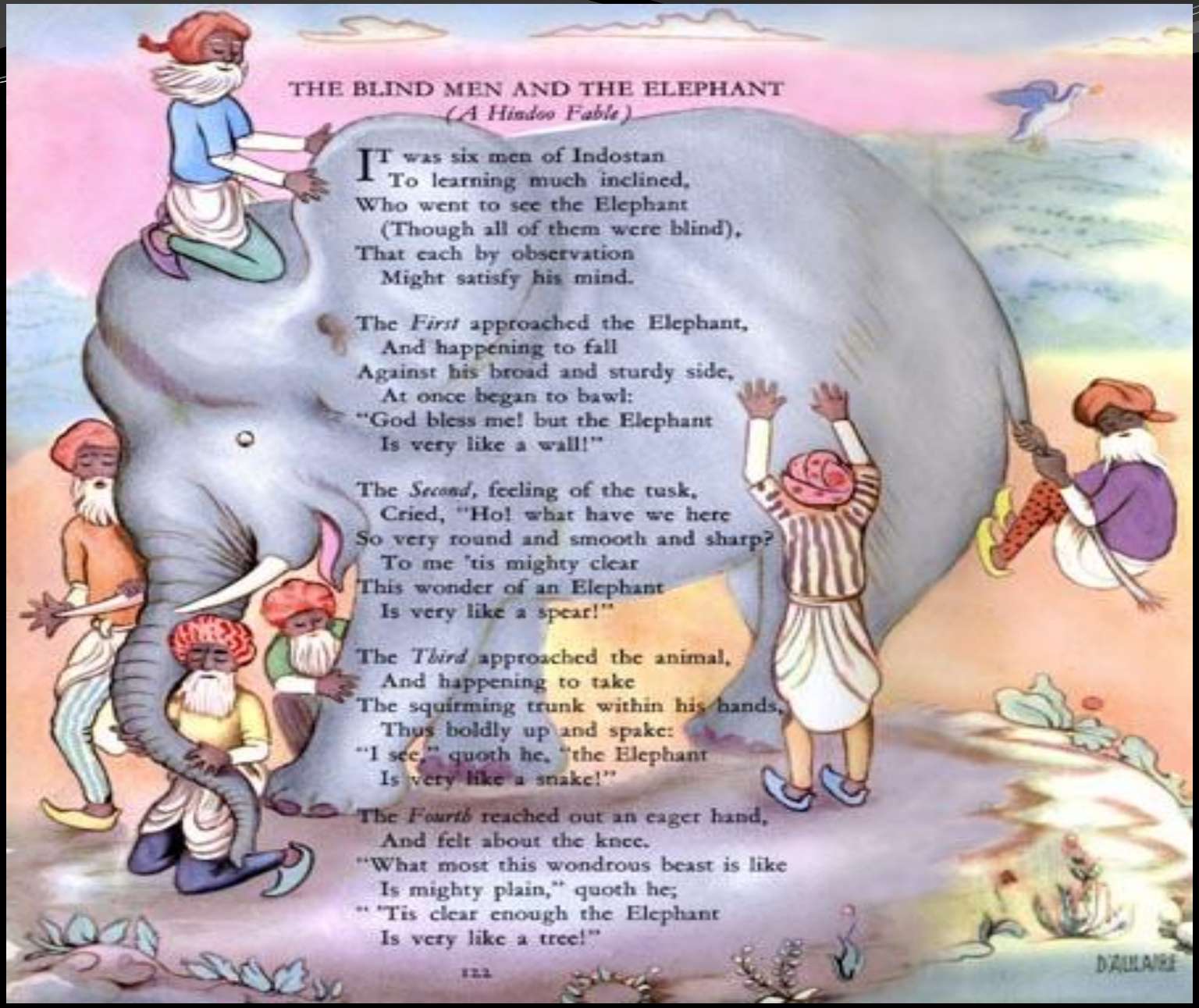
- **19 studies showed huge heterogeniety (75%) for CV events or MI**
- **Propensity matched or RCT participants showed no associated cardiovascular risk with PPI**
- **13 studies showed no significant association between PPI use and overall mortality**

Should patients taking aspirin and clopidogrel be prescribed PPIs

- The 2008 ACCF/ACG/AHA Expert consensus document recommends use of PPIs for the prevention of gastrointestinal bleeding in patients on dual antiplatelet therapy, referring to evidence that combining a PPI with clopidogrel appears to result in less GI bleeding and
- **Evidence of a clinical effect of a drug interaction is lacking**

Recommendation

- **Clinicians should carefully weigh up the real danger of an increase gastrointestinal bleeding before thinking of avoiding the use of PPI or omeprazole in patient taking clopidogrel**


THE BLIND MEN AND THE ELEPHANT
(A Hindoo Fable)
IT was six men of Indostan
To learning much inclined,
Who went to see the Elephant
(Though all of them were blind),
That each by observation
Might satisfy his mind.
The First approached the Elephant,
And happening to fall
Against his broad and sturdy side,
At once began to bawl:
"God bless me! but the Elephant
Is very like a wall!"
The Second, feeling of the tusk,
Cried, "Ho! what have we here
So very round and smooth and sharp?
To me 'tis mighty clear
This wonder of an Elephant
Is very like a spear!"
The Third approached the animal,
And happening to take
The squirming trunk within his hands,
Thus boldly up and spake:
"I see," quoth he, "the Elephant
Is very like a snake!"
The Fourth reached out an eager hand,
And felt about the knee.
"What most this wondrous beast is like
Is mighty plain," quoth he;
"'Tis clear enough the Elephant
Is very like a tree!"
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