The COGENT Trial

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on Behalf of the COGENT Investigators

Aims

- 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.
- Patients were stratified based on two baseline factors: *H. pylori* serology (positive or negative) and concomitant use of any NSAID.
- All patients were to receive enteric coated aspirin at a dose of 75 to 325 mg.

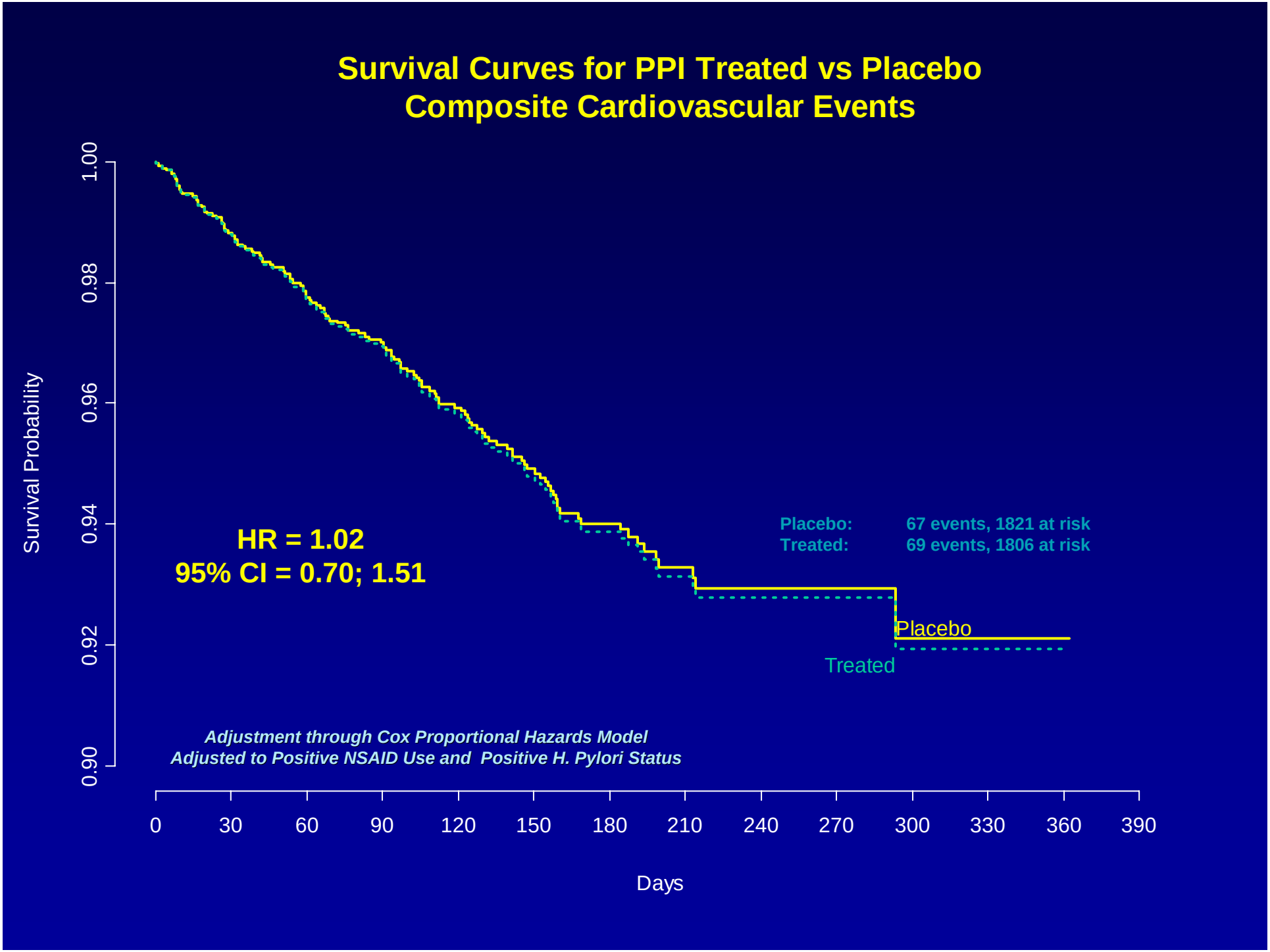
Methods

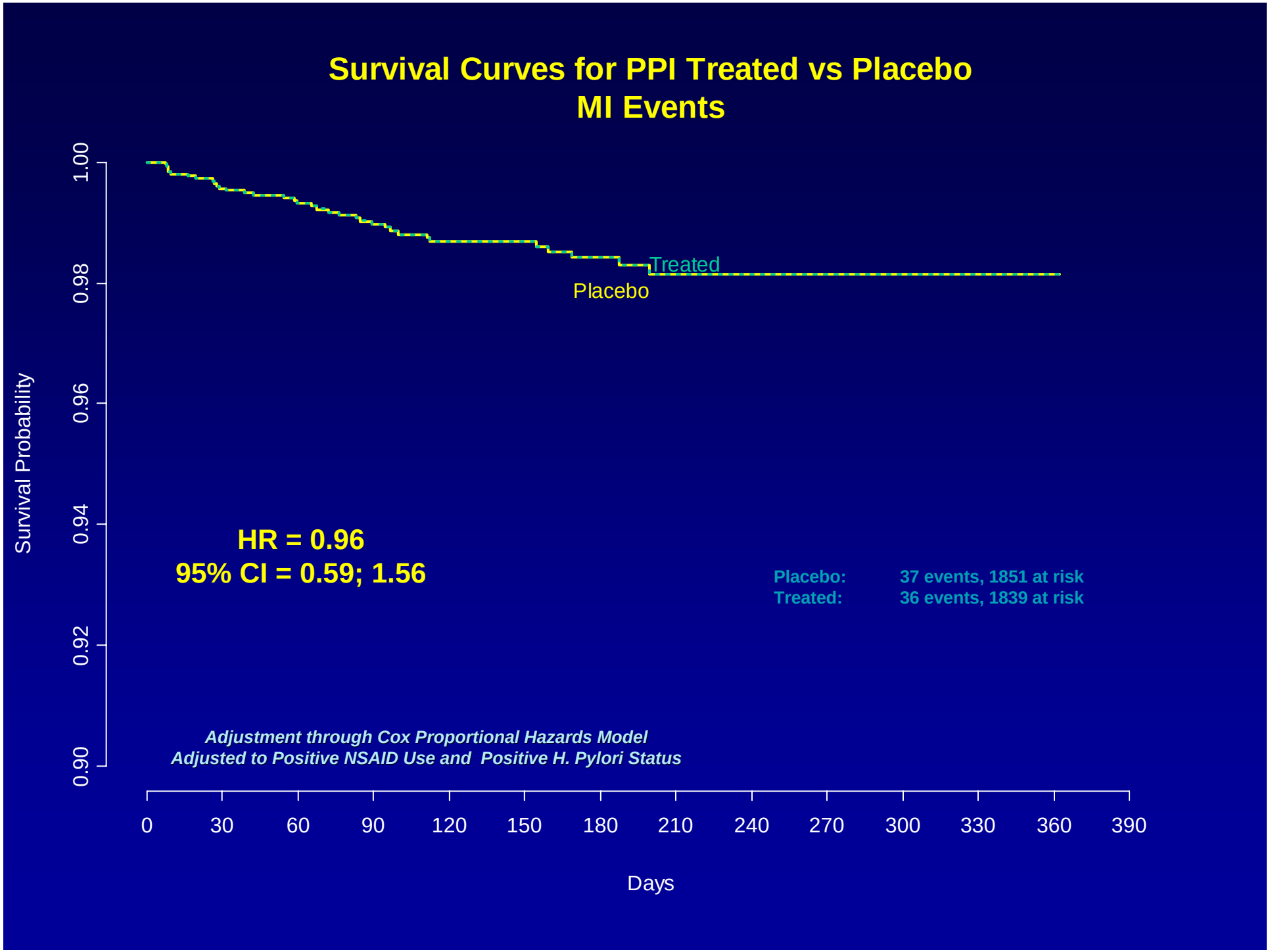
- The GI endpoint was upper GI bleeding, bleeding of presumed occult GI origin with decrease in hemoglobin of ≥ 2 g/dL or decrease in hematocrit ≥ 10%, symptomatic gastroduodenal ulcer confirmed by endoscopy or radiography, pain of presumed GI origin with underlying multiple erosive disease confirmed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

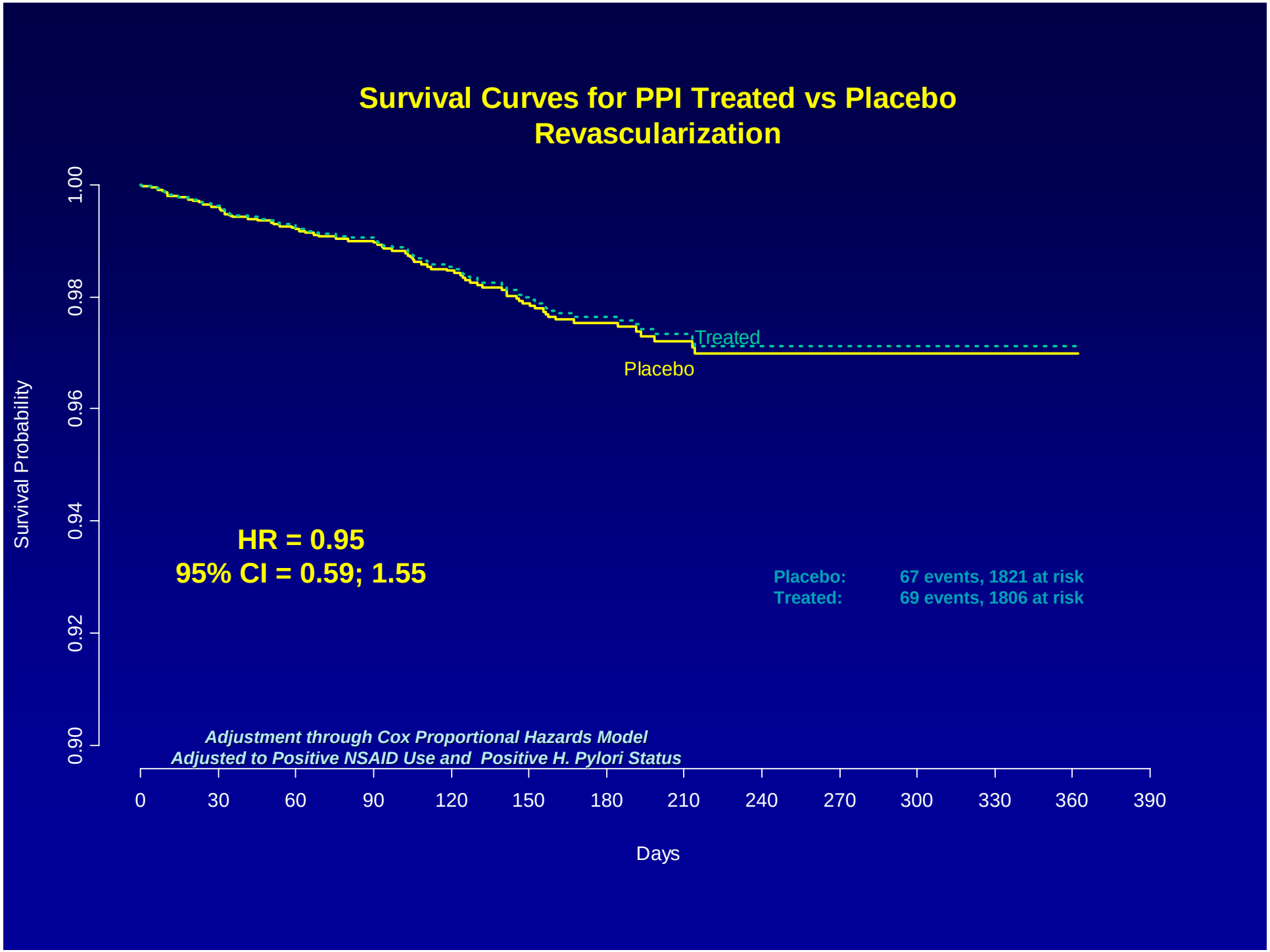
- The cardiovascular endpoint was the composite of cardiovascular death, non-fatal MI, CABG or PCI, or ischemic stroke.

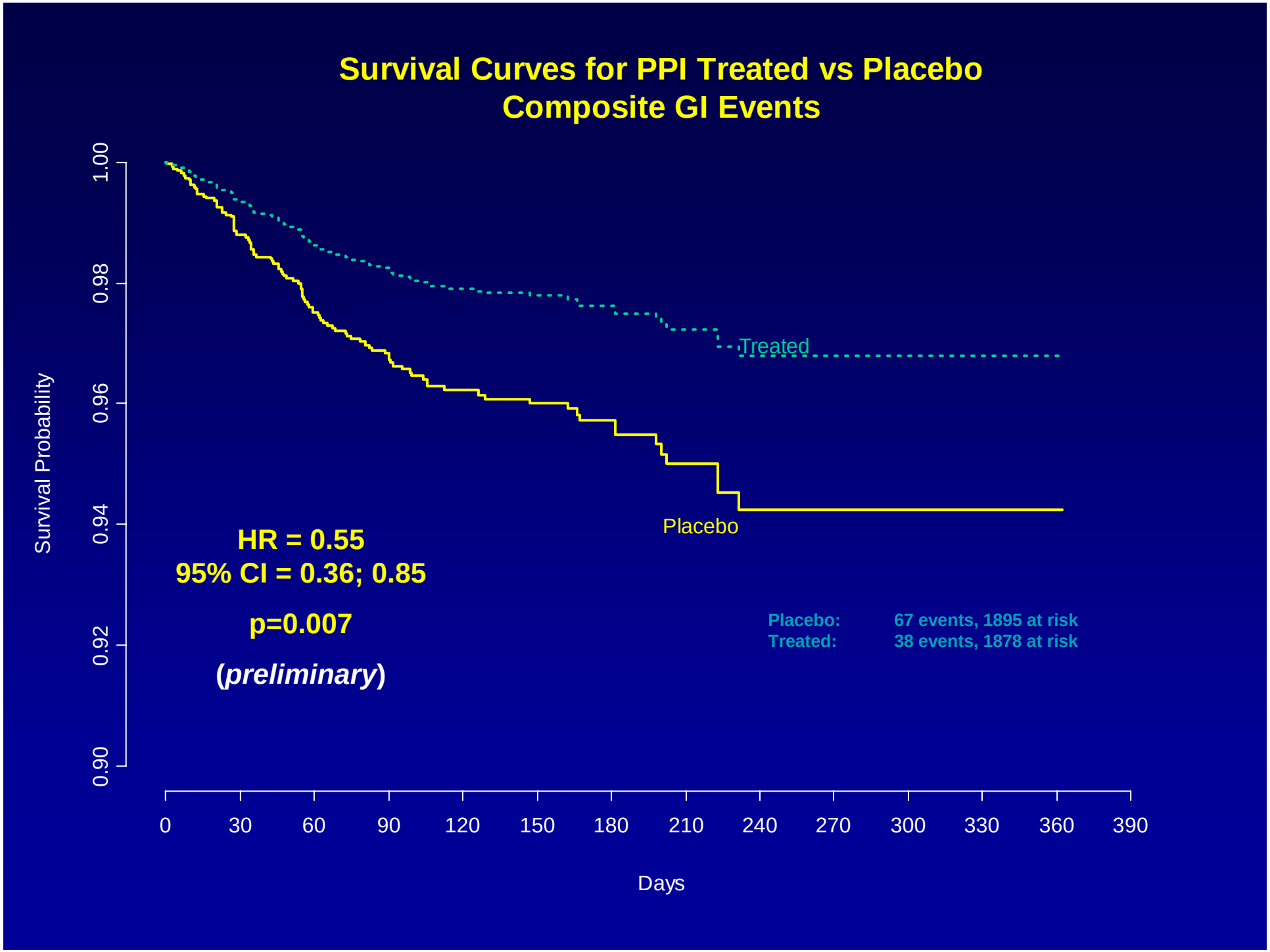
- Adjudication of events was performed by an independent committee of cardiologists and gastroenterologists.

- The initial planned sample size was 3200 patients, an accrual period of 1 year, and maximum follow up of 2 years. As a low rate of gastrointestinal events was observed as the trial was ongoing, the sample size target was increased to 4200 and then ~5000 (143 GI events). The study ended when the sponsor declared bankruptcy.


Survival Curves for PPI Treated vs Placebo
Composite Cardiovascular Events
Survival Probability
1.00
0.98
0.96
0.94
0.92
0.90
HR = 1.02
95% CI = 0.70; 1.51
Placebo: 67 events, 1821 at risk
Treated: 69 events, 1806 at risk
Placebo
Treated
Adjustment through Cox Proportional Hazards Model
Adjusted to Positive NSAID Use and Positive H. Pylori Status
0
30
60
90
120
150
180
210
240
270
300
330
360
390
Days


Survival Curves for PPI Treated vs Placebo
MI Events
Survival Probability
1.00
0.98
0.96
0.94
0.92
0.90
Treated
Placebo
HR = 0.96
95% CI = 0.59; 1.56
Placebo: 37 events, 1851 at risk
Treated: 36 events, 1839 at risk
Adjustment through Cox Proportional Hazards Model
Adjusted to Positive NSAID Use and Positive H. Pylori Status
0
30
60
90
120
150
180
210
240
270
300
330
360
390
Days


Survival Curves for PPI Treated vs Placebo
Revascularization
Survival Probability
1.00
0.98
0.96
0.94
0.92
0.90
Treated
Placebo
HR = 0.95
95% CI = 0.59; 1.55
Placebo: 67 events, 1821 at risk
Treated: 69 events, 1806 at risk
Adjustment through Cox Proportional Hazards Model
Adjusted to Positive NSAID Use and Positive H. Pylori Status
0
30
60
90
120
150
180
210
240
270
300
330
360
390
Days


Survival Curves for PPI Treated vs Placebo
Composite GI Events
Survival Probability
1.00
0.98
0.96
0.94
0.92
0.90
Treated
Placebo
HR = 0.55
95% CI = 0.36; 0.85
p=0.007
(preliminary)
Placebo: 67 events, 1895 at risk
Treated: 38 events, 1878 at risk
0
30
60
90
120
150
180
210
240
270
300
330
360
390
Days

Limitations

- Due to premature termination of trial, limited follow-up
  - However, most relevant for GI events, as most cardiac events early after ACS or PCI
  - No current PPI/clopidogrel data set has more adjudicated CV endpoints
- May not be directly applicable to PPIs other than omeprazole
  - Most commonly used PPI
  - One most indicted by *ex vivo* studies
- Special formulation of clopidogrel/PPI with different release kinetics, so may not be the same as taking clopidogrel and omeprazole off the shelf
  - If a major concern, then take the clopidogrel in the morning and the PPI at night

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
- Further research is needed to define the optimal strategy to reduce GI events in patients on antithrombotic therapy, though prophylactic PPIs seem very promising