Proton Pump Inhibitors In Patients Treated With Aspirin And Clopidogrel

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No potential conflict of interest

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Background

- Clopidogrel is a potent antiplatelet agent (through P2Y12 adenosine diphosphate receptor inhibition)
- Treatment with clopidogrel in addition to ASA has been proven to reduce cardiovascular events after coronary stenting and following the whole spectrum of acute coronary syndrome (ACS):
  - **CREDO** investigators. *Early and Sustained Dual Oral Antiplatelet Therapy Following Percutaneous Coronary Intervention. A Randomized Controlled Trial.* JAMA. 2002;288:2411-2420.
  - **CURE** investigators. *Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. NEJM* 2001; 345: 494–502.
  - **COMMIT** collaborative group. *Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial.* Lancet 2005; 366: 1607–21.

Background

- Clopidogrel is a prodrug converted to its metabolite by cytochrome P-450 isoenzymes (mainly CYP219)
- Numerous drugs are known to inhibit P-450 isoenzymes, such as proton pump inhibitors (PPIs)
- Mechanistic studies first suggested that PPIs might reduce the antiplatelet effect of clopidogrel, rising the question about the clinical significance of PPI – clopidogrel interaction

Background

- Recent published studies showed that the addition of a PPI to clopidogrel in ACS patients significantly increased the risk of recurrent cardiovascular events:
  - *Juurlink DN, Gomes T, Ko DT et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ 2009; 180(7). DOI: 10.1503/cmaj.082001*
  - *Ho MP, Maddox TM, Wang L et al. Risk of Adverse Outcomes Associated With Concomitant Use of Clopidogrel and Proton Pump Inhibitors Following Acute Coronary Syndrome. JAMA 2009; 301(9): 937-944.*
- Conflicting reports and expert opinions exist about the PPI-clopidogrel interaction and mainly its clinical significance

Aims

- Evaluate the prescription of a PPI in addition to ASA and clopidogrel in ACS patients
- Compare the clinical characteristics and therapeutic strategies of patients medicated or not with a PPI
- Determine if the addition of a PPI to ASA and clopidogrel was associated with a worst prognosis

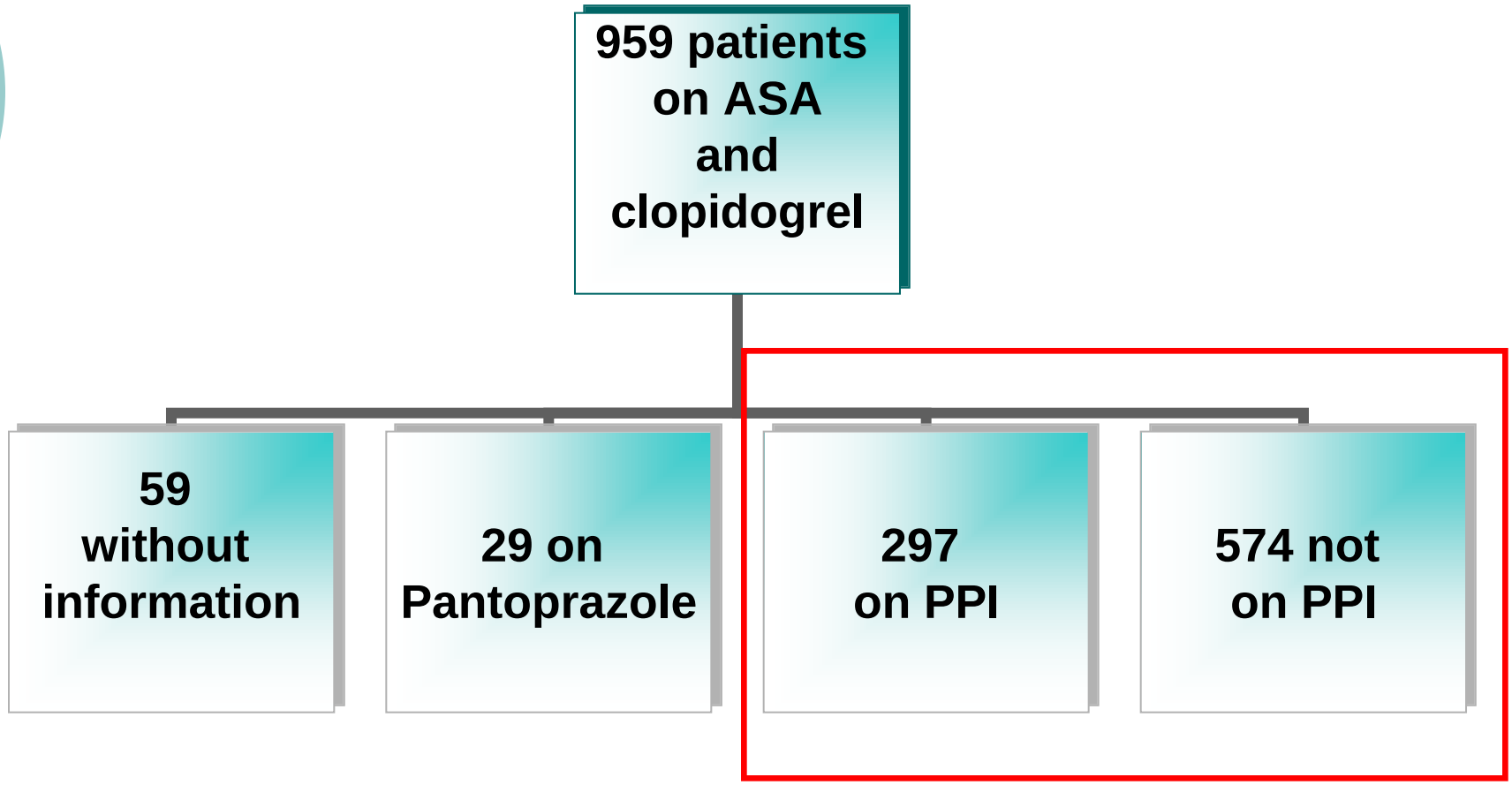
Methods

- Retrospective study - a total of 959 patients admitted with ACS and discharged with ASA and clopidogrel, from January 2004 to April 2008, were reviewed – we chose to analyze patients on ASA and clopidogrel as they represented the majority of ACS patients as well as the more relevant clinical scenario
- Patients were classified in two groups according to the association or not of a PPI to ASA and clopidogrel

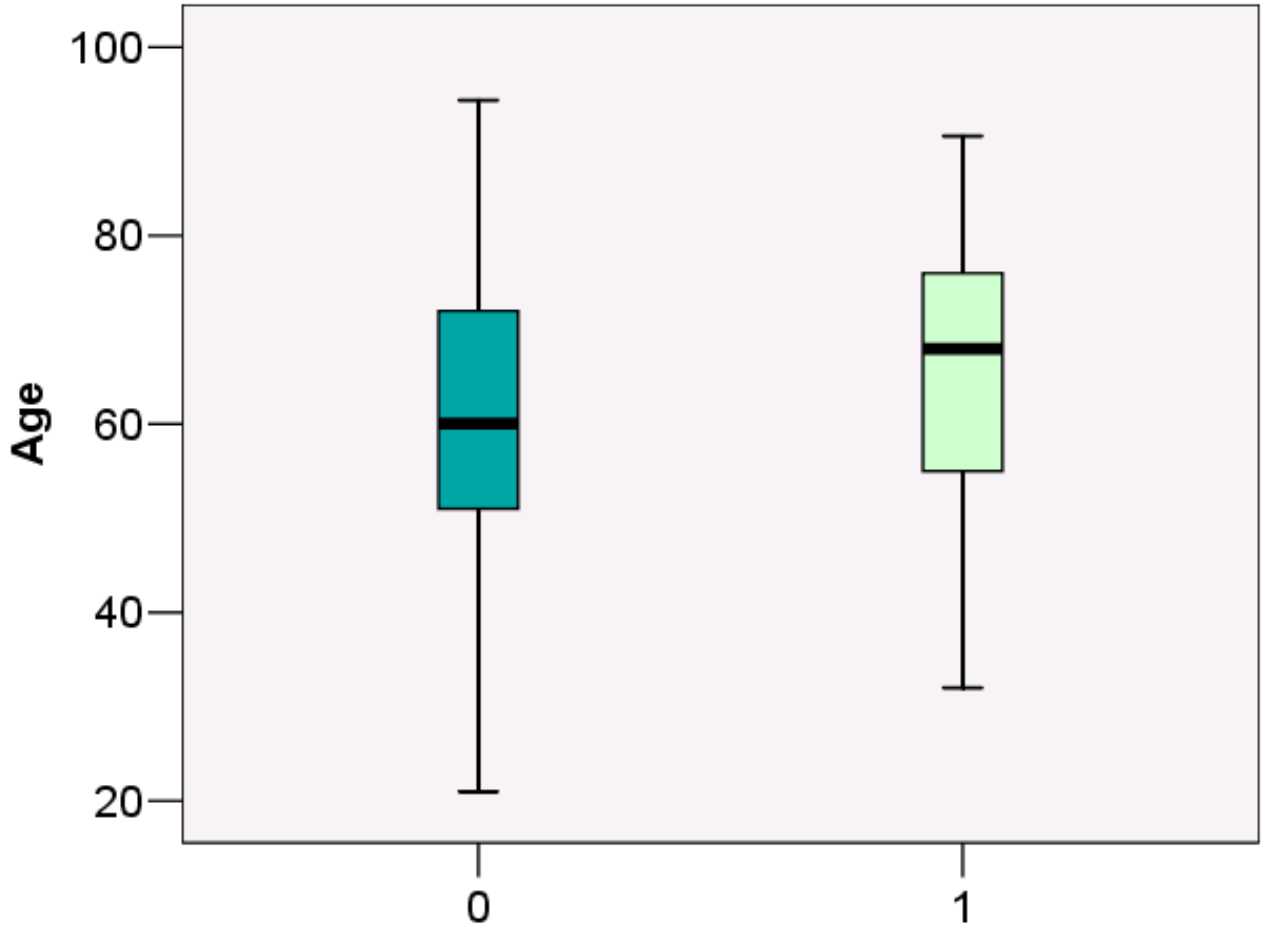
Methods

- All PPIs were considered except pantoprazole
  - Although pantoprazole can be metabolized by CYP219 isoenzyme, it preferentially uses other routes
- The prescription and clinical records were used to define exposure to PPI during dual antiplatelet therapy

Results

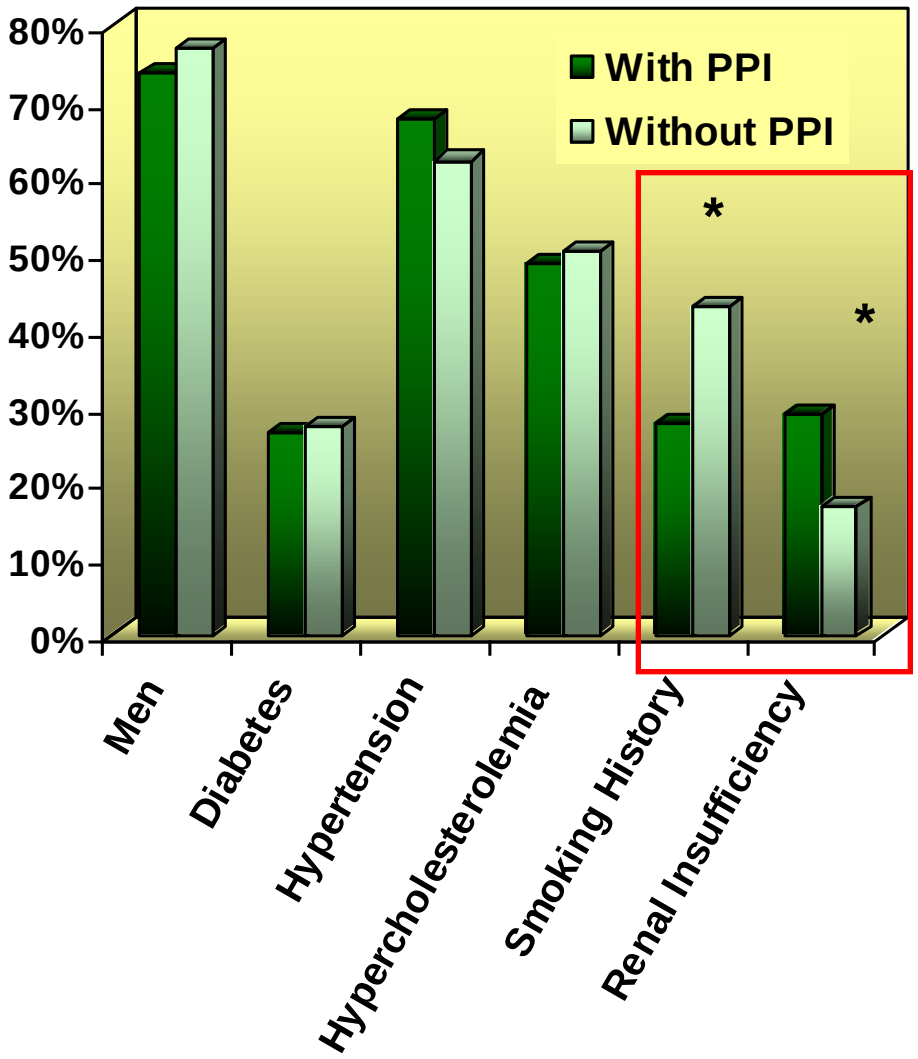

959 patients on ASA and clopidogrel
59 without information
29 on Pantoprazole
297 on PPI
574 not on PPI

Results
Baseline characteristics



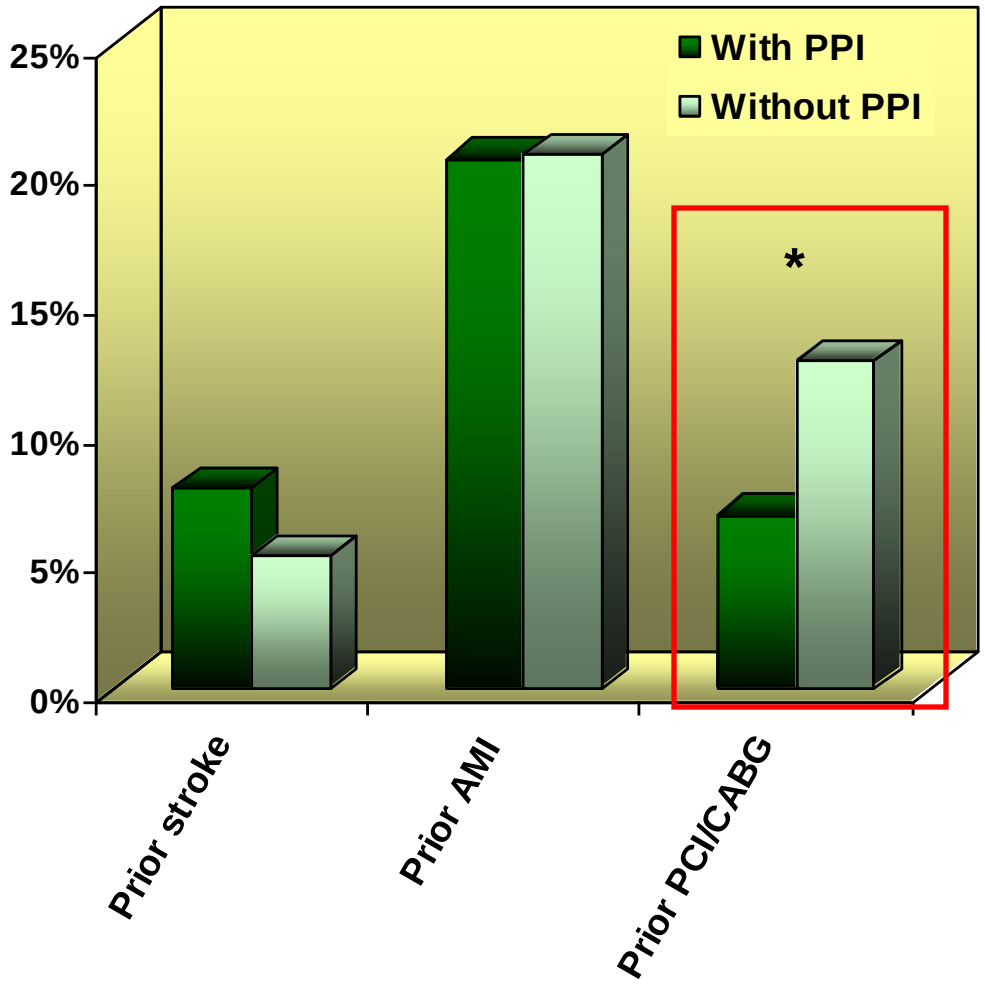
Mean ± SD	**61.1 ± 13.2 years**	**PPI**	**65.7 ± 13.2 years**	***p* < 0.001**

Results
Baseline characteristics



* $p < 0.05$

Results
Baseline characteristics

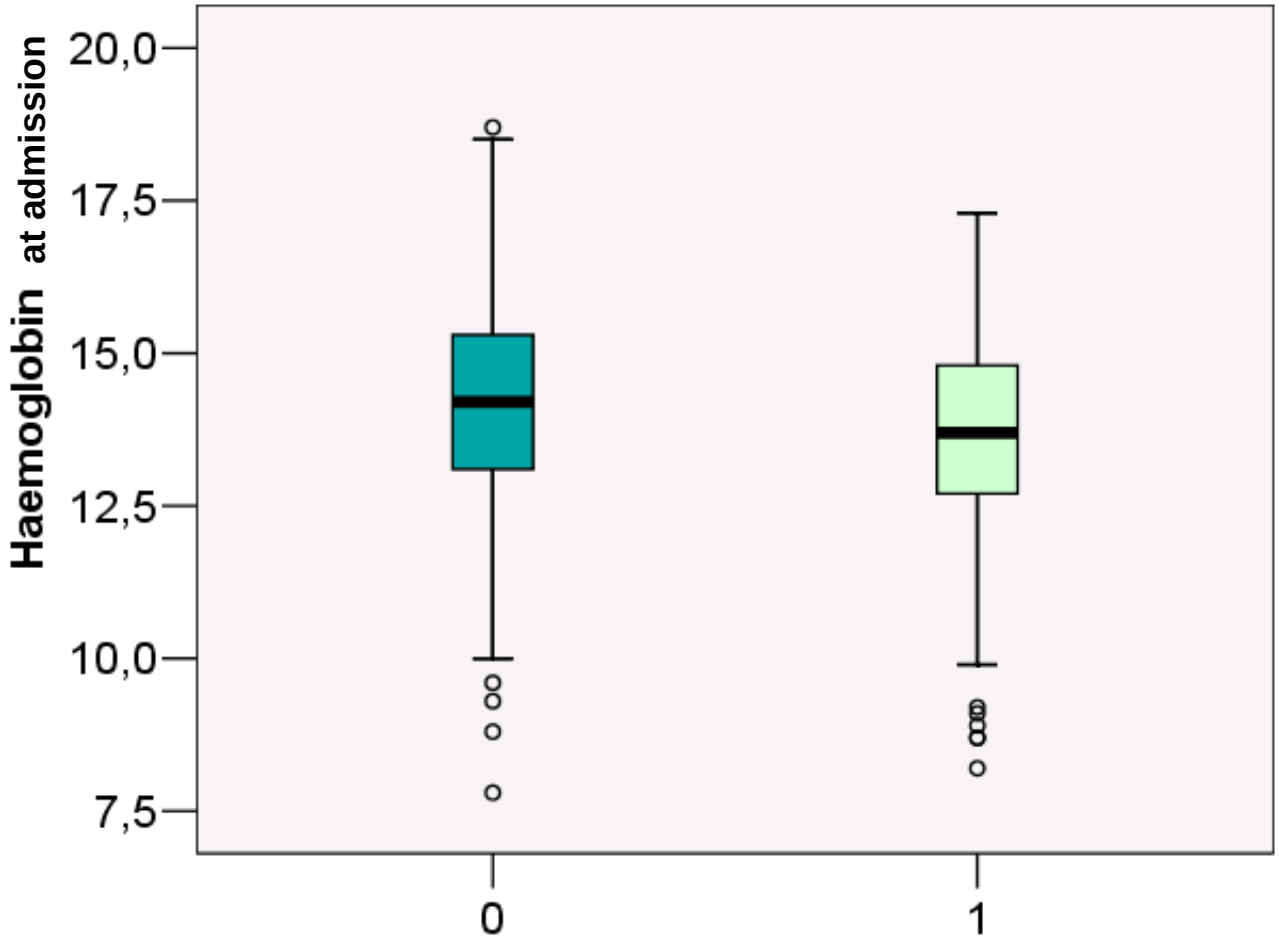


* $p < 0.05$

Results
At presentation

	With PPI n=297	Without PPI n=574	*p*
STEMI	36.7%	36.2%	NS
Killip Class > 1	24.1%	15.3%	0.002
Mean SBP (mmHg ±SD)	138 ± 27	140 ± 27	NS
Mean HR (bpm ±SD)	76 ± 18	75 ± 19	NS

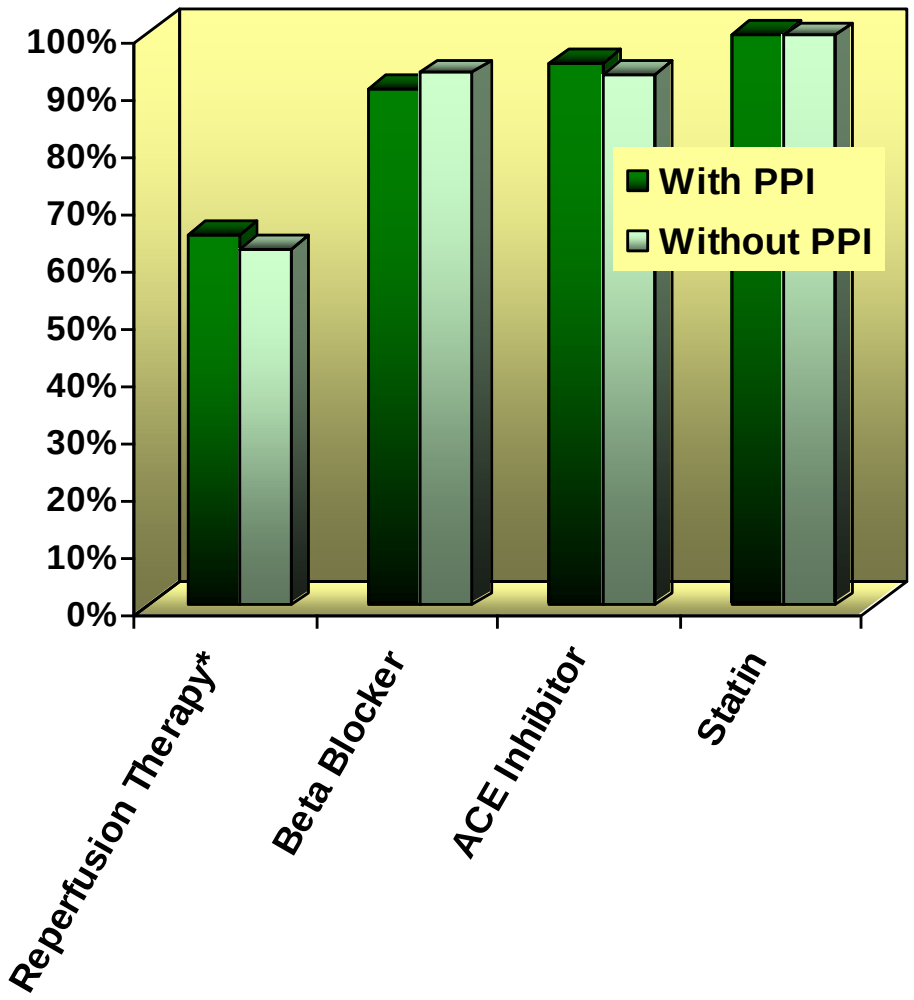
Results
Baseline characteristics



Mean ± SD	14.1 ± 1.8 g/dl		13.7 ± 2.1 g/dl

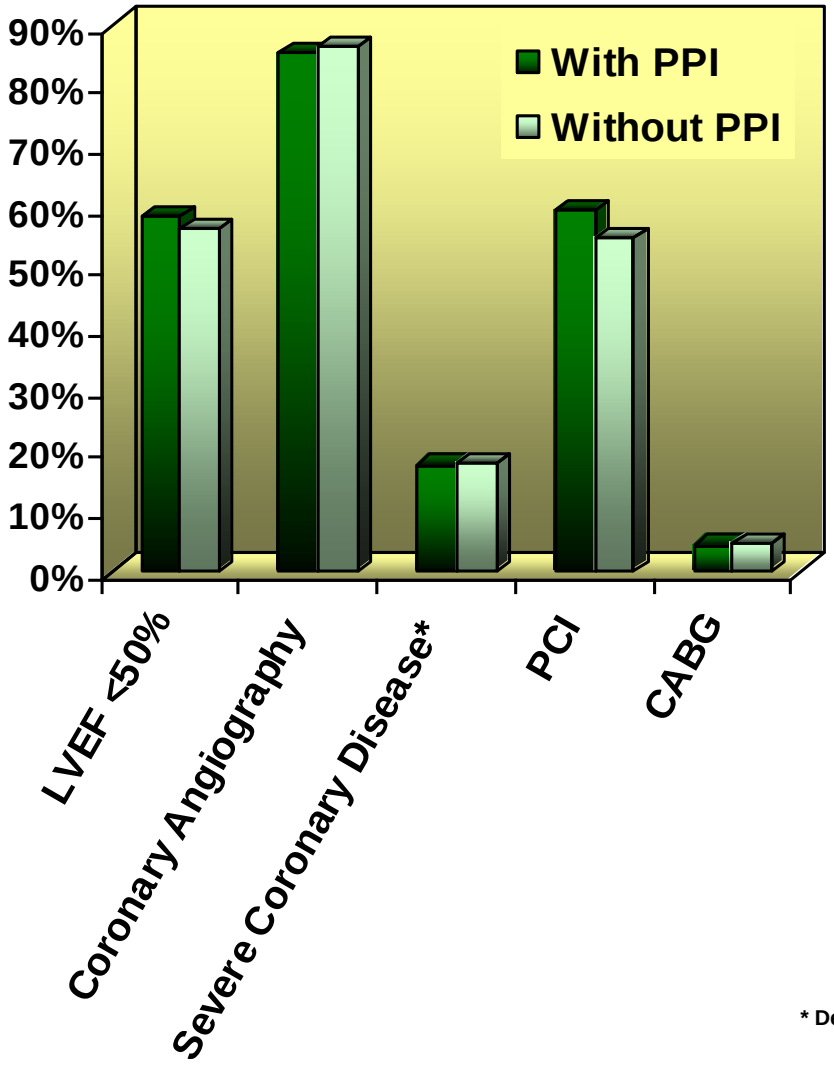
p= 0.001

Results
In-hospital medical treatment



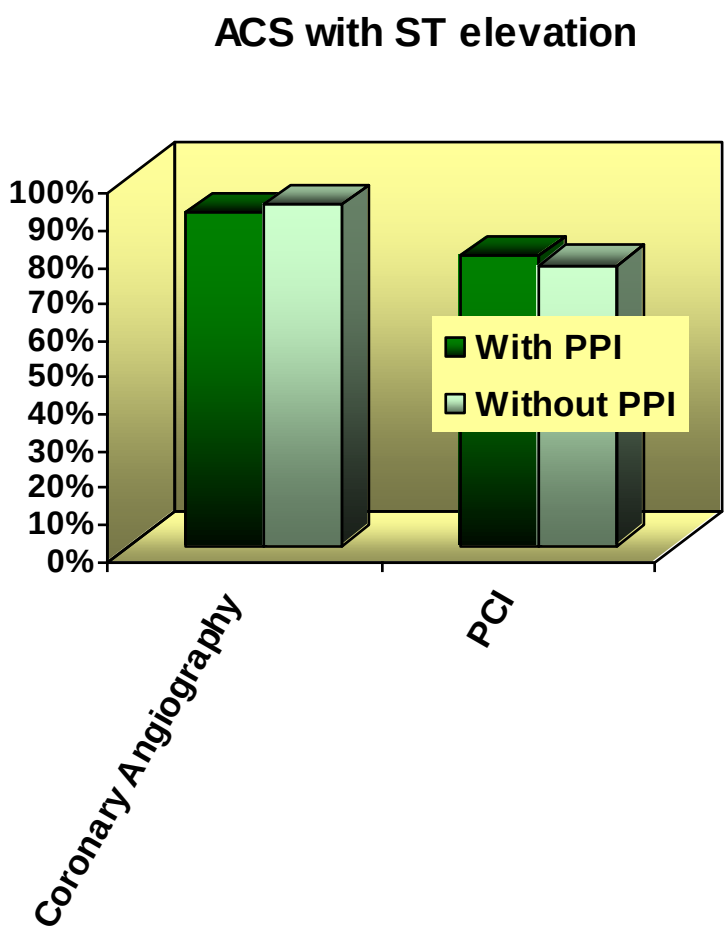
*Considering only STEMI patients

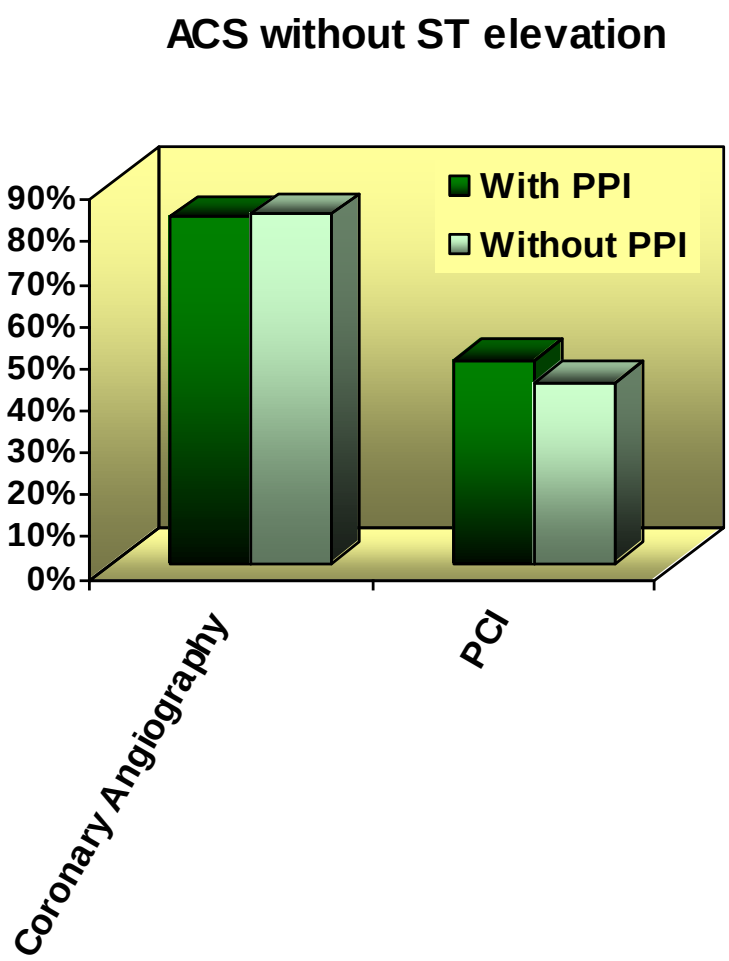
Results



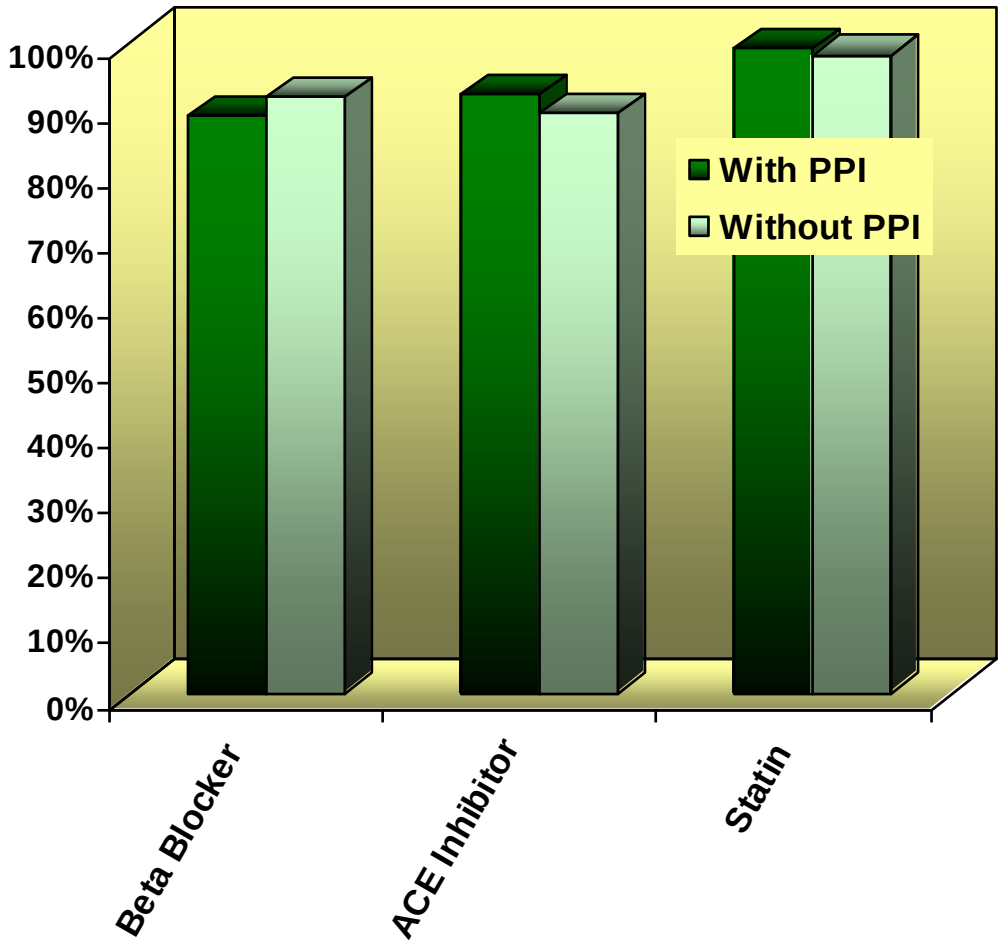
* Defined as three-vessel or left main disease

Results

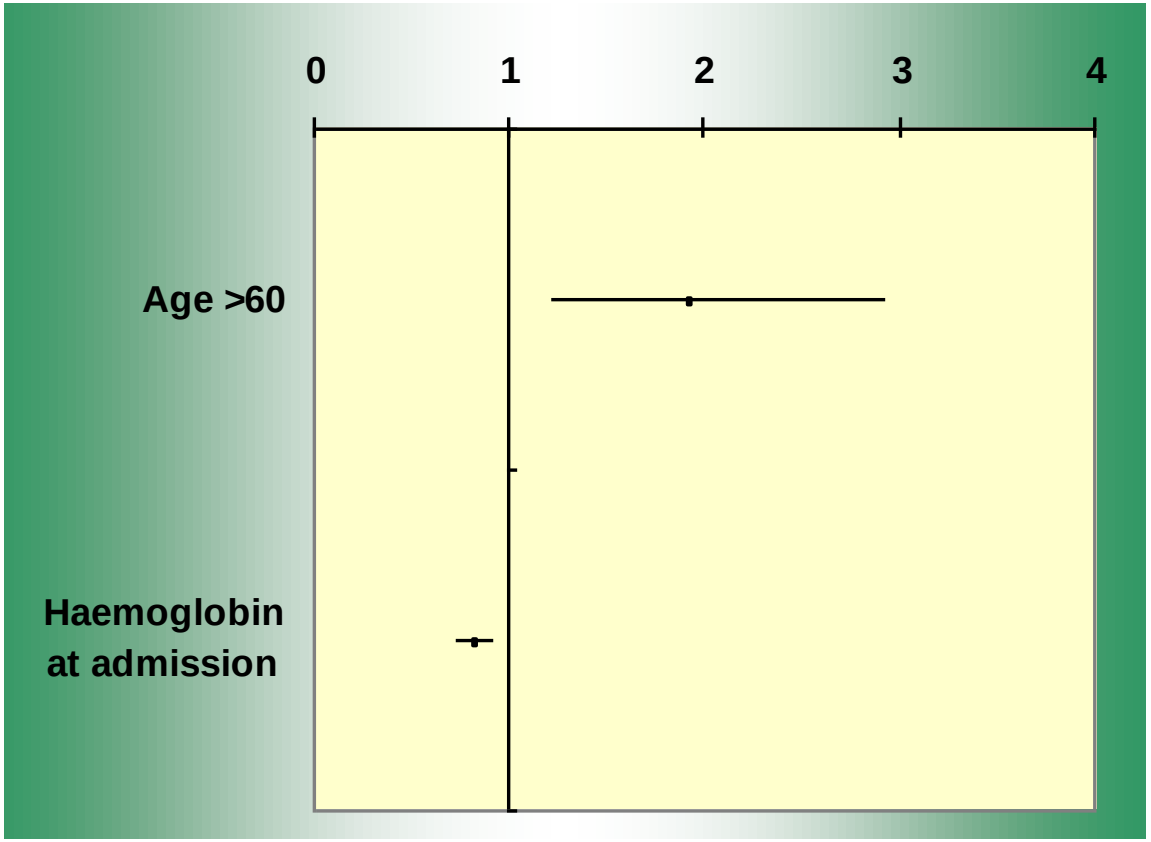

ACS with ST elevation
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
With PPI
Without PPI
Coronary Angiography
PCI


ACS without ST elevation
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
With PPI
Without PPI
Coronary Angiography
PCI

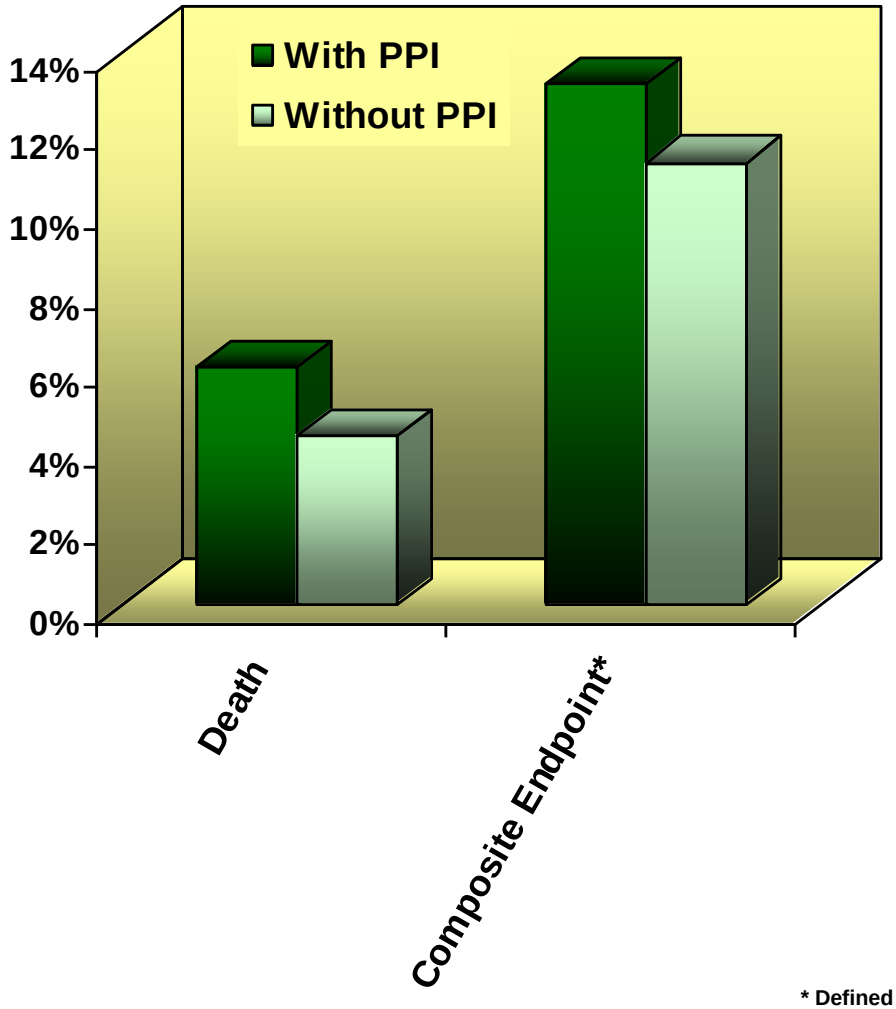
Results
Medical treatment at discharge



Independent predictors of PPI prescription

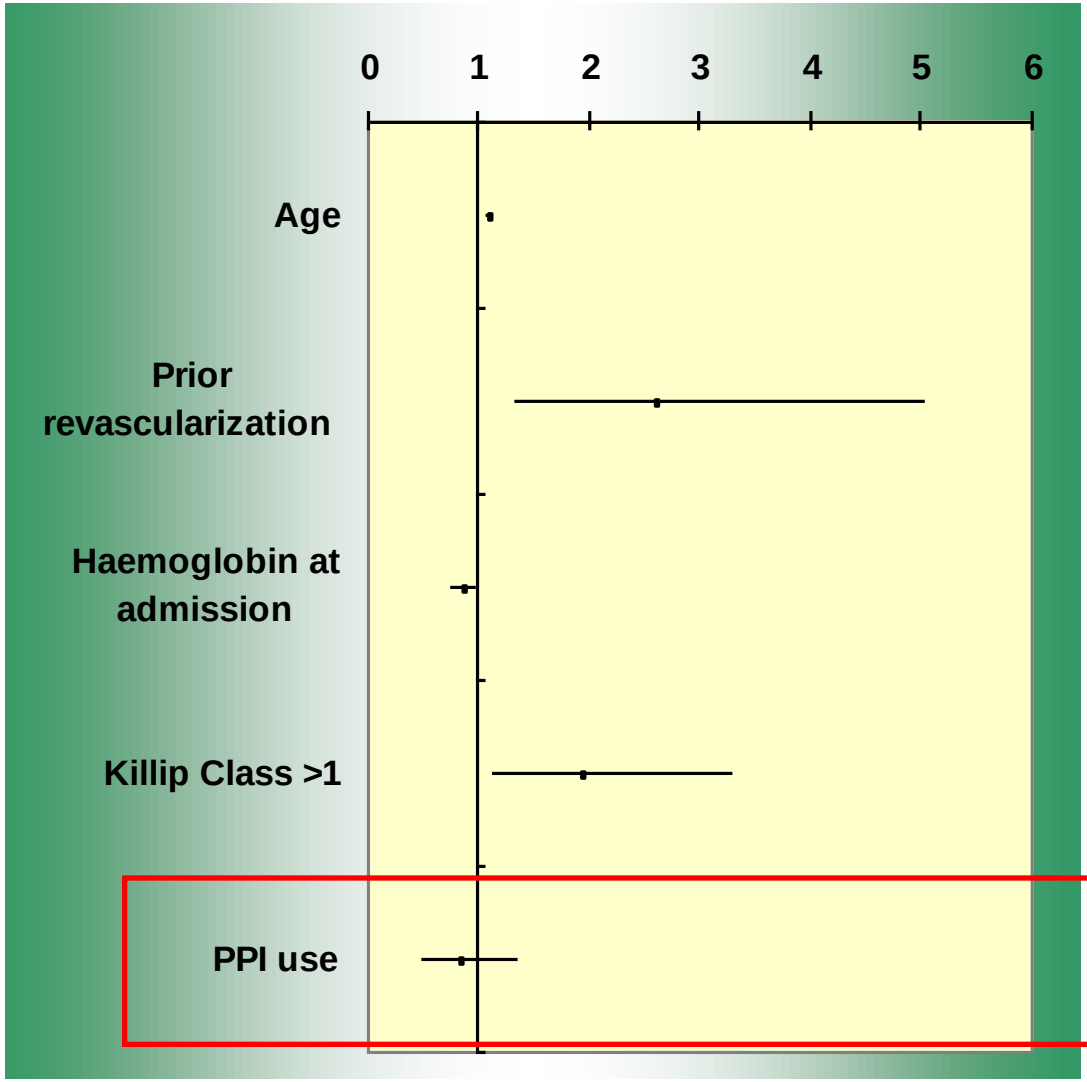


Results
Six-month follow-up

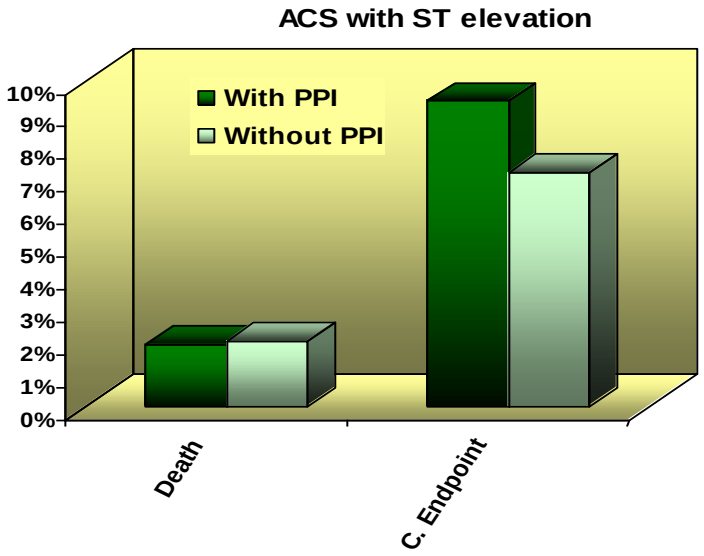


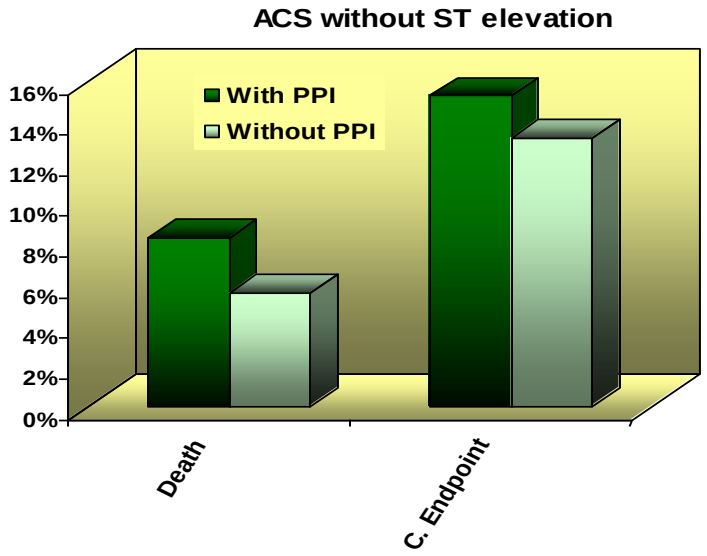
* Defined as all-cause mortality or rehospitalization for ACS

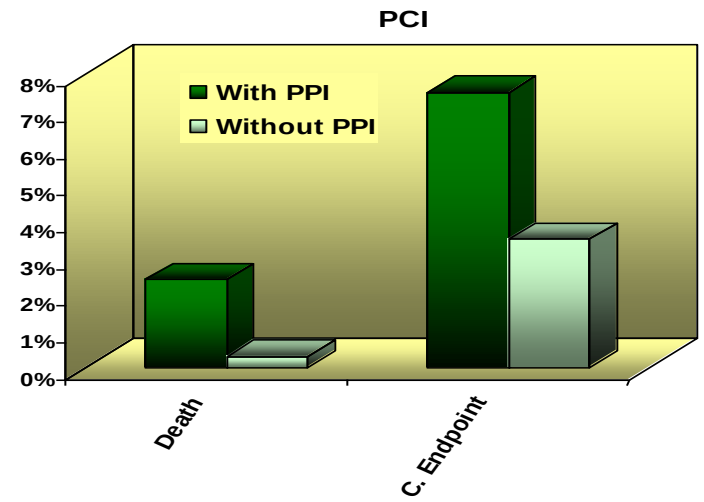
Results
Multivariate analysis
Composite Endpoint

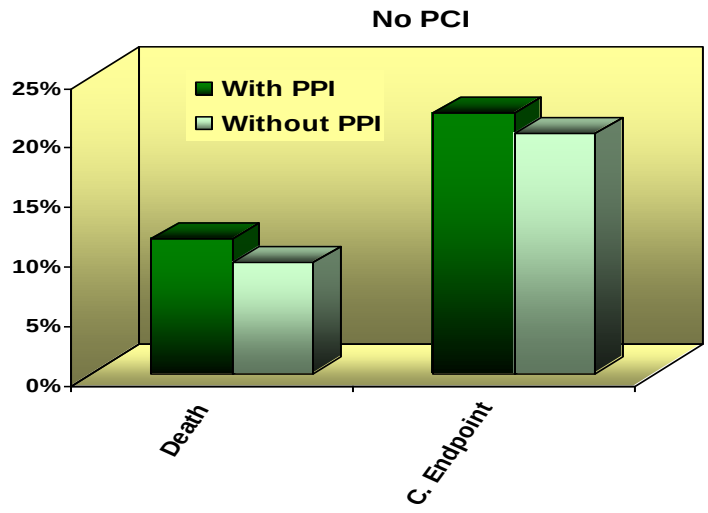


Results
Six-month follow-up
Stratification



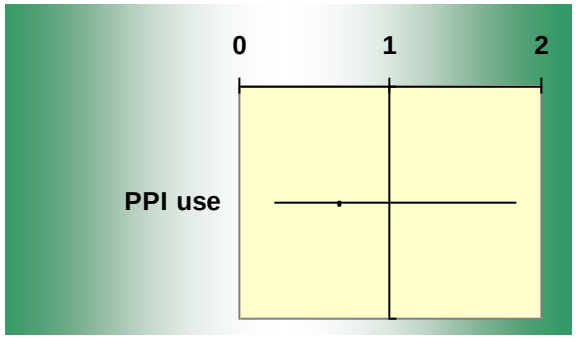




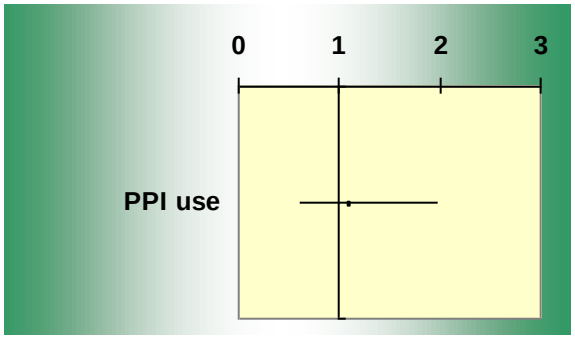


Results
Multivariate analysis
Composite Endpoint/Stratification

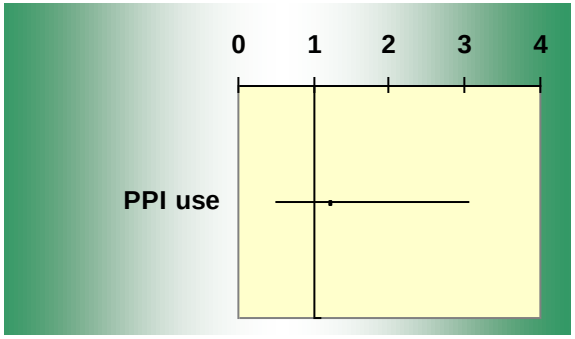
ACS with ST elevation



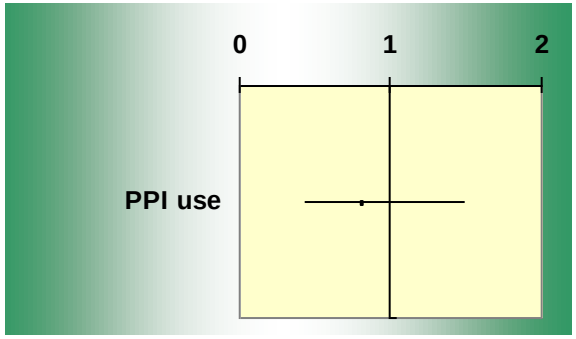
ACS without ST elevation



PCI



No PCI



Conclusions

- Patients on PPI were older, more often had renal insufficiency and less often had smoking history and history of previous revascularization; they more often presented with Killip class >1 and lower haemoglobin at admission
- There were no differences regarding in-hospital or discharge medical treatment, invasive procedure and coronary revascularization
- Independent and positive predictors of PPI prescription were older age and lower haemoglobin at admission

Conclusions

- PPI prescription in addition to aspirin and clopidogrel was not associated with a worst prognosis in patients with ACS, even after adjustment for potential confounding factors

Limitations

- This was an observational and nonrandomized study, and as such, both identified and unidentified confounders may have influenced the results
- Prescription and clinical records might be incomplete
- Therapeutic compliance was not assessed (namely ASA, clopidogrel and PPI)
- The number of patients assessed may have been insufficient

Limitations

- Randomized trials would be the preferential way to obtain definite conclusions about the clinical relevance of PPI-clopidogrel interaction

Thank you!