Aim: The goal of the present study was to evaluate the prognostic value of ongoing treatment with dual antiplatelet therapy (DAPT) *at admission*, and of smoking status on the outcome of patients with STEMI undergoing primary PCI (PPCI).

Methods and Results: Seven-hundred and thirteen consecutive STEMI patients undergoing PPCI, admitted between March 2009 and December 2011, were retrospectively enrolled. Rescue PCI was the only exclusion criterion. Primary end point was the combination of death for all causes, re-IMA, stroke, and target lesion revascularization. Patients already on DAPT at admission (26.4%) had a significant increase in the event rate at univariate analysis (HR 2.34, $p<0.001$), while current smokers (56.5%) had a lower event rate, as compared to non-smokers (HR 0.67, $p<0.05$). In smoking patients already on DAPT at admission, a higher event rate was observed than in non-smoking patients on DAPT. Cox regression analysis confirmed that smoking status (HR 0.69, $p<0.05$) and DAPT (HR 1.74, $p<0.01$) were significantly associated with a better and a worse outcome, respectively, underlying their role as independent prognostic factors.

Conclusions: For the first time, we have highlighted the indipendent prognostic value of smoking status and DAPT at admission in patients with STEMI undergoing PPCI. Patients on DAPT had a higher risk profile than patients not on DAPT; however, it cannot be excluded that at least some of the patients on DAPT were poor responders to clopidogrel. The paradoxical protective effect of smoking (smoking paradox), might be related to the known induction of CYP1A2, which would lead to an increased production of the active metabolite of clopidogrel. In light of these findings, it is reasonable to suggest that in patients already on DAPT with ASA and clopidogrel undergoing PPCI for STEMI, switching to a different $P2Y_{12}$ antagonist might be appropriate.