AIMS: Several studies have demonstrated that the mutant *2 allele of the CYP2C19 681G>A loss-of-function polymorphism is associated with diminished metabolism of clopidogrel into its active thiol metabolite and an attenuated platelet response to clopidogrel treatment. It is not known whether patients carrying the mutant CYP2C19*2 allele have a higher risk of stent thrombosis (ST) compared with homozygous CYP2C19*1 wild-type allele carriers following percutaneous coronary intervention (PCI). The aim of this study was to assess the impact of the CYP2C19 681G>A loss-of-function polymorphism on ST following PCI performed after pre-treatment with clopidogrel. METHODS AND RESULTS: The study population included 2485 consecutive patients undergoing coronary stent placement after pre-treatment with 600 mg of clopidogrel. Genotypes were determined with a TaqMan assay. The primary endpoint of the study was the incidence of definite ST within 30 days following PCI. Of the patients studied, 1805 (73%) were CYP2C19 wild-type homozygotes (*1/*1) and 680 (27%) carried at least one *2 allele (*1/*2 or *2/*2). The cumulative 30-day incidence of ST was significantly higher in CYP2C19*2 allele carriers (*1/*2 or *2/*2) vs. CYP2C19 wild-type homozygotes (*1/*1) [10 patients
(1.5%) in CYP2C19*2 allele carriers vs. 7 (0.4%) in CYP2C19 wild-type homozygotes (*1/*1), HR 3.81, 95% CI 1.45-10.02, P = 0.007; P = 0.006 after adjustment for confounding variables. The risk of ST was highest (2.1%) in patients with the CYP2C19 *2/*2 genotype (P = 0.002). CONCLUSION: CYP2C19*2 carrier status is significantly associated with an increased risk of ST following coronary stent placement.