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ABCB1 GENETIC VARIANTS, PHARMACODYNAMIC RESPONSE, AND CARDIOVASCULAR OUTCOMES FOLLOWING TREATMENT WITH CLOPIDOGREL AND PRASUGREL

ACC Poster Contributions
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Background: Clopidogrel and prasugrel are absorbed by intestinal enterocytes following oral administration and may be subject to efflux mediated by P-glycoprotein (P-gp, encoded by ABCB1, also known as MDR1). In vitro work suggests the C3435T genetic variant in ABCB1 is associated with altered disposition of several drugs.

Methods: We genotyped 293 healthy subjects in whom we measured platelet inhibition in response to clopidogrel and/or prasugrel and 2932 patients with ACS with planned PCI in TRITON-TIMI 38, a randomized trial of clopidogrel vs prasugrel for up to 15 months.

Results: Individuals homozygous for the 3435 T allele (14% of healthy study) had an absolute reduction in maximal platelet aggregation after a loading dose of clopidogrel that was 6.8 percentage points lower (ie less platelet inhibition) than that seen in CC or CT individuals (P=0.019), whereas there was no difference in response to prasugrel (1.3 percentage points higher; P=0.42). Among ACS patients treated with clopidogrel, TT homozygotes (27% of study) had a 72% increased risk of the primary efficacy endpoint of CV death, MI, or stroke (HR 1.72, P=0.002, Top Figure) compared with CC/CT patients. With prasugrel, TT homozygotes showed only a trend toward an increased risk of the primary endpoint that was not statistically significant (HR 1.25, P=0.24, Bottom Figure).

Conclusions: ABCB1 genotyping may identify individuals less likely to be protected from recurrent ischemic events in the setting of treatment with thienopyridines.