Overall, these results demonstrate that low-level anticoagulation is effective for reducing recurrent events in patients with ACS, including mortality. One of the most important findings of this study is the importance of appropriate dosing for anticoagulation in post-ACS patients. Traditional intensity anticoagulation using a different oral Xa inhibitor, apixaban, was shown to be harmful in patients with ACS [Alexander JH et al. *N Engl J Med* 2011]. The current trial shows efficacy at doses of rivaroxaban that are significantly lower than that used for atrial fibrillation (20 mg daily), with the greatest efficacy at the lowest dose of 2.5 mg twice daily. These results will need to be integrated with those of other recent trials to determine the optimal overall combination of antithrombotic therapy for patients with ACS.

Further reading: Mega JL et al. *N Engl J Med* 2011.

Escalating Clopidogrel by Involving a Genetic Strategy-TIMI 56

Written by Maria Vinall

Previous studies have shown that patients who are at risk of heart attack and are carriers of a CYP2C19 genetic variant that leads to reduced function of the cytochrome P450 oxidase enzyme have diminished platelet inhibition as a result of decreased conversion of clopidogrel to its active metabolite and a higher rate of major adverse cardiovascular events [Mega JL et al. *N Engl J Med* 2009]. Jessica L. Mega, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, reporting results of the EscaLating ClopidogrEl by InVolving A GeneTic StratEgy – Thrombolysis In Myocardial Infarction 56 (ELEVATE TIMI 56) trial, noted that tripling the maintenance dose of clopidogrel in CYP2C19*2 heterozygote patients (ie, the aforementioned carriers with 1 variant; 24% of the study population) achieved levels of platelet reactivity that were similar to the standard-dose clopidogrel in noncarriers. However, even higher doses of clopidogrel, up to 300 mg daily, did not result in optimal degrees of platelet inhibition in CYP2C19*2 homozygote patients (ie, carriers of 2 variants; 2% of the study population).

The ELEVATE TIMI 56 trial [NCT01235351] was a randomized, blinded, multicenter trial in patients with stable cardiovascular disease who were already taking 75 mg of clopidogrel daily. Patients were genotyped as CYP2C19*2 carriers (n=86) or noncarriers (n=247) and then randomized to treatment with clopidogrel for four 14-day treatment periods. Noncarriers were randomized to receive 75 mg and 150 mg of clopidogrel once daily (2 periods each in the various sequences). Carriers were randomized to receive 75 mg, 150 mg, 225 mg, and 300 mg clopidogrel once daily for one 14-day treatment period (each in various sequences). All patients took stable doses of aspirin (81 to 325 mg, daily). Platelet function testing was performed (vasodilator-stimulated phosphoprotein [VASP] phosphorylation and VerifyNow P2Y12 assays) after each 14-day treatment period. The primary endpoint was change in platelet inhibition with higher daily doses of clopidogrel.

In patients who received 75 mg daily, CYP2C19*2 heterozygotes had significantly higher on-treatment platelet reactivity than did noncarriers (VASP platelet reactivity index [PRI]: mean, 70.0% [95% CI, 66.0% to 74.0%] vs 57.5% [55.1% to 59.9%], and VerifyNow $P2Y_{12}$ reaction units [PRU]: mean, 225.6 [207.7 to 243.4] vs 163.6 [154.4 to 173.9]; $p<0.001$ for both comparisons). Among CYP2C19*2 heterozygotes, doses up to 300 mg daily significantly reduced platelet reactivity, with VASP PRI decreasing to 48.9% (44.6% to 53.2%) and PRU to 127.5 (109.9 to 145.2; $p<0.001$ for trend across doses for both). Whereas 52% of CYP2C19*2 heterozygotes were nonresponders (≥230 PRU) with 75 mg of clopidogrel, only 10% of these patients were nonresponders with 225 or 300 mg ($p<0.001$ for each vs 75 mg). Clopidogrel, 225 mg daily, reduced platelet reactivity in CYP2C19*2 heterozygotes to levels that were achieved with standard clopidogrel (75 mg daily) in noncarriers (mean ratios of platelet reactivity, VASP PRI, 0.92 [90% CI, 0.85 to 0.99], and PRU, 0.94 [90% CI, 0.84 to 1.04]). In CYP2C19*2 homozygotes, even with a 300-mg daily dose of clopidogrel, mean VASP PRI was 68.3% [95% CI, 44.9% to 91.6%] and mean PRU was 287.0 [95% CI, 170.2 to 403.8], comparable with that seen with the 75-mg dose. No significant increase in side effects occurred with increased dosage. There were no deaths, cerebrovascular events, or TIMI major or minor bleeding events.

Variants in the CYP2C19 gene influence the pharmacological and clinical response to the standard clopidogrel treatment; thus, patients with different CYP2C19 genotypes may require adjusted dosing of clopidogrel to achieve the most effective treatment. This intriguing proof-of-concept study sets the stage for a prospective long-term study of coronary artery disease-genotyped patients (and/or platelet function-directed management) that compares the efficacy and safety of high-dose clopidogrel with more potent antiplatelet therapies that are not metabolized by the cytochrome P450 oxidase enzyme (eg, prasugrel, ticagrelor).

Further reading: Mega JL et al. *JAMA* 2011.