GRACE: Long-Term Outcomes in NSTEMI and UA No Better Than in STEMI

Long-term cardiovascular (CV) morbidity and mortality rates are just as high for patients with non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA) as for patients with STEMI, according to a long-term analysis of data from the Global Registry of Acute Coronary Events (GRACE).

The late consequences of NSTEMI and UA are poorly recognized and often underestimated, according to Keith Fox, MD, University of Edinburgh, Scotland, who presented long-term findings from the GRACE study (published simultaneously online in the *European Heart Journal*).

In the long-term GRACE analysis, Prof. Fox and colleagues sought to evaluate the late clinical outcomes following STEMI, NSTEMI, and UA and to determine whether the GRACE risk score predicts long-term risk of all-cause mortality, CV death, and MI among patients with acute coronary syndrome (ACS). In total, 3721 patients from GRACE registry centers in the UK and Belgium were included in the long-term study.

After 5 years, a similar proportion of patients in each ACS category had died, including 19% of STEMI patients, 22% of NSTEMI patients, and 17% of UA patients. The majority of these deaths occurred after initial hospital discharge, regardless of index event. In STEMI patients, 66% of all deaths up to 5 years occurred after hospital discharge. By comparison, 86% of NSTEMI deaths and 97% of UA deaths up to 5 years occurred after hospital discharge in the GRACE cohort. Although rates of in-hospital mortality and MI were higher following STEMI, the cumulative rates of death were not different over the duration of follow-up in the STEMI (22%) and NSTEMI/UA groups (26%; p=0.21).

Despite high rates of CV medication use during the index hospitalization and 6 months following discharge, long-term CV morbidity was also high. Across all ACS groups, many patients experienced one or more late complications, including MI (12.7%), stroke (7.7%), revascularization (16.7%), or hospital readmission for suspected ACS (53.6%).

The GRACE risk score accurately predicted long-term outcomes in patients with STEMI, NSTEMI, and UA. Relative to low-risk patients, the risk of death was 2-fold higher in the intermediate-risk group (HR, 2.14; p<0.0001) and 6-fold higher in the high-risk group (HR, 6.36; p<0.0001). When examined according to index ACS event, baseline GRACE risk scores were highly predictive of in-hospital mortality, 5-year mortality, and the combined endpoint of CV death and MI in both the STEMI and NSTEMI/UA groups (p<0.0001 for all comparisons).

By accurately predicting long-term outcomes, the GRACE risk score can be used to identify which ACS patients are most likely to benefit from aggressive secondary prevention, Prof. Fox concluded.

CURE ACTIVE: No Loss of Clopidogrel Efficacy with the CYP2C19 Loss-of-Function Allele in Patients with ACS or AF

Genetic variations that are related to clopidogrel metabolism did not diminish clopidogrel efficacy in patients with acute coronary syndromes (ACS) or atrial fibrillation (AF), according to new data from two clinical trials. Guillaume Paré, MD, MSc, McMaster University, Hamilton, Ontario, Canada, presented new findings from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) and Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) trials.

The CYP2C19 gene is associated with the conversion of clopidogrel to its active metabolite. Variations in this gene include the loss-of-function CYP2C19 alleles (CYPC19*2 and CYPC19*3), which slow this conversion, and the gain-of-function CYP2C19 allele (CYPC19*17), which facilitates the metabolism of clopidogrel to its active form. To examine the influence of genetic variations on platelet response, Prof. Paré and colleagues evaluated safety and efficacy outcomes among patients who were enrolled in the CURE (n=5059) and ACTIVE (n=1156) trials according to CYP2C19 genotype (*2, *3, or *17).

In the CURE trial, there was no interaction between loss-of-function CYP2C19 alleles and the efficacy of clopidogrel relative to placebo (p=0.12). Clopidogrel provided a similar magnitude of protection against the primary endpoint compared with placebo in carriers of a loss-of-function allele (8.0% vs 11.6%; HR, 0.69; 95% CI, 0.49 to 0.98) and in those who did not carry a loss-of-function allele (9.5% vs 13.0%; HR, 0.72; 95% CI, 0.59 to 0.87).

By comparison, patients who were carriers of the CYP2C19 gain-of-function allele derived a greater benefit from clopidogrel than noncarriers (p=0.02) in the CURE trial. Clopidogrel significantly reduced the risk of the primary outcome versus placebo among gain-of-function allele carriers (7.7% vs 13.0%; HR, 0.55; 95% CI, 0.42 to 0.73) but not among noncarriers of the CYP2C19 gain-of-function allele (10.0% vs 12.2%; HR, 0.85; 95% CI, 0.68 to 1.05).

In the ACTIVE A trial, no differences in clopidogrel efficacy were observed between carriers and noncarriers of CYP2C19 loss-of-function alleles (p=0.87) or between carriers and noncarriers of the gain-of-function CYP2C19