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

allele (p=0.34). In both the CURE and ACTIVE A trials, bleeding risk among clopidogrel-treated patients did not vary according to CYP2C19 genotype.

In addition to ACTIVE A, future larger studies will be needed to rule out an adverse effect of CYP2C19 loss-of-function alleles on clopidogrel efficacy in patients with AF. However, the CURE trial provided strong data that support the continued use of clopidogrel in patients with ACS, regardless of CYP219 genotype status. In particular, conservatively managed ACS patients who carry the CYP2C19 loss-of-function allele should not be restricted from using clopidogrel at currently recommended doses, Prof. Paré concluded. Further studies will be needed to define the clinical role, if any, of the gain-of-function allele.

The Future of Hypertension Guidelines: Simplified Recommendations and Widespread Treatment

Physicians and other health care providers who manage patients with hypertension must try to reconcile an array of competing national and international blood pressure (BP) guidelines. More than 20 guidelines that are related to some aspect of BP management are available in Australia alone, said John Chalmers, MD, University of Sydney, Sydney, Australia. In this session on hypertension guidelines, Prof. Chalmers described current barriers to guideline implementation, as well as potential solutions to more widespread hypertension control.

Hypertension guidelines share some themes, such as the benefits of combination therapy. However, most guidelines offer divergent advice on specific strategies for hypertension screening and treatment. In 2010, Ferket and colleagues from Erasmus Medical Center, Rotterdam, The Netherlands, performed a systematic review of clinical guidelines on the management of cardiovascular risk factors, including hypertension [Ferket BS et al. *Arch Intern Med* 2010]. Across 27 guidelines from around the world, they found "no consensus on recommended target populations, treatment thresholds, or screening tests." This lack of consensus contributes to poor guideline adherence, with differences across guidelines giving clinicians an excuse for disregarding recommendations in lieu of their own treatment prejudices, Prof. Chalmers said.

Among the many areas of confusion are the different BP thresholds and targets that are described in current guidelines. These include thresholds for initiating antihypertensive therapy (eg, ≥160/90 mm Hg) and targets for antihypertensive treatment (eg, ≤130/80 mm Hg). BP thresholds and targets may vary in different patient groups according to the presence of comorbidities, such as diabetes, chronic kidney disease, and other risk factors. Different guidelines may also offer conflicting recommendations for the same category of patients. Together, these discrepancies can be very confusing and frustrating to the practicing clinician.

New Paradigm for Hypertension Management

Hypertension management may be shifting toward a new paradigm that addresses some of the barriers to guideline implementation. In 2009, Law and colleagues from the Queen Mary University, London, UK, performed a meta-analysis of 147 trials of antihypertension therapy [Law MR et al. *BMJ* 2009]. Most classes of antihypertension medications had a similar effect in reducing the risk of coronary heart disease (CHD) events and stroke. Antihypertensive treatment provided a similar magnitude of protection against CHD and stroke, regardless of pretreatment BP (≥110/70 mm Hg) or the presence or absence of cardiovascular disease at baseline. For all patients aged 60 to 69 years with a pretreated diastolic BP of 90 mm Hg, treatment with a 3-drug combination regimen at half-standard dose reduced the risk of CHD by 46% and reduced the risk of stroke by 62%. Single-agent treatment provided about half of this benefit. β-blockers provided additional protection following myocardial infarction, and calcium channel blockers (CCBs) provided an incrementally greater reduction in stroke compared with other classes.

According to Law and colleagues, these findings support a strategy of lowering BP in all persons of a certain age (eg, ≥60 years) rather than a strategy of screening patients for hypertension and treating only a subgroup of those who are screened. Under this treatment model, hypertension guidelines should be simplified to include therapy for all patients of a certain age and with all levels of BP. Treatment should start with low-dose therapy and build incrementally in patients who require more intensive BP control. Strong clinical trial evidence supports the use of diuretic therapy in combination with an angiotensin-converting enzyme inhibitor (ACEI), an angiotensin receptor blocker, or a CCB. Alternatively, combination therapy with an ACEI and a CCB may be appropriate for some patients. Many of these combinations are available as low-dose, single-pill, and fixed combinations.

Adopting this strategy for population-level hypertension control may remove many of the current barriers to BP management, including the challenges of identifying at-risk patients, determining when to initiate treatment, and defining treatment targets. In particular, the widespread use of fixed-dose combination therapies will enable many patients to start a low-dose regimen that provides significant protection against CHD and stroke, Prof. Chalmers concluded.