METABOLIC CARDIOVASCULAR DISEASE SURABAYA UPDATE (MECARSU)
SURABAYA METABOLIC SYNDROME UPDATE (SUMETSU)
SURABAYA DIABETES UPDATE (SDU)
SURABAYA OBESITY UPDATE (SOBU)

SYMPOSIUM

CABANG SURABAYA CABANG SURABAYA

Proceeding

THE QUADRUPLE JOINT SYMPOSIUM – 2018

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THEME: CARDIOMETABOLIC HEALTH TOWARD–2020
CHALLENGES in PREVENTION and TREATMENT of OBESITY, MetS, CMR, and the CMDs

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Follow the Leader GLP-1 Agonist Liraglutide Demonstrates Cardioprotective Effects

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The goals of antidiabetes treatment are to forestall the metabolic effects of high glucose levels and to prevent microvascular and macrovascular complications. Compelling data in type 2 diabetic patients support the conclusion that improved long-termglycemic control reduces the risk of microvascular complications. Based on several large outcome studies (e.g., the Diabetes Control Complications Trial and the UK Prospective Diabetes Study [UKPDS]), glycosylated hemoglobin (HbA1c) was established as a surrogate biomarker of glycemic control and therapeutic goals were set accordingly. Cardiovascular disease is the leading cause of death in patients with type 2 diabetes; more than 60% die of CV disease, and an even greater proportion have serious CV-related complications. Diabetes is associated with a two- to fourfold increase in the risk of coronary heart disease and death Patients with type 2 diabetes who have not had a myocardial infarction (MI) have a risk of infarction similar to that of nondiabetic patients who have had a prior MI. Pooled data from patients with acute coronary syndrome (ACS) in 11 independent Thrombolysis in Myocardial Infarction (TIMI) study group clinical trials from 1997 to 2006 suggest that, despite modern therapies for ACS, diabetes confers a significant adverse prognosis, with mortality rates of 7.2–8% during the first year after an event. Thus, while microvascular complications can lead to significant morbidity and premature mortality, the greatest cause of death in people with diabetes is by far CV disease.

The ability of glucose lowering to alter CV outcome is not as clear as itsability to reduce microvascular complications. The UKPDS demonstrated a nonsignificant 16% reduction in CV complications (combined fatal or nonfatal MI and sudden death) with intensive glycemic treatment. In an analysis of the study cohort, a continuous association was noted such that, for every percentage point of median HbA1c lowering, there was a statistically significant 18% reduction in CV disease events, with no glycemic threshold. Long-term follow-up demonstrated a significant 15% reduction in CV disease among patients in the intensive glycemic treatment group. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, which included 1,441 patients with type 1 diabetes, demonstrated a significant reduction in CV events (57%) in the intensively treated group after 17years of follow-up.

Cardiovascular safety concerns have been raised with respect to several antidiabetes compounds approved or under development for the treatment of type 2 diabetes. In July 2008, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee met to discuss the role of CV assessment in the premarketing and postmarketing settings. The FDA determined that concerns about CV risk should be more thoroughly addressed during drug development; their newly issued

guidelines will result in profound changes in the ways new antidiabetes drugs are evaluated and brought to market in the future.

In July 2008, the Endocrinologic and Metabolic Drugs Advisory Committee of the FDA met to discuss CV risk with oral antidiabetes agents and the role of risk assessment in the premarketing and postmarketing setting. After considering the discussion at this meeting, as well as other available data and information, the FDA determined that effects on CV risk should be more thoroughly addressed during antidiabetes agent development. The resulting FDA guidance document identifies several key areas that will need to be addressed by study sponsors:

- An upper bound of the 95% CI for the risk ratio of important CV events of <1.3 should be used as a key criterion for excluding unacceptable CV risk for new treatments of type 2 diabetes
- Study patients must include individuals with relatively advanced disease, elderly patients, and patients with some degree of renal impairment.
- A minimum of 2 years' CV safety data must be provided.
- All phase 2 and 3 studies should include a prospective independent adjudication of CV events. Adjudicated events should include CV mortality, MI, and stroke and can include hospitalization for ACS, urgent revascularization procedures, and possibly other end points.
- To satisfy the new statistical guidelines, the analysis of CV events may include a meta-analysis of all placebo-controlled trials, add-on trials (i.e., drug vs. placebo, each added to standard therapy), and active-controlled trials, and/or an additional single, large safety trial may be conducted that alone, or added to other trials, would be able to satisfy this upper bound before a new drug application/biologics license application (NDA/BLA) is approved.

Given FDA guidance for the assessment of cardiovascular (CV) safety, multiple clinical trials were designed to assess cardiovascular outcomes of GLP-1 RA therapy. Endpoints for major adverse cardiac events (MACE) were to be assessed based mainly on 3-point outcomes including death from all CV causes, non-fatal myocardial infarction, and non-fatal stroke. Several studies assessed additional endpoints, including hospitalization for unstable angina or heart failure.

Patients with diabetes often present with atherosclerosis and are at an increased risk for morbidity and mortality from cardiovascular disease (CVD). The risk for stroke, heart disease, and death from heart disease in patients with diabetes is twice that of patients without diabetes. While the benefit of intensive glycemic control is well established for microvascular complications, data on its effect on macrovascular complications have been disparate, with some studies showing benefit, some showing no difference, and others showing increased total and cardiovascular (CV) mortality. Intensive glycemic control must therefore be considered in the context of multifactorial risk reduction that has been shown to reduce CV mortality and events.

The drugs used in the treatment of diabetes have potential CV effects, either beneficial or harmful. In its 2008 Guidance for Industry publication, the US Food and Drug Administration (FDA) issued detailed recommendations to drug developers

for demonstrating that new and existing therapies will not result in an unacceptable increase in CV risk. The European Medicines Agency (EMA) issued similar guidelines in 2012 for drug developers to investigate and rule out potentially harmful drug interactions.

Current gold standard therapeutic strategies for T2DM target insulin resistance or ß cell dysfunction as their core mechanisms of action. However, the use of traditional anti-diabetic drugs, in most cases, does not significantly reduce macrovascular morbidity and mortality. Among emerging anti-diabetic candidates, glucagon like peptide-1 (GLP-1) based therapies carry special cardiovascular implications, exerting both direct as well as indirect effects.

Liraglutide relieves myocardial damage by promoting autophagy via AMPK-mTOR signaling pathway in zucker diabetic fatty rat. Glucagon-like peptide-1 receptor (GLP-1R) agonists are used to treat type 2 diabetes, and transient GLP-1 administration improved cardiac function in humans after acute myocardial infarction (MI) and percutaneous revascularization by Noyan et al. study. This study found benefits liraglutide include:

- Increased survival in mice post-MI.
- Prevented cardiac rupture post-MI
- Reduced infarct expansion post-MI
- Activates cardioprotective signaling pathways in the heart.
- Improved cardiac performance.
- Prevented ischemia–reperfusion injury of isolated hearts ex vivo.
- Camp and reduces apoptosis in neonatal mouse cardiomyocytes.

Findings of the LEADER trial show that liraglutide treatment may confer a reduced risk of cardiovascular events in patients with Type 2 diabetes and a high vascular risk. The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial was designed specifically to assess the cardiovascular safety profile of the glucagon-like peptide (GLP)-1 receptor agonist liraglutide when taken by this subgroup of diabetes patients.

The investigators - John Buse (University of North Carolina School of Medicine, Chapel Hill, USA) and colleagues - hypothesised that liraglutide would be noninferior to placebo for the primary outcome of nonfatal myocardial infarction or stroke, or cardiovascular death. In fact, liraglutide was statistically superior, with 13.0% of the liraglutide group and 14.9% of the placebo group having a primary outcome event over a median 3.8 years of follow-up, equating to a significant 13% risk reduction. The benefit was consistent across subgroups including age, race, diabetes duration and starting glycated haemoglobin level. This would equate to needing to treat 66 patients with liraglutide to prevent one primary outcome event over 3 years, the team reports in The New England Journal of Medicine. The 4668 patients randomly assigned to receive subcutaneous liraglutide took it at a dose of 1.8 mg per day. This group also had significantly improved microvascular outcomes compared with the 4672 patients taking placebo, with retinopathy or nephropathy event rates of 7.6% versus 8.9%.

LEADER patients were aged at least 50 years with co-existing cardiovascular disease or at least 60 years with one or more cardiovascular risk factors. All patients had a baseline glycated haemoglobin level of at least 7.0%, with the average being 8.7%.

Diabetes patients more prone to serious infections, research shows Study shows value of occupational therapy in the lives of young adults with diabetes Researchers identify potential enzyme as therapeutic target for type 2 diabetes Rates of adverse events and serious adverse events did not differ significantly by treatment. Rates of adverse events leading to discontinuation were significantly higher in the liraglutide than placebo group, at 9.5% versus 7.3%, because of higher rates of gastrointestinal events. The team note previous concerns about heart failure risk in patients taking diabetes medications, but this was not borne out in the current study, with hospitalisation for heart failure occurring no more often in the liraglutide group than the placebo group, at 4.7% and 5.3%, respectively. The LEADER trial had greater statistical power than most previous studies, and recruited patients whose blood glucose was poorly controlled at baseline.

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