Glycemic Control Influenced Heart Failure Risk

BY BRUCE JANCIN

FROM THE ANNUAL CONGRESS OF THE EUROPEAN SOCIETY OF CARDIOLOGY

STOCKHOLM – Suboptimal glycemic control is an independent risk factor for a linear increase in the rate of new-onset heart failure in patients with type 2 diabetes, a large Scottish prospective case-control study indicates.

Moreover, in type 2 diabetes patients who already have established heart failure, poor glycemic control is independently associated with increased mortality, Dr. Chim Choy Lang reported at the congress.

These were the key findings in a new analysis from the Tayside Study, which Dr. Lang directs. The ongoing project provides an unusual opportunity to prospectively follow a Scottish community, population 400,000.

"We can track patients with diabetes mellitus, looking at mean [hemoglobin A_{1c}] over time, and see who develops heart failure," he said in an interview.

The analysis was performed because controversy has arisen surrounding the relationship between glycemic control in type 2 diabetes and heart failure. Some recent evidence suggests tight metabolic control is actually associated with worse survival in the setting of heart failure.

"It should be noted that most of these studies were based on a single measure of HbA_{1c}. I think there's always cause for concern about that kind of analysis," observed Dr. Lang, a cardiologist at the University of Dundee.

Each 1% increase in HbA_{1c} was independently linked to a 19% increase in incident heart failure.

DR. LANG

He reported on more than 9,000 Tayside residents with type 2 diabetes, 841 of whom developed heart failure during 1991-2008. Each diabetic heart failure patient was matched by age, gender, and date of diagnosis of diabetes to five controls.

Analysis revealed that mean HbA_{1c} during the study period was associated in linear fashion with the risk of later developing heart failure. Each 1% increase in HbA_{1c} was independently linked to a 19% increase in incident heart failure after the researchers controlled for patients' mean arterial pressure and use of thiazolidinediones.

Further, in type 2 diabetic patients with diagnosed heart failure, each 1% increase in mean HbA_{1c} was independently associated with an adjusted 16% increase in all-cause mortality.

"I think our findings are an argument for tight glycemic control in diabetic patients with heart failure. The question is how to achieve that. I'm a big believer in metformin for that purpose," the cardiologist said.

Asked whether the increased risk of mortality documented in diabetic patients with poor glycemic control and heart failure is a marker for poor adherence to standard heart failure medications or is due to the adverse effects of high blood glucose, Dr. Lang said that's a key unsettled question.

"We have the ability to look at treatment adherence in this cohort and are doing so at the moment," he added.

He declared having no financial conflicts in connection with the study, which was conducted free of industry involvement. ■

Daily Fondaparinux Cuts Risk of Complications, Death

BY KERRI WACHTER

FROM NEW ENGLAND JOURNAL OF MEDICINE

Daily fondaparinux significantly reduced the relative risk of symptomatic thromboembolic complications or death by 85% – without increasing the incidence of bleeding – in a study of some 3,000 patients with acute symptomatic lower-limb superficial-vein thrombosis.

"Fondaparinux also reduced the risk of symptomatic recurrence of superficial-vein thrombosis and, more important, its extension to the saphenofemoral junction – a finding that is clinically relevant because such extension is considered to increase the risk of deep-vein thrombosis and pulmonary embolism, thereby prompting escalation of therapy (for example, to full-dose anticoagulation or surgery)," Dr. Hervé Decousus and his coinvestigators reported.

The results may help fill in knowledge gaps about the appropriate treatment for superficial-vein thrombosis. Currently, therapeutic strategies range from no treatment to the use of anti-inflammatory drugs, anticoagulant agents, or even surgery.

Investigators in the study, known as the Comparison of Arixtra in Lower Limb Superficial Vein Thrombosis with Placebo (CALISTO) trial, compared the efficacy and safety of the specific factor Xa inhibitor fondaparinux with placebo in reducing symptomatic venous thromboembolic complications or death from any cause. The study comprised 3,002 patients with acute, isolated superficial-vein thrombosis of the legs (N. Engl. J. Med. 2010;363:1222-32).

Patients 18 years or older with acute, symptomatic lower-limb superficial-vein thrombosis at least 5-cm long were eligible for the study. They were excluded from the study if they met various specific criteria, such as a documented history of SVT within the past 3 months or DVT or PE within the past 6 months.

Between March 2007 and May 2009, a total of 3,002 patients were enrolled and randomized to receive 2.5 mg subcutaneous fondaparinux per day or daily subcutaneous placebo for 45 days. Overall, 1,481 patients in the fondaparinux group and 1,467 in the placebo group completed the follow-up visit at day 75, wrote Dr. Decousus of the Centre Hôpitalier Universitaire Saint-Étienne in France, and his coinvestigators.

Patients could choose whether to self-administer the injections, were encouraged to use graduated compression stockings, and were allowed to take acetaminophen or topical NSAIDs as needed. Concomitant treatment with other thrombolytic, anticoagulant, or antiplatelet agents was prohibited.

The primary efficacy outcome – the composite of death from any cause, symptomatic confirmed PE or DVT, or confirmed symptomatic extension to the saphenofemoral junction or symptomatic recurrence of superficial-vein thrombosis up to day 47 – occurred in a significantly greater percentage of those in the placebo group (5.9% vs. 0.9%; relative risk with fondaparinux, 0.15). Twenty patients would need to be treated to prevent one death, PE, DVT, extension to the saphenofemoral junction or symptomatic recurrence of superficial-vein thrombosis.

In addition, the incidence of each component of the primary efficacy outcome was significantly reduced in the fondaparinux group, except for the incidence of death, which did not differ significantly. The risk of the composite of DVT or PE was significantly reduced by 85% with fondaparinux, compared with placebo (0.2% vs. 1.3% affected in each group, respectively). To prevent one DVT or PE, 88 patients would need to be treated.

"This benefit was evident within the first days after treatment was initiated, supporting the adequacy of the prophylactic dose of 2.5 mg of fondaparinux and in accord with the substantial efficacy data already available with respect to a dose of 2.5 mg of fondaparinux in various clinical settings," the investigators wrote.

In addition, more patients in the placebo group underwent surgery for superficial-vein thrombosis than in the fondaparinux group (3.5% vs. 0.5% by day 77), including ligation of the saphenofemoral junction. Major bleeding had occurred in one patient in each group by day 47. The rates of clinically relevant nonmajor, minor, and total bleeding and arterial thromboembolic complications did not differ significantly between groups.

The study was supported by GlaxoSmithKline, which markets Arixtra (fondaparinux). In addition, 8 of the 11 study authors reported significant financial relationships with several pharmaceutical companies, including GlaxoSmithKline. ■

VIEW ON THE NEWS

Consider Cost in Drug Approvals

While overall efficacy and safety information are crucial for the approval and widespread use of a new drug, so is cost effectiveness, Dr. Lee Goldman and Dr. Jeffrey Ginsberg wrote in a commentary.

The study authors determined that 88 patients would need to be treated with fondaparinux to prevent one nonfatal episode of deep-vein thrombosis or pulmonary embolism (N. Engl. J. Med. 2010;363:1278-80). "In New York City, the price of a 45-day regimen of 2.5 mg of fondaparinux once daily ranged from $2,124 to $7,380 at four major pharmacies. Even at the lowest quoted price and considering the 98.3% estimated adherence rate, the cost of the treatment for 1,500 patients would be about $3.13 million," they wrote.

"On the basis of the incremental 1-year costs for the medical care of a patient with a pulmonary embolus or deep-vein thrombosis, an estimated $250,000 or so in medical care costs would be averted, resulting in a net cost of fondaparinux treatment of about $2.88 million, or about $1,900 per treated patient, without any lives saved."

No clinical trial phases assess this information. Likewise, decisions regarding Medicare reimbursement do not "consider the cost or cost-effectiveness of the agent itself or of the strategy into which it is incorporated," wrote Dr. Goldman and Dr. Ginsberg.

"We recommend that the Food and Drug Administration give serious thought to mandating phase 3.5 trials to document the costs, the effects on quality of life, and the cost-effectiveness of new interventions so as to reach a consensus regarding their worthiness."

DR. GOLDMAN *is executive vice president of Health and Biomedical Sciences and dean of the Faculties of Health Sciences and Medicine at Columbia University, New York.* DR. GINSBERG *is professor of hematology and thromboembolism at McMaster University, Hamilton, Ont. They reported that they have no financial conflicts.*