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HEART FAILURE

Heart Failure, Saxagliptin, and Diabetes Mellitus: Observations from the SAVOR-TIMI 53 Randomized Trial

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contraindicated in patients with heart failure, until observational data demonstrated an acceptable safety profile.[15,16] Patients with both DM and heart failure are relatively under-represented in clinical trials that either excluded them[34–36] or enrolled <5% of the population.[37,38] Therefore, the 2105 patients with previous heart failure in the SAVOR-TIMI 53 trial represent 1 of the largest cohorts of such patients with DM studied.[1]

There are presently no known mechanisms by which DPP-4 inhibition could precipitate heart failure. The hemodynamic effects of glycemic modulation in myocardium accustomed to years of hyperglycemia are unknown and could potentially exacerbate cardiac dysfunction because glycemic changes may unfavorably alter the balance of free fatty acid oxidation and glycolysis.[39] Intensive glycemic control increased the risk of heart failure in 1 of the large glucose-lowering trials[40] but not in 2 others.[36,38] In contrast to the thiazolidinediones, there is no signal of volume overload observed in the SAVOR-TIMI 53 trial with saxagliptin, nor did saxagliptin raise levels of NT-proBNP. However, interestingly, treatment with the glitazones increases levels of natriuretic peptides in some studies[41] but not all studies.[7] The cardiovascular consequences of DPP-4 inhibition on other peptide substrates, such as natriuretic peptides or bradykinins, are also unknown, nor was there evidence of direct myocardial toxicity with saxagliptin as reflected by the similar change in concentrations of high-sensitivity troponin T and high-sensitivity C-reactive protein between treatment groups.

With the possible exception of metformin[15,16] and insulin,[42] most reported studies to date evaluating effects on heart failure of specific glucose-lowering medications either increased the risk of heart failure or were insufficiently powered and therefore often discordant.[33] Moreover, the trials of metformin and insulin by design enrolled patients with recently