ADA/EASD Panel Urges Caution on TZD Use

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In light of new information regarding thiazolidinediones, the American Diabetes Association and the European Association for the Study of Diabetes have updated their diabetes treatment guidelines to urge "greater caution" in the use of TZDs, particularly in patients with heart failure.

However, they did not fundamentally change last year's original consensus algorithm, which included the thiazolidinediones as one of three possible choices—along with insulin and sulfonylureas—in patients who do not achieve hemoglobin A_{1c} (HbA_{1c}) levels below 7% with the first-line therapies of lifestyle modification and metformin (Diabetes Care 2006;29:1963-72; Diabetologia 2006;49:1711-21).

The panel concluded that the increased risk of heart failure or fractures is not 'of a magnitude to warrant [TZDs'] removal' from the treatment algorithm.

The update, due to be published in January 2008 in both Diabetes Care and Diabetologia, also included information about sitagliptin, which was not yet approved by the Food and Drug Administration at the time the original document was written. As monotherapy, sitagliptin is expected to decrease HbA_{1c} by 0.5%-0.8%. It has the advantage of being weight neutral, but it also has disadvantages, including limited experience and high cost, according to the ADA/EASD panel of seven authors led by Dr. David M. Nathan, director of the Diabetes Center at Massachusetts General Hospital and professor of medicine at Harvard Medical School, Boston.

But TZDs were the main topic of the update, deemed necessary because of the enormous amount of attention that the class of drugs received during 2007, beginning with the widely publicized meta-analysis by Dr. Steven E. Nissen concluding that rosiglitazone was associated with a significant increase in the risk of myocardial infarction (N. Engl. J. Med. 2007;356:2457-71). At least four additional meta-analyses—including one from the manufacturer and one by the FDA—also called into question the safety of rosiglitazone with regard to the risk of MI, with a putative 30%-40% relative increase in risk.

However, another meta-analysis of essentially the same data found no significant increased risk of cardiovascular mortality for either rosiglitazone or pioglitazone (Lancet 2007;370:1129-36), while the interim analysis from the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) study revealed no significant effect on MI but did confirm the risk for heart failure (N. Engl. J. Med. 2007;357:28-38). Meanwhile, yet another meta-analysis suggested a protective effect for pioglitazone (JAMA 2007;298:1180-8).

In addition to the MI concern with rosiglitazone, the previously recognized risk of fluid retention and heart failure that occurs with both rosiglitazone and pioglitazone has now been quantified as approximately twofold. This information is included in a "black box" warning on the labels for both TZDs. Both drugs have also been associated with an increased risk for fractures, particularly in women. The majority of these were in the distal upper or lower limb, not the classic sites of osteoporotic fractures.

Despite these developments, the ADA/EASD panel concluded that the data on MI for both drugs are not definitive, and that the increased risk of heart failure or fractures is not "of a magnitude to warrant their removal as one of the possible second-step medications in our algorithm," particularly since they do have at least one advantage over either insulin or sulfonylureas: They are far less likely to cause hypoglycemia. Thus, the panel opted to compromise by urging clinicians to consider carefully whether to use TZDs versus insulin or sulfonylureas, as well as to consider what is known about the differences between the two available TZDs.

"We are mindful of the importance of not changing this consensus guideline in the absence of definitive or compelling new data. Future updates are planned to consider further revisions of the algorithm, guided by the evidence base and clinical experience with the newer classes of glucose-lowering medication," Dr. Nathan and the other panel members wrote. ■