RESPONSE TO COMMENTS ON INZUCCHI ET AL.

Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–149

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Mazzucchelli et al. (1) are incorrect in stating that the recently updated American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) Position Statement on the management of hyperglycemia in type 2 diabetes (2) favors newer drug classes to sulfonylureas because of lower hypoglycemia rates. The risk of hypoglycemia is important to consider, but it is merely one factor influencing optimal drug selection. Most agents that have become available over the past 15 years, including thiazolidinediones, incretin-based therapies, and sodium–glucose cotransporter 2 inhibitors, are associated with much lower hypoglycemia rates when compared with insulin or insulin secretagogues. Nonetheless, each of these classes has its own adverse effects and/or potential concerns with long-term use—issues with which clinicians and patients must also contend.

Mazzucchelli et al. also appear to minimize the risk of hypoglycemia with the sulfonylurea gliclazide. While likely to a lesser degree than certain other members of this class (3), this drug, based on its mechanism of action, does predispose to hypoglycemia. Indeed, in one study, its addition to metformin led to a more than fivefold increased risk of hypoglycemia as compared with the thiazolidinedione pioglitazone (4). In another trial, it resulted in a nearly twofold higher risk of hypoglycemia than the dipeptidyl peptidase-4 inhibitor vildagliptin (5). Although severe episodes were rare, even mild-moderate hypoglycemia was associated with an increased risk of cardiovascular events (6). So, this is a side effect of antihyperglycemic therapy that must be considered when developing a drug strategy for patients with type 2 diabetes, particularly those at risk, such as the elderly and those with chronic kidney disease. It should also be noted that because insulin itself is excreted by the kidneys, even sulfonylureas that are not renally metabolized must still be used cautiously when glomerular filtration is reduced. As to ischemic preconditioning, we, too, are not convinced of its clinical relevance, which is why a "?" was placed before its mention in Table 1 in the Position Statement's update (2).

Landman et al. (7) question whether the Position Statement should be viewed as a treatment guideline, in which case it would fall short due to the absence of a systematic review and Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. The writing group was charged by the ADA and EASD with developing a statement on antihyperglycemic therapy to represent the organizations' views on the range of therapeutic options in type 2 diabetes. As we pointed out in the original 2012 publication (8), we tried to incorporate the best available evidence, but, where solid support did not exist, we relied on the experience and insight of the writing group, complemented by an extensive review by global experts and ultimate endorsement by the professional practice committees of both organizations. When the original statement (8) was put together in 2012 and when we reconvened for the update 3 years later, the body of evidence in this area was (and remains) sparse, with few long-term comparative effectiveness studies and no head-to-head trials contrasting the effects of treatments on long-term vascular complications. It is interesting to note that published recommendations regarding type 2 diabetes therapies that have attempted to implement international standards for clinical practice guidelines (9) came to very similar conclusions as our writing group did. At present, the only

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rational approach to glucose-lowering therapy in type 2 diabetes is to consider targets, efficacy, side effects, and cost when individualizing a treatment program for a patient, while incorporating his or her preferences, needs, and values. As more robust comparative data emerge, we may be able to be more specific and evidence-based in our recommendations.

As related to disclosures, the authors submitted theirs based on the prevailing guidelines of the ADA and EASD at their main clinical journals, *Diabetes Care* (10) and *Diabetologia* (11), at the time of publication.

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