COMMENTS AND RESPONSES

Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A Consensus Statement From the American Diabetes Association and the European Association for the Study of Diabetes

Response to Jellinger, Lebovitz, and Davidson

Drs. Jellinger, Lebovitz, and Davidson (1) take issue with three features of the consensus algorithm (2). First, they protest that the "therapeutic target A1C of 7%" will miss the opportunity to reduce complications, including microvascular and cardiovascular disease, as much as lower A1C targets that are "achievable safely". Second, they suggest that the consensus algorithm ignores the importance of achieving postprandial glucose control, and third, that the algorithm ignores the "heterogeneity of the pathogenesis of phenotypic type 2 diabetes." They further note a "philosophical problem" in our "rejection of newer, well-proven treatments because they lack multiyear clinical trials." The American College of Endocrinology/American Association of Clinical Endocrinologists (ACE/AACE) response is disappointing in the failure to read the algorithm carefully and in its reliance on observational and epidemiologic data and analyses rather than on the clinical trial data that are universally accepted as the best means of establishing the effectiveness of interventions and balancing side effects and adverse events against demonstrated benefits.

Specifically, the algorithm emphasizes that the A1C goal for the individual patient should be as close to the nondiabetic range as safely possible. However, the best direct clinical trial data regarding control and complications were in the Diabetes Control and Complications Trial and U.K. Prospective Diabetes Study, both of which aimed for normal glycemia but achieved mean A1C levels of 7% (3,4). Based on these data, the consensus group recommended ≥7% A1C as a level that requires a change in therapy. The data cited by Jellinger, Lebovitz, and Davidson supporting the benefits of lower A1C are all secondary analyses of trial data or are epidemiologic studies of the association between A1C and cardiovascular disease (CVD) (5), which should not be used to impute causality or support an added benefit of lower A1C on CVD. The ongoing ACCORD [Action to Control Cardiovascular Risk in Diabetes] study is examining the effects on CVD of even tighter glucose control than has been achieved in previous studies (6). We continue to recommend waiting for the results of that controlled clinical trial before we conclude on the basis of observational data that even more intensive therapy is warranted. The unpublished studies from an AACE consensus conference that are cited by Jellinger, Lebovitz, and Davidson to support more intensive therapy obviously require peer review before they can be considered acceptable data.

The enthusiasm of Jellinger, Lebovitz, and Davidson for the importance of postprandial glycemia is just not warranted by the data, which they seem to recognize when they state that "the clinical significance of this has not yet been established." Although the role of postprandial glycemia in diabetes complications is far from established, the consensus guidelines include adjustment of therapy based on preprandial and postprandial glucose levels if necessary to obtain acceptable glycemic control. However, no clinical trial of type 2 diabetes has conclusively established an added benefit of therapy that specifically lowers postprandial glycemia on A1C or complications.

We agree that the failure to appreciate the heterogeneity in pathogenesis of type 2 diabetes may interfere with selecting interventions that are most likely to be effective. However, since there are few if any studies that separate patients with type 2 diabetes by phenotype or genotype, and select and/or adjust interventions based on the results, we were reluctant to suggest a consensus algorithm that relies on these factors.

The "philosophical problem" cited by Jellinger, Lebovitz, and Davidson represents a profound disagreement between the AACE and the consensus group. Diabetes is a chronic, degenerative disease. Interventions must be demonstrably effective for periods that make sense in the context of this long-term disease. The consensus group used effectiveness in lowering A1C as the primary criterion for judging the available medications, giving more weight to long-term than short-term studies. Secondary considerations included safety, side effects, tolerability and patient acceptance, other factors that might reduce complications independent of glycemia, and cost. Using these criteria, the consensus group was not persuaded that any of the new medications should be included in the algorithm at this time. Of course, as new data are generated, there may be sufficient evidence to support the addition of newer interventions to the algorithm.

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