COMMENT ON AMERICAN DIABETES ASSOCIATION

Approaches to Glycemic Treatment. Sec. 7. In *Standards of Medical Care in Diabetes—2016*. Diabetes Care 2016; 39(Suppl. 1):S52–S59

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The *Standards of Medical Care in Diabetes—2016* (1) released by the American Diabetes Association in the classic January issue supplement made no relevant change for insulin therapy in type 2 diabetes—an issue that probably concerns about 6 million U.S. adults using diabetes medication (2). Although we agree that the basal insulin regimen is a convenient way to start insulin therapy when needed for most patients, we have some concerns about advancing to combination injectable therapy to cover postprandial glucose excursions.

At the level of two injections per day, three options are offered after basal insulin failure: adding a glucagon-like peptide 1 (GLP-1) receptor agonist (GLP-1-RA), adding a mealtime insulin injection, or transitioning to twice-daily premixed insulin analogs. The meta-analysis of Eng et al. (3) is quoted to support the option of adding a GLP-1-RA. However, the only trial with the declared aim to compare a basal-plus regimen (adding once-daily main-meal fast-acting insulin to basal insulin once daily) with a GLP-1-RA added to basal insulin once daily (ref. 23 in Eng et al. [3]) demonstrated the superiority of basal insulin plus GLP-1-RA. At least two recent randomized controlled trials (4,5) had the specific aim to compare a basal-plus regimen with a twice-daily premixed insulin regimen in long-standing type 2 diabetes with suboptimal glycemia despite oral therapies and basal insulin: the basal-plus regimen was found to be noninferior (5) or inferior (4) to a premixed regimen in terms of reduction of HbA_{1c} and was associated with more nocturnal hypoglycemic events (5). The evidence so far produced indicates that the three options are at least equally effective and should have the same scientific dignity. Our suggestion is to offer the three options at the same level of evidence; i.e., all options should have a full line.

At the level of three or more injections per day, all of the previous three options converge on the basal-bolus insulin regimen. Implicit in this statement is the tacit assumption that the basal-bolus still represents the "the gold standard" in reaching goals of glycemic control. A meta-analysis (6) of 13 randomized controlled trials published until 2015 and involving 5,255 patients did not find any significant difference in the efficacy of basal-bolus versus premixed regimens for HbA_{1c} decrease (0.09% [95% CI −0.03 to 0.21]); event rate for overall hypoglycemia, weight change, and daily insulin dose were similar between regimens. Our suggestion is to offer the two final options (basal-bolus up to four injections per day and premixed up to three injections per day) at the same level of evidence by putting the basal-bolus as intensification of basal-plus (left part of Fig. 7.2 in ref. 1) and the thrice-daily premixed as intensification of twice-daily premixed insulin analogs (right part of Fig. 7.2 in ref. 1).

At last, something should be added for those patients who fail to reach their HbA_{1c} target despite full intensified insulin regimens (basal-bolus or premixed): as this population may be as high as >50% (6), this may represent one future challenge for the *Standards of Medical Care in Diabetes*.

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