COMMENT ON GENUTH

Should Sulfonylureas Remain an Acceptable First-Line Add-on to Metformin Therapy in Patients With Type 2 Diabetes? No, It's Time to Move On! Diabetes Care 2015;38: 170–175

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Genuth (1) discusses in a Counterpoint article several arguments against the use of sulfonylureas (SUs) as an add-on therapy to metformin. We understand that in this format he makes arguments against the use of SUs; however, we could not appreciate his oversimplification by ignoring within-class differences. Specifically, the safety of gliclazide is not recognized.

In the 2013 Dutch type 2 diabetes guidelines from the Dutch College of General Practitioners, gliclazide is recommended as the preferred second treatment option over other SUs. A large observational cohort study showed that monotherapy with glimepiride, glibenclamide, and glipizide was associated with a higher mortality and cardiovascular risk, while gliclazide was associated with a risk comparable to metformin (2). Additionally, one of the main advantages of gliclazide is its safety in severe renal failure (3). These drugs are used for many years, even decades, in a population with a high lifetime risk of developing renal impairment (3). Furthermore, two meta-analyses showed that of all SUs, gliclazide has the lowest hypoglycemia risk (4). For example, when compared with glimepiride, there appears to be 50% reduction in the hypoglycemic event rate (5). In all randomized trials published, only one severe hypoglycemia event for gliclazide has ever been reported, and this patient was using insulin in addition to gliclazide (4). Only two randomized trials, both with a sample size of around 1,000 patients, compared the use of a dipeptidyl peptidase-4 inhibitor to gliclazide and showed a comparable hypoglycemia event rate (4).

Within-class differences should be included in this discussion, and we challenge all trial designers to compare potential new glucose-lowering agents to the safest of all SUs: gliclazide. Even today, studies are started that use glibenclamide as a comparator (NCT00696982, NCT01867502, NCT02145611, and NCT02318693) for which we can only think of one goal—to amplify the safety of new glucose-lowering agents.

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