COMMENT 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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Inzucchi et al. (1) suggested that the newer class of hypoglycemic drugs should be preferred to sulfonylureas because of a safer profile with a superimposable hypoglycemic effect. In particular, they state that sulfonylureas are not indicated in chronic kidney disease because of an increased risk of hypoglycemia and potentially cardiovascular death. We challenge this conclusion, in main part, because sulfonylureas have been considered as a class, without taking into account specific properties of each drug—particularly gliclazide, which can be safely prescribed to patients with chronic kidney disease (2). Sulfonylureas have been prescribed to subjects with type 2 diabetes for more than 50 years and have been shown to reduce microvascular complications. We recognize that older sulfonylureas can cause dangerous side effects when used in particular clinical settings. Newer sulfonylureas with higher β-cell specificity, different cellular targets, and different metabolisms have been developed. In particular, gliclazide has been shown to decrease microvascular complications in type 2 diabetes without serious adverse effects. If compared with other sulfonylureas, gliclazide shows the following specificities: *1*) gliclazide is completely metabolized by liver and thus can be prescribed even to patients with severe renal insufficiency, and *2*) gliclazide shows a highest affinity and specificity for its cellular target—the pancreatic K_{ATP}—while other sulfonylureas also interact with myocardial K_{ATP}, blunting cardiac ischemic preconditioning, and with Epac2A/Rap (also a β-cell substrate of incretins), providing a cellular basis to explain their stronger potency as insulin secretagogues (3).

Do and how do these characteristics of gliclazide translate into clinical practice? In patients with renal insufficiency, gliclazide can be safely prescribed at the usual dosage without increasing the risk of severe hypoglycemia, while other sulfonylureas cannot. Gliclazide does not inhibit ischemic cardiac preconditioning, while other sulfonylureas do. The clinical importance of cardiac ischemic preconditioning is still unclear. In the case of glyburide, retrospective studies have produced inconclusive results on the association of glyburide use and cardiovascular death, suggesting that ischemic preconditioning could be of little clinical importance. It is reassuring, however, that gliclazide compared with other sulfonylureas is always associated with the best cardiovascular outcomes (4).

In prospective controlled studies, severe hypoglycemia due to gliclazide has been reported rarely (5); little is known in real life. We have looked at patients admitted for severe hypoglycemia to the emergency department of a teaching hospital in Genova, Italy: 339 admissions were recorded in 48 months and only one was associated with gliclazide (prescribed to a patient with alcoholic liver disease and intoxicated by alcohol at the time of admission) (R.C., personal communication).

Finally, it should be taken into account the low cost of gliclazide and the convenient once-daily administration of its slow-release formulation. Based on these observations, it is tempting to conclude that today gliclazide could be considered one of the "best" oral hypoglycemic drugs: "Do not throw the baby out with the bath water."

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