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Sulfonylureas (SUs) act directly on pancreatic β-cells and stimulate insulin secretion in type 2 diabetes patients. Over 60 years of experience have provided a good understanding of the benefits and risks of SU use.

Good efficacy, with the risk of hypoglycemia

Firstly, the efficacy and durability of SUs have been confirmed. Results from many trials and meta-analyses indicate that SUs have good efficacy on glucose control (glycated hemoglobin [HbA_{1c}] levels are reduced by around 1.25%-1.78% in monotherapy and by around 0.47%-1.30% when added to metformin).[1] In the ADOPT study (A Diabetes Outcome Progression Trial), the SU glyburide showed early and better efficacy in lowering HbA_{1c} over 6 months when compared with metformin or rosiglitazone treatment. In the ADVANCE trial (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation),[2] the intensive treatment based on gliclazide modified release (MR) showed good glycemic control over 5 years, and the mean HbA_{1c} at final visit was 6.5%.

The most common side effect of SU use is hypoglycemia. However, if properly used and begun at lower doses, this risk could be avoided or lowered. It was confirmed by several randomized controlled trials—including UKPDS (United Kingdom Prospective Diabetes Study), ADVANCE, ACCORD (Action to Control CardiOvascular Risk in Diabetes), and VADT (Veterans Affairs Diabetes Trial)—that there is a high rate of severe hypoglycemia in patients on intensive treatment. However, a meta-analysis[3] including real-world studies indicated that the proportion of people experiencing severe hypoglycemia is comparable between SU (5%) and non-SU therapies (5%), but higher in insulin treatment (20%); this probably reflected the fact that SUs were cautiously used in real-world clinical practice.

Improvement as regards diabetic complications

The UKPDS study[4] showed that intensive blood glucose control by either SUs or insulin substantially decreased the risk of microvascular complications, as compared with the conventional group (a 25% risk reduction [7-40; P=0·0099] in microvascular end points). The results from ADVANCE[2] also demonstrated that intensive treatment based on gliclazide MR was associated with lower risk of microvascular complications.

In addition, ADVANCE showed that intensive treatment based on gliclazide MR did not increase the risk of mortality and macrovascular diseases.[2] A meta-analysis[5] including 37 650 patients suggested that when SUs were used in combination with metformin, neither risk of all-cause mortality nor risk of cardiovascular mortality increased.

Affordability and good accessibility

There are 415 million people with diabetes globally, and this figure keeps growing, with 80% of diabetes patients living in low-to-middle–income countries. Therefore, treatment for diabetes should take affordability into consideration. Analysis of annual drug costs showed that the cost of SUs were the lowest among oral medications. What's more, SUs have been in clinical use for more than 60 years, in some places or countries with limited resources; SUs and metformin are considered essential medications with good accessibility.

Guidelines from the American Diabetes Association (ADA) and the International Diabetes Federation (IDF) and the latest Chinese Diabetes Society (CDS) guideline, all recommended use of SUs for type 2 diabetes inadequately controlled by metformin monotherapy. Therefore, sulfonylureas should stay and be used in individualized treatment as appropriate for each patient. ■

References

1. Hirst JA, Farmer AJ, Dyar A, Lung TW, Stevens RJ. Estimating the effect of sulfonylurea on HbA_{1c} in diabetes: a systematic review and meta-analysis. *Diabetologia.* 2013;56(5):973-984.
2. ADVANCE Collaborative Group; Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2008;358(24):2560-2572.
3. Edridge CL, Dunkley AJ, Bodicoat DH, et al. Prevalence and incidence of hypoglycaemia in 532,542 people with type 2 diabetes on oral therapies and insulin: a systematic review and meta-analysis of population based studies. *PLoS One.* 2015;10(6):e0126427.
4. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998;352 (9131):837-853.
5. Varvaki Rados D, Catani Pinto L, Reck Remonti L, Bauermann Leitão C, Gross JL. The association between sulfonylurea use and all-cause and cardiovascular mortality: a meta-analysis with trial sequential analysis of randomized clinical trials. *PLoS Med.* 2016;13(4):e1001992.

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Type 2 diabetes (T2D) is an increasing public health problem worldwide and is difficult to stop, worrisome because of the consequences of associated complications and health costs, lower quality of life, and shorter life expectancy, having an important social impact.[1] Treatment goals have been better defined, including among other issues selection of/accessibility to drugs, education, and treatment adherence, as well as more individualized treatment strategies with the aim of avoiding therapeutic inertia. Guidelines for T2D treatment are essential, but there are discrepancies in the criteria that underlie the algorithms they are based on. Recommendations change often as new drugs expand the therapeutic possibilities and clinical trials provide evidence of efficacy, tolerability, and safety; also, it is prudent to adapt the recommendations to each country, as situations can markedly differ.

Among insulin secretagogues, sulfonylureas (SUs)—in monotherapy or in combination—are recognized to have great efficacy in T2D and in maturity-onset diabetes of the young (MODY), as well as in other specific clinical situations.[2,3] Broad experience and accumulating evidence support a prominent place for SUs among oral agents for diabetes treatment and hold that in particular situations, they are irreplaceable.[4] Also, SUs are used as comparators in most trials for new molecules research.[5-8]

As 80% of diabetics live in low- or middle-income countries, SUs—owing to their effectiveness, safety, and low cost—are particularly important for the control of T2D. Notably, as regards safety, not all SUs are alike; eg, gliclazide has been shown to have a significantly lower risk for hypoglycemia than other drugs of this class.[9-11]

Most patients with T2D have a substantial and specific risk of cardiovascular (CV) disease. The conclusion of a long-standing controversy over use of SUs as regards CV morbidity-mortality is that there is no increased risk, though mechanisms of a possible added CV benefit remain unclear. Note that in CV outcome studies (after US Food and Drug Administration drug approval), the newer antihyperglycemic agents were assessed on top of "standard of care," with approximately 40% to 50% of patients already taking baseline SUs.[12-16] In conclusion, SUs are necessary in management of T2D today for many reasons. There are different SUs (with intraclass differences) to choose from, they are easily available, and they are appropriate, even preferably so, in specific clinical situations (during Ramadan, renal failure, in the elderly, MODY, etc). Efficacy, tolerability, costs, and accessibility place SUs in a privileged place. The World Health Organization considers metformin and gliclazide to be essential medicines as oral agents in the treatment of T2D.[17] Therefore, SUs must stay. ■

References

1. International Diabetes Federation. IDF Diabetes Atlas, Eighth Edition 2017. Available at: http://www.diabetesatlas.org/. Accessed April 1, 2018.
2. Kalra S, Bahendeka S, Sahay R, et al. Consensus recommendations on sulfonylurea and sulfonylurea combinations in the management of type 2 diabetes mellitus - International Task Force. *Indian J Endocrinol Metab.* 2018;22(1):132-157.
3. Sadikot S, Jothydev K, Zargar AH, et al. Clinical practice points for diabetes management during RAMADAN fast. *Diabetes Metab Syndr.* 2017;11(suppl 2):S811-S819.
4. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2008;358(24):2560-2572.
5. Charbonnel B, Schernthaner G, Brunetti P, et al. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. *Diabetologia.* 2005;48(6):1093-1104.
6. Gallwitz B, Guzman J, Dotta F, et al. Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial. *Lancet.* 2012;379(9833):2270-2278.
7. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet.* 2009;373(9662):473-481.
8. Ridderstråle M, Andersen KR, Zeller C, et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. *Lancet Diabetes Endocrinol.* 2014;2(9):691-700.
9. Chan SP, Colagiuri S. Systematic review and meta-analysis of the efficacy and hypoglycemic safety of gliclazide versus other insulinotropic agents. *Diabetes Res Clin Pract.* 2015;110(1):75-81.
10. Singh AK, Singh R. Is gliclazide a sulfonylurea with difference? A review in 2016. *Expert Rev Clin Pharmacol.* 2016;9(6):839-851.
11. Douros A, Yin H, Yu OHY, et al. Pharmacologic differences of sulfonylureas and the risk of adverse cardiovascular and hypoglycemic events. *Diabetes Care.* 2017;40(11):1506-1513.
12. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373(22):2117-2128.
13. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2016;375(4):311-322.
14. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377(7):644-657.
15. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2016;375(19):1834-1844.
16. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2015;373(3):232-242.
17. World Health Organization. 20th WHO model list of essential medicines. Available at: http://www.who.int/medicines/publications/essentialmedicines/en/. Published March 2017. Amended August 2017.

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New strategies to combat the burden of diabetes are needed. Globally, glycemic control rates remain far from target. Recent trends focus on early diagnosis and treatment options that are disease modifying, individualized, timely, and efficacious. With new classes of antidiabetic therapies, cost is becoming a more critical concern. Precision medicine seeks to translate to real-life situations the results observed in study populations from strictly controlled clinical trials. Beyond these pursuits, a focus on the prevention of complications spotlights antidiabetic agents that have cardioprotective and/or renoprotective effects.

Recently published trends in the incidence of diabetes-related complications in the United States from 1990 through 2010 indicate that there has been no progress in the prevention of end-stage renal disease despite impressive declines in macrovascular event rates.[1]

An investigator-initiated posttrial follow-up of the ADVANCE study population (ADVANCE-ON [Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation posttrial ObservatioNal study]) has clearly provided evidence that gliclazide modified release (gliclazide MR) is a unique sulfonylurea molecule with renal benefits.[2] *The underlying molecular mechanisms of gliclazide MR–related renal protection are not yet clearly understood, as they cannot be attributed solely to efficacy and glycemic control rate.*

Despite being an old member of an old class, recent in vitro studies with the gliclazide molecule suggest that it might modify diabetes-related chronic complications beyond the antihyperglycemic effect. Gliclazide, due to its specific chemical structure, is a free radical scavenger, as shown by several in vitro studies using resonance spectroscopy.[3,4] *Is that structural feature only a peculiar chemical property of the molecule, or does this feature come into play in the diabetic organ damage process? The answer lies in two separate in vitro studies: gliclazide delays low-density-lipoprotein oxidation and advanced glycation end product (AGE) formation.*[5,6] *These findings suggest that gliclazide is not only an antihyperglycemic agent, but may also inhibit the macromolecular denaturation occurring within the diabetic milieu by preventing oxidation and glycosylation.*

In conclusion, gliclazide—a unique member of a conventional class, sulfonylureas—should stay within the treatment arsenal for diabetes, as it is inexpensive, efficacious, safe, and has a potentially disease-modifying profile. ■

References

1. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990–2010. *N Engl J Med.* 2014;370(16):1514-1523.
2. Wong MG, Perkovic V, Chalmers J, et al; ADVANCE-ON Collaborative Group. Long-term benefits of intensive glucose control for preventing end-stage kidney disease: ADVANCE-ON. *Diabetes Care.* 2016;39(5):694-700.
3. Karakaya M, Kurekci M, Eskiyurt B, Sert Y, Cırak C. Experimental and computational study on molecular structure and vibrational analysis of an antihyperglycemic biomolecule: gliclazide. *Spectrochim Acta A Mol Biomol Spectrosc.* 2015;135:137-146.
4. Noda Y, Mori A, Cossins E, Packer L. Gliclazide scavenges hydroxyl and superoxide radicals: an electron spin resonance study. *Metabolism.* 2000;49(2 suppl 1):14-16.
5. O'Brien RC. Luo M. The effects of gliclazide and other sulfonylureas on low-density lipoprotein oxidation in vitro. *Metabolism.* 1997;46(12 suppl 1):22-25.
6. Li W, Ota K, Nakamura J, et al. Antiglycation effect of gliclazide on in vitro AGE formation from glucose and methylglyoxal. *Exp Biol Med (Maywood).* 2008; 233(2):176-179.

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The past three decades have seen an epidemic rise in the incidence of diabetes, especially type 2 diabetes (T2D), in developing countries. South-East Asia has almost 84 million people with diabetes, and this figure will rise to 156 million (an 86% increase) by 2045.[1] Against this backdrop, currently, about one-quarter of T2D patients are treated with sulfonylureas (SUs).[2] These drugs effectively lower blood sugar at relatively low cost and can be taken once a day for better long-term adherence to treatment.

The principal arguments for a stance that SUs "should go" are the side effects of hypoglycemia, also weight gain together with the suspicion that SUs as a class increase cardiovascular risk. However, not all SUs are the same, as each of them have different half-lives and clearance pathways and different pharmacokinetic and pharmacodynamic properties, which include variations in their binding affinities to receptors.[3] Furthermore, the frequency of hypoglycemia is significantly different with different SUs. For instance, in the European GUIDE study (GlUcose control In type 2 diabetes: Diamicron modified release versus glimEpiride), gliclazide modified release (MR) was associated with approximately 50% less hypoglycemic episodes than glimepiride.[3]

With regards to cardiovascular safety, ever since the UGDP study (University Group Diabetes Program) suggested an elevated cardiovascular risk with tolbutamide, and despite UKPDS (United Kingdom Prospective Diabetes Study) reporting the contrary, SUs tend to be regarded with suspicion.[2] However, several landmark trials successfully demonstrated the mortality and morbidity benefits associated with SU therapy. The ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) and ADVANCE-ON (ADVANCE posttrial ObservatioNal study) trials reported that an intensive glucose-lowering regimen (gliclazide MR–based regimen) was associated with a significant risk reduction for combined major macrovascular and microvascular events, including a remarkable 46% relative risk reduction for end-stage renal disease (ESRD), and that benefit was continued for up to 9.9 years.[4] Likewise, the STENO-2 trial (Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria), which also followed a gliclazide-based intensive-glucose-control regimen, reported significant cardiovascular (CV) benefits in the trial period that were extended till 21.2 years.[5] In addition, a recent meta-analysis (N=167 327) showed that gliclazide had the lowest risk of all-cause and CV-related mortality when compared with other SUs.[6]

In the past decade, glucagon-like peptide 1 (GLP-1) agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, and sodium glucose cotransporter 2 (SGLT2) inhibitors have been approved for treatment of T2D. Their novel modes of action—not associated with hypoglycemia, weight gain, or increased CV risk in the short term—may have contributed to the impression that SUs are now redundant. This notion is being put to the test in the CAROLINA trial (CARdiovascular Outcome study of LINAgliptin versus glimepiride in type 2 diabetes).[2] As of now, many guidelines recommend SUs (especially gliclazide for CV-disease patients) along with other hypoglycemic agents as a second-line treatment, depending on patient characteristics and clinical judgment. Along with the existing literature, if new evidence should emerge (both from randomized trials and high-quality observational studies) that the modern SUs are as safe as the other agents, they will certainly stay as an important alternative for the management of T2D. ■

References

1. International Diabetes Federation. *IDF Diabetes Atlas, 8th ed.* Brussels, Belgium: International Diabetes Federation, 2017. Available at: http://www.diabetesatlas.org.
2. Riddle MC. Modern sulfonylureas: dangerous or wrongly accused? *Diabetes care.* 2017;40(5):629-631.
3. Sola D, Rossi L, Schianca GP, et al. Sulfonylureas and their use in clinical practice. *Arch Med Sci.* 2015;11(4):840-848.
4. Wong MG, Perkovic V, Chalmers J, et al. Long-term benefits of intensive glucose control for preventing end-stage kidney disease: ADVANCE-ON. *Diabetes Care.* 2016;39(5):694-700.
5. Gæde P, Oellgaard J, Carstensen B, et al. Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial. *Diabetologia.* 2016;59(11):2298-2307.
6. Simpson SH, Lee J, Choi S, Vandermeer B, Abdelmoneim AS, Featherstone TR. Mortality risk among sulfonylureas: a systematic review and network meta-analysis. *Lancet Diabetes Endocrinol.* 2015;3(1):43-51.

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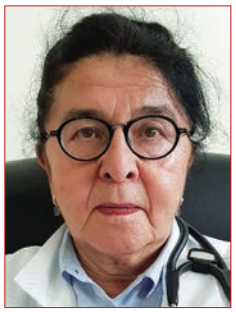

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Type 2 diabetes mellitus (T2DM), with a prevalence in Russia of about 4 million patients according to the latest registry data, is a problem that has reached the scale of crisis and has become a serious medical, social, and economic burden.[1] The situation is aggravated by the fact that almost half of the patients do not have satisfactory control of their diabetes, which leads to a predictable risk of premature death and disabling complications. This failure can be considered a problem of nonadherence to treatment or a problem of improper drug choice.

The complexity of T2DM pathogenesis and pleiotropic factors requiring intervention, such as hyperglycemia, hypoglycemia, weight gain, kidney damage, dyslipidemia, and arterial hypertension, substantiate the need for a personalized pharmacological strategy. At the core of such a strategy, the evidence base (convincing facts) and expert opinion should take into consideration the economic justification of the costs of treatment. The widely discussed results of the trials EMPA-REG OUTCOME ([Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) and LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results—a long term evaluation) are certainly promising, but with budgetary constraints, the availability of these expensive drugs will be limited.

The choice of metformin as a first-line drug in T2DM patients who have been educated in diabetes and who have no contraindications to metformin use does not stir up controversy. The second-line drug choice is also not difficult. Analysis of global trends in the use of antidiabetic agents shows that about half of T2DM patients receive sulfonylureas (SU) as second-line therapy.[2] The results of ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) and ADVANCE-ON (ADVANCE posttrial ObservatioNal study) trials allow us to differentiate gliclazide modified release (MR) from other therapies owing to its long-term and safe glucose-lowering effect and the opportunity it provides to reduce the risks of chronic kidney disease (CKD) progression and macrovascular outcomes.

Most importantly, the intensive glucose-lowering strategy used in the ADVANCE trial was obviously safe with regard to the risk of hypoglycemia. Studies on the drug's mode of action are currently underway, and new intracellular molecules involved in the exocytosis of insulin granules have been identified, eg, Epac 2 (exchange protein directly activated by cyclic adenosine monophosphate 2). This small molecule interacts with the sulfonylurea receptor 1 (SUR1) and exerts an antiapoptotic action. Additional data show that exocytosis of granules is not a mechanical effect triggered by the occupation of the receptor, but a process that requires complex intracellular interaction. Pharmacogeneticists are focused on the cytochrome system (CYP2C9) involved in the pharmacokinetics and pharmacodynamics of SU agents, which are characterized by high ethnic variability.[3] Such genotyping is available and useful, as it makes possible the identification of additional causes of unsatisfactory glycemic control when using drugs of this class. Thus, arming physicians with an analysis of the role of various factors involved in glucose metabolism in different patients, forming the cardiometabolic phenotype of a particular patient, could help in choosing treatment to reduce cardiovascular morbidity and mortality in T2DM.

In conclusion, SUs—keeping in mind that there are intraclass differences in effect and benefits—do have a place in treatment of T2DM and should stay. ■

References

1. Dedov II, Shestakova MV, Vikulova OK. Epidemiology of diabetes mellitus in the Russian Federation: clinical and statistical analysis according to the data of Federal registry of diabetes mellitus [in Russian]. *Sakharniy Diabet.* 2017;20(1):13-41.
2. Montvida O, Shaw J, Atherton JJ, Stringer F, Paul SK. Long-term trends in antidiabetes drug usage in the U.S.: real-world evidence in patients newly diagnosed with type 2 diabetes. *Diabetes Care.* 2018;41(1):69-78.
3. Mosikian A, Dolgorukova A, Zalevskaya A. Possible approaches to CYP2C9-guided prescription of sulfonylureas in Russia. *Pharmacogenomics.* 2016;17(18):2115-2126.