"The place of sulfonylureas in the management of type 2 diabetes continues to divide opinion. Their ability to meaningfully lower plasma glucose concentration remains undisputed, and current research suggests cardiovascular safety concerns about third-generation drugs especially are probably overstated. The global impact of DPP-4 and SGLT-2 inhibitors on sulfonylurea prescribing is growing and is likely to increase further as these classes become a more cost-effective option."

Sulfonylureas: historic to contemporary role in the management of type 2 diabetes

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Sulfonylureas continue to play an important role in the management of type 2 diabetes, despite the introduction of new agents with superior tolerability and fewer side effects. This review provides a historical perspective on sulfonylurea use and describes how the evolving evidence base continues to influence decision making, consensus treatment advice, and the general positioning of this class. Third-generation drugs (gliclazide modified release [MR] and glimepiride) remain a cost-effective glucose-lowering option with similar efficacy to dipeptidyl peptidase-4 (DPP-4)/sodium-glucose cotransporter-2 (SGLT-2) inhibitors and thiazolidinediones as add-on therapy to metformin. Mean reductions in HbA_{1c}% with sulfonylureas are sufficient to impact microvascular complications after 5 to 10 years treatment and probably cardiovascular disease in the longer term. However, therapeutic choice should consider higher rates of hypoglycemia, especially in renal disease, and weight gain with sulfonylureas. These agents are effective in some forms of monogenetic diabetes but as insulin secretagogues do not improve overall β-cell function. In summary, glucose-lowering potency and cost continue to make sulfonylureas an important treatment choice across the global health economy. Newer-generation agents also mitigate hypoglycemia risk and weight gain, but lack of evidence of cardiovascular mortality benefits in patients with type 2 diabetes is likely to be an increasingly important factor in treatment algorithms.

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Introduction

Sulfonylureas are orally administered organosulfur-containing sulfonamide antibiotic derivatives widely used in the management of type 2 diabetes.[1,2] They are most often employed as second-line glucose-lowering therapies, with an estimated 30% to 45% of patients, or 15 million people worldwide, using them as part of their diabetes treatment.[3,4] In England, over 8 million prescriptions for sulfonylureas have been issued every year since 2009.[5] These agents have remained in the armamentarium of most diabetes clinics for over 50 years now, despite unprecedented scrutiny and speculation over their side effects.[6]

This chronological review examines the controversies surrounding sulfonylureas and discusses how this group of drugs have been able to evade redundancy at a time when numerous newer and arguably better glucose-lowering drugs are being marketed. It will describe sulfonylurea research directly influencing clinical practice and contextualize the place of these drugs in current and future treatment algorithms. Modification of the hydrocarbon backbone of the basic organosulfur structure

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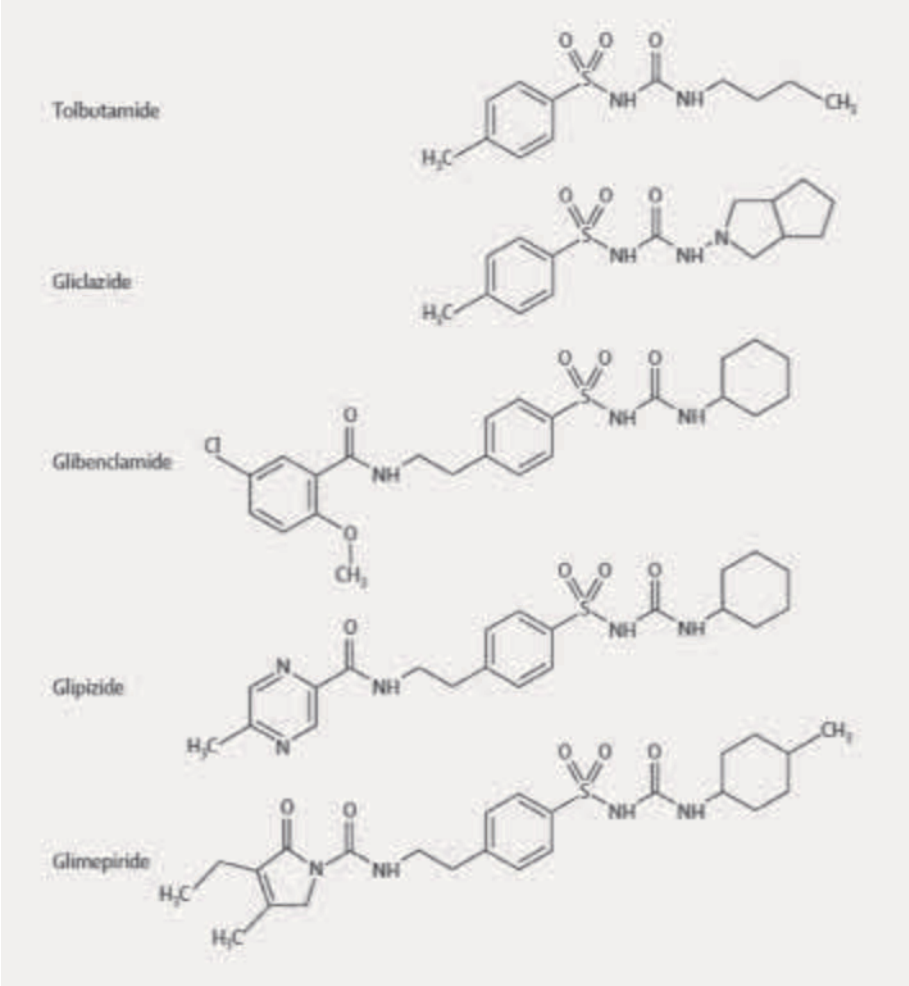

Figure 1. *Structures of first-, second-, and third-generation sulfonylureas.*
First-generation sulfonylurea, tolbutamide; second-generation, gliclazide (regular), glibenclamide, and glipizide; third-generation, gliclazide modified release (MR) and glimepiride.[7]
Adapted from reference 8: *Abdelmoneim et al.* Diabetes Obes Metab. *2012;14(2):130-138.*

changes its pharmacodynamic and pharmacokinetic properties, theoretically enabling the development of new and improved "generations" of sulfonylureas (see *Figure 1* for structures of first-, second-, and third-generation sulfonylureas[8]).[2] These aim to improve clinical performance, minimize hypoglycemia, and allay concerns over cardiovascular safety. Whether contemporary sulfonylureas have met these requirements is also considered, particularly in respect to increasingly abundant cardiovascular outcome data for other glucose-lowering drugs.

Early cardiovascular concerns in the UGDP era (1970 – 1980)

The safety of certain sulfonylureas was first questioned in 1970 after publication of the University Group Diabetes Program (UGDP) results.[9] This controversial trial reported that tolbutamide, a first-generation sulfonylurea, may be associated with an increased risk of cardiovascular death and prompted the US Food and Drug Administration to withdraw the drug and impose a "black box" warning on all sulfonylureas. Despite subsequent widespread criticism of its methodology, publication of the UGDP results dramatically affected prescribing patterns in the US and triggered a tranche of research into the effects of sulfonylureas on the cardiovascular system. They are now known to stimulate insulin release by binding to sulfonylurea receptor 1 (SUR1) membrane receptors and inhibiting adenosine triphosphate (ATP)-sensitive potassium (K^+) influx channels on the pancreatic β-cell.[10] It is proposed that transient ischemia-induced opening of myocardial and vascular smooth muscle ATP-sensitive K^+ channels has a protective effect through reduced cardiac afterload and peripheral vasodilation, a phenomenon referred to as ischemic preconditioning. Nonselective binding and closure of ATP-sensitive K^+ channels are therefore potentially deleterious, and sulfonylurea effects on preconditioning have been proposed as an explanation for the results of UGDP.[11] Sulfonylureas appear to have a range of affinities for different sulfonylurea-receptor isoforms, resulting in significant variation in their ability to interfere with ATP-sensitive K^+ channel activity.[8] Interestingly, tolbutamide, like gliclazide, has a low affinity for sulfonylurea receptor 2A (SUR2A) on cardiac myocytes, whereas other sulfonylureas are less β-cell specific and therefore potentially more cardiotoxic. Further evidence that this class of drugs have differing binding affinities comes from animal work. In rodent models, nicorandil-induced ischemic preconditioning is abolished by glibenclamide but not by gliclazide.[12] In summary, it would appear first- and second-generation sulfonylureas have less-selective binding properties, which may have adverse effects on cardiac tissue. Despite UGDP, the class survived this highly uncertain time and progressed into the era of the glucose-lowering "mega" trials.

Reassurance from the large cardiovascular outcome trials (1993-present day)

Current glucose-lowering targets are based on evidence gathered from landmark randomized trials comparing intensive management with routine care. The first to demonstrate a clear link between intensity of glucose control and the development of early vascular complications was the DCCT (Diabetes Control and Complications Trial). In this multicenter study in people with type 1 diabetes, a glycated hemoglobin (HbA_{1c}) difference of approximately 2% sustained over a me-

dian of 6.5 years reduced the risk of retinopathy, neuropathy, and nephropathy by over 50%.[13] Whether these important findings could be replicated within the much larger population of people with type 2 diabetes remained uncertain until publication of the UKPDS (United Kingdom Prospective Diabetes Study) in 1998.[14] UKPDS confirmed the benefits of sulfonylurea (mostly glibenclamide and chlorpropamide) and insulin-based treatment intensification, as compared with conventional treatment, on similar microvascular outcomes as DCCT but this time in people with newly diagnosed type 2 diabetes. A small substudy of UKPDS did show that the addition of metformin to a sulfonylurea was associated with an increased risk of all-cause mortality compared with sulfonylurea monotherapy (UKPDS34).[15] In posttrial observational follow-up of both UKPDS and DCCT, microvascular disease benefits were maintained and cardiovascular and overall mortality benefits emerged.[16,17] Overall, UKPDS did not confirm the findings of UGDP and in fact suggested intensive treatment with sulfonylureas was both safe and effective. Importantly, it should be noted that as a range of drugs and treatment strategies were used in the treatment arms of this glucose-lowering study, it is impossible to make firm conclusions about the effect of individual therapies. In the glucose-lowering arm of the ADVANCE study (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR controlled examination) over 10 000 patients with type 2 diabetes for at least 10 years and at least one cardiovascular risk factor were randomized to either intensive (HbA_{1c} <6.5%) or standard control.[18] ADVANCE confirmed the findings of UKPDS in terms of microvascular benefits and—because all participants in the intensive arm of the study initially received gliclazide MR—further consolidated confidence in the use of "modern" sulfonylureas.[19]

SELECTED ABBREVIATIONS AND ACRONYMS

ACCORD	Action to Control CardiOvascular Risk in type 2 Diabetes
ADOPT	A Diabetes Outcome Progression Trial
ADVANCE	Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR controlled Examination
ATP	adenosine triphosphate
CANVAS	CANagliflozin cardioVascular Assessment Study
CAROLINA	CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes
CI	confidence interval
DCCT	Diabetes Control and Complications Trial
DPP-4	dipeptidyl peptidase-4
EMPA-REG OUTCOME	(Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA_{1c}	glycated hemoglobin
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results
MACE	major adverse cardiovascular events
OR	odds ratio
SGLT-2	sodium-glucose cotransporter-2
SUSTAIN-6	Trial to Evaluate Cardiovascular Outcomes with Semaglutide in Subjects with Type 2 Diabetes
TOSCA.IT	Thiazolidinediones Or Sulfonylureas and Cardiovascular Accidents.Intervention Trial
UGDP	University Group Diabetes Program
UKPDS	United Kingdom Prospective Diabetes Study

Staying power? Glycemic control efficacy, hypoglycemia, and weight gain (1970 – present day)

Type 2 diabetes mellitus is caused by pancreatic β-cell dysfunction and target-cell resistance to the effects of insulin. Because these primary cellular defects typically worsen over time, multiple interventions are usually required to minimize progressive hyperglycemia once a diagnosis is made. The timing and extent of treatment intensification is largely determined by the ensuing metabolic compromise and requires careful consideration of the relative merits of available glucose-lowering pharmacotherapy. Initial treatment is usually with the biguanide metformin in conjunction with lifestyle and dietary changes. Current guidance from the European Association for the Study of Diabetes/American Diabetes Association (EASD/ADA) and the American College of Endocrinology/American Association of Clinical Endocrinologists (ACE/AACE) recommends individualized thresholds for the sequential addition and titration of second- and third-line glucose-lowering therapies when mutually agreed targets are not achieved with metformin alone.[20-22] These include agents within the following groups: sulfonylureas, thiazolidinedione, dipeptidyl peptidase-4 (DPP-4) inhibitor, glucagon-like peptide-1 receptor agonist (GLP-1 RA), sodium-glucose cotransporter-2 (SGLT-2) inhibitor, and basal insulin. Unfortunately, despite the need for additional treatment, there is often a significant delay in sequential intensification, possibly because of anticipated unacceptable side effects or inconvenience of proposed medication choices.[23] Sulfonylureas have been part of treatment algorithms for type 2 diabetes since their introduction in 1956, partly because in the short-term they reliably reduce plasma glucose.

By stimulating remaining endogenous insulin secretion, sulfonylureas improve glycemic control when used as monotherapy, in combination therapy, or with insulin. In a systematic review of 31 double-blind randomized controlled trials (including 3956 patients) with median duration of 16 weeks (range 3 weeks to 3 years), sulfonylurea monotherapy lowered HbA_{1c} concentration by 1.5% compared with placebo, by 1.62% compared with other oral glucose-lowering therapy (metformin or troglitazone), and by 0.46% compared with insulin.[24] Similar reductions in HbA_{1c} were found in a systematic review of 27 randomized controlled trials (involving 11 198 patients in total and each trial lasting at least 3 months) comparing different drug classes, including sulfonylureas, thiazolidinediones, GLP-1 RAs, and DPP-4 inhibitors, added

to maximally titrated or tolerated metformin in patients with inadequate glycemic response. For all drugs, and for sulfonylureas specifically, the weighted mean difference in HbA_{1c} concentration from baseline was 0.79% (95% confidence interval [CI], −0.90 to −0.68; $P<0.05$) and 0.79% (−1.15 to −0.43; $P<0.05$), respectively.[25] In summary, trial data continues to demonstrate that contemporary sulfonylureas are potent glucose-lowering therapies with equal if not superior clinical efficacy to many emergent newer drugs.

The most frequently encountered and clinically important side effects of sulfonylureas are hypoglycemia and weight gain. These by-products of glucose-independent insulin secretion have always been an area of major concern for clinicians and patients alike but notably are not features of new diabetes treatments such as incretin (DPP-4 and GLP-1 RA)-based therapies and SGLT-2 inhibitors. Hypoglycemia is possibly the most feared adverse effect of diabetes treatment and contributes significantly to patient distress and the therapeutic inertia discussed earlier.[23] The importance of low blood glucose has taken on new meaning over the last 10 years as it has become increasingly linked to cardiovascular mortality and some of the deleterious proinflammatory responses more commonly associated with hyperglycemia.[26] Both high and low HbA_{1c} are linked to all-cause mortality and cardiovascular disease, and the results of meta-analyses suggest that hypoglycemia nullifies benefits accrued by the effort of intensive glucose lowering.[27,28] The ACCORD trial (Action to Control CardiOvascular Risk in type 2 diabetes) demonstrated increased cardiovascular death with an intensive glucose-lowering regimen targeting an HbA_{1c} of less than 6.0%.[29] Unsurprisingly, severe hypoglycemic episodes occurred more frequently in the intensively managed group and were identified as a risk factor for mortality in secondary analyses of the trial. Like UKPDS and ADVANCE, it is not possible to tease out the role of individual therapies in the complex glucose-lowering algorithms of ACCORD, or even to conclude with confidence that hypoglycemia is the reason for its surprising outcome. However, since its publication, drugs with the capacity to cause hypoglycemia have been on the decline. For example, there has been a significant reduction in sulfonylurea use in the United States, United Kingdom, and other European countries over the last 10 years, as clinicians and patients opt for therapies with fewer propensities for hypoglycemia or weight gain.[30-32] The elderly and patients with poor renal function carry a higher risk of hypoglycemia, so sulfonylurea use in these subgroups has become a particular concern. Although all sulfonylureas can cause hypoglycemia, it appears that some may carry a higher risk than others.[33] Differences in chemical structure and pharmacodynamic properties between sulfonylureas probably explain the variation in hypoglycemia risk. Several conventional and network meta-analyses of trial data has shown differential effects of sulfonylureas, with glibenclamide generally being associated with a higher risk of hypoglycemia compared with gliclazide, glimepiride, and glipizide.[34-36]

Cardiovascular outcome trials and direction of future guidance (2008 – present)

The last decade has seen an unprecedented rise in the number of new pharmacotherapies for type 2 diabetes.[37] In 2008, in response to concerns about the cardiovascular safety of diabetes drugs, the US Food and Drug Administration issued a directive that clinical trials of new agents should include outcome data to demonstrate they are not associated with increased cardiovascular risk.[38] Unlike sulfonylureas, which predate these requirements, many of these drugs have been or are being tested in this way as a prerequisite to gaining regulatory approval. This level of scrutiny provides additional reassurance that a new therapy is not going to increase cardiovascular risk, or if the study design allows for enough power, it can also sometimes demonstrate cardiovascular benefit. This has recently been shown to dramatic effect in the EMPA-REG OUTCOME ([Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), CANVAS (CANagliflozin cardioVascular Assessment Study), LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results), and SUSTAIN-6 (Trial to Evaluate Cardiovascular Outcomes with Semaglutide in Subjects with Type 2 Diabetes) phase 3 cardiovascular outcome trials, where highly relevant cardiovascular mortality benefits were demonstrated for the SGLT-2 inhibitors empagliflozin and canagliflozin and the GLP-1 RAs liraglutide and semaglutide in people at high risk of or with preexisting cardiovascular disease.[39-42] Such results are extremely powerful, providing clinicians with long–sought-after knowledge that the glucose-lowering therapies they are advising for their patients are firstly safe and secondly may have a beneficial effect on cardiovascular disease.

Since completion of these trials, other GLP-1 receptor agonists have been tested in cardiovascular outcome trials, adding further to the encouraging evidence base for this new class.[43,44] There is also safety data available for the DPP-4 inhibitors, with three trials indicating that sitagliptin, saxagliptin and alogliptin are noninferior to placebo in major adverse cardiovascular events (MACE)-defined primary outcome trials.[45-47]

This increasing level of confidence cannot currently be extended to sulfonylureas, where, more than 40 years after the publication of UGDP, the association between incident cardiovascular disease and sulfonylurea use remains far from clear. The availability of high-quality outcome trial evidence assessing named sulfonylureas is relatively limited and is probably going to be increasingly confined to noninferiority comparator studies with newer agents.

The TOSCA.IT trial (Thiazolidinediones Or Sulfonylureas and Cardiovascular Accidents.Intervention Trial) compared the thiazolidinedione pioglitazone with a randomly allocated sulfonylurea (gliclazide [50%], glimepiride [48%], or glibenclamide [2%]) as second-line add-on therapy in 3000 people with

type 2 diabetes. The number of primary outcome cardiovascular events after 2.1 years of follow-up was almost identical in both arms of the study, although there were more hypoglycemic episodes associated with sulfonylurea use.[48] The CAROLINA study (CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes) is investigating the impact of the DPP-4 inhibitor linagliptin on cardiovascular outcomes compared with glimepiride and is due to report its findings in late 2018.[49]

Meta-analyses of sulfonylurea clinical trial data have tended to show no consistent association with MACE outcomes, while acknowledging the general heterogeneity of available data. In one study, the MACE risk estimate was not increased (odds ratio [OR], 1.08; 95% CI, 0.86-1.36; *P*=0.52), and the authors suggested that longer-term cardiovascular outcome studies were necessary to fully assess cardiovascular safety of sulfonylureas.[50] Another used a network analysis to indicate that the risk of all-cause and cardiovascular mortality was lower with gliclazide and glimepiride than with glibenclamide (all-cause mortality for gliclazide: relative risk, 0.65, 95% CI, 0.53-0.79).[51] Of all the sulfonylurea trials included, only glipizide was associated with an increased risk of all-cause mortality (OR, 1.68; 95% CI, 1.06-2.66) and cardiovascular mortality (OR, 2.1; 95% CI, 1.09-3.72), whereas neither gliclazide nor glimepiride were associated with significantly increased all-cause mortality (OR, 0.92; 95% CI, 0.49-1.72) or cardiovascular mortality (OR, 1.94; 95% CI, 0.86-4.39).

Evidence from meta-analyses of studies that were limited to new-generation sulfonylureas indicate no consistent association, either increased or decreased, between all-cause mortality or cardiovascular mortality and sulfonylurea use in people with type 2 diabetes. Observational data appears similarly uncertain. In a French registry study of patient outcomes after myocardial infarction, mortality was significantly lower in people with diabetes previously treated with sulfonylureas compared with those on other oral medication, insulin, or no medication.[52] Arrhythmia and ischemic complications were also less common in the gliclazide group and glimepiride groups. Conversely, other researchers using the Swedish National Diabetes Register observed that second-line treatment with DPP-4 inhibitors and thiazolidinediones was associated with reduced mortality risk compared with sulfonylureas.[53] Others have found both increased and decreased risk of cardiovascular events and death associated with sulfonylureas.[54,55] Future management guidance is likely to attach increasing importance to the ability of glucose-lowering therapies to address cardiovascular comorbidities associated with type 2 diabetes. Medications that have evidence of efficacy in high-risk cases—eg, obesity, existing heart disease, and microalbuminuria—are likely to be promoted in this role. The lack of this in the case of sulfonylureas is already beginning to affect some prescribing behaviors and may have major implications for these drugs.

Glycemic control durability (1990s – present)

In the late 1990s, speculation mounted that chronic use of first- and second-generation sulfonylureas may expedite β-cell failure and hasten the need for insulin therapy in type 2 diabetes. Sulfonylurea-mediated K^+ ATP channel closure resulting in unregulated cellular hyperexcitation was proposed as a trigger to "secondary loss" of insulin secretion or even β-cell death.[56] Therapy with sulfonylureas is associated with a gradual loss of glucose control and a greater rate of medication "failure" than either metformin or thiazolidinediones. Findings from the ADOPT trial (A Diabetes Outcome Progression Trial) showed that sulfonylurea monotherapy is sustainable for approximately 2.75 years before additional therapy is needed, although at this stage, there appears to be little difference in β-cell function between metformin, rosiglitazone, and glibenclamide.[57] More recently, mouse model work suggests that K^+ ATP channel suppression caused by sulfonylurea administration probably results in a transitory reversible impairment of β-cell secretory capacity with no evidence of accelerated apoptosis.[58] How or indeed whether these observations relate to sulfonyl-urea actions in humans remains uncertain, but they have led to suggestions that sustained or tonic β-cell stimulation may be best avoided. Newer compounds that act in a glucose-dependent fashion to promote phased insulin release may have better glycemic control durability. In recent clinical trials, DPP-4 inhibitors have been associated with improved β-cell function and an increase in time to insulin initiation.[45,46] There is also some evidence from real-world studies that treatment is maintained longer with dual therapy consisting of metformin and a DPP-4 inhibitor than with metformin and a sulfonylurea.[59,60] Head-to-head randomized comparisons over several years would be needed to determine whether newer drugs are more durable than sulfonylureas in clinical practice.

K^+ channel closure: a unique action put to good use in monogenetic diabetes (2000 – present)

Uncoupling of β-cell-stimulus – insulin-secretion coupling is of particular use if intracellular ATP production is impaired or there is a defect in K^+ ATP channel closure. Such abnormalities are seen in genetic mutations of the glycolytic pathway or the SUR1 membrane receptor, as occurs in some forms of neonatal and monogenetic diabetes. Sulfonylureas have proven highly successful as a treatment modality for these specific and relatively rare conditions.[61] As we enter the era of personalized medicine, it seems likely that further mutations and genetic variation in β-cell insulin release pathways will be identified. These may represent further opportunities for highly effective, targeted sulfonylurea therapy.

Conclusion

The place of sulfonylureas in the management of type 2 diabetes continues to divide opinion. Their ability to meaningfully lower plasma glucose concentration remains undisputed, and current research suggests cardiovascular safety concerns

about third-generation drugs especially are probably overstated. The global impact of DPP-4 and SGLT-2 inhibitors on sulfonylurea prescribing is growing and is likely to increase further as these classes become a more cost-effective option. Newer competitors have the advantage of lower rates of hypoglycemia, are not associated with weight gain, and most have undergone rigorous cardiovascular safety testing before being approved for use. The knowledge that some of these glucose-lowering drugs have additional probably pleiotropic actions that improve cardiovascular outcomes and mortality in high-risk populations with type 2 diabetes is an extremely powerful incentive to prescribe over traditional and less-certain drugs. This trend is likely to continue. However, the actions of insulin secretagogues are tried and increasingly tested, and they have certainly survived previous challenges to their place at the top of second-line choices for glucose management. Some 80% of patients in low- and middle-income countries continue to use these drugs. It seems inevitable that sulfonylureas will need to demonstrate hard evidence of survival benefits in future head-to-head comparisons with other drugs if they are to retain their mass appeal once the affordability of newer agents is no longer an issue. ■

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