"Prescribing therapy in older patients requires additional knowledge of age-associated changes in pathophysiology, pharmacokinetics, and pharmacodynamics, use of multiple medicines, and drug-drug interactions; this adds to the challenges of managing diabetes in the elderly. The emphasis is on achieving blood glucose levels that prevent and minimize vascular complications of diabetes but also minimize the risk of safety issues."

Sulfonylureas in specific clinical situations: elderly

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Type 2 diabetes is a worldwide pandemic and is an especially important health issue for the aging population. Conditions in the elderly diabetic population are more complex than in younger diabetics. The emphasis is on achieving blood glucose levels that not only prevent or minimize vascular complications of diabetes but also minimize the risk of safety issues. An ideal antihyperglycemic agent in the elderly should have good and sustained efficacy, less hypoglycemic risk, be weight neutral, and be well tolerated and easy to use. The elderly are also at an increased risk of microvascular and macrovascular complications from longer duration of diabetes, poor glycemic control, and more comorbidities. Agents with cardiovascular and renal benefit would be preferred, and those that are at least neutral in that respect are needed. Despite the emergence of newer agents, sulfonylureas (SUs) remain the most common choice after metformin in the treatment of type 2 diabetes. Advantages of SUs include their high and sustained glucose-lowering effect, wide treatment dosage window, oral administration, time-tested experience with their use, their wide availability throughout most of the world, and their low cost. Outcome studies—UKPDS (United Kingdom Prospective Diabetes Study) and ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR controlled Examination)—both showed that intensive therapy with a SU-based treatment improved long-term outcomes. Gliclazide has been included in the World Health Organization's 2013 Model List of Essential Medicines and is specifically recommended in the Dutch guidelines on type 2 diabetes. Unique features of gliclazide include its relatively low hypoglycemic risk, weight neutrality, once-daily oral administration, cardiovascular neutrality, and renal benefit, in line with the clinical needs seen in the elderly.

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Introduction

Type 2 diabetes is a worldwide pandemic and is an especially important health problem for the aging population. Approximately one-quarter of people over the age of 65 years have diabetes and one-half of older adults have pre-diabetes, and this proportion is expected to increase rapidly in the coming decades.[1]

Comprehensive diabetes management is essential to tackle the problem. Our treatment goal is to relieve symptoms and prevent or delay the related complications. Individualized therapy should be carefully considered for each patient, including the glycemic target and the treatment choice.

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Diabetes in the elderly: general considerations for management

The conditions in the elderly diabetic population are more complex than in younger diabetics. Older individuals with diabetes have higher rates of premature death, functional disability, accelerated muscle loss, and coexisting illnesses—such as hypertension, coronary heart disease, and stroke—than those without diabetes. Older adults with diabetes also are at greater risk than other older adults for several common geriatric syndromes, such as polypharmacy, cognitive impairment, urinary incontinence, injurious falls, and persistent pain. These conditions may affect an older adult's ability to self-manage diabetes.[2] The elderly are at increased risk of hypoglycemia, particularly those with frailty, undernutrition, or dementia, and the glucose concentration window between awareness of hypoglycemia and impairment of the brain is more narrowed than in others, which may lead to cognitive decline[3] and other major adverse outcomes. Poor glycemic control is also associated with a decline in cognitive function,[4] and longer duration of diabetes is linked with worsening cognitive function as well.

Thus, prescribing therapy in older patients requires additional knowledge of age-associated changes in pathophysiology, pharmacokinetics, and pharmacodynamics, use of multiple medicines, and drug-drug interactions; this adds to the challenges of managing diabetes in the elderly. The emphasis is on achieving blood glucose levels that prevent and minimize vascular complications of diabetes but also minimize the risk of safety issues. An ideal antihyperglycemic agent in the elderly should have good, sustained efficacy with less hypoglycemic risk and be weight neutral, well tolerated, and easy to use. Regarding the effect on body weight, weight loss would be ideal for the overweight and obese type 2 diabetes mellitus patients, but this may not be the case for those relatively aged and with normal body mass index (BMI). As lean body mass is also reduced when people lose weight, the elderly may feel weakness due to muscle wastage or even sarcopenia. In such cases, weight neutral agents would be a better choice. The elderly are also at an increased risk of microvascular and macrovascular complications in those with longer-duration diabetes, poor glycemic control, and more comorbidities. Agents with cardiovascular and renal benefit would be preferred, and those with at least neutrality in this regard are needed.[5,6]

Selected abbreviations and acronyms

ADVANCE	Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR controlled Examination
ADVANCE-ON	ADVANCE ObservatioNal study
EASYDia	ObsErvationAl Study to analYze titration of Diamicron MR 60 mg in daily clinical practice in a large population with uncontrolled type 2 diabetes
gliclazide MR	gliclazide modified release
HbA_{1c}	glycated hemoglobin
NICE	National Institute for Health and Care Excellence
STRATEGY	Efficacy and Safety of Metformin and Sitagliptin Based Triple Antihyperglycemic Therapy
SU	sulfonylurea
TOSCA.IT	Thiazolidinediones Or Sulfonylureas and Cardiovascular Accidents.Intervention Trial
UKPDS	United Kingdom Prospective Diabetes Study
Xrise	Treatment of Type 2 Diabetes with a Breakable Extended Release Gliclazide Formulation in Primary Care

Sulfonylureas in diabetes management in the elderly

Despite the emergence of newer agents, sulfonylureas (SUs) remain one among several dual-therapy choices after metformin and can be used as first-line therapy if metformin is not tolerated or is contraindicated, as recommended by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) position statement, the United Kingdom's National Institute for Health and Care Excellence (NICE) guidelines, and the Chinese Diabetes Society (CDS) guidelines. Advantages of SUs include their high and sustained glucose-lowering effect, wide treatment dosage window, oral administration, time-tested experiential evidence, wide availability throughout most of the world, and low cost. The outcome studies UKPDS (United Kingdom Prospective Diabetes Study)[7] and ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR controlled Examination)[8] both showed that intensive therapy with SU-based treatment improved long-term outcomes.

Although all SUs have the same general mechanism of action, their pharmacokinetic properties are influenced by factors such as dosage, rate of absorption, duration of action, route of elimination, tissue specificity, and binding affinity for pancreatic β-cell receptors. The result is a class of agents with similar glycated hemoglobin (HbA_{1c})-lowering efficacy, but well-documented differences in terms of effects on hypoglycemia, and cardiovascular and renal safety.

The SU class is associated with an increased risk of hypoglycemia, which varies between agents. Glibenclamide (also known as glyburide) has the highest risk of hypoglycemia, and gliclazide has the lowest.[9] In a small trial that compared the effect of glibenclamide and gliclazide on the frequency of hypoglycemic events and glycemic control in the elderly, results revealed that while both were similar for glycemic control after 6 months of treatment, the incidence of hypoglycemic episodes was significantly greater with glibenclamide than with gliclazide.[10] The majority of the hypoglycemic episodes occurred within 1 month of initiating treatment with either agent. A subgroup analysis of participants over the age of 75 (n=53) from a head-to-head comparison of gliclazide modified re-

lease (gliclazide MR) versus glimepiride also found that most hypoglycemic episodes in people over 75 years old occurred at the lowest treatment doses (15 out of 22 episodes on 30-60 mg gliclazide MR, and 48 out of 56 episodes on glimepiride 1-2 mg).[11] Glibenclamide and glimepiride are long acting, and the formation of active metabolites increases the risk for prolonged and severe hypoglycemia, particularly in the elderly.[12,13] The risk is significantly lower with gliclazide, partly due to metabolism to inactive metabolites. Moreover, a gradual increase in drug concentrations with the modified release formulations further reduces the risk for hypoglycemia when compared with the sharp increase in drug plasma concentrations observed with glibenclamide and glimepiride. A review assessed the comparative safety and efficacy of four commonly available SUs (glibenclamide, gliclazide, glimepiride, and glipizide) for the treatment of older people with type 2 diabetes for the World Health Organization's Essential Medicines List (EML) for adults.[14,15] Based on safety, efficacy, cost, and availability of SUs, the review recommended that glibenclamide should not be used in people older than 60 years of age and that gliclazide should be added to the EML for use in the elderly with type 2 diabetes (with other SUs, but not glibenclamide, as acceptable alternatives). Meanwhile, the Dutch type 2 diabetes management guideline also specifically recommends gliclazide as the preferred second-line drug, instead of SUs as a class.[16]

Other antihyperglycemic agents in diabetes management

New oral antihyperglycemic agents are emerging, including dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose cotransporter-2 (SGLT-2) inhibitors. Although cardio and renal benefits have been demonstrated for SGLT-2 inhibitors, this class would not be widely used in the elderly because of the decreased efficacy under conditions of impaired renal function, and also because of hypotension with related falls and fractures, genital infection, and weight loss with possible muscle wastage or even sarcopenia. On the other hand, DPP-4 inhibitors are quite suitable for the elderly, with good safety and tolerability profiles. However, efficacy of both classes is moderate. For most of the patients, especially those with relatively higher baseline HbA_{1c} levels, besides metformin, these new agents need to be combined with SUs to reach the glycemic target.

In the recently published STRATEGY study (Efficacy and Safety of Metformin and Sitagliptin Based Triple Antihyperglycemic Therapy),[17] Weng and coauthors firstly enrolled 5535 type 2 diabetic patients in a study of the combined effect of metformin with sitagliptin, on which less than half achieved an HbA_{1c} level under 7%. After 16 weeks, the authors randomized 2202 of those not achieving an HbA_{1c} level under 7% to either of the SUs glimepiride (mean dose, 1.8 mg) or gliclazide (mean dose, 42.3 mg), to the meglitinide repaglinide (mean dose, 2.0 mg), or to the α-glucosidase inhibitor acarbose (mean daily dose, 161.4 mg) for an additional 24 weeks, leading to a reduction in HbA_{1c} level from an approximate baseline of 7.7% by 0.65%, 0.70%, 0.61%, and 0.45%, respectively. Incidences of hypoglycemia (either requiring assistance or defined as a capillary glucose concentration ≤3.9 mmol/L with or without symptoms), as one of the predefined special interest adverse effects, were 8.9%, 3.6%, 6.1%, and 0.5% in glimepiride, gliclazide, repaglinide, and acarbose groups in the triple-therapy stage, respectively. Lower incidences of hypoglycemia were reported in both gliclazide (P=0.0003) and acarbose (P<0.0001) groups than that reported in the glimepiride group. Gliclazide is the only SU that does not bind to Epac2 (exchange protein directly activated by cAMP 2), a stimulating factor of insulin exocytosis that is involved in the amplifying pathway of insulin secretion by glucagon-like peptide-1 (GLP-1)-based therapy. As a consequence, by not binding to Epac2, gliclazide may not overstimulate insulin release. Thus, when DPP-4 inhibitors are combined with gliclazide, the risk of hypoglycemia is lower than for other DPP-4/SU combinations.

Focus on the sulfonylurea gliclazide

The efficacy and safety profiles of gliclazide MR have been well established in the long-term randomized controlled trial of ADVANCE and the real-world evidence of EASYDia (ObsErvationAl Study to analYze titration of Diamicron MR 60 mg in daily clinical practice in a large population with uncontrolled type 2 diabetes). It is also demonstrated as weight neutral in ADVANCE and EASYDia.[8,18] Additionally, the recently published TOSCA.IT trial (Thiazolidinediones Or Sulfonylureas and Cardiovascular Accidents.Intervention Trial) provided evidence of long-term cardiovascular safety.[19]

The renal protective effect demonstrated in ADVANCE and ADVANCE-ON (ADVANCE ObservatioNal study) in the intensive-treatment group, in which gliclazide MR was the backbone therapy, has been well recognized. Gliclazide MR provides renal benefits at all stages of diabetic kidney disease. More particularly, for patients with normal renal function at baseline, there is an 84% reduction in the risk of end-stage renal disease and unique primary prevention, with a 9% reduction in the risk of developing albuminuria. Abdelmoneim et al, in a Canadian nested case-control study (n=21 325), found 14% increased odds of acute-coronary-syndrome–related hospitalization and/or death with glibenclamide in elderly subjects in a ~5.4-year median follow-up, compared with gliclazide.[20] Lee et al, in a Korean retrospective cohort study (n=2854), compared glimepiride with gliclazide and found no difference in renal outcome after 4.7 years of median follow-up, although an increased risk of progression to doubling of creatinine and end-stage renal disease for patients aged 62 years or older were observed with glimepiride compared with gliclazide.[21] Another advantage of gliclazide MR is the wide treatment window, together with low hypoglycemic risk, which allows the physician to safely titrate the dosage to reach target effect.

Data from the Xrise trial (Treatment of Type 2 Diabetes with a Breakable Extended Release Gliclazide Formulation in Primary Care)[22] showed such a power in the real-life setting. The elderly may face more difficulties transitioning to new treatment regimes, so titrating the same agent they are already using would be more acceptable and easy to follow.

Conclusion

Gliclazide MR possesses many of the properties desired of a type 2 diabetes drug in the elderly. It is a simple and convenient therapy with a good efficacy and safety profile. More importantly, it is an agent with long-term cardiovascular safety and renal protective data. ■

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