"The pharmacology of sulfonylurea (SU) is modified in the setting of renal impairment, leading to the accumulation of metabolites with hypoglycemic potential. Thus, hypoglycemia is clearly an adverse effect that should be monitored in patients on SU therapy, particularly if they have renal impairment. Of note, it is also important to consider that, regardless of the diabetes treatment, renal failure is, per se, associated with the incidence of hypoglycemia."

# Sulfonylureas in specific clinical situations: renal impairment

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***This article reviews evidence on the use of sulfonylureas (SUs) in patients with renal impairment. The review begins with a focus on the pharmacology of SUs in renal impairment, with a special interest on hypoglycemia, the most important medical risk in this situation, and then provides a brief overview of national/international guideline recommendations. This is followed by a look at the impact of SUs on renal outcomes, eg, urinary albumin excretion, as well as harder end points, such as doubling of serum creatinine or end-stage renal failure.***

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## Introduction

Diabetes is a chronic condition that is dramatically increasing throughout the world.[1,2] Of note, diabetes, particularly type 2 diabetes (T2D), is associated with aging and obesity and characterized by chronic hyperglycemia, leading to long-term complications. Among them, renal impairment is common, affecting up to 40% of diabetes patients.[3] Diabetic kidney disease, which is considered the leading cause of end-stage renal disease (ESRD), is mainly due on the one hand to chronic renal lesions associated with hyperglycemia, and on the other hand to deterioration of kidney function associated with aging. The analysis of data from a national registry in Sweden shed light on the importance of the consequences of renal impairment in T2D, showing a clear, graded relationship between albuminuria status and all-cause death.[4]

The treatment of diabetes is now considered a multi-target intervention[5-7] even though diabetologists often remain largely influenced by a "glucocentric" view, where diabetes treatment mostly involves the treatment of hyperglycemia. Of interest, blood glucose targets must be individualized to each patient, and French guidelines, for example, suggest setting glycated hemoglobin ($HbA_{1c}$) targets that are higher (ie, more relaxed) in case of renal impairment, when the estimated glomerular filtration rate (eGFR) is below 30 mL/min.[8] However, whether alone or in combination with other medications such as statins and renin angiotensin aldosterone system (RAAS) blockers, the treatment of hyperglycemia remains a cornerstone of diabetes care. In T2D, in addition to lifestyle modifications, and when there is not an imperative indication for insulin, oral medications are often preferred by physicians and patients. Among oral antidiabetic drugs (OADs), sulfonylureas (SUs) are very important, often used as second-line treatment if glycemic control is not achieved with metformin or even as first-line treatment when metformin is contraindicated and/or not tolerated. As SUs are widely used and recommended, this review examines in depth the use

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of SUs in the context of chronic renal impairment. Several health outcomes such as hypoglycemia and development of renal impairment must be considered. This article reviews evidence about the use of SUs in patients with renal impairment, including legal mentions and national/international guideline recommendations. The effect of SUs on renal outcomes will also be addressed.

## Pharmacology of sulfonylurea in renal impairment

SUs are a class of drug considered insulin-producing agents, which lead to the production of insulin through direct interaction with potassium channel receptors at the surface of the pancreatic β-cells.[9] Renal impairment is thought to affect the pharmacodynamics of SU but not the effect of the drug or its metabolites on β-cells.

The management of SU in diabetic patients with renal failure was nicely reviewed by Charpentier et al[10] in 2000. Interestingly, because SUs are metabolized by the liver, renal failure does not greatly modify the pharmacokinetics of these drugs. The direct elimination of SUs through urine is limited. However, SU metabolites produced by hepatic transformation are responsible for a very significant part of the action of SU. These metabolites are eliminated mainly in urine and partly in feces. As an example, gliclazide is transformed into seven metabolites—accounting for approximately 70% of the dose administered—found in the urines. However, some data also suggest that a large proportion of a key gliclazide metabolite undergoes biliary elimination.[9] Thus, in patients with renal impairment, the modified urinary excretion of SU metabolites has a large impact on the hypoglycemic power of SU, increasing the hypoglycemic effect.

The main adverse event associated with use of SU in patients with renal failure is clearly hypoglycemia, shown to be particularly dangerous in patients with renal impairment.[11] Thus, the degree of renal impairment must be taken into account, as it is a risk factor for hypoglycemia both in type 1 diabetes (T1D) and T2D patients.[12,13] It is also important to be attentive to patients with end-stage renal failure, as elimination half-life of SUs and their metabolites is increased in uremic patients, leading to a potentially dangerous accumulation.

Finally, the legal mentions of these drugs clearly indicate the contraindication of SU in severe renal failure and that SU use should probably be stopped in patients with an eGFR lower than 30 mL/min, considering that other OADs with a lower risk of hypoglycemia have an approved indication in this clinical situation.

### Selected abbreviations and acronyms

| | |
|---|---|
| ADVANCE | Action in Diabetes and Vascular disease: PreterAx and DiamicroN Controlled Evaluation [study] |
| ADVANCE-ON | ADVANCE ObservatioNal study |
| CANVAS | CANagliflozin cardioVascular Assessment Study |
| CAROLINA | CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes |
| DCCT/EDIC | Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications [study] |
| DIALOG | French Observational Survey to Assess Hypoglycemia in Insulin-treated Diabetic Patients |
| eGFR | estimated glomerular filtration rate |
| ESRD | end-stage renal disease |
| $HbA_{1C}$ | glycated hemoglobin |
| LEADER | Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results |
| NICE | National Institute for Health and Care Excellence |
| OAD | oral antidiabetic drug |
| SU | sulfonylurea |
| T2D | type 2 diabetes |
| UKPDS | United Kingdom Prospective Diabetes Study |

## Clinical consequences: risk of hypoglycemia

As explained above, the pharmacology of SU is modified in the setting of renal impairment, leading to the accumulation of metabolites with hypoglycemic potential. Thus, hypoglycemia is clearly an adverse effect that should be monitored in patients on SU therapy, particularly if they have renal impairment. Of note, it is also important to consider that, regardless of the diabetes treatment, renal failure is, per se, associated with the incidence of hypoglycemia. Indeed, the incidence of severe hypoglycemia was clearly shown to be associated with renal failure in the ADVANCE trial (Action in Diabetes and Vascular disease: PreterAx and DiamicroN Controlled Evaluation)[13] and also in the DIALOG study (French Observational Survey to Assess Hypoglycemia in Insulin-treated Diabetic Patients), an observational study in T1D and T2D patients.[12]

In this context, the population-based cohort study from England published by Van Dalem[14] rather recently looked at new users of OAD and subsequent hypoglycemia. Data were derived from the clinical practice research data link containing over 11 million patients, including 120 803 patients with initial OAD treatment. The mean duration of follow-up was 3.7 years in patients aged 67 years. Of note, an indication bias is probable in this observational study where more SU users had poorer renal function than metformin users or users of other non-insulin diabetic agents. Patients on SU-only treatment had a hazard ratio of 2.5 (with metformin-only treatment as the reference group). Interestingly, there was a clear, graded relationship between daily dose and risk of hypoglycemia. Thus, those patients using the highest daily dose had a more than 3 times greater risk for hypoglycemia than metformin-only users.

In addition, the risk of hypoglycemia was clearly increased when derangement of renal function was more marked (eGFR

lower than 30 mL/min/1.73m²), intermediate in those with renal function defined as an eGFR of 30-59 mL/min/1.73m², and lower in those with renal function defined as an eGFR >60 mL/min/1.73m².

The authors also examined the relationship between hypoglycemia and the different SUs. In a fully adjusted model that took into account age, sex, body mass index, alcohol use, smoking status, cardiovascular disease, chronic heart failure, and use of loop diuretics, the adjusted hazard ratio compared with current metformin-only use was 1.97 (1.35-2.87) in glimepiride users, 7.48 (4.89-11.44) in glibenclamide users, 2.11 (1.24-3.58) in glipizide users, and 2.50 (2.21-2.83) in gliclazide users.

Despite that study's very large scale, it did not provide a very high level of evidence about hypoglycemia related to SU and other drugs in patients with renal impairment. A direct head-to-head comparison of sitagliptin and glipizide treatments in patients with renal failure gave a higher level of evidence.[15] In that controlled trial including 426 T2D patients with renal impairment (approximately one-fourth of the study population had severe renal failure) randomized at a 1 to 1 ratio to sitagliptin or glipizide treatment groups, glipizide was noninferior to sitagliptin with regard to effect on $HbA_{1c}$ levels. However, the 1-year incidence of hypoglycemia was greater in glipizide-randomized patients than in sitagliptin-randomized patients: 17% versus 6.2%. The same statistically significant trend was found for severe hypoglycemia, which was twice as frequent with glipizide (2.8%) compared with sitagliptin (1.4%).

Though not a primary outcome, the change in eGFR did not significantly differ between the two treatment arms.

## Guidelines on renal impairment and antidiabetic drugs

The international Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend avoiding SUs that are mainly excreted through the urines (eg, glyburide/glibenclamide). However, SUs that are mainly metabolized in the liver, such as gliclazide, can be used at usual doses in patients with renal impairment, with potential dose reduction for those with an eGFR under 30 mL/min/1.73m².[16]

In December 2015, the National Institute for Health and Care Excellence (NICE) issued an updated guideline on management of T2D in adults. Important new information was given about the use of SU in such patients, now recommended as a first intensification step.[17] In those patients with renal impairment, no clear message is given about the use of SUs, but the general aim to avoid overtreatment that leads to hypoglycemia must be kept in mind.

The French language diabetes society – SFD *(Société Francophone du diabète),* issued an expert consensus of management of diabetic patients with impairment of renal function in 2011.[18] Altogether, the recommendations were rather weak regarding SU utilization and renal impairment. They concluded that the use of SU was possible with chronic renal failure but required a dosage adjustment in order to limit the hypoglycemic risk (grade B).

In the French guidelines from the National Authority for Health—HAS *(haute autorité de santé)*—on drug strategy for glycemic control in T2D patients, issued in 2013, we were reminded that renal failure is of special interest for hypoglycemia.[19] Treatment must thus take renal function into account, and the drug dosage adapted, particularly for metformin. In patients with GFR below 30, acceptable drugs are insulin, repaglinide, α-glucosidase inhibitor, and DPP-4 inhibitor with adapted dosage. SUs are not to be given in this situation.

## Sulfonylurea and renal outcomes

Several studies have examined the relationship between SUs and renal outcome. Among several important issues in this context are the relevant end points indicative of renal protection. The development of microalbuminuria and the progression to proteinuria are important end points, largely considered in older trials. However, with the recent identification of an important decrease in renal function in patients without albuminuria,[20] the preferred hard end point for renal function should be modification of eGFR rather than a change in albumin/protein excretion, although the two are complementary.[21]

The composite end point consisting of time to renal replacement therapy and sustained doubling of baseline serum creatinine or renal death (whichever comes first) should be investigated in priority, even though it is rarely significant.

In the UKPDS trial (United Kingdom Prospective Diabetes Study), patients considered at early stages of T2D were randomly assigned to intensive blood glucose therapy with either insulin or SU (here glibenclamide, chlorpropramide, or glipizide) or to a more liberal strategy to manage blood glucose primarily with diet. The randomization was rather complex, as people from the control nonintensive-treatment group with symptoms of frank hyperglycemia could enter a secondary randomization to receive insulin or one of the three SUs mentioned previously.[22]

The general findings of the UKPDS were that in the long term, intensive blood glucose control allowed a significant reduction in $HbA_{1C}$ by 0.9%, leading to a reduced incidence of microvascular complications, including the occurrence of microalbuminuria and proteinuria. When considering harder end points, as previously mentioned, the doubling of serum creatinine was very significantly decreased with a 74% reduction in relative risk. The analysis of the specific effect of SU vs other options in the intensive therapy group did not show a beneficial effect of SUs over other options.[22]

**Effects of intensive compared with standard glucose control on albuminuria**

| Outcome | Intensive, *n* (%) | Standard, *n* (%) | Hazard ratio (95% confidence interval) | *P* value |
|---|---|---|---|---|
| New-onset microalbuminuria | 1318 (33.5) | 1434 (36.3) | 0.91 (0.85-0.98) | 0.012 |
| New-onset macroalbuminuria | 162 (3.0) | 231 (4.3) | 0.70 (0.57-0.85) | 0.0004 |
| Progression of albuminuria by ⩾1 stage[a] | 1298 (23.3) | 1410 (25.3) | 0.90 (0.84-0.97) | 0.0077 |
| Regression of albuminuria by ⩾1 stage[b] | 1003 (61.2) | 914 (56.3) | 1.15 (1.05-1.26) | 0.0020 |
| Regression to normoalbuminuria | 922 (56.3) | 814 (50.2) | 1.20 (1.09-1.31) | 0.0002 |

[a]From normoalbuminuria to either microalbuminuria or macroalbuminuria, or from microalbuminuria to macroalbuminuria.
[b]From macroalbuminuria or microalbuminuria to normoalbuminuria, or from macroalbuminuria to microalbuminuria.

***Table I.*** *Renal outcome associated with blood glucose intensive therapy in the ADVANCE trial.*

***Abbreviation:*** *ADVANCE, Action in Diabetes and Vascular disease: PreterAx and DiamicroN Controlled Evaluation.*
***After reference 23:*** *Perkovic et al.* Kidney Int. *2013;83(3):517-523. © 2013. International Society of Nephrology.*

Of great interest, the UKPDS post monitoring trial[24] was very helpful for analyzing the long-term effect of the initial intervention of the UKPDS trial. In fact, after the completion of the trial, participants were invited to take part in a nonrandomized observational follow-up lasting 10 years. No difference regarding $HbA_{1c}$ was found at that time between patients initially randomized to intensive or conventional treatment. This helped to appreciate the so-called "memory effect": 10 years of equivalent blood glucose control were not sufficient to fade the beneficial effect on complications observed in the first years of the trial. Thus, regarding renal outcomes, those patients randomized to intensive therapy were still less likely to have a renal event, confirming initial results issued at the end of the UKPDS princeps trial. Of interest, this result was concordant with the findings from the DCCT/EDIC study (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications) performed in T1D patients, also confirming the ultimate translation of positive prevention on renal intermediate outcomes, such as urinary albumin excretion, to harder end points, such as the development of renal impairment.[25]

On the basis of a recent review, concordant conclusions were drawn from an observational study performed in the US Veterans Administration medical system.[26] The comparative effectiveness of incident OADs on kidney function was examined using the Veterans Administration database, considering a retrospective cohort of over 93 000 diabetic patients with an eGFR of 60 mL/min/1.73m² or better. The primary composite end point was a 25% or greater decline in eGFR from baseline or a diagnosis of ESRD. Approximately 61 000 patients were on metformin, 30 000 on SU, and a very small proportion on rosiglitazone. The annual cumulative incidence of the composite outcome was significantly higher for SU than for metformin: 1.20 (1-1.28). When reanalyzing data considering the propensity score–matched analysis, results where rather similar. Unfortunately, SU prescription was considered as a whole and it was not possible to investigate any specific differences between the different SU medications usually prescribed in the United States.

Considering the US Veterans Administration medical system, Hung et al also compared the second-line agents for the treatment of T2D in the prevention of kidney function decline.[27] Comparing insulin and SU, a primary outcome very similar to that in the previously mentioned paper was considered. There was a borderline nonsignificant increased risk in insulin versus SU users: adjusted hazard ratio of 1.27 (0.99-1.63).

Lastly, we compared the "intensive therapy" arm of the ADVANCE trial, based on gliclazide modified release (gliclazide MR) and the "conventional" arm based on any therapy but gliclazide MR.[28] At the end of follow-up, more than 90% of ADVANCE participants randomized to the intensive-therapy group, in which the $HbA_{1c}$ target was 6.5%, were on gliclazide MR, whereas 57% of participants in the standard group were on other SUs. Although the aim of the study was not to compare two treatment arms, we must consider that the renal outcome was clearly and significantly less frequent in the intensive group than in the standard group *(Table I).*[23]

The result must be viewed with caution, as the aim of this trial was not to compare gliclazide MR with other drugs, but rather to compare an intensive strategy (based on this drug) including a target of $HbA_{1c}$ at 6.5% vs a standard strategy (not using gliclazide MR) that had a more liberal blood glucose target.

Similar to the UKPDS post-trial monitoring, the ADVANCE trial also evaluated if an additional 5-year follow-up with pure observational design resulted in a modified impact on study outcomes *(Table II, page 146).*[29] As in the princeps trial, those patients initially randomized to intensive therapy had a persistent reduced risk for renal outcomes even though blood glucose was no longer different between initial allocation groups during the ADVANCE-ON (ADVANCE ObservatioNal study) study period.

A trial comparing SU versus other drugs with regard to renal outcome is still expected. The CAROLINA trial (CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes) is designed to assess whether

| Study Cohort and Outcome | In-Trial Period | | | | Overall Follow-up | | | |
|---|---|---|---|---|---|---|---|---|
| | Intensive control (N=5571) | Standard control (N=5569) | Hazard ratio (95% CI) | *P* value | Intensive control (N=5571) | Standard control (N=5569) | Hazard ratio (95% CI) | *P* value |
| | *no. (%)* | | | | *no. (%)* | | | |
| **Glucose-control cohort** | | | | | | | | |
| Death from any cause | 498 (8.9) | 533 (9.6) | 0.93 (0.83–1.06) | 0.28 | 1139 (20.4) | 1126 (20.2) | 1.00 (0.92–1.08) | 0.91 |
| Major macrovascular events | 557 (10.0) | 590 (10.6) | 0.94 (0.84–1.06) | 0.32 | 1089 (19.5) | 1077 (19.3) | 1.00 (0.92–1.08) | 0.93 |
| Death from cardiovascular causes | 253 (4.5) | 289 (5.2) | 0.88 (0.74–1.04) | 0.12 | 490 (8.8) | 498 (8.9) | 0.97 (0.86–1.10) | 0.63 |
| Myocardial infarction | 190 (3.4) | 188 (3.4) | 1.01 (0.83–1.24) | 0.92 | 368 (6.6) | 354 (6.4) | 1.02 (0.89–1.19) | 0.75 |
| Stroke | 236 (4.2) | 245 (4.4) | 0.96 (0.81–1.15) | 0.68 | 491 (8.8) | 477 (8.6) | 1.01 (0.89–1.15) | 0.82 |
| Major clinical microvascular events† | 212 (3.8) | 246 (4.4) | 0.86 (0.72–1.03) | 0.11 | 390 (7.0) | 417 (7.5) | 0.92 (0.80–1.05) | 0.23 |
| End-stage renal disease | 7 (0.1) | 20 (0.4) | 0.35 (0.15–0.83) | 0.02 | 29 (0.5) | 53 (1.0) | 0.54 (0.34–0.85) | 0.007 |
| Death from renal causes | 17 (0.3) | 20 (0.4) | 0.85 (0.45–1.62) | 0.62 | 48 (0.9) | 53 (1.0) | 0.89 (0.60–1.31) | 0.56 |
| Retinal photocoagulation or diabetes-related blindness | 195 (3.5) | 216 (3.9) | 0.90 (0.74–1.09) | 0.29 | 332 (6.0) | 337 (6.1) | 0.97 (0.83–1.13) | 0.69 |
| Major hypoglycemia | 150 (2.7) | 81 (1.5) | 1.85 (1.42–2.42)‡ | <0.001 | 445 (8.0) | 373 (6.7) | 1.19 (1.04–1.36)‡ | 0.009 |

† The definition of major clinical microvascular events was based on the ADVANCE-ON trial protocol, which included in that category a requirement for renal-replacement therapy, death from renal disease, and development of severe diabetes-related eye diseases.
‡ This is the relative risk rather than the hazard ratio. The relative risk was estimated with the use of a log-binomial model.

***Table II.*** *Renal outcome associated with blood glucose intensive therapy in the ADVANCE-ON study.*
***Abbreviation:*** *ADVANCE-ON, Action in Diabetes and Vascular disease: PreterAx and Diamicron Controlled Evaluation ObservatioNal study.*
***After reference 29:*** *Zoungas S et al.* N Engl J Med. *2014;371(15):1392-1406.© 2014. Massachusetts Medical Society.*

linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is noninferior to a SU, glimepiride, on a combined cardiovascular outcome (3-point major adverse cardiovascular events [MACE-3P]).[30] Such a cardiovascular end point was also the primary outcome of other cardiovascular outcome studies; however, a secondary renal outcome is now very often predefined.

This was the case for the recently published LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results) and CANVAS program (CANagliflozin cardioVascular Assessment Study). If this end point is now considered vs DPP-4 inhibitors, even in a post-hoc analysis, the CAROLINA trial might bring some evidence regarding the respective renal efficacy of linagliptin and glimepiride.

## Limitations and conclusions

This article is based on a selection of key references and cannot be considered a systematic review. In addition, we focused on SUs limited to chlorpropramide, glipizide, gliclazide, glibenclamide (often named glyburide, in the American literature), and glimepiride.

Of note, some new evaluation techniques have emerged to compare medications that were not directly evaluated in a head-to-head comparison, such as network analysis. To the best of my knowledge, no such data have been published on renal outcome and OADs. The implementation of the CAROLINA trial—comparing canagliflozin and glimepiride—regarding MACE (but also renal events as secondary outcomes) will be another important result to help tailor treatment with OADs in patients with T2D.

In clinical practice, SUs are a widely prescribed class of OAD. SU drugs can be used in patients with renal impairment, provided a dosage adaptation is performed. Particular attention must be given to the risk for hypoglycemia. A head-to-head comparison of SU with other drugs and even between the different SUs within the class is still awaited, even though DDP-4 inhibitors have been shown to be less prone to provoke hypoglycemia than glipizide in patients with moderate-to-severe renal failure.

Some key points to remember are that hypoglycemia is the main risk factor associated with SU in renal impairment; that in case of severe renal impairment, SUs should be avoided and treatment chosen from other medications that pose a smaller hypoglycemic risk; and that SUs (especially gliclazide) have been shown to provide a significant benefit for renal outcome in the ADVANCE trial. ■

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