Diabetes Epidemiology and Management 1 (2021) 100002

Contents lists available at ScienceDirect

Diabetes Epidemiology and Management

journal homepage: www.elsevier.com

Review

Sulphonylureas in the management of type 2 diabetes: To be or not to be?

André J. Scheen

Division of Diabetes, Nutrition and Metabolic Disorders, CHU Liège, and Division of Clinical Pharmacology, Center for Interdisciplinary Research on Medicines (CIRM), Liège University, Liège, Belgium

ARTICLE INFO

Article history:
Received 5 February 2021
Accepted 9 February 2021
Available online 26 February 2021

Keywords:
Cardiovascular safety
Guidelines
Hypoglycaemia
Oral antidiabetic drug
Sulphonylurea

ABSTRACT

Sulphonylureas (SUs) for a long time occupied an essential role in the management of type 2 diabetes (T2D) as an alternative or a complement to metformin. However, the launch of new oral antidiabetic drugs (OADs), firstly DPP-4 inhibitors (gliptins) and more recently SGLT2 inhibitors (gliflozins), has markedly changed the scene. Indeed, in contrast to SUs, these new OADs (of course more expensive) offer the advantage of a very low risk of hypoglycaemia and a beneficial impact on bodyweight. Furthermore, while gliptins showed good cardiovascular safety, gliflozins have proven to exert both a cardiovascular and renal protection in patients at high risk. This article discusses the current place to be reserved to SUs in the treatment of T2D, after a short recall about the risk of hypoglycaemia and the cardiovascular safety. Contrasted positions still remain in the international literature which translate into different guidelines between countries, especially due to economic constraints. SUs keep a place in the management of T2D, yet it becomes more and more limited. For sure, SU should be avoided among elderly frailty people and patients at high risk of hypoglycaemia.

Introduction

Sulphonylureas (SUs), commercialized in the late fifties, were the first pharmacological class of oral antidiabetic agents (OADs). They were discovered in France by Auguste Loubatières and his team. These agents stimulate insulin secretion by closing potassium channels in beta-cells of Langerhans islets. SU-stimulated insulin secretion is independent of plasma glucose level. As a consequence, SUs are associated with a high risk of hypoglycaemia [1,2]. For a long time, the only drug alternative was biguanides. Among this pharmacological class, metformin is the only medication available in clinical practice because other ones were withdrawn from the market because of an excessive risk of lactic acidosis [3]. Most obvious advantages of SUs for the management of type 2 diabetes (T2D) are their low cost as well as a large clinical experience since more than 60 years. During this long period, several generations of SUs were commercialized [2]. SUs belonging to more recent generations offer some advantages compared to agents of the first generation, yet without completely avoiding the risk of hypoglycaemia.

In the last decade, dipeptidyl peptidase-4 inhibitors (DPP-4is or gliptins) were commercialized and are increasingly used in clinical practice [4]. More recently, sodium-glucose cotransporter type 2 inhibitors (SGLT2is or gliflozins) became also available for the treatment of T2D [5]. These new OADs offer the advantage of causing a negligible risk of hypoglycaemia. Furthermore, DPP-4is are weigh neutral and SGLT2is are generally associated with a moderate weight loss resulting from increased glucosuria. These weight effects contrast with those of SUs, which most often cause weight gain (especially soon after the initiation of the therapy), an effect not well accepted by T2D patients who are generally overweight or obese. Finally, gliptins have proven their cardiovascular (CV) safety [4,6] while gliflozins are now recognized to be associated with a reduction of major cardiovascular events (MACEs) and hospitalisations for heart failure as well as with a specific renal protection, especially in T2D patients with albuminuria [6,7]. Of major interest, all these favourable effects are independent of glucose control [7]. In the same time, CV safety of SUs [8,9] still remains a matter of debate [10–12], as discussed later.

Given all these findings, while metformin keeps a privileged place as first-line drug in the pharmacological therapy of T2DM (even if it was recently challenged in patients at high CV risk in cardiology guidelines) [13], the question of which place should be reserved to SUs compared to gliptins and gliflozins deserves further evaluation, besides the strict pharmaco-economic (lowest cost of SUs !) point of view.

E-mail address: andre.scheen@chuliege.be

https://doi.org/10.1016/j.deman.2021.100002

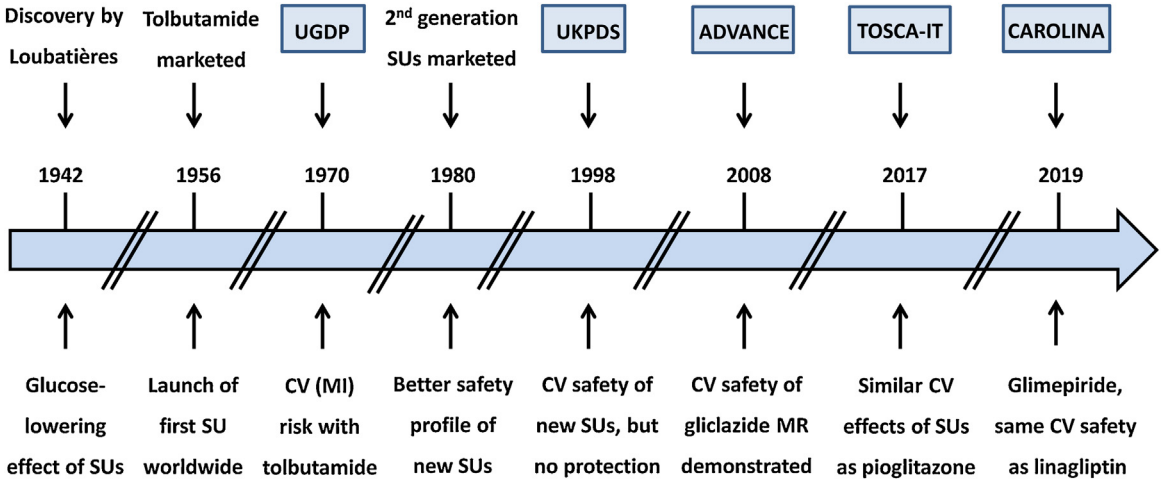

Fig. 1. Key steps of the history of sulphonylureas. CV : cardiovascular. MI : myocardial infarction. MR : modified release. SU : sulphonylureas.

SUs and risk of hypoglycaemia

of a glucose-independent stimulation of insulin secretion, carry a risk of hypoglycaemia. This represents a first argument in favour of metformin, a molecule that is not associated with hypoglycaemic episodes [3]. SUs can cause severe hypoglycaemias, which may progress to loss of consciousness and coma requiring emergency hospitalisations, with a relative risk at least multiplied by 3 versus other OADs [14]. This risk is higher when SUs are introduced in patients with only modestly increased glycated haemoglobin (HbA1c) or in elderly frailty patients with T2D. As a consequence, SUs should be stopped («therapeutic de-escalation") in patients at high risk of hypoglycaemia. Reducing the dose or even stopping the drug should also be considered in people who have a (too) good glucose control with low HbA1c levels, for instance below 6.5 % (48 mmol/mol), or in some cases < 7 % (53 mmol/mol) [15]. These excellent results may make clinicians happy but may expose SU-treated T2D patients to a high risk of hypoglycaemia.

With the commercialization of DPP-4is, SUs have now serious competitors. Indeed, when added to metformin monotherapy, DPP-4is are associated with a 5 to 10-fold lower risk of hypoglycaemias, with almost no severe episodes, for a similar quality of glucose control compared with SUs. This difference has been observed both in randomised controlled trials (RCTs) [16,17] and in real-life observational studies as shown, for instance in a study that used a French health insurance database [18]. As far as SGLT2is are concerned, a meta-analysis of five RCTs involving 4 300 patients with T2D not well controlled with metformin alone also showed a risk of hypoglycaemia reduced by almost 10 times with gliflozins versus SUs [19].

A question, which arose already a long time ago [20], is to determine whether all SUs share a same risk of hypoglycaemia when combined with metformin. A first meta-analysis published in 2013 did not report major differences between the different molecules [14]. However, a network meta-analysis, which was published two years later, showed a lower risk of hypoglycaemia with gliclazide [21]. These findings confirm the results of the GUIDE head-to-head trial that showed a lower risk of hypoglycaemia with gliclazide than with glimepiride [22]. In the ADVANCE ("*Action in Diabetes and VAscular disease: preterax and diamicroN modified release Controlled Evaluation* study"), which analysed the effects of an intensified glucose control with gliclazide modified release, the incidence of severe hypoglycaemic episodes was uncommon, yet more frequent in the intensive-control group (2.7 % versus 1.5 % in the standard-control group) [23]. A UK database collected in real-life conditions reported an increased risk of hypoglycaemia with glibenclamide (glyburide) and glimepiride compared with gliclazide and glipizide [24].

Another important clinical question is to know whether SU-induced hypoglycaemic episodes, especially severe episodes, could increase the risk of MACEs. A UK observational study showed that the shift from metformin monotherapy to a metformin-SU combination is associated with a 25–30 % increase of myocardial infarctions and of all-cause mortality, while, in the same time, a seven-fold increase of severe hypoglycaemia was noticed; however, an obvious causal relationship could not be demonstrated [25]. In a post-hoc analysis of the already cited ADVANCE study [26], the occurrence of severe hypoglycaemia was associated with an increased risk of MACEs and death rate, but again a clear-cut direct relationship could not be established; the conclusion of the Authors was that severe hypoglycaemic episodes should be considered as a marker of vulnerability of exposed patients rather than a causal factor of MACEs and mortality [26].

SUs and cardiovascular risk

The CV safety of SUs remains a matter of debate, after more than 40 years of controversies [10,11], even if recent studies reported reassuring findings (Fig. 1). The CV safety of SUs was first challenged by the results of the US UGDP (*"University Group Diabetes Program"*) [27]. Indeed, with a first-generation SU (tolbutamide), an increased percentage of mortality linked to a myocardial infarction was noticed compared to a placebo; nevertheless, the number of events was low, confounding factors were disturbing and the study was criticized from a statistical point of view [28]. The UKPDS (*"United Kingdom Prospective Diabetes Study"*) was planned at the end of the seventies to investigate the benefit/risk ratio of an intensification of glucose control with insulin or more recent SUs (chlorpropamide, glibenclamide/glyburide) [29]. Reassuring results were reported with SUs (Table 1), yet in the intensive group, the improvement of glucose control was not associated with a significant reduction of the incidence of CV events, especially myocardial infarction [29]. This observation contrasted with a significant reduction in CV events in a subgroup of obese patients treated with metformin [30]. Of note, in a limited subgroup of patients with newly diagnosed T2D who were treated with a metformin-SU combination, a worse CV prognosis was reported. This intriguing finding was attributed by the investigators to be due to chance [30], yet similar observations were collected in a meta-analysis of nine observational studies [31].

Table 1
Randomised controlled trials that investigated the cardiovascular safety of sulphonylureas. Results are expressed by hazard ratio (with 95 % confidence intervals) of SUs versus comparators.

RCTs	Sulphonylurea	Comparator	Follow-up (years)	N SU/ comparator	All cause mortality	CV mortality	Myocardial infarction	Stroke	MACEs
UKPDS [29]	Chlorpropamide,	Diet alone	11.1	619/1138	1.02 (0.82–1.27)	NA	0.87 (0.68–1.12)	1.01 (0.65–1.58)	NA
	Glibenclamide	Diet alone	11.1	615/1138	0.91 (0.73–1.15)	NA	0.78 (0.60–1.01)	1.38 (0.52–2.08)	NA
ADVANCE [23]	Modified release gliclazide (intensified arm)	Standard treatment	5.0	5571/5569	0.93 (0.83–1.06)	0.88 (0.74–1.04)	0.98 (0.78–1.23) non fatal	1.02 (0.85–1.24) non fatal	0.94 (0.84–1.06)
TOSCA-IT [38]	Glibenclamide Glimepiride Gliclazide	Pioglitazone	4.8	1493/1535	0.91 (0.62–1.33)	NA	1.15 (0.65–2.08) non-fatal	1.27 (0.65–2.44) non-fatal	1.04 (0.79–1.35)
CAROLINA [40]	Glimepiride	Linagliptin	6.3	3010/3023	1.10 (0.94–1.28)	1.00 (0.80–1.23)	0.97 (0.78–1.22)	1.16 (0.89–1.52)	1.02 (0.88–1.19)

HR: hazard ratio. CI: confidence interval. MACEs: major cardiovascular events. NA: not available. NS: not significant. RCTs: randomised controlled trials. SU: sulphonylurea.

Table 2
Two selected meta-analyses of randomised controlled trials and observational studies that investigated the effects of sulphonylureas versus comparators on cardiovascular complications.

References	Type of studies	Mode of comparison	All-cause mortality	CV mortality	Myocardial infarction	Stroke	MACEs
Versus metformin							
Monami et al 2013 [34]	2-4 RCTs	MH-OR	1.29 (0.80–2.13)	NA	NA	NA	0.95 (0.34–2.70)
Bain et al 2017 [35]	RCTs + observational studies	HR	1.37 (1.03–1.84)	1.38 (0.90–2.16)	1.21 (0.78–1.99)	1.40 (0.92–2.22)	NA
Versus DPP-4is							
Monami et al 2013 [34]	7 RCTs	MH-OR	1.40 (0.74–2.65)	1.50 (0.49–4.52)	NA but NS	4.51 (1.60–12.66)	1.85 (1.20–2.87)
Bain et al 2017 [35]	RCTs + observational studies	HR	2.03 (1.22–3.58)	4.42 (1.92–13.00)	2.54 (1.14–6.57)	9.40 (3.27–41.90)	NA

CV: cardiovascular. HR: hazard ratio. MACEs: major cardiovascular events. M–H OR: Mantel-Haenszel odds ratio. NA: not available. NS : not significant. RCTs: randomised controlled trials.

Table 3
Advantages et disadvantages of sulphonylureas compared with newer oral antidiabetic agents.

	Sulphonylureas	Gliptins	Gliflozins
Advantages	Good lowering-glucose activity	Excellent tolerance	Negligible hypoglycaemia
	Long experience	Negligible hypoglycaemia	Weight loss
	Low cost	Weight neutrality	Reduction in blood pressure
		Confirmed CV safety	CV protection Reduction in heart failure Renal protection
Disadvantages	Hypoglycaemia	Lower glucose-lowering potency	Genital mycotic infections Euglycaemic ketoacidosis
	Weight gain	Higher cost	Other (rare) various safety concerns
	Controverted CV safety		Higher cost

CV : cardiovascular.

Afterwards, several observational studies that compared different monotherapies showed that patients with T2D treated with SUs have a higher risk of CV events and mortality when compared to patients treated with metformin and the difference is even more marked when compared with gliptins. Differences were still present after appropriate matching for a number of known confounding factors (age, renal function, ...) to avoid, as much as possible, biases inherent to observational retrospective studies [12,32,33]. Results were summarized in several meta-analyses, two of them are depicted in Table 2 [34,35]. These real-life findings, in addition to those from some RCTs, have contributed to discredit the use of SUs in clinical practice, particularly among patients with antecedents of CV disease or at risk to develop such complications.

However, three large prospective RCTs gave reassuring results regarding the use of SUs in the management of T2D (Table 1) [36]. First, ADVANCE showed that the intensification of glucose control with gliclazide modified release was not associated with an increase in the incidence of CV events (and, as already mentioned, a very low risk of severe hypoglycaemia was recorded in the SU-treated group in this study) [23,37]. Second, TOSCA-IT (*"Thiazolidinediones Or Sulphonylureas and Cardiovascular Accidents-Intervention Trial")* [38] reported that the incidence of CV events was comparable in patients treated with a SU (glibenclamide, glimepiride or gliclazide) or treated with pioglitazone, a drug that showed some CV benefits in the PROactive (*"PROspective pioglitAzone Clinical Trial In macroVascular Events")* study [39]. And, third, CAROLINA (*"CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes")* [40], probably the most recent convincing trial, showed no difference in the incidence of MACEs in patients at high CV risk with T2D treated with the glimepiride, a SU of last generation, or the DPP-4i linagliptin, a medication whose CV safety versus placebo was demonstrated in the CARMELINA (*"CARdiovascular and renal Microvascular outcomE study with LINAgliptin in patients with type 2 diabetes mellitus at high vascular risk")* trial [41].

As for hypoglycaemia, already discussed above, it is important to know whether all SUs share the same CV safety profile [42]. Indeed, first-generation SU most probably showed a higher risk compared with second-generation, and not used anymore. Among SUs of second generation, it has been recommended not to use glibenclamide (glyburide) because this SU causes more hypoglycaemia (see above), interferes with ischemic preconditioning [8], and may be associated with an increased incidence of CV events compared with other second-generation SUs [43]. However, this conclusion may be challenged by the results of recent studies. For instance, an analysis of a UK database failed to show any significant differences in CV events between long-acting SUs (glibenclamide/glyburide, glimepiride) and short-acting SUs (gliclazide, glipizide) [24]. In a network meta-analysis of 18 studies, the relative risk of CV-related mortality (0.60, 95 % CI 0.45-0.84) was significantly lower with gliclazide compared with glibenclamide (glyburide), but not significantly different compared with glimepiride [44]. Recent review papers summarized emerging evidence suggesting better CV profile of gliclazide over other SUs [45,46]. However, in absence of a dedicated head-to-head trial, this remains an open question.

Nevertheless, because of the neutral results of ADVANCE [23,37] and of CAROLINA [40], available findings should favour the use of gliclazide modified release or glimepiride, two SUs that proved CV safety in these two large prospective studies. However, divergent findings still remain and unanimity is not obvious in this matter [24].

Two contrasted position statements

Currently, two opposing opinions are present in the literature. Some people consider that there is almost no more place for SUs, when taking into account alternative new medications that showed advantages compared with older agents (Table 3) [47]. On the contrary, others made plea for maintaining a right place of SUs in the therapeutic armamentarium of T2D [48–50], especially in countries with limited resources [51]. As already mentioned, gliclazide modified release has some supporters [45,46,52], especially, but not exclusively, after the publication of the results of ADVANCE [23,37]. Similarly, the recent favourable results of CAROLINA [40] have contributed to increase a positive opinion regarding the SU glimepiride [53].

Considering these contrasting opinions, it is not astonishing that the use of SUs in clinical practice is highly different between countries, as reflected by differences between national and international guidelines [54] (see below). It is interesting to note that 40%–50 % of patients with T2D included in the CV outcome trials with DPP-4is or SGLT2is were treated with a SU (alone or more often combined with metformin and/or insulin) as background therapy. Furthermore, SUs were maintained throughout the trials in most instances and benefits were also shown in these patients [6]. The proportion of T2D patients treated with SUs is the highest in countries with limited resources where more recent but expensive medications are not available or not reimbursed by the social security. As an example, in a prospective observational multicentre study carried out in Sub-saharan Africa, the metformin-SU combination concerns almost the totality of T2D patients treated with a dual therapy [55]. Such an association keeps also a privileged place in numerous African English-speaking countries, countries from Asia (including India) and Middle-East [56].

SUs in recent diabetes guidelines

Differences in the place of SUs in international and national guidelines have been examined in a dedicated paper that also pro-

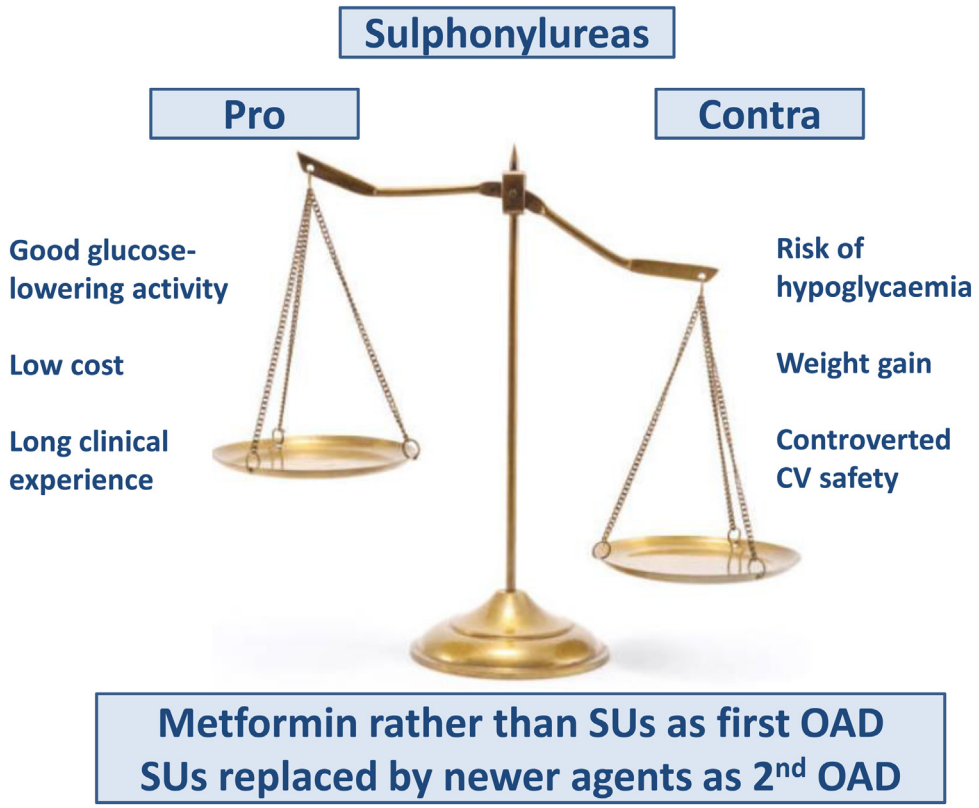

Fig. 2. Benefit-risk balance regarding the use of sulphonylureas for treating type 2 diabetes. CV : cardiovascular. OAD : oral antidiabetic drug. SU : sulphonylureas.

posed a critical appraisal of the reasons for these differences [54]. In the present paper, only most important international guidelines will be discussed. Detailed analysis of other guidelines such as the American Association of Clinical Endocrinologists (AACE), the Canadian Diabetes Association (CDA) and the UK National Institute for Health and Care Excellence (NICE) guidelines, as well as other national guidelines, may be found elsewhere [54].

In the guidelines developed by the World Health Organization to provide guidance on selection of medicines for treatment intensification in T2D, the first recommendation is to give a SU to patients who do not achieve glycaemic control with metformin alone or who have contraindications to metformin (strong recommendation, moderate-quality evidence) [57]. SUs should be added to metformin in patients not at HbA1c target and SUs with a better safety record for hypoglycaemia (e.g. gliclazide) should be preferred in patients for whom hypoglycaemia is a concern [57].

The International Diabetes Federation (IDF) Guidelines Task Force recommends metformin as the preferred first-choice with regard to monotherapy, but other glucose-lowering drugs are recommended if metformin is not tolerated, preferably an SU (not glibenclamide), an alpha-glucosidase inhibitor or a DPP-4i, and similar choices are recommended for dual (second-line) therapy after metformin failure [58,59].

In the ADA/EASD (American Diabetes Association/ European Association for the Study of Diabetes) consensus report, published in 2018 [60] and confirmed in 2020 [61], metformin is recommended as initial therapy, with further management based on whether or not T2D patients have established atherosclerotic CV disease, chronic kidney disease and/or heart failure. In those patients without such complications, three subgroups are individualized: (i) patients with a compelling need to minimise hypoglycaemia, for whom SUs are last-choice therapy; (ii) those with a compelling need to minimise weight gain or promote weight loss, for whom SUs are also last-choice therapy; and (iii) those where cost is a major issue, who are the only patients for whom use of SUs after metformin is recommended. In T2D patients with aforementioned CV or renal complications, SUs are not recommended or only proposed as the last choice of glucose-lowering drug therapy [60,61].

Of note, most of these recommendations are consensus-based rather than evidence-based guidelines. Several reasons may explain the differences between those guidelines: the target audience (general practitioners versus specialists), cost-effectiveness (considerations of the cost of implementing the guidelines), access to therapies (e.g. gliclazide, which is the preferred SU in numerous European and international guidelines, is not available in the USA and thus not highlighted in American guidelines), ease of implementation (taking into account the complexities involved in implementing one treatment strategy over another), outcomes to be considered (subjective short-term quality outcomes versus long-term objective outcomes) ... [54]. The ADA-EASD consensus report does not provide guidelines for particular drug classes among patients without compelling indications resulting from comorbidities. In a majority of patients in the absence of atherosclerotic CV disease, chronic kidney disease and/or heart failure, a later-generation SU may still appear as the most cost-effective agent, even in a first world setting. This is probably the reason why SUs remain the most widely prescribed second-line therapy in numerous countries despite the negative narrative regarding the risk of hypoglycaemia and CV events potentially related with SUs over recent years [54]. Of note, in several national recommendations, including those published in 2013 (without updated version since that time) by the Haute Autorité de Santé (HAS) in France, SUs are still considered as first choice after failure of metformin monotherapy, except in patients with a high risk of hypoglycaemia [62].

Economic constraints seem to play a major role to influence the choice among the different medications after failure of met-

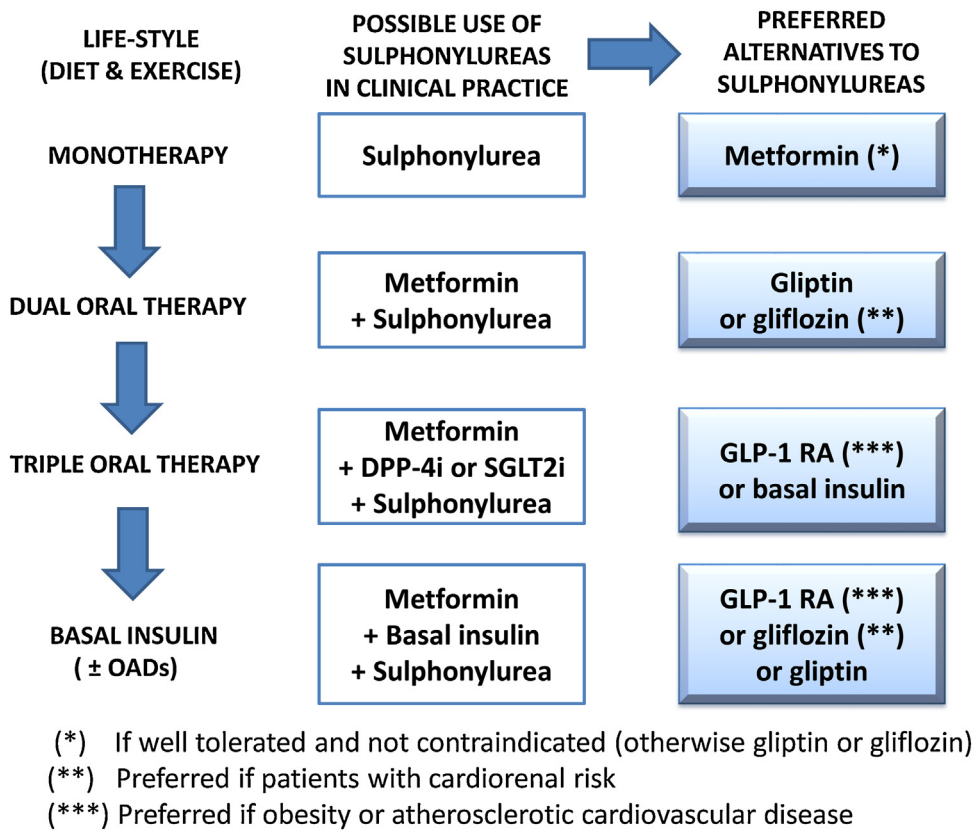

Fig. 3. Place of sulphonylureas in the management of type 2 diabetes and preferred pharmacological alternatives (meglitinides, alpha-glucosidase inhibitors and thiazolidinediones not considered here). GLP-1 RA : glucagon-like peptide-1 receptor agonist. OADs : oral antidiabetic drugs.

formin monotherapy [51]. According to a recent paper published by an expert opinion from a European consensus panel, current local treatment guidelines in European countries still widely proposed SUs as second-line treatment after metformin and not necessarily replaced by newer glucose-lowering medications. The conclusion was that routine utilization of SUs as second-line agents continues to be acceptable in resource-constrained settings [63]. Current guidelines, developed by experts from Africa, Asia, and the Middle East, promote the safe and smart use of SUs in combination with other glucose-lowering drugs. According to them, individualization of treatment, using SUs in combination with other drugs, backed with careful monitoring and patient education, ensures maximum benefits with minimal side effects [53]. A similar conclusion was adopted by a group of French-speaking experts from sub-Saharan Africa, especially because of economic constraints and limited access to drug therapies [64].

Place of SUs in clinical practice

The positioning of SUs in a modern treatment algorithm for patients with T2D has been recently reviewed by an Expert opinion from a European consensus panel [63]. According to current local treatment guidelines in many European countries, SUs are still widely proposed as second-line treatment after metformin and are often ranked at the same level as newer glucose-lowering medications [63]. The advantages and disadvantages of SUs are shown in Fig. 2 and compared with those of DPP-4is and SGLT2is in Table 3. From a theoretical point of view, SUs may be used in all the spectrum of T2D, from early stage as monotherapy in addition to life-style measures to a later stage as add-on therapy to basal insulin, with dual oral (add-on to metformin) or triple therapy (as add-on to metformin plus a gliptin or a gliflozin) as intermediate steps. However, for each step, an alternative treatment may be considered, when taking into account some advantages offered by other pharmacological options (Fig. 3). Using SUs in place of SGLT2is and GLP-1RAs may deprive patients of key advantages and potentially important cardiorenal benefits [63]. The choice should be personalized based upon the patient's clinical profile and preference, but also after taking into account the local possibilities and differences between medication costs, especially in countries with low resources.

Conclusion

SUs have long been the only alternative to metformin or considered as an ideal complementary therapy in case of failure of metformin monotherapy. The availability of newer OADs offer different advantages, especially a very low risk of hypoglycaemia, no weight gain and for SGLT2is a CV and renal protection. As a consequence, SUs fall off their pedestal, especially in T2D patients at high risk of hypoglycaemia, CV disease and/or renal insufficiency. Nevertheless, SUs remain largely prescribed even in countries where newer drugs are available. Of course, this is even more obvious in countries where more expensive OADs are not available or not reimbursed, and thus SUs represent the only therapeutic solution. In those countries where DPP-4is and SGLT2is are available, the use of SUs is progressively decreasing everywhere, but the speed and importance of the decline may markedly vary between countries. When the use of SUs is considered, it is mandatory to take into account the risk of hypoglycaemia in an individualized approach centred to the patient with T2D.

Declaration of Competing Interest

A.J. Scheen has received lecturer/advisor/investigator fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis, NovoNordisk, Sanofi and Servier.

He worked as clinical investigator in the TECOS, EMPA-REG OUTCOME, CANVAS-R and DECLARE-TIMI 58, LEADER AND HARMONY OUTCOME trials.

References

[1] Levine R. Sulfonylureas: background and development of the field. Diabetes Care 1984;7(Suppl 1):3–7.
[2] Groop LC. Sulfonylureas in NIDDM. Diabetes Care 1992;15:737–54.
[3] Scheen AJ, Lefebvre PJ. Oral antidiabetic agents. A guide to selection. Drugs 1998;55:225–36.
[4] Scheen AJ. The safety of gliptins : updated data in 2018. Expert Opin Drug Saf 2018;17:387–405.
[5] Scheen AJ. An update on the safety of SGLT2 inhibitors. Expert Opin Drug Safety 2019;18:295–311.
[6] Scheen AJ. Cardiovascular effects of new oral glucose-lowering agents: DPP-4 and SGLT-2 inhibitors. Circ Res 2018;122:1439–59.
[7] Scheen AJ. Sodium-glucose co-transporter type 2 inhibitors for the treatment of type 2 diabetes mellitus. Nature Rev Endocrinol 2020;16:556–77.
[8] Brady PA, Terzic A. The sulfonylurea controversy: more questions from the heart. J Am Coll Cardiol 1998;31:950–6.
[9] Brady PA, Jovanovic A. The sulfonylurea controversy: much ado about nothing or cause for concern? J Am Coll Cardiol 2003;42:1022–5.
[10] Abdelmoneim AS, Eurich DT, Light PE, Senior PA, Seubert JM, Makowsky MJ, et al. Cardiovascular safety of sulphonylureas: over 40 years of continuous controversy without an answer. Diabetes Obes Metab 2015;17:523–32.
[11] Pop LM, Lingvay I. The infamous, famous sulfonylureas and cardiovascular safety: much ado about nothing? Curr Diabetes Rep 2017;17:124.
[12] Scheen AJ. Cardiovascular safety of DPP-4 inhibitors compared to sulphonylureas : results of randomized controlled trials and observational studies. Diabetes Metab 2018;44:386–92.
[13] Scheen AJ. Challenging 2019 ESC guidelines for the management of type 2 diabetes. Diabetes Metab 2020;46:181–5.
[14] Monami M, Dicembrini I, Kundisova L, Zannoni S, Nreu B, Mannucci E. A meta-analysis of the hypoglycaemic risk in randomized controlled trials with sulphonylureas in patients with type 2 diabetes. Diabetes Obes Metab 2014;16:833–40.
[15] Tseng CL, Soroka O, Maney M, Aron DC, Pogach LM. Assessing potential glycemic overtreatment in persons at hypoglycemic risk. JAMA Intern Med 2014;174:259–68.
[16] Scheen AJ. DPP-4 inhibitors in the management of type 2 diabetes: a critical review of head-to-head trials. Diabetes Metab 2012;38:89–101.
[17] Zhang Y, Hong J, Chi J, Gu W, Ning G, Wang W. Head-to-head comparison of dipeptidyl peptidase-IV inhibitors and sulfonylureas - a meta-analysis from randomized clinical trials. Diabetes Metab Res Rev 2014;30:241–56.
[18] Detournay B, Halimi S, Robert J, Deschaseaux C, Dejager S. Hypoglycemia hospitalization frequency in patients with type 2 diabetes mellitus: a comparison of dipeptidyl peptidase 4 inhibitors and insulin secretagogues using the French health insurance database. Vasc Health Risk Manag 2015;11:417–25.
[19] Chen Z, Li G. Sodium-glucose co-transporter 2 inhibitors compared with sulfonylureas in patients with type 2 diabetes inadequately controlled on metformin: a meta-analysis of randomized controlled trials. Clin Drug Investig 2019;39:521–31.
[20] Shorr RI, Ray WA, Daugherty JR, Griffin MR. Individual sulfonylureas and serious hypoglycemia in older people. J Am Geriatr Soc 1996;44:751–5.
[21] Andersen SE, Christensen M. Hypoglycaemia when adding sulphonylurea to metformin: a systematic review and network meta-analysis. Br J Clin Pharmacol 2016;82:1291–302.
[22] Schernthaner G, Grimaldi A, Di Mario U, Drzewoski J, Kempler P, Kvapil M, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. Eur J Clin Invest 2004;34:535–42.
[23] Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–72.
[24] Douros A, Yin H, Yu OHY, Filion KB, Azoulay L, Suissa S. Pharmacologic differences of sulfonylureas and the risk of adverse cardiovascular and hypoglycemic events. Diabetes Care 2017;40:1506–13.
[25] Douros A, Dell'Aniello S, Yu OHY, Filion KB, Azoulay L, Suissa S. Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population based cohort study. BMJ 2018;362:k2693.
[26] Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, Billot L, et al. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363:1410–8.
[27] University Group Diabetes Program. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: sections I and II. Diabetes 1970;19:747–830.
[28] University Group Diabetes Program. A study of the effects of hypoglycemia agents on vascular complications in patients with adult-onset diabetes. VI. Supplementary report on nonfatal events in patients treated with tolbutamide. Diabetes 1976;25:1129–53.
[29] UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53.
[30] UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:854–65.
[31] Rao AD, Kuhadiya N, Reynolds K, Fonseca VA. Is the combination of sulfonylureas and metformin associated with an increased risk of cardiovascular disease or all-cause mortality?: a meta-analysis of observational studies. Diabetes Care 2008;31:1672–8.
[32] Farah D, Leme GM, Eliaschewitz FG, Fonseca MCM. A safety and tolerability profile comparison between dipeptidyl peptidase-4 inhibitors and sulfonylureas in diabetic patients: a systematic review and meta-analysis. Diabetes Res Clin Pract 2019;149:47–63.
[33] Azoulay L, Suissa S. Sulfonylureas and the risks of cardiovascular events and death: a methodological meta-regression analysis of the observational studies. Diabetes Care 2017;40:706–14.
[34] Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2013;15:938–53.
[35] Bain S, Druyts E, Balijepalli C, Baxter CA, Currie CJ, Das R, et al. Cardiovascular events and all-cause mortality associated with sulphonylureas compared with other antihyperglycaemic drugs: a Bayesian meta-analysis of survival data. Diabetes Obes Metab 2017;19:329–35.
[36] Leiter LA. Latest evidence on sulfonylureas: what's new? Diabetes Ther 2020;11:15–22.
[37] Zoungas S. ADVANCE in context: the benefits, risks and feasibility of providing intensive glycaemic control based on gliclazide modified release. Diabetes Obes Metab 2020;22(Suppl 2):5–11.
[38] Vaccaro O, Masulli M, Nicolucci A, Bonora E, Del Prato S, Maggioni AP, et al. Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial. Lancet Diabetes Endocrinol 2017;5:887–97.
[39] Scheen AJ. Outcomes and lessons from the PROactive study. Diabetes Res Clin Pract 2012;98:175–86.
[40] Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. JAMA 2019;322:1155–66.
[41] Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. JAMA 2018;321:69–79.
[42] Riveline JP, Danchin N, Ledru F, Varroud-Vial M, Charpentier G. Sulfonylureas and cardiovascular effects: from experimental data to clinical use. Available data in humans and clinical applications. Diabetes Metab 2003;29:207–22.
[43] Ferrannini E, DeFronzo RA. Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes. Eur Heart J 2015;36:2288–96.
[44] 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;3:43–51.
[45] Singh AK, Singh R. Is gliclazide a sulfonylurea with difference? A review in 2016. Expert Rev Clin Pharmacol 2016;9:839–51.
[46] Colagiuri S, Matthews D, Leiter LA, Chan SP, Sesti G, Marre M. The place of gliclazide MR in the evolving type 2 diabetes landscape: a comparison with other sulfonylureas and newer oral antihyperglycemic agents. Diabetes Res Clin Pract 2018;143:1–14.
[47] Genuth S. Should sulfonylureas remain an acceptable first-line add-on to metformin therapy in patients with type 2 diabetes? No, it's time to move on! Diabetes Care 2015;38:170–5.
[48] Abrahamson MJ. Should sulfonylureas remain an acceptable first-line add-on to metformin therapy in patients with type 2 diabetes? Yes, they continue to serve us well! Diabetes Care 2015;38:166–9.
[49] Khunti K, Chatterjee S, Gerstein HC, Zoungas S, Davies MJ. Do sulphonylureas still have a place in clinical practice? Lancet Diabetes Endocrinol 2018;6:821–32.
[50] Webb DR, Davies MJ, Jarvis J, Seidu S, Khunti K. The right place for sulphonylureas today. Diabetes Res Clin Pract 2019;157:107836.
[51] Mohan V, Cooper ME, Matthews DR, Khunti K. The standard of care in type 2 diabetes: re-evaluating the treatment paradigm. Diabetes Ther 2019;10:1–13.
[52] Khunti K, Hassanein M, Lee MK, Mohan V, Amod A. Role of gliclazide MR in the management of type 2 diabetes: report of a symposium on real-world evidence and new perspectives. Diabetes Ther 2020;11:33–48.
[53] Wexler DJ. Sulfonylureas and cardiovascular safety: the final verdict? JAMA 2019, http://dx.doi.org/10.1001/jama.2019.14533. September 19.
[54] Amod A. The place of sulfonylureas in guidelines: why are there differences? Diabetes Ther 2020;11:5–14.

[55] Diop SN, Baldé N, Sidibé AT. La bithérapie antidiabétique orale en pratique médicale courante en Afrique subsaharienne : résultats d'une étude observationnelle multicentrique sur six mois. Med Mal Metab 2018;12:306–12.
[56] Kalra S, Bahendeka S, Sahay R, Ghosh S, Md F, Orabi A, 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;22:132–57.
[57] Roglic G, Norris SL. Medicines for treatment intensification in type 2 diabetes and type of insulin in type 1 and type 2 diabetes in low-resource settings: synopsis of the World Health Organization Guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in nonpregnant adults with diabetes mellitus. Ann Intern Med 2018;169:394–7.
[58] Aschner P. New IDF clinical practice recommendations for managing type 2 diabetes in primary care. Diabetes Res Clin Pract 2017;132:169–70.
[59] International Diabetes Federation. Recommendations for managing type 2 diabetes in primary care. Belgium: International Diabetes Federation; 2017 (latest accessed Feburary 4, 2021) https://www.idf.org/e-library/guidelines/128-idf-clinical-practice-recommendations-for-managing-type-2-diabetes-in-primary-care.html.
[60] Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2018;61:2461–98.
[61] Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, et al. update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2019;2020(63):221–8.
[62] Haute Autorité de Santé (HAS). Stratégie médicamenteuse du contrôle glycémique du diabète de type 2 : recommandations; 2013 [Epub]; Available from: http://www.has-sante.fr/portail/upload/docs/application/pdf/2013-02/10irp04_reco_diabete_type_2.pdf (latest accessed Feburary 4, 2021).
[63] Consoli A, Czupryniak L, Duarte R, Jermendy G, Kautzky-Willer A, Mathieu C, et al. Positioning sulphonylureas in a modern treatment algorithm for patients with type 2 diabetes: expert opinion from a European consensus panel. Diabetes Obes Metab 2020;22:1705–13.
[64] Diop SN, Djrolo F, Sidibé AT, Baldé NM, Monabeka HG, Epaka ME, et al. Consensus pour la prise en charge de l'hyperglycémie dans le diabète de type 2 en Afrique subsaharienne. Rédigé par un groupe d'experts africains du diabète. Med Mal Metab 2019;13:210–6.