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Profiles of sulfonylurea use in Diabetes Mellitus type 2: an analysis of clinical practice over the last 10 years

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ABSTRACT

Aims: Describing the evolution over time in the use of sulfonylureas (SUs) and the characteristics of patients at first prescription and at interruption of treatment with SUs.
Methods: Retrospective evaluation of data from the Italian Association of Diabetologists (AMD) Annals registry (2010–2020), about T2D patients who started treatment with SUs. The longitudinal probability of remaining on SUs was estimated by Kaplan Meier survival curves.
Results: SU prescription decreased from 30.7 % (2010) to 12.9 % (2020). Patients started on SU were 68.2 ± 11.2 years old, mostly males (55.5 %), with diabetes duration = 10.1 ± 8.3 years, BMI = 29.7 ± 5.5 kg/m2, and HbA1c = 8.3 ± 1.7 % [67 mmol/mol]. After one year, the probability of staying on SU was 85.4 %, 75.9 % after two years, 68.2 % after 3 years, 56.6 % after 5 years. Patients who discontinued SUs had higher BMI and HbA1c, were younger, more often males and treated with insulin. Over time, the percentage of subjects switched to metformin, DPP4i, SGLT2i, and GLP1RA increased, whereas use of glinides, glitazones, acarbose and insulin declined.
Conclusions: These data suggest a consensus, slowly, but increasingly aligning with the current National indications of dismissing SUs for the treatment of T2D. The new drugs for diabetes should represent a preferable choice in all patients who do not have specific contraindications.

1. Introduction

Among the oral hypoglycemic drugs, sulfonylureas (SUs) are the ones used the longest [1,2]. They exert their hypoglycemic action by stimulating insulin secretion in a glucose-independent manner, through the interaction with specific receptors (Sulphonyl Urea Receptor 1, SUR1) localized on the surface of pancreatic β-cells, which act as the regulatory subunit of ATP-dependent K^+ channels [3-7].

Around 10–15 % of patients with type 2 diabetes (T2D) have a poor initial response to SUs monotherapy ("primary failure"); these subjects usually have low fasting C-peptide levels (<1 ng/ml) and high fasting blood glucose (280–300 mg/dl) [8]. Every year, approximately 5 % of

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patients treated with SUs experience secondary failure, and after 15 years only 25–30 % of patients manage to maintain satisfactory metabolic control [9-12]. In association with metformin, in short-term direct comparison studies (24–52 weeks), SUs have demonstrated superior efficacy to acarbose [13] and dipeptidyl-peptidase 4 inhibitors (DPP4i) [13-17], similar to pioglitazone and to glucagon-like-peptide 1 receptor agonists (GLP1RA), and equal to or less than sodium-glucose-cotransporter 2 inhibitors (SGLT2i) [18]. In longer-term comparisons (2–4 years), the efficacy of SUs becomes similar or inferior to DPP4i, and inferior to pioglitazone, SGLT2i [18-21] and GLP1RA [22]. Overall, this trend of rapid but transient action on hyperglycemia is compatible with experimental data showing that SUs have a pro-apoptotic effect at the β-cell level [10,23,24].

Alongside the high rates of failure, it is important to acknowledge that treatment with SUs is associated with weight gain and risk of hypoglycemia [25-27], both particularly enhanced when SUs are used in combination with insulin. In direct comparison trials, glibenclamide is associated with a higher risk of hypoglycemia than other molecules of the same class [28-30].

In addition to this, ATP-dependent K^+ channel subtypes are found in many cell types, including cardiomyocytes. The clinical relevance of this phenomenon has been debated for decades [31-35]. Meta-analyses of randomized clinical trials have provided conflicting results: some have observed a significant increase in mortality from all causes [36] and in the incidence of stroke [37] in subjects treated with SUs, while others, with selection criteria of the most restrictive trials, reported no significant statistical differences between groups [38-40]. Overall, evidence suggests that gliclazide has greater cardiovascular safety than other molecules of the same class [41].

Indeed, SU molecules are not equivalent to each other [42] and should not be considered as one and the same. Glibenclamide is considered the most powerful but less selective among the molecules still used today; gliclazide apparently respects more faithfully the biphasic nature of insulin secretion [43,44] and has potential vascular protective effects [45-47]. More recent is the introduction of a third-generation SUs, glimepiride, characterized by a longer action [48], allowing single daily administrations. Also glibenclamide and gliclazide-MR have kinetics compatible with once-daily administration while others require at least two administrations for 24-hour coverage (gliclazide, glipizide, gliquidone); some are mainly eliminated by the kidneys (glibenclamide, gliclazide, glipizide), whereas others are mainly eliminated by the bilio-fecal route (gliquidone, glimepiride). Consistent with this, there are important differences regarding safety: glibenclamide is associated with a higher risk of hypoglycemia [49] while gliclazide is associated with a lower risk [50].

The various molecules differ also for myocardial affinity, and this could translate into the differences reported for cardiovascular safety: in observational studies, cardiovascular morbidity and mortality was least associated with gliclazide, and most with glibenclamide [51-61].

SUs can interact with numerous drugs that can alter its kinetics and efficacy. Some act as enhancers, as in the case of acetylsalicylic acid, dicoumarol, allopurinol, probenecid; others as inhibitors, such as rifampin, barbiturates, diuretics, diphenylhydantoin [62]. Because SUs are metabolized by the liver and excreted as metabolites via the kidneys, in the event of severe impairment of hepatic and renal function, accumulation of the drug may occur with risk of serious and prolonged hypoglycemic crises. SUs should also be discontinued during acute cardiovascular episodes during which a temporary switch to insulin therapy is appropriate. Other conditions in which the use of SUs is contraindicated are: pregnancy [63-65], breastfeeding [66,67], allergy to sulphonamides and acute stress conditions (infections, surgical interventions).

The aim of this study is to describe the profiles of use of SUs for the treatment of T2D, and the characteristics of patients at first prescription and at interruption of treatment with this class of drugs. The evolution over time in the use of this therapeutic approach was also investigated, considering a time span ranging from 2010 to 2020.

2. Subjects

This is a retrospective, transversal and longitudinal study based on data obtained from the register of the Association of Diabetologists (AMD) called "AMD Annals", established in 2004 to monitor the quality of diabetes care in Italy. The database includes information on all patients with T2D treated at 282 diabetes centers in Italy, from January 1st 2010 to December 31st 2020. In order to participate in the initiative, the centers had to be equipped with electronic record systems capable of guaranteeing, in addition to the normal management of patients in their care, the extraction of standardized information for the creation of the AMD Data File. The latter represents the core tool, as it provides all the information necessary for the description of process and outcome indicators.

Patient data from all participating centers were collected, coded and stored anonymously, and then analyzed centrally. Available data included demographic, clinical and biochemical information. This study relied on pre-existing data and did not require direct patient involvement.

3. Materials and methods

3.1. Population selection

As previously mentioned, the analysis concerned patients with T2D managed between 2010 and 2020. The population analyzed is represented by the active patients for each year, i.e. all the subjects for whom there was a pharmacological prescription and a recording of weight or blood pressure during the index year. The cohort under study is represented by all patients who had started treatment with SUs during the period examined.

3.2. General descriptive data

The data analyzed were socio-demographic and clinical characteristics. Continuous values were reported as means ± standard deviation (SD); categorical variables are reported as percentages (%). If not reported in the medical record, LDL values were calculated using the Friedwald formula. LDL cholesterol was calculated only if the total cholesterol, HDL and triglyceride values determined on the same date were present in the record and if triglycerides levels did not exceed 400 mg/dL. Glomerular filtration rate (GFR) was calculated with the CKD-Epi formula. Pharmacological treatments were deduced from the ATC codes of the prescriptions recorded, while the complications from the ICD9-CM codes (reported in supplementary Table 1). From the clinical characteristics, the percentages of patients suffering from retinopathy, albuminuria or with a history of cardiovascular disease or previous CV event (heart attack/stroke/coronary or peripheral revascularization/coronary or peripheral bypass) were obtained. The information about HbA1c was used to stratify the population into 4 groups (HbA1c < 7.0 % [<53 mmol/mol]; 7.0–8.0 % [53–64 mmol/mol]; 8.1–9.0 % [65–75 mmol/mol]; > 9.0 % [>75 mmol/mol]).

3.3. Data analysis

For patients who started therapy with SUs in the index period, the following information was collected, both relating to the start of therapy and the time of discontinuation: age, sex, smoking habit, HbA1c, total cholesterol, LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), triglycerides, systolic blood pressure (SBP), diastolic blood pressure (DBP), BMI, glomerular filtration rate (GFR), albuminuria, class of anti-hyperglycemic drugs (metformin, glinides, glitazones, DPP4i, GLP1RA, acarbose, SGLT2i, insulin, basal insulin, rapid insulin), anti-hyperglycemic therapeutic scheme (oral monotherapy, dual oral

therapy, three or more oral drugs, schedules containing GLP1RA, insulin + oral therapy, insulin only), antihypertensive therapy (yes/no), hypolipidemic therapy (yes/no), cardiovascular complications (heart attack, stroke, coronary revascularization/reperfusion, peripheral revascularization/reperfusion), and diagnosis of retinopathy. For all the variables considered, the denominator was made up of patients with at least one detection during the index year. If the same patient had multiple visits during the index year, those that were the closest to the beginning and interruption of SU therapy were evaluated.

To examine the probability of remaining on SU therapy over the years, Kaplan Meier survival curves were used.

4. Results

Over the years examined, the percentage of subjects receiving SU treatment progressively decreased, going from 30.7 % in 2010 to 12.9 % in 2020 (Fig. 1).

4.1. Characteristics of patients at the time of initiation of SU therapy

In the period between 2010 and 2020, a total of 216,002 patients with T2D were started on SU therapy. Their characteristics are shown in Table 1. The subjects started on SU therapy had a fairly advanced age (68.2 ± 11.2 years), male prevalence was 55.5 %, duration of diabetes of approximately 10 years, most individuals were overweight or obese (average BMI = 29.7 ± 5.5 kg/m2) and with high average HbA1c values (8.3 % [67 mmol/mol]). One in 5 patients had a glomerular filtration rate < 60 ml/min and one in three had albuminuria.

The drugs most often used in association with SUs were metformin (79.8 %), DPP4i (19.4 %) and insulin (15.7 %). Most often, SUs were administered in the context of dual or triple oral therapy. The antihyperglycemic treatments and therapeutic schedules used at the start of SU therapy are shown in Table 2.

4.2. Discontinuation of SU treatment

During the observation period, 84,513 patients out of the 216,002 who were started on SU therapy (39.1 %) discontinued treatment with SUs after a median of 1.7 years (interquartile range 0.6–3.5 years), while 131,489 patients were still treated with SUs after a median of 3.5 years (interquartile range 1.5–6.1 years). The probability of still being on SUs was 85.4 % after one year of therapy, 75.9 % after two years, 68.2 % after 3 years and decreased to 56.6 % after 5 years (Fig. 2).

Table 1
Characteristics of patients started on sulfonylurea therapy in the years 2010–2020 (N = 216,002).

Characteristics	% or mean ± SD
Age (years)	68.2 ± 11.2
Sex (% males)	55.5
Diabetes duration (years)	10.1 ± 8.3
Smoking (% yes)	17.4
BMI (kg/m2)	29.7 ± 5.5
HbA1c (%) [mmol/mol]	8.3 ± 1.7 [56]
HbA1c classes	
<7.0 % [<53 mmol/mol]	20.2
7.0–8.0 % [53–64 mmol/mol]	29.0
8.1–9.0 % [65–75 mmol/mol]	20.3
>9.0 % [>75 mmol/mol]	23.8
N/A	6.6
SBP (mmHg)	137.6 ± 19.1
DBP (mmHg)	78.6 ± 10.0
Total cholesterol (mg/dl)	181.8 ± 41.8
HDL cholesterol (mg/dl)	48.2 ± 13.1
LDL cholesterol (mg/dl)	103.2 ± 35.1
Triglycerides (mg/dl)	157.5 ± 103.5
eGFR < 60 ml/min (%)	20.2
Micro-macroalbuminuria (%)	35.6
Cardiovascular complications (%)	15.0
Retinopathy (%)	15.0

BMI: body mass index; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HbA1c: glycated hemoglobin; HDL: high density lipoprotein; LDL: low density lipoprotein; N/A: not available; SBP: systolic blood pressure.

The characteristics of patients who discontinued SU treatment and those who continued therapy are summarized in Table 3. Compared to subjects who continued SU therapy, those who discontinued it were younger, with a higher male prevalence, higher BMI and HbA1c values, and more frequently diagnosed with cardiovascular complications and retinopathy. The antihyperglycemic treatments and therapeutic schemes used at the time of interruption of SU therapy and those of patients who continued SUs are shown in supplementary Table 2. Patients who discontinued SUs were less often treated with DPP4i, SGLT2i, and GLP1RA, and were more often treated with insulin. Fig. 3 reports the treatments and therapeutic schedules at the time of discontinuation of SU therapy and immediately after discontinuation.

After the interruption of SU therapy, the proportion of subjects treated with DPP4i and insulin increased the most, but the numbers for SGLT2i, glinides and GLP1RA use were also increased. Discontinuation

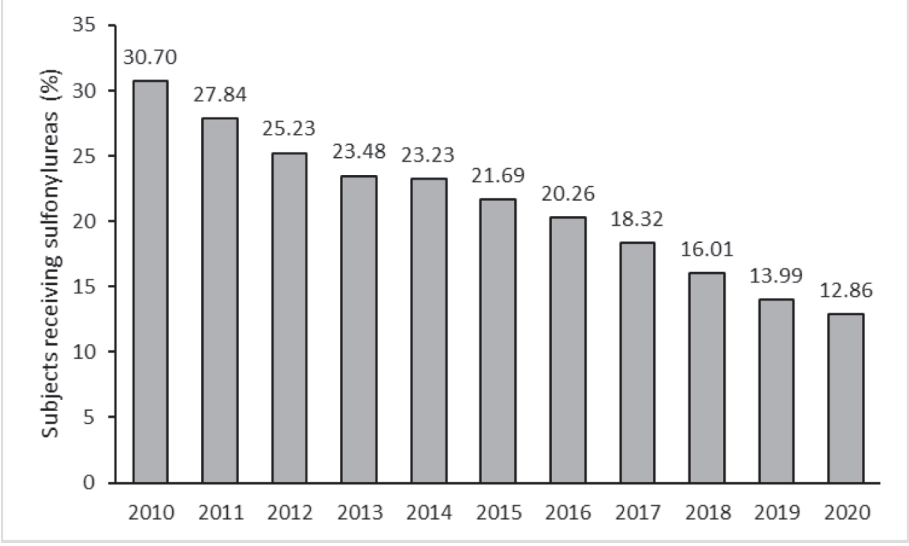

Fig. 1. Prevalence of use of sulfonylureas therapy in the years considered.

Table 2
Antihyperglycemic treatments and therapeutic schemes used at the beginning of SU therapy.

Treatment	%
Metformin	79.8
Glinides	4.3
DPP4i	19.4
Thiazolidinediones	7.3
SGLT2i	2.0
GLP1RA	5.2
Acarbose	2.8
Insulin	15.7
Therapeutic scheme	
Oral monotherapy	11.9
Dual oral therapy	46.4
≥ 3 oral medications	22.1
Patterns with GLP1RA	5.2
Insulin + oral therapy	14.5

DPP4i: dipeptidyl-peptidase 4 inhibitors; GLP1RA: glucagon-like-peptide 1 receptor agonists; SGLT2i: sodium-glucose-cotransporter 2 inhibitors.

of SU therapy was associated with a reduction in regimens with two or more oral anti-hyperglycemic drugs, an increase in monotherapies and the appearance of therapeutic regimens with insulin alone.

The trend of HbA1c values after the first SU prescription is shown in Fig. 4, stratified into two groups of subjects who interrupted the treatment and those who continued it. The figure shows graphically that the beginning of SU therapy is followed by a significant reduction in average HbA1c levels within the first 12 months, followed by a slight but steady rise, which remains consistent throughout a 5 year follow-up. Overall, during the observation period, subjects who eventually discontinued SU treatment had higher HbA1c values.

4.3. Discontinuation of SUs: Variations in therapeutic approaches over time

Table 4 reports the characteristics of patients who discontinued SU therapy, dividing the entire observation period into three groups based on the index year during which the therapy was modified: 2010–2012, 2013–2016, 2017–2020.

In more recent years, therapy has been discontinued in slightly younger subjects, with lower BMI and slightly lower HbA1c values. In particular, the proportion of subjects with HbA1c < 7.0 % [<53 mmol/mol] has increased. The prevalence of subjects with lower eGFR and cardiovascular complications appears to have reduced over time. The treatments and therapeutic schemes adopted immediately after the interruption of SUs in the three time groups are shown in Table 5.

Over the years, after the interruption of SU therapy, the percentage of subjects who were treated with metformin, DPP4i, SGLT2i, and GLP1RA increased, whereas the use of glinides, glitazones, acarbose and insulin became sparser.

As for therapeutic schemes, the proportion of subjects who, after the interruption of SUs, were treated with two or more oral agents or with GLP1RA increased over time, and less individuals were put on insulin therapy, especially as exclusive therapy.

Consistent with these observations, preliminary data from a sneak peek of the AMD Annals relating to the year 2022 show that the prescription of SUs has decreased further, to 7.7 %, with HbA1c = 7.5 ± 1.2 % [59 mmol/mol] and with a concomitant increase in prescriptions of GLP1RA and SGLT2i (Fig. 5). These data depict the prescriptive attitude of diabetologists who are increasingly attentive to the indications of the Guidelines, although there is still much space for improvement.

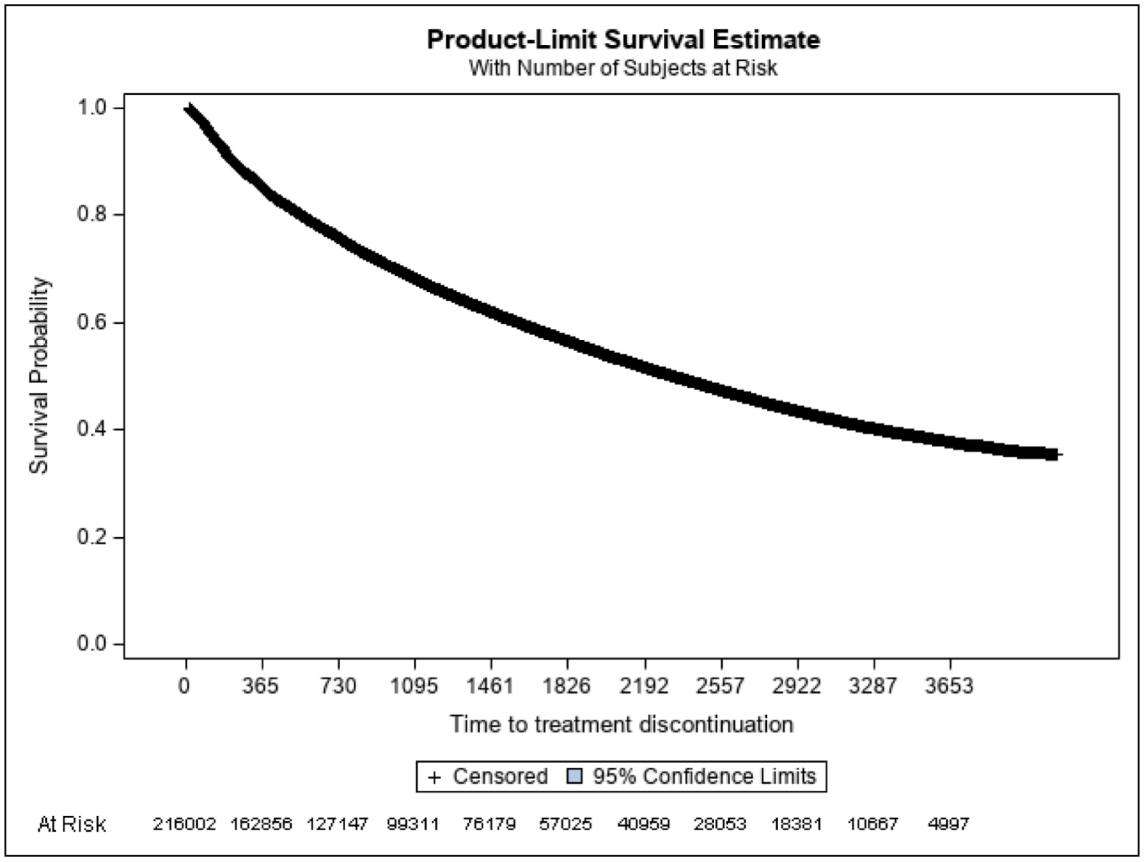

Fig. 2. Probability of remaining on sulfonylureas therapy over time, Kaplan-Meier curve.

Table 3
Characteristics of patients on sulfonylureas therapy at the time of discontinuation or, for patients still on treatment, at the last available visit.

Characteristics	Still in treatment with SUs	Discontinued treatment with SUs
N	131.489	84.513
Age (years)	73.4 ± 11.2	68.5 ± 11.2
Sex (% male)	54.9	57.0
Diabetes duration (years)	10.2 ± 8.3	10.1 ± 8.1
Smoking (% yes)	16.2	19.3
BMI (kg/m^2)	28.9 ± 5.4	29.8 ± 5.9
HbA1c (%) [mmol/mol]	7.5 ± 1.3 [58]	8.1 ± 1.8 [65]
HbA1c classes		
<7.0 % [<53 mmol/mol]	30.4	24.8
7.0–8.0 % [53–64 mmol/mol]	29.1	22.0
8.1–9.0 % [65–75 mmol/mol]	13.1	15.3
>9.0 % [>75 mmol/mol]	9.4	21.0
N/A	17.9	16.9
SBP (mmHg)	137.0 ± 18.7	135.2 ± 18.4
DBP (mmHg)	77.1 ± 9.7	77.7 ± 9.8
Total cholesterol (mg/dl)	167.6 ± 39.5	173.4 ± 41.4
HDL cholesterol (mg/dl)	47.9 ± 13.0	47.1 ± 13.0
LDL cholesterol (mg/dl)	92.5 ± 33.2	96.5 ± 34.2
Triglycerides (mg/dl)	140.5 ± 81.0	154.2 ± 105.2
eGFR < 60 ml/min (%)	30.9	29.4
Micro-macroalbuminuria (%)	37.1	37.1
Cardiovascular complications (%)	12.7	18.5
Retinopathy (%)	12.2	19.4

BMI: body mass index; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HbA1c: glycated hemoglobin; HDL: high density lipoprotein; LDL: low density lipoprotein; N/A: not available; SBP: systolic blood pressure; SUs: sulfonylureas.

5. Discussion

On July 28th 2021, approved by the Superior Health Institute (ISS), the new guidelines for the "Treatment of type 2 diabetes" were published by the Italian Society of Diabetology (SID) and the Association of Diabetologists (AMD) [42]. They present some innovations compared to previous editions (Standard of Care for Diabetes Mellitus, 2018) [68], and the most striking one is that SUs disappear from the therapeutic algorithm for T2D because the systematic review of studies on these drugs has highlighted an unfavorable benefit/risk ratio compared to other, more modern, therapeutic options. It is therefore recommended not to prescribe these molecules to people with diabetes who do not already use them and to proceed with their progressive replacement in those who are already under treatment, accepting the evidence produced by clinical studies on the cardiovascular and renal benefits of SGLT2i and GLP1RA, which are therefore placed in a prominent position within therapeutic algorithms.

The AMD-SID guidelines for the treatment of diabetes have both medical and legal value on national (Italian) territory. They are the only guidelines in the international scenario which strongly advise against the prescription of SUs to new patients and recommend de-prescribing them for patients already under treatment. This is in consideration that new classes of hypoglycemic drugs, in particular SGLT2i and GLP1RA, and to a lesser extent DPP4i, have expanded the possibility of targeting patients with diabetes safely, thanks also to a significantly lower incidence of side effects and hypoglycemic risk, and to their protective action against the onset and progression of complications.

Overall, this situation puts the decision-making process of an Italian diabetologist under an ethical, and scientific scrutiny, where complying with prescriptive appropriateness means choosing whether to continue taking SUs or implement a therapeutic switch in favor of newer, safer, classes of drugs, even in the presence of acceptable glycemic compensation.

The AMD Annals demonstrate a progressive decrease in the prescription of SU by Italian diabetologists (from 30.7 % in 2010 to 7.7 % in 2022), highlighting a prescribing attitude that is increasingly aware of the cost/benefit imbalance of SUs and, since 2018, attentive to the indications of the guidelines.

The data also point to the relatively large number of patients who were started on SU therapy between 2010 and 2020. It is striking to notice that SU therapy is still being prescribed in patients at high risk of hypoglycemic events (such as elderly patients, with low glomerular filtration rate), or in those with higher BMI or HbA1c, completely disregarding the national guidelines. This persistence is a hallmark of therapeutic inertia [69], a common plague affecting the modern clinical society, including diabetology, but it also hints that there is a remaining margin for further improvement, by educational interventions and by spreading the discussion about the potential damages of an unsupported therapeutic decision.

Unfortunately, reasons for changes of therapy, were not recorded in a

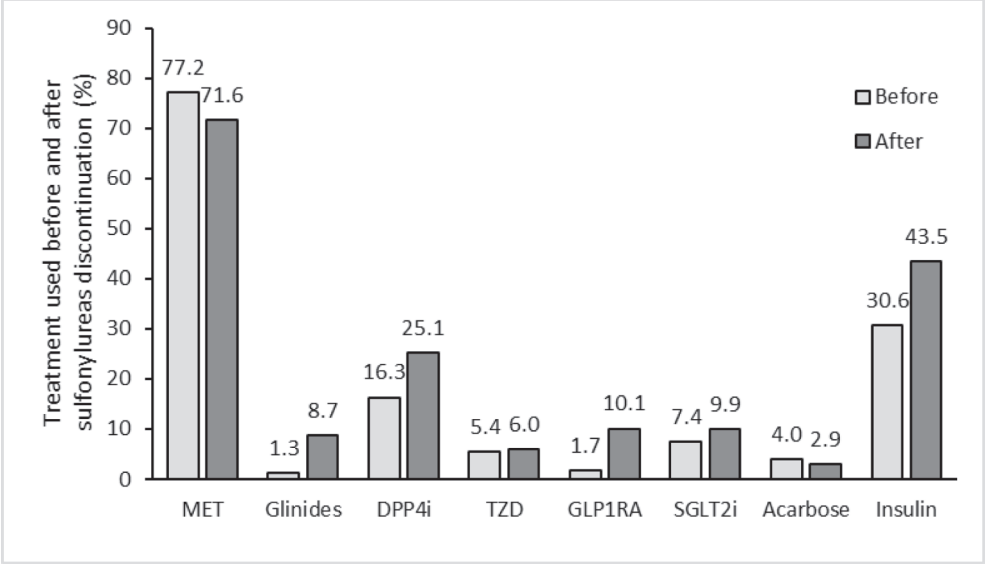

Fig. 3. Treatments used before and after discontinuation of sulfonylurea therapy. DPP4i: dipeptidyl-peptidase 4 inhibitors; GLP1RA: glucagon-like-peptide 1 receptor agonists; SGLT2i: sodium-glucose-cotransporter 2 inhibitors, TZD: thiazolidinediones.

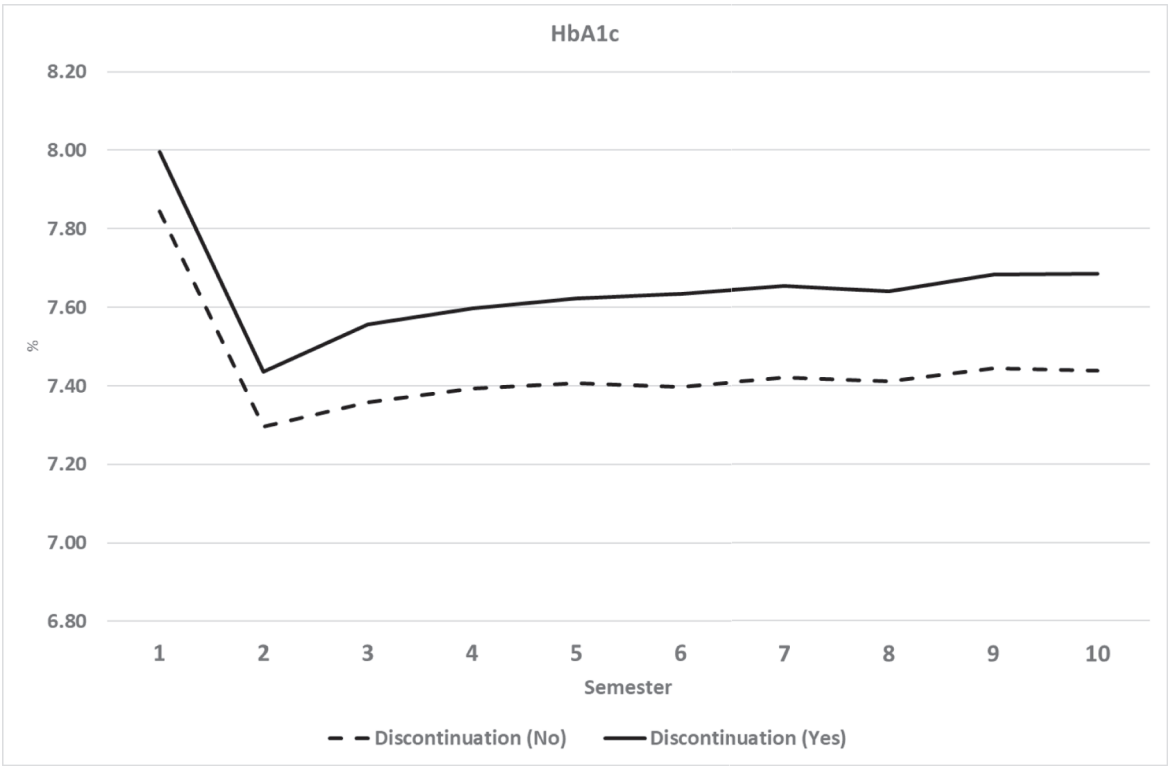

Fig. 4. Time trend of HbA1c (%) values in subjects who discontinued therapy with sulfonylureas and in those who continued therapy.

Table 4
Characteristics of patients on sulfonylureas therapy at the time of discontinuation, based on the time of discontinuation.

Characteristics	2010–2012	2013–2016	2017–2020
No	33.721	37.46	13.332
Age (years)	69.2 ± 11.0	68.2 ± 11.3	68.1 ± 11.4
Sex (% male)	56.3	57.5	57.0
Diabetes duration (years)	9.7 ± 8.3	9.9 ± 8.1	10.9 ± 8.5
Smoking (% yes)	19.9	18.1	20.7
BMI (kg/m2)	29.9 ± 5.7	29.9 ± 6.0	29.5 ± 5.8
HbA1c (%) [mmol/mol]	8.2 ± 1.8 [66]	8.1 ± 1.8 [65]	8.0 ± 1.8 [65]
HbA1c classes			
<7.0 % [<53 mmol/mol]	22.9	25.3	27.2
7.0–8.0 % [53–64 mmol/mol]	21.8	22.1	22.2
8.1–9.0 % [65–75 mmol/mol]	15.2	15.5	14.8
>9.0 % [>75 mmol/mol]	21.8	21.0	19.6
N/A	18.4	16.0	16.3
Systolic blood pressure (mmHg)	136.1 ± 18.7	134.5 ± 18.3	134.8 ± 18.0
Diastolic blood pressure (mmHg)	77.9 ± 10.0	77.6 ± 9.7	77.7 ± 10.0
Total cholesterol (mg/dl)	175.5 ± 41.8	172.4 ± 41.0	171.8 ± 41.4
HDL cholesterol (mg/dl)	47.7 ± 13.5	46.8 ± 12.9	46.5 ± 12.6
LDL cholesterol (mg/dl)	98.2 ± 34.7	95.4 ± 33.6	95.6 ± 34.5
Triglycerides (mg/dl)	140.5 ± 81.0	154.7 ± 104.8	155.8 ± 108.9
eGFR < 60 ml/min (%)	31.9	28.2	27.8
Micro-macroalbuminuria (%)	37.1	37.2	36.5
Cardiovascular complications (%)	17.7	14.8	10.7
Retinopathy (%)	19.1	14.6	19.1

BMI: body mass index; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HbA1c: glycated hemoglobin; HDL: high density lipoprotein; LDL: low density lipoprotein; N/A: not available; SBP: systolic blood pressure; SUs: sulfonylureas.

Table 5
Treatments and therapeutic schemes used upon discontinuation of SUs based on the observation period.

Treatment	2010–2012	2013–2016	2017–2020
Metformin	69.0	72.2	76.4
Glinides	13.0	6.7	3.5
DPP4i	22.7	26.3	28.2
Thiazolidinediones	6.3	5.9	5.3
SGLT2i	4.7	12.4	17.6
GLP1RA	7.0	9.8	17.7
Acarbose	3.3	2.7	2.1
Insulin	45.6	43.1	39.2
Therapeutic scheme			
Oral monotherapy	22.0	19.7	16.6
Dual oral therapy	20.8	24.0	25.1
≥ 3 oral medications	5.1	5.4	7.7
Patterns with GLP1RA	6.8	9.5	16.8
Insulin + oral therapy	27.9	26.8	23.4
Insulin only	15.2	12.6	8.4

DPP4i: dipeptidyl-peptidase 4 inhibitors; GLP1RA: glucagon-like-peptide 1 receptor agonists; SGLT2i: sodium-glucose-cotransporter 2 inhibitors.

standardized form in our electronic charts, thus precluding the possibility to explore this aspect. However, comparisons between patients who were still on treatment with SUs at the end of the study period and those who discontinued SUs during the follow-up (Table 3) revealed that the major divergence points were the age of the patients, higher in average for the group who was kept on SUs, HbA1c and BMI, both slightly higher in average for patients who have been de-prescribed SUs. At this point we can only speculate that these parameters might have influenced the decision-making process, as a prescribing doctor might opt to maintain the status quo of an elderly patient who is accustomed to a therapeutic regimen, and even more so in the presence of good blood glucose control and weight management, in spite of the national guidelines stating the opposite.

On the other hand, although reasons for discontinuation are not

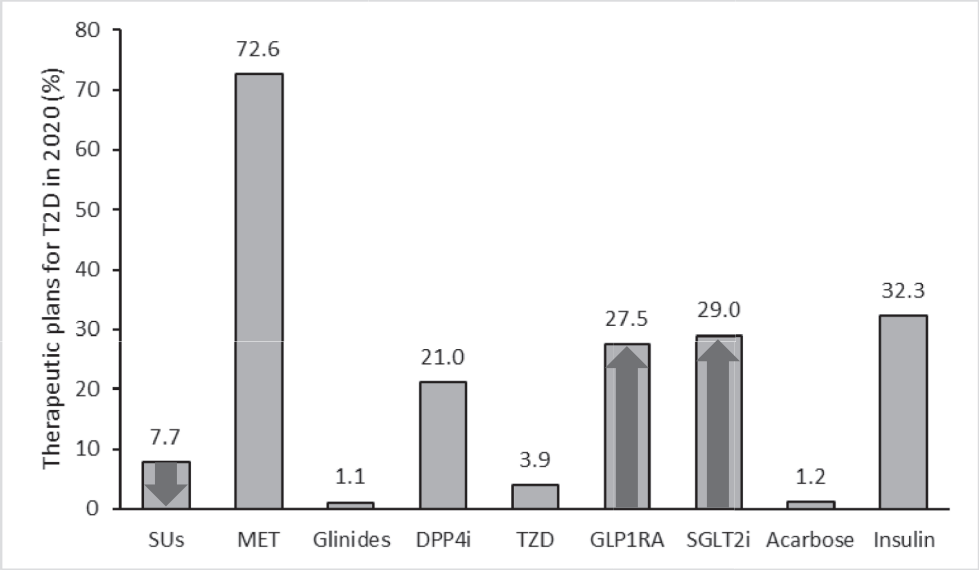

Fig. 5. Distribution of patients with type 2 diabetes by drug class, data from AMD Annals 2022. DPP4i: dipeptidyl-peptidase 4 inhibitors; GLP1RA: glucagon-like-peptide 1 receptor agonists; SGLT2i: sodium-glucose-cotransporter 2 inhibitors, SUs: sulfonylureas; TZD: thiazolidinediones.

available in our study, it is important to acknowledge that in cases of SU discontinuation, unbearable hypoglycemia episodes, weight gain and the benefits of the newer drugs are all likely explanations. Our data show that the therapy of choice was more often metformin, DPP4i, SGLT2i, or GLP1RA than glinides, glitazones, acarbose or insulin, depicting a virtuous scenario in which the decision-making process is guided by scientific evidences and national prescription indications from the Italian regulatory authority of drugs (AIFA), consistent with the recent campaign promoting the adherence to current Italian guidelines [42], that have been released with the endorsement of the Ministry of Health.

The availability of innovative pharmaceuticals that are increasingly easier to handle, flexible, safe, with fewer adverse effects and, above all, increasingly aimed at specific targets for the correction of well-defined pathophysiological alterations, represents a fundamental step forward in the treatment of T2D, allowing the diabetologist to individualize the hypoglycemic therapy for each individual patient. This goal of personalized medicine requires from the side of the doctor an intensive therapeutic attitude, with full understanding of the mechanisms of action and possible side effects of drugs prescribed and the willingness of revising the therapeutic strategy even for minor deviations from the target, which, if neglected, might eventually give rise to long exposure of patients to high glycemic values, increase the risk of complications and affect negatively the quality of life of the person with diabetes.

The priority in the treatment of T2D should be assigned to the improvement of outcomes (cardiovascular, renal events and mortality), therefore, the newer drugs should be preferred over SUs, in light of the minimal hypoglycemic risk associated with their use, their positive (GLP1RA, SGLT2i) or neutral (DPP4i) CV effects, their protective renal effects (SGLT2i $\gg$ GLP1RA $>$ DPP4i), their neutral (DPP4i) or positive (GLP1RA, SGLT2i) action on body weight, and, finally, their greater durability and ease of use, without titration and without the need for stringent self-monitoring. No study has demonstrated an improvement in CV and renal risk in patients with T2D treated with SU.

It is important to mention that we are not preaching a complete ban on SUs as hypoglycemic agents. These molecules find their application niche inn rare forms of diabetes, and are, indeed, extremely effective for the treatment of neonatal diabetes [70] and some forms of monogenic diabetes, depending on the genetic defect that defines the specific pathologic phenotype [70,71].

The new drugs for diabetes should represent a preferable choice in all patients with T2D who do not have specific contraindications to their use, both for individuals with new onset of the disease and without complications, and for subjects with established cardiovascular disease or at very high risk.

CRediT authorship contribution statement

Fabio Baccetti: Investigation. **Cristiano Crisafulli:** Investigation. **Francesco Andreozzi:** Writing – review & editing. **Gaia Chiara Mannino:** Writing – original draft, Visualization, Conceptualization. **Antonio Nicolucci:** Visualization, Software, Resources, Formal analysis, Data curation, Conceptualization. **Andrea Michelli:** Visualization, Investigation, Conceptualization. **Cesare Miranda:** Investigation. **Riccardo Candido:** Investigation. **Paolo Di Bartolo:** Project administration, Funding acquisition. **Graziano Di Cianni:** Project administration, Funding acquisition. **Giuseppina Tiziana Russo:** Writing – review & editing, Visualization, Investigation, Formal analysis. **Domenico Mannino:** Writing – original draft, Visualization, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2024.111781.

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