https://doi.org/10.46389/rjd-2022-1078
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2022; volume 29, issue 1, pages 83-91

Original Research

Drivers of vildagliptin prescription for Romanian patients with type 2 diabetes, the TREND study

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Received: 31 January 2022 / Accepted: 18 March 2022

Abstract

Background and aims: Vildagliptin is a dipeptidyl-peptidase-4 inhibitor, used in the treatment of type 2 diabetes mellitus, associated with a slightly better HbA_{1c} reduction compared to other molecules in its class, who may be used, in adjusted dose, irrespective of the estimated glomerular filtration rate, including in end-stage kidney disease and which demonstrated an excellent safety profile. Vildagliptin is fully reimbursed in Romania within the National Diabetes Program. The main aim of this study was to evaluate which are the most important vildagliptin's prescription drivers. **Materials and methods:** In this cross-sectional, non-interventional study data for 1918 patients in who vildagliptin treatment was considered was collected in a consecutive-case population-based scenario. Data were collected from 106 diabetologists working in 61 cities from 36 Romanian counties. The median cases completed by a doctor was 18 (ranging from 1 to 31 responses, inter quartile range between 15 and 20). **Results:** The majority of vildagliptin's associations were to prior metformin treatment (83.6% of the cases), among those who in 48.7% of the cases vildagliptin was added as early as possible to maximize the benefit according to the VERIFY study results. In 9.6% of the cases, vildagliptin was associated with sulfonylurea. In prescribing vildagliptin, the most important driver was the improvement of glycemic control, considered by 72.6% of the responders as being extremely important, followed by the importance of cardiovascular protection (65.5% – extremely important), hypoglycemia avoidance (61.9% – extremely important) and the possibility of safely use in chronic kidney disease (59.1% – extremely important). About 59.9% of the responders considered it appropriate to intensify the diabetes therapy with vildagliptin after 3 months of metformin treatment and 31.2% considered it adequate to add vildagliptin right at the T2DM diagnosis alongside metformin if this would have been possible in the reimbursement algorithm. **Conclusions:** Vildagliptin is considered a valuable intervention in the treatment of T2DM, its benefits being emphasized in case of its early use in the course of T2DM. The most important factor in considering vildagliptin for a patient is the improvement of glycemic control. The excellent safety profile and possibility to use irrespective of eGFR is considered a key advantage for vildagliptin.

Keywords: vildagliptin, dipeptidyl peptidase 4 inhibitors, glycemic control, drug safety.

Background and aims

Dipeptidyl-peptidase 4 inhibitors (DPP4i) are a class of diabetes drugs, acting by inhibiting the dipeptidyl-peptidase 4 enzyme [1], which is responsible for inactivating the incretin hormones (mainly glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide). Thus, DPP4i are prolonging the endogenous effect of incretin hormones, thus leading to improvements in the glycemic control, mediated mainly by enhancing the pancreatic beta-cell activity and consequently increasing glucose-dependent pancreatic insulin secretion [2]. Their

glucose-lowering activity is more pronounced for the post-prandial glycemia rather than fasting glycemia [3].

Currently, DPP4i are recommended as second-line therapy after metformin in patients in which there is a compelling need to reduce hypoglycemia risk and as a third-line therapy in patients in which there is a need to minimize weight gain or to promote weight loss and a glucagon-like peptide 1 receptor agonist is not tolerated [4].

According to current guidelines, DPP4i are known to have an intermediate efficacy on glycemic control, are not associated with hypoglycemia risk, are neutral regarding body weight, cardiovascular risk, renal risk, and are administered using the oral route [4]. Among diabetes therapies, the DPP4i are recognized as having the lowest rate of adverse therapeutic effects, being among the best-tolerated therapies, with the associated lowest discontinuation rates including here the use in frail patients [5]. In Romania, the following DPP4i are available and fully reimbursed for patients with type 2 diabetes mellitus (T2DM): Vildagliptin, Sitagliptin, and Saxagliptin.

Vildagliptin is a DPP4i fully reimbursed in Romania for patients with T2DM and available individually (Dalmevin ™) as well as in fixed combination with metformin (Daltex ™). According to the reimbursement algorithm, vildagliptin may be prescribed in double therapy after metformin, after sulfonylurea as well as on triple therapy after metformin + sulfonylurea [6]. Vildagliptin has a similar efficacy profile with the other DPP4i, the key differentiating component being its renal safety, vildagliptin being the only DPP4i available in Romania which may be used, in adjusted dose, irrespective of the patient's eGFR, including the use in end-stage kidney disease [7].

The use of vildagliptin in T2DM was evaluated in several clinical trials in which an efficacy slightly higher than other molecules from the DPP4i class was observed, irrespective of the scenario of use, in parallel with an excellent safety profile, including here hypoglycemia, cardiovascular safety as well as other therapeutic adverse effects [8–10]. When used after metformin, vildagliptin proved a similar HbA_{1c} reduction but obtained in parallel with a significantly lower rate than gliclazide as well as being weight neutral, in contrast to gliclazide intervention which led to a significant increase in body weight [11]. In the elderly (aged higher than 65 years) drug-naïve patients with T2DM vildagliptin was non-inferior to metformin regarding the glycemic control efficacy and had a significantly lower rate of gastrointestinal adverse effects [12]. Furthermore, in a pooled analysis, with data extracted from vildagliptin's clinical development, it was observed that vildagliptin had an excellent safety profile: it was not associated with increased risk of hepatic adverse or serious adverse events vs. comparator, no increased risk for adjudicated cardiovascular events were observed relative to all comparators studies and was not associated to increased risk for pancreatitis or infections [13].

Regarding the early intervention with vildagliptin in the course of T2DM, it has to be mentioned that the verify trial demonstrated that the combination therapy of metformin + vildagliptin immediately after the diagnosis of T2DM leads to a significantly improved long-term prognosis and a significantly decreased risk of treatment failure [14].

Considering all this efficacy and safety premises, vildagliptin emerges as a valuable intervention for patients with T2DM, with emphasis on patients in early stages of T2DM, elderly and frail patients as well as patients with decreased eGFR or at risk of further eGFR decreases. The aims of the therapeutic role of vildagliptin within TrEatment GuideliNes for Type 2 Diabetes (TREND) study are to evaluate the profile of patient which are prescribed vildagliptin as well as to identify the most important drivers for vildagliptin prescription in Romania.

Material and methods

Study design

The therapeutic role of vildagliptin within TrEatment GuideliNes for Type 2 Diabetes (TREND) study is a cross-sectional, multi-centric, nationwide, a non-interventional survey designed to evaluate diabetologists perception regarding the drivers for prescribing vildagliptin to patients with type 2 diabetes. The responders were

https://doi.org/10.46389/rjd-2022-1078

diabetologists working in the main Romanian cities who completed an anonymized electronic data collection form regarding a consecutive-case series of patients with type 2 diabetes, attending scheduled outpatient visits. The study was sponsored by Medochemie Romania. Responders were asked to complete the collection form with data for patients in who they considered adding vildagliptin in the treatment regimen.

Data collection

For the aim of the study, between 12th of March 2021 and 10th of June 2021, using a secured electronic collection form (SurveySparrow ™), 1918 responses of consecutive patients with T2DM were collected from 106 diabetologists working in 61 cities from 36 Romanian counties. The median cases completed by a doctor was 18 (ranging from 1 to 31 responses, inter quartile range between 15 and 20).

The questionnaire was designed to evaluate six main components:

1. The profile of the patient (demographic, medical history, presence of complications of co-morbidities, hypoglycemic events) who may benefit from adding vildagliptin to its treatment regiment
2. Which are the main drivers for choosing a diabetes therapy
3. Which are the main drivers for choosing vildagliptin for a patient with T2DM
4. What are the main expected benefits after the addition of vildagliptin?
5. When is the optimal moment during the clinical course of T2DM to add vildagliptin?
6. Whether there are improvements needed to the vildagliptin's reimbursement protocol for patients with T2DM.

Data collection was managed by Medochemie Romania.

Statistical analysis

Data was collected using the Survey Sparrow ™ electronic data collection form. Data management and data analysis were performed using International Business Machines' Statistical Package for Social Sciences (IBM SPSS) version 28.0, (IBM Corp. Armonk, New York, United States of America).

Results are presented as the mean ± standard deviation for numerical variables with Gaussian distribution, median and [interquartile range] for ordinal variables, and numerical variables with non-parametric distributions and absolute and relative frequencies for categorical variables.

To evaluate the statistical significance of the differences between the studied sub-groups unpaired t-student tests (differences between two means), ANOVA tests (differences between more than two means), Mann-Whitney U tests (differences between two medians), Kruskal-Wallis tests (differences between more than two medians) and Chi-square tests (differences between relative frequencies) were used.

In this study, a threshold value for significance of $p<0.05$ was used.

Results and discussions

Patient's characteristics

In the TREND study, 1918 individual patients data were collected: 1002 women (52.2%) and 916 (47.8%) men. The patients of which data were analyzed had a median age (Figure 1) of 63 years [interquartile range = 13], median diabetes duration of 5 years [interquartile range = 6] with a right-skewed distribution of values (skewness=1.32; Figure 2).

In the studied sample, the most frequent antidiabetic medication therapy class was metformin (93.4%) followed by DPP4 inhibitors (50.8%). It is to be noted that due to the study design (physicians were asked to complete a patient's profile which may benefit from having vildagliptin in their treatment regimen) the use of the DPP4i in the studied sample is artificially increased since many of those patients were already on vildagliptin treatment, initiated at a previous visit (of the 975 reported uses of DPP4i, 922 patients were previously initiated on

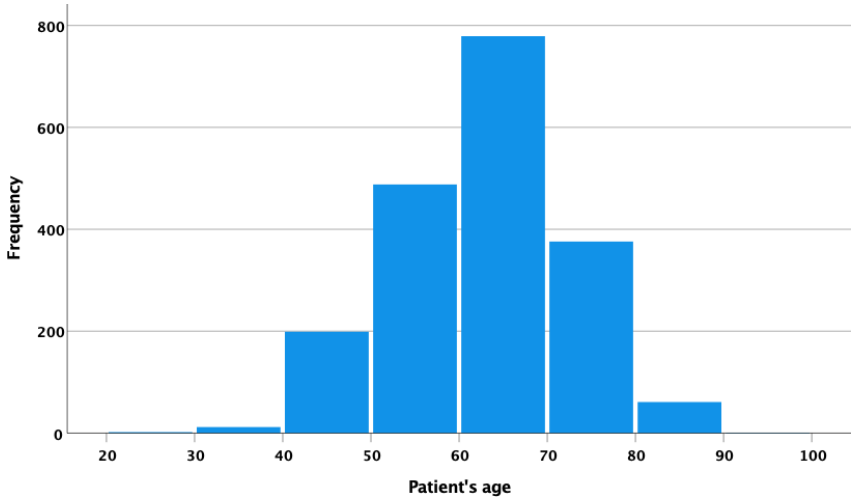

Figure 1: Histogram of patient's age.

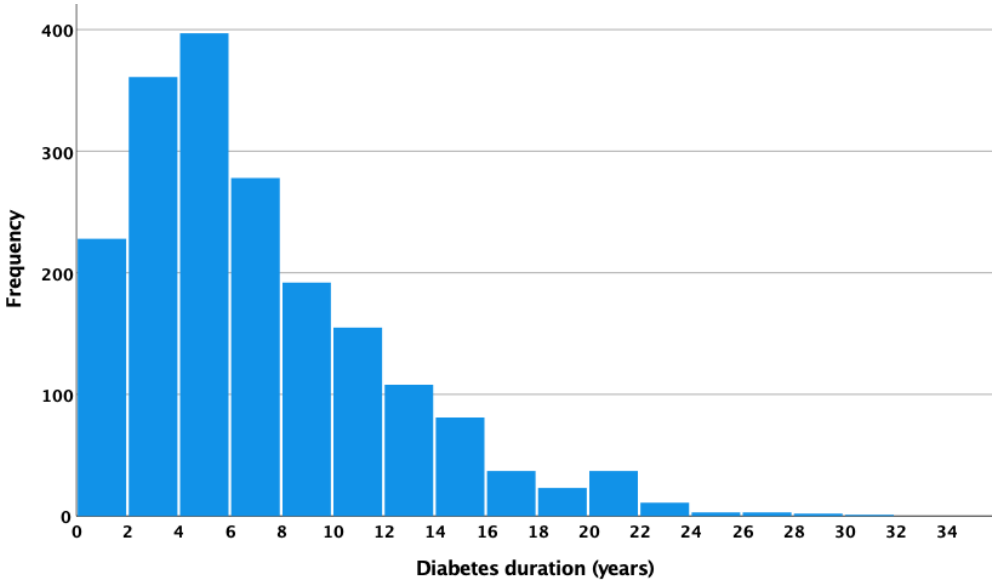

Figure 2: Distribution of diabetes duration.

vildagliptin). The low reported use of GLP1-RA (0.4%) is also explained by the study design: there is an extremely low probability that a patient already on GLP1-RA may benefit from vildagliptin addition since this therapeutic step needs GLP-1RA discontinuation and more, it is not covered by the reimbursed algorithms (Table 1).

Table 1: Frequency of use for the antidiabetic therapy classes.

	Count	Frequency of use (%)
Metformin	1792	93.4
DPP4i	975	50.8
Sulfonylurea	666	34.7
Insulin	202	10.5
SGLT2i	33	1.7
Meglitinides	20	1.0
GLP-1 RA	8	0.4
Thiazolidinediones	5	0.3

Glycemic control. Complications and co-morbidities

The median HbA_{1c} (Figure 3) in the study sample was 7.7% [interquartile range = 1], its distribution values having a low right-skew (1.643)

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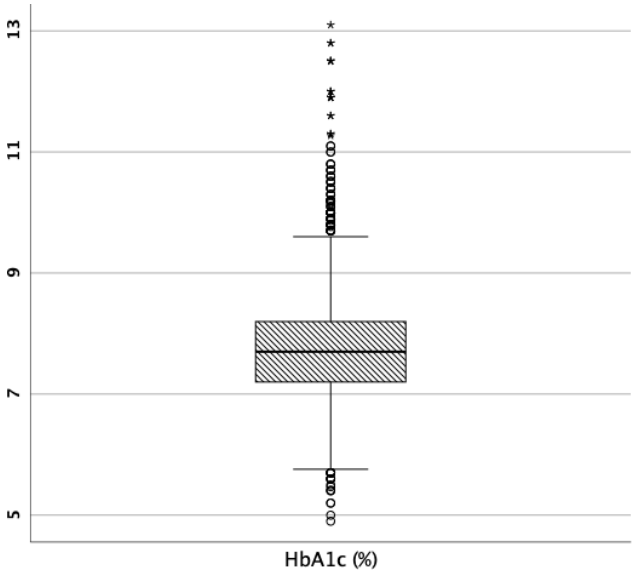

Figure 3: Box and whiskers plot for HbA_{1c} values distribution.

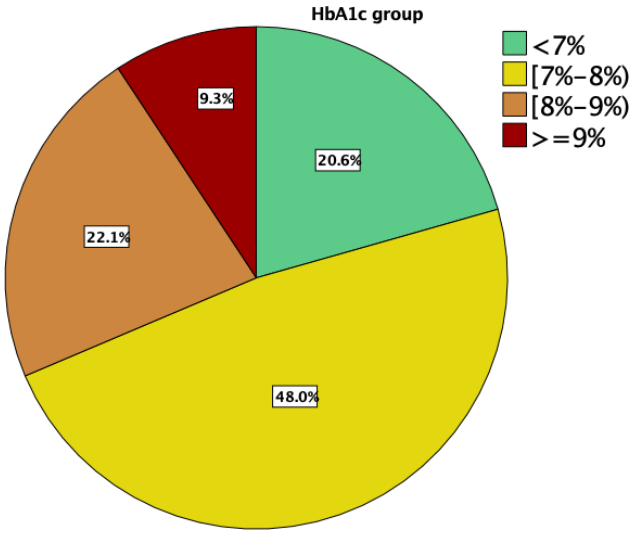

Figure 4: Distribution of HbA_{1c} values.

and a high kurtosis (7.173). The low interquartile range and increased kurtosis are explained by the study design: patients in which the benefit of adding vildagliptin (or other DPP4i) are patients with a glycemic control close to the targets, patients with more than 1% point over the individualized HbA_{1c} target having a low probability of achieving adequate glycemic control after the addition of the DPP4i.

Most patients (48.0%) had an HbA_{1c} value between 7% and 8%, followed by the 8–9% subgroup (22.1%). About 20.6% of the patients had an HbA_{1c} value below 7% (Figure 4).

The most frequent co-morbidity reported in the studied sample was hypertension (64.2%) followed by dyslipidemia (56.7%) and diabetic neuropathy (50.1%). The occurrence of clinically relevant diabetes complications and co-morbidities is presented in Figure 5. Considering that the complications and co-morbidities were reported only if known at the date of the evaluation and proactive screening for complications and co-morbidities was not part of the present study, the presence of complications of co-morbidities which may be asymptomatic or oligo-symptomatic was expected to be lower than in populational studies which reported results of proactive screenings for diabetes complications and co-morbidities.

A major discrepancy was observed regarding reporting the chronic kidney disease: a prevalence of 13.2% for CKD at the dichotomous reporting among diabetes complications was reported, however, when reporting the estimated glomerular filtration rate, it was observed that only 35.0% of the patients had an eGFR higher than 60 ml/min (Table 2, Figure 6).

In the studied sample, the median eGFR was 83.65 ml/min, with an associated interquartile range of 26.0 ml/min (Figure 7).

In the studied sample, 26.7% of the patients had at least one monthly hypoglycemic event (irrespective of severity), while 4.6% of them had at least one monthly daytime hypoglycemic event, respectively 2.3% at least one nocturnal severe hypoglycemic event (Table 3).

In prescribing vildaliptin, the most important driver was the improvement of glycemic control, considered by 72.6% of the responders as being extremely important, followed by the importance of cardiovascular protection (65.5% considered it as extremely important), hypoglycemia avoidance (61.9% considered it as extremely important) and the possibility of safely use in chronic kidney disease (59.1% of responders considering it extremely important). The least important factors considered when choosing vildagliptin for the patient with T2DM were the treatment compliance, availability of fixed combination therapy, and the treatment's impact on the body weight.

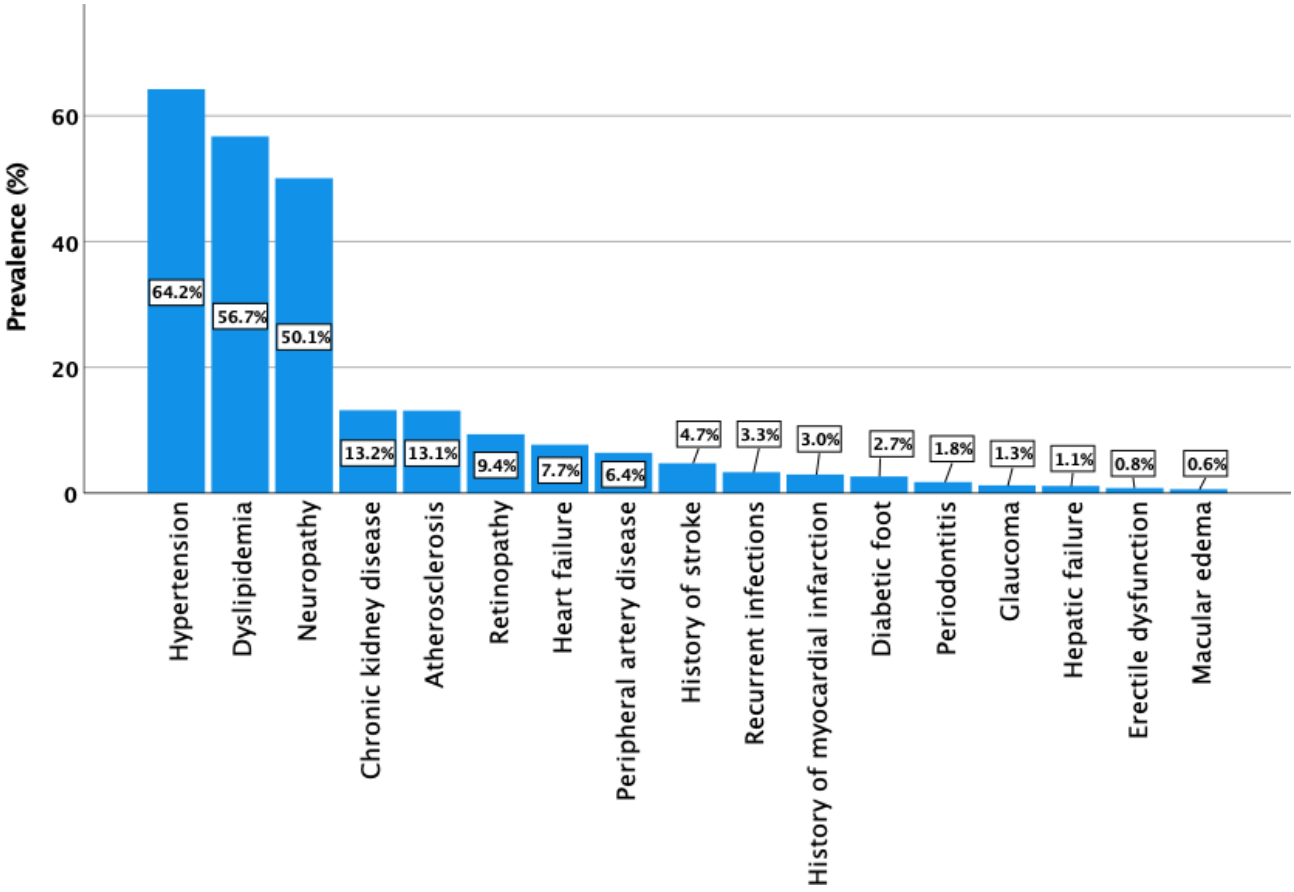

Figure 5: Prevalence of diabetes complications and co-morbidities.

Table 2: Distribution CKD stages.

	Frequency	Percent	Cumulative percent
Stage 1	672	35.0	35.0
Stage 2	929	48.4	83.5
Stage 3a	213	11.1	94.6
Stage 3b	85	4.4	99.0
Stage 5	9	0.5	99.5
End-stage CKD	10	0.5	100.0
Total	1918	100.0	

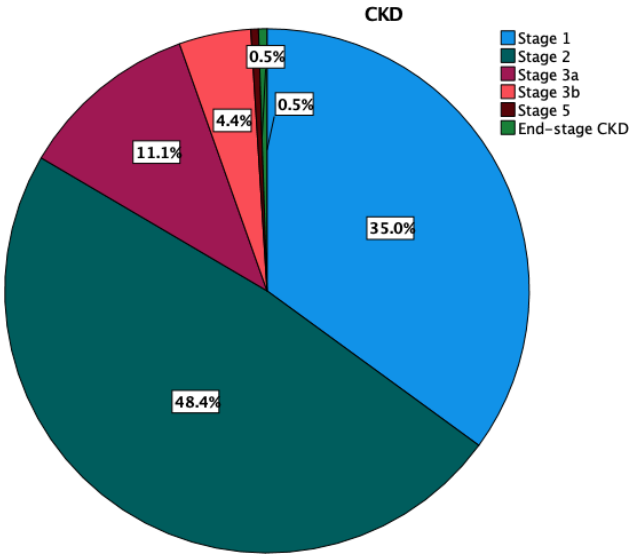

Figure 6: Distribution of eGFR values.

The responder's perception regarding the importance of several factors in choosing vildagliptin for the patient with T2DM is presented in Table 4 and Figure 8.

In the studied sample, 99.6% of the individuals responded that they are willing to early intensify the treatment of diabetes to avoid complications.

The majority of vildagliptin's associations were to prior metformin treatment (83.6% of the cases), among which is 48.7% of the cases vildagliptin was added as early as possible to maximize the benefit according to

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the VERIFY study results. In 9.6% of the cases, vildagliptin was associated with sulfonylurea respectively in 5.5% to insulin and 1.2% associated with a sodium-glucose co-transporter 2

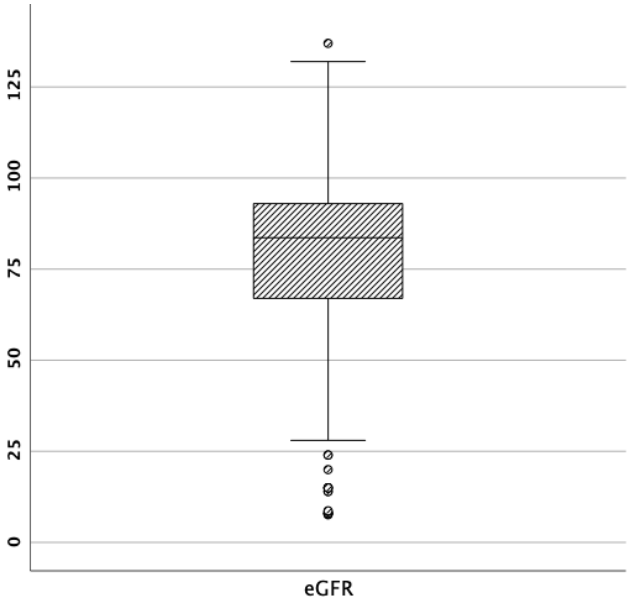

Figure 7: Box and whiskers plot for eGFR value.

even if not reimbursed by the health insurance company.

About 59.9% of the responders considered it appropriate to intensify the diabetes therapy with vildagliptin after 3 months of metformin treatment and 31.2% considered it adequate to add vildagliptin right at the T2DM diagnosis alongside metformin if this would have been possible in the reimbursement algorithm. A 79.5% of the responders considered to be a major advantage in the possibility of safely using vildagliptin in elderly patients, with eGFR rates lower than 30 ml/min.

Conclusions

Vildagliptin is considered a valuable intervention in the treatment of T2DM, its benefits being emphasized in case of its early use in the course of T2DM. The most important factor in considering vildagliptin for a patient is the

Table 3: Distribution of hypoglycemic events frequency.

	Number of monthly events					
	0	1	2	3	4	>=5
Hypoglycemia	73.3%	5.3%	7.3%	5.1%	3.6%	3.0%
Daytime severe hypoglycemia	95.4%	2.7%	1.1%	0.5%	0.2%	0.1%
Nocturnal severe hypoglycemia	97.7%	1.5%	0.6%	0.2%	0%	0%

Table 4: Importance of several factors in the therapeutic decision for patients with T2DM.

	Extremely important (%)	Very important (%)	Average importance (%)	Little importance (%)	Not important at all (%)
Glycemic control	72.6	26.5	0.9	0.0	0.1
Cardiovascular protection	65.5	32.5	1.9	0.0	0.1
Hypoglycemia's avoidance	61.9	33.7	4.2	0.2	0.1
Safety of use in chronic kidney disease	59.1	34.9	5.6	0.4	0.1
Possibility to use when eGFR decreases	56.3	34.9	8.2	0.5	0.1
Treatment compliance	51.5	36.6	11.1	0.7	0.1
Availability in fixed combination therapy	50.4	36.2	12.3	1.0	0.2
Body weight	49.5	44.0	6.5	0.1	0.1

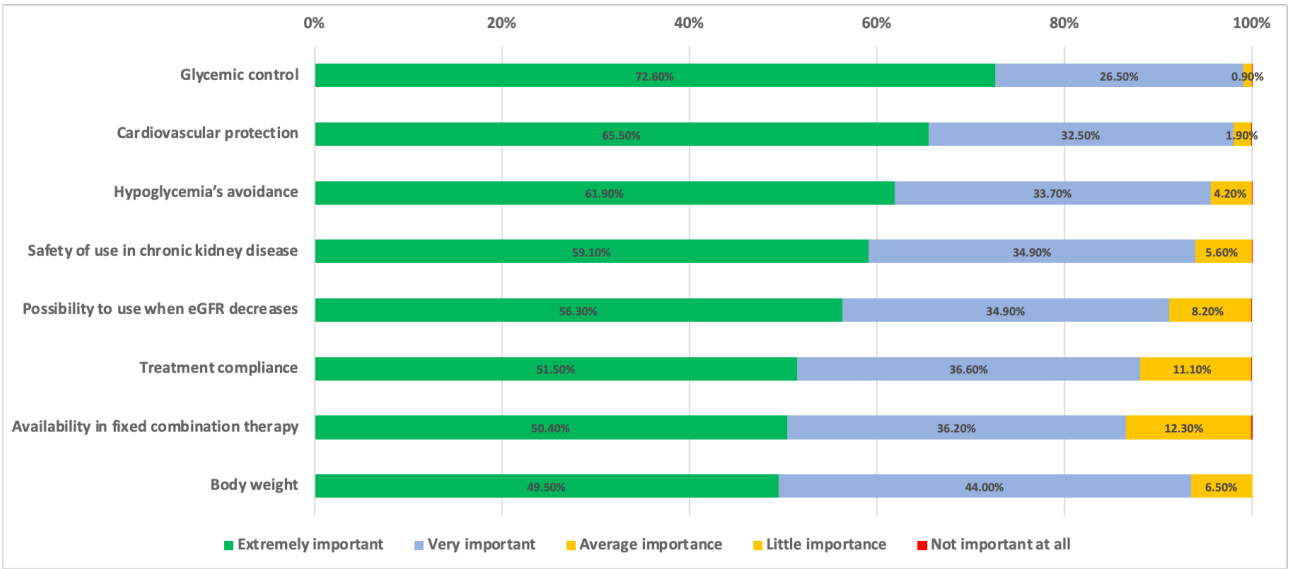

Figure 8: Responder's perception regarding therapeutic decision factors in patients with T2DM.

improvement of glycemic control. The excellent safety profile and possibility to use irrespective of eGFR is considered a key advantage for vildagliptin.

Disclosure

The study and data collection were sponsored by Medochemie S.R.L. Romania

Conflict of interest

The authors declare no conflict of interest.

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immune system, the skin and in patients with impaired renal function from a large pooled database of Phase II and III clinical trials. *Diabetes Obes Metab*. 12(6):495–509. doi: 10.1111/j.1463-1326.2010.01214.x.

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