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A multicenter, epidemiological study of the treatment patterns, comorbidities and hypoglycemia events of patients with type 2 diabetes and moderate or severe chronic kidney disease – the ‘LEARN’ study

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ABSTRACT
Objective Management of patients with type 2 diabetes (T2DM) and stage 3 to 5 chronic kidney disease (CKD) is challenging. The aim of the ‘LEARN’ study was to describe treatment patterns employed in this population and to record comorbidities, glycemic control and hypoglycemia episodes in routine clinical practice in Greece.

Research design and methods ‘LEARN’ was a non-interventional, multicenter, cross-sectional study conducted in Greece between 15 February 2013 and 4 July 2013. A total of 120 adult patients were enrolled from four hospital sites in different geographic regions of Greece.

Results Participants had a mean age of 69.1 ± 10.3 years and a male/female ratio of 2:1. Nearly all patients (99.2%) suffered from at least one comorbidity, with hypertension (95.8%) and hyperlipidemia/dyslipidemia (78.3%) being the most prevalent. Of the overall study population, 57.5% was managed with insulin therapy only, 30.8% with oral antidiabetics only and 11.7% with a combination of insulin and oral antidiabetics. The overall rate of glycemic control, defined as glycated hemoglobin (HbA1c) ≤ 7.0% during the most recent assessment, was 55.0%. This rate was significantly higher among those receiving oral antidiabetics only (73.0%) compared to insulin only (47.8%) or a combination of both types of treatment (42.9%) (p = 0.03). Moreover, patients receiving oral antidiabetics only had experienced fewer hypoglycemia episodes over the last 7 days prior to the study visit (0.1 ± 0.4) compared to patients receiving insulin only (0.9 ± 1.7) (p = 0.03).

Conclusions Although this is an observational study, it seems that oral antidiabetic therapy might be advantageous for heavily burdened T2DM patients with moderate or severe CKD in terms of glycemic control and hypoglycemia episodes. More data preferably from randomized trials is needed in order to validate this hypothesis.

Introduction
According to the International Diabetes Federation, an alarming 56.3 million Europeans 20–79 years old suffer from diabetes and the prevalence is expected to increase by 22.4% by 2035. This is mostly attributed to a sharp increase in the prevalence of overweight and obesity, the aging population, and the frequency of unhealthy diet and physical inactivity. It has been estimated that type 2 diabetes (T2DM) increases the risk of developing chronic kidney disease (CKD) 2.6-fold while it is the most common cause of end stage renal disease (ESRD) accounting for 44% of the new ESRD cases. CKD is defined as either kidney damage or Glomerular Filtration Rate (GFR) < 60 mL/min/1.73 m² for ≥ 3 months; kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies. There are five stages of CKD defined as follows: stage 1: kidney damage with GFR ≥ 90, stage 2: kidney damage with GFR 60–89, stage 3: GFR 30–59, stage 4: GFR 15–29, stage 5 (kidney failure) ≤ 15 (or dialysis). Moreover, apart from CKD, diabetes is a risk factor for various other comorbidities, including hypertension, dyslipidemia, atherosclerosis, depression, sleep disorders and cancer, as well as the risk of death from any cause. Specifically, a recent retrospective study reviewing medical records of over 125,000 patients reported that 99% of patients with T2DM were either at high risk of developing cardiovascular disease (CVD) or had established CVD. Moreover, in another study the proportion of patients with T2DM and uncontrolled or treated hypertension has been estimated to be near 67%.

The frequency of inadequate glycemic control in the T2DM patient has been reported to commonly be above 50% and even as high as 76% to 14%. Glycemic control in patients with diabetes and CKD is an especially difficult but imperative endeavor in order to prevent and control diabetes complications. It has been established that achievement of glycated hemoglobin (HbA1c) levels below 7% prevents microvascular complications of the disease. However, the
risk of hypoglycemia episodes is especially high in diabetic patients with stage 3–5 CKD, as a result of decreased renal gluconeogenesis, uremic malnutrition and impaired catecholamine release. This increased risk of hypoglycemia limits the ability to intensively treat hyperglycemia in diabetic patients with CKD. The 2012 National Kidney Foundation guidelines recommend not treating to an HbA1c target of <7.0% in patients at risk of hypoglycemia and suggest that the target HbA1c be extended above 7.0% in individuals who in addition to an increased risk of hypoglycemia suffer from comorbidities or have a limited life expectancy.

The management of the T2DM CKD patient is further complicated by the following factors. Certain dialysis strategies exacerbate hypo- and hyperglycemia, while as renal function worsens issues of drug accumulation become apparent and abnormalities in glucose homeostasis lead to impairments in the production of and sensitivity to insulin, limiting therapeutic options.

To our knowledge there is no data on the frequency of glycemic control and hypoglycemia episodes among patients with advanced CKD and T2DM in Greece. However, the prevalence of diabetes, as well as of many of the risk factors associated with the disease, namely obesity, hypertension, dyslipidemia, and depression, in the Greek population has largely increased over recent years suggesting that there is likely an increased morbidity burden for the diabetic patient with renal impairment. In light of the above and taking into account the introduction of new therapeutic strategies for the diabetic patient with renal impairment over recent years it was considered of interest to assess the rate of glycemic control in this patient population in Greece and to collect data on their therapeutic management. Moreover, the present study aimed at assessing the comorbidity burden and hypoglycemia episodes in patients with T2DM and moderate to advanced CKD as well as at exploring potential factors that may complicate the treatment choice in these patients, in daily clinical practice in Greece.

**Subjects and methodology**

**Study design and setting**

The ‘LEARN’ study was a non-interventional, multicenter, cross-sectional study. A total of 120 patients were planned to be enrolled and were actually enrolled from four hospital sites, located throughout Greece, regularly treating T2DM patients with CKD. Six physicians (four nephrologists, a general practitioner and an internal medicine physician) enrolled patients. Participants were recruited between 15 February 2013 (first subject in) and 4 July 2013 (last subject out).

Data collected pertaining to patients was recorded on electronic Case Report Forms (eCRFs). Data recorded included patients’ demographic and anthropometric characteristics; the therapeutic management for T2DM; information on the underlying CKD, hemodialysis, peritoneal dialysis and recent glomerular filtration rate (GFR); as applicable; comorbidities; medications for comorbidities; results of the most recent HbA1c laboratory test (in order to determine the proportion of the patients on target for HbA1c). GFR was calculated with the Modification of Diet in Renal Disease (MDRD) method. The treatment target for T2DM was set as HbA1c ≤7%, i.e. patients were considered to have adequately controlled diabetes if their HbA1c levels were ≤7%.

Furthermore, patients were asked to complete a hypoglycemia evaluation questionnaire in order to assess the hypoglycemia rate in the study population. The questionnaire also included questions pertaining to patients’ reactions to their most recent hypoglycemia episode, worries/concerns, actions taken to prevent hypoglycemia events, and activity limitations.

The study was conducted under real-life conditions of daily clinical practice and in accordance with ethical principles that have their origin in the Declaration of Helsinki (ICH-GCP guidelines) and all applicable national and EU laws and regulations.

**Subjects**

A total of 120 male or female patients ≥18 years old with T2DM and stage 3–5 CKD with moderate or severe renal impairment or with ESRD (GFR <60 mL/min/1.73 m²) as a complication of T2DM receiving any type of antidiabetic treatment were enrolled in the study. Major exclusion criteria included the presence of type 1 diabetes and serious ongoing uncontrolled infection or sepsis or any other reason of acute derangement of diabetes and/or renal function at the investigators discretion.

All patients were informed about the nature of the study and signed the informed consent form prior to the conduct of any study related procedures.

**Study objectives**

The primary objective of this study was to show treatment patterns employed for the management of patients with T2DM and CKD stages 3 to 5 in routine clinical practice in Greece. Secondary objectives included recording of comorbidities of study population, as well as the estimation of the proportion of HbA1c well controlled vs. uncontrolled patients and the percentage of hypoglycemia in the patient population. Furthermore, the study aimed to explore potential factors that may complicate the treatment choice in these patients, in daily clinical practice in Greece.

**Statistical analysis**

**Subgroups of interest**

For statistical analysis purposes, the study population was divided into two groups according to the most recent HbA1c value recorded in the study visit. The first group comprised patients attaining the HbA1c target levels (HbA1c ≤7%); and the second comprised those failing to attain the HbA1c target levels (HbA1c >7%).

In addition, the study population was divided into three subgroups depending on the type of their current antidiabetic treatment modality. More specifically the three groups have been defined as: patients treated only with insulin...
therapy for diabetes; patients treated with oral antidiabetic agents only; and patients treated with a combination of insulin and oral antidiabetics. The aforementioned groupings aimed to assess the study-specific endpoints in the different subpopulations of interest.

**Statistical methods**

The population set used for statistical analysis comprised all eligible enrolled patients who provided adequate evaluable data. The Wilcoxon–Mann–Whitney or Kruskal–Wallis non-parametric statistical tests were applied in order to assess the significance of the difference in continuous variables, while the Nemenyi statistical test was applied as post-hoc analysis in order to determine the source of statistical significance. The association between categorical variables was examined by Pearson's chi-squared test or Fisher's exact test, when applicable.

The correlation between continuous variables was examined by Spearman's rank correlation or Pearson's correlation coefficient as appropriate. The significance of the difference in continuous variables, while parametric statistical tests were applied in order to assess the correlation between continuous variables, when appropriate.

With regard to patient-reported outcomes as seen in the study-specific questionnaire, descriptive statistics (mean, standard deviation [SD], median and range) have been calculated for each separate item.

In order to examine how the impact of age (<65; 65–<75; >75 years), gender, type of antidiabetic treatment, time since T2DM diagnosis and actions taken to prevent the occurrence of hypoglycemia episodes (according to questionnaires’ respective items) may impact HbA1c levels (<7%; >7%), binary logistic regression has been applied. Initially, all the aforementioned factors were tested using a univariate logistic regression model, and only age and type of antidiabetic treatment reached statistical significance, thus these two factors were further examined in a multivariate logistic regression model.

Similarly, the impact of age group, gender, type of antidiabetic treatment and time since T2DM diagnosis on the count (frequency) of low blood sugar events (as reported by the patient during the last 7 days) as well as on the count of confirmed low blood sugar events was examined by Poisson regression model. In the context of sensitivity analysis, since Poisson models for low blood sugar events fitted poorly due to overdispersion (Scaled Pearson X2 ≥ 1) negative binomial models have been used instead.

All statistical tests were two-sided and were performed at a 0.05 significance level. Statistical analyses have been conducted using the statistical software package SAS v9.3.

**Results**

**Patient characteristics**

A total of 120 T2DM participants with stage 3–5 CKD were recruited from four hospital sites located in four different regions of Greece (Attica, West Greece, West Macedonia, and Thessaly). No protocol violations were recorded and all patients were included in the statistical analysis. Participants had a mean age of 69.1 ± 10.3 years and a male to female ratio of 2:1. The participants’ anthropometric and CKD characteristics are displayed in Table 1.

In terms of the overall population’s T2DM characteristics, the median time elapsed between the diagnosis of T2DM and the study visit was 20.0 years (range 1.1–60.3), while the mean HbA1c levels were 7.0 ± 1.1%.

**Estimation of HbA1c: well controlled vs. uncontrolled patients**

According to the most recent laboratory assessment of HbA1c conducted prior to the study visit, 55% (95% CI, 45.7–64.1%) of the study population were well controlled for their T2DM (HbA1c ≤7%), while 45% (95% CI, 35.9–54.4%) were poorly controlled. Patient distribution according to CKD stage and HbA1c target attainment is displayed in Figure 1.

**Treatment management patterns**

In terms of antidiabetic therapy received for T2DM, 57.5% of the overall population was managed with insulin therapy...
only, while 30.8% was managed only with oral antidiabetics and the remaining 11.7% with a combination of insulin and oral antidiabetics (Table 2). The most common antidiabetic medication was insulin glargine for the overall population, but also for the subpopulations meeting and not meeting the HbA1c target (28.3, 25.8 and 31.5%, respectively).

A statistically significant difference ($p = 0.03$) was observed between well controlled (HbA1c $\leq 7\%$) and poorly controlled (HbA1c $> 7\%$) patients with regard to their distribution among the three antidiabetic treatment patterns (Figure 2). In particular, 40.9% of patients meeting the HbA1c target were managed with oral antidiabetics compared to 18.5% of those not meeting the target. The rate of glycemic control was 73.0% among those receiving only oral antidiabetics, 47.8% among those receiving insulin only and 42.9% among those receiving a combination of both types of antidiabetic treatment (Table 2).

Among patients receiving only insulin antidiabetic therapy the most common chemical treatment categories were ‘intermediate-acting combined with fast-acting insulin’ (36.2, 30.3 and 41.7%, respectively, for the overall patient population, and those with well and poorly controlled diabetes), followed by long-acting insulin only (26.1, 30.3 and 22.2%, respectively). Among patients receiving only oral antidiabetic medications, biguanides monotherapy (specifically metformin) was the most common treatment category for the overall population (24.3%) as well as for those with well controlled diabetes (33.3%). Sulfonylureas monotherapy was most common (30.0%) among those with poorly controlled diabetes receiving only oral antidiabetics (Table 2).

The rates of glycemic control among specific chemical drug categories of oral antidiabetics were 73.7% among those

### Table 2. Antidiabetic medications in the overall population as well as in the subgroups of well controlled and poorly controlled diabetes.

<table>
<thead>
<tr>
<th>Type of therapy</th>
<th>Overall population $n = 120$</th>
<th>HbA1c $\leq 7%$ $n = 66$</th>
<th>HbA1c $&gt; 7%$ $n = 54$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC Chemical Category$^a$</td>
<td>$N$</td>
<td>%</td>
<td>$N$</td>
</tr>
<tr>
<td>Insulin therapy, only</td>
<td>69</td>
<td>57.5</td>
<td>33</td>
</tr>
<tr>
<td>Intermediate-acting combined with fast-acting insulin* only</td>
<td>25</td>
<td>20.8</td>
<td>10</td>
</tr>
<tr>
<td>Long-acting insulin only</td>
<td>18</td>
<td>15.0</td>
<td>10</td>
</tr>
<tr>
<td>Fast-acting insulin and long-acting insulin</td>
<td>10</td>
<td>8.3</td>
<td>4</td>
</tr>
<tr>
<td>Fast-acting insulin only</td>
<td>9</td>
<td>7.5</td>
<td>5</td>
</tr>
<tr>
<td>Intermediate-acting combined with fast-acting insulin* and long-acting insulin</td>
<td>3</td>
<td>2.5</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate-acting insulin only</td>
<td>2</td>
<td>1.7</td>
<td>2</td>
</tr>
<tr>
<td>Intermediate-acting and fast-acting insulin</td>
<td>1</td>
<td>0.8</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate-acting combined with fast-acting insulin* &amp; fast-acting insulin</td>
<td>1</td>
<td>0.8</td>
<td>–</td>
</tr>
<tr>
<td>Combination of insulin and oral antidiabetics</td>
<td>14</td>
<td>11.7</td>
<td>6</td>
</tr>
<tr>
<td>Biguanides only</td>
<td>9</td>
<td>7.5</td>
<td>9</td>
</tr>
<tr>
<td>Sulfonylureas only</td>
<td>6</td>
<td>5.0</td>
<td>3</td>
</tr>
<tr>
<td>Biguanides and DPP-4 inhibitors and sulfonylureas</td>
<td>5</td>
<td>4.2</td>
<td>3</td>
</tr>
<tr>
<td>DPP-4 inhibitors only</td>
<td>4</td>
<td>3.3</td>
<td>4</td>
</tr>
<tr>
<td>DPP-4 inhibitors and sulfonylureas</td>
<td>4</td>
<td>3.3</td>
<td>3</td>
</tr>
<tr>
<td>Biguanides and sulfonylureas</td>
<td>3</td>
<td>2.5</td>
<td>1</td>
</tr>
<tr>
<td>Biguanides and DPP-4 inhibitors</td>
<td>2</td>
<td>1.7</td>
<td>2</td>
</tr>
<tr>
<td>Biguanides and sulfonylureas and thiazolidinediones</td>
<td>1</td>
<td>0.8</td>
<td>–</td>
</tr>
<tr>
<td>Biguanides and DPP-4 inhibitors and thiazolidinediones</td>
<td>1</td>
<td>0.8</td>
<td>–</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1.7</td>
<td>2</td>
</tr>
<tr>
<td>Oral antidiabetic therapy, only</td>
<td>37</td>
<td>30.8</td>
<td>27</td>
</tr>
<tr>
<td>Biguanides only</td>
<td>9</td>
<td>7.5</td>
<td>9</td>
</tr>
<tr>
<td>Sulfonylureas only</td>
<td>6</td>
<td>5.0</td>
<td>3</td>
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<td>4.2</td>
<td>3</td>
</tr>
<tr>
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<td>4</td>
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<td>4</td>
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<td>4</td>
<td>3.3</td>
<td>3</td>
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<td>2</td>
</tr>
<tr>
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<td>–</td>
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<tr>
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<td>0.8</td>
<td>–</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1.7</td>
<td>2</td>
</tr>
</tbody>
</table>

$^a$Recorded medications were coded with the use of the ATC Drug Classification dictionary by WHOCC for Drug Statistics Methodology.

$^*$The category ‘intermediate-acting combined with fast-acting insulin’ may also include insulin available as intermediate or fast-acting formulations, if the type of formulation was not specified.

Fixed dose combinations are indicated by the term 'combined'.
receiving a dipeptidyl peptidase 4 (DPP-4) agent (sitagliptin or vildagliptin), 61.5% for biguanides (metformin), and 52.6% for any sulfonylurea (glimepiride or gliclazide) either alone or in combination with other oral agents or insulin.

In addition, a statistically significant difference was observed in treatment types between patients with different CKD stages (p < 0.001). Specifically, oral antidiabetics were more frequently used in patients with stage 3 CKD (49.2% vs. 5.3% for stage 4 and 11.1% for stage 5), while insulin therapy only was more common among stages 4 (63.2%) and 5 (86.1%) vs. stage 3 (40.0%) CKD patients.

The overall rate of glycemic control was 55.5% among CKD stage 5 patients, regardless of treatment type. The respective rate was 75% among patients with CKD 5 treated with oral antidiabetics only.

Nearly all patients (99.2%) were receiving medications other than their antidiabetic treatment. The most common therapeutic subgroups were lipid modifying agents (74.2%), antithrombotic agents (64.2%), calcium channel blockers (61.7%), agents acting on the renin–angiotensin system (57.5%) and beta-blockers (55.0%).

Comorbidities

Of the overall population, all but one patient (99.2%) suffered from at least one comorbidity. The most common groups of comorbidities were vascular disorders (96.7%) followed by metabolism and nutrition disorders (89.2%). Comorbidities present in more than one third of the patient population by MedDRA preferred term (PT) were: hypertension (95.8%), hyperlipidemia/dyslipidemia (78.3%), hyperuricemia (37.5%), myocardial ischemia (36.7%), secondary hyperparathyroidism (35.8%) and diabetic retinopathy (35.8%).

Among patients with well and poorly controlled T2DM, 98.5% and 100% suffered from at least one comorbidity. The list of comorbidities by MedDRA system organ class (SOC) and PT of the overall patient population and the subpopulations of well and poorly controlled diabetes are presented in Table 3.

Hypoglycemia episodes

In the last 7 days prior to the study visit, a total of 31.7% of the overall patient population perceived having a hypoglycemia episode(s) and 28.2% had confirmed hypoglycemia episodes. The proportion of patients experiencing patient-reported and confirmed hypoglycemia events was lower for patients meeting the HbA1c target (27.3% and 25.4%, respectively) than for those not meeting the target (37.0% and 31.5% respectively).

Similarly, the mean number of hypoglycemia episodes (whether patient-perceived or confirmed) during the last 7
days was lower in patients meeting the HbA1c target vs. those not meeting the HbA1c target (Table 4). In addition, the number of self-perceived (p = 0.04) as well as confirmed (p = 0.03) hypoglycemia events was statistically significantly lower among patients receiving only oral antidiabetic treatment compared to those receiving only insulin antidiabetic treatment (Table 4).

In the overall study population, the hypoglycemia event-free rate was 19.3%. This proportion was significantly higher among the patient subgroup meeting the HbA1c target (27.7%) compared to those not meeting the target (9.3%) (p = 0.01); as well as among patients on oral antidiabetic treatment only (65.2%) vs. those receiving only insulin treatment (34.8%) or on a combination of insulin and oral antidiabetic treatment (0%) (p < 0.001).

Moreover, a total score indicating the importance patients place on actions they may take to prevent the occurrence of hypoglycemia episodes was calculated from 12 specific measures of the patient-completed questionnaire, with a higher score representing increased importance. This score could range from 0 (not important at all) to 20 (extremely important). A significant difference was observed between patients receiving only oral antidiabetics vs. those receiving insulin (mean score 42.4 ± 22.2 vs. 55.8 ± 18.9, p = 0.007), but not among those with well controlled (47.5 ± 21.6) vs. poorly controlled (54.4 ± 19.2) diabetes. In addition, no significant differences between the study subgroups based on HbA1c target attainment and treatment pattern was demonstrated for any of the remaining items analyzed in the patient-completed questionnaires, i.e. feelings about the most recent hypoglycemia episode, worries/concerns, activity limitations and awareness of hypoglycemia.

Healthcare resource utilization (i.e. number of hospitalizations and emergency room visits) was low (median: 0; range: 0–2, for both hospitalizations and emergency rooms visits for the entire study population irrespective of the HbA1c target attainment) for the year prior to the study visit.

Factors affecting attainment of HbA1c target levels and frequency of hypoglycemia episodes

In terms of factors appearing to affect the attainment of HbA1c target levels, both age and antidiabetic treatment patterns were assessed as statistically significant in the multivariate logistic regression model applied. Younger patients (<65 years old) appear more likely to achieve HbA1c target levels than those aged over 75 years. Likewise, patients treated with oral antidiabetics only were found to be 3.59 times (95% CI: 1.45–8.90; p = 0.01) more likely to attain their HbA1c levels than those receiving insulin monotherapy (Table 5).

Furthermore, the group of patients receiving only oral antidiabetics appeared to be 79% (Incidence ratiooral antidiabetics vs. insulin treatment only: 0.21 [95% CI: 0.08–0.55]; p = 0.002) less likely to experience patient-perceived hypoglycemic episodes compared to those receiving insulin only. The respective percentage based on the incidence rate ratio of the confirmed hypoglycemic episodes is 85% (IRR oral antidiabetics vs. insulin treatment only: 0.15 [95% CI: 0.05–0.46]; p = 0.001) (Table 5).

Discussion

The rate of glycemic control in the overall study population defined as HbA1c levels ≤7.0% was 55.0%. This rate is higher than that reported in previous studies of patients with T2DM (independent of the presence of kidney disease) in which the rates of control varied from 47.3%14 to 27%25, 25%26 and 24%13. Notably, in the present study the rate of glycemic control was higher among patients receiving only oral antidiabetics compared to those receiving only insulin antidiabetic
treatment. Multivariate logistic regression models estimated that patients treated with oral antidiabetics only are 3.59 times (95% CI: 1.45–8.90; \( p = 0.01 \)) more likely to attain their HbA1c levels \(<7\%\) than those receiving insulin monotherapy (Table 5). This finding is in support with those of other studies. Specifically, in a cross-sectional study conducted in Brazil between 2006 and 2007, the rate of glycemic control was 10% among insulin-treated and 36% among non-insulin treated patients\(^{25}\). In a similar study conducted in Venezuela during 2007, the respective rates were 10% and 30%\(^{26}\). In both studies, although an effect of diabetes duration on the rates of glycemic control was identified, insulin treatment was associated with poorer glycemic control compared to diet only or diet and oral antidiabetic treatment even in the subgroup of patients with a recent (within the last 5 years) diabetes diagnosis\(^{25,26}\). An age effect on glycemic control was identified in the present study. In particular, younger patients (≤65 years old) were shown to be more likely to attain HbA1c target levels than those aged over 75 years.

The higher rate of glycemic control observed in the present study is likely attributed to the introduction of newer antidiabetic treatments in the therapeutic armamentarium of T2DM patients with renal impairment over the last 7 years. It’s worth mentioning that the rates of glycemic control were 73.7% among patients receiving a DPP-4 agent and 61.5% among patients receiving metformin, whether these agents were received as monotherapy or in combination with other oral antidiabetics or insulin. There is ample evidence that incretin-based therapies, which include DPP-4 agents, have improved glycemic control in the setting of CKD\(^{27–31}\). Of the DPP-4 agents, those used in the present study were sitagliptin and vildagliptin. Sitagliptin was the first agent of this class to be introduced into the market in 2007 and vildagliptin followed in 2007\(^{29}\). These agents offer the advantage of a negligible risk for the development of hypoglycemia as well as weight neutrality, i.e. neither a significant weight loss nor gain. Moreover, these two agents are approved and can be used in patients with moderate or severe renal impairments\(^{22,33}\), unlike metformin\(^{29}\). Another interesting finding of this study is that physicians sometimes use metformin in the CKD 3–5 patient population (24.3%), where metformin is not indicated.

Among patients on dialysis the glycemic control rate was 55.5%. The vast majority of this patient population (86.1%) was treated only with insulin antidiabetic therapy, 11.1% only with oral antidiabetics, while 2.8% were treated with a combination of insulin and an oral antidiabetic. The glycemic control rate among patients on dialysis receiving only oral antidiabetics was 75%. Due to the small number of patients on dialysis receiving oral antidiabetics in the present study (4 of 36) no definitive conclusions can be drawn as to the advantage offered by this treatment modality. However, these observations warrant the conduct of further studies in a real-life clinical setting, designed to assess a cause and effect relationship between the use of oral antidiabetics and glycemic control of the diabetic CKD patient population, including those on dialysis.

In the last 7 days prior to the study visit, 28.2% of the overall patient population experienced one or more hypoglycemia episode. Treatment with oral antidiabetics appeared to offer an advantage both in the frequency of hypoglycemia episodes as well as in the hypoglycemia event-free rate. Specifically, with regard to the number of hypoglycemic episodes during the last 7 days, patients treated only with oral antidiabetics appear to be 79% less likely to experience hypoglycemia compared to those being only on insulin antidiabetic therapy (\( p = 0.001 \)). In addition, the proportion of patients never experiencing a hypoglycemia event was significantly higher among patients on oral antidiabetic treatment only (65.2%) vs. those receiving only insulin treatment (34.8%) or a combination of insulin and oral antidiabetic treatment (0%) (\( p < 0.001 \)). The benefit of oral antidiabetics vs. insulin treatment in terms of a lower frequency of hypoglycemia episodes has been implied in a previous study\(^{34}\). Controlling the frequency and severity of hypoglycemia episodes is of crucial importance as hypoglycemia is linked with severe complications such as dizziness, disorientation, fatigue, convulsions, coronary ischemia and even death\(^{35–36}\). A relatively large retrospective cohort study of patients with or without CKD and with or without diabetes identified that patients with CKD had a higher risk of mortality, while the risk of hypoglycemia was shown to be the highest among patients with both diabetes and CKD\(^{19}\). The results of the present study suggest that there is room for improvement in terms of the

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### Table 5. Factors influencing HbA\(_1c\), target level attainment and hypoglycemia incidence.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Categories</th>
<th>Incidence rate ratios</th>
<th>95% CI</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multivariate logistic regression model for factors influencing HbA(_1c), target level attainment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>≤65 years vs. &gt;75 years</td>
<td>2.85</td>
<td>1.01</td>
<td>8.04</td>
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<tr>
<td></td>
<td>&gt;65–≤75 years vs. &gt;75 years</td>
<td>0.89</td>
<td>0.35</td>
<td>2.24</td>
</tr>
<tr>
<td><strong>Antidiabetic treatment patterns</strong></td>
<td>Oral antidiabetics only vs. insulin treatment only</td>
<td>3.59</td>
<td>1.45</td>
<td>8.90</td>
</tr>
<tr>
<td></td>
<td>Combination of oral antidiabetics vs. insulin treatment only</td>
<td>1.08</td>
<td>0.32</td>
<td>3.61</td>
</tr>
<tr>
<td><strong>Negative binomial model of factors influencing the number of confirmed hypoglycemia episodes during the last 7 days prior to the study visit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antidiabetic treatment patterns</strong></td>
<td>Oral antidiabetics only vs. insulin treatment only</td>
<td>0.21</td>
<td>0.08</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>Combination of oral antidiabetics vs. insulin treatment only</td>
<td>0.76</td>
<td>0.25</td>
<td>2.31</td>
</tr>
</tbody>
</table>

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occurrence of hypoglycemia episodes in this patient population. Since hypoglycemia may often be induced by antidiabetic therapies, employment of newer therapeutic strategies offering an advantage in terms of hypoglycemia episodes is advised.

In the present study, the population was heavily burdened by comorbidities, with 99.2% reporting at least one comorbidity. Of the patients, 95.8% suffered from hypertension and 78.3% from hyperlipidemia/dyslipidemia. These findings underscore the difficulties in managing this patient population and support the need for a multidisciplinary approach.

The findings of the study are somewhat limited by concerns that the measurement of HbA1C may be affected by the severity of renal impairment or the hematological complications of kidney disease, such as iron deficiency, hemolysis, shorter red blood cell lifespan, or acidosis. HbA1C levels may underestimate glycemic control in T2DM patients undergoing hemodialysis due to renal anemia and the use of erythropoietin. Glycated albumin has been suggested as an alternate optimal marker of glycemic control in these patients.

Notably, this concern applies to about 30% of our patient population comprising patients undergoing dialysis, since the remaining 70% were not undergoing dialysis. Moreover, HbA1C remains the most commonly used measure of long-term glycemic control in clinical studies.

In terms of other limitations of observational studies, such as patient selection bias and influence of confounding factors, the following steps were taken: physicians were requested to consecutively enroll the first 30 patients (based on the site-specific target) attending their clinic that met the study-specific eligibility criteria in order to minimize patient selection bias. Additionally, the possible influence of confounding factors on the outcomes of this study has been accounted for in the statistical analyses by use of multivariable analyses.

Another limitation of the study was that the hypoglycemia rate was estimated retrospectively for a short time-period of 7 days. However, the short recall period of hypoglycemic episodes was chosen in order to minimize the likelihood of recall (information) bias between patients with and without hypoglycemic events. Additionally, interview bias was avoided by using a questionnaire that was self-administered in paper-and-pencil mode. However, it is noted that the questionnaire used in the study was neither a validated nor a standardized instrument, thus limiting the comparability of the patient-reported outcomes to the results of other studies. Moreover, self-administered questionnaires are prone to bias due to the fact that certain participants may have wanted to check answers that portrayed them favorably, while others may have exaggerated their symptoms and severity.

With regard to external validity, i.e., the ability to generalize the study results to a more universal population, the small number of study centers (n = 4) makes it difficult to generalize the results to the general population of diabetic patients with moderate to severe CKD in Greece. Regardless, the study was conducted in a real life clinical setting in various regions of Greece by both specialized nephrologists and general practitioners/internists and offers a snapshot of real world clinical outcomes and observations. Notably, the study population was nearly equally distributed among those meeting and not meeting the HbA1C target allowing for meaningful comparisons among these study subgroups.

In conclusion, the present study indicates that, in Greece, patients with T2DM and moderate or severe CKD represent a population heavily burdened by comorbidities. Moreover, the study suggests that there is room to improve the glycemic control rate and to decrease the frequency of hypoglycemia episodes. The majority of patients regardless of CKD stage were mainly treated with insulin monotherapy; however, an advantage was observed in terms of glycemic control, number of hypoglycemia episodes and hypoglycemia event-free rate in the patient subgroup receiving only oral antidiabetic treatments. Further studies are warranted investigating the benefit of oral antidiabetics in general, but also of particular therapeutic categories, for the diabetic patient with moderate or severe renal impairment.

**Transparency**

**Declaration of funding**

Novartis Greece was the sponsor of the study. The sponsor was responsible for medical writing and review of the manuscript.

**Declaration of financial/other relationships**

G.R., E.P. and C.V. have disclosed that they are employees of Novartis Hellas SACI. C.K., I.S. and D.G. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

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