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Chronic kidney disease in type 2 diabetic patients followed-up by primary care physicians in Switzerland: prevalence and prescription of antidiabetic drugs

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Summary

QUESTION UNDER STUDY: The aim of this study was to assess the prevalence of chronic kidney disease (CKD) among type 2 diabetic patients in primary care settings in Switzerland, and to analyse the prescription of antidiabetic drugs in CKD according to the prevailing recommendations.

METHODS: In this cross-sectional study, each participating physician was asked to introduce anonymously in a web database the data from up to 15 consecutive diabetic patients attending her/his office between December 2013 and June 2014. Demographic, clinical and biochemical data were analysed. CKD was classified with the KDIGO nomenclature based on estimated glomerular filtration rate (eGFR) and urinary albumin/creatinine ratio.

RESULTS: A total of 1 359 patients (mean age 66.5 ± 12.4 years) were included by 109 primary care physicians. CKD stages 3a, 3b and 4 were present in 13.9%, 6.1%, and 2.4% of patients, respectively. Only 30.6% of patients had an entry for urinary albumin/creatinine ratio. Among them, 35.6% were in CKD stage A2, and 4.1% in stage A3. Despite prevailing limitations, metformin and sulfonylureas were prescribed in 53.9% and 16.5%, respectively, of patients with advanced CKD (eGFR <30 ml/min). More than a third of patients were on a dipeptidyl-peptidase-4 inhibitor across all CKD stages. Insulin use increased progressively from 26.8% in CKD stage 1–2 to 50% in stage 4.

CONCLUSIONS: CKD is frequent in patients with type 2 diabetes attending Swiss primary care practices, with CKD stage 3 and 4 affecting 22.4% of cases. This emphasizes the importance of routine screening of diabetic nephropathy based on both eGFR and urinary albumin/creatinine ratio, the latter being largely underused by primary care physicians. A careful individual drug risk/benefit balance assessment is mandatory to avoid the frequently observed inappropriate prescription of antidiabetic drugs in CKD patients.

***Key words**: type 2 diabetes; chronic kidney disease; antidiabetic drugs; primary care*

Abbreviations

ACR	albumin/creatinine ratio
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
DPP-4	dipeptidyl-peptidase-4
eGFR	estimated glomerular filtration rate
GLP-1	glucagon-like peptide-1
KDIGO	Kidney Disease: Improving Global Outcomes
T2D	type 2 diabetes

Introduction

Chronic kidney disease (CKD) in diabetic patients is on the rise owing to the increased prevalence of type 2 diabetes (T2D) and the aging population [1]. However, we are lacking data for the prevalence of CKD in the diabetic population followed-up by primary care physicians in Switzerland although it is well recognised that in the last decades diabetic nephropathy has become one of the leading causes of end-stage renal disease.

In Switzerland, recommendations for the use of antidiabetic drugs in CKD were elaborated in 2012 by the Swiss Society of Endocrinology and Diabetology (SSED) [2]. Whether these recommendations have reached PCPs and are followed by them is not clear and has never been evaluated. Therefore, the goal of this cross-sectional study was to examine the prevalence of CKD stages in T2D patients followed-up by PCPs in Switzerland and to examine accordingly the prescription of antidiabetic drugs.

Methods

Data were collected from December 2013 to June 2014 in Switzerland by performing a cross-sectional survey of ambulatory diabetic patients visiting their physicians. The criterion for recruitment was T2D. An exclusion criterion was type 1 diabetes. Randomisation of participating physicians was as follows: for the German and French linguistic regions of Switzerland, around 109 physicians were recruited randomly among general practitioners and internists. No

physician from the Italian-speaking part of Switzerland was included in the study. The participating physicians were asked to collect the data from up to 15 consecutive diabetic patients. The data were entered anonymously in a web database elaborated by PNN AG (www.pnn.ch). One hundred and nine physicians participated in the survey. Each participating physician received 30 CHF per included patient. The maximum amount paid was 450 CHF (for 15 patients) even if the physician included more than 15 patients. Informed consent was obtained from each patient.

Demographic and clinical data, complications related to diabetes and details of antidiabetic, antihypertensive and lipid lowering therapies and aspirin treatment were collected using a standardised web questionnaire. Estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [3]. The age-related eGFR decline was estimated using simple linear regression stratified by sex. For the evaluation of albuminuria, only the albumin/creatinine ratio (ACR) was considered for classification, in accordance with Kidney Disease: Improving Global Outcomes (KDIGO) [3] as shown in table 1. In this manuscript we report the data for CKD stages and detailed antidiabetic therapy. The history of hypoglycaemia was assessed by asking patients to rate the frequency of hypoglycaemic events according to the following categorisation: never, low, medium and high.

This study was supported by Boehringer Ingelheim and Lilly for the logistics of data collection but not for data analysis and manuscript preparation, which was performed independently by the authors. The study was approved by the Ethics Committee of the Canton de Vaud.

Results

In the German-speaking region of Switzerland, 134 physicians were willing to participate (134/4097 = 3.2% of primary care physicians including general medicine, internal medicine and general internal medicine). Among them, 76 finally introduced at least one case in the database (76/134 = 56.7%). In the French-speaking regions of Switzerland, 61 physicians were willing to participate (61/1416 = 4.3% of primary care physicians (including general medicine, internal medicine and general internal medicine). Among them, 33 finally introduced at least one case in the web database (33/61 = 54%). The representation of primary care physicians per population was similar in the German- and French-speaking regions. Finally, a total of 109 primary care physicians from 20 German- or French-speaking cantons participated in the study with a total of 1359 patients included for analysis. The characteristics of enrolled patients are presented in table 2. There were a majority of male and Caucasian patients. Average age was of 66.5 ± 12.4 years (mean ± standard deviation [SD]) with the majority (57.5%) being in the 60–80 year age group. Mean duration of diabetes was 9.3 years and mean body mass index (BMI) was 30.2 kg/m^2, with only 16% having a normal BMI.

Stages of chronic kidney disease

The distribution of eGFR according to the CKD-EPI equation is presented in table 2. Since dose adaptation of oral

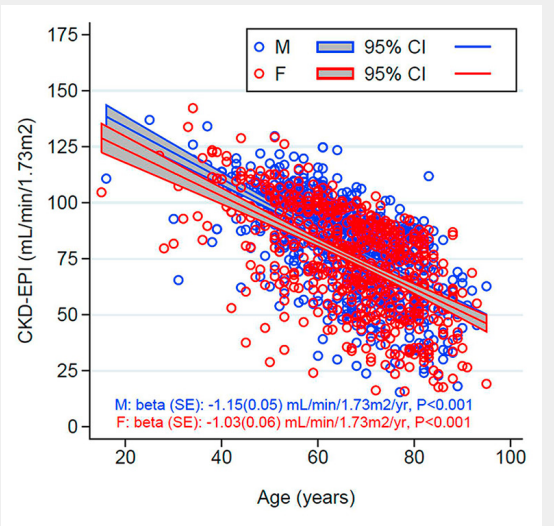


Figure 1

Beta coefficient and standard error (SE) from simple linear regression.
CI = confidence interval; CKD-EPI = chronic kidney disease-epidemiology collaboration

Table 1: KDIGO 2012 CKD classification by GFR categories and urinary albumin/creatinine ratio.

Prognosis of CKD by eGFR and ACR				**Albuminuria categories**		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
			ACR	<3 mg/mmol	3–30 mg/mmol	>30 mg/mmol
GFR categories (ml/min/1.73 m^2)	G1	Normal or high	≥90	+/–	+	++
	G2	Mildly decreased	60–89	+/–	+	++
	G3a	Mildly to moderately decreased	45–59	+	++	+++
	G3b	Moderately to severely decreased	30–44	++	+++	+++
	G4	Severely decreased	15–29	+++	+++	+++
	G5	Kidney failure	<15	+++	+++	+++

ACR = urinary albumin/creatinine ratio; CKD = chronic kidney disease; GFR = glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes
+/– low risk (if no other markers of kidney disease, no CKD)
+ moderately increased risk
++ high risk
+++ very high risk

antidiabetic drugs is recommended only with an eGFR <60 ml/min/1.73 m^2, and equations are less reliable for eGFRs >60 ml/min/1.73 m^2, we chose to group values over 60 ml/min/1.73 m^2 as CKD stages 1–2. CKD stages were possible to calculate in only 1 354 patients because 5 patients had unreliable values, presumably owing to an error of data entry. Estimated GFR was ≥60 ml/min/1.73 m^2 in 77.6% of patients. CKD stages 3a, 3b and 4 were present in 13.9%, 6.1%, and 2.4%, respectively. Nobody presented with CKD stage 5. By plotting the CKD stages according to age and sex (fig. 1), it was possible to estimate the age- and sex-related decline in renal function, using simple linear regression. The estimated decline in renal function was –1.15 (0.05) ml/min/1.73m^2/y (p <0.001) for men and –1.03 (0.06) ml/min/1.73 m^2/y (p <0.001) for women. For the evaluation of albuminuria, only 416 patients (30.6% of total) had an entry for ACR. Of these, 35.6% were in CKD stage A2 and 4.1% in stage A3. When an eGFR of <60 ml/min/1.73 m^2 and/or the presence or albuminuria were considered to indicate the presence of significant nephropathy, 45.4% of diabetic patients had significant nephropathy and 22.4% needed adjusted antidiabetic therapies according to Swiss recommendations because of an eGFR <60 ml/min/1.73 m^2. More than 70% were reported to follow a healthy way of life throughout all CKD stages.

Antidiabetic therapy and chronic kidney disease stages

Metformin and DPP-4 (dipeptidyl-peptidase-4) inhibitors were the two most commonly prescribed oral antidiabetic therapies (74% and 34.2% respectively), whereas the use of sulfonylureas was less frequent (20.5%). Insulin was prescribed in 28.9% of cases. Among the 1 359 patients, 6.3%, 37.7%, 38.3%, 15.7% and 1.9%, respectively, had no, one, two, three and four pharmacological antidiabetic therapies (fig. 2a). Because over three-quarters of individuals were either on mono- or dual therapy, we chose to examine more precisely which classes of antidiabetic therapy were prescribed. Metformin was the preferred option for monotherapy (57.1%) followed by insulin (19.8%) and sulfonylureas (9.2%) (fig. 2b). The combination of metformin and a DPP-4 inhibitor was the preferred option for dual therapy (47.3%) followed by metformin and insulin (22.1%) and metformin and a sulfonylurea (14.3%) (fig. 2c).

The prescription of each class of antidiabetic therapy according to CKD stage is presented in figure 3. Metformin was the preferred option at all stages of CKD except for CKD stage 4. In spite of the prevailing contraindications for its use in CKD stage 3b or more, metformin was prescribed in 57.8% and 43.8%, respectively, of patients with CKD stages 3b or 4. DPP-4 inhibitors were prescribed approximately the same at all CKD stages, with a slight trend towards more use with advancing CKD stages (34%, 33.5%, 37.3%, 37.5% for stages 1–2, 3a, 3b and 4, respectively). Insulin use increased progressively from 26.8% in CKD stage 1–2 to 50% in CKD stage 4. Sulfonylureas were prescribed in 21.0%, 20.7%, 19.3% and 9.4% for stages 1–2, 3a, 3b and 4, respectively. GLP-1 (glucagon-like peptide-1) agonists were prescribed in 7.0%, 4.8%, 1.2% and 3.1% for stages 1-2, 3a, 3b and 4, respectively. Prescriptions of glinides, glitazones and alpha-glucosidase inhibitors were all under 5% throughout CKD stages. Inappropriate therapy with regard to eGFR was frequently observed, especially for metformin in patients with CKD stage 3b or more (table 3).

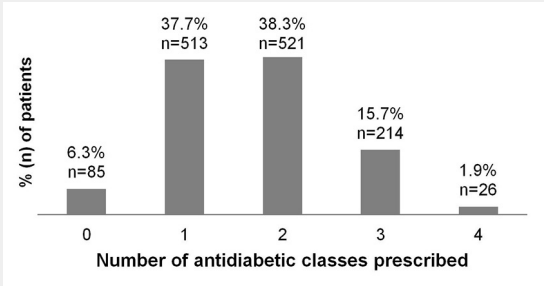
Regarding the question about hypoglycaemia, 611 answers were missing. While stratifying the response according to CKD stage, we chose to group low, medium and high frequency as "yes" and never as "no". Among the 748 patients who answered to the question about hypoglycaemia, the prevalence of patients with episodes of hypoglycaemia were increased at CKD stages 3 and 4 (25%, 34%, 61.4% and 47.6% in CKD stages 1–2, 3a, 3b and 4, respectively) (fig. 4) and was significantly correlated with CKD stage (p <0.0001).

Table 2: Characteristics of type 2 diabetic patients enrolled in the study.

	Number	%	Mean (standard deviation)
Sex: M/F	782/577	57.5/42.5	
Ethnicity: C/A	1 338/21	98.5/1.6	
Age (y)	1 359		66.5 (12.4)
<40 y	34	2.5	
40–60 y	335	24.7	
60–80 y	781	57.5	
>80 y	209	15.4	
Duration of diabetes (y)			9.3 (8.8)
Body mass index (kg/m^2)			30.2 (5.7)
<25 kg/m^2	217	16	
25–30 kg/m^2	537	39.5	
30–35 kg/m^2	364	26.8	
35–40 kg/m^2	152	11.2	
>40 kg/m^2	88	6.5	
CKD stage (GFR in ml/min/1.73 m^2):			
Stage 1–2 (≥60)	1 051	77.6	
Stage 3a (45–59)	188	13.9	
Stage 3b (30–44)	83	6.1	
Stage 4 (15–29)	32	2.4	

A = African descent; C = Caucasian; CKD = chronic kidney disease; F = female; GFR = glomerular filtration rate; M = male

Discussion



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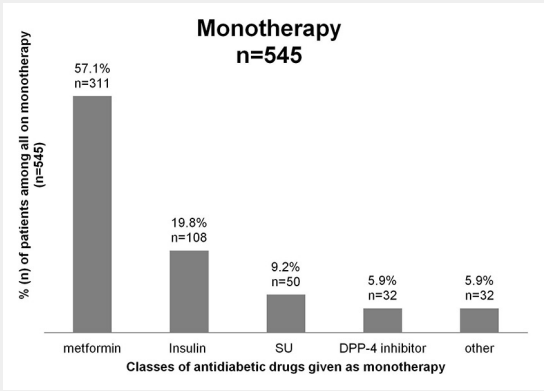

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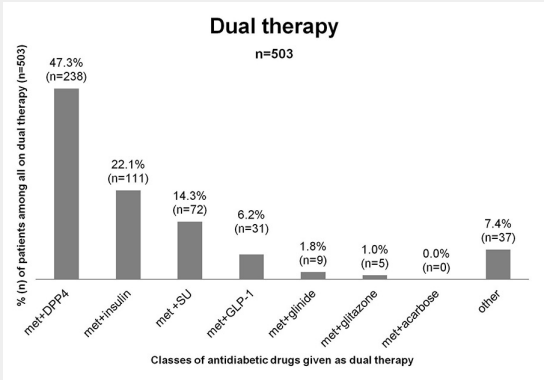

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Figure 2

Antidiabetic therapy in diabetic patients treated in primary care practices. Number of classes prescribed (2a), classes of drugs prescribed as monotherapy (2b), classes of drugs prescribed as dual therapy (2c).
DPP-4 = dipeptidyl-peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 agonist; met = metformin; SU = sulfonylurea

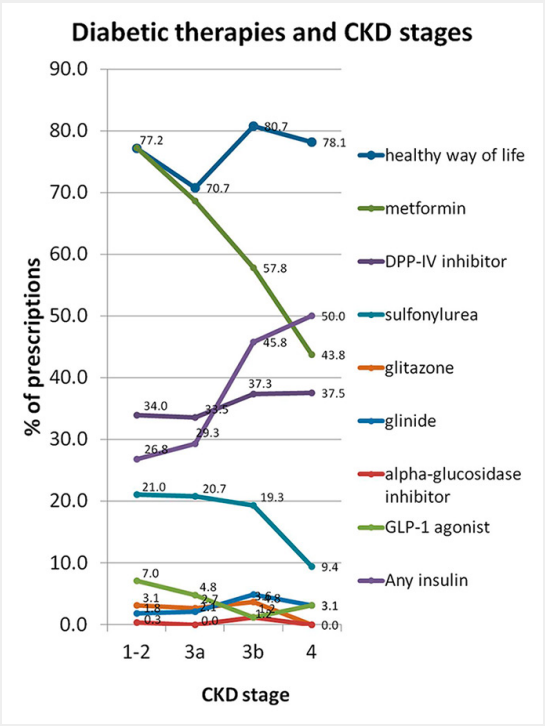

Figure 3

Antidiabetic class prescriptions (%) and chronic kidney disease (CKD) stage.
DPP-IV = dipeptidyl-peptidase-4; GLP-1 = glucagon-like peptide-1

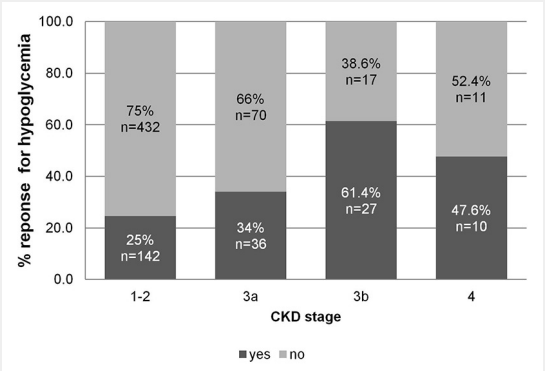

Figure 4

Presence of hypoglycaemia and chronic kidney disease (CKD) stage.

Table 3: Inappropriate antidiabetic therapies according to prevailing recommendations.

Drug and recommendations	**% prescriptions**
Metformin in CKD stage ≥3b	53.9%
Sulfonylurea in CKD stage ≥3b*	16.5%
GLP-1 in CKD stage ≥4	3.1%
Inappropriate dual therapy:	
Sulfonylurea and glinide	0.2%
GLP-1 agonist and DPP-4 inhibitor	0.5%

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; DPP-4 = dipeptidyl peptidase-4
* Sulfonylureas are contraindicated in CKD stage 3 except for gliclazide, which can be given until an eGFR of 40 ml/min. For simplification, we examined the prescriptions in CKD stage ≥3b

Prevalence of significant chronic kidney disease in type 2 diabetes treated in primary care practices in Switzerland.

To our knowledge, this study is the first to assess CKD prevalence and diabetes management in T2D patients treated in a primary care setting in Switzerland. We found that CKD stage 3–5 is common in T2D patients (22.4%). This is in agreement with a recent USA observational study which reported a CKD stage 3–5 prevalence of 25.8% in a population of 9 339 T2D patients treated by primary care physicians [4]. In contrast, this prevalence was much lower in Finland (16.2%) in a study with a similar design but a smaller number of patients than ours [5]. The estimated decline in renal function was –1.15 (0.05) ml/min/1.73 m^2/y ($p < 0.001$) for men and –1.03 (0.06) ml/min/1.73 m^2/y ($p < 0.001$) for women, much higher than the estimated decline in the general population Colaus study (–0.58 ml/min/1.73 m^2/y; average age = 51.1 y) [6], or the decline among the Colaus 65–75-year-old group (–0.91 ml/min/1.73 m^2/y, Murielle Bochud, Peter Vollenweider personal communication, unpublished results).

When combining patients with both eGFR and ACR values available, the rate of CKD stage 3–5 and/or albuminuria, was 45.4% in Switzerland and 34.7% in the Finnish study [5]. However, this rate could be inaccurately estimated in our study as ACR values were available for only 30.6% of patients. Underutilisation of ACR annual screening in T2D patients followed-up in primary care has previously been reported. In a cross-sectional study conducted in 2004 in the French-speaking part of Switzerland, annual screening for albuminuria was performed in only 49% of patients [7]. Similarly, a more recent retrospective Swiss study of T2D patients admitted to a general internal medicine clinic in 2009 showed a screening rate of 56% in patients with new onset diabetes and 66% in patients with previously diagnosed T2D [8]. In a USA primary care setting, ACR testing was performed in only 47.1% of T2D patients [4]. These results further emphasise the need to improve primary care physician adherence to routine screening and follow-up of diabetic nephropathy using both eGFR and ACR, as recommended by current guidelines [9].

Patterns of prescribed antidiabetic regimens in primary care practice

In our study, metformin was the preferred option overall (74%), as monotherapy (57.1%) or dual therapy (92.7%). Our data are in line with those from the United Kingdom primary care setting, in which close to 90% of patients received metformin as initial monotherapy or combination therapy [10]. These practices are in accordance with current American Diabetes Association / European Association for the Study of Diabetes (ADA-EASD) guidelines (2015), which recommend metformin as first-line pharmacological therapy in T2D [11]. The other monotherapy options included insulin (19.8%), sulfonylureas (9.2%) and DPP-4 inhibitors (5.9%). The reason why each class was chosen as monotherapy instead of metformin was not investigated in the present study. According to ADA-EASD guidelines, if metformin is contraindicated or poorly tolerated, physicians should consider one of the six other classes including insulin [11]. At the time of the study, there was no scientific evidence supporting superiority of any antidiabetic class as second choice. When prescribing antidiabetic therapy, physicians need to take into account efficacy, hypoglycaemia risk, effect on weight, side effects, costs and patient preference. According to the UK National Institute for Health and Care Excellence (NICE) guidelines, sulfonylureas can also be considered as first-line therapy in nonobese patients, or when a rapid response to therapy is required because of severe hyperglycaemia [12].

Most patients in our study were on dual therapy. In patients with long-standing and complicated diabetes, a combined regimen of antidiabetic drugs is often required to achieve glycaemic targets. Among dual therapies, combination of metformin and a DPP-4 inhibitor was the preferred option, probably because both target different pathways without the sulfonylurea or insulin side effects of weight gain and hypoglycaemia.

Appropriateness of prescription of antidiabetic agents according to degree of renal impairment

The kidneys are involved in the metabolism and clearance of almost all antidiabetic agents [2]. Therefore, prescribing antidiabetic drugs in patients with diabetes and CKD is challenging, with special concerns regarding safety issues and the need for appropriate dosage adjustment according to eGFR.

Metformin is currently recommended as first-line pharmacological therapy in T2D unless there are contraindications [11]. Contraindications to metformin use mainly relate to renal function as this drug is primarily excreted unchanged by the kidney. Renal failure leads to drug accumulation that potentially enhances the risk of lactic acidosis, a rare (4.3/100 000 patient/years) but potentially fatal condition [13].

The SSED clinical practice guidelines, published in 2012 and valid when the study was conducted, propose a cut-off of eGFR <45 ml/min/1.73 m^2 for stopping metformin [2]. In contrast, other guidelines (NICE, ADA-EASD, Canadian Diabetes Association) allow metformin use with great caution in stable CKD stage 3b only with appropriate dosage reduction and close monitoring of renal function [14–16]. The Swiss label for metformin (Glucophage®) has consequently been updated to emphasise that metformin may be maintained in moderate stable CKD (eGFR 30–60 ml/min/1.73 m^2) with dosage reduction (maximum dosage 1 000 mg/d), and close monitoring of eGFR, unless there are conditions that interfere with the metabolism/excretion of lactic acid (liver disease, heart failure, acute illness).

Despite prevailing limitations with regard to renal function, our study showed that the use of metformin in T2D patients with CKD stage 3b or more was very common (53.9%). In real-life practice, poor adherence to the metformin label / guidelines for kidney impairment has been reported worldwide, ranging between 4.5–30% in outpatient settings [17–21]. The OREDIA French cross-sectional observational study reported metformin use in 33% of T2D patients with renal contraindications (eGFR <30 ml/min/1.73 m^2) [17]. Also, the USA retrospective database analysis of 344 770 outpatient electronic medical records showed that metformin was used in 21.5%, 19.8% and 20.1%, respect-

ively of patients with moderate, severe and end-stage CKD [18].

This study was not intended to assess the theoretical knowledge of primary care physicians on diabetic CKD management. Inaccurate renal function assessment, under-recognition/awareness of CKD as well as lack of application of guidelines, rather than lack of knowledge, could be possible explanations for inappropriate prescription of metformin in CKD [4, 17]. The aim of the original metformin label was to provide a margin of safety to minimise the risk of metformin-associated lactic acidosis. However, issues of safe use of metformin in moderate CKD (stage 3) are being questioned and the cut-off for renal safety is controversial. A recent systematic review assessed the risk of metformin-associated lactic acidosis in patients with impaired renal function [22]. This review found that: (i) although metformin clearance is decreased proportionally with eGFR decline, drug levels remain generally within therapeutic range without a significant increase in lactate levels when eGFR is >30 ml/min/1.73 m^2; (ii) data suggesting increased risk of lactic acidosis in metformin-treated patients with CKD are limited; (iii) no randomised controlled trial has been conducted to assess the safety of metformin in significantly impaired kidney function. Experts supporting metformin use in moderate CKD argue that, if metformin is avoided in moderate CKD because of the fear of lactic acidosis, alternative use of sulfonylureas or insulin may enhance the mortality/morbidity risk associated with hypoglycaemia. Moreover, limited observational data suggest cardiovascular benefits of metformin in patients with moderate CKD compared with other antidiabetic agents [23, 24]. In our opinion, it is important to continue to educate physicians and patients on the risk of metformin use in CKD and in specific situations with risk of acute kidney injury.

Sulfonylureas can be used as second-line therapy in combination with metformin if the glycated haemoglobin target is not achieved [10]. In our study, dual therapy with sulfonylureas or glinides and metformin were not the preferred option, presumably because of the risk of hypoglycaemia and weight gain. Renal failure is an independent risk factor of hypoglycaemia and thus iatrogenic hypoglycaemia is a major concern [25]. We found a significant increase in hypoglycaemic risk with advancing CKD stages. In Switzerland, gliclazide is the only sulfonylurea that can be used in patients with eGFR 40–60 ml/min/1.73 m^2 [2]. In our study, sulfonylurea use did not decrease in patients with CKD stage 3a and was inappropriate (in CKD stages 3b–4) in 16.5% of cases. This is consistent with OREDIA data, which reported that over 20% of patients were still taking sulfonylureas despite prevailing renal contraindications (eGFR <30 ml/min/1.73 m^2) [16]. Similar findings were seen in the RIACE study and the USA EMR-based analysis, where the use of sulfonylureas remained frequent in severe CKD (18.1% and 22%, respectively) [17, 24].

DPP-4 inhibitors are incretin-based therapies approved in Europe since 2007. They are positioned as second-line therapy after metformin [10]. In Switzerland, available DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin) are approved and used across all stages of CKD including end-stage renal disease (except for saxagliptin). All need dosage adjustments with declining eGFR except for linagliptin, which can be administrated at all CKD stages at a dose of 5 mg daily [2]. In our study, DPP-4 inhibitor use was relatively frequent at all CKD stages (over one third of patients) increasing more in CKD stage 3b–4, which is in agreement with the current ADA consensus conference on diabetic kidney disease [26]. Some emerging data suggest potential renoprotective effects with linagliptin and saxagliptin (decrease in ACR), independent of their glucose lowering effects [27, 28], and larger clinical trials are underway to assess this issue further. Cardiovascular safety of DPP-4 inhibitors was demonstrated in three large dedicated trials [28–30]. In our view, physicians need to be cautious with the prescription of DPP-4 inhibitor therapy in diabetic patients with advanced CKD and a history of heart failure [29, 30].

Currently available GLP-1 agonists (exenatide, liraglutide, dulaglutide) are injectable incretin-based therapies used as second- or third-line therapy [10]. Renal impairment may alter the pharmacokinetic properties of exenatide leading to decreased renal elimination and higher systemic exposure. The clinical experience in CKD patients is quite limited. Moreover, several case reports of GLP-1 agonist induced acute kidney failure due to either acute tubulointerstitial nephritis or acute tubular necrosis (trigged in part by dehydration resulting from the gastrointestinal and diuretic effects of these drugs) raised some renal safety concerns [31]. In Switzerland, GLP-1 receptor agonists are contraindicated if eGFR <30 ml/min/1.73 m^2 and should be used with great caution with eGFR of 30–60 ml/min/1.73 m^2, especially in the elderly and in the case of diuretic and/or renin-angiotensin system inhibitor treatment [2]. Patients should be educated to report rapidly situations with increased risk of dehydration. In our study, GLP-1 agonist therapy was appropriate in most cases.

Glitazones were rarely used in our study population across all CKD stage, presumably because Swissmedic (the Swiss Agency for Therapeutic Products) has limited their use to 2 years because of the safety signal regarding bladder cancer. Moreover, pioglitazone use in CKD can aggravate water and sodium retention.

In our study, close to half of the patients with CKD stage 4 were on insulin therapy. Insulin can be used at all CKD stages; however, prevention of insulin-induced hypoglycaemia especially in the elderly is a critical issue [32]. Total insulin requirements are generally reduced when eGFR falls below 60 ml/min/1.73 m^2, because the kidneys clear about 25–50% of circulating insulin [31]. Data on pharmacokinetics and pharmacodynamics of insulin preparations in patients with CKD are scarce. Basal insulin analogues are the preferred option in T2D patients with CKD over NPH insulin as the former were reported to offer less variability and less hypoglycaemia in T2D patients with a history of frequent overnight hypoglycaemia [33]. CKD diabetic patient education should focus on frequent self-monitoring of blood glucose and prevention of hypoglycaemia.

Limitations of the study: We cannot exclude that physicians accepting to participate to the study were more compliant with current recommendations than those who refused. Furthermore, patients selected for data collection obviously

represent a group more adherent to visits to physician offices and in this case men may be underrepresented. Although type 1 diabetes was an exclusion criterion, we cannot exclude that some patients with latent autoimmune diabetes in adults or with chronic pancreatitis were included in the study, which may have biased the results toward a higher prescription of insulin. When creatinine is measured within the primary care practice, eGFR is regrettably not always calculated and can be a cause of unawareness by primary care physicians of chronic kidney disease, which may explain some misleading prescriptions. In this study, we do not have the proportion of primary care physicians relying on eGFR for their patient evaluation. Estimated GFR may have been slightly overestimated in the 40% of patients over 70 years of age with the CKD-EPI [34]. The reported frequency of following a "healthy way of life" may have been overestimated as no detail was provided on how the specific counselling was done.

Conclusions

CKD is frequent in T2D patients attending primary care practices, with advanced CKD (eGFR <60 ml/min/1.73 m^2) present in 22.4% of cases. This emphasises the importance of routine screening for and follow-up of diabetic nephropathy based on both eGFR and ACR, the latter being largely underused in primary care in Switzerland.

Accurate renal function evaluation and a careful individual drug risk/benefit balance assessment are mandatory to avoid the frequently observed inappropriate antidiabetic therapy. In CKD diabetic patients attending primary care physicians in Switzerland, metformin was the preferred option followed by DPP-4 inhibitors, insulin and sulfonylureas. However, metformin was frequently prescribed in advanced CKD. Safety of metformin (lactic acidosis) in moderate CKD is controversial. In our opinion, metformin can be used with great caution in moderate and stable CKD with dosage reduction, careful monitoring of eGFR, and appropriate patient education to stop treatment transiently if at risk of dehydration.

The new class of DPP-4 inhibitors is an interesting alternative when metformin is contraindicated in CKD patients, although ongoing safety studies have not yet shown any superiority to other AD therapy in terms of cardiovascular outcomes or renal function decline.

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Figures (large format)

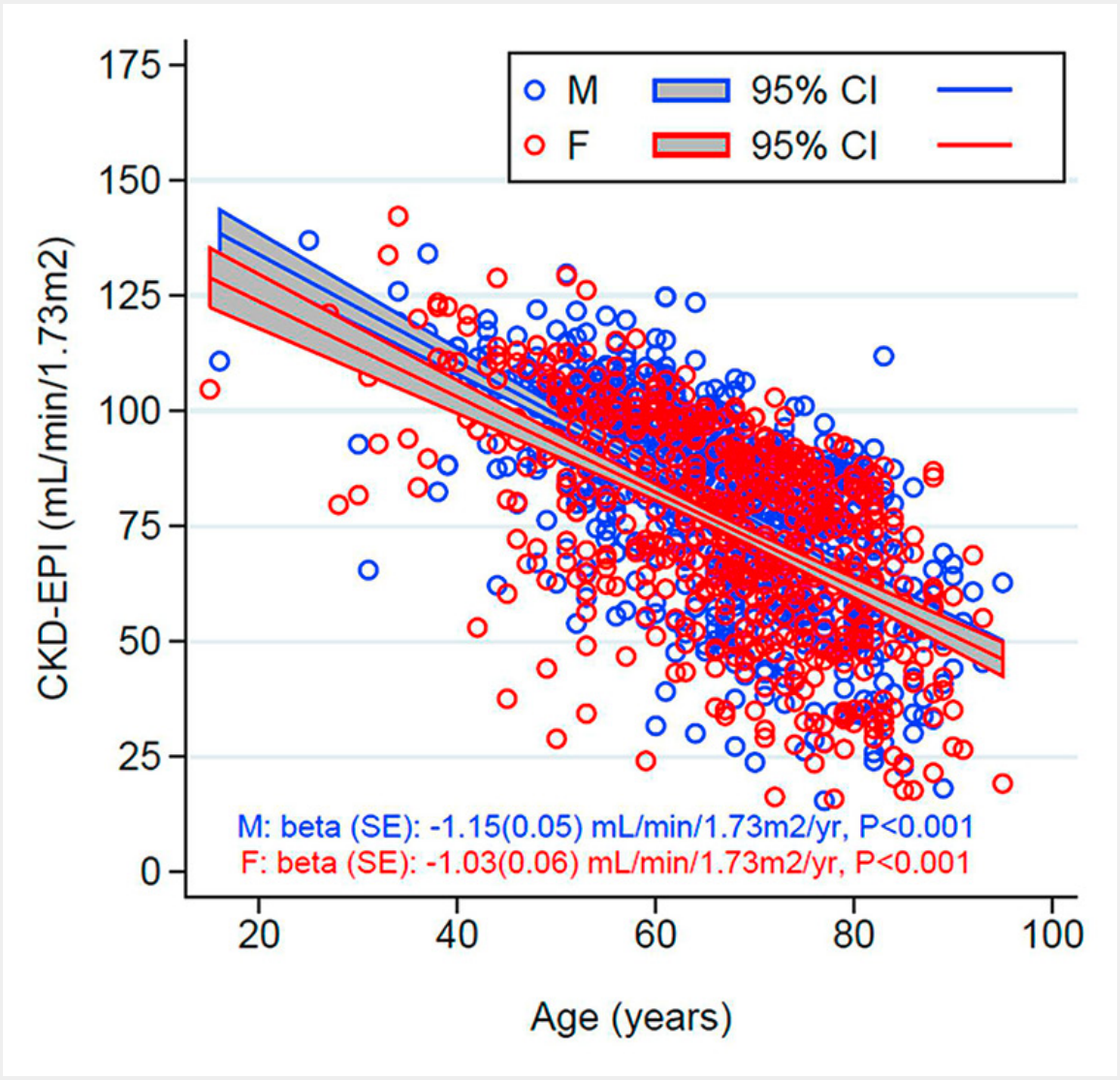
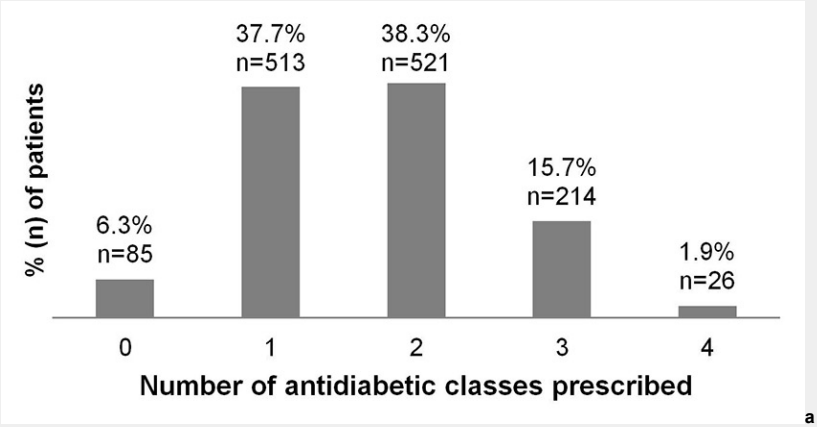


Figure 1

Beta coefficient and standard error (SE) from simple linear regression.
CI = confidence interval; CKD-EPI = chronic kidney disease-epidemiology collaboration



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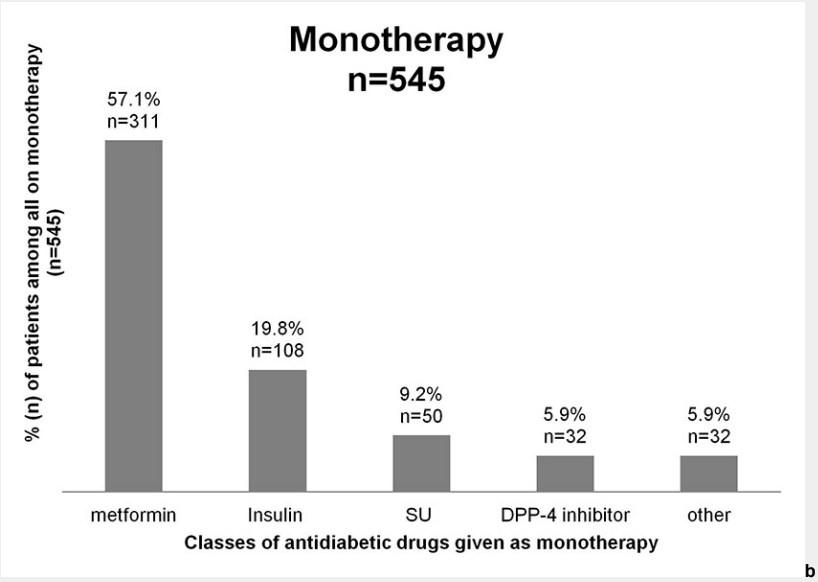

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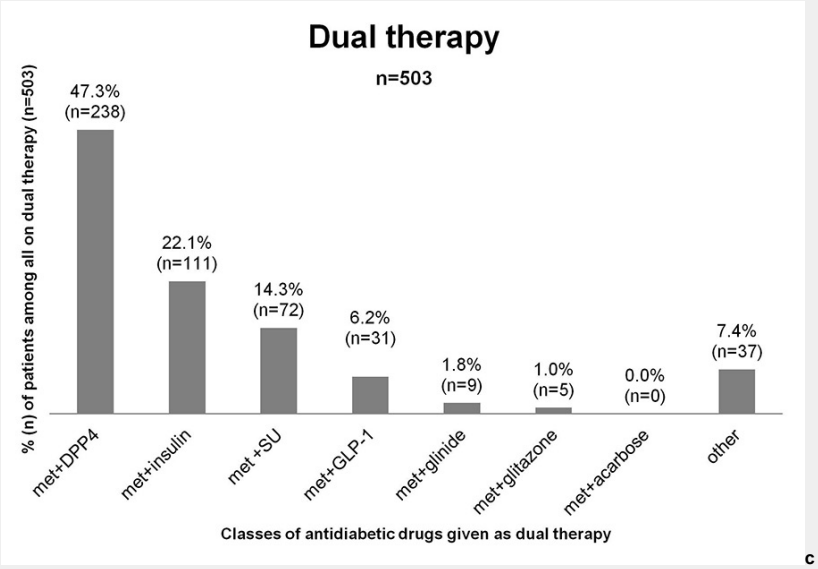

c

Figure 2

Antidiabetic therapy in diabetic patients treated in primary care practices. Number of classes prescribed (2a), classes of drugs prescribed as monotherapy (2b), classes of drugs prescribed as dual therapy (2c).

DPP-4 = dipeptidyl-peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 agonist; met = metformin; SU = sulfonylurea

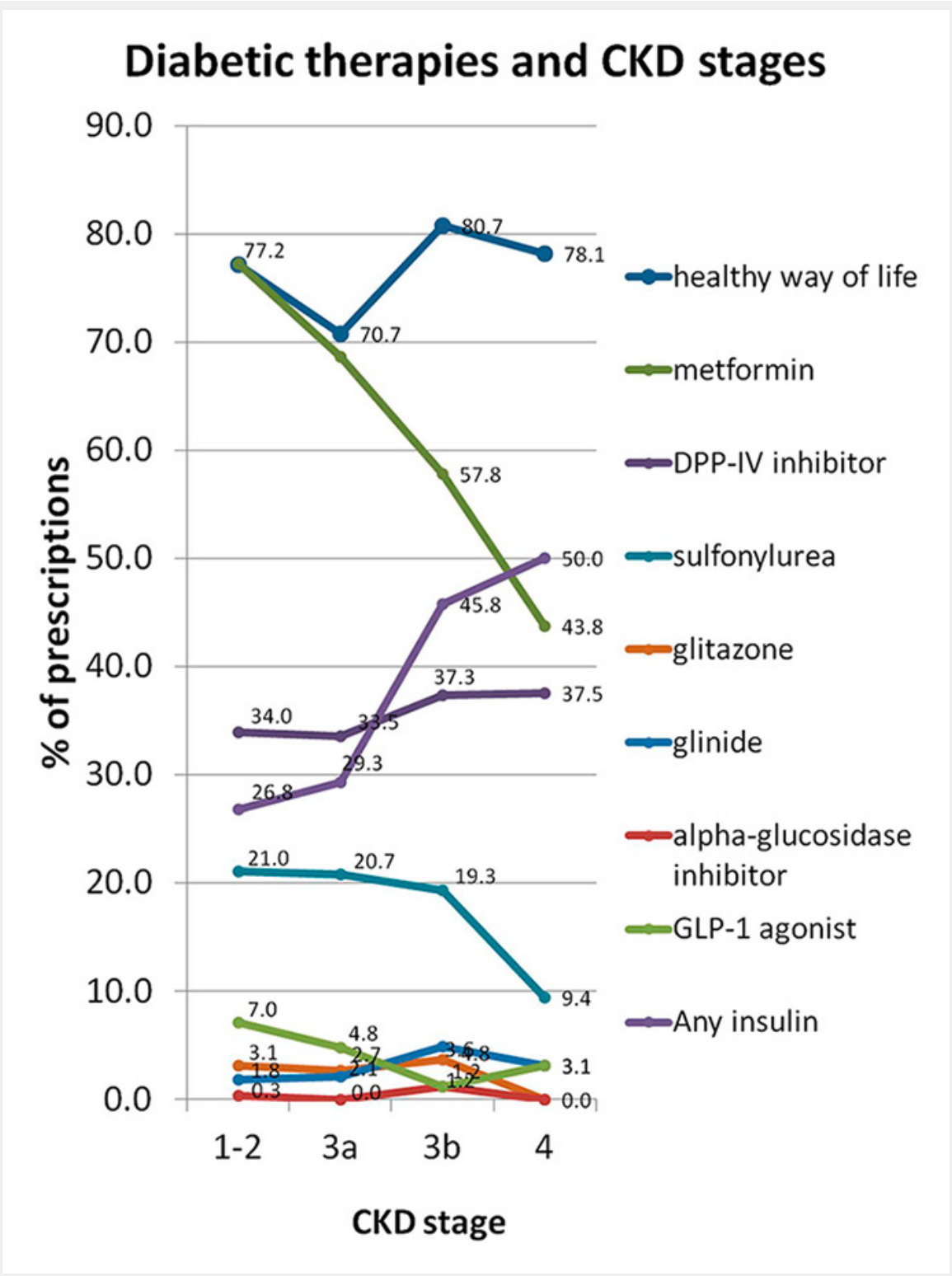

Figure 3

Antidiabetic class prescriptions (%) and chronic kidney disease (CKD) stage.
DPP-IV = dipeptidyl-peptidase-4; GLP-1 = glucagon-like peptide-1

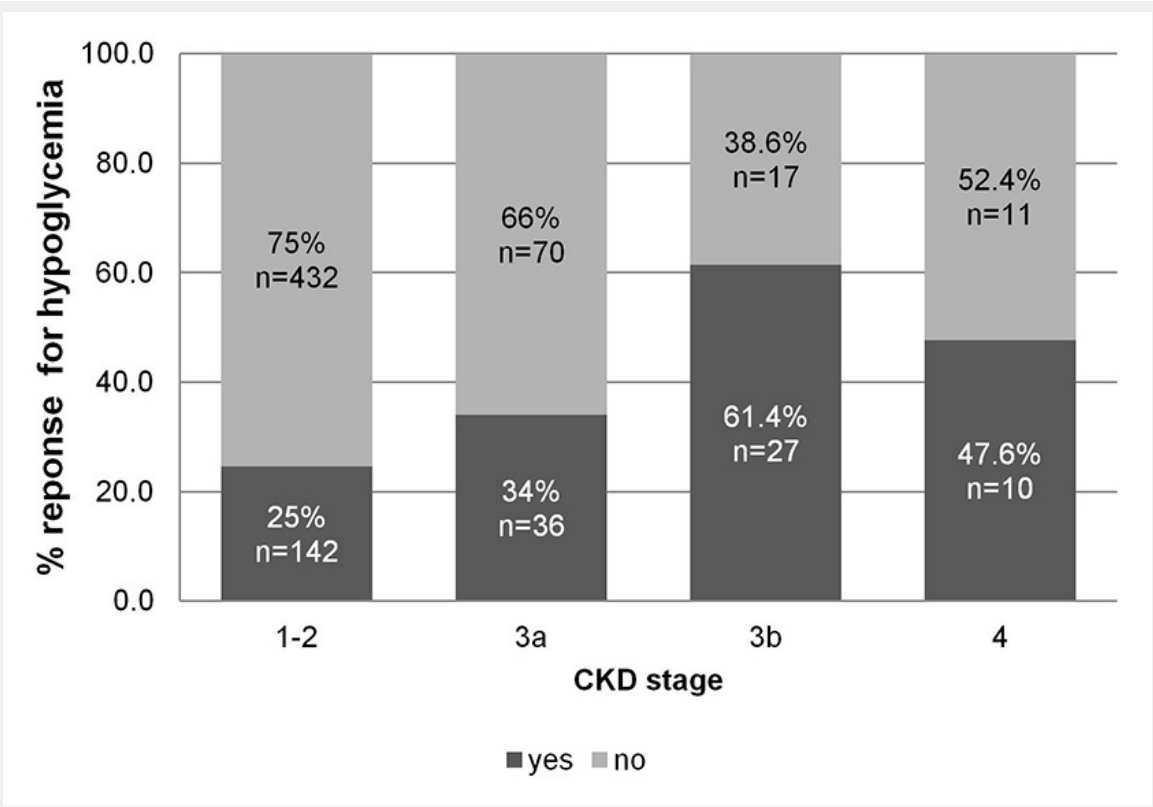

Figure 4

Presence of hypoglycaemia and chronic kidney disease (CKD) stage.