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Quality of prescribing in chronic kidney disease and type 2 diabetes

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IS GUIDELINE-ADHERENT PRESCRIBING ASSOCIATED WITH QUALITY OF LIFE IN PATIENTS WITH TYPE 2 DIABETES?

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ABSTRACT

Background: Guideline-adherent prescribing for treatment of multiple risk factors in type 2 diabetes (T2D) patients is expected to improve clinical outcomes. However, the relationship to Health-Related Quality of Life (HRQoL) is not straightforward since guideline-adherent prescribing can increase medication burden. The aim of study was to test whether guideline-adherent prescribing and disease-specific medication burden are associated with HRQoL in patients with T2D.

Methods: This was a cross-sectional study including 1,044 T2D patients from the e-VitaDM/ZODIAC study in 2012 in the Netherlands. Data from the diabetes visit, such as laboratory and physical examinations and prescribed medication, and from two HRQoL questionnaires, the EuroQol-5D-3L (EQ5D-3L) and the World Health Organization Well-Being Index (WHO-5) were collected. Seven indicators assessing prescribing of renin-angiotensin-aldosterone system (RAAS) inhibitors, statins, and potentially inappropriate drugs from a diabetes indicator set were used. Disease-specific medication burden was assessed using a modified version of the Medication Regimen Complexity Index (MRCI). Associations were tested with regression models, adjusting for age, gender, diabetes duration, comorbidity, BMI and smoking.

Results: The mean MRCI was 7.1, the median EQ5D-3L score was 0.86 and the mean WHO-5 score was 72. Prescribing of RAAS inhibitors and statins was not significantly associated with HRQoL. The indicators assessing inappropriate prescribing included small numbers of patients; prescribing of glibenclamide and dual RAAS blockade was not significantly associated with HRQoL, whereas the indicators assessing inappropriate prescribing of metformin and overprescribing in elderly included too few patients and were excluded from the analysis. Finally, also the MRCI was not associated with HRQoL.

Conclusions: We found no evidence for associations between guideline-adherent prescribing or disease-specific medication burden and HRQoL in T2D patients. This gives no rise to refrain from prescribing intensive treatment in T2D patients as recommended, but the interpretation of these results is limited by the cross-sectional study design and the low number of patients included in some indicators.

INTRODUCTION

Clinical guidelines for managing patients with type 2 diabetes (T2D) recommend pharmacotherapy to reduce levels of risk factors such as glycated haemoglobin (HbA_{1c}), blood pressure, low-density lipoprotein (LDL)-cholesterol and albuminuria.^{1,2} These recommendations are based on clinical trials assessing the efficacy and safety of these treatments. Patients receiving treatment according to these recommendations show improved intermediate³ and hard clinical outcomes.⁴ It is expected that improved clinical outcomes have a positive effect on health-related quality of life (HRQoL) in patients with T2D.⁵ However, following treatment recommendations may also have a negative effect on HRQoL by increasing medication burden and inducing an increased risk for adverse drug events.⁶ Medication burden proved to be negatively associated with physical and general HRQoL in various patient populations.⁷⁻⁹ In addition, prescribing more medication may increase the risk of unsafe or inappropriate prescribing. Previously it was found that the use of inappropriate drugs is associated with reduced general and mental HRQoL in elderly patients.¹⁰ Also, adverse drug events resulting from inappropriate drugs use can negatively influence HRQoL.^{8,11}

Several studies have assessed the association between glucose regulating drugs and HRQoL. These studies found that prescribing of insulin may be associated with lower general but not mental HRQoL^{12,13} and prescribing of various oral glucose regulating drugs is not associated with differences in HRQoL.^{13,14} Furthermore, one study found that intensive multitherapy for glycaemic, blood pressure and cholesterol control was associated with better general HRQoL compared with usual care.¹⁵ On the other hand, another study found that an increase in the number of glucose, blood pressure and cholesterol regulating drugs did not change HRQoL in T2D patients.¹⁶ Data on the effect of prescribing drug treatment other than glucose regulating drugs or potentially inappropriate drugs in T2D patients on HRQoL is unavailable.

Therefore, the primary aim of this study in T2D patients was to assess the relationship of (I) guideline-adherent prescribing of renin-angiotensin-aldosterone system (RAAS) inhibitors and statins, (II) potentially inappropriate drug prescribing, and (III) disease-specific medication burden with general HRQoL. Secondly, the relationship with mental HRQoL will be explored.

METHODS

A cross-sectional study was conducted using data from the e-VitaDM/ZODIAC study.¹⁷ In short, 1,614 patients with T2D from 69 general practices in the Drenthe region of the Netherlands agreed to participate in a cohort study to investigate the effect of e-health on HRQoL. The database contains routinely collected data from the annual diabetes visit extracted from medical records from these patients. Furthermore, several questionnaires, including the EuroQoL 5 dimensions with 3 levels (EQ5D-3L) and the World Health Organization Well-Being Index (WHO-5) were filled out by the patients either at the general practice or at home. All patients with complete questionnaires, data registered during the yearly extensive diabetes control, and prescription data available were included in this study. All patients with a diagnosis date after 2012, were excluded from the analysis.

This study was approved by the Medical Ethical Review Committee of Isala, Zwolle, the Netherlands, and was registered under Clinicaltrials.gov number NCT01570140.

Patient characteristics

The e-VitaDM/ZODIAC database includes structured data on age, gender, physical examination, laboratory measurements, diabetes-related complications and prescribed medication. Age and diabetes duration (categorized on recently diagnosed ≤ 2 years, less recently diagnosed 2-10 years, and older diagnosed >10 years) were calculated using the date from the annual diabetes visit. Gender, body mass index (BMI) and smoking (smoking or non-smoking) were determined at the annual diabetes visit. Medication included glucose, blood pressure, and cholesterol regulating drugs. Comorbidities were grouped under coronary artery disease, including history of angina pectoris, coronary artery bypass grafting, myocardial infarct, percutaneous coronary intervention and heart failure, and cerebrovascular disease, including history of cerebrovascular accident and transient ischemic attack.

The quality of prescribing was assessed using the prescribing quality indicators which were systematically developed and validated in the Netherlands.¹⁸

Prescribing of recommended drugs

Three indicators assessing the recommended prescribing of RAAS inhibitors and statins were included.¹⁸ The indicators focused on prescribing of angiotensin-converting-enzyme inhibitors (ACE-i) or angiotensin-II-receptor-blockers (ARBs) when multiple antihypertensives are prescribed; prescribing of ACE-i or ARBs when albuminuria is present; and prescribing of statins in patients aged 55 to 80 years (Table 7.1).

Table 7.1: Definition of quality indicators used in this study.

Recommended prescribing
1. The percentage of patients with T2D between 55 and 80 years that is prescribed a statin
2. The percentage of patients with T2D 18 years or older treated with two or more antihypertensives that is prescribed an ACE-i or ARB
3. The percentage of patients with T2D 18 years or older treated with antihypertensives and with micro- or macro-albuminuria [†] that is prescribed an ACE-i or ARB
Inappropriate prescribing
4. The percentage of patients with T2D 18 years or older treated with SU-derivatives that is prescribed glibenclamide
5. The percentage of patients with T2D 18 years or older with an eGFR <30 ml/min/1.73m ² that is prescribed metformin
6. The percentage of patients with T2D 80 years or older with a normal HbA _{1c} level (<53 mmol/mol) that is prescribed two or more glucose regulating drugs
7. The percentage of patients with T2D 18 years or older treated with RAAS inhibitors that is prescribed a combination of an ACE-i and ARB (dual RAAS blockade)

T2D: type 2 diabetes; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; SU-derivatives: sulfonylurea derivatives; eGFR: estimated glomerular filtration rate; HbA_{1c}: glycated haemoglobin; RAAS: renin-angiotensin-aldosterone system.

[†] Micro-albuminuria is defined as albumin/creatinine ratio ≥ 2.5 mg/mmol and <25 mg/mmol for males, ≥ 3.5 mg/mmol and <35 mg/mmol for females. Macro-albuminuria is defined as albumin/creatinine ratio ≥ 25 mg/mmol for males, ≥ 35 mg/mmol for females.

Prescribing of potentially inappropriate drugs

Four indicators assessing the prescribing of potentially inappropriate drugs were included.¹⁸ They focused on prescribing of the non-recommended glibenclamide among sulfonylurea derivative users, prescribing of the contra-indicated metformin among patients with an impaired renal function (eGFR <30 ml/min/1.73m²), potential overprescribing of glucose regulating drugs in elderly (≥ 80 years) with low HbA_{1c} values (HbA_{1c} <53 mmol/mol), and prescribing of potentially unsafe dual RAAS blockade (Table 7.1).

Disease-specific medication burden

To assess disease-specific medication burden, we calculated the burden of taking glucose, blood pressure, and cholesterol regulating drugs using a modified version of the Medication Regimen Complexity Index (MRCI).¹⁹ The MRCI comprises of three sections, which are giving burden scores for administration modality, dosing frequency and additional directions. For administration modality, the scores 1 and 4 were used for tablets and injections respectively. For dosing frequency, a score of 1 was used for drugs prescribed once daily, a score of 2 for drugs prescribed twice daily and so on. Furthermore, different scores are used for additional instructions

for use. In our dataset, however, data on additional instructions (such as take with a specific fluid or at a specified time) was incomplete. Therefore we used a modified MRCI score, as has been proposed previously.²⁰ Data on the number of pills prescribed per time was complete and used in the analysis. A score of 1 was used for drugs which had multiple units per time or half a unit per time. Each prescribed drug received an overall score by adding the scores in the sections.

Health-related quality of life

The primary outcome of this study was general HRQoL, assessed by the EQ5D-3L.²¹ The EQ5D-3L consists of five questions regarding five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. For each question three answer categories are possible; no problems, some problems or extreme problems. This questionnaire has been validated for the Dutch population.²² The outcome scores range from -0.333 to 1.0, where 1.0 represents perfect HRQoL. The secondary outcome of this study was mental HRQoL, assessed by the WHO-5.²³ The WHO-5 consists of five questions regarding positive mood, vitality and general interest. For each question six answer categories are possible, ranging from constant to never. The WHO-5 score ranges from 0 to 100.

Statistical analysis

Means with standard deviations are reported for normally distributed variables, medians with the inter-quartile range for non-normally distributed variables and percentages for categorical variables. Regression analysis was used to test for associations between the indicators of guideline-adherent prescribing and the HRQoL measures. The residuals of the EQ5D-3L outcome were not normally distributed and therefore did not meet the assumption for linear regression. Since transformation of the variable did not improve the normality, we dichotomized this variable on the median EQ5D-3L score and logistic regression was performed. The WHO-5 scores did satisfy the assumptions for performing linear regression. Two different models were assessed. Model 1 was a crude model and model 2 tested whether the effects sized of the associations were changed by possible confounders. The included confounders were age, gender, diabetes duration, BMI, smoking status and history of coronary artery disease and cerebrovascular disease. Regression models for indicators including less than 50 patients were not assessed, considering the low power, in particular for the adjusted models. P-values below 0.05 were considered statistically significant. All analyses were conducted using Stata version 14.2 Special Edition (Stata Corp., College Station, TX).

Sensitivity analysis

A sensitivity analysis was performed where groups for HRQoL based on the EQ5D-3L were determined on a perfect score (=1) compared to suboptimal score (<1).

RESULTS

Of the 1,614 patients that agreed to participate in the study, patients were excluded from the analysis because they did not have complete data on both the EQ5D-3L and WHO-5 questionnaires (n=423), there was no data available of the annual diabetes control visit (n=125), and when there was no prescription data available (n=22), leaving 1,044 primary care patients with T2D in this study. Of these, 1,035 completed the EQ5D-3L, and 1,011 the WHO-5 questionnaire. The patients were on average 65 years old, 44% was female and the median diabetes duration was 6 years. The mean HbA_{1c} was 50 mmol/mol, the average systolic blood pressure was 136 mmHg, the average LDL-cholesterol 2.4 mmol/l and the median albumin-creatinine ratio (ACR) was 0.7 mg/mmol. Furthermore, 82% of the patients were prescribed glucose regulating drugs, 75% blood pressure regulating drugs, and 78% statins. The score on the MRCI for these three therapeutic classes was on average 7.1 (standard deviation (SD): 4.1) (Table 7.2). The outcome of the indicators for current use ranged from 79% to 86%, while the indicators on inappropriate prescribing ranged from 0% to 15% (Figure 7.1). The indicators focusing on prescribing of metformin with impaired renal function and overprescribing of glucose regulating drugs in the elderly included 1 and 41 patients respectively, and were therefore excluded from the further analysis.

EQ5D-3L

The median score of the total population on the EQ5D-3L questionnaire was 0.86 (interquartile range: 0.81-1.00) (Table 7.2). None of the indicators on recommended prescribing of statins or ACE-i/ARBs, or the indicators on inappropriate prescribing were significantly associated with EQ5D-3L scores in the logistic regression. Higher MRCI scores were significantly associated with lower EQ5D-3L scores. However, after adjustment for age, gender, diabetes duration, BMI and history of coronary disease this association lost significance (Figure 7.2). The sensitivity analysis using a perfect EQ5D-3L score versus all other scores showed similar results (data not shown).

Table 7.2: Baseline characteristics of the study population

Patient characteristics	N (%)	Mean (\pmSD)
<i>Patient characteristics</i>		
Age (years)	1,044 (100)	65.2 (\pm 9.8)
\leq 55 years	152 (14.6)	49.0 (\pm 5.2)
55-80 years	827 (79.2)	66.7 (\pm 6.4)
$>$ 80 years	65 (6.2)	83.4 (\pm 2.6)
Female gender	458 (43.9)	
Diabetes duration (years)	1,036 (99.2)	6 [3; 10] ^a
\leq 2 years	254 (24.5)	1.0 (\pm 0.8)
2-10 years	586 (56.6)	6.4 (\pm 2.3)
$>$ 10 years (incl. missing values)	196 (18.9)	14.5 (\pm 4.9)
Smoking 2012 (yes)	156 (14.9)	
<i>Physical examination</i>		
Systolic blood pressure 2012 (mmHg)	1,037 (99.3)	135.9 (\pm 15.2)
BMI (kg/m ²)	1,031 (98.8)	29.9 (\pm 5.0)
Normal weight (\leq 25 kg/m ²)	136 (13.0)	23.5 (\pm 1.2)
Overweight (25-30 kg/m ²)	464 (44.4)	27.5 (\pm 1.4)
Obese ($>$ 30 kg/m ²)	431 (41.3)	34.4 (\pm 4.3)
<i>Laboratory measurements</i>		
HbA _{1c} 2012 (mmol/mol)	1,037 (99.3)	49.6 (\pm 8.3)
LDL-cholesterol 2012 (mmol/l)	1,015 (97.2)	2.4 (\pm 0.8)
ACR 2012 (mg/mmol)	945 (90.5)	0.7 [0.3-1.5] ^a
eGFR 2012 (ml/min/1.73m ²)	1,036 (99.2)	80.8 (\pm 12.1)
Poor kidney function ($<$ 30 ml/min/1.73m ²)	1 (0.1)	28.7 (-)
<i>Medication</i>		
Glucose regulating drugs	853 (81.7)	
Metformin	785 (75.2)	
SU-derivatives	311 (29.8)	
Glibenclamide	3 (0.3)	
Insulin	141 (13.5)	
Blood pressure regulating drugs	782 (74.9)	
Diuretics	346 (33.1)	
Beta blocking agents	426 (40.8)	
Calcium channel blockers	179 (17.2)	
RAAS inhibitors	587 (56.2)	
Statins	811 (77.7)	
Medication Regimen Complexity Index	1,044 (100)	7.1 (\pm 4.1)
<i>Comorbidities</i>		
CAD	203 (19.4)	
CBVD	71 (6.8)	

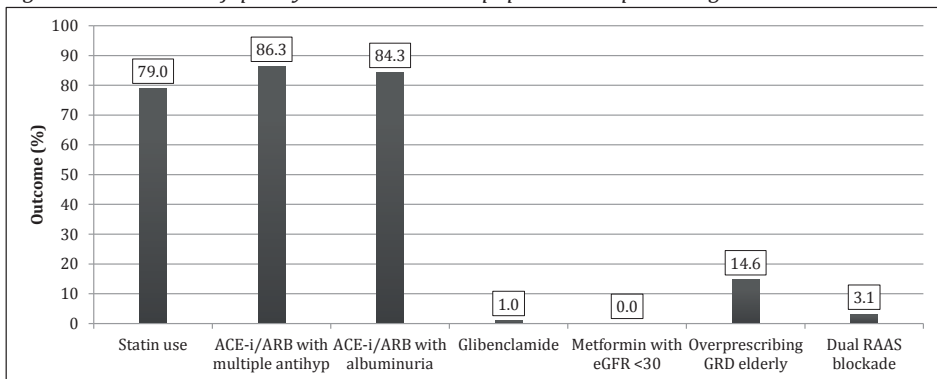
Table 7.2: Baseline characteristics of the study population (continued)

Patient characteristics	N (%)	Mean (\pm SD)
<i>HRQoL questionnaires</i>		
EQ5D-3L	1,035 (99.1)	0.86 [0.81-1.00] ^a
WHO-5	1,011 (96.8)	71.9 (\pm 17.8)

SD: standard deviation; BMI: body mass index; HbA_{1c}: glycated haemoglobin; LDL-cholesterol: low-density lipoprotein-cholesterol; ACR: albumin/creatinine ratio; eGFR: estimated glomerular filtration rate; SU-derivatives: sulfonylurea derivatives; RAAS: renin-angiotensin-system; CAD: coronary artery disease; CBVD: cerebrovascular disease; HRQoL: health-related quality of life; EQ5D-3L: Euroqol 5 dimensions questionnaire with 3 levels; WHO-5: World Health Organization Well-Being Index.

^a Median with inter quartile range

Figure 7.1: Outcome of quality indicators in this population in percentages.

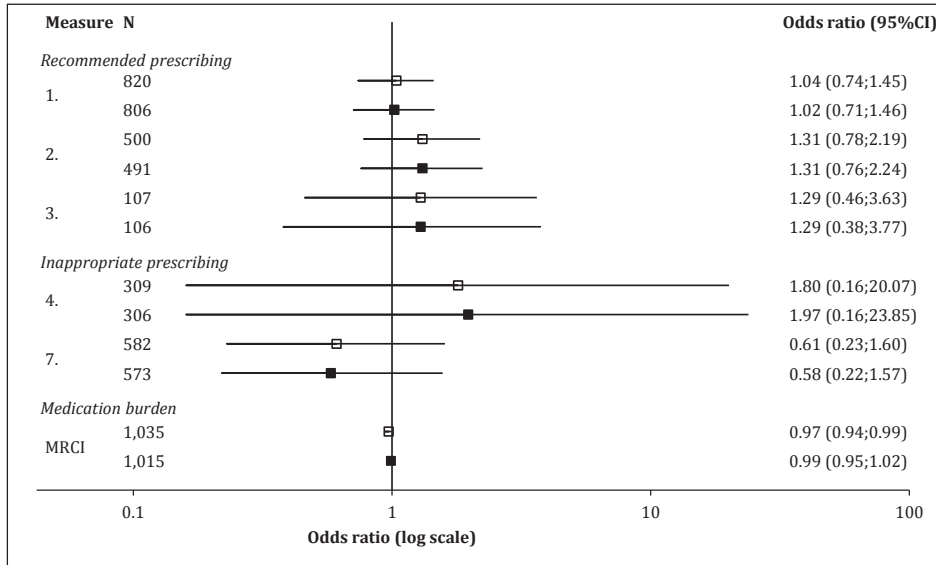


ACE-i: angiotensin-converting-enzyme inhibitors; ARBs: angiotensin-II-receptor-blockers; antihyp: antihypertensives; eGFR: estimated glomerular filtration rate; GRD: glucose regulating drugs; RAAS: renin-angiotensin-aldosterone system.

WHO-5

The mean score on the WHO-5 questionnaire of the total population was 72 (SD: 17) (Table 7.2). None of the indicators on recommended prescribing of RAAS-inhibitors or statins, or the indicators on inappropriate prescribing were significantly associated with higher or lower WHO-5 scores in linear regression. The MRCI for the glucose, blood pressure, and cholesterol regulating drugs was also not associated with WHO-5 scores. Adjustments did not alter the results (Figure 7.3).

Figure 7.2: Overview of odds ratios of guideline-adherent prescribing quality indicators and medication burden with EQ5D-3L scores



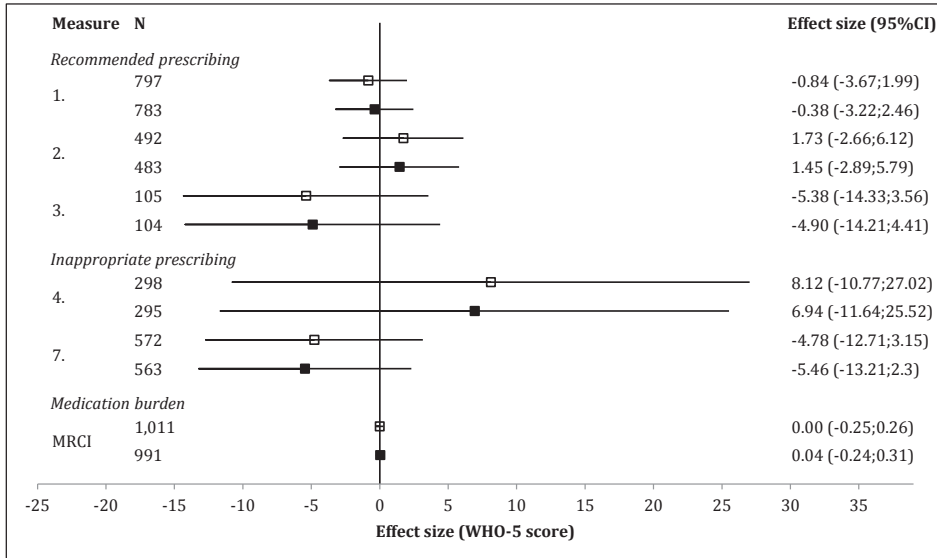
□ represents unadjusted odds ratios; ■ represents adjusted odds ratios; indicator 1: statin prescribing among patients 55-80 years of age; indicator 2: angiotensin-converting-enzyme-inhibitor/angiotensin-II-receptor-blockers prescribing among patients with multiple antihypertensive treatment; indicator 3: angiotensin-converting-enzyme-inhibitor/angiotensin-II-receptor-blockers prescribing among patients with albuminuria; indicator 4: glibenclamide prescribing among patients with sulfonylurea derivate treatment; indicator 7: dual renin-angiotensin-aldosterone system blockade among patients with renin-angiotensin-aldosterone system-inhibitor treatment; MRCI: medication regimen complexity index.

DISCUSSION

We found no evidence for an association between guideline-adherent prescribing of RAAS-inhibitors or statins and either general or mental HRQoL in T2D patients. Also prescribing of potentially inappropriate medication and having a higher disease-specific medication burden were not associated with HRQoL in patients with T2D.

Our study supports previous findings that prescribing more cardio-protective medication, as recommended by the guidelines, does not influence general or mental HRQoL.¹⁶ This is in contrast to another study, where the association was observed between intensive multitherapy for cardiometabolic risk factors and better general HRQoL.¹⁵ This multitherapy, however, included education and support for improving lifestyle, monthly visits and extensive blood glucose monitoring in addition to medication treatment. Therefore, it is unclear whether the medication

Figure 7.3: Overview of effect sizes of guideline-adherent prescribing quality indicators and medication burden with WHO-5 scores



□ represents unadjusted effect sizes; ■ represents adjusted effect sizes; indicator 1: statin prescribing among patients 55-80 years of age; indicator 2: angiotensin-converting-enzyme-inhibitor/angiotensin-II-receptor-blockers prescribing among patients with multiple antihypertensive treatment; indicator 3: angiotensin-converting-enzyme-inhibitor/ angiotensin-II-receptor-blockers prescribing among patients with albuminuria; indicator 4: glibenclamide prescribing among patients with sulfonylurea derivate treatment; indicator 7: dual renin-angiotensin-aldosterone system blockade among patients with renin-angiotensin-aldosterone system-inhibitor treatment; MRCI: medication regimen complexity index.

treatment in itself influenced the HRQoL. Our findings suggest this may not be the case. The improved lifestyle and diabetes control might be responsible for the improved HRQoL, which has been shown before.²⁴⁻²⁷

The prescribing of potentially inappropriate drugs in elderly patients has found to be associated with reduced general and mental HRQoL.¹⁰ Such findings can be confounded by indication, that is, people who are prescribed more drugs, including potentially inappropriate drugs, may have a poorer health status, which in turn is associated with poorer HRQoL. Our study looked at the prescribing of specific inappropriate drugs in T2D patients, including glibenclamide and dual RAAS blockade. Our findings suggest that general or mental HRQoL is not affected by prescribing of such medication. Possibly, the patients receiving these potentially inappropriate drugs do not perceive any harm at that moment and therefore it did not affect their HRQoL. On the other hand, in this population, only three out of 311 eligible patients were prescribed glibenclamide, and only 18 out of 587 eligible

patients were prescribed dual RAAS blockade, which limited the power for these two analyses.

Surprisingly, we also did not find a significant association between the MRCI for glucose, blood pressure, and cholesterol regulating drugs and general or mental HRQoL. Previously, a negative association was found between the overall MRCI and HRQoL in relatively young medication users.⁹ Our finding suggests that in patients with a chronic disease, such as T2D, the disease-specific medication burden does not have a significant impact on their HRQoL.

We found no associations between guideline-adherent prescribing and HRQoL, at least when assessed with the EQ5D-3L and WHO-5. Previous research also used other questionnaires, such as the 36-item Short Form Survey. This makes it difficult to compare the results between studies and may explain the inconsistent results found previously. The EQ5D-3L is a widely used and accepted method to assess general HRQoL, and previously differences between treatments have been detected using the EQ5D-3L.^{12,28} The T2D patients in this study were relatively well controlled, which might influence the generalizability. On the other hand, the HRQoL was comparable to other T2D populations.^{14,16}

This is a first study testing the association between quality indicators of guideline-adherent prescribing and HRQoL in T2D patients. These indicators are part of a larger indicator set to assess quality of prescribing care in T2D, which has previously been validated for content, feasibility, and associations with intermediate outcomes.¹⁸ The analyses were adjusted for several possible confounders. Due to the cross-sectional design of the study, however, it is not possible to assess cause-effect relationships between prescribing and HRQoL. A large proportion of the patients had a high EQ5D-3L score, which we therefore categorized. The categorization may have reduced the power needed to detect significant effects. Furthermore, because of a small number of patients included in two indicators for prescribing of inappropriate drugs, these were excluded from the analyses.

In conclusion, we found no evidence that guideline-adherent prescribing and disease-specific medication burden are related to HRQoL in relatively well-controlled T2D patients. This gives no reason to refrain from prescribing guideline-recommended treatment in T2D patients, at least from a HRQoL perspective, but the interpretation of these results is limited by the cross-sectional study design and the low number of patients included in some indicators.

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