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Quality of prescribing in chronic kidney disease and type 2 diabetes

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PRESCRIBING QUALITY AND
PREDICTION OF CLINICAL
OUTCOMES IN PATIENTS WITH
TYPE 2 DIABETES: A PROSPECTIVE
COHORT STUDY

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ABSTRACT

Background: We assessed whether prescribing quality indicators (PQIs) for type 2 diabetes care are associated with better intermediate outcomes. Special focus was on clinical action indicators measuring start or intensification of treatment when indicated.

Methods: Data were used from the Groningen Initiative to Analyse Type 2 Diabetes Treatment (GIANTT) database, including >26,000 T2D patients. Eleven PQIs measuring prescribing of glucose lowering drugs, statins, antihypertensives, and renin-angiotensin-aldosterone system (RAAS) inhibitors were evaluated. Associations were tested between receiving the recommended treatment in 2012 as measured by each PQI and the related outcome in the following year (glycated haemoglobin, low-density lipoprotein-cholesterol, systolic blood pressure (SBP), albuminuria) using regression models.

Results: Three clinical action PQIs focusing on treatment with glucose lowering drugs were associated with better glycated haemoglobin levels (-5.5 mmol/mol [-9.3,-1.7]; -8.2 mmol/mol [-9.5,-6.9]; -8.8 mmol/mol [-10.1,-7.5]). One current use and two clinical action PQIs on treatment with statins were associated with better low-density lipoprotein-cholesterol levels (-0.29 mmol/l [-0.32,-0.27]; -0.97 mmol/l [-1.04,-0.90]; -0.64 mmol/l [-0.72,-0.56]). Two clinical action PQIs on treatment with antihypertensives were associated with better SBP (-8.63 mmHg [-10.62,-6.63]; -9.95 mmHg [-11.96,-7.95]). The clinical action PQI on treatment with RAAS inhibitors was associated with a lower risk of albuminuria (OR:0.19 [0.08,0.48]). The PQIs on current use of RAAS inhibitors were not associated with a lower risk of albuminuria.

Conclusions: Nine PQIs for type 2 diabetes treatment, including eight clinical action indicators, were associated with better intermediate cardiovascular and renal outcomes, which supports their validity for clinical practice.

INTRODUCTION

Guidelines for management of type 2 diabetes (T2D) recommend a stepwise approach to initiate, intensify, and maintain medication treatment in patients with T2D.^{1,2} These recommendations are based on evidence from studies on the efficacy and safety of such treatment. It is expected that prescribing as advised in the guidelines will lead to better patient outcomes. Whether patients are treated according to the recommendations can be measured with prescribing quality indicators (PQIs).

PQIs are used for internal and external evaluation of the quality of prescribing. Internal evaluation includes monitoring the quality of care and giving feedback to healthcare professionals, while external evaluation includes benchmarking or pay-for-performance systems.³ Using indicators in feedback-and-audit programs can lead to better quality of care.^{4,5} Nonetheless, when PQIs are, for example, poorly defined or disregard a need for personalized treatment, prescribing according to the PQIs may not be beneficial for all patients.⁶ To ensure that the use of PQIs leads to better patient outcomes, their predictive validity needs to be assessed.⁷

There are several types of PQIs.⁸ Clinical action indicators measure whether treatment is timely started or intensified.⁹ Such action indicators are considered more clinically relevant than the traditional indicators focusing on current medication use.⁹⁻¹² Studies showed that several clinical action indicators were predictive of better intermediate patient outcomes.¹³⁻¹⁵ Recently, a new set of PQIs for T2D care was developed that included twenty indicators focusing on treatment with glucose lowering drugs, statins, antihypertensives, renin-angiotensin-aldosterone system (RAAS) inhibitors, and medication safety.¹⁶ These PQIs were considered face, content, and operationally valid, but their predictive validity has not yet been assessed. Eleven indicators in this set are expected to have an impact on patient outcomes. Eight of these are clinical action indicators and three focus on current medication use. The aim of this study is to test whether these eleven PQIs are predictive of better intermediate cardiovascular and renal outcomes of patients with T2D.

METHODS

A retrospective cohort study was conducted using data from the Groningen Initiative to Analyse Type 2 Diabetes Treatment (GIANTT) database.¹⁷ The GIANTT database contains longitudinal data extracted from medical records of patients

with T2D managed in primary care in the north of the Netherlands. The data covers 80% of all general practices in the province of Groningen. All patients that were managed for their T2D in one of the practices for the whole year 2012 were included. The GIANTT database contains all routinely collected data, including information on age, gender, physical examination, laboratory values, comorbidity, and prescribed medication.

The Medical Ethical Committee of University Medical Center Groningen ascertained that the study did not need formal approval with regards to the Medical Research Involving Human Subjects Act, since it used anonymized data from existing databases.

Indicators

The eleven indicators used in this study were defined in the set developed previously (Table 6.1).¹⁶ The eight clinical action indicators focus on start or intensification of treatment with glucose lowering drugs, statins, antihypertensives, and RAAS inhibitors. The three current use indicators focus on prescribing of statins and RAAS inhibitors. Quality of care was assessed in 2012 using these indicators. The clinical action indicators included patients whose last available risk factor value (glycated haemoglobin (HbA_{1c}), low-density lipoprotein(LDL)-cholesterol, systolic blood pressure (SBP), or albuminuria) in 2011 showed insufficient control, and measured the quality of care by looking at whether treatment was initiated or intensified or the risk factor value had returned to control in 2012 (Table 6.1, and Appendix 4, Table S5.2 for PQI definitions). Treatment start and intensification was measured by comparing the medication prescribed in the last four months of 2012 to the last four months of 2011. Current use indicators measured whether the recommended treatment was prescribed in the last four months of 2012 (Figure 6.1). The period of four months was chosen because prescriptions for chronic medication usually have a maximum duration of three months in the Netherlands.

Outcomes

The outcomes were the follow-up values of HbA_{1c}, LDL-cholesterol, SBP, and albuminuria, depending on the PQI (Table 6.1). Albuminuria was dichotomized into normoalbuminuria (albumin/creatinine ratio (ACR) <2.5 mg/mmol for males and <3.5 mg/mmol for females) and micro-/macroalbuminuria (ACR ≥2.5 mg/mmol for males and ≥3.5 mg/mmol for females). Follow-up was defined as the first value in 2013, provided that this was at least thirty days and not more than 365 days after the indicator date. The indicator date was defined as the date of the prescription or the risk factor value that determined the numerator of the PQI in 2012.

Table 6.1: Definition of indicators with the relevant intermediate outcomes and general outcome in a cohort of type 2 diabetes patients in primary care

Indicator	Intermediate patient outcome	Indicator outcome in GIANTT (% , nominator/ denominator)
1. The percentage of patients with T2D between 18 and 70 years with an elevated HbA _{1c} level (>53 mmol/mol) in the previous year, that started with glucose lowering drugs or that reached the HbA _{1c} target level (≤53 mmol/mol)	Blood glucose	73.1 (174/238)
2. The percentage of patients with T2D between 18 and 70 years on monotherapy metformin and with an elevated HbA _{1c} level (>53 mmol/mol) in the previous year, that is intensified with glucose lowering drugs or that reached the HbA _{1c} target level (≤53 mmol/mol)	Blood glucose	61.1 (618/1,012)
3. The percentage of patients with T2D between 18 and 70 years with two or more non-insulin glucose lowering drugs and with an elevated HbA _{1c} level (>53 mmol/mol) in the previous year, that started with insulin or that reached the HbA _{1c} target level (≤53 mmol/mol)	Blood glucose	38.8 (446/1,150)
4. The percentage of patients with T2D between 55 and 80 years that is prescribed a statin	LDL-cholesterol	71.7 (13,123/18,301)
5. The percentage of patients with T2D between 18 and 80 years with an elevated LDL-cholesterol level (>2.5 mmol/l) in the previous year, that started with a statin or that reached the LDL-cholesterol target level (≤2.5 mmol/l)	LDL-cholesterol	32.1 (1,100/3,429)
6. The percentage of patients with T2D between 18 and 80 years treated with simvastatin and with an elevated LDL-cholesterol level (>2.5 mmol/l) in the previous year, that switched to atorvastatin or rosuvastatin or that reached the LDL-cholesterol target level (≤2.5 mmol/l)	LDL-cholesterol	46.3 (1,105/2,389)
7. The percentage of patients with T2D between 18 and 70 years of age with an elevated systolic blood pressure (>140 mmHg) in the previous year, that started with antihypertensives or that reached the systolic blood pressure target level (≤140 mmHg)	Blood pressure	56.9 (562/988)
8. The percentage of patients with T2D between 18 and 70 years treated with monotherapy antihypertensives and with an elevated systolic blood pressure (>140 mmHg) in the previous year, that is intensified with antihypertensives or that reached the systolic blood pressure target level (≤140 mmHg)	Blood pressure	55.3 (588/1,064)
9. The percentage of patients with T2D between 18 and 70 years with micro- or macro-albuminuria [†] in the previous year, that started with an ACE-i or ARB or that returned to normo-albuminuria [†]	Albuminuria	59.5 (132/222)
10. The percentage of patients with T2D 18 years or older treated with two or more antihypertensives that is prescribed an ACE-i or ARB	Albuminuria	87.4 (12,789/14,627)

Table 6.1: Definition of indicators with the relevant intermediate outcomes and general outcome in a cohort of type 2 diabetes patients in primary care (continued)

Indicator	Intermediate patient outcome	Indicator outcome in GIANTT (% , nominator/denominator)
11. 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	Albuminuria	84.5 (2,451/2,901)

GIANTT: Groningen Initiative to Analyse Type 2 diabetes Treatment; T2D: type 2 diabetes; HbA_{1c}: glycated haemoglobin; LDL-cholesterol: low-density lipoprotein-cholesterol; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker.

[†] Micro-/macro-albuminuria is defined as albumin/creatinine ratio ≥ 2.5 mmol/l for males and ≥ 3.5 mmol/l for females. Normo-albuminuria is defined as albumin/creatinine ratio < 2.5 mmol/l for males and < 3.5 mmol/l for females.

Patient characteristics

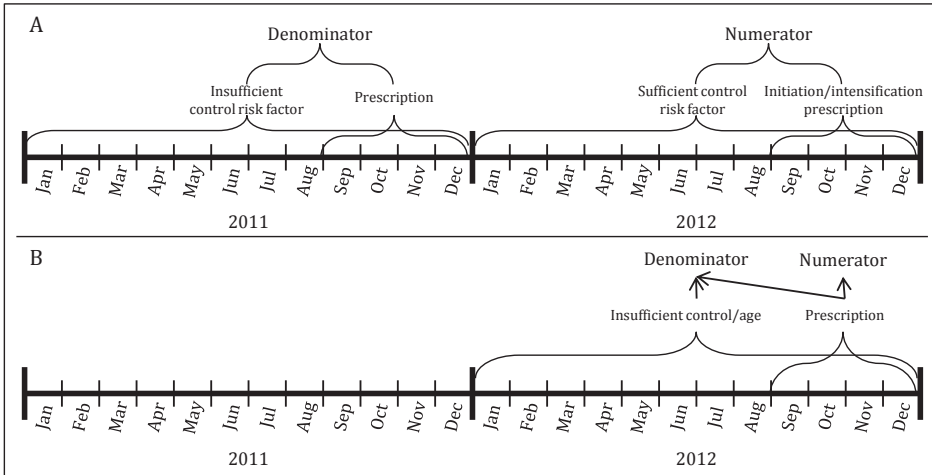
Patient characteristics were included in the models to test whether they would influence the associations between the PQIs and the intermediate patient outcomes. This included age (determined on January 1st, 2012), gender, diabetes duration (categorized on recently diagnosed ≤ 2 years, less recently diagnosed 2-10 years, and older diagnosed > 10 years), baseline risk factor (HbA_{1c}, LDL-cholesterol, SBP, or albuminuria in 2011 for clinical action indicators and in 2012 for current use indicators), time between indicator and outcome date, body mass index (normal < 25 kg/m², overweight 25-30 kg/m², obese ≥ 30 kg/m²), and smoking status (yes/no). Furthermore, the following comorbidities were considered: history of cardiovascular disease, peripheral vascular disease, renal complications, diabetic complications, malignancies, and psychological comorbidities (Appendix 5, Table S6.1).

Statistical analysis

Descriptive statistics were used to describe the population in 2012. To test whether the PQIs are predictive of better outcomes, the associations between the indicators and patient outcomes were assessed using linear regression for the continuous outcomes (HbA_{1c}, LDL-cholesterol, SBP values) and logistic regression for the dichotomous outcome (albuminuria).

For each PQI, three separate models were defined for patients with or without good quality of care as defined by the indicator. Model 1 was the primary model, which was adjusted for baseline HbA_{1c}, LDL-cholesterol, SBP, or albuminuria values, depending on the indicator tested. Model 2 tested whether adjusting for

Figure 6.1: Clinical action and current use indicators



A: figure of clinical action indicator. Patients are selected in the denominator when the last available measurement showed insufficient control of the risk factor and there was either no or a predefined treatment prescribed in the last four months of 2011. Patients are selected in the numerator when the last available measurement showed sufficient control of the risk factor and/or a predefined treatment was prescribed in the last four months of 2012. This is a measurement of the initiation or intensification of treatment. B: figure of current use indicators. Patients are selected in the denominator based on either age determined on 1 Jan 2012, insufficient control in the last available measurement of the risk factor in 2012, or a predefined prescription in the last four months of 2012. Patients are selected in the numerator when a predefined treatment was prescribed in the last four months of 2012.

other patients characteristics changed the associations. We included age in this model, and covariates from the predefined list with a p-value below 0.20 using backward selection. When the association is changed by adjusting for a patient characteristic, this could indicate a shortcoming of the indicator. When this is the case, the indicator needs adaptation to reduce unwanted sensitivity to heterogeneity in the underlying patient population. Possibly older patients are prescribed differently than younger patients and have more difficulty with reaching target values. Therefore, Model 3 tested whether patient's age modified the associations by including an interaction term with age. The effect sizes are presented by the estimated differences in outcomes for linear regression and odds ratios (ORs) for logistic regression. The effect sizes were considered statistically significant when the p-value was below 0.05. All analyses were conducted using Stata version 14.1 Special Edition (Stata Corp., College Station, TX).

Sensitivity analysis

LDL-cholesterol and albuminuria values are less frequently available than HbA_{1c} and SBP values. Therefore, a sensitivity analysis was performed extending the follow-up period for the LDL-cholesterol and albuminuria outcomes, that is, allowing for a period of up to 548 days after the indicator date. Furthermore, time between indicator and outcome date may vary between patients, and could influence the association between the indicator and the outcome.¹⁸ A second sensitivity analysis tested for a possible interaction between the indicator and the time between indicator and outcome date.

Role of the funding source

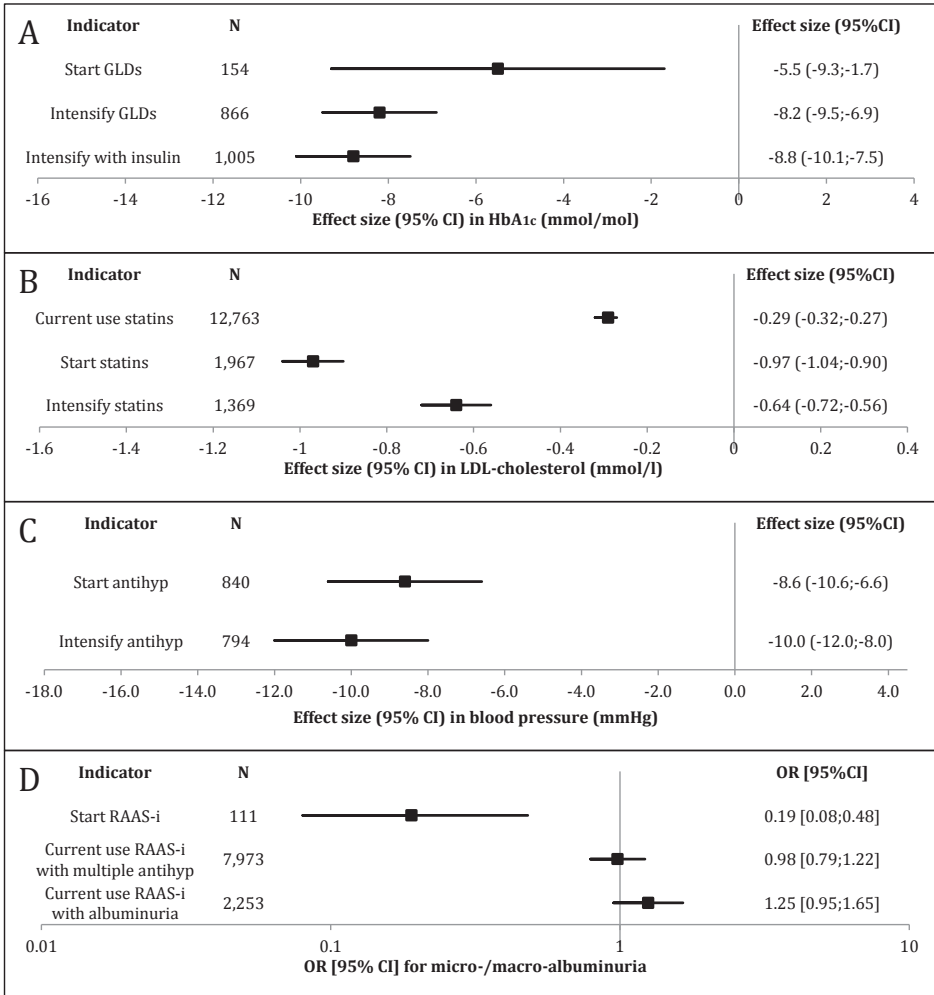
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

In total, 26,321 primary care patients with T2D were included in this study (Table 6.2). At baseline in 2012, they were on average 66.8 years old and 51% was female. The median diabetes duration was 5 years. The percentages of patients with an HbA_{1c}, LDL-cholesterol, SBP, or ACR value were 91%, 81%, 88%, and 69% respectively. Mean HbA_{1c} was 52.0 mmol/mol, mean LDL-cholesterol was 2.61 mmol/l, mean SBP was 140.5 mmHg, and 12% of patients had micro- or macro-albuminuria. Of all patients, 77% were prescribed glucose lowering drugs, 67% were prescribed statins, and 76% were prescribed antihypertensives (Table 6.2).

All three clinical action indicators on start or intensification of treatment with glucose lowering drugs were associated with better HbA_{1c} values at follow-up (Figure 6.2A). Indicator 1 focusing on start of treatment with any glucose lowering drug was associated with an average HbA_{1c} decrease of 5.5 mmol/mol [95%CI -9.3, -1.7]. Indicator 2 focusing on intensification of treatment in patients on metformin monotherapy was associated with an HbA_{1c} decrease of 8.2 mmol/mol [-9.5, -6.9]. Similarly, indicator 3 focusing on initiation of insulin in patients being on multiple non-insulin glucose lowering drugs, was associated with an HbA_{1c} decrease of 8.8 mmol/mol [-10.1, -7.5]. These associations remained similar after adjusting for patient characteristics (effect sizes -5.2 mmol [-9.0, -1.4]; -8.5 mmol [-9.9, -7.2]; -8.9 mmol [10.1, -7.5] respectively, Appendix 5, Table S6.2). The effect

Figure 6.2: Forrest plots showing the effect sizes (A, B, C) and odds ratios (D) for the association between the indicators and the intermediate patient outcomes



95% CI: 95% confidence interval; GLD: glucose lowering drug; HbA_{1c}: glycated haemoglobin; LDL-cholesterol; low-density lipoprotein-cholesterol; antihyp: antihypertensives; RAAS-i: RAAS inhibitors; OR: odds ratios.

A: linear regression associations of the indicators on glucose lowering drugs with HbA_{1c} values in percentages. B: linear regression associations of the indicators on statin use with LDL-cholesterol values. C: linear regression associations of the indicators on antihypertensive treatment with blood pressure values. D: odds ratios of indicators on RAAS inhibitors for risk of having micro- or macro-albuminuria.

size of indicator 3 was modified by age ($p=0.049$). Being younger was associated with larger reductions in HbA_{1c} values (Appendix 5, Figure S6.2).

Both the current use indicator and the two clinical action indicators on treatment with statins were associated with better LDL-cholesterol values at follow-up (Figure 6.2B). Indicator 4 focusing on current use of statins was associated with an LDL-cholesterol decrease of 0.29 mmol/l [-0.32, -0.27]. The clinical action indicators 5 and 6 focusing on start and intensification with statins were associated with LDL-cholesterol decreases of 0.97 [-1.04, -0.90] and 0.64 mmol/l [-0.72, -0.56] respectively. These associations remained similar after adjusting for patient characteristics (effect sizes -0.30 [-0.33, -0.27]; -0.97 [-1.03, -0.90]; -0.62 [-0.70, -0.54] respectively, Appendix 5, Table S6.2). There was no significant effect modification by age.

Both clinical action indicators focusing on start and intensification of antihypertensives were associated with better SBP values at follow-up (Figure 6.2C). Indicator 7 focusing on start of treatment was associated with an SBP decrease of 8.63 mmHg [-10.62, -6.63] and indicator 8 on intensification of treatment was associated with an SBP decrease of 9.95 mmHg [-11.96, -7.95]. These associations remained similar after adjusting for patient characteristics (effect sizes -8.38 [-10.36, -6.39] and -9.47 [-11.47, -7.46] respectively, Appendix 5, Table S6.2). There was no significant effect modification of age.

Of the PQIs focusing on treatment with RAAS inhibitors, the clinical action indicator on starting with RAAS inhibitors was significantly associated with the albuminuria values at follow-up (OR: 0.19 [95%CI 0.08, 0.48]). No significant associations were found for indicators 10 and 11 (Figure 6.2D), which focus on current use of RAAS inhibitors (OR: 0.98 [0.79, 1.22]; OR: 1.25 [0.95, 1.65]). These associations remained similar after adjusting for patient characteristics (OR: 0.12 [0.04, 0.34]; OR: 0.94 [0.75, 1.18]; OR: 1.22 [0.92, 1.62] respectively, Appendix 5, Table S6.2). The effect size of indicator 10 was modified by age ($p=0.044$) but no significant differences were found between the associations according to different age quartiles (Appendix 5, Table S6.3).

The first sensitivity analysis, where the follow-up period was extended to 548 days for the LDL-cholesterol and albuminuria outcomes, did not alter the results (Appendix 5, Figure S6.1). The second sensitivity analysis found one significant effect modification by time between indicator and outcome date. For indicator 6, the association between the indicator and the LDL-cholesterol outcome was stronger for patients with more time between these two dates (Appendix 5, Figure S6.2).

DISCUSSION

Overall, nine out of the eleven PQIs were predictive of better patient outcomes in the following year. All eight clinical action indicators on start and intensification of glucose lowering drugs, statins, antihypertensives, and RAAS inhibitors were predictive of better intermediate cardiovascular and renal outcomes. Of the three current use indicators, only the PQI on current use of statins was predictive of better LDL-cholesterol outcomes. The other two indicators on current use of RAAS inhibitors were not significantly associated with the albuminuria outcome.

Clinical action indicators give more insight for the health care provider than current use indicators.^{9,12,19} Previous studies found associations between clinical action indicators and intermediate patient outcomes. A review found evidence that indicators assessing whether glucose and lipid lowering treatment was intensified were predictive of better HbA_{1c} and LDL-cholesterol outcomes.¹³ Other studies confirmed these findings.^{14,15} While the review did not find an association between intensification of treatment and better SBP outcomes,¹³ a more recent study did find such an association.¹⁴ In our study, all clinical action indicators were predictive of better outcomes, including PQIs for various treatment steps to reduce glucose, blood pressure, cholesterol, and albuminuria. The indicators tested in our study differ from most of the previously defined indicators, that is, they also consider patients as receiving adequate treatment when they return to control without a start or intensification of medication treatment. This provides more fair assessment of the quality of care, which may include also interventions on lifestyle, drug dosing, or adherence. In addition, the PQIs we tested were developed using a structured method, providing support for their content and face validity.^{7,16} The development process of previously tested indicators was not always clear.^{14,15}

PQI focusing on current use of medication are widely used. These are easy to calculate but they do not capture actions of a health care provider in patients who are not sufficiently controlled. Previous studies found mixed results for the predictive validity of these indicators on better intermediate patient outcomes. One study found an association between current use of lipid lowering drugs and better LDL-cholesterol values,¹⁴ which our study confirmed for current use of statins. No associations were found for current use of RAAS inhibitors with albuminuria values,¹⁴ which our study confirmed for patients with or without micro- or macro-albuminuria. Guidelines recommend the use of RAAS inhibitors because of their albuminuria lowering effect.^{1,20} Indicators for prescribing of RAAS inhibitors are used in multiple indicator sets for T2D care but also for chronic kidney disease management.²¹⁻²³ Their lack of association with patient outcomes suggests that

these indicators have no predictive validity. However, this lack of association can also be caused by our use of a dichotomous albuminuria outcome, which is less sensitive to detect changes than a continuous outcome. A continuous variable for albuminuria could not be used due to the presence of values under the detection limit. Since it is not yet certain that patients will benefit from prescribing according to these indicators, they should only be used for internal evaluation to give insight for the health care professionals.

The models were adjusted for the baseline risk factor value, because one can expect that someone with a high baseline risk factor value will have a higher value at the outcome compared to patients with a lower baseline value, despite receiving similar treatment.²⁴ The models were additionally adjusted for a range of patient characteristics to test for the possible influence of the heterogeneity of the patient population. None of the associations were significantly altered by the adjustments, which was also in line with previous findings for other quality indicators.¹⁸ For one indicator, the association was modified by age but remained significant for all age groups. Therefore none of the tested PQIs needs case-mix adjustment when comparing the quality of care between practices or against a benchmark.

This is a first study testing the predictive validity of clinical action indicators that were developed using a systematic structured approach. We used a database with routinely collected data from a large proportion of patients with T2D cared for in primary care practices to test the predictive validity. The PQIs were tested for associations with intermediate patient outcomes, assuming that this leads to better hard patient outcomes. Previously, however, not all PQIs that were associated with better intermediate outcomes were found to be predictive of better hard patient outcomes.²⁵ Therefore, additional analyses are needed to test the predictive validity of the PQI on hard patients outcomes.

In conclusion, all eight clinical action PQIs on start and intensification of treatment with glucose lowering drugs, statins, antihypertensives, and RAAS inhibitors and one current use PQI on statins are well defined and beneficial for patients. Therefore these PQIs can be used for internal and external evaluation of the quality of T2D care. Both indicators on current use of RAAS inhibitors do not have sufficient evidence of predictive validity at this point, and should only be used in internal evaluation programs.

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