Development and validation of prescribing quality indicators for patients with type 2 diabetes

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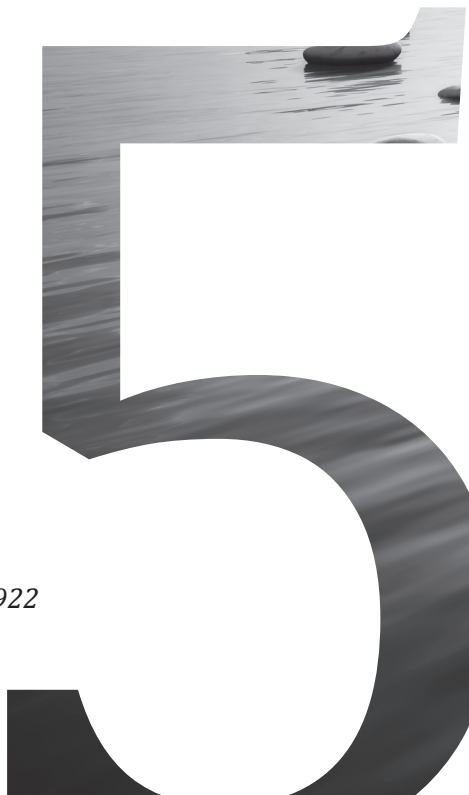

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Abstract

Background: Quality indicators are used to measure whether healthcare professionals act according to guidelines, but few indicators focus on the quality of pharmacotherapy for diabetes. The aim of this study was to develop and validate a set of prescribing quality indicators (PQIs) for type 2 diabetes in primary care, and to apply this set in practice. To take into account the stepwise treatment of chronic disease, clinical action indicators were specifically considered.

Methods: Potential PQIs were derived from clinical practice guidelines and evaluated using the RAND/UCLA Appropriateness Method, a modified Delphi panel. Thereafter, the feasibility of calculating the PQIs was tested in two large Dutch primary care databases including >80,000 diabetes patients in 2012.

Results: 32 PQIs focusing on treatment with glucose, lipid, blood pressure and albuminuria lowering drugs, and on vaccination, medication safety and adherence were assessed by ten experts. After the Delphi panel, the final list of twenty PQIs was tested for feasibility. All PQIs definitions were feasible for measuring the quality of medication treatment using these databases. Indicator scores ranged from 18.8% to 90.8% for PQIs focusing on current medication use, clinical action and medication choice, and from 2.1% to 37.2% for PQIs focusing on medication safety.

Conclusions: Twenty PQIs focusing on treatment with glucose, lipid, blood pressure and albuminuria lowering drugs, and on medication safety in type 2 diabetes were developed, considered valid and operationally feasible. Results showed room for improvement, especially in initiation and intensification of treatment as measured with clinical action indicators.

Introduction

Adequate medication treatment for patients with type 2 diabetes (T2D) is an integral and important part of clinical guidelines. Such guidelines emphasize treatment with glucose, lipid, blood pressure and albuminuria lowering drugs.[1,2] Furthermore, guidelines provide recommendations with regards to appropriateness and safety of medication use. Quality indicators measure whether healthcare professionals prescribe according to these guidelines. They are used to monitor quality of care, compare and reward healthcare professionals, and can be part of feedback and audit programs.[3] Earlier research using such quality indicators showed that a sizable part of the patients with T2D may receive suboptimal treatment.[4-6]

Most of the available quality indicators for T2D care measure whether risk factors are monitored and target levels are achieved, whereas few focus on the quality of prescribing.[7] Indicators focusing on prescribing are more direct measures of actions of the healthcare professionals, and can be a meaningful addition in quality assessments to support providers to prescribe appropriately.[8] The Quality Outcomes Framework (QOF) in the UK and the Healthcare Effectiveness Data and Information Set (HEDIS) in the USA only include some indicators focusing on prescribing of medication in diabetes.[9,10] In the Netherlands, the Dutch College of General Practitioners (Nederlands Huisartsen Genootschap, NHG) and the Dutch Institute for Rational Use of Medicine (Instituut voor Verantwoord Medicijngebruik, IVM) include respectively seven and three indicators measuring the use of glucose lowering, blood pressure lowering and lipid lowering drugs in patients with diabetes.[11,12] Most of these prescribing quality indicators (PQIs) assess whether patients receive recommended medication treatment, including some focusing on current medication use and specific first-choice medication, and some focusing on medication adherence.

Other aspects of treatment can be relevant, including timely start and intensification of medication, and medication safety.[8,13] Quality indicators focusing on timely start and intensification of treatment take sequential data into account and give credit for appropriate clinical action.[14,15] Previous studies illustrated that such clinical action indicators may better reflect guideline recommendations and be more clinically meaningful than indicators that measure whether patients are treated or achieve specific targets.[14-16] Furthermore, indicators on medication safety are considered important by healthcare providers.[17] Martirosyan *et al.*[18] developed and validated a comprehensive set of thirteen PQIs for T2D, including clinical action indicators. However, these PQIs were derived from guidelines which were published more than 10 years ago, and the definitions of these PQIs

required detailed clinical data that is not routinely collected for quality measurement purposes.

Therefore, the specific aims of our study are (I) to develop an up-to-date and comprehensive set of PQIs covering different aspects of treatment quality for T2D patients, (II) to assess the feasibility to calculate the PQIs using data routinely collected in primary care, and (III) to identify priority areas for improvement in T2D patients based on the PQIs estimates.

Methods

We followed the recommended steps for developing quality indicators.[19,20] We based the indicators on literature, clinical guidelines and expert consultations. A group of experts assessed the indicators. Thereafter, the feasibility to calculate the PQIs using data from actual practice was assessed.[21]

Selection of prescribing quality indicators

The initial list of PQIs was based on the current national and international guidelines.[1,2,22,23] Recommendations for medication treatment from these guidelines with level A or B evidence were extracted and converted in a list of potential PQIs by four members of the research team. This list was then discussed with an experienced clinician to refine the definitions, and with two patient representatives to ascertain that all relevant topics from the patient perspective were covered.

Content and face validation

To assess the content and face validity of the PQIs, the RAND/UCLA Appropriateness Method (RAM) was used.[24] This three-round modified Delphi method combines evidence (content validity) with expert opinion and consensus (face validity). It is considered an appropriate method for assessing the validity of indicators.[21,25] General practitioners and internists specialized in diabetes care were approached. A financial compensation was offered to the experts for their time.

During the first round, the experts individually scored the PQIs on three criteria using a 9-point Likert scale. Two of these criteria represent content validity, i.e. whether the PQI reflected the guidelines adequately ('correct reflection of guidelines') and whether the definitions were correctly formulated ('definitions'). The third criterion, whether following the PQIs would result in health gain for the patient ('health gain'), was included as a general reflection of both content and face validity. The experts could give comments and propose changes or new PQIs during the first round. The second round was a consensus meeting where the

experts discussed discrepancies and were able to change, add and remove PQIs. This discussion was chaired by a moderator (PD). During the third round, the experts received a list of adjusted PQIs including explanations for the changes, deletions, and additions made. This round was similar to the first round, assessing the criteria 'correct reflection of guidelines' and 'health gain', and one new criterion, which assessed whether the PQI measured a necessary aspect of quality of care ('necessary aspect'), reflecting face validity.

Operational feasibility

The feasibility to calculate the PQIs using routinely collected data (operational feasibility) was assessed using data from the Groningen Initiative to Analyse Type 2 Diabetes Treatment (GIANTT)[26] and Zwolle Outpatient Diabetes project Integrating Care Study (ZODIAC)[27,28] databases in 2012. The GIANTT database includes longitudinal data extracted from medical records of >25,000 T2D patients managed in primary care in a region in the north of the Netherlands in 2012. The ZODIAC database includes data extracted from medical records of >55,000 T2D patients managed in primary care in regions in the east and west of the Netherlands in 2012. GIANTT includes all routinely collected data from general practices. In contrast, the ZODIAC database only includes data from the yearly visit. Both databases include structured information on age, gender, physical examination, laboratory measurements, comorbidity and prescribed medication. Age and gender were determined on 1 January 2012, while for physical examinations and laboratory measurements the most recent values in 2011 and 2012 (GIANTT) or the values from the yearly visits in 2011 and 2012 (ZODIAC) were collected. Current use of medication was defined as having a documented prescription at the yearly visit in ZODIAC, and as use of a medication at any time within the last 4 months of the calendar year in GIANTT. An indicator's definition was considered feasible when all indicator components could be calculated using the available data, i.e. the inclusion and exclusion criteria, required measurements and prescribed medication. Indicators were considered less appropriate for monitoring and benchmarking healthcare professionals when they were applicable for <2% of the total patient population. Priority areas for improvement were identified using arbitrary cut-off points of >15% for the medication safety indicator scores and <60% for all other indicator scores.

Two sensitivity analyses were performed. First, we recalculated the clinical action indicators focusing on starting and intensifying treatment including in the denominator also the patients without measurements of a risk factor (glycated haemoglobin (HbA_{1c}), low-density lipoprotein(LDL)-cholesterol, blood pressure, albumin/creatinine ratio) in the previous year. This allows for the inclusion of

newly diagnosed patients for whom the risk factor measurements were not available or recorded in the database in the previous year. Second, we performed a sensitivity analysis for the GIANTT data where current use of medication was defined as use of a medication at any time in the whole year instead of the last 4 months of the year. This allows for the inclusion of patients as being treated, who did receive a repeat prescription from the practice in the latter part of the year. Two safety indicators were excluded from this sensitivity analysis, which assess medication use in relation to the last risk factor measurement in the current year. Including any use of medication for these indicators would lead to misclassification of patients whose medication was changed during the year because of the risk factor measurement.

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.

Statistical analysis

A PQI was considered content and face valid when (I) all criteria in the third round of the RAM method were rated with a median score of seven or more, and (II) the criteria were rated without disagreement. Disagreement among the experts was calculated using the ratio of the InterPercentile Range Adjusted for Symmetry over the InterPercentile Range, where a score of <1 indicates poor agreement.[24]

To assess to what extent a PQI can provide reliable scores for comparison of healthcare professionals, we calculated the minimum number of patients required with a moderate precision of 10 percentage points for all indicators, except for the medication safety indicators. A precision of 5 percentage points was used for safety indicators with a score of more than 5% and 1 percentage point for safety indicators with a score of 5% or less.

All analyses on expert and PQI scores were conducted using Stata version 13.1 Special Edition (Stata Corp., College Station, TX).

Results

Content and face validity

The expert panel included four general practitioners and six internists. An initial list of 32 PQIs was composed to be rated by the expert panel. This list included indicators focusing on clinical action, current medication use and medication choice for glucose (n=11), lipid (n=4), blood pressure (n=4), and albuminuria

(n=3) lowering drugs. Furthermore, indicators on medication safety (n=6), vaccination (n=1), and treatment adherence (n=3) were included.

First round

In the first round, the following indicators were scored with certainty (median score≥7) and agreement: all indicators on medication safety, and all indicators on clinical action and medication choice of albuminuria lowering drugs. Furthermore, three indicators on clinical action for glucose, lipid and blood pressure lowering drugs, and one medication choice for glucose lowering drugs scored sufficient. The other nineteen indicators scored insufficient on one or more criteria (Appendix 4, Table S5.1).

Second round

Twelve PQIs were changed during the consensus meeting. For eight of these twelve PQIs, only the age restriction was altered (Appendix 4, Table S5.1, PQI **1**, **2**, **8**, **9**, **10**, **12**, **14** and *12B* [later discarded]). Regarding the other four PQIs, one was split into two indicators to differentiate between patients currently receiving or starting the recommended metformin treatment (Appendix 4, Table S5.1, PQI **5**). Another PQI was restricted to focus on patients starting with the recommended second-step gliclazide treatment (Appendix 4, Table S5.1, PQI **7**). Furthermore, the target level of blood pressure was changed from 140 mmHg to 160 mmHg in one PQI (Appendix 4, Table S5.1, PQI *12A* [later discarded]). Finally, the denominator of the PQI focusing on medication safety of simultaneous use of renin-angiotensin-aldosterone system (RAAS) inhibitors was changed from everyone into patients on RAAS treatment (Appendix 4, Table S5.1, PQI **20**).

Discarded and added indicators

The remaining fourteen indicators from the initial list were discarded. Of these fourteen, three PQIs assessing current use of different classes of glucose lowering drugs were discarded because they included all patients without addressing their need for specific treatment (Appendix 4, Table S5.1, PQI *1A, 1B, 1C*). The experts decided that these volume-based PQIs, which are included in the NHG indicator set to describe the population, did not reflect quality of care. Two PQIs focusing on clinical action for treatment of blood glucose and two PQIs focusing on clinical action for treatment of blood pressure were discarded because they focus on older patients for whom the guideline recommendations are less clear (Appendix 4, Table S5.1, PQI *4B, 4C, 15C, 17*). The PQI on simultaneous use of pioglitazone with insulin was discarded as not needed since this combination is seldom prescribed in practice (Appendix 4, Table S5.1, PQI *10*). One PQI focusing on medication

choice of simvastatin was removed by the experts because the preference was not reflecting a quality of treatment aspect (Appendix 4, Table S5.1, PQI *14*). The medication safety indicator on monitoring potassium in patients with a prescription of a RAAS inhibitor or a diuretic was discarded because the indicator only assesses yearly measurements, whereas such monitoring should be conducted before and after initiation of these drugs (Appendix 4, Table S5.1, PQI *21*). Finally, the indicators focusing on vaccination and treatment adherence were discarded because they may partly reflect patient behaviour that is not under the physicians' control (Appendix 4, Table S5.1 *23*, *24*, *25*, *26*).

Four PQIs were added, including three on starting treatment with metformin, sulphonylurea derivatives (SU-derivatives) and angiotensin-converting-enzyme inhibitor (ACE-i) and one on medication safety in older patients (Appendix 4, Table S5.1, PQI **4**, 6, **16**, **19**).

Third round

The resulting list of 22 PQIs was rated again by all expert from the panel in the third round. Twenty-one of these indicators were scored sufficient on all three criteria. The new PQI focusing on starting treatment with SU-derivatives among all starters of a second glucose lowering drug, was scored insufficient on 'health gain' and therefore discarded (Appendix 4, Table S5.1, PQI 6). Furthermore, the PQIs focusing on clinical action for high blood pressure received many comments on the risk factor target levels for different age groups. Therefore, we proposed to combine both PQIs and asked the experts to rate the PQI again. This new PQI scored sufficient on all criteria (Appendix 4, Table S5.1, PQI **11**). The final list of twenty PQIs included sixteen indicators on treatment with glucose lowering (n=7), lipid lowering (n=3), blood pressure lowering (n=2), and albuminuria lowering drugs (n=4), including eight clinical action indicators, one current medication use and seven medication choice indicators, and four indicators on medication safety (Table 5.2 and Appendix 4, Table S5.1).

Operational feasibility

This final list of PQIs was then applied in the GIANTT and ZODIAC databases, including 26,321 respectively 56,808 T2D patients in 2012 (Table 5.1).
Operational definitions could be made for all PQIs using the available data (Appendix 4, Table S5.2). All indicators had sufficient number of eligible patients for reliable calculation in these large primary care cohorts (Table 5.2).

For three of the indicators, the percentage of eligible patients was less than 2% of the total population. These indicators focus on start of glucose lowering drugs, the start of ACE-i/angiotensin-II-receptor-blockers (ARBs) and the percentage

Table 5.1: Patient characteristics in 2012

	GIANTT		ZODIAC	
Variables	**N (%)**	**Mean (±SD)**	**N (%)**	**Mean (±SD)**
Age (years)	26,321 (100)	67.3 (±11.9)	56,808 (100)	67.1 (±12.0)
Male gender (%)	12,965 (49.3)		28,581 (50.3)	
Physical examination				
Systolic blood pressure (mmHg)	23,069 (87.6)	140.5 (±17.7)	45,263 (79.7)	137.2 (±16.5)
High systolic blood pressure (>140 mmHg)	9,921 (37.7)	156.2 (±13.1)	15,697 (27.6)	154.5 (±11.6)
Laboratory measurements				
HbA_{1c} (mmol/mol)	23,843 (90.6)	52.0 (±9.6)	44,731 (78.7)	50.6 (±9.9)
Elevated HbA_{1c} (>53 mmol/mol)	9,474 (36.0)	60.7 (±9.2)	13,542 (23.8)	62.0 (±9.3)
LDL-cholesterol (mmol/l)	21,259 (80.8)	2.6 (±0.9)	43,495 (76.6)	2.5 (±0.9)
Elevated LDL-cholesterol (>2.5 mmol/l)	9,669 (36.7)	3.4 (±0.7)	18,089 (31.8)	3.3 (±0.7)
Albumin/creatinine ratio (mg/mmol)	18,084 (68.7)	0.7 [0.0-1.9][a]	38,830 (68.4)	1.0 [0.4-2.3][a]
Micro/Macro-albuminuria[†]	3,265 (12.4)	7.1 [4.4-14.7][a]	7,801 (13.7)	6.2 [4.0-12.0][a]
Serum creatinine	22,271 (84.6)	78 [66-92][a]	43,888 (77.3)	77 [66-91][a]
Medication[‡]				
Glucose lowering drugs	20,267 (77.0)		36,843 (81.0)	
0	7,341 (27.9)		10,116 (22.3)	
1	11,842 (45.0)		21,882 (48.1)	
2	6,345 (24.1)		12,406 (27.3)	
3	782 (3.0)		1,040 (2.3)	
4	11 (0.0)		25 (0.1)	
5	0 (0.0)		1 (0.0)	
Insulin	3,783 (14.4)		6,734 (14.8)	
Non-insulin glucose lowering drugs	18,980 (72.1)		35,354 (77.8)	
Metformin	17,219 (65.4)		32,215 (70.9)	
SU-derivatives	7,859 (29.9)		15,299 (33.7)	
Gliclazide	5,030 (19.1)		3,034 (6.7)	
Glibenclamide	163 (0.6)		487 (1.1)	
Acarbose	9 (0.0)		30 (0.1)	
TZD	341 (1.3)		723 (1.6)	
DPP-4 inhibitors	1,168 (4.4)		1,485 (3.3)	
Other glucose lowering drugs	326 (1.2)		167 (0.4)	
Statins	17,674 (67.2)		33,095 (72.8)	
Simvastatin	10,719 (40.7)		21,835 (48.0)	
Atorvastatin	4,007 (15.2)		5,290 (11.6)	
Rosuvastatine	2,278 (8.7)		2,523 (5.6)	
Antihypertensives	20,089 (76.3)		34,560 (76.0)	
0	6,236 (23.7)		10,900 (24.0)	

Table 5.1: Patient characteristics in 2012 (continued)

	GIANTT		ZODIAC	
Variables	**N (%)**	**Mean (±SD)**	**N (%)**	**Mean (±SD)**
1	5,458 (20.7)		11,668 (25.7)	
2	6,667 (25.3)		12,098 (26.6)	
3	5,676 (21.6)		8,308 (18.3)	
4	2,150 (8.2)		2,365 (5.2)	
5	134 (0.5)		131 (0.3)	
Diuretics	12,033 (45.7)		15,495 (34.1)	
Beta blocking agents	10,725 (40.8)		18,712 (41.2)	
Calcium channel blocker	6,158 (23.4)		9,937 (21.9)	
RAAS inhibitors	15,714 (59.7)		26,155 (57.5)	
ACE-i	9,909 (37.7)		16,871 (37.1)	
ARB	6,307 (24.0)		10,499 (23.1)	
Other antihypertensives (ATC code: C02)	460 (1.8)		604 (1.3)	

GIANTT: Groningen Initiative to Analyse Type 2 diabetes Treatment; ZODIAC: Zwolle Outpatient Diabetes project Integrating Care Study; SD: standard deviation; HbA_{1c}: glycated haemoglobin; LDL-cholesterol: low-density lipoprotein-cholesterol; SU-derivatives: sulphonylurea derivatives; TZD: thiazolidinedione; DPP-4 inhibitors: dipeptidyl peptidase-4 inhibitor; RAAS: renin-angiotensin-aldosterone system; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; ATC: anatomical Therapeutic Chemical Classification System.

[a] Median and interquartile range are reported. † Micro/Macro-albuminuria is defined as an ACR ≥2.5 mg/mmol for males and ≥3.5 mg/mmol for females. ‡ For the GIANTT database, medication use in last 4 months of 2012; for the ZODIAC database, medication prescription at the yearly visit in 2012.

of patients with a low estimated glomerular filtration rate (eGFR) treated with metformin (Table 5.2).

Looking at the level of performance, several priority areas for improvement can be identified (Table 5.2). Starting with insulin scored low (38.8/42.9% for the GIANTT/ZODIAC population respectively). Furthermore, starting with statins (32.1/33.1% respectively) and intensification of statins (46.3/45.5% respectively) scored low, as did starting (56.9% in GIANTT) and intensification of antihypertensives (55.3/57.1% respectively). First-choice treatment with glicazide showed a large difference between the two populations. Finally, the medication safety indicator on use of metformin in patients with impaired kidney function (24.8/37.2% respectively of patients at risk) and potential overprescribing of glucose lowering drugs in elderly patients scored relatively high (18.2/21.3% respectively of patients at risk).

Including patients with unknown risk factor level in the previous year for the clinical action indicators resulted in including substantially more patients and also higher PQI scores for the indicators on starting treatment. The differences were especially large for the ZODIAC population (increases with more than 15% for glucose lowering drugs and more than 25% for the other starting PQIs, Appendix 4, Table S5.3A) and the PQI focusing on start with ACE-i or ARB in GIANTT (increases with more than 30%, Appendix 4, Table S5.3B). Furthermore, when measuring drugs use at any time in 2012 compared to only the last 4 months, resulted in an almost 10% higher quality score for choosing ACE-i as start medication among all starts of RAAS treatment (Appendix 4, Table S5.4, PQI 16). This shift was mainly the result of including fewer patients in the denominator (Appendix 4, Table S5.4).

Discussion

A new set of twenty indicators for measuring the quality of medication treatment in diabetes care was developed and validated. The included PQIs focus on current medication use, clinical action and medication choice for the treatment of relevant risk factors, and on medication safety. The indicators were derived from evidence-based guideline recommendation and approved by a panel of Dutch diabetes experts. All of the indicators could be operationalized using routinely collected data from two primary care databases in the Netherlands. However, some indicators may be less appropriate for monitoring and benchmarking healthcare professionals due to low numbers of eligible patients. The set of PQIs allowed identification of several priority areas for improvement, including timely start of insulin, timely start and intensification of statins and antihypertensives, prescription of metformin in patients with impaired renal function and potential overtreatment for blood glucose management in older patients.

Our set of PQIs covers a range of quality aspects, including current medication use, clinical action, medication choice and medication safety. It includes one PQI that measures current use of statins and a few PQIs on medication choice, which are similar to PQIs in existing sets. For example, the PQIs on the treatment with statins[10-12,18,29] and with ACE-i/ARBs,[9,11,12,18,29] and medication choice for glucose lowering drugs[12] are implemented in various quality assessment programs.[9,10,12] Furthermore, our set includes eight clinical action indicators, some of which were previously proposed as being more clinically relevant for physicians than indicators measuring the current medication use or achievement of specific targets.[8,14-16,30] The medication safety PQIs included in this set are new and were not

Table 5.2: Operational feasibility in GIANTT and ZODIAC database

	GIANTT		
Indicator	**Outcome score(%)**	**Nominator/ denominator**	**Percentage of eligible patients**
Glucose lowering drugs			
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)	73.1	174/ 238	0.9
2.† The percentage of patients with T2D between 18 and 70 years treated with 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)	61.1	618/ 1,012	3.8
3.† The percentage of patients with T2D between 18 and 70 years treated 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)	38.8	446/ 1,150	4.4
4.‡ The percentage of patients with T2D 18 years or older that started with metformin among all starters of oral glucose lowering drugs	78.7	841/ 1,069	4.1
5.‡ The percentage of patients with T2D 18 years or older treated with glucose lowering drugs that is prescribed metformin	86.3	14,984/ 17,353	65.9
6.‡ The percentage of patients with T2D 18 years or older treated with two non-insulin glucose lowering drugs that is prescribed a combination of metformin and an SU-derivative	87.0	4,865/ 5,589	21.2
7.‡ The percentage of patients with T2D 18 years or older that started with gliclazide among all starters of an SU-derivative	67.5	666/ 986	3.7
Lipid lowering drugs			
8.§ The percentage of patients with T2D between 55 and 80 years that is prescribed a statin	71.7	13,123/ 18,301	69.5
9.† 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)	32.1	1,100/ 3,429	13.0

			ZODIAC				
	N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison	Outcome score(%)	Nominator/ denominator	Percentage of eligible patients	N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison
	76	8,353	80.9	178/ 220	0.4	60	15,323
	92	2,376	66.1	846/ 1,280	2.3	87	3,821
	92	2,088	42.9	687/ 1,603	2.8	95	3,335
	65	1,688	88.4	8,299/ 9,383	16.5	40	238
	46	69	88.1	30,360/ 34,451	60.6	41	67
	44	205	90.8	10,686/ 11,769	20.7	33	155
	85	2,249	18.8	835/ 4,431	7.8	59	754
	78	113	76.1	24,428/ 32,079	56.5	70	124
	84	643	33.1	1,436/ 4,342	7.6	86	1,113

Table 5.2: Operational feasibility in GIANTT and ZODIAC database (continued)

	GIANTT		
Indicator	**Outcome score(%)**	**Nominator/ denominator**	**Percentage of eligible patients**
10.† 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)	46.3	1,105/ 2,389	9.1
Blood pressure lowering drugs			
11.† The percentage of patients with T2D between 18 and 70 years 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)	56.9	562/ 988	3.8
12.† 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)	55.3	588/ 1,064	4.0
Albuminuria lowering drugs			
13.‡ The percentage of patients with T2D 18 years or older treated with two or more antihypertensives that is prescribed an ACE-i or ARB	87.4	12,789/ 14,627	55.6
14.† 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¶	59.5	132/ 222	0.8
15.‡ 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	84.5	2,451/ 2,901	11.0
16.‡ The percentage of patients with T2D 18 years or older that started with an ACE-i among all patients that started with RAAS treatment	70.5	920/ 1,305	5.0
Medication safety			
17. The percentage of patients with T2D 18 years or older treated with SU-derivatives that is prescribed glibenclamide	2.1	163/ 7,859	29.9
18. The percentage of patients with T2D 18 years or older with an eGFR <30 ml/min/1.73m^2 that is prescribed metformin	24.8	91/ 367	1.4

ZODIAC						
N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison	Outcome score(%)	Nominator/ denominator	Percentage of eligible patients	N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison
96	1,053	45.5	1,587/ 3,488	6.1	96	1,552
95	2,511	63.4	724/ 1,142	2.0	90	4,435
95	2,350	57.1	816/ 1,428	2.5	95	3,743
43	77	84.6	19,381/ 22,902	40.3	51	125
93	10,980	61.0	326/ 534	0.9	92	9,719
51	457	82.6	5,517/ 6,676	11.8	56	470
80	1,612	65.3	5,057/ 7,742	13.6	88	639
781‖	2,614	3.2	487/ 15,299	26.9	1,190#	4,397
287¶	20,551	37.2	196/ 527	0.9	359††	38,694

Table 5.2: Operational feasibility in GIANTT and ZODIAC database (continued)

	GIANTT		
Indicator	**Outcome score(%)**	**Nominator/ denominator**	**Percentage of eligible patients**
19. 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 lowering drugs	18.2	377/ 2,070	7.9
20. 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)	3.2	502/ 15,714	59.7

GIANTT: Groningen Initiative to Analyse Type 2 diabetes Treatment; ZODIAC: Zwolle Outpatient Diabetes project Integrating Care Study; T2D: type 2 diabetes; HbA1c: glycated haemoglobin; SU-derivative: sulphonylurea derivative; LDL-cholesterol: low-density lipoprotein-cholesterol; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; RAAS: renin-angiotensin-aldosterone system; eGFR: estimated glomerular filtration rate. † Clinical action indicator. ‡ Medication choice indicator. § Current medication use. ¶ Micro- or macro-albuminuria is defined as albumin/creatinine ratio ≥2.5 mg/mmol for males and ≥3.5 mg/mmol for females. Normo-albuminuria is defined as albumin/creatinine ratio <2.5 mmol/l for males and <3.5 mmol/l for females. # Precision of 1 percentage point allowed. †† Precision of 5 percentage point allowed.

included in the previous indicator sets. On the other hand, our PQI set does not include an indicator on the influenza immunization which is included in other sets.[9,11] This indicator was discarded by experts because it could in part reflect behaviour of patients instead of healthcare professionals. The same goes for the indicators focusing on medication adherence.

The PQIs in our set can be divided into indicators that measure the treatment at one point in time, and indicators that make use of sequential data. The latter include the clinical action indicators taking the chronic aspect of diabetes care into account, but also the indicators looking at medication choice when treatment is started. Although such indicators may have a higher face and content validity, the use of additional information can introduce new validity problems. For example, the scores of the PQIs will be influenced by the quality and completeness of data for individual patients in consecutive years. Some PQIs included a low number of patients due to the definitions of patients eligible for starting treatment, where eligible patients could only be identified when the related risk factor measurement from the year before was known. Especially for recently diagnosed patients, such measurements may not be available. Our first sensitivity analysis

ZODIAC						
N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison	Outcome score(%)	Nominator/ denominator	Percentage of eligible patients	N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison
229[¶]	2,911	21.3	891/ 4,178	7.4	258[††]	3506
1,189[‖]	1,991	4.9	1,274/ 26,155	46.0	1,781[#]	3,867

showed that including patients with unknown risk factor measurements in the previous year may lead to higher PQI scores, especially for the PQIs focusing on starting treatment. This could be due to a high prevalence of well-controlled patients among those without a measurement in the previous year or due to a high number of newly diagnosed patients. Also, the misclassification of treatment starters can occur due to a relatively short observation period in the previous year that is used to identify patient who were not yet treated. Our second sensitivity analysis showed that looking at use of treatment at any time point of 12 months in comparison to the last four months, led to including fewer eligible patients and a substantial change in the PQI scores, in particular in the PQIs focusing on start of first-choice drugs. These PQIs do not depend on risk factor measurements, but only include information on drugs use. To reduce misclassification of treatment starts, these indicators could be improved by including an additional requirement that at least one laboratory measurement should be available in the previous year. This indicates that there was a practice visit without a recorded prescription. Finally, several PQIs in our set are restricted to specific cut-off levels of a risk factor as part of the inclusion criteria. This may lead to misclassification of patients that are temporarily well-controlled.[8,31]

PQIs can be used for different purposes, i.e. for monitoring quality of prescribing care, for providing feedback to the healthcare professionals, for research purposes to assess changes over time or after an intervention, and for external benchmarking.[13] However, it is important to be aware that a score of 100% is never pursued. There might be valid reasons why a patient does not receive the recommended treatment, such as an intolerance to a drug or patient's refusal. The PQIs of this set could be used for the first three purposes, but they lack a precision for benchmarking at general practice level.[32] The number of patients with T2D

needed per general practice for measuring the quality of prescribing with a precision of 10 percentage point (5 or 1 percentage point for medication safety PQI) ranged from 67 to 38,694. An average general practice in the Netherlands manages around 100 patients with T2D. Furthermore, three PQIs included less than 2% of the total cohort population. When the measured care is applicable to such a small percentage of patients, it can be less appropriate for monitoring purposes. The PQIs including low numbers of patients could instead be more relevant for alerting systems.

Our study has some strengths and limitations. Our initial set was selected using only level A and B evidence recommendations from recent national guidelines, which are similar to international guidelines on most aspects. In some cases, for example, for the indicator on starting statin treatment as a function of LDL-cholesterol, an adaptation might be relevant to incorporate additional risk factors to comply with other guidelines. We confirmed that also topics considered relevant from the patient perspective were included. An expert panel specialised in diabetes care assessed the face and content validity of the PQIs. Judgments made by this panel may not be representative of all diabetes healthcare professionals. However, the number of experts satisfies the requirement to include 7-15 experts to the panel according to the RAM,[24] and it has been argued that using techniques combining evidence with consensus improves the quality of the indicators.[21] We tested the operational validity in different databases, including the ZODIAC database that is representative for the routinely collected data used for monitoring and benchmarking in the Netherlands. Therefore, using this database for testing the operational validity showed that this set of PQIs, including clinical action indicators, can be applied on a national level in Dutch practice. The PQIs can be applied in other settings on the condition that there is a database available that includes information at patient level regarding age, physical examinations, laboratory measurements and prescribed medication. Finally, although our indicators give a good indication of the quality of pharmacotherapy, this cannot be seen as an assessment of overall quality of diabetes care. Other aspects, such as monitoring of patients and outcome parameters might be important as well.

In conclusion, a set of twenty PQIs for patients with T2D was developed and validated, using the RAM method and routinely collected primary care data. This set complements existing T2D quality indicator sets with PQIs that focus on clinical action and medication choice for treatment with glucose lowering, lipid lowering, blood pressure lowering and albuminuria lowering drugs, and medication safety. These PQIs can be used to point out priority areas for improvement and in audit and feedback programs.

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References

1. Rutten GEHM, De Grauw WJC, Nijpels G, et al. NHG-Standard Diabetes mellitus type 2 (derde herziening) [The Dutch College of General Practitioners-Practice Guideline Diabetes mellitus type 2 (third revision)]. Huisarts Wet 2013; 56(10): 512-25.
2. American Diabetes Association. Standards of Medical Care in Diabetes - 2014. Diabetes Care 2014; 37(S1): S14-S80.
3. Campbell SM, Hann M, Hacker J, Durie A, Thapar A, Roland MO. Quality assessment for three common conditions in primary care: validity and reliability of review criteria developed by expert panels for angina, asthma and type 2 diabetes. Qual Saf Health Care 2002; 11(2): 125-30.
4. Hellemons ME, Denig P, de Zeeuw D, Voorham J, Lambers Heerspink HJ. Is albuminuria screening and treatment optimal in patients with type 2 diabetes in primary care? Observational data of the GIANTT cohort. Nephrol Dial Transplant 2013; 28(3): 706-15.
5. Sidorenkov G, Haaijer-Ruskamp FM, de Zeeuw D, Denig P. A longitudinal study examining adherence to guidelines in diabetes care according to different definitions of adequacy and timeliness. PLoS One 2011; 6(9): e24278.
6. Modesti A, Bartaloni R, Bellagamba F, et al. Health care delivery in type 2 diabetes. A survey in an Italian primary care practice. Prim Care Diabetes 2015; 9(1): 9-14.
7. Calsbeek H, Ketelaar NA, Faber MJ, Wensing M, Braspenning J. Performance measurements in diabetes care: the complex task of selecting quality indicators. Int J Qual Health Care 2013; 25(6): 704-9.
8. O'Connor PJ, Bodkin NL, Fradkin J, et al. Diabetes performance measures: current status and future directions. Diabetes Care 2011; 34(7): 1651-9.
9. National Institute for Health and Care Excellence (NICE). Quality Outcomes Framework (QOF). 2014. http://www.nice.org.uk/standards-and-indicators/qofindicators. (accessed 2015-05-13.
10. National Committee for Quality Assurance. National Committee for Quality Assurance (NSQA) Healthcare Effectiveness Data and Information Set (HEDIS) 2016. 2016. http://www.ncqa.org/Portals/0/HEDISQM/HEDIS2016/HEDIS%202016%20List%20of%20Measures.pdf (accessed 09-05-2016).
11. van Althuis TR, Bouma M, The Dutch College of General Practitioners [Nederlands Huisartsen Genootschap (NHG)]. Overview and definitions of diabetes indicators in general practice [Overzicht en definitie van diabetesindicatoren huisartsenzorg], 2015.
12. Lambooij A, de Metz J, Essink R, Nijpels M, Warnier M. Monitor Prescribing Behaviour General Practitioners 2015 [Monitor Voorschrijfgedrag Huisartsen 2015]. Utrecht, The Netherlands: Institute for Rationale Use of Medicine [Instituut voor Verantwoord Medicijngebruik (IVM)], 2015.
13. Denig P, F. H-R, Pont L. Assessment of quality of prescribing using quality indicators. In: Elseviers M, ed. Drug Utilization Research: Methods and Applications. Chichester, West Sussex : Hoboken, NJ: John Wiley & Sons Inc.; 2016: 433-42.
14. Rodondi N, Peng T, Karter AJ, et al. Therapy modifications in response to poorly controlled hypertension, dyslipidemia, and diabetes mellitus. Ann Intern Med 2006; 144(7): 475-84.

15. Kerr EA, Lucatorto MA, Holleman R, Hogan MM, Klamerus ML, Hofer TP. Monitoring performance for blood pressure management among patients with diabetes mellitus: too much of a good thing? Arch Intern Med 2012; 172(12): 938-45.
16. Voorham J, Denig P, Wolffenbuttel BH, Haaijer-Ruskamp FM. Cross-sectional versus sequential quality indicators of risk factor management in patients with type 2 diabetes. Med Care 2008; 46(2): 133-41.
17. Martirosyan L, Markhorst J, Denig P, Haaijer-Ruskamp FM, Braspenning J. A pilot qualitative study to explore stakeholder opinions regarding prescribing quality indicators. BMC Health Serv Res 2012; 12: 191.
18. Martirosyan L, Braspenning J, Denig P, et al. Prescribing quality indicators of type 2 diabetes mellitus ambulatory care. Qual Saf Health Care 2008; 17(5): 318-23.
19. Campbell SM, Kontopantelis E, Hannon K, Burke M, Barber A, Lester HE. Framework and indicator testing protocol for developing and piloting quality indicators for the UK quality and outcomes framework. BMC Fam Pract 2011; 12: 85.
20. Kotter T, Blozik E, Scherer M. Methods for the guideline-based development of quality indicators--a systematic review. Implement Sci 2012; 7: 21.
21. Campbell SM, Braspenning J, Hutchinson A, Marshall M. Research methods used in developing and applying quality indicators in primary care. Qual Saf Health Care 2002; 11(4): 358-64.
22. De Grauw WJC, Kaasjager HAH, Bilo HJG, et al. Landelijk Transmurale Afspraak Chronische nierschade [Dutch Transmural Agreement Chronic Kidney Disease]. Huisarts Wet 2009; 52(12): 586-97.
23. International Diabetes Federation. Global Guideline for Type 2 Diabetes. 2012. (www.idf.org)
24. Fitch K, Bernstein SJ, Aguilar MD, et al. The RAND/UCLA Appropriateness Method User's Manual. 1700 Main Street, P.O. Box 2138, Santa Monica, CA, USA: RAND; 2001.
25. Naylor CD. What is appropriate care? N Engl J Med 1998; 338(26): 1918-20.
26. Voorham J, Denig P. Computerized extraction of information on the quality of diabetes care from free text in electronic patient records of general practitioners. J Am Med Inform Assoc 2007; 14(3): 349-54.
27. Hendriks SH, van Hateren KJ, Groenier KH, et al. Sex Differences in the Quality of Diabetes Care in the Netherlands (ZODIAC-45). PLoS One 2015; 10(12): e0145907.
28. van Hateren KJ, Drion I, Kleefstra N, et al. A prospective observational study of quality of diabetes care in a shared care setting: trends and age differences (ZODIAC-19). BMJ open 2012; 2(4).
29. NQF NQF. National Voluntary Consensus Standards for Ambulatory Care Using Clinically Enriched Data: A Consensus Report. Washington, DC: NQF, 2010.
30. Weiler S, Gemperli A, Collet TH, et al. Clinically relevant quality measures for risk factor control in primary care: a retrospective cohort study. BMC Health Serv Res 2014; 14: 306.
31. Aron D, Pogach L. Quality indicators for diabetes mellitus in the ambulatory setting: using the Delphi method to inform performance measurement development. Qual Saf Health Care 2008; 17(5): 315-7.
32. van Doorn-Klomberg AL, Braspenning JC, Feskens RC, Bouma M, Campbell SM, Reeves D. Precision of individual and composite performance scores: the ideal number of indicators in an indicator set. Med Care 2013; 51(1): 115-21.