Biochemical Urine Testing of Medication Adherence and Its Association With Clinical Markers in an Outpatient Population of Type 2 Diabetes Patients: Analysis in the DIAbetes and LifEstyle Cohort Twente (DIALECT)

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OBJECTIVE

To assess adherence to the three main drug classes in real-world patients with type 2 diabetes using biochemical urine testing, and to determine the association of nonadherence with baseline demographics, treatment targets, and complications.

RESEARCH DESIGN AND METHODS

Analyses were performed of baseline data on 457 patients in the DIAbetes and LifEstyle Cohort Twente (DIALECT) study. Adherence to oral antidiabetics (OADs), antihypertensives, and statins was determined by analyzing baseline urine samples using liquid chromatography–tandem mass spectrometry. Primary outcomes were microvascular and macrovascular complications and treatment targets of LDL cholesterol, HbA_{1c}, and blood pressure. These were assessed cross-sectionally at baseline.

RESULTS

Overall, 89.3% of patients were identified as adherent. Adherence rates to OADs, antihypertensives, and statins were 95.7%, 92.0%, and 95.5%, respectively. The prevalence of microvascular (81.6% vs. 66.2%; *P* = 0.029) and macrovascular complications (55.1% vs. 37.0%; *P* = 0.014) was significantly higher in nonadherent patients. The percentage of patients who reached an LDL cholesterol target of ≤2.5 mmol/L was lower (67.4% vs. 81.1%; *P* = 0.029) in nonadherent patients. Binary logistic regression indicated that higher BMI, current smoking, elevated serum LDL cholesterol, high HbA_{1c}, presence of diabetic kidney disease, and presence of macrovascular disease were associated with nonadherence.

CONCLUSIONS

Although medication adherence of real-world type 2 diabetes patients managed in specialist care was relatively high, the prevalence of microvascular and macrovascular complications was significantly higher in nonadherent patients, and treatment targets were reached less frequently. This emphasizes the importance of objective detection and tailored interventions to improve adherence.

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Optimal medication adherence is of utmost importance in patients with type 2 diabetes, because nonadherence can lead to disease progression, complications, mortality, and increased health care costs (1,2). The challenge of adequate therapy in type 2 diabetes is illustrated by the lasting high incidence of diabetes complications and failure to reach treatment targets of HbA_{1c}, LDL cholesterol, and blood pressure (BP) (3–5). Because patients with type 2 diabetes have a high prevalence of multimorbidity, they are often required to take multiple drugs, which poses adherence challenges. Medication adherence is especially important for patients with advanced disease, who are often on multiple therapies and at high risk of nonadherence (1). Medication adherence can be assessed in several ways, such as patient self-report, health care professional direct observation, and use of pharmacy data or electronic monitoring. However, there is no method that can be qualified as the gold standard of accurately assessing medication adherence (6). The biggest drawback of self-report is that patients tend to overreport adherence to avoid disapproval of health care professionals (7). A promising new tool to objectively assess medication adherence is biochemical urine testing using liquid chromatography–tandem mass spectrometry (LC-MS/MS) (8,9). LC-MS/MS is an extremely specific and sensitive instrument with a detection limit in the low nanogram range in a spot urine or blood sample. Medications can be detected for between four and six half-lives of the drug, thus providing an objective snapshot of drug adherence (10).

Although there is a previous small study on prevalence of nonadherence determined by LC-MS/MS in primary care (10), we aimed with this larger study to assess the prevalence of nonadherence to oral antidiabetics (OADs), antihypertensives, and statins in a real-life population of type 2 diabetes patients managed in a specialist setting using urine testing by LC-MS/MS. In addition, we determined associations of nonadherence with baseline demographics, treatment targets, and diabetes complications.

RESEARCH DESIGN AND METHODS

Study Design

This study was performed in the DIABetes and LifEstyle Cohort Twente (DIALECT) cohort (3). DIALECT is an observational prospective cohort study performed in the Ziekenhuis Groep Twente Hospital (Almelo and Hengelo, the Netherlands) and designed to investigate the effect of lifestyle and dietary habits on outcomes in patients with complicated type 2 diabetes treated in specialist care. The primary aim of DIALECT is to identify targets for the improvement of treatment quality by a systematic assessment of both pharmacological and nutritional management. DIALECT consists of two identical inclusion periods. Patients in the DIALECT-1 population were recruited between September 2009 and January 2016 (n = 400). Recruitment of DIALECT-2 started from that moment on, and recruitment will continue until a total of 850 participants is reached. Our study was performed according to the guidelines of good clinical practice and the Declaration of Helsinki. Written informed consent was obtained from all patients before participation. The study was approved by the local institutional review boards (Medisch Ethische Toetsingscommissie reg. nos. NL57219.044.16 and 1009.68020) and is registered in the Netherlands Trial Register (NTR5855).

Population

The study population consisted of patients with type 2 diabetes aged ≥18 years treated in the specialist outpatient clinic as part of routine secondary care. In the Netherlands, criteria for referral from primary to secondary health care are inability to achieve adequate glycemic control (defined as failure to achieve the HbA_{1c} target, which is usually ≤7% [53 mmol/mol]) with OADs or a standard insulin regimen, macroalbuminuria and/or estimated glomerular filtration rate (eGFR) ≤60 mL/min, or multiple cardiovascular complications (4). Patients on renal replacement therapy or patients with insufficient knowledge of the Dutch language were excluded from participation.

Study Procedures and Baseline Characteristics

Eligible patients were selected from the electronic patient file as described in detail previously (3). All data were obtained at baseline. At the outpatient clinic, anthropometric measurements, sociodemographic characteristics, medical history, lifestyle behaviors, and current medications of participants who gave informed consent were recorded. BMI was calculated as weight divided by height squared (kg/m^2). Nonfasting blood tests were taken at baseline visit to determine serum albumin-to-creatinine ratio (ACR), LDL cholesterol, and HbA_{1c}. To obtain nonbiased data on medication adherence, 24-h urine was collected from 8 A.M. to 8 A.M. the next morning while patients were on their usual medication. Patients had signed previously for future studies of frozen blood/urine samples and were not aware that their urine would be checked for medication adherence. A separate single morning void urine was used to assess the urinary ACR. Blood samples, 24-h urine collection, and morning void urine were stored in a biobank at −80°C to allow for future analysis. BP was measured in a supine position by an automated device (Dinamap; GE Medical Systems, Milwaukee, WI) for 15 min with a 1-min interval. The mean systolic and diastolic BPs of the last three measurements were used for further analysis (3). The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula (11). Physical activity was assessed using the validated Short Questionnaire to Assess Health-Enhancing Physical Activity (12). An activity score was calculated based on minutes of activity per day multiplied by an intensity factor. We scored which patients met the Dutch Healthy Exercise Norm of 30 min of moderate to intense activity per day for at least 5 days per week (13). Adherence to the Dutch Guidelines for a Healthy Diet was assessed using the Dutch Healthy Diet index (14).

Urine samples were analyzed in December 2018 from all participants who were included between the start of the study in September 2009 and December 2018, totaling a population of 632 participants. For the current study, we excluded patients who did not have a prescription for any detectable drugs (n = 11), those for whom no shipment for analysis was available (n = 119), and those for whom no urine was available for secondary analysis (n = 45), leaving a total of 457 participants for analysis (Fig. 1).

Treatment Targets

Participants were considered to be well controlled if their HbA_{1c} was ≤7% (53 mmol/mol), in line with the Dutch guidelines for type 2 diabetes (13). Similarly, patients were considered to be at target if the serum LDL cholesterol was ≤2.5 mmol/L for primary prevention and <1.8 mmol/L for secondary prevention (15). BP targets were derived from international guidelines for diabetes management (16,17). In patients with diabetic kidney disease (DKD), the BP target was set according to the Kidney Diseases Improving Global Outcomes guidelines (17). Patients with DKD without albuminuria (eGFR <60, no albuminuria) had a BP target of <140/90 mmHg, whereas patients with albuminuria had a BP target of <130/80 mmHg. For patients with type 2 diabetes without DKD, the European Association for the Study of Diabetes guidelines were used, which stipulate a BP target of <140/85 mmHg (16).

Diabetes Complications

Microvascular disease was defined as the presence of either DKD, neuropathy, or retinopathy. Presence of these complications was assessed cross-sectionally at baseline. DKD was defined as an eGFR <60 mL/min with or without albuminuria. Neuropathy was assessed using monofilament and VibraTip. Retinopathy was assessed at 1- to 2-year intervals by an ophthalmologist. Macrovascular disease was defined as the presence of either coronary heart disease, cerebrovascular disease, or peripheral artery disease. Coronary heart disease was defined as the presence of one of the following in medical history: physician-diagnosed unstable angina pectoris, myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft. Cerebrovascular disease was defined as a history of transient ischemic attack or cerebrovascular accident. Peripheral artery disease was defined as the presence of one of the following in medical history: proven artery disease by angiogram or magnetic resonance angiogram, percutaneous transluminal angioplasty, or peripheral artery bypass graft.

Measurement of Adherence

Urine samples were obtained at baseline from collections of 24-h urine. The samples were stored at the local site at −80°C and subsequently transported on dry ice by a courier to the biobank at the University Medical Center Groningen. Thereafter, the samples were shipped to the laboratory at the University Hospitals of Leicester NHS Trust and stored at −80°C. Urine samples were analyzed by LC-MS/MS using an Agilent 1290 HPLC interfaced with an Agilent 6490 triple quad mass spectrometer (Santa Clara, CA) (8). The LC-MS/MS assay is a qualitative yes/no method to detect the presence and absence of medications. The assay is accredited by the United Kingdom Accreditation Service, the premier laboratory validation organization of the U.K. The assay has a high sensitivity, with limits of detection of the medications analyzed between 10 and 110 ng/mL (in-house data). Also, the assay is highly specific, because it uses separation by chromatograms and mass to charge ratios to identify analytes. Because of its high sensitivity and specificity, LC-MS/MS–based detection of analytes is a well-established technique used in forensics and detection of illegal performance-enhancing drugs in elite sports (18,19). The nondetection of a prescribed medication in urine implies that it was not ingested for at least 4–6 half-lives before sample collection, which can vary from a few hours to a few days. Furthermore, Lane et al. (20) previously demonstrated in a retrospective study that pharmacokinetic parameters like half-lives, median concentration in plasma, and volume of distribution do not affect the diagnosis of nonadherence.

Urine samples were screened for OADs, antihypertensives, and statins. Detectable OADs included biguanides, sulfonylurea derivatives, dipeptidyl peptidase-4 inhibitors, and thiazolidinediones. Of the sulfonylurea derivatives, the drugs tolbutamide and glibenclamide give no rise to urinary excretion of metabolites and are therefore not detectable. Detectable antihypertensives included diuretics (thiazide, low ceiling, high ceiling, and potassium saving), β-blockers, calcium channel blockers, ACE inhibitors, angiotensin II receptor blockers, and other antihypertensives interfering in the renin-angiotensin system. Of the antihypertensives, hydralazine, barnidipine, methyldopa, ketanserin, and clonidine give no rise to urinary excretion of metabolites and are therefore not detectable. Of the statins, only atorvastatin and rosuvastatin give rise to urinary excretion of metabolites and are therefore detectable.

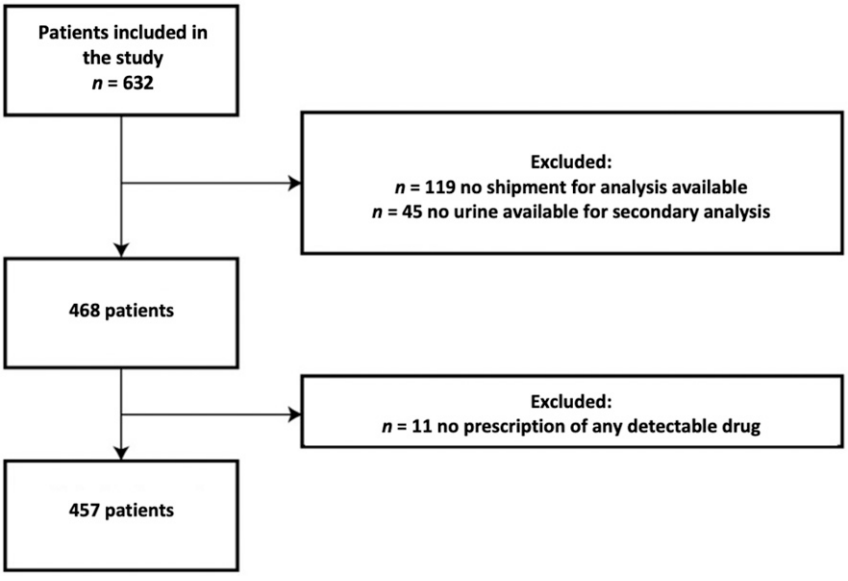

Figure 1—Patient recruitment flowchart.

Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows (version 24.0; IBM Corp., Armonk, NY). Differences between the groups were tested using the independent samples *t* test for normally distributed variables, Mann-Whitney *U* test for skewed variables, and χ^2 test for dichotomous variables.

Normally distributed data are presented as means ± SDs. Skewed variables are presented as medians (interquartile ranges [IQRs]). Dichotomous variables are presented as numbers (percentages). A two-tailed P value <0.05 was considered statistically significant. Normality of data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests of normality and by visually inspecting the frequency of histograms of each variable.

The population was divided into two groups according to their overall biochemical results. Patients were considered adherent if all screened medications were detected in the urine and nonadherent if at least one of the screened medications was not detected. Determinants of nonadherence were studied using binary logistic regression analysis based on complete cases with overall adherence as dependent variable. Confounders were based on relevant differences in baseline characteristics and previous literature. All univariate variables with a P value <0.20 were included in a forward logistic regression model together with other relevant pathophysiological variables. Variables that remained significant were tested in each model, until full adjustment.

Discrepancies

Because medication lists were obtained electronically, discrepancies were noted between prescribed medication in the electronic health record and medication detected in urine. Of the total number of prescribed drugs that gave rise to urinary excretion of metabolites (n= 1631), 24 discrepancies were found (Supplementary Fig. 1).

RESULTS

Baseline Characteristics

Overall, the study population consisted of 457 participants with type 2 diabetes (Table 1). The average age was 64.2 ± 9.0 years, and the average diabetes duration was 11 (7–19) years, reflecting a population with advanced type 2 diabetes, as can be anticipated in a referred care population like DIALECT.

Adherence

Of the total population, 408 patients were adherent (89.3%). The two groups were comparable and had similar mean age, sex composition, BMI, waist-to-hip ratio, duration of diabetes, alcohol intake, physical activity, Dutch Healthy Diet index, and urine ACR. There were more current smokers (28.6% vs. 15.0%; P = 0.015) and HbA_{1c} (7.9 ± 3.5% [62.9 ± 14.5 mmol/mol] vs. 7.4 ± 3.2% [57.4 ± 11.2 mmol/mol]; $P < 0.01$) and LDL cholesterol levels were higher (2.2 ± 0.9 vs. 2.0 ± 0.7 mmol/L; P = 0.022) in the nonadherent group compared with the adherent group. Furthermore, a significantly greater number of total prescribed medications was seen in the nonadherent group (8 [7–9] vs. 7 [5–8] medications; $P < 0.01$). Adherence rates to OADs, antihypertensives, and statins were 95.7%, 92.0%, and 95.5%, respectively.

Target Achievement

The percentage of people who reached an LDL cholesterol target of ≤2.5 mmol/L was significantly lower (P = 0.029) in the nonadherent group compared with the adherent group (67.4% vs. 81.1%) (Fig. 2). However, no significant association was found between adherence and an LDL cholesterol target of <1.8 mmol/L (P = 0.40). There were no statistically significant differences between the groups in the percentages of people who reached the HbA_{1c} and BP targets (26.5% vs. 38.8%; P = 0.09 and 41.7% vs. 44.4%; P = 0.46, respectively).

Diabetes Complications

The percentages of both microvascular and macrovascular complications were significantly higher in the nonadherent group (81.6% vs. 66.2%; P = 0.029 and 55.1% vs. 37.0%; P = 0.014, respectively). Within the individual components of microvascular disease, the prevalence of DKD was 18.8% higher in the nonadherent versus the adherent group (P = 0.012). There were no statistically significant differences in the prevalence of neuropathy and retinopathy between the groups (51.0% vs. 37.6%; P = 0.07 and 30.6% vs. 25.2%; P = 0.41, respectively).

Determinants of Nonadherence

Binary logistic regression (Table 2) indicated that higher BMI, current smoking, elevated serum LDL cholesterol, high HbA_{1c}, presence of DKD, and presence of macrovascular disease were significantly associated with nonadherence. No significant association was found for number of screened drugs, former smoking, and neuropathy. Univariate analyses of all the variables that were considered for the multivariable model are shown in Supplementary Table 1. Furthermore, the sensitivity analysis with patients for whom all data were available of the variables used in the multivariable model is shown in Supplementary Table 2.

CONCLUSIONS

In this report, we present the assessment of adherence to OADs, antihypertensives, and statins in a real-life population with type 2 diabetes managed in routine specialist clinical practice using urine testing by LC-MS/MS. To our knowledge, this is the first large study to report adherence in the real-world setting to measure adherence objectively and report the association of adherence with microvascular and macrovascular complications. Generally, both the overall medication adherence and the adherence to the specific drug classes were relatively high compared with that seen in other studies. However, in nonadherent patients, treatment targets were reached less frequently, and the prevalence of microvascular and macrovascular complications at baseline was higher. This demonstrates a window of opportunity for early detection and interventions in cases of nonadherence.

Much of the evidence regarding poor medication adherence in diabetes is based on retrospective or observational studies that collect data from claim databases using a broad range of definitions. The reported incidence of poor medication adherence in patients with type 2 diabetes varies widely, primarily because of different underlying subpopulations and different methodological approaches to measure adherence (1). Previously, in a small observational study in type 2 diabetes patients attending different primary care practices, Patel et al. (10) reported an LC-MS/MS nonadherence rate of 28.1% to antidiabetic, antihypertensive, and/or lipid-lowering medications. Nonadherence to statins was the highest at 23.7%, and

Table 1—Baseline characteristics by overall adherence in DIALECT-1 and DIALECT-2 population

	Total population	Adherent	Nonadherent	*P*
Patients	457	408 (89.3)	49 (10.7)	—
Age, years	64.2 ± 9.0	64.3 ± 8.9	63.7 ± 10.2	0.68
Male sex	281 (61.5)	252 (61.8)	29 (59.2)	0.73
Prescribed drugs	7 (5–9)	7 (5–8)	8 (7–9)	<0.01*
Screened drugs	4 (2–5)	4 (2–5)	4 (3–5)	0.025*
Detected drugs	3 (2–5)	4 (2–5)	3 (1–4)	<0.01*
Diabetes duration, years	11 (7–19)	12 (7–19)	11 (5–19)	0.52
BMI, kg/m^{2}[a]	32.9 ± 6.0	32.7 ± 5.9	33.9 ± 6.4	0.19
Waist-to-hip ratio[a]	1.01 ± 0.09	1.01 ± 0.09	1.02 ± 0.08	0.26
Smoking status				0.047*
Current	75 (16.4)	61 (15.0)	14 (28.6)	
Former	243 (53.2)	222 (54.4)	21 (42.9)	
Never	139 (30.4)	125 (30.6)	14 (28.6)	
Alcohol intake per week, units[a]				0.39
None	153 (35.5)	133 (34.6)	20 (42.6)	
1–13	218 (50.6)	195 (50.8)	23 (48.9)	
≥14	60 (13.9)	56 (14.6)	4 (8.5)	
Physical activity (adherence to Dutch Healthy Exercise Norm)[a]	239 (53.6)	217 (54.7)	22 (44.9)	0.20
DHD index[a]	70.5 ± 13.5	70.5 ± 13.7	70.5 ± 12.1	0.98
ACR, mg/mmol[a]	12.5 ± 49.4	11.7 ± 48.7	20.0 ± 54.8	0.30
LDL cholesterol, mmol/L[a]	2.0 ± 0.7	2.0 ± 0.7	2.2 ± 0.9	0.022*
LDL cholesterol ≤2.5 mmol/L	344 (79.6)	313 (81.1)	31 (67.4)	0.029*
LDL cholesterol <1.8 mmol/L	185 (40.5)	168 (41.2)	17 (34.7)	0.40
HbA_{1c}, % (mmol/mol)[a]	7.5 ± 3.2 (58.0 ± 11.7)	7.4 ± 3.2 (57.4 ± 11.2)	7.9 ± 3.5 (62.9 ± 14.5)	<0.01*
HbA_{1c} on target	171 (37.5)	158 (38.8)	13 (26.5)	0.09
Systolic BP, mmHg[a]	139 ± 16	138 ± 16	141 ± 17	0.24
Diastolic BP, mmHg[a]	76 ± 9	76 ± 9	77 ± 9	0.47
BP on target[a]	200 (44.2)	180 (44.4)	20 (41.7)	0.46
Complications				
Microvascular diseases	310 (67.8)	270 (66.2)	40 (81.6)	0.029*
Retinopathy[a]	117 (25.8)	102 (25.2)	15 (30.6)	0.41
Neuropathy[a]	178 (39.0)	153 (37.6)	25 (51.0)	0.07
DKD	194 (42.5)	165 (40.4)	29 (59.2)	0.012*
Macrovascular diseases	178 (38.9)	151 (37.0)	27 (55.1)	0.014*
Insulin use	300 (65.6)	264 (64.7)	36 (73.5)	0.22

Data are presented as *n* (%), mean ± SD, or median (interquartile range) for nominal, normally distributed, and nonnormally distributed data, respectively. Patients for whom every screened drug was detected in the urine were considered adherent. All other patients were considered nonadherent (i.e., absence of at least one detectable drug in the urine sample). DHD, Dutch Healthy Diet. [a]Missing values for BMI (*n* = 2), waist-to-hip ratio (*n* = 8), alcohol intake (*n* = 26), physical activity (*n* = 11), DHD index (*n* = 19), ACR (*n* = 31), LDL cholesterol (*n* = 25), HbA_{1c} (*n* = 1), systolic BP (*n* = 1), diastolic BP (*n* = 1), BP target (*n* = 4), retinopathy (*n* = 3), and neuropathy (*n* = 1). *Statistically significant difference between the groups ($P < 0.05$).

nonadherence to OADs was 9.3%. In their study, adverse effects such as myalgia or the poor perception of statins in the general population were given as possible explanations for the high rates of nonadherence to statins. In contrast to these high rates of nonadherence to statins, we found nonadherence rates of only 4.5%. This difference can be partly explained by the more severe population managed in a specialist center, as compared with the primary care setting in the Patel et al. study. Additionally, we should note that the statin subgroup in our population covered less than half of our cohort patients, because the most prescribed statin subtype, simvastatin, does not give rise to urinary excretion of metabolites and was therefore not detectable.

In a post hoc analysis of a small trial (*n* = 98), De Jager et al. (21) assessed medication adherence using LC-MS/MS to analyze serum samples in patients with apparent resistant hypertension using three or more antihypertensives. They reported that 68% of patients were partly nonadherent and 16% were completely nonadherent; the rate for the latter (aligning with our definition) is still twice as high as the 8% antihypertensive nonadherence rate we found. We speculate that two mechanisms may have been responsible for this difference. On the one hand, our additional underlying condition (diabetes) could

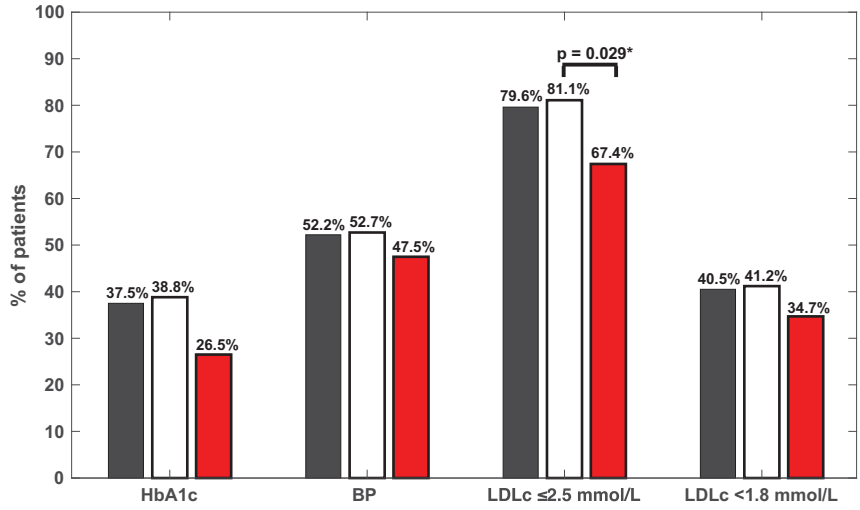

Figure 2—Achievement of LDL cholesterol (LDLc), HbA_{1c}, and BP targets by adherence. Black bars, total population; white bars, adherent; red bars, nonadherent. HbA_{1c} target, ≤7% (53 mmol/mol). BP targets, <140/90 mmHg for eGFR <60 without albuminuria; <140/85 mmHg for eGFR >60 without albuminuria; and <130/80 mmHg for patients with albuminuria. *P < 0.05, significant difference between adherent and nonadherent patients.

have enhanced adherence. On the other, the high number of antihypertensives in the trial conducted by De Jager et al. could have worsened adherence.

A possible explanation for the relatively high degree of medication adherence in our population could be that patients treated in specialist care may feel more urgency to adhere to their treatment in comparison with patients treated in primary care. This is supported by comparing our study results with the results of the Patel et al. (10) study, where an LC-MS/MS nonadherence rate of 28.1% to antidiabetic, antihypertensive, and/or lipid-lowering medications was reported. Another hypothesis regarding the high rates of medication adherence in general could be the presence of microvascular and macrovascular complications, which could be a motivation for patients to take their medication. However, this is not supported by data from our study, because nonadherent patients had more microvascular and macrovascular complications. Furthermore, the well-organized pharmacy service in the Netherlands, where medication is often delivered automatically, could also improve medication adherence. Further research is needed to assess the role of diabetes complications and automatic refills versus self-initiated refills in medication adherence.

In a cohort like DIALECT, it is important to take the possibility of selection bias into account, (i.e., selection of highly motivated patients). We can refute this if we take the criteria for referral from primary to secondary health care in the Netherlands into consideration. Patients in DIALECT are treated in a specialist setting because their type 2 diabetes was not optimally controlled in primary care. In addition, a vast majority of patients developed diabetes complications. Moreover, the average BMI of 32.9 kg/m^2 reflects a predominantly obese population. These data are not in line with patients who are highly motivated. However, despite the high prevalence of diabetes complications and high BMI, serum LDL cholesterol, and HbA_{1c} levels, this population is motivated in its own way, and they show this by taking their medication properly, with high rates of adherence as a result.

Usually, by determining nonadherence using an objective method like LC-MS/MS, bias can be introduced if patients take their medication just before baseline visit, the so-called "white coat adherence." However, patients in this study were not aware that their urine would be checked for medication adherence. Therefore, the results in our study are a true reflection of adherence, which is a major strength of this study. A limitation of this study is that no analyses could be conducted on the associations between specific drug classes/individual drugs and adherence, because the sample size was not adequate to make meaningful analyses (data not shown).

Apparently, nonadherence in our population was not recognized by patients' health care professionals. However, it is important to actively search for nonadherence, recognizing that poor medication adherence contributes to suboptimal clinical benefits. Health care professionals should in particularly be alert for nonadherence if a patient smokes or fails to reach LDL cholesterol or HbA_{1c} targets. The multifactorial nature of poor medication adherence implies that a broader strategy is needed to manage nonadherence. It is important to note that the utility of the LC-MS/MS assay is an evolving and rapidly developing field over the last 3–4 years. Currently, it is possible to analyze the most common cardiovascular medications, except aspirin and simvastatin. However, the prescription of simvastatin has decreased since other potent statins have become generic medications; the cost difference that used to make simvastatin the cheaper option to prescribe no longer exists. In the course of time, this could increase the utility of the LC-MS/MS assay in both clinical trials and real-world settings. Additional prospective studies are needed to compare the effects of pharmacokinetic parameters of individual medications on the diagnosis of nonadherence. The role of using prescription

Table 2—Determinants of overall medication nonadherence

Variable	OR (95% CI)	*P*
BMI	1.054 (1.001–1.110)	0.046
Current smoking	2.471 (1.138–5.364)	0.022
HbA_{1c}	1.042 (1.015–1.069)	0.002
Serum LDL cholesterol	1.714 (1.134–2.591)	0.011
DKD	2.286 (1.162–4.497)	0.017
Macrovascular disease	2.233 (1.145–4.343)	0.018

Fully adjusted logistic regression model with nonadherence as study outcome. OR, odds ratio.

refill information to estimate medication adherence is well established and broadly used. Future research should be aimed at examining the agreement between this method (LC-MS/MS) and other established methods for identifying poor adherence, like prescription refill–based methods.

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