Adherence to Oral Glucose-Lowering Therapies and Associations With 1-Year HbA_{1c}: A Retrospective Cohort Analysis in a Large Primary Care Database

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OBJECTIVE

The impact of taking oral glucose-lowering medicines intermittently, rather than as recommended, is unclear. We conducted a retrospective cohort study using community-acquired U.K. clinical data (Clinical Practice Research Database [CPRD] and GoDARTS database) to examine the prevalence of nonadherence to treatment for type 2 diabetes and investigate its potential impact on HbA_{1c} reduction stratified by type of glucose-lowering medication.

RESEARCH DESIGN AND METHODS

Data were extracted for patients treated between 2004 and 2014 who were newly prescribed metformin, sulfonylurea, thiazolidinedione, or dipeptidyl peptidase 4 inhibitors and who continued to obtain prescriptions over 1 year. Cohorts were defined by prescribed medication type, and good adherence was defined as a medication possession ratio ≥0.8. Linear regression was used to determine potential associations between adherence and 1-year baseline-adjusted HbA_{1c} reduction.

RESULTS

In CPRD and GoDARTS, 13% and 15% of patients, respectively, were nonadherent. Proportions of nonadherent patients varied by the oral glucose-lowering treatment prescribed (range 8.6% [thiazolidinedione] to 18.8% [metformin]). Nonadherent, compared with adherent, patients had a smaller HbA_{1c} reduction (0.4% [4.4 mmol/mol] and 0.46% [5.0 mmol/mol] for CPRD and GoDARTs, respectively). Difference in HbA_{1c} response for adherent compared with nonadherent patients varied by drug (range 0.38% [4.1 mmol/mol] to 0.75% [8.2 mmol/mol] lower in adherent group). Decreasing levels of adherence were consistently associated with a smaller reduction in HbA_{1c}.

CONCLUSIONS

Reduced medication adherence for commonly used glucose-lowering therapies among patients persisting with treatment is associated with smaller HbA_{1c} reductions compared with those taking treatment as recommended. Differences observed in HbA_{1c} responses to glucose-lowering treatments may be explained in part by their intermittent use.

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Between a third and a half of medicines prescribed for type 2 diabetes (T2DM), a condition in which multiple medications are used to control cardiovascular risk factors and blood glucose (1,2), are not taken as prescribed (3–6). However, estimates vary widely depending on the population being studied and the way in which adherence to recommended treatment is defined.

The impact of continuing to take glucose-lowering medicines intermittently, but not as recommended, is unknown. Medication possession (expressed as a ratio of actual possession to expected possession), derived from prescribing records, has been identified as a valid adherence measure for people with diabetes (7). Previous studies have been limited to small populations in managed-care systems in the U.S. and focused on metformin and sulfonylurea oral glucose-lowering treatments (8,9). Further studies need to be carried out in larger groups of people that are more representative of the general population.

The Clinical Practice Research Database (CPRD) is a long established repository of routine clinical data from more than 13 million patients registered with primary care services in England. These data now include demographic data, diagnostic codes, biochemistry results, and prescribing records from clinicians who have achieved high standards of data completeness. The Genetics of Diabetes and Audit Research Tayside Study (GoDARTS) database is derived from integrated health records in Scotland with primary care, pharmacy, and hospital data on 9,400 patients with diabetes.

We sought to establish the prevalence of medication nonadherence, measured from routinely collected data in patients with T2DM and its relationship with reductions in glycated hemoglobin (HbA_{1c}) with prescribed glucose-lowering medications. Specifically, we wished to determine whether poor response to oral glucose-lowering drugs could be due in part to reduced adherence. We hypothesized that there would be an association between the number of tablets potentially available for a newly prescribed glucose-lowering medication (if all prescriptions were filled) over 1 year (expressed as a percentage) and the observed reduction in HbA_{1c}.

RESEARCH DESIGN AND METHODS

Design

We performed a retrospective cohort study using routine clinical data obtained from community-acquired U.K. clinical data. The primary end point of the study was HbA_{1c} reduction over 1 year.

Data Sources

We selected patients from the CPRD and the GoDARTS cohort. The CPRD contains anonymized longitudinal health records from 680 general practices across the U.K. amounting to 13.2 million patients (10). We selected patients prescribed metformin, sulfonylurea, dipeptidyl peptidase 4 inhibitors (DPP4i), or thiazolidinediones. Prescriptions for glucagon-like peptide-1 receptor agonists were not included in the analysis given the limited information available and difficulty in determining daily doses for injectable therapies.

GoDARTS contains electronic health record data from primary care, hospitals, and pharmacies (11). It includes >9,400 patients with T2DM who have given explicit consent for use of the information in research. In addition to the types of data available through CPRD, it includes information on the dispensing of prescribed medication.

Population

In both data sets, the date of diagnosis was based on the earliest record of a first prescription of a glucose-lowering drug prescribed, a diabetes diagnostic code, or the first HbA_{1c} >6.5% (48 mmol/mol). Patients were included in a cohort for analysis if there was a record of treatment with a glucose-lowering medication for a period of at least 1 year.

Patients were excluded from the analysis if they were younger than 35 years old when diagnosed; had forms of diabetes other than T2DM, including gestational diabetes mellitus; had a diabetes duration <1 year; had previously been prescribed or were currently taking insulin; or were prescribed a thiazolidinedione or a DPP4i as monotherapy (where the characteristics of patients prescribed these treatments as monotherapy differed from other treatments and treatment combinations). We restricted consideration to the first period of treatment on each drug for each person. An individual patient could contribute 12-month periods of observation for different drugs but could not contribute data for two or more drugs concurrently.

Derived Variables

The medication possession ratio (MPR) was calculated by using prescription data (or, for GoDARTS, the dispensing data) from the date of the first prescription for that patient to the next prescription after 365 days from the first prescription date. The 1-year period for calculating adherence was considered valid if *1*) there were no gaps between prescriptions longer than 6 months (a gap of >6 months was considered "stopping" the drug), *2*) there was no change in treatment (either a drug being started or stopped) in the period of 3 months prior to the drug start date up until the date of the first prescription after 1 year, and *3*) data were available from three or more prescriptions (with nonzero daily dose information). MPR was defined as the number of days of available medication divided by the number of days between the first and last prescription dates, multiplied by 100. The number of days of available medication was calculated by dividing the quantity prescribed by the daily dose. In some instances (25% of 15,336,948 prescription records in CPRD), the daily dose was recorded as zero. Where dose information was not available for any of the prescriptions for a patient over the 12-month prescription period, MPR was not calculated. For those where there were at least three valid prescriptions, but dose was missing from others, we removed the prescription with missing dose and the time between that prescription and the next from the denominator (7% of cases). Patients with MPR ≥120% were excluded from the analysis.

HbA_{1c} Response at 1 Year

Baseline HbA_{1c} was the closest HbA_{1c} value to the drug start date in a time window between 3 months before to 7 days after. The 12-month HbA_{1c} values used were those nearest to the date 1 year after the drug was started, with a time window from 3 months before to 3 months after. Response was calculated as 12-month HbA_{1c} minus baseline HbA_{1c}. For the response to be valid, there had to be no change in treatment (either a drug being started or stopped)

in the period from the baseline HbA_{1c} date to the 12-month HbA_{1c} date. Invalid responses were excluded from analysis. Response could not be calculated on 6% of patients owing to missing HbA_{1c} data.

Additional Clinical Variables

We extracted age and BMI from the data as baseline variables at the time a glucose-lowering drug was started. The values used were those that were the closest to the drug start date in a time window between 6 months before to 7 days after. Medication doses over 1 year were calculated as a mean percentage maximum dose for that medication, weighted by the number of days the patient was on that dose.

Statistical Analyses

We categorized adherence into MPR groups: <70%, 70% to <80%, 80% to <90%, 90% to <100%, and >100%. For the analyses presented here, we defined nonadherence as an MPR <80% and adherence as an MPR ≥80% (12).

To assess the impact of MPR category on response, we used regression models, adjusted for baseline HbA_{1c}, for each drug, and all data combined. Models used MPR category (coded as a factor) and baseline HbA_{1c} as independent variables and change in HbA_{1c} over 12 months as the outcome. Only baseline HbA_{1c} was adjusted for, as this explains the most variation in response (R^2 = 0.32). We did not adjust for other features in these models. For each drug and overall, we plotted 95% CIs for change in HbA_{1c} adjusted by baseline HbA_{1c}, and *P* values for comparison of the extreme categories were derived from the regression analysis. All analyses were carried out in R, version 3.0.2 (13).

Ethics

Approval for the study was granted by the CPRD Independent Scientific Advisory Committee (ISAC 13_177R) and for GoDARTS by the East of Scotland Regional Ethics Committee (09/21402/44).

RESULTS

Analysis of CPRD Data Set

A total of 32,634 patients were included for analysis with 38,100 instances of starting a new treatment (periods of treatment) and continuing for at least 1 year. The characteristics of included patients are shown by treatment cohort in Table 1. The mean duration of diabetes was shorter for those in the metformin and sulfonylurea cohorts, consistent with use of metformin earlier in the course of the disease. The mean proportion of the maximum dose of each drug also varied by treatment. Overall, 28.7% of patients were taking no other noninsulin glucose-lowering treatments, 51.8% were taking one other treatment, and 19.1% were taking two other treatments (Supplementary Table 1). Additional glucose-lowering drug treatment for patients in each cohort is shown in Supplementary Table 2, with the majority taking metformin alongside other treatments.

The proportion of nonadherent patients was 13.3% (*n* = 38,100 periods of treatment; 32,634 patients), ranging from 9.1% and 8.6% for DPP4i inhibitors and thiazolidinediones, respectively, up to 18.8% with metformin (Table 2). For all therapies, participants with MPRs ≥90% experienced the greatest reductions in baseline-adjusted HbA_{1c} (Fig. 1). With lower MPRs, there was a consistent observed smaller reduction in HbA_{1c} changes with all therapies (Fig. 1).

Adherent, compared with nonadherent, patients consistently had greater HbA_{1c} reductions in all drug classes (Table 2). Overall, HbA_{1c} decrements were −0.75% (95% CI −0.78, −0.72) (−8.2 mmol/mol [95% CI −8.5, −7.9]) and −1.14% (95% CI −1.16, −1.13) (−12.5 mmol/mol [95% CI −12.7, −12.4]) for nonadherent and adherent patients, respectively (Table 2). The mean difference overall between adherent and nonadherent groups in baseline-adjusted 1-year HbA_{1c} was −0.40% (95% CI −0.43, −0.37) (−4.4 mmol/mol [95% CI −4.7, −4.0]). This between-group difference varied across drugs from −0.38% (95% CI −0.44, −0.31) (−4.1 mmol/mol [95% CI −4.8, −3.4]) with sulfonylureas to −0.57% (95% CI −0.64, −0.49) (−6.2 mmol/mol [95% CI −7.0, −5.4]) with thiazolidinediones (Table 2).

Analysis of GoDARTS Cohort

A total of 2,284 patients were included for analysis, with 2,622 instances of starting a new treatment (periods of treatment) and continuing for at least 1 year. The characteristics of included patients are shown by treatment cohort in Table 1 and, similarly to CPRD, the different characteristics of the cohort reflect the stage of treatment at which the treatment was started. Overall, 34% of patients were taking no other noninsulin glucose-lowering treatments, 44% were taking one other treatment, and

Table 1—Clinical characteristics of included patients within each cohort at baseline

	Metformin	Sulfonylurea	Thiazolidinedione	DPP4i
CPRD				
N	13,823	10,070	9,088	5,119
Age (years)	65.1 (10.8)	64.0 (10.8)	63.4 (10.4)	64.1 (10.3)
Female sex, *n* (%)	5,351 (39)	3,924 (39)	3,398 (37)	1,894 (37)
Duration of diabetes (years)	4.9 (4.0)	5.2 (3.8)	6.7 (4.8)	7.8 (4.9)
BMI (kg/m^2)	30.5 (5.7)[a]	31.1 (6.0)[b]	31.4 (6.0)[c]	32.5 (6.1)[d]
HbA_{1c} (mmol/mol)	70.5 (15.0)	72.0 (15.5)	72.0 (13.9)	71.1 (13.6)
HbA_{1c} (%)	8.6 (1.4)	8.7 (1.4)	8.7 (1.3)	8.7 (1.2)
Dose (% maximum dose)	59.7 (19)[e]	32.1 (16.7)[f]	56.2 (18.4)[g]	97.8 (10.3)[h]
Weight change over 12 m (kg)	−1.4 (4.0)[i]	2.0 (4.5)[j]	2.8 (4.5)[k]	−0.9 (4.0)[l]
GoDARTS				
N	927	729	677	244
Age (years)	66.3 (10.2)	65.3 (10.5)	63.7 (9.8)	65.3 (9.8)
Female sex, *n* (%)	41	40	39	43
Duration of diabetes (years)	5.3 (4.0)	6.0 (3.7)	8.4 (5.2)	6.7 (4.6)
BMI (kg/m^2)	31.4 (5.7)[m]	31.6 (5.8)[n]	32.1 (5.7)[o]	32.9 (5.9)[p]
HbA_{1c} (mmol/mol)	67.9 (13.4)	70.2 (14.7)	72.9 (13.0)	70.5 (11.3)
HbA_{1c} (%)	8.3 1.23	8.6 1.34	8.8 1.18	8.6 1.10
Dose (% maximum dose)	55 (18)[q]	28 (16)[r]	73 (41)[s]	99.6 (0.1)[t]

Data are mean (SD) unless otherwise indicated. m, months. Missing data: [a]2,174; [b]1,618; [c]1,202; [d]621; [e]1,500; [f]402; [g]190; [h]70; [i]3,805; [j]2,849; [k]2,392; [l]1,389; [m]15; [n]12; [o]4; [p]5; [q]43; [r]61; [s]24; [t]41.

22% were taking two other treatments (Supplementary Tables 3 and 4).

The proportion of nonadherent patients was 15.1% (n = 2,622 periods of treatment and 2,284 patients), ranging from 10.7% with DPP4i up to 18.1% with metformin (Table 2). For all therapies, participants with an MPR ≥90% experienced the greatest reductions in baseline-adjusted HbA_{1c} (Fig. 1). With lower MPRs, there was a consistent observed smaller reduction in HbA_{1c} across all therapies (Fig. 1). There was no clear evidence of a differential response to any one therapy for groups of patients with differing MPR.

Overall HbA_{1c} decrements were −0.63% (95% CI −0.74, −0.52) (6.9 mmol/mol [95% CI −8.1, −5.7]) and −1.09% (95% CI −1.14, −1.04) (−11.9 mmol/mol [−12.5, −11.4]) for nonadherent and adherent patients, respectively (Table 2). The mean difference overall between adherent and nonadherent groups in baseline-adjusted 1-year HbA_{1c} was −0.46% (95% CI −0.58, −0.34) (−5.0 mmol/mol [95% CI −6.3, −3.7]). This between-group difference varied across drugs from −0.34% (95% CI −0.58, −0.1) (−3.7 mmol/mol [95% CI −6.3, −1.1]) with sulfonylurea to −0.75% (95% CI −1.22, −0.28) (−8.2 mmol/mol [95% CI −13.3, −3.1]) with DPP4i (Table 2).

CONCLUSIONS

These findings show an association between adherence to oral glucose-lowering treatment, measured by the proportion of medication obtained on prescription over 1 year, and the corresponding decrement in HbA_{1c}, in a population of patients newly starting treatment and continuing to collect prescriptions. The association is consistent across all commonly used oral glucose-lowering therapies, and the findings are consistent between the two data sets examined, CPRD and GoDARTS. Nonadherent patients, taking on average <80% of the intended medication, had about half the expected reduction in HbA_{1c}.

This is the largest study that we are aware of to examine the association between adherence to oral glucose-lowering treatment in T2DM over 1 year and change in HbA_{1c}. The study uses two independent data sets: a representative

Table 2—Adherence by treatment and HbA_{1c} response from baseline to 1 year, showing overall decrement in HbA_{1c} by group

Drug	N	Percentage of patients with MPR <80%	Change in HbA_{1c} from baseline to 12 months for patients with MPR <80% (95% CI)	Change in HbA_{1c} from baseline to 12 months for patients with MPR ≥80% (95% CI)	Difference between change in HbA_{1c} from baseline to 12 months for patients with <80% MPR ≥80% (95% CI)	P
CPRD						
All treatments	38,100	13.3	−0.75 (−0.78, −0.72)	−1.14 (−1.16, −1.13)	−0.40 (−0.43, −0.37)	<0.001
			[−8.2 (−8.5, −7.9)]	[−12.5 (−12.7, −12.4)]	[−4.4 (−4.7, −4.0)]	
Metformin	13,823	18.8	−0.78 (−0.82, −0.74)	−1.16 (−1.18, −1.14)	−0.38 (−0.42, −0.34)	<0.001
			[−8.5 (−9.0, −8.1)]	[−12.7 (−12.9, −12.5)]	[−4.2 (−4.6, −3.7)]	
Sulfonylurea	10,070	11.9	−0.85 (−0.91, −0.79)	−1.23 (−1.24, −1.20)	−0.38 (−0.44, −0.31)	<0.001
			[−9.3 (−10.0, −8.6)]	[−13.4 (−13.6, −13.1)	[−4.1 (−4.8, −3.4)]	
Thiazolidinedione	9,088	8.6	−0.66 (−0.73, −0.59)	−1.24 (−1.25, −1.21)	−0.57 (−0.64, −0.49)	<0.001
			[−7.2 (−8.0, −6.4)]	[−13.4 (−13.7, −13.2)]	[−6.2 (−7.0, −5.4)]	
DPP4i	5,119	9.1	−0.40 (−0.50, −0.30)	−0.83 (−0.87, −0.81)	−0.44 (−0.54, −0.33)	<0.001
			[−4.4 (−5.5, −3.3)]	[−9.1 (−9.5, −8.8)]	[−4.8 (−5.9, −3.6)]	
GoDARTS						
All	2,622	15.1	−0.63 (−0.74, −0.52)	−1.09 (−1.14, −1.04)	−0.46 (−0.58, −0.34)	<0.001
			[−6.9 (−8.1, −5.7)]	[−11.9 (−12.5, −11.4)]	[−5.0 (−6.3, −3.7)]	
Metformin	972	18.1	−0.59 (−0.73, −0.43)	−1.08 (−1.14, −1.01)	−0.49 (−0.66, −0.32)	<0.001
			[−6.4 (−8.0, −4.7)]	[−11.8 (−12.5, −11.0)]	[−5.4 (−7.2, −3.5)]	
Sulfonylurea	729	16.2	−0.77 (−0.99, −0.56)	−1.11 (−1.20, −1.02)	−0.34 (−0.58, −0.1)	<0.005
			[−8.4 (−10.8, −6.1)]	[−12.1 (−13.1, −11.1)]	[−3.7 (−6.3, −1.1)]	
Thiazolidinedione	677	11.4	−0.70 (−0.95, −0.44)	−1.28 (−1.37, −1.18)	−0.59 (−0.86, −0.32)	<0.001
			[−7.6 (−10.4, −4.8)]	[−14.0 (−15.0, −12.9)]	[−6.4 (−9.4, −3.5)]	
DPP4i	244	10.7	0.12 (−0.32, 0.56)	−0.63 (−0.79, −0.48)	−0.75 (−1.22, −0.28)	<0.005
			[1.3 (−3.5, 6.1)]	[−6.9 (−8.6, −5.3)]	[−8.2 (−13.3, −3.1)]	

HbA_{1c} is reported in % [mmol/mol]. HbA_{1c} change adjusted by baseline HbA_{1c}.

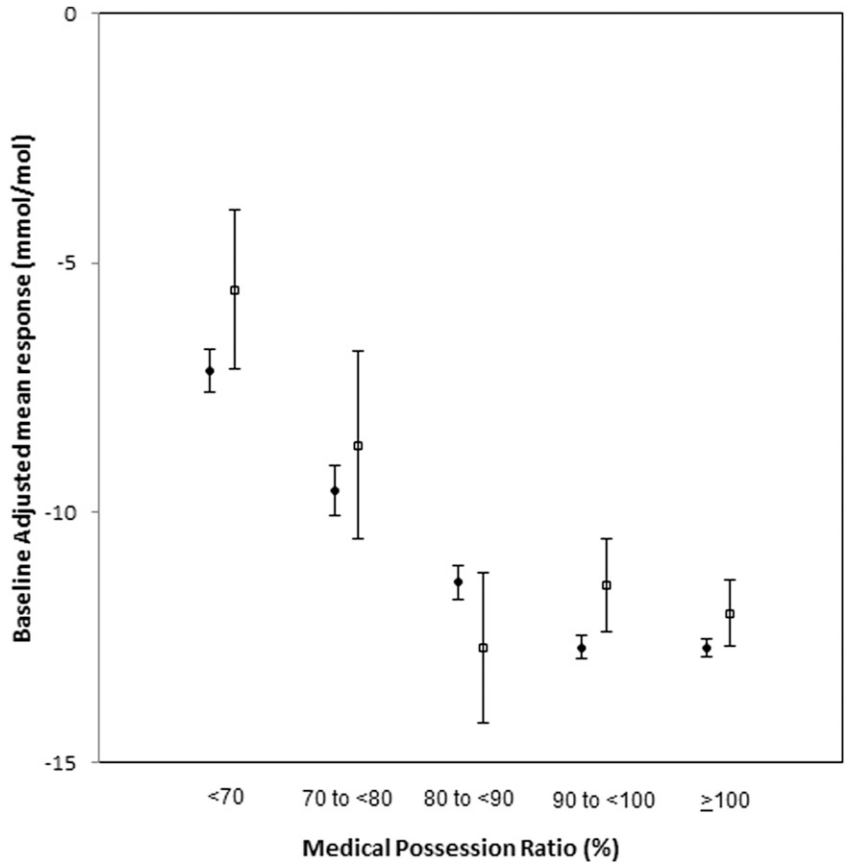

Figure 1—Difference in HbA_{1c} change for both CPRD and GoDARTS ($P < 0.00001$). Plot of HbA_{1c} (mmol/mol) change over all drugs in 12 months for each data set by MPR category (baseline-adjusted absolute change in HbA_{1c}). ●, CPRD; □, GoDARTS.

primary care data set from across England and an electronic medical record data set from a region in Scotland. Both data sets have detailed information about dosage adjustment over the period of the study (14) and include systematic records of clinical and laboratory measurements at three to six monthly intervals. Results were consistent across both studies. Although the Scottish data use prescription encashment, the similar results in CPRD support the use of issued prescription data for studying medication adherence.

There are a number of issues that could be further explored in greater depth to provide information about factors associated with nonadherence. These include whether adherence differs when a medication is used as first, second, or third line and the extent to which there is an interaction with the type of medication. In addition, there is potential for starting a drug to change adherence to other concurrent medication. However, because our study is limited by use of different populations in examining the different drugs, we are unable to directly address these questions, and our study does not provide evidence of comparative effectiveness between the drugs.

Although direct comparisons of adherence rates are not possible, high adherence levels reported for patients taking drugs commonly found in combination therapy (e.g., DPP4i) may reflect a greater personal investment in disease self-management. Differences in baseline characteristics of patients using DPP4i between England and Scotland may reflect differences in local usage of the class of drugs, as there is no difference in national guidance. Similarly, the higher levels of change in HbA_{1c} found for patients taking metformin and sulfonylurea may also reflect an earlier stage in the course of their diabetes.

There is the possibility for time-dependent confounding, and this is something we have not explored in this study. We have limited our data to only simple models and those cases where there were no changes in diabetes drugs during the 1-year period of interest. However, this does not exclude other potential changes that may impact adherence, such as changes in dose, incidence of side effects, or changes in other medications or comorbidities. It will be of interest to examine predictors of adherence, both at baseline when starting medication and over the time course of taking the drug. Development of in-depth models to explore this would be an important next step for further research focusing on the relationship between adherence and achieved HbA_{1c}.

There are a number of different ways to measure adherence to medication. Overall adherence rates are consistently overestimated by self-report (15). Direct measurement (for example, with electronic dispensing measurement) has potential to modify behavior because it is intrusive. Data on medication prescribing and dispensing are widely used and have evidence to support their validity (7), and medicine availability is a necessary prerequisite for being able to take the medicine. Medication hoarding (obtaining medicine but not then using it) has been identified as an issue in the psychiatric literature but not more generally for long-term conditions (16). In another study, perceptions of higher levels of hoarding in older people relating to medicines' nonadherence were not supported (17).

The focus of this study is on the relationship of quality of taking medication and impact on HbA_{1c}. The MPR is used to report adherence as an increasingly accepted measure of medication use. There are some patterns of medication use that may result in misleading metrics for MPR, but the most common, failure to persist with medication, is accounted for in this analysis by exclusion of patients with a 6-month or longer break in prescribing (18). It also excludes individuals starting treatment in the first year after diagnosis, again a group where overall adherence and persistence are likely to differ from those at a later stage of their illness.

In addition, this retrospective study was not able to identify sufficient patients within the data set to provide information about glucagon-like peptide-1 receptor agonist treatment. We have not addressed adherence to insulin therapy in this analysis.

A number of previous studies have used retrospective databases of electronic

health records to examine factors that might predict adherence. A recent large cohort database examined overall adherence to oral therapy for T2DM, taking into account changes of therapy. It concluded that overall adherence was 69%, with individuals newly started on treatment being significantly less likely to adhere (19). There are few studies providing estimates of adherence to treatment and its relationship with glycemic control: we have identified only two, both focused on sulfonylurea and metformin treatment and of relatively small size. In one, based in southwest Michigan, 677 patients with diabetes were reviewed, and a 10% increase in nonadherence was associated with a 0.14% (1.5 mmol/mol) rise in HbA_{1c} (9). A larger study in South Carolina of 1,668 patients found that the mean MPR for those reaching an HbA_{1c} target of 7.0% (53 mmol/mol) was 81% (8).

Low medication adherence is related to increased mortality (20). The mean difference in HbA_{1c} between patients with MPR $<$80% and $\geq$80% is between 0.37% and 0.55% (4 mmol/mol and 6 mmol/mol), equivalent to up to a 10% reduction in death or an 18% reduction in diabetes complications (21). The small numbers with adherence $<$70% mean that exploring the impact of this on HbA_{1c} and its relationship with other lifestyle factors requires a larger study population. Further work is now needed to demonstrate the extent to which improved compliance leads to improvements in HbA_{1c}.

Data obtained from real-time monitoring of medication collection may provide feedback to patients and their clinicians to indicate whether medication use might be suboptimal. Further work is needed to establish the intervals over which data become meaningful and whether analysis with other routinely collected data improves identification of low adherence to treatment.

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