# Treatment choice, medication adherence and glycemic efficacy in people with type 2 diabetes: a UK clinical practice database study

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## ABSTRACT

**Objective** Using primary care data obtained from the UK Clinical Practice Research Datalink, this retrospective cohort study examined the relationships between medication adherence and clinical outcomes in patients with type 2 diabetes.

**Research design and methods** Data were extracted for patients treated between 2008 and 2016, and stratified by oral antihyperglycemic agent (OHA) line of therapy (mono, dual or triple therapy). Patients were monitored for up to 365 days; associations between medication possession ratio (MPR) and outcomes at 1 year (glycated hemoglobin A1c (HbA1c), weight and hypoglycemia incidence) were assessed using linear regression modeling and descriptive analyses.

**Results** In total, 33 849 patients were included in the study (n=23 925 OHA monotherapy; n=8406 OHA dual therapy; n=1518 OHA triple therapy). One-year change in HbA1c was greater among adherent (−0.90 to −1.14%; −9.8 to −12.5 mmol/mol) compared with non-adherent patients (−0.49 to −0.69%; −5.4 to −7.5 mmol/mol). On average, adherent patients had higher hypoglycemia event rates than non-adherent patients (rate ratios of 1.24, 1.10 and 2.06 for OHA mono, dual and triple therapy cohorts, respectively) and experienced greater weight change from baseline. A 10% improvement in MPR was associated with −0.09% (−1.0 mmol/mol), −0.09% (−1.0 mmol/mol) and −0.21% (−2.3 mmol/mol) changes in HbA1c for OHA mono, dual and triple therapy cohorts, respectively.

**Conclusions** For patients with type 2 diabetes, increasing medication adherence can bring about meaningful improvements in HbA1c control as the requirement for treatment escalation increases. Regimens associated with weight loss and the avoidance of hypoglycemia were generally associated with better medication adherence and improved glycemic control.

## Significance of this study

### What is already known about this subject?

► The glucose-lowering efficacy of type 2 diabetes medications may only be realized through optimal patient adherence; a factor negatively impacted by treatment-related side effects such as weight gain and hypoglycemia.

### What are the new findings?

► Using real-world data from 33 849 patients with type 2 diabetes in UK clinical practice, this study found that across oral antihyperglycemic agent (OHA) lines of therapy (mono, dual or triple therapy), regimens typically associated with weight loss and lower incidence of hypoglycemia were generally associated with better medication adherence, which in turn was related to improved glycemic control.

### How might these results change the focus of research or clinical practice?

► For patients with type 2 diabetes requiring therapy escalation across the OHA treatment paradigm, data from this study have identified important determinants of optimal medication adherence and glycemic management.

## INTRODUCTION

Optimal glycemic management is essential to avoid the downstream health and economic consequences of type 2 diabetes, both at a patient and population level. In addition to dietary and lifestyle factors, choice of medication for type 2 diabetes represents a key determinant of the achievement and maintenance of glycemic control.

The evolution of type 2 diabetes is characterized by elevations in glycated hemoglobin A1c (HbA1c) levels over time and an ongoing requirement to adjust medication with respect to glucose-lowering efficacy, patient preferences and side effect profiles. In patients newly diagnosed with type 2 diabetes, metformin (MET) or sulfonylurea (SU) are common first-line therapeutic strategies.[1] These therapies often elicit a good, initial glucose-lowering response; however, in patients who experience intolerable side effects (including gastrointestinal symptoms and/or hypoglycemia) or do not achieve sufficient glycemic control with these therapies (initially or over time as the disease progresses), there is a requirement

to escalate to alternative monotherapy or combination regimens. These may include other oral antihyperglycemic agents (OHA) such as thiazolidinedione (TZD), sodium-glucose co-transporter-2 inhibitors (SGLT-2i) and dipeptidyl peptidase-4 inhibitors (DPP-4i) or injectable regimens including glucagon-like peptide-1 (GLP-1) and insulin-based therapies.[1] These alternative classes of medication are each associated with unique efficacy and side effect profiles which, on their own or in combination, may determine patient adherence and levels of glycemic control.[2]

The glucose-lowering potential of medication may only be realized through optimal medication adherence. Factors recognized by patients with diabetes to negatively impact their adherence to medication include the incidence of treatment-related side effects, particularly weight gain and hypoglycemia.[3] Research evaluating the impact of administering OHAs intermittently, rather than as recommended,[1] found that patients with type 2 diabetes and decreasing levels of medication adherence were consistently associated with a smaller HbA1c reductions compared with adherent patients.[4] In clinical terms, the UK Prospective Diabetes Study demonstrated that each 1% (11 mmol/mol) reduction in HbA1c reduced the risk of diabetes-related death by 21%, myocardial infarction by 14%, stroke by 12% and microvascular complications by 37%.[5] In economic terms, Baxter and colleagues reported that by maintaining HbA1c levels recommended by the National Institute for Health and Care Excellence, cost reductions could total £299 million over 5 years across the UK adult type 2 diabetes population, rising to £4.5 billion over 25 years.[6] In general, poor medication adherence in type 2 diabetes has been found to negatively influence time to treatment intensification,[7] rate of hospitalizations[8] and healthcare expenditure[9] related to diabetes-related morbidity and mortality.

Given that type 2 diabetes is characterized by the need to adjust treatments to maintain glycemic control over time, and that different treatments can elicit different levels of adherence due to side effect profiles, there is a requirement to establish the inter-relationships between these factors and HbA1c outcomes. Associations between treatment, outcomes and adherence have previously been evaluated[4 10 11]; however, such research has focused on specific classes of therapy or restricted populations, without addressing the evolution of type 2 diabetes and outcomes associated with OHA therapy escalation in a general clinical practice population. In light of this, the present retrospective cohort study aimed to generate evidence, based on a large cohort of patients with type 2 diabetes treated in UK clinical practice, to quantify inter-relationships between OHA treatment choice, line of therapy, medication adherence, HbA1c, weight and hypoglycemia, which may inform clinical management and health policy.

## RESEARCH DESIGN AND METHODS
### Study design
This study retrospectively analyzed patients with type 2 diabetes who were prescribed one of three treatment regimens (OHA monotherapy, dual or triple therapy) between 1 January 2008 and 31 December 2016. The index date was defined as the date of treatment initiation, and the baseline data period was defined as the quarter prior to the index date. Data were extracted quarterly, with measurements based on the last available record for each study variable within each period. Patients were monitored for up to 365 days post-index date, or until death, treatment cessation, treatment intensification to a non-examinable regimen, lost to follow-up or the end of the study period.

### Data source
The Clinical Practice Research Datalink (CPRD; formerly the General Practice Research Database) contains primary care data for approximately 11.3 million individuals registered with selected general practitioners in the UK.[12] In this study, patient-level data were extracted from the CPRD to obtain patient demographic and lifestyle information, as well as information on medical diagnoses, symptoms, referrals, hospitalizations, deaths and prescriptions, for each patient. Prescriptions are generated directly within the system and contain the name of the preparation, instructions for use, route of administration, dose and number of tablets for each entry. Primary care data derived from the CPRD have been validated and demonstrated to be of high quality[13 14] and used in previous observational research of diabetes,[15–17] including the assessment of adherence and HbA1c.[4]

### Population
Patients eligible for inclusion in this study were aged ≥18 years at index date with a diagnosis of type 2 diabetes, based on a Read code for type 2 diabetes or a prescription record of OHA. Patients with gestational or type 1 diabetes (based on read codes for type 1 diabetes or a prescription record indicating first-line insulin therapy), diagnosis of polycystic ovary syndrome or malignant disease prior to index date and/or during follow-up were excluded.

For each treatment cohort, eligible patients were required to have at least a 365-day record of prescription coverage and a minimum of two prescriptions filled for the medication(s) comprising a given regimen. OHA monotherapy included all patients prescribed one OHA over the study period; OHA dual therapy included patients with at least two instances of two simultaneously prescribed OHAs with no instances of additional OHA prescriptions; OHA triple therapy included patients with at least two instances of three simultaneously prescribed OHAs with no instances of additional OHA prescriptions. Patients with prior insulin usage or in receipt of regimens including GLP-1 were excluded due to

inadequate recording of injectable regimens (ie, dose and preparation).

By design, patients may have been included in more than one cohort at different times during the study period, provided they met the eligibility criteria for each cohort. Therapy change post-index was defined as cessation of one or more of the medication(s) comprising each regimen and/or initiation of a new treatment.

### Derived variables

Descriptive analyses were undertaken to compare patient profiles, outcomes and patterns of medication adherence within and across treatment cohorts. Patient outcomes of interest included 1-year HbA1c and weight change from baseline (for patients with 365 days of follow-up data), 1-year hypoglycemic event incidence (total events and rate per 1000 patient-years) and medication adherence.

Consistent with methodological approaches advocated by the International Society for Pharmacoeconomics and Outcomes Research, medication adherence was assessed by calculating the medication possession ratio (MPR).[18] In this study, MPR was defined as the total number of days of available medication (calculated as the quantity of drug prescribed divided by the daily dose), divided by the length of the analysis period. For dual and triple OHA therapies, overall MPR was calculated as the average MPR of all medications comprising each regimen.

If prescription coverage was <365 days for a given regimen (due to therapy change or discontinuation) or periods between prescriptions were >6 months apart, the analysis period was shortened to coincide with the expected end date of the last valid prescription. Where dose information was absent for prescriptions within the analysis period, but present for a minimum of three prescriptions, the invalid prescriptions were omitted; and the time between the invalid prescription and the next valid prescription was subtracted from the denominator of the MPR calculation.

Patients with an overall MPR of ≥80% (MPR ≥0.80) were considered adherent to treatment; non-adherence was defined as MPR <0.80. Consistent with the approach of previous studies, patients with MPR calculated as >120% were excluded from the analysis.[4]

### Statistical analyses

For baseline patient and treatment characteristics, descriptive analyses for continuous variables (number of patients, mean, SD, median, minimum and maximum values) and categorical variables (the number and proportions of patients) were reported. Statistical significance of between-group comparisons was estimated using $\chi^2$ tests (categorical variables) and analysis of variance (continuous variables) to determine significant differences at the 5% level of testing.

Multivariate regression analyses were based on a general-specific selection methodology, with covariates excluded at the 5% level of statistical significance. Overall model fit was determined by appropriate goodness-of-fit statistics, including the $R^2$ statistic, likelihood ratio test and Akaike information criterion and Bayesian information criterion. All analyses were undertaken using R software for statistical computing.

Linear regression modeling was used to determine the association between patient variables, HbA1c and medication adherence. In patients with 365 days of follow-up data, multivariate regression modeling was used to assess the influence of observed covariates (demographic, clinical and socioeconomic factors, other prescriptions, comorbidities and center effects) on MPR and HbA1c change over 1 year.

## RESULTS

### Patient characteristics

A total of 159 799 patients aged ≥18 years within the CPRD database were identified as having type 2 diabetes between 1 January 2008 and 31 December 2016. After inclusion and exclusion criteria were applied, 33 849 patients were considered eligible for this study. Of these, 23 925 patients were prescribed OHA monotherapy and met the inclusion criteria for this treatment cohort, while 8406 patients were eligible for inclusion in the OHA dual therapy cohort and 1518 patients were included OHA triple therapy cohort (online supplementary figure S1).

At baseline, patients included in the OHA monotherapy subgroup tended to have lower body weight (94.4±21.9 kg; body mass index (BMI) 32.9±6.6 kg/m$^2$), a shorter duration of diabetes (0.7±1.3 years), lower baseline HbA1c (7.8%±1.6%; 62±17.5 mmol/mol) and fewer total prescriptions (19.9±18.9). In contrast, the OHA triple-therapy cohort had increased body weight at baseline (98.2±21.8 kg; BMI 33.4±6.6 kg/m$^2$), a longer duration of diabetes (3.0±1.8 years), higher baseline HbA1c (9.1%±1.5%; 76±16.4 mmol/mol), greater total prescriptions (26.9±22.6) and a higher likelihood of receiving lipid-lowering and antihypertensive therapies; potentially reflective of treatment escalation due to the progressive nature of diabetes and comorbid diseases. Other variables including baseline age, proportion of male patients, clinical measurements and type 2 diabetes-related event history were comparable across treatment cohorts. Within each OHA cohort, MET, SU and DPP-4i were the most commonly prescribed regimens (table 1).

### Patient outcomes

Treatment with OHA monotherapy was associated with a mean HbA1c reduction of −0.8% (−8.7 mmol/mol) over 1 year compared with −0.9% (−9.8 mmol/mol) and −1.0% (−10.9 mmol/mol) in patients treated with OHA dual and triple therapy, respectively (table 2). Across treatments and cohorts, patients who were adherent to therapy (MPR ≥0.80) generally experienced significantly greater reductions in HbA1c over 1 year (−0.90 to −1.14%; −9.8 to −12.5 mmol/mol) than those considered non-adherent (−0.49 to −0.69%; −5.4 to −7.5 mmol/mol).

**Table 1** Baseline characteristics of patients with type 2 diabetes in each oral antihyperglycemic agent (OHA) therapy cohort

| | OHA therapy cohort | | |
| --- | --- | --- | --- |
| | OHA monotherapy (n=23 925) | OHA dual therapy (n=8406) | OHA triple therapy (n=1158) |
| **Baseline patient characteristics** | | | |
| Age (years), mean (SD) | 59.2 (12.9) | 56.9 (11.9) | 56.6 (10.6) |
| Male sex, n (%) | 14 356 (60.0%) | 5475 (65.1%) | 1061 (69.9%) |
| Current smoker, n (%) | 2388 (10.0%) | 750 (8.9%) | 123 (8.1%) |
| Duration of diabetes (years), mean (SD) | 0.7 (1.3) | 1.9 (1.8) | 3.0 (1.8) |
| BMI (kg/m$^2$), mean (SD) | 32.9 (6.6) | 32.8 (6.6) | 33.4 (6.6) |
| HbA1c (%), mean (SD) | 7.8 (1.6) | 8.6 (1.6) | 9.1 (1.5) |
| HbA1c (mmol/mol), mean (SD) | 62 (17.5) | 70 (17.5) | 76 (16.4) |
| **Regimens, n (%)** | | | |
| OHA monotherapy | 23 925 (100.0%) | – | – |
| MET | 21 628 (90.4%) | – | – |
| SU | 1758 (7.3%) | – | – |
| DPP-4i | 423 (1.8%) | – | – |
| Other | 116 (0.5%) | – | – |
| OHA dual therapy | – | 8406 (100.0%) | – |
| MET+SU | – | 4871 (57.9%) | – |
| MET+DPP-4i | – | 2448 (29.1%) | – |
| MET+TZD | – | 466 (5.5%) | – |
| MET+SGLT-2i | – | 232 (2.8%) | – |
| SU+DPP-4i | – | 223 (2.7%) | – |
| Other | – | 166 (2.0%) | – |
| OHA triple therapy | – | – | 1518 (100.0%) |
| MET+SU+DPP-4i | – | – | 985 (64.9%) |
| MET+SU+TZD | – | – | 210 (13.8%) |
| MET+DPP-4i+SGLT-2i | – | – | 119 (7.8%) |
| MET+DPP-4i+TZD | – | – | 104 (6.9%) |
| MET+SU+SGLT-2i | – | – | 68 (4.5%) |
| Other | – | – | 32 (2.1%) |
| **Prescriptions** | | | |
| Mean (SD) | 19.9 (18.9) | 22.8 (19.4) | 26.9 (22.6) |
| Patients in receipt of lipid-lowering therapy, n (%) | 17 462 (73.0%) | 6512 (77.5%) | 1274 (83.9%) |
| Patients in receipt of antihypertensive therapy, n (%) | 14 460 (60.4%) | 5037 (59.9%) | 973 (64.1%) |
| **Complications at baseline, n (%)** | | | |
| Microvascular complications* | 429 (1.79%) | 393 (4.68%) | 210 (13.83%) |
| Macrovascular complications† | 932 (3.90%) | 261 (3.10%) | 92 (6.06%) |
| Other complications‡ | 88 (0.37%) | 62 (0.74%) | 42 (2.77%) |

*Microvascular complications include diabetic nephropathy, neuropathy (comprising neuropathy, ulcer and amputation) and retinopathy (comprising retinopathy, blindness and macular edema).
†Macrovascular complications include congestive heart failure, ischemic heart disease, myocardial infarction and stroke.
‡Other complications include nausea, gastrointestinal complications, edema, urinary tract infection, acute pancreatitis, fracture, ketoacidosis and hypoglycemia.
BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; HbA1c, glycated hemoglobin A1c; MET, metformin; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

**Table 2** One-year change in glycated hemoglobin A1c (HbA1c), weight and hypoglycemia incidence, stratified by oral antihyperglycemic agent (OHA) therapy cohort and medication possession ratio (MPR) category

| Regimen | N | One-year HbA1c change (%), mean (95% CI) | One-year HbA1c change (mmol/mol), mean (95% CI) | One-year weight change (kg), mean (95% CI) | Hypoglycemia event rate, n (per 1000 patient-years) |
|---|---|---|---|---|---|
| OHA monotherapy | 23 925 | −0.8 (−0.9 to −0.8) | −8.7 (−9.8 to −8.7) | −2.5 (−2.6 to −2.3) | 189 (7.9) |
| MPR<80% | 4401 | −0.55 (−0.61 to −0.49) | −6.0 (−6.7 to −5.4) | −1.64 (−1.94 to −1.34) | 29 (6.6) |
| MPR≥80% | 19 524 | −0.90 (−0.93 to −0.87) | −9.8 (−10.2 to −9.5) | −2.65 (−2.80 to −2.50) | 160 (8.2) |
| Difference* | | −0.35 (−0.41 to −0.28); p<0.001 | −3.8 (−4.5 to −3.1); p<0.001 | −1.01 (−1.34 to −0.67); p<0.001 | 131 (RR 1.24; p=0.303) |
| OHA dual therapy | 8406 | −0.9 (−1.0 to −0.9) | −9.8 (−10.9 to −9.8) | 0.6 (0.4 to 0.8) | 152 (18.1) |
| MPR<80% | 1610 | −0.69 (−0.79 to −0.58) | −7.5 (−8.6 to −6.3) | 0.31 (−0.22 to 0.83) | 27 (16.8) |
| MPR≥80% | 6796 | −0.97 (−1.02 to −0.92) | −10.6 (−11.1 to −10.1) | 0.67 (0.46 to 0.88) | 125 (18.4) |
| Difference* | | −0.28 (−0.40 to −0.17); p<0.001 | −3.1 (−4.4 to −1.9); p<0.001 | 0.36 (−0.20 to 0.93); p=0.210 | 98 (RR 1.10; p=0.757) |
| OHA triple therapy | 1518 | −1.0 (−1.1 to −0.9) | −10.9 (−12.0 to −9.8) | 0.5 (0.0 to 0.9) | 58 (38.2) |
| MPR<80% | 291 | −0.49 (−0.74 to −0.25) | −5.4 (−8.1 to −2.7) | 0.26 (−0.65 to 1.17) | 6 (20.6) |
| MPR≥80% | 1227 | −1.14 (−1.25 to −1.04) | −12.5 (−13.7 to −11.4) | 0.50 (0.03 to 0.97) | 52 (42.4) |
| Difference* | | −0.65 (−0.92 to −0.38); p<0.001 | −7.1 (−10.1 to −4.2); p<0.001 | 0.24 (0.79 to 1.27); p=0.642 | 46 (RR 2.06; p=0.096) |

*Difference relates to MPR ≥80% versus MPR <80%.
RR, rate ratio.

On average, OHA monotherapy was associated with weight loss over 1 year (−2.5 kg); within this cohort, weight reductions were greater among adherent (−2.65 kg) compared with non-adherent (−1.64 kg) patients. In the dual and triple OHA cohorts, weight tended to increase, more so for adherent (+0.50 to +0.67 kg) compared with non-adherent (+0.26 to +0.31 kg) patients; however, this overall result included a trend of weight gain for SU and TZD-based regimens, and weight loss for DPP-4i and SGLT-2i-based regimens (table 2; online supplementary Table S1).

Despite having higher baseline HbA1c, the incidence of recorded hypoglycemia events (per 1000 patient-years) was greatest in the OHA triple-therapy cohort (38.2), compared with patients receiving OHA monotherapy and dual-therapy regimens (7.9 and 18.1, respectively). Within the OHA monotherapy cohort, treatment with SU was associated with a higher hypoglycemia event rate (15.4) versus MET and DPP-4i therapies (7.3 and 9.5, respectively). Similarly, the incidence of hypoglycemia was generally higher among patients who received dual-therapy and triple-therapy regimens containing SU, compared with those containing DPP-4i, TZD and/or SGLT-2i agents (online supplementary Table S1). Observed event rates were higher among adherent versus non-adherent patients in the OHA monotherapy (8.2 vs 6.6), dual-therapy (18.4 vs 16.8) and triple-therapy (42.4 vs 20.6) cohorts, reflecting an increase in hypoglycemia incidence among adherent patients across therapy lines (table 2).

### Levels of adherence and glycemic control

Medication adherence was highest in the OHA monotherapy cohort (81.6%), followed by dual-therapy (80.8%) and triple-therapy (80.8%) cohorts (online supplementary Table S1). Adherence by regimen (MPR ≥0.80; 95% CI) for OHA monotherapy was highest for DPP-4i agents (89.8%; 87.0% to 92.7%). For the two most commonly observed dual OHA therapies, MET+DPP-4i (29% of patients) was associated with a higher level of adherence (83.3%; 81.8% to 84.8%), compared with MET+SU (58% of patients) that had the lowest adherence (79.6%; 78.5% to 80.7%). In patients treated with triple OHA therapies, medication adherence across regimens was similar.

As shown in figure 1, increasing levels of medication adherence were typically associated with greater 1-year HbA1c reductions across all lines of OHA therapy. In absolute terms, the OHA triple-therapy cohort had the greatest level of HbA1c change (−0.17 to −1.20%; −1.9 to −13.1 mmol/mol), followed by the dual (−0.60 to −1.04%; −6.6 to −11.4 mmol/mol) and monotherapy (−0.49 to −0.94%; −5.4 to −10.3 mmol/mol) cohorts.

### Predictors of adherence and glycemic control

Factors predictive of MPR were evaluated for each OHA cohort in linear regression analyses. Across OHA cohorts, patient age, baseline HbA1c, change in BMI and/or change in total cholesterol were significant variables related to MPR variability (table 3). Consistent with observations of patient outcomes, coefficient estimates for change in BMI were negative in the OHA monotherapy cohort, and positive in patients receiving OHA dual therapy. Using a regression model that predicted 1-year change in HbA1c as a function of MPR, it was estimated that a 10% improvement in MPR, when all other variables were held constant, was associated with a −0.09% (−1.0 mmol/mol), −0.09% (−1.0 mmol/mol) and −0.21%
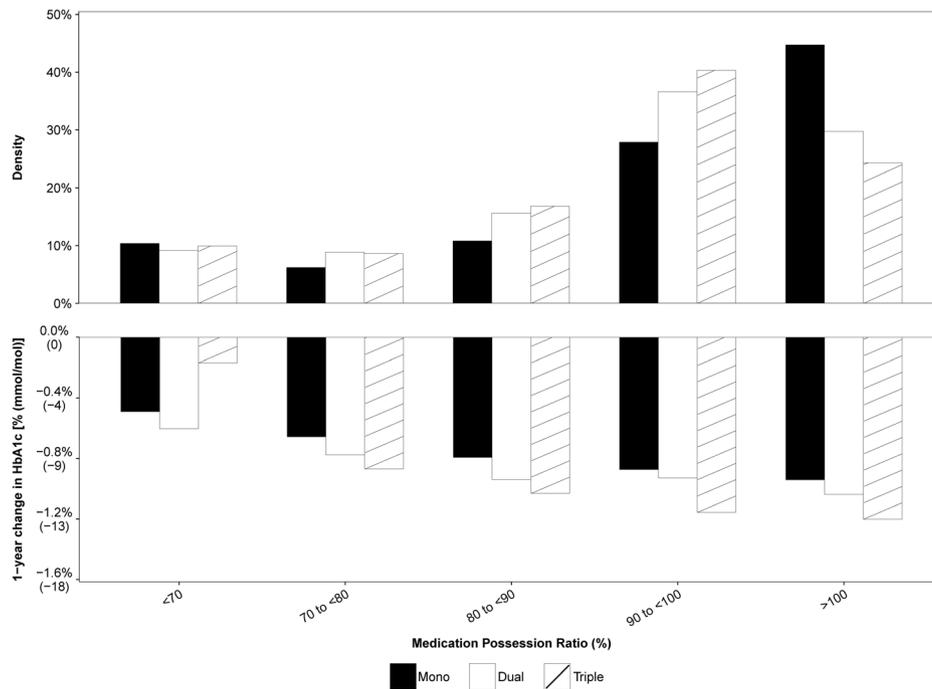
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**Figure 1** One-year change in glycated hemoglobin A1c (HbA1c), stratified by medication possession ratio category and oral antihyperglycemic agent therapy cohort.

(−2.3 mmol/mol) change in HbA1c for OHA mono, dual and triple therapy, respectively.

## CONCLUSIONS

Using real-world data from 33 849 patients with type 2 diabetes in UK clinical practice, this study sought to evaluate the evolution of type 2 diabetes and outcomes associated with OHA therapy escalation as a function of medication adherence. Analyses found that reduced medication adherence was associated with smaller HbA1c reductions among patients treated with OHA monotherapy, dual-therapy and triple-therapy regimens. One-year reductions in HbA1c were greater among adherent (−0.90 to −1.14%; −9.8 to −12.5 mmol/mol) compared with non-adherent patients (−0.49 to −0.69%; −5.4 to −7.5 mmol/mol) and a 10% improvement in MPR was associated with a −0.09% (−1.0 mmol/mol), −0.09% (−1.0 mmol/mol) and −0.21% (−2.3 mmol/mol) change in HbA1c for OHA monotherapy, dual therapy and triple therapy, respectively. Collectively, these findings support the notion that modest increases in medication adherence can bring about meaningful improvements in HbA1c control as the requirement to escalate therapy increases.

On average, hypoglycemia was more frequent among adherent patients compared with non-adherent patients, with rate ratios of 1.24, 1.10 and 2.06 associated with OHA monotherapy, dual therapy and triple therapy, respectively. Within each OHA cohort, adherent patients tended to lose more weight (OHA monotherapy) or gain more weight (OHA dual and triple therapy) compared with non-adherent patients. These findings are consistent

with a regimen–outcome interaction that may be mediated via medication adherence. For instance, across the OHA treatment paradigm, regimens typically associated with weight loss and lower incidence of hypoglycemia were generally associated with better medication adherence and improved glycemic control.

The health economic value of type 2 diabetes medication is driven by its expected therapeutic profile, in addition to patient and clinician treatment preferences. Key barriers to achieving good medication adherence include treatment-related hypoglycemia and weight gain[3]; in this context, guidelines suggest that DPP-4i or SGLT-2i therapies are associated with weight loss or neutrality and low risk of hypoglycemia, while TZD regimens cause weight gain and SU-based therapies are associated with both weight gain and moderate hypoglycemia risk.[19] Data arising from this study coincide with such guidance and extend this notion to demonstrate that patients treated with OHA regimens associated with weight loss and lower hypoglycemia frequency tended to achieve better adherence and HbA1c control. Importantly, this was observed across all lines of OHA therapy, suggesting that adherence may be an increasingly important determinant of glycemic control as patients escalate from OHA monotherapy to dual-therapy and triple-therapy regimens.

To our knowledge, this is the first study to evaluate a large general cohort of UK patients with type 2 diabetes in order to assess the associations between adherence and clinical outcomes across the OHA treatment paradigm. This research builds on existing studies that demonstrate associations between adherence and HbA1c control,[4]

**Table 3** Multiple linear regression model predicting 1-year glycated hemoglobin A1c (HbA1c) change as a function of medication possession ratio (MPR), stratified by oral antihyperglycemic agent (OHA) therapy cohort

| | Multivariate model | | | |
|---|---|---|---|---|
| | Value | SE | t-value | p-value |
| **OHA monotherapy** | | | | |
| Change in HbA1c **(%)** | | | | |
|    MPR (%) | −0.892 | 0.076 | −11.680 | 0.000 |
|    Constant | −0.002 | 0.073 | −0.030 | 0.974 |
| **MPR (%)** | | | | |
|    Age (years) | 0.002 | 0.000 | 10.110 | 0.000 |
|    Change in BMI (kg/m$^2$) | −0.003 | 0.001 | −2.760 | 0.006 |
|    Baseline HbA1c (%) | −0.002 | 0.002 | −1.400 | 0.162 |
|    Change in total cholesterol | −0.016 | 0.002 | −7.270 | 0.000 |
|    Constant | 0.827 | 0.019 | 42.780 | 0.000 |
| **OHA dual therapy** | | | | |
| Change in HbA1c (%) | | | | |
|    MPR (%) | −0.859 | 0.155 | −5.550 | 0.000 |
|    Constant | −0.133 | 0.143 | −0.930 | 0.353 |
| **MPR (%)** | | | | |
|    Age (years) | 0.002 | 0.000 | 6.320 | 0.000 |
|    Change in BMI (kg/m$^2$) | 0.004 | 0.001 | 2.420 | 0.015 |
|    Baseline HbA1c (%) | −0.007 | 0.002 | −3.400 | 0.001 |
|    Change in total cholesterol | −0.012 | 0.003 | −4.230 | 0.000 |
|    Constant | 0.874 | 0.023 | 37.300 | 0.000 |
| **OHA triple therapy** | | | | |
| Change in HbA1c (%) | | | | |
|    MPR (%) | −2.058 | 0.348 | −5.920 | 0.000 |
|    Constant | 0.840 | 0.319 | 2.630 | 0.009 |
| **MPR (%)** | | | | |
|    Age (years) | 0.001 | 0.001 | 2.170 | 0.031 |
|    Change in BMI (kg/m$^2$) | −0.001 | 0.004 | −0.220 | 0.823 |
|    Baseline HbA1c (%) | −0.013 | 0.005 | −2.610 | 0.009 |
|    Change in total cholesterol | −0.016 | 0.008 | −1.930 | 0.054 |
|    Constant | 0.941 | 0.063 | 15.050 | 0.000 |

BMI, body mass index.

and hypoglycemia and cardiovascular risk,[20] in specific patient populations or for individual treatments.

There are several important limitations associated with this research. Observational studies that stratify outcomes by therapy type are potentially subject to the bias of 'confounding by indication', where observed patterns within the data are a function of the patient phenotype, which may in turn dictate the prescription of a specific therapy. Potential confounding factors may not be captured within the CPRD database (such as educational and professional status); thus, predicting causality between treatment and outcome should be interpreted with these limitations in mind. To further minimize the impact of confounding in this study, homogenous OHA cohorts were selected for analysis; and stratification and statistical adjustment were used as the principal

methods of accounting for differences in patient type and prescribing choice on study outcomes.

An additional limitation of CPRD-derived data relates to the under-reporting of hypoglycemia, as patients may often self-manage an event and not present to a physician. While there are no data to confirm this, we consequently expect that fewer hypoglycemic events were captured by the CPRD and that such events were more likely to be severe. As a result, data describing hypoglycemia incidence, and its influence on medication adherence and clinical outcomes, may be underestimated in this retrospective study. The under-reporting of hypoglycemia may have additionally led to spurious comparisons between OHA regimens; for example, the relatively high hypoglycemia event rate observed in patients treated with MET monotherapy compared with SU

(7.3 vs 15.4 events per 1000 patient-years, respectively) may be attributed to the comparatively low number of patients (21 628 vs 1758) and recorded events (158 vs 27) in the SU monotherapy cohort. Moreover, although the high incidence of hypoglycemia observed in the OHA triple-therapy cohort may reflect greater HbA1c reductions and/or treatment regimens associated with higher hypoglycemia risk, patient numbers are comparatively low in this cohort, and associated data should thus be interpreted with caution. Finally, we were unable to adequately assess medication adherence in patients treated with injectable agents, including GLP-1 receptor agonist and insulin-based therapies, due to a paucity of CPRD data characterizing factors including doses, preparations or the full range of potential treatment-related side effects. Examining the impact of OHA dosing frequency on medication adherence and treatment outcomes was beyond the design and objectives of the present study; however, as dosing frequency may represent an important determinant of patient adherence and subsequent outcomes, this relationship is indicated as an area for future research.

In conclusion, improving HbA1c is the cornerstone of type 2 diabetes therapy, which serves to manage glycemic control and reduce the risks of diabetes-related complications, morbidity and mortality. Improvements in HbA1c are determined by treatment choice and medication adherence; factors which are interrelated and further confounded by patient type and place in the OHA treatment paradigm. This retrospective study of routinely collected UK primary care data sought to evaluate associations between medication adherence and clinical outcomes among patients with type 2 diabetes treated with OHA regimens. Across all lines of OHA therapy examined, lower MPR was associated with smaller HbA1c reductions, suggesting that increased medication adherence can bring about meaningful improvements in HbA1c control as the requirement to escalate therapy increases. Across the OHA treatment paradigm, regimens associated with weight loss and the avoidance of hypoglycemia were generally associated with better medication adherence and improved glycemic control.

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