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Recent Metformin Adherence and the Risk of Hypoglycaemia in the Year Following Intensification with a Sulphonylurea

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Abstract

Aims: People with unrecognized suboptimal adherence to antihyperglycemic medications may have their regimens intensified, potentially exposing them to high risk of adverse events. We evaluated whether recent low adherence to metformin monotherapy is associated with hypoglycaemia following sulphonylurea addition.

Methods: We assembled a retrospective cohort of veterans who filled a new prescription for metformin from 2001 through 2011 and intensified treatment with a sulphonylurea after 1 year of metformin use. We calculated metformin adherence from pharmacy data using the proportion of days covered in the 180-day period before intensification. The primary outcome was hypoglycaemia, defined as a hospitalization or emergency department visit due to hypoglycaemia or an outpatient blood glucose measurement <3.3 mmol/L in the year following intensification. Cox proportional hazards models compared the risk of hypoglycaemia between participants with low (<80%) and high (≥80%) adherence. Adherence was also modelled as a continuous variable using restricted cubic splines.

Results: Of 187,267 participants who initiated metformin monotherapy, 49,424 added a sulphonylurea after 1 year. The median adherence was 87% (IQR 50, 100), and 43% had adherence <80%. Hypoglycaemia rates were 23.1 (95% confidence interval [CI] 21.1,25.4) and 24.5 (95% CI 22.7,26.4) per 1000 person-years among low and high adherence participants, respectively (adjusted hazard ratio 0.95, 95% CI 0.84,1.08). The risk of hypoglycaemia was similar across all levels of adherence when adherence was modelled as a continuous variable.

Conclusions: We found no evidence that past low adherence to metformin monotherapy was associated with hypoglycaemia following intensification with a sulphonylurea.

Keywords

type 2 diabetes mellitus; medication adherence; hypoglycaemia; metformin; sulphonylureas

Introduction

Antihyperglycemic medications are an important part of diabetes management. However, adherence to these medications is often suboptimal. Overall antihyperglycemic medication adherence among people with type 2 diabetes mellitus is estimated to be 36–85%, and up to a third of individuals who are prescribed metformin discontinue the drug within one year (1,2). Many factors affect medication adherence, including cost, side effects, number of concurrent medications, beliefs about medications, and relationship with provider (2–4). The level of adherence to antihyperglycemic medications can impact both short-term diabetes treatment goals, including glycosylated haemoglobin (HbA_{1c}), and long-term clinical outcomes including cardiovascular, cerebrovascular and renal events, among others (5–9).

While it is ideal to address any problems with adherence prior to intensifying treatment, in clinical practice providers often decide to intensify therapy based on physiologic or laboratory measurements regardless of the level of medication adherence, due to challenges or barriers to objectively ascertaining past medication use. When an individual with type 2 diabetes mellitus on metformin has elevated HbA_{1c} levels due to nonadherence, the provider may decide to intensify antihyperglycemic therapy by adding another agent such as a sulphonylurea to the current regimen. However, if the individual decides to take the medications more regularly from that point forward, he or she could be exposed to a more intensive regimen than was necessary, increasing the risk for hypoglycaemic events. We conducted a retrospective cohort study to evaluate whether recent low adherence to metformin monotherapy was a risk factor for early hypoglycaemia events following intensification of therapy with a sulphonylurea.

Participants and Methods

Study design and data sources

We used national U.S. Veterans Health Administration (VHA) databases including administrative, clinical and laboratory data linked through identifiers designed for research to construct a retrospective cohort of veterans with type 2 diabetes. Sources of data include: dispensed medication information (fill date, days supply, number of pills); demographic data; diagnostic and procedure information from inpatient and outpatient encounters coded as *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*(10); and laboratory test results and vital signs (blood pressure, height, weight) from standard clinical sources. For participants enrolled in Medicare or Medicaid, additional data were obtained from the U.S. Centers for Medicare and Medicaid Services (CMS) through an interagency exchange agreement (11). Dates of death were obtained from the National Death Index (NDI) prior to 2011, and VHA vital status files were used as a supplement to identify subsequent dates of death from 2011 to 2012. The institutional review boards of VHA Tennessee Valley Healthcare System approved this study.

Study population

The study population included veterans aged 18 years or older who received regular care at VHA. Regular care was defined as having at least one inpatient or outpatient encounter or a prescription fill every 360 days in the prior 2 years. We identified new users of metformin from October 2001 to September 2011, with at least 365 days of baseline data and no antihyperglycemic drug fill in the past 180 days. Participants were excluded if they did not refill metformin at least once during the initial 12 months of therapy. This criterion was added to exclude participants who did not refill due to gastrointestinal intolerance or other side effects to metformin. Metformin initiators who refilled their medication at least once became eligible for the intensification cohort when they first filled sulphonylurea (glibenclamide, glipizide or glimepiride) prescription (Supplemental Fig. S1). The time on metformin monotherapy was required to be at least 12 months to assess adherence. Participants were not required to have a metformin supply on hand at the time of intensification with sulphonylurea.

Participants receiving hospice care or dialysis at the time of intensification (Supplemental Table S1), and those with missing birthdate or gender were excluded.

Exposures

The exposure of interest was recent metformin adherence at therapy intensification with a sulphonylurea. Prescription refill records were used to define adherence as a continuous variable representing the proportion of metformin days covered (PDC) during the 6-month period prior to intensification (12)(Supplemental Fig. S1).

Based on previous studies, we dichotomized the comparison groups in our study population for the primary analysis into participants with low (<80%) and high (≥80%) metformin adherence at intensification (12,13). Follow-up began after intensification and continued for up to a year until study outcome, regimen change (filled a third antihyperglycemic agent), loss to follow-up (181 days without VHA contact), death, or end of study (September 30, 2012) (Supplemental Fig. S1).

Primary outcome: Hypoglycaemia

The primary outcome was time to first hypoglycaemia within one year of intensification with a sulphonylurea. Recurrent events were not considered in the study. Hypoglycaemia was a composite of 3 event types: hospitalization for hypoglycaemia, emergency department visit due to hypoglycaemia, or an outpatient blood glucose measurement <3.3 mmol/L. Hospitalization for hypoglycaemia was identified by a primary discharge diagnosis of hypoglycaemia or poisoning by insulin or other antidiabetic agents (ICD-9-CM codes 251.0, 251.1, 251.2, 270.3 or 962.3 in the primary position only). Hypoglycaemia events identified through emergency department visits had a discharge diagnosis ICD-9-CM code of 251.0, 251.1, 251.2, 962.3, or 270.3, and a concurrent Current Procedural Terminology (CPT) code of 99281, 99282, 99283, 99284, 99285, or 99288 (to identify emergency encounters) (14).

Secondary outcome

For the secondary analysis, we described median HbA_{1c} measurements in low versus high adherence participants at baseline and 12 months after intensification, among those alive during the study period. We also compared the adjusted proportion (by baseline HbA_{1c}) of participants with >11 mmol/mol (1.0%) decrease in HbA_{1c} during the study period.

Covariates

Baseline covariate information was collected from up to 730 days prior to intensification (t_1). Covariates included age (continuous), sex, race (white, black, other), year of metformin initiation, indicators of healthcare use (hospitalized during past year, nursing home use, number of outpatient visits, Medicare or Medicaid utilization), physiologic variables (body mass index [BMI], blood pressure (systolic, diastolic), HbA_{1c} level, low density lipoprotein [LDL] level, proteinuria, serum creatinine, and calculated estimated glomerular filtration rate [eGFR] using the Chronic Kidney Disease Epidemiology Collaboration formula (15), duration of metformin monotherapy (proxy for diabetes duration), selected medications, smoking, and selected comorbidities (See Supplemental Table S2 for further details).

We also considered the type (glipizide, glibenclamide, and glimepiride) and dose of sulphonylurea added. Initial defined daily dose (DDD) was calculated as: 10mg for glipizide, 10mg for glibenclamide, and 2mg for glimepiride according to the World Health Organization (WHO)(16).

Multiple imputation was conducted (30 imputations) for missing covariates using an iterative Markov chain Monte Carlo (MCMC) method for both the construction of propensity scores and for the final outcome model in the primary analysis (17). For continuous variables, restricted cubic splines were included in the final outcome model to account for nonlinearity (18).

Data cleaning and quality control

For blood glucose values obtained in the outpatient setting, we excluded non-numeric values (such as “high” or “low”) and converted non-absolute values to absolute values so that a blood glucose value >22.2 would be coded as 22.2, and a blood glucose value <3.9 would be coded as 3.9. If a participant had hypoglycaemia based on the outpatient blood glucose or emergency room visit definition which led to a hospitalization within 48 hours, the event was counted as a single event attributed to the hospitalization. Similarly, if a participant had hypoglycaemia based on an outpatient blood glucose which led to an emergency visit, the event was attributed to the emergency room visit.

Statistical analyses

The primary analysis evaluated the time to first hypoglycaemia event among participants with low adherence versus high adherence, using a Cox proportional hazards model adjusting for baseline covariates. The study population was weighted using propensity score matching weights (19). The propensity scores modelled the probability of low adherence based on covariate information and service network of care, and the weights scaled the high and low adherence groups to resemble a 1:1 matched cohort. Results of the propensity score

models are presented in separate figures and tables (Supplemental Fig. S2 and Table S3). For the secondary analysis, we described the median HbA_{1c} at baseline and at 12 months after intensification among participants who survived and had a baseline HbA_{1c} measurement. Using a logistic regression model adjusting for baseline HbA_{1c}, we estimated the adjusted proportion of participants with >11 mmol/mol (1.0%) decrease in HbA_{1c} for low and high adherence patients.

Subgroup and sensitivity analyses

We examined whether the association between low adherence and risk of hypoglycaemia differed by two potential effect modifiers, sulphonylurea type and dose. Subgroup analyses were conducted for participants who intensified treatment with glibenclamide versus glipizide or glimepiride, and for those who added a high dose of sulphonylurea (≥ 1 DDD) versus a low dose of sulphonylurea (<1 DDD).

For the sensitivity analysis, we modelled medication adherence as a continuous variable using restricted cubic splines in a Cox proportional hazard model adjusting for baseline covariates (18). This analysis was performed to examine whether there was a nonlinear association between adherence and the hypoglycaemia outcome, or if there was a tipping point where the risk of hypoglycaemia increased.

Results

Study population

We identified 187,267 participants who initiated metformin monotherapy, 49,424 of whom intensified therapy with a sulphonylurea after being on metformin monotherapy for at least one year and did not meet other exclusion criteria (Fig. 1). The intensification cohort participants were 96% male and 84% white, and the median age was 63 years (interquartile range [IQR] 57, 72). The median metformin adherence in the 6 months prior to intensification was 87% (IQR 50, 100) (Supplemental Fig. S3): 47% (IQR 16, 63) among low adherence participants and 100% (IQR 94, 100) among high adherence participants. A total of 21,419 participants (43%) had low adherence. Prior to propensity score weighting, low adherence participants were slightly younger, were less often white, had shorter duration of metformin monotherapy and higher HbA_{1c} at intensification, and were on fewer outpatient medications (Table 1). The median total number of outpatient laboratory blood glucose measurements during the 1-year follow-up period was 4 (IQR 2, 6) in both low adherence and high adherence participants.

Primary Outcome: Hypoglycaemia

Of the 49,424 study participants, 1100 (2.2%) had a hypoglycaemia event during the first year of intensification (10 hospitalizations, 143 emergency department visits, and 947 outpatient events); 10.7% were censored for death, end of study, or were no longer in contact with the VHA. Among low adherence participants, 456 (2.1%) had a hypoglycaemia event (3 hospitalizations, 62 emergency department visits, and 391 outpatient events), and among high adherence participants, 644 (2.3%) had a hypoglycaemia event (7 hospitalizations, 81 emergency department events, and 556 outpatient events). The rates of hypoglycaemia per

1000 person-years were 23.1 (95% confidence interval [CI] 21.1, 25.4) and 24.5 (95% CI 22.7, 26.4) for low and high adherence participants, respectively. After propensity score weighting and further adjusting for baseline covariates in the Cox model, the risk of hypoglycaemia among low adherence participants was similar to that among high adherence participants (adjusted hazard ratio [HR] 0.95, 95% CI 0.84, 1.08) (Table 2).

Subgroup and Sensitivity and analyses

Subgroup analyses results were consistent with the main findings (Table 2). When adherence was modelled as a continuous variable using restricted cubic splines, there was no evidence of a linear or nonlinear association between levels of adherence and risk of hypoglycaemia (Fig. 2).

Relationship between adherence and change in HbA_{1c}

The median baseline HbA_{1c} for low and high adherence participants was 58 mmol/mol (7.5%) (IQR 51, 70 [6.8, 8.6]) and 56 mmol/mol (7.3%) (IQR 50, 64 [6.7, 8.0]), respectively. The median HbA_{1c} at 12 months for participants who were alive and had a baseline measurement was 52 mmol/mol (6.9%) (IQR 45, 61 [6.3, 7.7]) among low adherence participants and 51 mmol/mol (6.8%) (IQR 45, 57 [6.3, 7.4]) among high adherence participants (Supplemental Fig. S4). The median absolute HbA_{1c} change from baseline to 12 months was -3 mmol/mol (0.3%) (IQR -13, 0 [-1.2, 0]) among low adherence participants and -3 mmol/mol (0.3%) (IQR -10.9, 0 [-1.0, 0]) among high adherence participants. The adjusted proportion of patients with >11 mmol/mol (1.0%) decrease in HbA_{1c} estimated from the logistic regression model accounting for baseline HbA_{1c} was 27.0% (95% CI 26.3, 27.6) and 22.8% (95% CI 22.1, 23.6) among high and low adherence participants, respectively.

Discussion

In our study of veterans with type 2 diabetes, we found no evidence that recent low metformin monotherapy adherence was associated with an increased risk of developing early hypoglycaemia after intensifying treatment with a sulphonylurea. A smaller proportion of low adherence participants had a >11 mmol/mol (1.0%) decrease in HbA_{1c} compared to high adherence participants when accounting for baseline HbA_{1c}. The risk of hypoglycaemia appeared to be similar across different levels of recent adherence to metformin when we modelled adherence as a continuous variable in our sensitivity analysis. We had limited power to evaluate the association in those with very low adherence (<30%) as indicated by the wide confidence intervals.

While it is important to evaluate medication adherence, this study does not suggest that intensifying treatment in the presence of recent nonadherence is associated with higher risk of hypoglycaemia. Improvements in HbA_{1c} levels were seen in participants with low and high adherence. In a study of hypertension, Rose and colleagues found that antihypertensive treatment intensification improved blood pressure control similarly among participants with different levels of adherence (20). The authors argue that while addressing adherence is important, it may not be a necessary step prior to intensifying therapy for hypertension.

Similarly, for antihyperglycemic drug therapy among people with type 2 diabetes mellitus, clinicians may intensify treatment based on HbA_{1c} or glucose measurements before addressing adherence issues, and our study suggests this may lead to favourable changes in glycaemic control without a greater risk of hypoglycaemia.

Two previous studies have explored the relationship between antihyperglycemic medication adherence and the outcome of hypoglycaemia, although the specific research questions differed. Quilliam and colleagues examined whether the risk of hypoglycaemia differed depending on the adherence and change in regimen during the first 6 months of metformin, sulphonylurea, or thiazolidinedione therapy (19). The overall rates of hypoglycaemia were similar to our observed event rates (0.9–2.6%). They found that the hazard of hypoglycaemia was higher among participants switching to combination therapy compared to metformin users who were highly adherent; however, they did not specifically evaluate how the observed adherence could relate to hypoglycaemia after switching to combination therapy. Hsu and colleagues used a cross-sectional design to examine the relationship between self-reported adherence and adverse safety events including hypoglycaemia (22). They did find that lower adherence by self-report was associated with more adverse safety outcomes by self-report (prevalence ratio [PR] 1.21, 95% CI 1.04, 1.41), but the specific results for hypoglycaemia were not reported, and the temporal relationship could not be established due to the cross-sectional study design.

The national VHA population is an ideal population to study medication adherence and evaluate how it relates to clinical outcomes such as hypoglycaemia, because most people receive their medications through the VHA pharmacy at lower costs and have detailed records of prescription medication fills and healthcare encounters. As in any observational study, unmeasured confounding could have impacted our results, but we were able to use advanced survival methods to balance many potential confounders in the comparison groups by applying propensity score weighting and covariate adjustment.

A limitation of our study is that we did not examine post-intensification adherence to sulphonylurea. Because the VA often dispenses 90-day supply of medications to promote high adherence, the ability to detect meaningful changes in adherence after intensification would have required a longer follow-up. Another limitation is that hypoglycaemia is often not captured in medical records because many people do not present to the hospital or obtain glucose measurements even when they have a moderate to severe event. In addition, Veterans may not receive all care at VHA facilities, so events may be missed. Our data are supplemented by Medicare and Medicaid encounter information, which should have reduced missed events. We also lack information on certain confounders including participant education or provider quality of care. Finally, the cohort included mostly white men, typical of a U.S. veteran population (23) and should be considered when generalizing the study results to other populations.

In conclusion, we found no evidence that low metformin monotherapy adherence was a risk factor for early hypoglycaemia events following intensification with a sulphonylurea. In addition, the risk of hypoglycaemia did not appear to change across different levels of adherence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Cramer JA. A systematic review of adherence with medications for diabetes. *Diabetes Care*. 2004 5;27(5):1218–1224. [PubMed: 15111553]
2. Rubin RR. Adherence to pharmacologic therapy in patients with type 2 diabetes mellitus. *Am J Med*. 2005 5;118 Suppl 5A:27S–34S.
3. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence*. 2016 7;10:1299–1307. [PubMed: 27524885]
4. Linetzky B, Jiang D, Funnell MM, Curtis BH, Polonsky WH. Exploring the role of the patient–physician relationship on insulin adherence and clinical outcomes in type 2 diabetes: Insights from the MOSAIC study. *J Diabetes*. 2017 6;9(6):596–605. [PubMed: 27368146]
5. Kim N, Agostini JV, Justice AC. Refill adherence to oral hypoglycemic agents and glycemic control in veterans. *Ann Pharmacother*. 2010 5;44(5):800–808. [PubMed: 20388863]
6. Krapek K, King K, Warren SS, George KG, Caputo DA, Mihelich K, et al. Medication adherence and associated hemoglobin A1c in type 2 diabetes. *Ann Pharmacother*. 2004 9;38(9):1357–1362. [PubMed: 15238621]
7. Lawrence DB, Ragucci KR, Long LB, Parris BS, Helfer LA. Relationship of oral antihyperglycemic (sulfonylurea or metformin) medication adherence and hemoglobin A1c goal attainment for HMO patients enrolled in a diabetes disease management program. *J Manag Care Pharm*. 2006 7;12(6):466–471. [PubMed: 16925454]
8. Pladevall M, Williams LK, Potts LA, Divine G, Xi H, Lafata JE. Clinical outcomes and adherence to medications measured by claims data in patients with diabetes. *Diabetes Care*. 2004 12;27(12):2800–2805. [PubMed: 15562188]
9. Lau DT, Nau DP. Oral antihyperglycemic medication nonadherence and subsequent hospitalization among individuals with type 2 diabetes. *Diabetes Care*. 2004 9;27(9):2149–2153. [PubMed: 15333476]
10. National Center for Health Statistics. International Classification of Diseases, Ninth Revision, Clinical Modification. Washington, DC: Public Health Service, US Dept of Health & Human Services; 1988.
11. Information Exchange Agreement (IEA) between the Department of Health and Human Services, Centers for Medicare & Medicaid Services, and Department of Veterans Affairs, Veterans Health Administration. 2009.
12. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: terminology and definitions. *Value Health*. 2008 1;11(1):44–47. [PubMed: 18237359]
13. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. *Curr Med Res Opin*. 2009 9;25(9):2303–2310. [PubMed: 19635045]
14. American Medical Association. CPT® (Current Procedural Terminology) [Internet]. 2018 Available from: <https://www.ama-assn.org/practice-management/cpt-current-procedural-terminology>

15. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009 5 5;150(9):604–12. [PubMed: 19414839]
16. The World Health Organization (WHO) ATC/DDD Index 2018 [Internet]. Available from: https://www.whocc.no/atc_ddd_index/
17. Schafer JL, Graham JW. Missing data: our view of the state of the art. *Psychol Methods.* 2002 Jun;7(2):147–177.
18. Croxford R Restricted Cubic Spline Regression : A Brief Introduction. *Proc SAS Glob Forum 2016 Conf Cary NC SAS Inst Inc* [Internet]. Available from: <http://support.sas.com/resources/papers/proceedings16/5621-2016.pdf>
19. Franklin JM, Eddings W, Austin PC, Stuart EA, Schneeweiss S. Comparing the performance of propensity score methods in healthcare database studies with rare outcomes. *Stat Med.* 2017 5;36(12):1946–1963. [PubMed: 28208229]
20. Rose AJ, Berlowitz DR, Manze M, Orner MB, Kressin NR. Intensifying therapy for hypertension despite suboptimal adherence. *Hypertension.* 2009 9;54(3):524–529. [PubMed: 19581506]
21. Quilliam BJ, Ozbay AB, Sill BE, Kogut SJ. The association between adherence to oral antidiabetic drugs and hypoglycaemia in persons with Type 2 diabetes. *Diabet Med.* 2013;30(11):1305–1313. [PubMed: 23586474]
22. Hsu KL, Fink JC, Ginsberg JS, Yoffe M, Zhan M, Fink W, et al. Self-reported Medication Adherence and Adverse Patient Safety Events in CKD. *Am J Kidney Dis.* 2015 10;66(4):621–629. [PubMed: 25979348]
23. National Center for Veterans Analysis and Statistics. Veteran Population. [Internet] Available from: https://www.va.gov/vetdata/veteran_population.asp

Novelty statement:

- Providers often intensify antihyperglycemic treatment for individuals with type 2 diabetes mellitus based on laboratory measurements without accurate assessment of adherence, potentially exposing those with low adherence to a more intensive regimen than necessary.
- This retrospective cohort study, which included incident users of metformin intensifying treatment, found that recent low adherence to metformin monotherapy was not associated with hypoglycaemia in the year following intensification with a sulphonylurea.
- While it is important for providers to evaluate medication adherence, this study does not suggest that intensifying treatment in the presence of recent nonadherence is associated with a higher risk of hypoglycaemia.

Figure 1.
Flowchart of eligible study participants

Figure 2.

Association of adherence and risk of hypoglycaemia in the year following metformin intensification, following multiple imputation and adjusting for baseline covariates; adherence is modelled as a continuous variable using restricted cubic splines, with median adherence (87%) as the reference

Table 1.

Characteristics of study participants before and after propensity score weighting

Characteristic *	Full cohort N=49,424			Weighted cohort N=34,385		
	Recent Low Adherence to Metformin N= 21,419	Recent High Adherence to Metformin N= 28,005	SD†	Recent Low Adherence to Metformin N=17,186	Recent High Adherence to Metformin N= 17,199	SD†
Age, years, median (IQR)	62 (56, 71)	64 (59, 72)	0.16	63 (57, 72)	63 (57, 72)	0.002
Women (%)	4.9	3.6	0.07	4.2	4.2	<0.001
Race, (%)						
Black	16.2	9.1	0.21	12	12.4	<0.001
Hispanic/ Other	5.3	3.6	0.08	4.5	4.5	0.001
Available %	91.3	92.2	0.03	91.6	91.6	<0.001
Days on metformin monotherapy, median (IQR)‡	748 (277, 1377)	913 (484, 1501)	0.21	847 (370, 1437)	744 (379, 1414)	<0.001
Initiated glibenclamide (%)	38.8	36.5	0.05	37.6	37.8	0.004
Sulphonylurea initial dose, DDD, median (IQR)	0.5 (0.5, 1.0)	0.5 (0.3, 1.0)	0.08	0.5 (0.5, 1.0)	0.5 (0.4, 1.0)	0.001
HbA _{1c} , mmol/mol, median(IQR) [% , median (IQR)]	59 (51, 71) [7.5 (6.8, 8.6)]	56 (50, 64) [7.3 (6.7, 8.0)]	0.24	57 (50, 67) [7.4 (6.7, 8.3)]	57 (50, 66) [7.4 (6.7, 8.2)]	0.004
Available %	90.7	92.5	0.07	99.7	99.7	0.002
Low density lipoprotein, mmol/L, median (IQR)	2.1 (1.7, 2.6)	2.4 (1.9, 3.1)	0.33	2.3 (1.8, 2.9)	2.3 (1.8, 2.9)	0.001
Available %	82.7	86.2	0.10	99.6	99.6	0.002
Glomerular filtration rate (ml/min), median (IQR)	82 (66, 99)	80 (65, 95)	0.10	80 (65, 97)	80 (65, 97)	0.005
Available %	88.2	89.4	0.04	99.7	99.7	0.001
Creatinine, umol/L, median (IQR)	88 (80, 106)	88 (80, 106)	0.03	88 (80, 106)	88 (80, 106)	0.004
Systolic blood pressure, mm/Hg, median (IQR)	133 (122, 144)	132 (121, 142)	0.08	132 (122, 144)	132 (122, 143)	<0.001
Diastolic blood pressure, mm/Hg, median (IQR)	77 (69, 84)	76 (68, 82)	0.13	76 (69, 83)	76 (69, 83)	0.003
Available %	98.4	98.9	0.04	99.9	99.9	0.003
Body mass index (kg/m ²), median (IQR)	31.9 (28.3, 36.2)	32.1 (28.6, 36.4)	0.03	31.9 (28.4, 36.2)	31.9 (28.4, 36.3)	0.002
Available %	97.5	98.3	0.06	99.9	99.9	0.003
Proteinuria (%)			0.06			0.004
Negative	50	51		50	50	
Trace to +4	18	18		18	18	
Not tested or no result	32	31		32	32	
Baseline Co-morbidities (%)						
Malignancy	6	6	0.03	6	6	0.001
Liver/ respiratory failure‡	1	1	0.03	1	1	0.001
HIV	0.3	0.3	0.02	0.3	0.3	<0.001
Congestive heart failure	6	6	0.01	6	6	0.001
Cardiovascular disease	22	25	0.06	24	24	0.001

Characteristic *	Full cohort N=49,424			Weighted cohort N=34,385		
	Recent Low Adherence to Metformin N= 21,419	Recent High Adherence to Metformin N= 28,005	SD [†]	Recent Low Adherence to Metformin N=17,186	Recent High Adherence to Metformin N= 17,199	SD [†]
Serious mental illness	18	18	0.001	18	18	0.002
Smoking	14	12	0.04	13	13	0.001
Obstructive pulmonary disease/ asthma	13	14	0.03	13	13	<0.001
Cardiac valve disease	2	2	0.01	2	2	0.001
Arrhythmia	8	9	0.03	8	8	0.001
Parkinson's	0.4	0.5	0.004	0.5	0.5	<0.001
Osteoporosis	2	2	0.10	2	2	<0.001
History of falls/ fractures	1	1	0.04	1	1	0.001
Oxygen use	0.3	0.3	0.01	0.3	0.4	0.001
Use of Medications (%)						
ACE Inhibitors	60	65	0.11	62	63	0.001
ARBs	11	13	0.08	12	12	0.001
Calcium channel blockers	24	27	0.07	26	26	0.001
Beta blockers	42	49	0.14	46	45	0.004
Other anti-hypertensive medications	23	27	0.09	24	24	0.003
Statin and other lipid lowering agents [†]	69	80	0.26	74	74	0.001
Antiarrhythmics, digoxin and inotropes	2	2	0.02	2	2	<0.001
Anticoagulants, platelet inhibitors	6	7	0.06	6	6	0.002
Nitrates	11	13	0.06	12	12	<0.001
Aspirin	21	23	0.04	22	22	0.002
Thiazide/potassium-sparing diuretics	36	41	0.09	38	38	0.002
Loop Diuretics	12	14	0.05	13	13	0.001
Antipsychotics	8	8	0.02	8	8	<0.001
Oral glucocorticoids	12	13	0.05	12	12	0.001
Alpha blockers	14	18	0.10	16	15	0.002
Indicators of Healthcare Utilization						
Hospitalized at VA in last year (%)	13	11	0.06	8	8	0.001
Hospitalized at VA in prior 90 days (%)	5	5	0.03	4	4	0.001
Nursing home encounter (%)	0.04	0.04	0.001	0.04	0.04	0.001
Outpatient visits, median (IQR)	6 (3, 10)	6 (4, 10)	0.04	6 (3, 10)	6 (3, 10)	0.002
Medicare utilization	25	27	0.04	26	26	<0.001
Medicaid utilization	10	9	0.03	10	10	0.001
Number of outpatient medications, median (IQR)	12 (8, 16)	13 (9, 18)	0.21	12 (9, 17)	12 (9, 17)	0.003
Year of Metformin Initiation			0.05			0.002

Characteristic *	Full cohort N=49,424		SD †	Weighted cohort N=34,385		SD †
	Recent Low Adherence to Metformin N= 21,419	Recent High Adherence to Metformin N= 28,005		Recent Low Adherence to Metformin N=17,186	Recent High Adherence to Metformin N= 17,199	
2001–2002	4.4	4.5		4.5	4.5	
2003	17.7	17.9		17.6	17.6	
2004	19.5	20.4		19.8	19.8	
2005	21.2	22.1		21.6	21.6	
2006	21.6	20.7		21.4	21.5	
2007	15.6	14.2		15.1	15.0	

* Abbreviations: interquartile range (IQR), standardized differences (SD), angiotensin converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB)

† Standardized differences (SD) are reported. Standardized differences are the absolute difference in means or percent divided by an evenly weighted pooled standard deviation, or the difference between groups in number of standard deviations.

‡ Days on metformin monotherapy is an approximation of the duration of diabetes since participants were free of all hypoglycemic medications for 180 days prior to starting metformin.

Table 2.

Adjusted hazard ratio and 95% confidence intervals for the risk of hypoglycaemia among low adherence participants versus high adherence participants

	Low adherence	High adherence
Primary analysis	N=21,419	N=28,005
First hypoglycaemia events	456	644
Person-years	19,707	26,316
Unadjusted rate/1000 person-years (95% CI)	23.1 (21.1, 25.4)	24.5 (22.7, 26.4)
Adjusted hazard ratio [†] (95% CI)	0.95 (0.84, 1.08)	Ref
Subgroup analysis by sulphonylurea type		
Glibenclamide	N=8,309	N=10,223
First hypoglycaemia events/ person-years	180/7,801	260/9,781
Unadjusted rate/1000 person-years (95% CI)	23.1 (19.9, 26.7)	26.6 (23.5, 30.0)
Adjusted hazard ratio [†] (95% CI)	0.89 (0.72, 1.10)	Ref
Glipizide or glimepiride	N=13,110	N=17,782
First hypoglycaemia events/ person-years	276/11,907	384/16,535
Unadjusted rate/1000 person-years (95% CI)	23.2 (20.6, 26.1)	23.2 (21.0, 25.7)
Adjusted hazard ratio [†] (95% CI)	1.00 (0.84, 1.18)	Ref
Subgroup analysis by sulphonylurea dose		
DDD ≥ 1	N=7,248	N=8,611
First hypoglycaemia events/ person-years	161/6,577	220/8,038
Unadjusted rate/1000 person-years (95% CI)	24.5 (21.0, 28.6)	27.4 (24.0, 31.2)
Adjusted hazard ratio [†] (95% CI)	0.94 (0.75, 1.18)	Ref
DDD<1	N=14,171	N=19,394
First hypoglycaemia events/ person-years	295/13,130	424/18,278
Unadjusted rate/1000 person-years (95% CI)	22.5 (20.0, 25.2)	23.2 (21.1, 25.5)
Adjusted hazard ratio [†] (95% CI)	0.96 (0.82, 1.13)	Ref

* Primary analysis does not require persistence on metformin, but participants are censored after 180 days without VHA contact or if they fill a third antihyperglycemic agent

[†]Propensity score weighted (with matching weights), covariate-adjusted hazard is derived from Cox proportional hazards model for time to outcome, adjusting for baseline covariates