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Weight change after initiation of oral hypoglycemic monotherapy for diabetes predicts 5-year mortality: an observational study

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Abstract

Purpose—To investigate whether weight change in the first year after initiating an oral hypoglycemic agent (OHA) for type 2 diabetes treatment is associated with mortality in a national cohort.

Procedures—We prospectively followed Veterans Health Administration patients with type 2 diabetes initiating treatment with an OHA and not receiving any other diabetes pharmacotherapy for at least one year. Information on OHAs, weight, co-morbidities, other medications, demographics, and laboratory measurements was obtained from electronic medical records. Logistic regression was used to estimate 5-year mortality odds by weight change during the first year after OHA treatment initiation.

Findings—Patients (mean age 65 years, 97% male, mean BMI 32.3 kg/m²) initiating OHA monotherapy between 2003–8 totaled 145,198 (metformin n=89,111, glipizide n=27,100, glyburide n=25,226, rosiglitazone n=3,761). Most patients (65%) maintained a stable weight (change ≤ 5% from baseline) during the first year after OHA initiation. Those losing > 5% of baseline weight had a significantly higher odds of death over the subsequent 5-years ranging from

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Conflicts of Interest

None.

Contribution Statement

B.M.K. developed the research question, researched the data, and wrote the manuscript. E.J.B. and K.P.M. assisted in the development of the research question, reviewed/edited the manuscript, and researched the data. N.L.S. assisted in the development of the research question and reviewed/edited the manuscript. All authors reviewed and approved this final version of the manuscript.

1.64 to 2.13 depending on OHA type. In the metformin group, weight gain > 5% of baseline was also associated with higher odds of 5-year mortality. The same results were obtained after conducting three sensitivity analyses that excluded patients for the following reasons: weight loss in the one year prior to OHA initiation, weight change > 100 lbs, or weight change > 50 lbs.

Conclusions—Weight loss was associated with higher odds of 5-year mortality among patients initiating an OHA, as was weight gain for metformin only.

Keywords

Weight change; oral hypoglycemic medication; mortality; epidemiology; prospective research

1. Introduction

Oral hypoglycemic agents (OHAs) are the most common initial pharmacologic treatments for type 2 diabetes. These medications are known to be associated with changes in weight. The most common choices for initial treatment are metformin or sulfonylureas (1). Metformin is typically associated with weight loss of 1-2 kg over the first year (2, 3). The other agents are associated with a weight gain over the first year (approximately 1.5 kg for sulfonylureas and 1.5-2.5 kg for thiazolidinediones) (2, 3).

Although patients often have changes in their weight after initiating a medication to treat type 2 diabetes, little is known about whether this weight change is associated with diabetes outcomes, including mortality. One report examined the association between weight change and mortality after the initial diagnosis of diabetes, but there were several methodological limitations that diminished the interpretability of the results including lack of adjustment for important confounding factors and the inability to measure weight change from the initiation of glucose lowering medications in a high proportion of study patients (4).

Given the lack of information in the literature on whether weight changes following the initiation of commonly used OHAs for type 2 diabetes treatment predict outcomes of this disease, we investigated the relationship between weight change during the first year of treatment with an OHA and the 5-year cumulative risk of mortality in a national cohort of US veterans. Since weight reduction is recommended in overweight or obese patients who develop type 2 diabetes, we were interested in whether a mortality benefit might exist among patients who fulfilled this recommendation (5).

2. Methods

2.1 Research design and setting

We assembled a new-user cohort study of US veterans receiving healthcare from the Veterans Health Administration (VHA) who initiated monotherapy with an OHA. VA Puget Sound Health Care System Institutional Review Board reviewed and approved this research.

2.2 Data source

A national electronic medical record captures information from all medical care delivered and prescriptions dispensed within VHA facilities. Demographic, comorbidity, laboratory,

and medication use data from January 1, 2003 to December 31, 2013 were obtained from the VHA national databases. Baseline co-morbidities were identified using ICD-9 codes from outpatient visits at VHA facilities in the year prior to initiation of an OHA. The most recent laboratory results within the year before OHA initiation were used in our analysis for baseline labs, and the hemoglobin A1c level (A1c) closest to the date one year after medication initiation was used as the A1c at 1-year follow-up. Medication use was obtained from pharmacy records.

2.3 Cohort Entry Inclusion Criteria

Veterans enrolled in the VHA between January 1, 2004 and December 31, 2007 who received a new prescription for a sulfonylurea (glipizide or glyburide), metformin, or rosiglitazone were eligible for this analysis. Follow-up of patients commenced one year after the initial prescription for an OHA and ended on December 31, 2013 or at the time of death, whichever occurred first.

2.4 Exclusion criteria

To capture new users of OHAs, we excluded patients with any prior prescriptions for hypoglycemic medications. The VHA provides a pharmacy benefit to eligible participants that exceeds what is available in some other U.S. health plans. As it is possible to enroll in multiple U.S. health plans, some participants use the VHA for the pharmacy benefit but receive most of their clinical care in another setting. To eliminate subjects using the VHA only for pharmacy services and not for healthcare visits, patients were excluded if they had not received prescriptions for non-diabetes medications in the year prior to the first OHA prescription. For this same reason, we excluded patients who did not have an outpatient visit to a VHA facility in the year prior to the initial OHA prescription. We also excluded patients who initiated multiple hypoglycemic agents concurrently and those requiring additional hypoglycemic agents within the first year of therapy as our aim was to assess weight change among those on OHA monotherapy for one year.

2.5 Exposures

OHA monotherapy included new users of a sulfonylurea (glipizide or glyburide), metformin, or rosiglitazone. The key exposure of interest was weight change in the first year after starting an OHA. Follow-up time for mortality started one year after OHA initiation. Weight was captured at three time points: one year prior to OHA initiation, at the time of initiation, and one year after diabetes medication initiation. The weight recorded closest to each of these time points was used in our analysis. Weights were considered to be potentially erroneous if they were recorded as <100 pounds or >500 pounds and were excluded. The weight change over the first year was calculated weight at one year after initiation minus weight at the time of OHA initiation. Height was recorded as the median of all values. BMI was calculated as weight in kilograms divided by height in meters squared. All covariates considered were measured at the time of OHA initiation unless otherwise mentioned.

2.6 Outcome

Mortality status and date of death was obtained from VA Vital Status files through December 31, 2013. Accuracy of death ascertainment using these files is similar to the National Death Index (6). Cause of death is not available within these files. The main outcome of interest in this analysis is 5-year mortality cumulative risk.

2.7 Statistical Analysis

Unadjusted and adjusted odds ratios (ORs) and 95% CIs were calculated using logistic regression with 5-year mortality as the dependent variable. We did not employ the Cox proportional hazards model for analysis of our data due to violation of the proportional hazards assumption. Our final multivariable logistic regression models included many covariates to adjust for potential confounding: demographic characteristics, co-morbidities, alcohol consumption, tobacco use, use of other medications, and laboratory measurements. In particular, we considered and adjusted for the use of other medications known to be associated with weight changes (mainly cardiac and mental health medications) as well as co-morbid conditions that potentially might result in weight loss as shown in Supplemental Table S1. All analyses were performed with stratification by initial OHA (glipizide, glyburide, metformin, or rosiglitazone) to eliminate the possibility of confounding due to differential associations between weight change and mortality by type of pharmacotherapy. The variance inflation factor (VIF) was used to assess the potential for multicollinearity, but all multivariable models exhibited a $VIF < 4$, indicating that multicollinearity was unlikely. A test for first order multiplicative interaction in multivariable logistic regression models was performed to assess whether associations between one-year weight change categories and mortality differed by level of baseline BMI categories. A significant interaction would suggest that the level of general adiposity at baseline as measured by BMI alters the association between weight change and mortality.

To determine whether a non-linear association between weight change and mortality existed, we used restricted cubic spline models with 4 knots for assessment of the relationship between the continuous weight change variable and 5-year cumulative mortality risk (Supplemental Figure 1) (7). Since weight change was significantly associated with 5-year mortality in a non-linear manner, we transformed the variable into categories of weight stability, loss, and gain. A cutoff of 10 pounds was used for absolute weight change and a cutoff of 5% was used for proportional weight change, with stable weight defined as a change of no more than ± 10 pounds or $\pm 5\%$. Sensitivity analyses were performed with exclusions based on different cutoffs for plausible 1-year weight changes (± 100 lbs, ± 50 lbs), since very large gains or losses could potentially indicate other medical problems or improperly recorded data. A sensitivity analysis was also performed with exclusion of patients who lost weight during the year prior to medication initiation since these patients may have had other underlying conditions that would predispose them to earlier mortality and further weight loss during follow-up. All analyses were performed using Stata version 14 (College Station, TX, USA).

3. Results

A total of 200,131 patients received an initial OHA prescription between January 1, 2004 and December 31, 2007. After exclusions were made, our final cohort consisted of 145,198 patients who initiated pharmacotherapy for diabetes with an OHA and who received no other diabetes pharmacotherapy during the first year of treatment (Figure 1). The majority of patients were started on metformin for the initial management of their diabetes (61.4%), with sulfonylureas as the next most common choice (18.7% started on glipizide and 17.4% on glyburide), followed by a smaller number starting on rosiglitazone (2.6%). Other OHAs were excluded from our study due to their small sample size. The cumulative mortality rate at 5 years was 20.4% after the first treatment year. During the first year of treatment, 3,644 deaths occurred, with the following mortality risk by medication during this time interval: metformin 1.4%, glipizide 4.8%, glyburide 4.0%, and rosiglitazone 3.5%. Characteristics of study patients and co-morbidities and medication use by type of OHA monotherapy are shown in Table 1 and Supplemental Table S1, and by weight change during the one-year follow-up in Supplemental Table S2. The lower risk of death associated with metformin might be explained at least in part by the younger mean age of these participants as well as a lower prevalence of heart and kidney disease in this group (Table 1 and Supplemental Table S1). All variables had less than 10% missing information except race, A1c at medication initiation, and baseline cholesterol levels, where missing data ranged from 14 to 23%. Weight measurements were taken on average 79 days prior to OHA initiation and 112 days after the end of the one year period following OHA initiation.

The mean weight in all patients at OHA initiation was 219.9 pounds and the mean weight after 1 year of medication exposure was 216.6 pounds. Most patients maintained a stable weight during this 1-year time period based on an absolute weight change between -10 to +10 pounds. Metformin users had a decreased average weight one year after medication initiation compared with small average weight increases in the other medication groups. Overall average A1c level decreased from 7.2% to 6.7% during the first year of OHA use, and was of similar magnitude across the different medications one year after OHA initiation (Table 1).

In univariate analyses (Table 2), stable weight measured either absolutely or proportionally was associated with lower risk of mortality for most of the comparisons. Patients had higher odds of 5-year mortality associated with weight loss of more than 10 pounds or a proportional loss of greater than 5% during the first year for all medications. Patients who initiated metformin and glipizide and gained more than 5% body weight had higher odds of 5-year mortality, while an absolute weight gain of more than 10 pounds was associated with a higher 5-year mortality risk among metformin initiators but a lower risk among glyburide and rosiglitazone initiators. Kaplan-Meier survival curves of proportional weight change for each medication demonstrate lower 5-year mortality among the stable weight group as well as better overall survival in the metformin group (Figure 2). Additional unadjusted analyses found lower odds of mortality with higher baseline BMI and non-white race for each OHA. Older age at baseline was significantly associated with higher 5-year mortality in all medication groups, while the same was true for male sex except for rosiglitazone initiators. A non-linear association was seen between both absolute and proportional weight change

over one year and mortality, as shown in plots of the restricted cubic spline models (Supplemental Figure S1).

Adjustment for multiple covariates in logistic regression models confirmed higher odds of 5-year mortality with weight loss in the first year after medication initiation for all medications, as defined by either proportional or absolute weight change (Table 3).

Associations between these multiple covariates and odds of 5-year mortality are shown in Supplemental Table S3. In the metformin group, weight gain was also associated with higher odds of 5-year mortality compared to stable weight, but no significant association was seen between absolute or proportional weight gain and mortality in the other medication groups. These findings persisted when sensitivity analyses were performed to exclude patients who had the largest weight gains or losses using two different cut-points for implausible weight change as shown in Table 3.

We assessed the presence of interaction between baseline BMI categories and weight change categories as shown in Table 2 during the first year after medication initiation in relation to the odds of 5-year mortality (Supplemental Figure S2). This interaction was only significant in the metformin group. Among patients on metformin, the higher risk of mortality associated with weight loss diminished with baseline BMI of 35 kg/m² or greater.

We also performed a sensitivity analysis excluding patients from the analysis who lost weight during the year prior to medication initiation. During the year prior to medication initiation, participants gained 1.4 pounds on average, but 44% of them lost weight, with the average weight loss being 8.1 pounds. These results were not different compared to those from the main analysis.

4. Discussion

Our results indicate that weight loss in the year after OHA initiation was associated with higher odds of 5-year mortality among a national study of U.S. veterans in analyses adjusted for multiple potential confounding variables, including co-morbidities including renal disease, use of other medications, laboratory measurements, and demographics. We performed a sensitivity analysis to test whether our findings were indicative of continued weight loss that preceded the initiation of an OHA but did not find that the results changed after excluding patients with weight loss during the one year prior to OHA initiation, arguing against the weight loss occurring after OHA initiation merely reflecting a process that had begun prior to starting treatment for diabetes. This finding represents another paradox with regard to weight and mortality, but this time in reference to weight change, as weight loss is generally recommended to persons with new onset type 2 diabetes due to the association between overweight/obesity and hyperglycemia, and would therefore be expected to predict better clinical outcomes. Our multivariable analyses found that weight stability during the year after OHA initiation was associated with lower odds of 5-year mortality. Significantly higher odds of 5-year mortality with weight gain compared to those maintaining a stable weight was only seen in metformin initiators. These associations did not vary by baseline BMI, except for metformin initiators, where the higher risk of mortality associated with weight loss was attenuated with greater baseline BMI, and did not appear

present in those with Class 2 obesity or greater at baseline. For initiators of glipizide, glyburide, and rosiglitazone monotherapy, though, the association between weight loss and higher risk of mortality was seen across the range of baseline BMI.

Most prior research examining the association between weight and mortality in patients with type 2 diabetes has focused on a static, one-time, weight measurement and not weight change, and was typically not limited to patients with newly diagnosed diabetes or newly initiating an OHA. These studies have reported conflicting results, but most often have identified a lower risk of mortality in patients with type 2 diabetes with BMI in the overweight or mildly obese category (8–12). Similar conflicting findings have been reported by studies that have specifically examined the association between BMI at the time of type 2 diabetes diagnosis and mortality, with several reports demonstrating the lowest risk of mortality among the overweight or mildly obese at the time of diagnosis (13, 14). However, a recent study found no difference in risk of mortality in overweight or obese patients compared to normal weight patients with newly diagnosed type 2 diabetes (15).

To our knowledge, only one prior longitudinal study has specifically examined the association between weight change and mortality in patients with newly diagnosed type 2 diabetes (4). This study included 8486 Swedish patients followed over a median of 4.6 years and found higher risks of both all-cause and cardiovascular mortality with an increased BMI during the 18 months after the diagnosis of diabetes but no difference in risk among those losing weight compared to those with stable BMI (4). However, this study included a heterogeneous group of patients receiving a variety of treatment regimens ranging from lifestyle change only to insulin plus oral agents. Furthermore, almost one-third of patients were already taking a glucose lowering agent at the time of diabetes diagnosis, precluding the ability to assess weight change from the initiation of these pharmacologic treatments (4). Also, bias due to confounding could not be excluded as adjustments were not performed for type of diabetes medication treatment, since weight is known to be affected by most medications used to treat diabetes, or for smoking status, which is also an important predictor of mortality as well as a known factor in determining body weight (16, 17). We avoided the issues present in this study by adjusting for multiple potential confounding factors, and by restricting our study to patients newly initiating one OHA and not receiving any additional pharmacologic treatment for diabetes for one year.

In patients with pre-existing type 2 diabetes, a few prior studies have investigated the association between weight change and mortality. Most of these were conducted prior to the modern era of diabetes management emphasizing tighter glycemic control and are therefore less applicable to current clinical practice (18). One of these studies found a higher hazard ratio for all-cause mortality in both men and women with pre-existing diabetes who lost 10 or more pounds over a 10-year period (19). A more recent study examined this association in patients with pre-existing cardiovascular disease and pre-existing type 2 diabetes (9). Weight loss was associated with a higher risk of mortality, with a hazard ratio of 1.13 per 1% loss of body weight (95% CI: 1.11 to 1.16) (9). This association was even stronger among patients who lost 7.5% of body weight (9). This study included patients on a wide range of treatments for pre-existing type 2 diabetes and did not control for treatment regimen, which

is an important potential confounder given the known effect of most hypoglycemic regimens on weight gain or loss.

Although seemingly paradoxical, several possible explanations exist for the association between weight loss and higher odds of mortality. The initial treatment recommendation for patients with diabetes is lifestyle changes, including both diet and exercise modifications (5). Patients who are unsuccessful in achieving glycemic treatment targets with these measures are then prescribed an OHA. The fact that our study population initiated treatment with an oral hypoglycemic medication likely indicated that they had demonstrated difficulties with improving their diabetes through lifestyle modifications. Therefore, the weight loss that occurred after starting a medication may indicate a different process than weight loss through lifestyle measures prior to requiring a medication. Patients who were diagnosed with diabetes and were able to adequately manage their disease through lifestyle modification would have been excluded, thereby creating a selection filter. Weight loss in our study population might therefore reflect a process potentially related to a pharmacologic effect associated with the initiation of the oral hypoglycemic medication. Patients tend to have modest weight changes on average as a known side effect from starting an OHA, so a weight loss of more than 10 pounds or more than 5% may indicate an underlying issue beyond the typical response. We attempted to adjust for serious undiagnosed medical problems related to weight loss through our sensitivity analysis excluding patients who lost weight in the year prior to starting an OHA. We also adjusted for smoking and many comorbid conditions potentially related to weight change and mortality, but the potential for residual confounding remains.

Unintentional weight loss has a graver prognosis than an intentional weight reduction (20). Given the size of our population, a medical record review to determine whether weight loss was intentional or unintentional was not feasible. Prior studies have found that unintentional weight loss is associated with higher risk of mortality, but that intentional weight loss is typically associated with lower risk of mortality unless the weight loss is large (>70 pounds) (20–22). Some of the prior studies also reported that intentional weight loss provided a mortality benefit among patients with diabetes, but this effect did not persist when analyzing populations where the intention to lose weight was not known (20, 21). However, whether unintentional weight loss due to any cause has the same dire prognosis is not known, for example, in response to the initiation of an oral hypoglycemic medication. The reason for the association between weight loss and higher risk of mortality in our data is not clear, but may be related to intentionality of weight loss.

Weight gain predicted higher mortality in the metformin group only. There is evidence from the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Studies that low adherence to this medication was associated with weight gain, although this effect only became apparent after about 6 years of follow-up (23). Thus, weight gain while taking metformin may be a marker for low adherence, which has been reported to be associated with higher mortality in a study of medication adherence to OHA in Quebec, Canada (24). Weight gain among metformin users might also reflect lesser adherence to healthy lifestyle recommendations regarding diet and exercise for type 2 diabetes management. Weight gain

with the other medications we examined would not be expected to indicate nonadherence, given that sulfonylureas and rosiglitazone promote weight gain rather than loss.

Our study had several strengths. By restricting our analysis to patients who received only one oral hypoglycemic medication for the first year of treatment, we aimed to reduce the heterogeneity found in other research where subjects may have received multiple medications for diabetes treatment including insulin. We were able to adjust for a large number of potential confounding factors given the high quality, universal medical record system in the VHA. The VHA mortality ascertainment file also has been shown to be highly accurate on a comparable level with the National Death Index (25). Our large sample size provided adequate power to assess our question of interest and also improves the generalizability of our findings since our population generally represents all veterans with diabetes who receive care from the VHA and demographically similar members of the U. S. population. As shown in Table 1 and Supplemental Table S1, there were notable differences in characteristics and comorbidities associated with mortality by oral hypoglycemic monotherapy, such as, for example, younger age, more prevalent tobacco use, and less prevalent coronary artery disease among metformin users. We therefore performed our analyses within strata defined by oral hypoglycemic medication, thereby removing the potential for bias due to the differing associations between these medications and mortality.

Our study was not without limitations. Cause of death is not available within the VHA records, and hence we were not able to establish whether higher mortality was due mainly to a few or many different causes. We did not have data on cardiorespiratory fitness, which is a possible confounder (26). We were not able to confirm that patients were actually taking their medication, only that they received a prescription for it. However, the accuracy of using an initial prescription as a proxy for ongoing medication use was addressed with a sensitivity analysis in an earlier paper from our group and was not found to alter the results (27). As discussed above, we were not able to determine the intentionality of weight loss. Since the study population consisted mainly of men, our findings may be less generalizable to women.

In conclusion, our findings can be viewed as paradoxical, since weight loss in the year following the initiation of OHA monotherapy was associated with higher odds of 5-year mortality and not an expected benefit. Weight stability in the year after initiating oral monotherapy was generally associated with lower odds of mortality. Metformin users who gained weight in the initial year of treatment had higher odds of mortality. The greater risk of death among metformin users who lost weight diminished with greater adiposity at baseline (Class 2 obesity or greater). The higher risk of mortality with weight loss for the sulfonylurea agents and rosiglitazone was seen across the entire range of baseline BMI. The reasons for the associations between the higher odds of 5-year mortality with weight loss in all treatments and with weight gain in metformin-treated patients are not readily apparent. Despite the absence of clear mechanistic explanations, these results are potentially useful in predicting long term outcomes after the initiation of OHAs. In addition, these results may help to stimulate further research on the associations between weight change and outcomes in type 2 diabetes, and additional insights may be gained by examining the intentionality of weight loss in relation to mortality, as well as specific causes of death.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Study flow chart.

Figure 2. Kaplan-Meier survival curves for proportional weight change stratified by initial hypoglycemic agent.

Table 1

Patient characteristics by oral hypoglycemic monotherapy

	Overall (SD) or %	Metformin	Glipizide	Glyburide	Rosiglitazone
Patients taking initial medication (n)	145198	89111	27100	25226	3761
5-year mortality (% of subjects)	20.4	14.2	32.2	28.6	26.7
Mean age, years (SD)	65.0 (11.4)	62.9 (10.9)	68.9 (11.4)	67.4 (11.5)	69.3 (10.8)
Sex, male (% of patients)	96.6	95.6	98.3	97.9	97.7
Race (% of patients)					
White	82.6	83.0	81.1	82.5	84.6
Black	14.3	13.8	16.1	14.4	12.6
Other	3.1	3.2	2.8	3.1	2.8
Mean A1c at medication initiation	7.2 (1.4)	7.2 (1.3)	7.3 (1.5)	7.5 (1.6)	6.8 (1.1)
Mean A1c at 1 year follow-up	6.7 (1.1)	6.6 (1.1)	6.7 (1.2)	6.8 (1.3)	6.5 (1.0)
Mean weight at medication initiation (lbs)	219.9 (45.9)	225.5 (46.4)	211.2 (44.0)	211.5 (43.9)	208.2 (42.1)
Mean weight at 1 year follow-up	216.6 (45.6)	219.6 (46.2)	211.5 (44.3)	212.3 (44.5)	209.3 (43.7)
Percent weight change (% of patients)					
Loss of >5%	25.1	29.7	18.6	16.4	17.3
Stable (−5% to +5%)	65.0	63.6	67.1	67.6	66.6
Gain of >5%	9.9	6.7	14.4	16.1	16.2
Absolute weight change (% of patients)					
Loss of >10 lbs	26.8	32.1	19.0	17.0	17.3
Stable (−10 to +10 lbs)	62.7	60.4	66.4	66.6	66.0
Gain of >10 lbs	10.5	7.5	14.6	16.4	16.7
BMI categories (% of patients)					
<25 kg/m ²	8.9	6.5	13.2	12.4	13.2
25-29.9 kg/m ²	31.0	28.1	35.7	35.4	36.2
30-34.9 kg/m ²	33.1	34.4	30.6	31.3	31.5
35-39.9 kg/m ²	17.0	19.1	13.5	13.8	13.0
40 kg/m ²	10.0	12.0	6.9	7.1	6.1

	Overall (SD) or %	Metformin	Glipizide	Glyburide	Rosiglitazone
Tobacco use diagnosis, %	23.1	24.7	20.3	21.4	13.4
Mean HDL at baseline	40.0 (11.6)	39.9 (11.3)	39.8 (12.3)	40.1 (11.9)	42.4 (12.3)
Mean LDL at baseline	103.2 (34.0)	104.5 (33.7)	100.2 (34.5)	102.1 (34.6)	98.6 (32.7)
Mean serum creatinine at baseline	1.12 (0.49)	1.04 (0.34)	1.31 (0.69)	1.21 (0.56)	1.33 (0.80)
Hypertension, %	81.4	80.5	84.0	81.6	82.0
Coronary artery disease, %	31.8	28.1	39.2	35.8	39.3
Myocardial infarction, %	6.9	6.2	8.5	7.7	6.6
Angina, %	4.2	4.0	4.9	4.4	3.9
Congestive heart failure, %	8.3	5.3	14.4	12.3	7.9
Peripheral vascular disease, %	8.4	6.9	11.5	10.2	9.9
Cerebrovascular disease, %	9.0	7.7	12.0	10.3	9.7

Table 2

Univariate logistic regression analyses of the relative odds of 5-year mortality by weight change for each diabetes monotherapy.

Initial oral hypoglycemic agent	Metformin			Glipizide			Glyburide			Rosiglitazone		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Percent weight change												
Loss of >5%	1.64	(1.75, 1.72)	<0.01	2.06	(1.92, 2.22)	<0.01	1.95	(1.80, 2.11)	<0.01	2.13	(1.74, 2.60)	<0.01
Stable (–5% to +5%)	ref			ref			ref			ref		
Gain of >5%	1.41	(1.30, 1.53)	<0.01	1.14	(1.05, 1.25)	<0.01	1.02	(0.93, 1.11)	0.70	0.92	(0.72, 1.17)	0.50
Absolute weight change												
Loss of >10 lbs	1.47	(1.41, 1.54)	<0.01	1.77	(1.65, 1.90)	<0.01	1.69	(1.56, 1.83)	<0.01	1.78	(1.45, 2.18)	<0.01
Stable (–10 to +10 lbs)	ref			ref			ref			ref		
Gain of >10 lbs	1.21	(1.12, 1.31)	<0.01	0.99	(0.91, 1.08)	0.86	0.87	(0.80, 0.95)	<0.01	0.70	(0.55, 0.90)	0.01
BMI categories												
<25 kg/m ²	ref			ref			ref			ref		
25-29.9 kg/m ²	0.45	(0.42, 0.48)	<0.01	0.46	(0.43, 0.50)	<0.01	0.49	(0.45, 0.54)	<0.01	0.45	(0.36, 0.57)	<0.01
30-34.9 kg/m ²	0.32	(0.30, 0.34)	<0.01	0.33	(0.31, 0.36)	<0.01	0.33	(0.30, 0.36)	<0.01	0.37	(0.30, 0.47)	<0.01
35-39.9 kg/m ²	0.27	(0.25, 0.29)	<0.01	0.27	(0.25, 0.30)	<0.01	0.29	(0.26, 0.33)	<0.01	0.33	(0.25, 0.45)	<0.01
40 kg/m ²	0.28	(0.26, 0.31)	<0.01	0.25	(0.22, 0.28)	<0.01	0.29	(0.25, 0.33)	<0.01	0.25	(0.16, 0.37)	<0.01
Weight at medication initiation	0.73	(0.72, 0.75)	<0.01	0.64	(0.62, 0.66)	<0.01	0.66	(0.64, 0.69)	<0.01	0.67	(0.61, 0.73)	<0.01
Weight at 1 year follow-up	0.72	(0.71, 0.74)	<0.01	0.63	(0.60, 0.65)	<0.01	0.65	(0.63, 0.67)	<0.01	0.65	(0.59, 0.71)	<0.01
Age, years	2.28	(2.23, 2.33)	<0.01	2.28	(2.21, 2.35)	<0.01	2.32	(2.25, 2.40)	<0.01	2.77	(2.50, 3.07)	<0.01
Sex (male)	2.65	(2.32, 3.03)	<0.01	1.67	(1.34, 2.08)	<0.01	2.15	(1.70, 2.72)	<0.01	1.29	(0.77, 2.16)	0.33
Race												
White	ref			ref			ref			ref		
Black	0.66	(0.61, 0.70)	<0.01	0.67	(0.61, 0.72)	<0.01	0.67	(0.61, 0.74)	<0.01	0.54	(0.40, 0.73)	<0.01
Other	0.60	(0.52, 0.69)	<0.01	0.72	(0.60, 0.86)	<0.01	0.61	(0.50, 0.75)	<0.01	0.78	(0.45, 1.33)	0.36

Table 3

Multivariable logistic regression analyses of the relative odds of 5-year mortality by weight change for each diabetes monotherapy, with sensitivity analyses that excluded subjects with less plausible changes in weight (± 100 lbs, ± 50 lbs).*

Medication	Metformin	Glipizide	Glyburide	Rosiglitazone
	Odds ratio of 5 year mortality (95% CI)	Odds ratio of 5 year mortality (95% CI)	Odds ratio of 5 year mortality (95% CI)	Odds ratio of 5 year mortality (95% CI)
Percent weight change				
Loss of >5%	1.43 (1.33, 1.53)	1.67 (1.48, 1.88)	1.90 (1.67, 2.17)	1.56 (1.05, 2.33)
Stable (−5% to +5%)	ref	ref	ref	ref
Gain of >5%	1.55 (1.37, 1.75)	1.09 (0.95, 1.25)	0.96 (0.83, 1.11)	1.02 (0.64, 1.60)
Absolute weight change				
Loss of >10 lbs	1.41 (1.31, 1.51)	1.64 (1.45, 1.85)	1.85 (1.62, 2.12)	1.63 (1.09, 2.44)
Stable (−10 to +10 lbs)	ref	ref	ref	ref
Gain of >10 lbs	1.49 (1.32, 1.68)	1.09 (0.94, 1.25)	0.95 (0.83, 1.10)	0.92 (0.58, 1.48)
Restricted to 100 lb weight change				
	Odds ratio of 5 year mortality (95% CI)	Odds ratio of 5 year mortality (95% CI)	Odds ratio of 5 year mortality (95% CI)	Odds ratio of 5 year mortality (95% CI)
Percent weight change				
Loss of >5%	1.42 (1.33, 1.53)	1.67 (1.48, 1.89)	1.91 (1.67, 2.18)	1.56 (1.05, 2.33)
Stable (−5% to +5%)	ref	ref	ref	ref
Gain of >5%	1.54 (1.36, 1.74)	1.10 (0.95, 1.26)	0.96 (0.83, 1.11)	1.02 (0.65, 1.61)
Absolute weight change				
Loss of >10 lbs	1.41 (1.31, 1.51)	1.64 (1.45, 1.86)	1.86 (1.62, 2.12)	1.63 (1.09, 2.44)
Stable (−10 to +10 lbs)	ref	ref	ref	ref
Gain of >10 lbs	1.48 (1.32, 1.68)	1.09 (0.95, 1.26)	0.95 (0.83, 1.10)	0.93 (0.58, 1.48)
Restricted to 50 lb weight change				
	Odds ratio of 5 year mortality (95% CI)	Odds ratio of 5 year mortality (95% CI)	Odds ratio of 5 year mortality (95% CI)	Odds ratio of 5 year mortality (95% CI)
Percent weight change				
Loss of >5%	1.42 (1.32, 1.52)	1.65 (1.46, 1.87)	1.90 (1.66, 2.17)	1.55 (1.04, 2.31)
Stable (−5% to +5%)	ref	ref	ref	ref
Gain of >5%	1.56 (1.37, 1.77)	1.08 (0.94, 1.25)	0.96 (0.83, 1.11)	1.03 (0.65, 1.62)
Absolute weight change				
Loss of >10 lbs	1.40 (1.31, 1.51)	1.62 (1.43, 1.83)	1.84 (1.61, 2.11)	1.61 (1.07, 2.41)
Stable (−10 to +10 lbs)	ref	ref	ref	ref
Gain of >10 lbs	1.50 (1.33, 1.70)	1.08 (0.94, 1.25)	0.96 (0.83, 1.10)	0.93 (0.58, 1.48)

* Analyses were adjusted for demographic characteristics including age (Table 1), co-morbidities including cardiovascular disease (Supplemental Table S1), alcohol consumption, tobacco use, use of other medications (Supplemental Table S1), baseline HDL concentration, baseline LDL concentration, baseline serum creatinine concentration, A1c level at the time of OHA initiation, and A1c level one year after OHA initiation.