

Impact of oral anti-hyperglycemic therapy on all-cause mortality among patients with diabetes in the Veterans Health Administration

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Objective: The objective of this analysis was to evaluate the impact of several classes of oral anti-hyperglycemic therapy relative to sulfonylurea monotherapy on all-cause mortality among a cohort of patients with diabetes from the Veterans Health Administration (VHA).

Research Design and Methods: A retrospective cohort study using data obtained from the VHA Diabetes Epidemiology Cohort was employed. Users of oral anti-hyperglycemic therapy were classified into the following cohorts: sulfonylurea monotherapy, metformin monotherapy, metformin + sulfonylurea, TZD use alone or in combination with other oral agents (TZD users), and no drug therapy. All-cause mortality was the outcome of interest. Multivariate mixed models incorporating a propensity score to account for imbalance among cohorts were used to estimate drug effects on mortality with associated 95% confidence intervals (95% CI).

Results: 39,721 patients with diabetes were included in the study. Adjusted odds ratios and 95% CIs for all-cause mortality were 0.87 (0.68, 1.10) for metformin monotherapy users, 0.92 (0.82, 1.05) for metformin + sulfonylurea users, 1.04 (0.75, 1.46) for TZD users, relative to sulfonylurea monotherapy users.

Conclusions: We did not find any significant drug effect on all-cause mortality for any oral treatment cohorts relative to sulfonylurea oral-monotherapy.

The most influential study designed to assess long-term microvascular and macrovascular outcomes in patients with type 2 diabetes was the United Kingdom Prospective Diabetes Study (UKPDS). This study was specifically designed to assess the effects of “intensive glycemic control” versus a more liberal treatment target on the cardiovascular and microvascular complications of type 2 diabetes.(1,2) Despite several shortcomings,(3) the UKPDS answered the question of whether intensive blood glucose control is beneficial for people with type 2 diabetes – it definitely is, especially with regard to microvascular complications.(2) However, the UKPDS was less conclusive regarding the impact of specific oral anti-hyperglycemic treatments targeting a lower HbA1c level on the risk of macrovascular complications and all-cause mortality. Furthermore, thiazolidinediones were not available during the time period of the UKPDS.

Since the publication of the primary findings from the UKPDS, several observational studies conducted in Europe and Canada has assessed the effect of diabetes drug treatment on mortality, but has produced conflicting results.(4-8) A commonality across most of the observational studies conducted to date is that it has been difficult to draw conclusions because of the high potential for confounding by indication; that is, the tendency for patients with more severe disease both to be exposed to more aggressive therapy and to be more likely to experience an adverse outcome. The

direct effect of drug exposure has also been difficult to ascertain as many of the long-term studies assessed drug exposure only once, and then assessed mortality many years later.

We had the opportunity to study these issues in a large cohort of U.S. veterans via the implementation of advanced techniques for limiting confounding by indication with adjustment for a number of confounding variables obtained from survey data as well as integrated longitudinal prescription and medical administrative data. Specifically, we evaluated the impact of several classes of anti-hyperglycemic therapy relative to sulfonylurea monotherapy on all-cause mortality among a cohort of patients with diabetes.

Research Design and Methods

We used existing Veterans Health Administration (VHA) data from the Diabetes Epidemiology Cohort (DEpiC) which is an ongoing study of virtually all VHA patients with diabetes since October, 1996. The creation of the DEpiC has been previously described.(9) (10) We restricted our study to those who responded to the 1999 Large Health Survey of Veteran Enrollees (LHSVE) between April, 1999 and April 2000.(11) The LHSVE selected a stratified random sample of over 1,500,000 VHA patients identified in the summer of 1999, representing nearly 43% of the entire VHA enrollee population. The core survey included questions on health status measured by the Veterans RAND 36-item Health Survey (VR-36); occurrence of medical and mental conditions; body mass index; and many socio-

demographic factors including health behaviors and social support. Vital status was ascertained from the Beneficiary Identification and Record Locator Subsystem (BIRLS) file, and data from CMS to ensure greater accuracy.

From the DEpiC integrated database, we selected those individuals that were at least 18 years old and alive as of December 31, 2000. In an effort to minimize the variability in glycosylated hemoglobin (HbA1c) lab assay methodology, we restricted our analyses to those patients that received care from medical facilities that used assays certified by the National Glycohemoglobin Standardization Program.(12)

We used a retrospective cohort design. Drug utilization information was available from October 1, 1998 – September 30, 2000 and mortality status was obtained from calendar year 2001. Each patient had a fixed 1-year ‘window of drug exposure’, followed by a 15-month period where drug exposure was not assessed prior to death or a randomly assigned study termination date. Current use of therapy was assessed during the ‘window of drug exposure’, irrespective of prior therapy. We included the criterion of surviving the 15 months after the ‘window of drug exposure’ due to the concern that many events may occur in the year or so prior to death that can influence treatment choice and outcomes, and that these influences may not represent a stable phase of care and long-term risks or benefits.

Overall, drug exposure was classified into the following cohorts: sulfonylurea monotherapy, metformin

monotherapy, metformin + sulfonylurea, TZD users, and no drug therapy. TZD users consisted of those on monotherapy (7%), those on TZD + sulfonylurea (64%), those on TZD + metformin (7%), and those on triple combination therapy (22%). There were few deaths in the various TZD sub-groups: TZDs alone (2 deaths), TZD + metformin (2 deaths), TZD + sulfonylureas (33 deaths), and TZD + metformin + sulfonylureas (11 deaths); therefore, these sub-groups were pooled (TZD users). Users of insulin either alone or in combination were excluded from all analyses. All doses and dosage forms were combined for each drug class. Users of sulfonylurea monotherapy made up the reference cohort for all analyses because of its large size and relevance to prior literature.

Patients within the VHA receive care from specific medical facilities, and in an effort to account for possible inter-correlation between patients in the same facility we used a mixed logit model for the mortality outcome where facility was treated as an independent cluster, and a random effect was added to the intercept.(13,14) From the mixed logit model, odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated to assess the relationship between drug use and mortality.

Adjustment for confounding factors was accomplished via the propensity score methodology.(15,16) The propensity score represents the likelihood of receiving one of the treatments given an individual’s characteristics. This method has the appeal of being able to control for many covariates in a very efficient

manner. The list of covariates that were assessed during the 'window of drug exposure' and included in the propensity score can be found in the Appendix

(<http://care.diabetesjournals.org>). To ease the complexity of using the propensity score methodology for an exposure variable that is not dichotomous we created five separate propensity scores, using logistic regression, for each of the treatment groups relative to the reference group. The c-statistic was used to test the performance of each propensity score model. The c-statistic is equivalent to the area under the receiver operating curve, and ranges from 0.5 to 1 with 1 indicating perfect prediction and 0.5 indicating a chance prediction. The generated propensity scores were then included as a covariate in the respective mixed logit models.

Several variables from the 1999 LHSVE had relatively high rates of missing (up to 8.4%), which were assumed to be at random.⁽¹⁷⁾ Incomplete lab profiles were also common, but may be due to the fact that a particular test was not done rather than an actual missing observation. Regardless, up to 25.2% did not have complete lab profiles. In an effort to preserve the sample size and enhance generalizability to the rest of the VHA population, we used an 'unavailable' category for several covariates, including several continuous covariates that were converted to nominal variables for this purpose.

Several sensitivity analyses were performed to evaluate the robustness of the design and analysis. It is possible that HbA1c is in the causal pathway between drug

treatment and mortality. In an effort to evaluate the effect of HbA1c, we performed the analysis without adjusting for HbA1c. Based on data from the LHSVE, the VHA was not the sole source of medical care for 44.8% of patients in this cohort; therefore, we also conducted an analysis that included only those that used the VHA as the sole source of medical care. We also used an alternative design in which the 'window of drug exposure' was fixed as October 1, 1998 through September 30, 2000, mortality was assessed in calendar year 2001, and the period between exposure and mortality was variable for each individual depending on the date of death or the random study termination date. An analysis excluding those with any missing information was also conducted.

Results

We identified 39,721 patients with diabetes that responded to the LHSVE and received care from 125 different medical facilities across the nation. Of these, 19,053 (48.0%) were in the reference (sulfonylurea monotherapy) cohort, 2,988 (7.5%) were metformin monotherapy users, 13,820 (34.8%) were users of metformin in combination with sulfonylureas, 675 (1.7%) were TZD users, and 3,185 (8.0%) were not on any anti-hyperglycemic therapy.

A selection of patient characteristics is presented in Table 1. Several variables indicate a possible selection bias (confounding by indication), suggesting that the more aggressive treatment cohorts (oral combination therapy with metformin and TZD users) had more advanced diabetes. Mean HbA1c was 6.6% for

those not on drug therapy, and was about 7% for both the sulfonylurea and metformin monotherapy cohorts, and was about 8% for the metformin + sulfonylurea combination and TZD users. In general, relative to the sulfonylurea monotherapy cohort, metformin + sulfonylurea combination users and TZD users had more advanced disease as indicated by several diabetes severity indicators including, diabetes duration, HbA1c, proportion of patients receiving care from a diabetes specialist, and the mean number of diabetes-related physician visits. On the other hand, sulfonylurea monotherapy users were the oldest (68.2 years), and had higher Charlson scores, higher LDL-C, higher creatinine, slightly worse health status, and a higher percentage of patients with a history of MI and CHF relative to metformin use either alone or in combination with sulfonylureas.

The c-statistics from the propensity score models were 0.69 for metformin users, 0.75 for metformin + sulfonylurea users, 0.85 for TZD users, and 0.71 for non-users. c-statistics between 0.7 and 0.8 are generally considered as acceptable and between 0.8 and 0.9 as excellent.(18) Since several of the propensity score model c-statistics were below 0.8, it is possible there may be residual confounding caused by some of the strongest predictors of drug use. Therefore, these variables were identified (age, diabetes duration, HbA1c, creatinine, diabetes-related physician visits, and utilization of lipid lowering and hypertension medications) and included in the subsequent multivariate analyses along with the propensity score to

control for any residual confounding imposed by these variables.

The highest unadjusted mortality rate was for the TZD user cohort (7.1%), and the lowest was among metformin monotherapy users (2.7%). The unadjusted logit models suggested that metformin monotherapy users, metformin + sulfonylureas users, and that not on drug therapy had a reduced risk of all-cause mortality; while TZD users experienced an increased risk of mortality. However, from the multivariate logit models, the risk of all-cause death was attenuated for all groups, and none remained statistically significant. (Table 2)

Table 3 contains the results of the various sensitivity analyses. After testing models without HbA1c, excluding those who may receive care outside the VHA, and evaluating an alternative study design, we found the original results were robust. In the alternate design the odds ratio for the TZD users changed direction, but was not significant, and was within the 95% confidence interval of the original analysis. When patients with incomplete data were excluded, sample sizes decreased substantially; there were 9,360 sulfonylurea monotherapy users, 1,607 metformin monotherapy users, 7,497 metformin + sulfonylurea users, 454 TZD users, and 1,596 that were not on any anti-hyperglycemic therapy. Despite the changes in sample size, the results are consistent with the original findings.

Conclusions

In this diabetic population of veterans, we found no significant drug effect on all-cause mortality. We had the unique ability to control for many

variables that are not typically available in database studies, including standardized lab values and several important patient-reported covariates and well-researched measures of comorbid conditions. Despite this, there may still have been some residual unmeasured confounding that we were unable to account for.

Previous research on the relationship between anti-hyperglycemic drug use and mortality has yielded mixed results. The UKPDS showed that among overweight patients, metformin reduced the risk of diabetes-related mortality and all-cause mortality vs. conventional therapy. However, metformin was also found to increase diabetes-related deaths and all-cause mortality when added to the maximum dose of sulfonylurea.(2) Several observational studies have also concluded that metformin, when added to sulfonylurea monotherapy increased the risk of all-cause mortality;(4-6) however, these studies may have been plagued by confounding by indication.(19) Our findings, which controlled for many potential confounding variables found no significant increase in mortality associated with metformin used alone or in combination with sulfonylureas. Recently, studies published by Johnson et al have concluded that metformin alone and in combination was associated with a reduced risk of mortality.(7,20) Our sample size and duration of follow-up may have limited our ability to detect any potential beneficial effect of drug therapy on all-cause mortality.

Several additional limitations should be recognized. The VHA

databases contain limited information on the use of non-VHA services; however, the DEpiC database used for this analysis does contain healthcare utilization information extracted from linked Medicare files through September, 2000. Given the generous pharmacy benefit in the VHA, the lower economic status of veterans compared to the general US population, and the lack of a Medicare pharmacy benefit during this study period, patients that required prescription pharmacotherapy probably filled their prescriptions at VHA pharmacies. Based on data from the LHSVE, the VHA was the sole source of medical care for 55.2% of patients in this cohort. When we limit our primary results to just those that used the VHA as the sole source of medical care, the direction and magnitude of the odds ratios do not change appreciably.

The accuracy of our findings are only as good as the data that are used to create them which can be a limitation with some sources of administrative databases. However, the agreement between information in the VHA administrative databases and written medical records has been reported to have adequate reliability for demographics (average kappa = 0.92), inpatient diagnoses (diabetes principal diagnosis kappa = 0.80, diabetes secondary diagnosis kappa = 0.82),(21) and several diabetes quality of care measures (HbA1c < 9.5% - kappa = 0.93; LDL < 130 - kappa = 0.83).(22) Also, the vital status ascertained through the BIRLS has been shown to be up to 94.5% accurate,(23) and when combined with CMS data, as was done for this study, is even higher.

A limitation of the dataset was the duration of retrospective data, hence our need to assess prevalent drug exposure during the 'window of drug exposure' only. We did evaluate the agreement between the mutually exclusive drug cohorts defined by utilization from October, 1998 to September, 1999 and from October, 1999 to September, 2000 and found that 88%, 71%, 71%, 91%, and 72% of sulfonylurea monotherapy users, metformin monotherapy users, metformin + sulfonylurea users, insulin users, and those on no drug therapy were classified the same in both years, respectively. TZD use was less consistent across years (31%) likely due to the availability of products during the time of this analysis. We also assessed the relationship between various levels of exposure of each drug class. When we limited the analysis to only those that used at least 90 days or 180 days of drug in the 12-month 'window of drug exposure', the conclusions did not change, suggesting our assumption that any indication of drug use for this prevalent cohort was a good indicator of chronic use.

It should be noted that troglitazone was introduced in January, 1997 but due to its association with severe liver toxicity, was withdrawn from the US market on

March 21, 2000. Most troglitazone users were switched to one of the other TZDs when it was removed from the market. These characteristics of the TZD market may have influenced prescribing practices around TZDs, but should not have impacted our multivariate results. Importantly, we found no excess mortality risk attributable to TZD use.

In conclusion, we found no significant drug effect on all-cause mortality for all oral treatment cohorts relative to sulfonylurea oral-monotherapy. The subject of future work should assess whether long-term exposure to oral anti-hyperglycemic medications have the potential to reduce all-cause or cause-specific mortality.

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Table 1 Select patient characteristics

	All Patients	Sulfonylurea monotherapy	Metformin monotherapy	Metformin + Sulfonylurea	TZD users†	No Drug
N	39,721	19,053	2,988	13,820	675	3,185
Age (years) ‡	66.9±10.1	68.2±10.0	64.9±10.2*	65.6±9.8*	67.1±9.4*	66.8±10.4*
Male (%)	98.0	98.3	96.9*	98.1	97.5	97.3*
Race (%)					*	
Black	12.7	12.6	12.7	13.2	8.7	11.8
White	78.4	78.6	78.7	77.5	80.9	80.0
Other	9.0	8.8	8.7	9.3	10.4	8.3
BMI (kg/m ²) ‡	29.9±5.3	29.6±5.2	30.4±5.5*	30.3±5.3*	30.7±5.5*	29.2±5.2*
Diabetes duration (%)			*	*	*	*
< 1 year ago	11.3	12.8	20.5	4.5	3.3	23.9
1 to 3 years ago	29.4	32.2	41.5	21.2	18.2	35.2
4 to 10 years ago	35.5	33.4	25.1	43.3	39.9	22.6
11 to 20 years ago	15.4	13.2	7.6	21.0	27.0	9.4
> 20 years ago	7.1	6.8	4.0	8.1	10.5	6.8
Missing	1.4	1.5	1.3	0.9	1.2	2.2
HbA1c (%)‡	7.4±1.4	7.2±1.3	7.0±1.2*	8.0±1.5*	7.9±1.4*	6.6±1.0*
Saw a diabetes specialist (%)	8.4	6.5	9.0*	10.0*	26.8*	7.9*
Diabetes-related physician visits‡	4.0±2.6	3.9±2.6	3.6±2.2*	4.4±2.6*	5.7±3.3*	3.6±2.2*
Anti-hypertensive meds (%)			*	*	*	*
None	11.3	10.3	13.6	10.9	4.9	18.2
One	23.1	21.7	25.4	24.2	16.0	26.0
More than one	65.6	68.0	61.1	64.9	79.1	55.8
Lipid lowering meds (%)	55.3	52.2	57.9*	60.1*	75.3*	46.5*
LDL-C (mg/dL)‡	108.4±28.1	108.8±28.2	107.7±27.4*	107.5±28.4*	109.4±29.2	109.6±26.9
Creatinine (mg/dL) ‡	1.15±0.48	1.21±0.57	1.06±0.25*	1.07±0.27*	1.37±0.59*	1.19±0.68
History of MI (%)	38.0	39.5	33.9*	36.7*	47.1*	36.4*
History of CHF (%)	11.6	13.6	7.0*	9.4*	21.0*	11.6*
SF-36V – MCS‡	44.4±13.3	44.2±13.2	45.1±13.6*	44.4±13.3	44.5±12.9	44.5±13.6
SF-36V – PCS‡	32.4±10.6	32.0±10.5	33.3±10.9*	32.6±10.5*	30.8±10.0*	33.0±11.1*
Charlson Score‡	2.2±1.5	2.3±1.6	1.9±1.3*	2.1±1.4*	2.7±1.6*	2.2±1.6*

‡ Means ± sd

† TZD use alone or in combination with other oral agents

* Significantly different from the Sulfonylurea monotherapy cohort; p-value <0.05 based on T-test for continuous variables and Chi-square test for categorical variables

Table 2 Unadjusted and adjusted odds ratios (95% confidence intervals) for all-cause mortality

	# deaths (%)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Sulfonylurea monotherapy	1,005 (5.3)	1.00	1.00
Metformin monotherapy	82 (2.7)	0.51 (0.40, 0.63)	0.87 (0.68, 1.10)
Metformin + Sulfonylurea	468 (3.4)	0.63 (0.56, 0.70)	0.92 (0.82, 1.05)
TZD alone or in combination w/ other oral agents	48 (7.1)	1.37 (1.02, 1.85)	1.04 (0.75 1.46)
No drug	132 (4.1)	0.78 (0.65, 0.94)	0.90 (0.74, 1.09)

* Adjusted for propensity score plus age, diabetes duration, HbA1c, creatinine, diabetes-related physician visits, and utilization of lipid lowering and hypertension medications

Table 3 Sensitivity analysis odds ratios (95% confidence intervals) for all-cause mortality

	Adjusted* (original) OR (95% CI)	Adjusted[†] (w/o HbA1c) OR (95% CI)	Adjusted* (VHA services only) OR (95% CI)	Adjusted* (Fixed 2yr exposure) OR (95% CI)	Adjusted* (Missing excluded) OR (95% CI)
Sulfonylurea monotherapy	1.00	1.00	1.00	1.00	1.00
Metformin monotherapy	0.87 (0.68, 1.10)	0.86 (0.68, 1.10)	0.93 (0.67, 1.29)	0.92 (0.72, 1.17)	0.76 (0.52, 1.18)
Metformin + Sulfonylurea	0.92 (0.82, 1.05)	0.95 (0.85, 1.08)	0.97 (0.82, 1.15)	0.94 (0.83, 1.06)	0.89 (0.75, 1.07)
TZD alone or in combination w/ other oral agents	1.04 (0.75, 1.46)	1.12 (0.81, 1.55)	1.14 (0.71, 1.81)	0.97 (0.70, 1.33)	1.18 (0.78, 1.77)
No drug	0.90 (0.74, 1.09)	0.88 (0.73, 1.07)	0.91 (0.70, 1.20)	0.86 (0.68, 1.10)	1.10 (0.85, 1.44)

* Adjusted for propensity score plus age, diabetes duration, HbA1c, creatinine, diabetes-related physician visits, and utilization of lipid lowering and hypertension medications

[†] Adjusted for propensity score (without HbA1c) plus age, diabetes duration, creatinine, diabetes-related physician visits, and utilization of lipid lowering and hypertension medications