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Thiazolidinedione Use is Associated with Improved All-Cause Mortality Compared with Sulfonylureas Among Diabetic Hemodialysis Patients

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To the Editor

Among diabetics on hemodialysis (HD), there are conflicting data as to whether thiazolidinedione (TZD) use improves or worsens survival.[1, 2] Ramirez et al. compared rosiglitazone and pioglitazone with non-TZD oral hypoglycemic agents and found 38% higher all-cause mortality and 59% higher cardiovascular mortality among rosiglitazone users, although no differences were seen for pioglitazone.[1] In contrast, Brunelli et al. compared any TZD use with non-users and found 53% lower all-cause mortality among non-insulin users who used TZDs; no significant difference was seen among insulin users.[2] Recent data in the general type 2 diabetic population have shown better survival among incident rosiglitazone versus glipizide users.[3] However, data from the general population may not apply to dialysis patients because of unique physiological circumstances, greater burden of illness among dialysis patients, and competing risks. We conducted this study to evaluate the comparative effectiveness of TZD use versus sulfonylurea (SU) use with respect to mortality among hemodialysis patients.

Methods

Data for this retrospective study were obtained from a randomly selected cohort of 14,643 prevalent adult patients receiving thrice-weekly in-center hemodialysis in one of 1247 facilities operated by a large US dialysis organization between 1-1-2005 and 1-16-2009. We identified 608 patients with incident use of TZD or SU during the study period. Use of a TZD or SU was taken as evidence that these patients were diabetic. Incident use was defined

as a new prescription, which started after a period of at least 90 days during which the patient was dialyzed at the clinic and was not receiving either medication. Incident TZD users were matched (1:n) with replacement to incident SU users on the basis of insulin use and on a propensity score based on age, sex, race, dry weight, catheter use, heart failure, and serum albumin.[4, 5] Patients were considered at-risk for the outcome of all-cause mortality immediately after the start of the new TZD or SU prescription and remained at risk until death, transfer of care, transplant, or end of study (2-21-2009). Standardized differences were used to compare matched groups; standardized difference >10% (or <-10%) signifies substantive imbalance.[6] Associations with mortality were estimated using Cox proportional hazard models. All analyses were performed using Stata 12 (StataCorp LP, College Station, TX). This study was deemed exempt by the Partners Healthcare Institutional Review Board.

Results

In the unmatched cohort, unadjusted Kaplan-Meier survival curves show an association between improved survival and TZD use when compared to SU use (Figure). Overall, 230 incident TZD users were matched to 434 incident SU users (94 TZD to 168 SU on insulin; 136 TZD to 266 SU not on insulin). Cumulative at-risk time was 966 patient-years; 207 deaths occurred. Baseline characteristics of TZD and matched SU users are presented in the Table; the two groups were similar in terms of all variables studied except that TZD users were more likely to have pre-existing liver disease and on average had a shorter dialysis vintage. Incident TZD users had a significantly lower risk of death: HR (95% CI) 0.70 (0.53–0.92). In contrast to the unadjusted analysis, there was suggestion of effect modification based on concurrent insulin status (p-interaction=0.06): HRs (95% CIs) for TZD versus SU were 0.57 (0.40–0.82) among patients not on insulin, and 0.99 (0.63–1.55) among insulin users.

Comments

For diabetics on HD, TZD use versus SU use was associated with 30% lower all-cause mortality. These findings are similar to the results obtained by Brunelli et al., which showed TZD use versus non-use was associated with lower mortality among non-insulin dependent diabetics, but no difference in mortality among insulin users. The present analysis suggested similar effect modification by insulin, however this finding should be interpreted carefully because it (narrowly) missed formal levels of statistical significance. In contrast, Ramirez et al. found that rosiglitazone users had greater mortality compared to patients using other oral hypoglycemic agents. Our study differs from prior studies in that it was limited to new users of TZD and SUs. New user designs are preferable for studies of comparative effectiveness because they enable appropriate adjustment for patient characteristics at the time treatment decisions were rendered. Also, results are not subject to bias due to differential survival that may have occurred after initial exposure to medication and prior to the period of observation (eg, depletion of susceptibles).[7] The precise mechanism by which TZDs may improve mortality is not well elucidated, but data indicate that TZD use may decrease catabolism by improving insulin sensitivity[8] and mitigate cardiovascular risk profiles.[9, 10] Despite the use of statistical methods to minimize confounding, residual confounding may still exist; however, the residual differences that were observed (more liver disease and earlier dialysis

vintage) should bias against TZDs, which would render our estimates conservative. Prospective studies are needed to confirm these results.

In conclusion, among diabetics on HD, incident TZD use versus SU use was associated with 30% lower all-cause mortality. This effect may be limited to patients not concurrently on insulin.

Acknowledgments

References

1. Ramirez SP, Albert JM, Blayney MJ, Tentori F, Goodkin DA, Wolfe RA, et al. Rosiglitazone is associated with mortality in chronic hemodialysis patients. JASN. 2009; 20(5):1094–101. [PubMed: 19357257]

2. Brunelli SM, Thadhani R, Ikizler TA, Feldman HI. Thiazolidinedione use is associated with better survival in hemodialysis patients with non-insulin dependent diabetes. Kidney international. 2009; 75(9):961–8. [PubMed: 19190679]

3. Wheeler S, Moore K, Forsberg CW, Riley K, Floyd JS, Smith NL, et al. Mortality among veterans with type 2 diabetes initiating metformin, sulfonylurea or rosiglitazone monotherapy. Diabetologia. 2013 Epub 2013/06/26.

4. Brunelli SM, Rassen JA. Emerging analytical techniques for comparative effectiveness research. AJKD. 2013; 61(1):13–7. [PubMed: 23021799]

5. Stuart EA. Matching methods for causal inference: A review and a look forward. Statistical science. 2010; 25(1):1–21. [PubMed: 20871802]

6. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Statistics in medicine. 2009; 28(25):3083–107. [PubMed: 19757444]

7. Johnson, ESBB.; Briesacher, BA.; Fleming, NS.; Gerhard, T.; Kornegay, CJ.; Nourjah, P.; Sauer, BSG.; Sedrakyan, A.; Stürmer, T.; West, SL.; Schneeweiss, S. AHRQ Publication No 11(12)-EHC054-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2012. The Incident User Design in Comparative Effectiveness Research. Effective Health Care Program Research Report No. 32. (Prepared under Contract No. HHSA290200500161).

8. Wang X, Hu Z, Hu J, Du J, Mitch WE. Insulin resistance accelerates muscle protein degradation: Activation of the ubiquitin-proteasome pathway by defects in muscle cell signaling. Endocrinology. 2006; 147(9):4160–8. [PubMed: 16777975]

9. Chu CS, Lee KT, Lee MY, Su HM, Voon WC, Sheu SH, et al. Effects of rosiglitazone alone and in combination with atorvastatin on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. The American journal of cardiology. 2006; 97(5):646–50. [PubMed: 16490430]

10. Marx N, Imhof A, Froehlich J, Siam L, Ittner J, Wierse G, et al. Effect of rosiglitazone treatment on soluble CD40L in patients with type 2 diabetes and coronary artery disease. Circulation. 2003; 107(15):1954–7. [PubMed: 12695287]
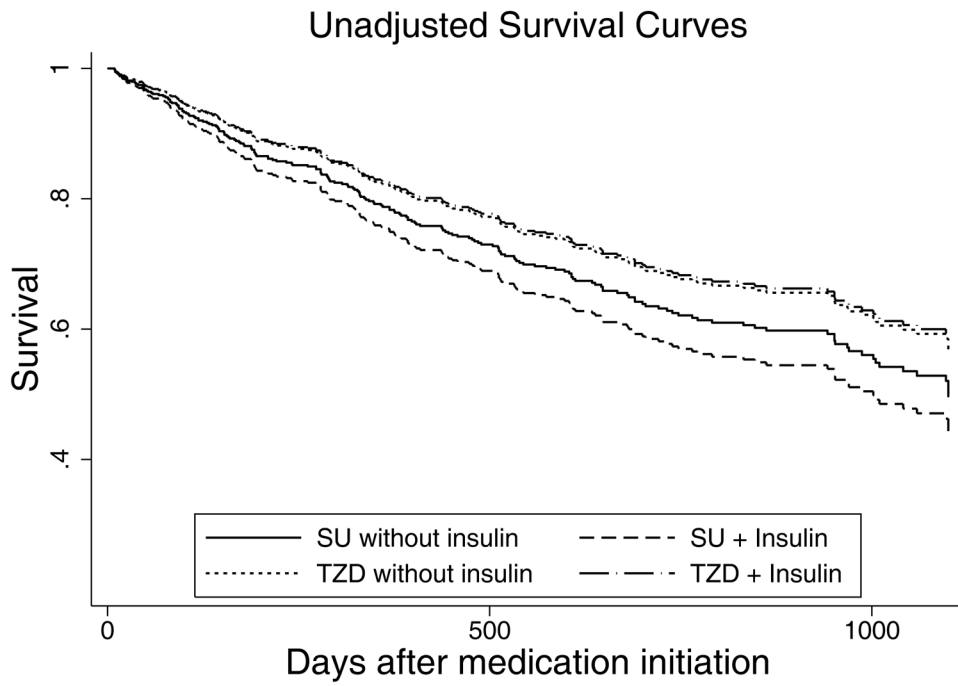
Unadjusted Survival Curves

Figure.
Kaplan-Meier survival curves showing the association between survival and incident TZD treatment compared to incident SU treatment when stratified on insulin use in the unmatched cohort.

Table

Baseline comparison of incident TZD users and matched incident SU users.[*]

	SU use (N=434)	TZD use (N=230)	Standardized difference
Age (years) [a,b]	64.9 +/− 11.8	64.2 +/− 11.4	−0.052
Female [a]	48.2%	51.3%	0.063
Black [a]	35.5%	33.9%	−0.033
Dry weight (kg) [a,b]	80.1 +/− 21.5	78.6 +/− 24.4	−0.065
Catheter use [a,b]	21.9%	23.9%	0.048
Heart failure [a]	22.1%	19.1%	−0.073
Albumin (g/dL) [a,b]	3.8 +/− 0.4	3.8 +/− 0.4	−0.007
Use of insulin [b,c]	38.7%	40.9%	0.044
Dialysis vintage (m) [b]	3.8 +/− 2.8	3.2 +/− 2.1	−0.213
Vascular disease [b]	4.8%	4.4%	−0.023
Hyperlipidemia [b]	20.3%	21.7%	0.036
Cancer [b]	1.6%	2.6%	0.072
Liver disease [b]	0.7%	3.0%	0.194
Creatinine (mg/dL) [b]	7.9 +/− 2.6	8.0 +/− 2.6	0.017
Phosphorus (mg/dL) [b]	5.3 +/− 1.6	5.2 +/− 1.6	−0.052
Corrected calcium (mg/dL) [b]	9.4 +/− 0.7	9.4 +/− 0.7	−0.035
Ln(Ferritin) (ln(ng/mL)) [b]	6.23 +/− 0.66	6.20 +/− 0.69	−0.056
Hemoglobin (g/dL) [b]	12.1 +/− 1.4	12.1 +/− 1.5	−0.027
Use of other oral diabetic medications [b]	4.8%	3.9%	−0.045

[a] Variable considered in propensity score.

[b] Considered as of the time of incident TZD/SU use.

[c] Groups were matched on this independently of propensity score.

[*] Data presented as mean +/− SD or n (%).