

Research Article

Frailty Attenuates the Impact of Metformin on Reducing Mortality in Older Adults with Type 2 Diabetes

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Special Issue on

Antidiabetic Drug-Metformin

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Submitted: 30 March 2014

Accepted: 26 May 2014

Published: 28 May 2014

ISSN: 2333-6692

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Keywords

- Metformin
- Frailty
- Mortality
- Type 2 diabetes

Abstract

Objective: To determine whether the protective effect of metformin against death is modified by frailty status in older adults with type 2 diabetes.

Research Design and Methods: We conducted a cohort study during October 1, 1999-September 30, 2006 among veterans aged 65-89 years old with type 2 diabetes but without history of liver, renal diseases, or cancers, who had sulfonylureas or metformin as the sole antidiabetic drug for ≥ 180 days. The Cox proportional hazard model was used to compare hazard rates of all-cause mortality between the metformin and sulfonylurea users adjusting for the propensity score of metformin use and covariates: age, race/ethnicity, diabetes duration, Charlson comorbidity score, statin use, smoking status, BMI, LDL, and HbA1c.

Results: In this cohort of 2,415 veterans, 307 (12.7%) were metformin users, 2,108 (87.3%) were sulfonylurea users, the mean age was 73.7 ± 5.2 years, the mean study period was 5.6 ± 2.3 years, the mean HbA1c at baseline was $6.7 \pm 1.0\%$, 23% had diabetes for ≥ 10 years, and 43.6% (N=1,048) died during the study period. For patients with and without frailty, the adjusted hazard ratio (HR) of death for metformin vs. sulfonylurea use were 0.92 (95% CI=0.90-1.31, p-value=0.19) and 0.69 (95% CI = 0.60-0.79, p-value<0.001), respectively. Logistic regression analyses showed that metformin (vs. sulfonylurea) was significantly associated with a decreased odds of frailty (OR: 0.66, 95% CI: 0.61-0.71, p-value <.0001)

Conclusion: Our study suggests that metformin could potentially promote longevity via preventing frailty in older adults with type 2 diabetes.

ABBREVIATIONS

U.S: United States; AMPK: AMP-Activated Protein Kinase; VAHCS: Veterans Administration Health Care System; VLHS: Veteran's Large Health Survey; HR: Hazard Ratio; CI: Confidence Interval; SD: Standard Deviation; LDL: Low-Density Lipoprotein; BMI: Body Mass Index; HbA1c: Hemoglobin A1c

INTRODUCTION

In the United States (US), the proportion of the population

aged ≥ 65 years is projected to increase to 19.6% (~71 millions) in 2030 [1]. The growing number of older adults increases demands on the public health system and on medical and social services. A major portion of these demands is attributed to burdens associated with type 2 diabetes, a prevalent aging-related disease that affects 26.9% of the U.S. population aged ≥ 65 years. Type 2 diabetes is reportedly a major predictor for frailty which may exacerbate insulin resistance in a vicious cycle, wherein impaired insulin action contributes to the disease process and the resulting impaired functional capacity further

impairs insulin action [2]. Therefore, it is important to identify practical interventions that would potentially reduce the burden associated with aging-related diseases, such as diabetes, and therefore to promote healthy aging and longevity. The need of these types of interventions is especially pressing for the U.S. veteran population in which 44% of individuals are aged ≥ 65 years [3]. In particular, the number of older adult veterans is expected to grow exponentially primarily as a result of aging Vietnam era Veterans: nearly 7 million veterans will be over the age of 65 in 2015.

Metformin (biguanide) is an insulin sensitizing medication commonly used for treating type 2 diabetes, which lowers blood glucose concentration by activating the enzyme AMP-activated protein kinase (AMPK) [4]. By its activation of the AMPK, metformin can then inhibit the production of inflammatory cytokines as well as malignant/metastatic progression of pre-malignant/senescent tumor cells [5,6], and hence increase the human lifespan [7,8]. Studies have also suggested that metformin could be a potential pharmacological strategy for reducing morbidity and promoting healthy aging via its insulin sensitizing effects mediated by calorie-restriction [7,9-11]. Consistent with these findings, it has been shown that metformin was associated with reduced all-cause mortality in patients with type 2 diabetes [12-14]. In a cohort study of 12,272 new oral anti-diabetic agent users from the Saskatchewan Health databases, Johnson et al. showed that the adjusted odds ratio (OR) for all-cause mortality for metformin monotherapy was 0.60 (95% CI=0.49-0.74) compared with sulfonylurea monotherapy, and the combination of sulfonylurea plus metformin therapy was also associated with reduced all-cause mortality (OR= 0.66, 95% CI=0.58-0.75) [12]. The cohort study of 2206 patients with type 2 diabetes from the Veterans Affairs Medical Center at Memphis Tennessee found that the adjusted hazard ratios (HR) for all-cause mortality between metformin users and non-metformin oral anti-diabetes agent users was 0.77 (p-value= 0.01), and the adjusted HR between metformin users and insulin users was 0.62, (p-value=0.04) [13]. In addition, a nested case-control study using patients with type 2 diabetes from the UK General Practice Research Database showed that patients exposed to a combination of sulfonylureas and metformin were at a decreased risk of all-cause mortality compared to patients exposed to sulfonylurea monotherapy (adjusted RR=0.77, 95% CI=0.70-0.85), and similar results were obtained when comparing metformin monotherapy with sulfonylurea monotherapy (adjusted RR=0.70, 95% CI=0.64-0.75) [14].

The effect of metformin on reduced mortality is primarily attributed to its pleiotropic effects on anti-inflammation and insulin sensitization [7,9-11]. This beneficial effect could be attenuated in the presence of frailty, a geriatric syndrome of physical decline over time that is most likely to be worsening over time [16,17]. This is because frailty may lead to worsening in insulin resistance [2,15], which then causes further decline of frailty [19]. Thus the mortality-reduction benefit of metformin could be countered in frail individuals who are more insulin resistant. Frailty, estimated at 7-15% of older adults in the United States, can lead to disability and institutionalization, and increased risk of death [16,18]. Because diabetes with macrovascular complications is a significant predictor of the

onset and progression of frailty [16], and insulin resistance is known to predict frailty onset [19], the goal of this study is to determine whether the protective effect of metformin against death is modified by frailty status in a clinical cohort of veterans with type 2 diabetes.

MATERIALS AND METHODS

Population

We drew our study sample from the 887,775 Veterans Administration Health Care System (VAHCS) enrollees who responded to the nationally representative Veteran's Large Health Survey (VLHS) in 1999 [20]. Patients who were younger than 65 years or older than 90 years in 1999 were excluded. To identify patients with type 2 diabetes, we restricted the cohort to individuals who had at least one primary care (including general medicine, geriatric, or diabetes clinic) visit as well as a diagnosis of type 2 diabetes (diagnosis using ICD-9 CM codes of 250.00 or 250.02) each year during fiscal year (FY) 1999 to FY2000 [21]. We further narrowed the study cohort to 2415 patients with type 2 diabetes who also met the following criteria: 1) having had prescription(s) for sulfonylureas or metformin as the sole class of glucose-lowering medication for ≥ 180 days; 2) no prescription for insulin or a thiazolidinedione (TZD) during the study period; 3) no liver or renal diseases during the study period; 4) no cancer diagnosis before the baseline (starting date of metformin or sulfonylureas); and 5) no missing data on any baseline covariates: age, ethnicity, Hemoglobin A1c (HbA1c), Body Mass Index (BMI), diabetes duration, age-adjusted Charlson comorbidity score [22], and smoking cessation status. All study procedures were approved by the Institutional Review Board of the University of Texas Health Science Center San Antonio.

Data sources

We used five VAHCS databases for this study. VAHCS Inpatient and Outpatient Medical SAS Datasets were used to identify the cohort of patients with type 2 diabetes and their associated characteristics, including demographic variables and comorbidities (based on diagnosis codes). Additional clinical variables were extracted from the VA Decision Support System (HbA1c and lipid laboratory test results and dates of measurements) and VAHCS Corporate Data Warehouse (height and weight values for deriving BMI). Medication prescription records were extracted from the VAHCS Pharmacy Benefits Management Services Database. Duration of diabetes was extracted from VLHS in 1999. Mortality data were extracted from the VAHCS Vital Status files [20].

Outcomes of interest

The outcome of interest in this study is the incidence rate of all-cause mortality during the study period. (i.e., the dependent variable in our analyses is the time interval between initiations of sulfonylurea or metformin to the date of death observed during the study period). Those who remained alive during the entire study period were treated as censored data. The study termination date for each patient corresponded to either September 30, 2006 (study ending date) or the date of death, whichever came first.

Predictors and measures

Medication exposure: For this study, we regarded sufficient

medication exposure as a minimum of 180 days as most clinical trials on these medications were 24 weeks or longer, and other studies have used a similar exposure cut-point [23]. The metformin group consisted of patients who had metformin prescription of any dose for ≥ 180 days but never had sulfonylurea for ≥ 180 days during the study period. Similarly, the sulfonylurea group consisted of patients who had sulfonylurea prescription for ≥ 180 days but never had metformin for ≥ 180 days during the study period.

Frailty status: Frailty status is defined as the presence (indicator) of any marker that is considered to be a major frailty characteristic, or if it was associated with frailty in prior studies using validated and widely-applied screening criteria for frailty [17]. Markers for frailty chosen were the occurrence of any of the following conditions during the study period: anemia [24], fluid electrolyte imbalance [25], fall, fracture, head injury, or other injury [17], coagulopathy [26], and weight loss [17]. Anemia was assessed by ICD9 = '280.0', '280.8', '280.9', '281', or '285.9', fluid electrolyte balance by ICD9 = '276', fall by ICD9 = 'E800', 'E801', 'E802', 'E803', 'E804', 'E850', 'E851', 'E852', 'E853', or 'E854', fracture by ICD9 = '820', head injury by ICD9 = '800', '801', '802', '803', '804', '850', '851', '852', '853', or '854', other injury by ICD9 = '805.6', '805.7', '806.6', '806.7', '807.0', '807.1', '808', '810', '811', '812', '813', '814', '818', '819', '821', '822', '823', '824', '825', '827', '828', or '829', coagulopathy by ICD9 = '286', '287.1', '287.3', '287.4', or '287.5', and weight loss by ICD9 = '260', '261', '262', or '263'.

Covariates

Covariates adjusted for in the analyses included demographic and clinical characteristics. Demographic characteristics included age, and race/ethnicity (Caucasian, African-American, Hispanic, others). Clinical characteristics included diabetes duration category in FY1999 (≤ 10 , > 10 years), age-adjusted Charlson comorbidity score, smoking cessation status, and the mean for LDL levels and HbA1c during the study period.

Statistical analysis

The Cox proportional hazard model adjusting for covariates and the propensity score of metformin use was conducted to compare hazard rates associated with mortality between the metformin and sulfonylurea groups. The hazard rate of mortality associated with metformin use was reported in relation to that due to sulfonylurea use. The interaction between frailty and metformin was assessed by the coefficient associated with the product of indicator of metformin use and the indicator of frailty. The Wald's test with p -value < 0.05 was considered significant. All statistical analyses were performed using SAS 9.1 (SAS Inc., Cary, NC).

RESULTS AND DISCUSSION

In our final cohort of 2,415 veterans, 2,108 (87.3%) had prescription(s) for sulfonylureas as the sole class of glucose-lowering medication, and 307 (12.7%) had prescription(s) for metformin as the sole class of glucose-lowering medication; 2,185 men (66.3% of the cohort) who had prescription(s) for statins. The mean age at cohort entry was 73.68 ± 5.25 years, and the mean study period (length of follow-up) was 5.30 ± 2.39 years.

The mean HbA1c at baseline was $6.69 \pm 0.90\%$, and the number of subjects with duration of type 2 diabetes greater than 10 years was 22.50%. In total, 1,048 patients (43.40%) died during the study period.

The characteristics of the subjects by metformin use are shown in Table 1. We observed heterogeneity (imbalance) in subjects' characteristics at baseline between the metformin and the sulfonylurea groups, and, some of these variables are associated with mortality. Based on chi-square tests, statin use, frailty-related diagnoses, age, co-morbidity, mean HbA1c, mean BMI, and mean LDL are significantly different between the metformin and sulfonylurea groups. The results in Table 1 suggested that in order to minimize the impact of baseline imbalance (e.g., confounding by indication) on the assessment of the association between metformin and mortality incidence, it is necessary to weight or stratify subjects by the propensity scores for metformin use.

Using Cox proportional hazard model adjusted for the propensity scores of metformin use (as inverse weights) as well as covariates, we observed significantly different hazard ratios associated with metformin by frailty as shown in Table 2. Metformin use was associated with a decreased Hazard Ratio (HR) for mortality. As shown in Figure 1, frailty modified the effect of metformin use on mortality, and this interaction effect was significant (p -value < 0.001). Among patients without frailty, the HR for metformin vs. sulfonylurea use was 0.69 (95% confidence interval (CI) = 0.60-0.79, p -value < 0.001). Among those who were frail, the HR for metformin use vs. sulfonylurea use was 0.92 (95% CI = 0.90-1.31, P -value = 0.19).

The effect of statin is worthy of attention: the HR for statin use vs. no statin use was 0.55 (95% CI = 0.50-0.60, p -value < 0.001). Higher mean HbA1c was associated with increased risk of mortality (HR = 1.45, 95% CI = 1.40-1.50, p -value < 0.001). BMI is curve linearly associated with mortality-- lower or higher BMI was associated with significant increased mortality rate risk (the linear BMI term is associated with HR = 0.903 P < 0.001 ; the quadratic BMI term is associated with HR = 1.001, p -value = 0.001). Mean LDL was positively associated with increased mortality incidence (HR = 1.003 for every 1mg/dL increase in LDL, 95% CI = 1.002-1.005, p -value < 0.001).

CONCLUSION

This study has shown that among older veterans with type 2

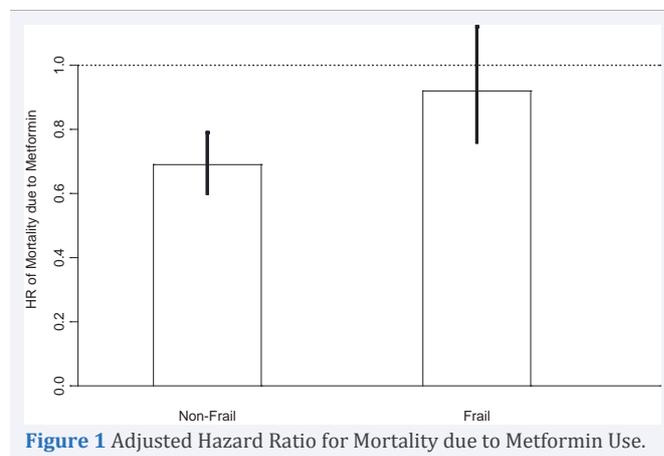


Figure 1 Adjusted Hazard Ratio for Mortality due to Metformin Use.

Table 1: Baseline Characteristics of the Study Population.

	Non-Metformin (n=2108)		Metformin (n=307)	
	Mean	SD	Mean	SD
Age	73.96	5.25	71.88	4.79
Male	98%		98%	
White/others	83%		84%	
Hispanic	7%		9%	
Black	10%		7%	
BMI (kg/m ²)	28.64	4.80	29.30	4.75
LDL (mg/dL)	101.86	26.26	97.87	22.77
Statin usage	64%		80%	
Hemoglobin A1c (%)	6.71	0.92	6.56	0.66
Diabetes duration >10 years	24%		14%	
Cancer diagnosis	2%		1%	
Charlson score	2.13	1.49	1.68	1.05
Frailty-related diagnosis	51%		37%	
Smoking cessation	17%		18%	

Abbreviations: CI: Confidence Interval; SD: Standard Deviation; LDL: Low-Density Lipoprotein; BMI: Body Mass Index; HbA1c: Hemoglobin A1c

Table 2: Cox Proportional Hazard Model for Death.

	HR	95% CI	P-value
Metformin	0.69	0.60 - 0.79	<0.001
Statin usage	0.55	0.50 - 0.60	<0.001
Frailty-related diagnosis	0.98	0.89 - 1.07	0.59
Metformin*frailty	1.33	1.17 - 1.52	<0.001
Cancer diagnosis	0.94	0.71 - 1.25	0.68
Age	1.06	1.05 - 1.06	<0.001
Male (vs. Female)	1.32	1.01 - 1.72	0.04
Charlson	1.28	1.26 - 1.31	<0.001
Hispanic (vs. white)	0.57	0.49 - 0.66	<0.001
Black (vs. white)	0.81	0.72 - 0.92	<0.001
Other (vs. white)	0.91	0.47 - 1.75	0.76
Mean HbA1c	1.45	1.40 - 1.50	<0.001
Mean BMI (kg/m ²)	0.90	0.87 - 0.94	<0.001
(Mean BMI) ²	1.002	1.001 - 1.003	0.001
Mean LDL (mg/dL)	1.003	1.002 - 1.005	<0.001
Smoking cessation	0.88	0.81 - 0.97	0.007
Diabetes duration >10 years	1.01	0.94 - 1.08	0.85

Abbreviations: CI: Confidence Interval; HR: Hazard Ratio; LDL: Low-Density Lipoprotein; BMI: Body Mass Index; HbA1c: Hemoglobin A1c

diabetes, metformin, compared to sulfonylurea, was associated with a 30% decreased risk of mortality among those without any frailty-related diagnoses, while metformin was not significantly associated with decreased risk of mortality among those with frailty-related markers. That is, our study of older veterans with type 2 diabetes suggests that the beneficial effect of metformin on reduced mortality was attenuated in patients who were identified as frail based on the presence of frailty-related diagnoses. Thus

our finding provides further insight regarding the variation of metformin impact on reduced mortality among the older adults of varying health status, such as age, drug exposure status, and diabetes duration as suggested in prior studies [12,13].

Frailty is a geriatric syndrome of physical decline that has been demonstrated to be associated with increased risk of death [16,17]. In the Cardiovascular Health Study (n = 5,317) by Fried et al [17], the HR for death in frail (vs. non-frail) individuals

was 2.24 (95% CI=1.51-3.33, p-value<0.001) after covariate adjustment. Further, frailty is also shown to predict other adverse health outcomes, including disability, falls, hospitalization, and unnecessary hospital readmission [17,27]. Interestingly, in our study, we found that frailty-related diagnoses modified the effect of metformin use on mortality, such that the observed mortality reduction was only observed in the older veterans without frailty-related diagnoses. Although among older veterans with frailty-related diagnoses, those who took metformin had 8% decrease in mortality compared to those who took sulfonylurea, this difference was not significant. We surmise that the attenuation of mortality benefit from metformin in the frail group observed in this study is because frail older adults are more insulin resistant, and have increased risk for death. In logistic regression analyses of the indicator of frailty-related diagnoses adjusting for the medication propensity scores as well as covariates associated with frailty in our study cohort showed that compared to sulfonylureas, metformin was significantly associated with a decreased odds of frailty (OR=0.66, 95% CI=0.61-0.71, p-value<0.001). Therefore, this suggests that metformin could be associated with reduced mortality mediated via reducing the onset of frailty.

Our results are consistent with those from prior similar studies in type 2 diabetes in that all have concluded that metformin is associated with reduced mortality compared to other anti-diabetic drugs [12-14,28], or placebo/no treatment [29]. However, since our study primarily focuses on an older population with an average age over 70 years, it is not surprising to see that the magnitude of the metformin effect found in our study differs from those in the prior studies. In a cohort of 2,206 veterans with diabetes (mean age of 63±11 years), metformin users had a 23% decreased risk for death after multivariate adjustment (but without adjusting for frailty) [13]. The effect of metformin found in this younger VA population is greater than the overall metformin effect found in our older cohort: 19% decreased risk for death that is derived by averaging the effects for those who were frail and those who were not.

Johnson et al. found that in a cohort of 12,272 diabetic individuals (mean age of 64 years) who were new users of oral anti-diabetic agents, those on metformin monotherapy or in combination with sulfonylurea were at a decreased risk for death compared to those taking sulfonylurea alone over an average follow-up period of 5 years: the covariate-adjusted effect of metformin was associated with 34-40% reduction in mortality [12]. Perhaps the most well-known long-term study is the United Kingdom Prospective Diabetes trial (UKPDS), which demonstrated that in 4,075 individuals (mean age of 53 years) with diagnosed diabetes for less than one year, treatment with metformin was associated with 36% improved survival compared with treatment with sulfonylureas, insulin, or diet [28]. The greater metformin effect found in Johnson et al. and UKPDS compared to ours could be due to that their cohorts had less progressive diabetes (indicated by their new initiation of anti-diabetic agents and diabetes duration) and hence less likely to be frail compared to our cohort. However, interestingly, the UKPDS showed that early addition of metformin in sulfonylurea-treated patients to improve glycemic control was associated with increased mortality compared to those continued on sulfonylurea alone over an average follow-up of approximately 10.5 years.

This detrimental effect of the combination with sulfonylureas deserves further investigation [29]. Two other related studies have also suggested the beneficial effect of metformin on mortality compared to sulfonylureas. Roumie studied a cohort slightly younger than ours and found a decreased rate of death or CVD outcomes (acute myocardial infarction and stroke) in metformin users compared to sulfonylurea users in a cohort of 253,690 patients: the adjusted HR was 1.21 (95% CI=1.13-1.30) for sulfonylurea users compared to metformin users [30]. Phung conducted a meta-analysis of 33 studies (n = 1,325,446), followed for a range of 0.46–10.4 years. In 17 studies that compared sulfonylurea with metformin, the relative risks of cardiovascular death for sulfonylurea relative to metformin was 1.26 (95% CI=1.17-1.35), and the relative risks of composite cardiovascular event (myocardial infarction, stroke, cardiovascular-related hospitalization or cardiovascular death) was 1.18 (95% CI=1.13-1.24) [31].

In this study, individuals taking insulin were excluded, 22.7% of the patients had duration of diabetes for more than 10 years, and the mean HbA1c at baseline was 6.71, which is within the recommended range for glycemic control of most patients with diabetes. Since the study cohort had a reasonable level of glycemic control, it is likely the metformin effect on frailty mediated via its insulin-sensitizing effect was limited. In fact, the regression analyses of the HbA1c adjusting for covariates showed that HbA1c level were similar between metformin and sulfonylurea groups. Thus the mechanism via which metformin reduced mortality in comparison to sulfonylureas could potentially be due to its less likelihood of causing hypoglycemia [33], better LDL-lowering effect [34], or even through reducing inflammation and preventing frailty [35].

The covariate effects on mortality found in this study are mostly consistent with those reported in the literature. For example, our results show that lower HbA1c, younger age, less comorbidity, shorter diabetes duration, and statin use are associated with decreased risk for mortality, while BMI is curve linearly associated with the rate of mortality (or a J-shaped association). However our study found that compared to non-Hispanic white, both black and Hispanic race/ethnic groups were associated with reduced mortality. In fact, the reduced mortality associated with the black race has been seen in other VA studies. Jha showed that the relative risk (RR) of mortality between black and white was 0.77 (95% CI=0.69-0.87; p-value =0.001) [39]. The study by Gosmanov which did not include Hispanics and did not adjust for social economic status (SES), suggested that the black race group was not associated with lower risk of mortality (HR=0.89, 95% CI=(0.72,1.10), p-value = 0.29) [13]. Another study by Young et al. conducted analyses of mortality, diabetic nephropathy, and cardiovascular disease in a national population of veterans with diabetes, which included Hispanics as well as several other ethnic groups (African American, Asian, and Native American) [40]. In this relatively younger population (mean age was 64.1 years), better overall short-term survival (over 18 months) was observed in most race/ethnic groups compared to Caucasians: African Americans and Hispanics had lower mortality compared to Caucasians, whereas Asians and Native Americans had similar mortality rates [40]. Although the explanation for this phenomena is not completely clear, some

have speculated that the observed survival benefit for veterans of ethnic minority groups compared to Caucasians may be related to the fact that factors such as SES, access to healthcare, and healthcare utilization, which may explain ethnic differences in mortality outside the VA system, are more homogeneous across ethnic groups within the VA population [40].

Our study has limitations. Confounding by indication could occur if patients with certain characteristics that are associated with the risk of mortality were also related to the use metformin or sulfonylureas. As shown in Table 1, there were some differences at baseline between the metformin and sulfonylurea as groups in our study. Nevertheless, we have managed to minimize the bias due to confounding by indication using the propensity score weighted technique in our analyses. Although we could not exclude residual confounding, such as lifestyle or behaviors, it would require a very large prevalence imbalance among exposure groups to explain our findings. Second, since the laboratory results came from individual VHA facilities, not a central laboratory, which could lead to imprecision in measurement. Third, our patients reflect a typical veteran population, with most patients being male. Finally, because frailty is typically measured using physical performance measures and administered questionnaires [17], in this study we were not able to directly measure frailty using an administrative dataset. The frailty variable used in this study was derived using diagnoses that have been associated with the Fried model of frailty from prior studies. Although the frailty variable used in this study has not been formally compared to a more widely known and applied frailty definition by Fried [17], it has been shown to be a significant predictor of hospital readmissions in a similar VA cohort [27].

Our study suggests that the metformin could potentially promote longevity via preventing frailty in older adults with type 2 diabetes, and early intervention with metformin before the onset of frailty could be key to assure the effect. Given the higher risk of death in our older population potentially as a result of frailty, we would expect that the mortality reducing effects of metformin would be more robust in populations who are younger and less frail than those in the present study.

ACKNOWLEDGEMENT

C.P.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. C.P.W. wrote the manuscript and researched data. C.L. reviewed/edited the manuscript. S.E.E. contributed to interpretation of the findings and writing the manuscript.

Funding acknowledgement

Dr. Wang's work on this study was partly sponsored by National Institute of Diabetes and Digestive and Kidney Diseases K25DK075092 and National Cancer Institute R21CA161180. Dr. Espinoza's work on this study was partly sponsored by Robert Wood Johnson Foundation, Harold Amos Medical Faculty Development Program.

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Cite this article

Meng S (2014) The Anticancer Effect of Metformin, the Most Commonly Used Anti-Diabetes Drug. *J Endocrinol Diabetes Obes* 2(2): 1030.