Association between metformin and abdominal aortic aneurysm in diabetic and non-diabetic US veterans

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ABSTRACT

We sought to examine the progression from abdominal aortic aneurysm (AAA) diagnosis to surgery and death among diabetics with and without exposure to metformin as well as non-diabetics.

We conducted a retrospective cohort study (January 2000 to July 2019) comparing 3 transitions (AAA surgery, death, and death after AAA surgery) among propensity score-matched metformin-exposed and unexposed diabetic veterans and non-diabetic veterans using the VA Informatics and Computing Infrastructure database. We fit an adjusted Cox proportional hazards model with transition-specific effects. There were 43,073 metformin-unexposed diabetics, 24,361 metformin-exposed diabetics and 56,006 non-diabetics. Compared with the non-diabetic cohort, both diabetic cohorts have a lower risk of surgery (no metformin (HR=0.740, 95% CI 0.706 to 0.776); with metformin (HR=0.770, 95% CI 0.730 to 0.813)). However, the non-metformin diabetic cohort has a higher risk of death (HR=1.024, 95% CI 1.004 to 1.045) and death after surgery (HR=1.086, 95% CI 1.013 to 1.165). The metformin-exposed diabetic cohort has a lower risk of death in the first 10 years after AAA diagnosis (HR=0.877, 95% CI 0.855 to 0.899), yet a higher risk of death 10 years after AAA diagnosis (HR=1.177, 95% CI 1.092 to 1.270) compared with non-diabetic cohort. Non-diabetics have the highest rate of AAA surgery compared with both diabetic cohorts. However, diabetics without metformin have the highest risk of death prior to, and after surgery. This research provides novel findings for patients diagnosed with AAA. The use of metformin after both AAA diagnosis and surgery should be further investigated.

INTRODUCTION

Abdominal aortic aneurysm, hereafter AAA, is a leading cause of death among the elderly.[1] Numerous studies have shown a negative association between diabetes and AAA incidence.[2–12] Furthermore, there has been evidence suggesting metformin is associated with a lower risk of AAA incidence, growth rate and mortality.[13–17] While previous results show the protective effect of both diabetes and metformin there have been no studies examining the clinical outcomes after AAA diagnosis and surgery among patients with diabetes and non-diabetic patients. We used a long study period (January 2000 to July 2019) and sought to analyze the progression from diagnosis to surgery and death using a multistate model (MSM) within the US Department of Veterans Affairs (VA) Healthcare System population of patients.

MATERIALS AND METHODS

Data source

This retrospective cohort study was conducted using data from the VA. The VA Informatics and Computing Infrastructure was used to obtain individual-level information on demographics, administrative claims, and pharmacy dispensation. The study used inpatient and outpatient claims coded with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), ICD-10-CM, Current Procedure Terminology (CPT), and pharmacy dispenses over the period of January 2000 to July 2019.

Cohort selection

We used a retrospective cohort of male patients with an ICD-9 or ICD-10 diagnosis code for AAA including 441.4x and I71.4x. The study index was based on the first date of AAA diagnosis. Index dates range from January 2000 to December 31, 2018. Patients were followed from index to death or end of study period (July 1, 2019). Patients were included in the study if they: (1) were at least 55 years old at diagnosis; (2) had at least 1 year between VA enrollment and index; and (3) had no AAA surgery prior to index. Cohorts were formed using diabetes status and metformin exposure prior to AAA diagnosis. Diabetes status was coded using ICD-9 or ICD-10 codes 249.x, 250.x, E10.x, and E11.x. Diabetics with at least 1 outpatient pharmacy dispense of metformin prior to AAA diagnosis were classified into metformin-exposed cohort. Diabetics without metformin exposure were classified into the diabetic non-metformin-exposed cohort. Patients with no diagnoses of diabetes or metformin exposure were classified into the non-diabetic cohort.

Table 1 Baseline demographic and comorbid characteristics

Variable	Diabetes		Non-diabetes	Standardized difference
	No metformin n=43,073	Metformin exposed n=24,361	n=56,006	
Race				
Black	3882 (9.01%)	1943 (7.98%)	4050 (7.23%)	0.077
Other/unknown	4905 (11.39%)	2290 (9.4%)	5671 (10.13%)	
White	34,286 (79.6%)	20,128 (82.62%)	46,285 (82.64%)	
Age (mean, SD)	72.27 (7.85)	69.65 (7.15)	70.36 (7.95)	0.349
Charlson comorbidity (mean, SD)	2.83 (2.25)	2.67 (1.91)	2.02 (2.03)	0.377
Pure hypercholesterolemia	4515 (10.48%)	2724 (11.18%)	6177 (11.03%)	0.032
Hyperlipidemia	24,594 (57.1%)	15,716 (64.51%)	34,153 (60.98%)	0.164
Hypertriglyceridemia	3957 (9.19%)	2760 (11.33%)	5048 (9.01%)	0.066
Hypertension	33,885 (78.67%)	20,030 (82.22%)	44,745 (79.89%)	0.076
Smoking	9820 (22.8%)	6559 (26.92%)	14,979 (26.75%)	0.093
BMI				
<18.5	332 (0.77%)	115 (0.47%)	279 (0.5%)	0.140
18.5–24.9	7106 (16.5%)	2959 (12.15%)	8334 (14.88%)	
25–29.9	15,695 (36.44%)	8242 (33.83%)	21,053 (37.59%)	
30+	19,660 (45.64%)	12,946 (53.14%)	26,118 (46.63%)	
Missing	280 (0.65%)	99 (0.41%)	222 (0.4%)	
Metformin MPR*100 (mean, SD)	– (–)	64.7 (31.5)	– (–)	
HbA1c (mean, SD)	6.67 (1.2)	7.14 (1.3)	– (–)	<0.001
Index year (mean, SD)	2010.42 (5)	2010.75 (4.36)	2010.31 (4.6)	0.098

BMI, body mass index; MPR, medication possession ratio.

Study outcome

The study outcome is surgery and/or death after diagnosis of AAA. AAA surgery was extracted from the hospital files using CPT codes 35801, 35102, 34800, 34802–34805, 34703, 34705, 34707, 35802, 35103, 34702, 34704, 34706, and 34708. Date of death was extracted from the VA vital status files. The time from index until the first AAA surgery and death was used as the outcome variable.

Statistical analysis

We used propensity score matching to minimize observable differences between cohorts. We fit a logistic regression model including demographic and comorbid factors listed in table 1 to predict treatment with metformin. We then used a greedy nearest neighbor algorithm to match from 1 to 3 non-metformin diabetic controls as well as from 1 to 3 non-diabetic controls. We use the largest standardized difference among the 3 cohorts as a measure of closeness. To analyze the risk of both surgery and death we use an MSM. MSMs extend competing risk analyses and are used in clinical trials and retrospective studies.[18–25] MSMs are composed of at least 3 states and the transitions between states. MSMs can be estimated using Cox proportional hazards models using appropriately created data. We used the mstate package in R for data set-up and the survival package to estimate the models.[26 27] We estimate unadjusted cumulative hazards via the Nelson-Aalen estimator. To account for demographic and comorbid factors, we fit a Cox proportional hazards model with transition-specific effects. Data management was preformed using SAS V.9.4 (SAS Institute) and analysis in R (R Core Team (2019). R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; URL http://www.R-project.org/).

RESULTS

Table 1 displays the baseline characteristics for the 43,073 patients with diabetes not on metformin, 24,361 diabetics on metformin and 56,006 non-diabetics. On average, patients were white, 82% in the metformin-exposed and non-diabetic cohorts and 79% in the no metformin cohort. Patients were slightly older in the non-metformin cohort, on average 72 years vs 69.9 and 70 in the metformin and non-diabetic cohorts. Diabetics not on metformin had the highest average Charlson comorbidity, 2.83, compared with the metformin exposed, 2.67, and non-diabetics, 2.02. Metformin-exposed patients have higher rates of hyperlipidemia, hypertriglyceridemia and hypertension. The metformin-exposed cohort and non-diabetics have similar rates of smoking, approximately 27%, while the non-metformin-exposed diabetic cohort has a lower rate, 22%. On average, patients exposed to metformin were adherent to metformin 64% of the time as calculated by the medication possession ratio. We display the average HbA1c at baseline for patients with diabetes. Metformin-exposed patients have, on average, a higher HbA1c at baseline than the unexposed (HbA1c 7.14 vs 6.67). Transition frequencies and unadjusted hazards appear in the online supplementary file 1.

In table 2, we find that compared with the non-diabetic cohort, both diabetic cohorts have a lower risk of surgery (no metformin (HR=0.740, 95% CI 0.706 to 0.776); metformin exposed (HR=0.770, 95% CI 0.730 to 0.813)). In terms of death, the non-metformin diabetic cohort has

Table 2 Multistate model for surgery, death and death after surgery

	Surgery	Death	Death after surgery
Variables	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Diabetic status (reference=non-diabetic)			
Diabetic no metformin	0.740 (0.706 to 0.776)	1.024 (1.004 to 1.045)	1.086 (1.013 to 1.165)
Diabetic with metformin	0.770 (0.730 to 0.813)	0.877 (0.855 to 0.899)	0.934 (0.855 to 1.021)
Diabetic with metformin after 10 y		1.177 (1.092 to 1.270)	1.307 (1.055 to 1.620)
Age	0.960 (0.957 to 0.963)	1.046 (1.045 to 1.047)	1.030 (1.026 to 1.035)
Race (reference=White)			
Black	1.059 (0.987 to 1.137)	0.877 (0.844 to 0.910)	0.953 (0.852 to 1.066)
Other/unknown	0.497 (0.455 to 0.542)	1.427 (1.391 to 1.465)	1.333 (1.180 to 1.505)
Charlson comorbidity	0.941 (0.931 to 0.952)	1.167 (1.161 to 1.173)	1.105 (1.084 to 1.126)
Pure hypercholesterolemia	1.078 (1.015 to 1.144)	0.899 (0.874 to 0.925)	0.955 (0.873 to 1.044)
Hyperlipidemia	1.050 (1.006 to 1.095)	0.875 (0.858 to 0.892)	0.916 (0.857 to 0.979)
Hypertriglyceridemia	1.258 (1.181 to 1.340)	0.892 (0.864 to 0.922)	0.795 (0.712 to 0.889)
Hypertension	1.022 (0.970 to 1.076)	0.993 (0.971 to 1.016)	1.110 (1.027 to 1.200)
Smoking	1.413 (1.352 to 1.477)	1.180 (1.153 to 1.207)	1.069 (0.998 to 1.144)
BMI (reference=18.5–24.9 normal)			
<18.5	1.093 (0.814 to 1.467)	1.796 (1.598 to 2.018)	1.354 (0.867 to 2.113)
25–29.9	1.112 (1.044 to 1.185)	0.764 (0.744 to 0.784)	0.805 (0.733 to 0.883)
30+	1.030 (0.967 to 1.097)	0.705 (0.687 to 0.723)	0.802 (0.732 to 0.879)
Missing	0.899 (0.625 to 1.291)	1.269 (1.125 to 1.432)	0.840 (0.543 to 1.300)
Index year	0.914 (0.909 to 0.918)	0.938 (0.935 to 0.940)	0.910 (0.903 to 0.918)

BMI, body mass index.

a higher risk (HR=1.024, 95% CI 1.004 to 1.045) and a higher risk after surgery (HR=1.086, 95% CI 1.013 to 1.165). The diabetic cohort with metformin has a lower risk of death compared with the non-diabetic cohort in the first 10 years after AAA diagnosis (HR=0.877, 95% CI 0.855 to 0.899). However, 10 years after AAA diagnosis the metformin-exposed cohort has a higher risk of death (HR=1.177, 95% CI 1.092 to 1.270). In terms of death after AAA surgery, the non-metformin diabetic cohort has a higher risk compared with the non-diabetic cohort (HR=1.086, 95% CI 1.013 to 1.165). Those exposed to metformin have no statistically significant different risk of death compared with the non-diabetic cohort within 10 years after AAA surgery. After 10 years we find that the risk of death is statistically significantly higher for those exposed to metformin compared with the non-diabetic cohort (HR=1.307, 95% CI 1.055 to 1.620).

DISCUSSION

This national retrospective cohort study of US veterans demonstrated non-diabetics have a higher rate of AAA surgery compared with both metformin-exposed and unexposed diabetics, yet diabetics without metformin have the highest risk of death prior to, and after surgery. Our findings provide a nuanced examination of the progression from AAA diagnosis to surgery, death and postsurgery survival. Interestingly, metformin-exposed diabetics have a lower risk of death within 10 years after diagnosis of AAA and prior to surgery compared with the non-diabetics. After 10 years post-AAA diagnosis, the risk for death among those exposed to metformin is higher compared with the non-diabetic cohort. Similarly, after 10 years, postsurgery metformin-exposed diabetics have an increased risk of death compared with the non-diabetic cohort. At baseline, the metformin-exposed cohort had a higher HbA1c suggesting poorer diabetic control. Further, patients with at least 10 years after AAA diagnosis were found to have a metformin adherence of 54% in the first 10 years. It is possible for these metformin-exposed patients, with poor adherence and diabetic control, to drive the results in the post-10-year period after surgery. Previous results have linked both diabetes and metformin use to a lower AAA incidence and growth rate. In a small sample of Canadian study a protective effect was shown for diabetes in terms of risk for AAA, a result found in other studies and systematic reviews.[3 5 6 11–13] In addition, the protective effect of diabetes for AAA was shown in data from 17 pooled large population prevalence studies (OR=0.80, 95% CI 0.70 to 0.90) and repeated in smaller population prevalence studies. Other risk factors such as older age, race, hypercholesterolemia, hyperlipidemia, and hypertension were shown to be associated with AAA surgery and/or death in the present study as well as other studies.[2 7 8]

While 1 study demonstrated metformin failed to have any effect on AAA rupture rates, a population-based study by Fujimura *et al* reported metformin reduces AAA growth rate and recent studies found similar results.[14 17 28 29] Metformin was associated with a lower risk of developing aortic aneurysm within a nested case–control of 4468 diabetics with and without aortic diseases.[16] In an animal model, AAA-induced mice treated with metformin had decreased rates of incidence, severity, and death from AAA.[30] Similar to our findings, Golledge *et al* demonstrated that metformin-exposed diabetics (adjusted HR=0.63, 95% CI 0.44 to 0.93), but not for unexposed patients with diabetes (adjusted HR=1.15, 95% CI 0.83 to 1.59), had a lower incidence of AAA events compared with non-diabetics in 3 Australian cohorts.[15]

The strengths of our study include the large sample and long study period. Furthermore, our analytic methods enabled us to estimate transition-specific effects for each of the predictors. While we believe our data and analysis are robust in evaluating metformin and the risk of surgery and death there are some limitations. First, our results may not be generalizable to people outside of the VA Healthcare System. The cohorts were not randomly assigned, and thus residual or unobserved confounding could bias the results. Our analysis mitigates this bias by using propensity score matching and covariate adjustment. Aneurysm size is not available in our data and could influence the risk of surgery and death among our cohorts. Additionally, a family history of AAA increases the risk of developing the condition and accentuates the risk. Importantly, this study lacks time-dependent HbA1c measures that could confound the results. However, the poorer outcomes for the metformin-exposed cohort after 10 years post-AAA surgery are intriguing and warrant further research.

Another limitation to claims database studies is medication adherence, which could impact the results as adherence was not evaluated in the MSMs. Despite these limitations, we feel that our data are robust given the large sample and long follow-up and can provide support to the scientific finding that metformin use in patients with diabetes reduces the rate of AAA surgery and/or death after AAA diagnosis.

CONCLUSION

A nationwide cohort of US veterans demonstrated non-diabetics have a higher rate of AAA surgery compared with both metformin-exposed and unexposed diabetics, yet diabetics without metformin have the highest risk of death prior to, and after surgery. This study presented several benefits of metformin; however, future research should be considered in understanding the risks and benefits of metformin exposure and the occurrence of AAA surgery and/or death within patients with diabetes and non-diabetic patients after AAA diagnosis.

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Competing interests None declared.

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