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Metformin prescription status and abdominal aortic aneurysm disease progression in the U.S. veteran population

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Abstract

Background: Identification of a safe and effective medical therapy for abdominal aortic aneurysm (AAA) disease remains a significant unmet medical need. Recent small cohort studies indicate that metformin, the world's most commonly prescribed oral hypoglycemic agent, may limit AAA enlargement. We sought to validate these preliminary observations in a larger cohort.

Methods: All patients with asymptomatic AAA disease managed in the Veterans Affairs Health Care System between 2003 and 2013 were identified by *International Classification of Diseases, Ninth Revision* codes. Those with a concomitant diagnosis of diabetes mellitus who also received two or more abdominal imaging studies (computed tomography, magnetic resonance imaging, or ultrasound) documenting the presence and size of an AAA, separated by at least 1 year, were included for review. Maximal AAA diameters were determined from radiologic reports. Further data acquisition was censored after surgical AAA repair, when performed. Comorbidities, active smoking status, and outpatient medication records (within 6 months of AAA diagnosis) were also queried. Yearly AAA enlargement rates, as a function of metformin treatment status, were compared using two statistical models expressed in millimeters per year: a multivariate linear

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Analysis and interpretation: NI, MM, BX, CC, RD
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regression (model 1) and a multivariate mixed-effects model with random intercept and random slope (model 2).

Results: A total of 13,834 patients with 58,833 radiographic records were included in the analysis, with radiology imaging follow-up of 4.2 ± 2.6 years (mean ± standard deviation). The average age of the patients at AAA diagnosis was 69.8 ± 7.8 years, and 39.7% had a metformin prescription within ±6 months of AAA. The mean growth rate for AAAs in the entire cohort was 1.4 ± 2.0 mm/y by model 1 analysis and 1.3 ± 1.6 mm/y by model 2 analysis. The unadjusted mean rate of AAA growth was 1.2 ± 1.9 mm/y for patients prescribed metformin compared with 1.5 ± 2.2 mm/y for those without ($P < .001$), a 20% decrease. This effect remained significant when adjusted for variables relevant on AAA progression: metformin prescription was associated with a reduction in yearly AAA growth rate of −0.23 mm (95% confidence interval, −0.35 to −0.16; $P < .001$) by model 1 analysis and 0.20 mm/y (95% confidence interval, −0.26 to −0.14; $P < .001$) by model 2 analysis. A subset analysis of 7462 patients with baseline AAA size of 35 to 49 mm showed a similar inhibitory effect (1.4 ± 2.0 mm/y to 1.7 ± 2.2 mm/y; $P < .001$). Patients' factors associated with an increased yearly AAA growth rate were baseline AAA size, metastatic solid tumors, active smoking, chronic obstructive pulmonary disease, and chronic renal disease. Factors associated with decreased yearly AAA growth rates included prescriptions for angiotensin II type 1 receptor blockers or sulfonylureas and the presence of diabetes-related complications.

Conclusions: In a nationwide analysis of diabetic Veterans Affairs patients, prescription for metformin was associated with decreased AAA enlargement. These findings provide further support for the conduct of prospective clinical trials to test the ability of metformin to limit progression of early AAA disease. (J Vasc Surg 2019;69:710–6.)

Keywords

Abdominal aortic aneurysm; Metformin; Veterans Affairs

The focus of abdominal aortic aneurysm (AAA) management is to prevent premature death from rupture. AAA rupture risk increases with increasing aortic diameter, and management guidelines recommend elective surgical intervention when diameter reaches or exceeds 5.5 cm in men and 5.0 cm in women.[1] Although the introduction of endovascular aneurysm repair has significantly reduced the risk for periprocedural morbidity and mortality, the identification and validation of effective medical therapies to suppress progression of early AAA disease remain a significant unmet medical need.[2]

Unfortunately, even though most AAAs are identified at an early stage of the disease, no medical intervention, including aggressive attempts to modify conventional cardiovascular risk factors with statins, angiotensinconverting enzyme inhibitors, angiotensin II type 1 receptor blockers (ARBs), or beta blockers as well as with antiproteolytic, anti-inflammatory, antiangiogenic, or immune-modulating agents, has proved effective in limiting progressive diameter enlargement or eventual rupture.[3,4]

Two small cohort studies and one population-based study have associated metformin therapy with reduced rates of AAA progression and reduced AAA prevalence, respectively, in diabetic patients.[5–7] Validating this association in a larger population has proved challenging

in that AAAs are less prevalent in diabetic patients, and few diabetics were included in previous AAA natural history studies (eg, 4.3% of AAA patients in the UK Small Aneurysm Trial [UKSAT]).[8]

In the U.S. Department of Veterans Affairs (VA) Health System population of patients, approximately 25% of patients are diabetic.[9] Given the concurrent prevalence of cigarette smoking history and other cardiovascular disease risk factors,[10,11] the VA population represents an ideal cohort in which to examine the relationship between diabetic medication prescription status and AAA disease progression. We queried the national VA data using the VA Informatics and Computing Infrastructure (VINCI) to evaluate the relationship between metformin prescription and AAA enlargement in a large, geographically diverse population of patients while controlling for other medications and relevant aneurysm-related demographic and environmental risk factors included in this data set.

METHODS

Approval for this project and wavier of informed consent were obtained from the Stanford University Institutional Review Board (Protocol 30669), the VA Research and Development Information System (AAL0002), and the Data Access Request Tracker (2016–03-167-D-A01).

Population of patients

Patients receiving care in the VA Health Care System between 2003 and 2013 with a diagnosis of AAA without rupture and diabetes *(International Classification of Diseases, Ninth Revision* [ICD-9] codes 441.4 and 250.x, respectively) were identified and selected for review. Inclusion criteria included men and women with the diagnosis of diabetes made either before or up to 6 months after the diagnosis of AAA to maximize the duration of exposure to diabetic medications. Eligible patients also received two or more radiographic imaging studies mentioning the presence and size of an AAA, separated by at least 1 year (Fig 1). The VINCI workspace was used to collect and query inpatient and outpatient records using Structured Query Language and SAS software (SAS Institute, Cary, NC).

Radiographic studies

Radiographic text records from January 2003 to December 2017 were queried according to *Current Procedural Terminology* codes (Supplementary Table I, online only). Eligible imaging studies included computed tomography (CT) scans of the abdomen and pelvis, with and without intravascular injection of contrast material, as well as abdominal ultrasound and magnetic resonance imaging (MRI) studies. The radiologic impression texts were then queried and included if the report contained “cm,” “centimeter,” “centimeters,” “mm,” “millimeter,” or “millimeters.”

AAA maximum diameter measurements

Maximum aortic diameters were determined from radiographic reports as noted. Thoracoabdominal aneurysms, aortic dissections, and mycotic aneurysms were excluded from analysis. If two measurements were reported, the largest of the two was recorded (eg,

"4.5 × 4.8-cm AAA": 48 mm was recorded). If three measurements were reported, the largest of the first two measurements was recorded (eg, "4.5 × 4.8 × 6.5-cm AAA": 48 mm was recorded). If no measurements were found regarding AAA size or exact measurement of the AAA size was not reported (eg, "AAA size stable"), the radiographic imaging report was excluded. Radiographic scans that included mention of AAA repair (eg, graft, endovascular aneurysm repair, endoleak) were censored from analysis; however, growth rates in these patients were included if two or more radiographic measurements were available before repair. The radiographic report with the first documented AAA diameter was noted as baseline AAA size. Erroneous and outlier AAA diameter measurements (eg, ≥20-mm deviation from neighboring measurements, except at end measurements) were removed after investigating yearly AAA growth trends at an individual patient level.

An AAA was determined to be present if the infrarenal aortic diameter was ≥29 mm at baseline. To increase the potential translational relevance of this review, a subcohort with baseline AAA diameter between 35 and 49 mm was also created.

AAA growth rates

Model 1—Multivariate linear regression.—To calculate yearly AAA growth rates, least squares linear regression was used to define the slope of AAA diameters over time between radiographic imaging studies. The first reported AAA diameter was noted as time zero, with subsequent radiographic examinations recorded in years from the initial examination. Baseline demographics, including, age, ethnicity, comorbidities, and medication use at time of AAA diagnosis, were controlled for using multivariable linear regression.

Model 2—Multivariate mixed-effects model.—A multivariate mixed-effects model with random slope and intercept was used to fit the yearly AAA growth rate.[12] Maximum likelihood estimates and unstructured covariance were used to account for the varying intervals between radiographic examinations and number of scans per patient. Baseline demographics including, age, ethnicity, comorbidities, and medication use at time of AAA diagnosis were incorporated using an interaction term with time.

Comorbidities and medication

Patients' demographic information at the time of AAA diagnosis was collected using outpatient ICD-9-associated codes. These data included the patient's age, gender, ethnicity, and relevant comorbidities. Outpatient diagnosis codes were collected, and a Charlson Comorbidity Index was created to calculate 17 co-morbidity categories according to ICD-9 codes.[13] Active smoking status at the time of AAA diagnosis was queried using a three-category smoking algorithm and investigated further with ICD-9 clinical modification codes (305.1x, 305.9, 649.0x, 989.84, and V15.82).[14] Outpatient medication records were also investigated. Diabetic and cardiovascular medication records were included if the medication was prescribed within a ±6-month window of the time of AAA diagnosis (Supplementary Table II, online only).

Statistical analysis

Data analysis was performed in Stata 14 (StataCorp LP, College Station, Tex). Descriptive statistics were used to evaluate baseline demographics and comorbidities. The primary analytic variable was the difference in growth rates between those patients with a prescription of metformin and those without. Significance was determined at the $P < .05$ value. All data were reported as the mean ± standard deviation, unless otherwise specified.

RESULTS

The entire cohort was composed of 13,843 remaining patients with 58,833 radiographic records (55.4% ultrasound, 43.3% CT, 1.3% MRI). The median number of radiographic studies per patient was 4 (range, 2–23; interquartile range, 2–5). The subcohort (AAA diameter at baseline, 3.5–4.9 cm) was composed of 7462 patients and 33,418 radiographic studies (53.2% ultrasound, 45.6% CT, 1.2% MRI; Fig 1).

The mean imaging follow-up interval of the entire cohort was 4.2 ± 2.6 years. The average age of the patients at time of AAA diagnosis was 69.8 ± 7.8 years, and the average baseline AAA diameter was 38.0 ± 7.1 mm. Other demographics and comorbidities of the patients are seen in Table I. Metformin was prescribed to 39.7% of patients around the time of AAA diagnosis. Other prescribed medications are noted in Table II. The overall mean yearly AAA growth rate was calculated to be 1.4 ± 2.0 mm/yin model 1 and 1.3 ± 1.6 mm/yin model 2. AAA growth rates according to starting diameter and radiology follow-up are displayed in the Supplementary Fig (online only).

The unadjusted mean AAA growth rate was 1.2 ±1.9 mm/y for patients prescribed metformin compared with 1.5 ± 2.2 mm/y for those without; metformin prescription was associated with a 20% reduction in growth rate. The distribution of yearly growth rates stratified by metformin use is seen Fig 2. When adjusting for comorbidities, metformin decreased the yearly AAA growth rate by −0.23 mm/y (95% confidence interval [CI], −0.35 to −0.16; $P < .001$) by model 1 analysis and 0.20 mm/y (95% CI −0.26 to −0.14; $P < .001$) by model 2 analysis.

Factors increasing yearly AAA growth rates on both models included baseline AAA size, active smoking, chronic obstructive pulmonary disease, chronic renal disease, and metastatic solid organ tumors. In addition to metformin, factors associated with reduced AAA growth rates included diabetes with complications and prescriptions for sulfonylureas or ARBs (Table III). Medications included in the regression that were not significantly associated with AAA growth rates are displayed in Supplementary Table III (online only).

In the subcohort (starting AAA size, 35–49 mm), the unadjusted mean growth rate was 1.4 ± 2.0 mm/y for patients with a metformin prescription compared with 1.7 ± 2.2 mm/y for those without, an 18.4% decrease in yearly growth rate. Adjusted for comorbidities, metformin decreased the yearly AAA growth rate by −0.27 mm/y (95% CI, −0.38 to −0.16; $P < .001$) by model 1 analysis and 0.21 mm/y (95% CI, −0.30 to −0.12; $P < .001$) by model 2 analysis.

DISCUSSION

Although AAA and cardiovascular disease share many common risk factors,[15,16] the paradoxical relationship between diabetes mellitus and AAA disease remains controversial and poorly understood.[17,18] In the VA-based Aneurysm Detection and Management (ADAM) trial, a concurrent diagnosis of diabetes reduced the average yearly growth rate of AAA (2.6 mm/y) enlargement by 42%.[19,20] In the UKSAT trial, AAA enlargement in diabetics was reduced by roughly 30% compared with nondiabetics (2.6 mm/y).[8] In this study, the average yearly enlargement rate for diabetic patients (~1.3 mm/y) was approximately 50% of that reported in the previous two studies, in populations in which only a small fraction of the patients were diabetic, providing further support for the hypothesis associating diabetes with AAA suppression. This study demonstrates additionally, for the first time in a population-based study, that metformin prescription is associated with an additional reduction in AAA enlargement rate beyond that associated with the presence of diabetes itself.[5,6]

Prescriptions for both ARBs and sulfonylureas were also associated with significant reductions in rates of AAA enlargement, although somewhat lower in magnitude than that evident with metformin (Table III). Importantly, the ARB effect was not mirrored by patients taking angiotensin-converting enzyme inhibitors. Extensive clinical and experimental evidence links angiotensin biology to AAA pathogenesis,[21] and a clinical trial testing the ability of telmisartan to suppress AAA enlargement recently completed enrollment and is pending final data analysis.[22] The broad application of ARBs in hypertension management, however, has substantially limited the pool of eligible, ARB-naive participants for AAA-related clinical trials, making this hypothesis difficult to test in practice. At least one population-based retrospective study has previously identified a negative association of sulfonylureas prescription and AAA prevalence in diabetic patients, although no information was available about influence on diameter enlargement in existing AAAs.[7]

Despite >60 years of worldwide use, the exact mechanism of action of metformin in diabetes management remains incompletely understood.[23] Metformin, an adenosine monophosphate-activated protein kinase agonist and a weak inhibitor of the mitochondrial electron transport chain, increases intracellular concentrations of adenosine monophosphate, which in turn lowers blood glucose concentration, enhances insulin sensitivity, and favorably modifies serum lipid profiles in diabetics. In cardiovascular diseases, accumulating evidence suggests that metformin suppresses reactive oxygen species production, proinflammatory nuclear factor kB activity, mammalian target of rapamycin pathway, autophagy, and mural angiogenesis[5,24–26] irrespective of diabetes status.[27]

To our knowledge, this study is the first to use national VA data to examine longitudinal AAA diameter changes and associations within this population of patients. The VINCI infrastructure allows long-term analysis of VA patients nationwide, with follow-up extending to15years. The high prevalence of diabetes in the VA population of AAA patients allows analysis of risk factor and demographic influences on AAA enlargement in diabetic patients, a population previously difficult to study. Given the relative under-representation of women in this data set as well as other VA-specific demographics and associated risks,

external validation in non-VA populations should be performed before these findings are extrapolated beyond the population of veteran patients.

This study has additional limitations that warrant further discussion. As no standardized clinical protocols exist for measuring and reporting aortic diameters in AAA disease, variation across modalities[28,29] and individual radiologist's interpretation methods may limit accuracy and precision in aggregated reports. Because our study methodology did not provide access to source images, AAA diameter data derived from clinical reports could not be independently verified. However, interobserver differences exist in all AAA diameter measure-ments,[30,31] and all reports evaluated in this study were performed by radiologists. A second limitation related to the inability to stratify AAA results on the basis of laboratory values or duration of diabetes mellitus in affected patients. The presence of diabetic complications as identified by ICD-9 coding was associated with a further decrease in yearly AAA growth, however, providing indirect insight into this relationship. Furthermore, we simplified our model to assume that metformin prescription status, along with other medications and comorbidities, including smoking status, did not change during the follow-up period. Finally, insulin prescription status was not evaluated as previous studies did not find a similar protective effect associated with insulin use in diabetic patients.[5–7]

CONCLUSIONS

In a nationwide analysis of diabetic VA patients, prescriptions for metformin, ARBs, and sulfonylureas were associated with decreased AAA progression. The rate of AAA enlargement in diabetic patients overall was significantly less than that previously reported in predominantly nondiabetic populations. Prospective testing is needed to validate the efficacy of metformin in limiting AAA disease progression in patients regardless of glycometabolic status.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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REFERENCES

1. Chaikof EL, Dalman RL, Eskandari MK, Jackson BM, Lee WA, Mansour MA, et al. The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. J Vasc Surg 2018;67:2–77.e2. [PubMed: 29268916]
2. Kraiss LW, Conte MS, Geary RL, Kibbe M, Ozaki CK. Setting high-impact clinical research priorities for the Society for Vascular Surgery. J Vasc Surg 2013;57:493–500. [PubMed: 23337859]

3. Rughani G, Robertson L, Clarke M. Medical treatment for small abdominal aortic aneurysms. Cochrane Database Syst Rev 2012;9:CD009536.
4. Golledge J, Norman PE, Murphy MP, Dalman RL. Challenges and opportunities in limiting abdominal aortic aneurysm growth. J Vasc Surg 2017;65:225–33. [PubMed: 27641464]
5. Fujimura N,Xiong J, Kettler EB,Xuan H,Glover KJ, Mell MW,et al. Metformin treatment status and abdominal aortic aneurysm disease progression. J Vasc Surg 2016;64:46–54.e8. [PubMed: 27106243]
6. Golledge J, Moxon J, Pinchbeck J, Anderson G, Rowbotham S, Jenkins J, et al. Association between metformin prescription and growth rates of abdominal aortic aneurysms. Br J Surg 2017;104:1486–93. [PubMed: 28650557]
7. Hsu CY, Su YW, Chen YT, Tsai SH, Chang CC, Li SY, et al. Association between use of oral-antidiabetic drugs and the risk of aortic aneurysm: a nested case-control analysis. Cardiovasc Diabetol 2016;15:125. [PubMed: 27585542]
8. Brady AR, Thompson SG, Fowkes FG, Greenhalgh RM, Powell JT; UK Small Aneurysm Trial Participants. Abdominal aortic aneurysm expansion: risk factors and time intervals for surveillance. Circulation 2004;110:16–21. [PubMed: 15210603]
9. Veterans Health Administration. Close to 25 percent of VA patients have diabetes. Available at: https://www.va.gov/health/NewsFeatures/20111115a.asp. Accessed January 16, 2018.
10. Veterans Health Administration. Survey of veteran enrollees' health and reliance upon VA. Available at: https:www.va.gov/HEALTHPOLICYPLANNING/SOE2011/SoE2011_Report.pdf# 2011 Accessed April 27, 2018.
11. Veterans Assari S. and risk of heart disease in the United States: a cohort with 20 years of follow up. Int J Prev Med 2014;5:703–9. [PubMed: 25013689]
12. Sweeting MJ, Thompson SG, Brown LC, Powell JT; RESCAN collaborators. Meta-analysis of individual patient data to examine factors affecting growth and rupture of small abdominal aortic aneurysms. Br J Surg 2012;99:655–65. [PubMed: 22389113]
13. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613–9. [PubMed: 1607900]
14. McGinnis KA, Brandt CA, Skanderson M, Justice AC, Shahrir S, Butt AA, et al. Validating smoking data from the Veteran's Affairs Health Factors dataset, an electronic data source. Nicotine Tob Res 2011;13:1233–9. [PubMed: 21911825]
15. Golledge J, Kuivaniemi H. Genetics of abdominal aortic aneurysm. Curr Opin Cardiol 2013;28:290–6. [PubMed: 23478885]
16. Golledge J, Norman PE. Atherosclerosis and abdominal aortic aneurysm: cause, response, or common risk factors? Arterioscler Thromb Vasc Biol 2010;30:1075–7. [PubMed: 20484703]
17. Lederle FA. The strange relationship between diabetes and abdominal aortic aneurysm. Eur J Vasc Endovasc Surg 2012;43:254–6. [PubMed: 22237512]
18. De Rango P, Farchioni L, Fiorucci B, Lenti M. Diabetes and abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 2014;47:243–61. [PubMed: 24447529]
19. Lederle FA, Johnson GR, Wilson SE, Chute EP, Littooy FN, Bandyk D, et al. Prevalence and associations of abdominal aortic aneurysm detected through screening. Aneurysm Detection and Management (ADAM) Veterans Affairs Cooperative Study Group. Ann Intern Med 1997;126:441–9. [PubMed: 9072929]
20. Bhak RH, Wininger M, Johnson GR, Lederle FA, Messina LM, Ballard DJ, et al. Factors associated with small abdominal aortic aneurysm expansion rate. JAMA Surg 2015;150:44. [PubMed: 25389641]
21. Xuan H, Xu B, Wang W, Tanaka H, Fujimura N, Miyata M, et al. Inhibition or deletion of angiotensin II type 1 receptor suppresses elastase-induced experimental abdominal aortic aneurysms. J Vasc Surg 2018;67:573–84.e2. [PubMed: 28434702]
22. Morris DR, Cunningham MA, Ahimastos AA, Kingwell BA, Pappas E, Bourke M, et al. TElmisartan in the management of abDominal aortic aneurYsm (TEDY): the study protocol for a randomized controlled trial. Trials 2015;16:274. [PubMed: 26081587]

23. Pierotti MA, Berrino F, Gariboldi M, Melani C, Mogavero A, Negri T, et al. Targeting metabolism for cancer treatment and prevention: metformin, an old drug with multi-faceted effects. Oncogene 2013;32:1475–87. [PubMed: 22665053]
24. Wang W, Xu B, Xuan H, Ge Y, Wang Y, Wang L, et al. Hypoxia-inducible factor 1 in clinical and experimental aortic aneurysm disease. J Vasc Surg 2017 12 11 [Epub ahead of print].
25. Victor VM, Rovira-Llopis S, Bañuls C, Diaz-Morales N, Lopez-Domenech S, Escribano-López I, et al. Metformin modulates human leukocyte/endothelial cell interactions and proinflammatory cytokines in polycystic ovary syndrome patients. Atherosclerosis 2015;242:167–73. [PubMed: 26188541]
26. Diaz-Morales N, Rovira-Llopis S, Bañuls C, Lopez-Domenech S, Escribano-Lopez I, Veses S, et al. Does metformin protect diabetic patients from oxidative stress and leukocyte-endothelium interactions? Antioxid Redox Signal 2017;27:1439–45. [PubMed: 28467723]
27. Cameron AR, Morrison VL, Levin D, Mohan M, Forteath C, Beall C, et al. Anti-inflammatory effects of metformin irrespective of diabetes status. Circ Res 2016;119:652–65. [PubMed: 27418629]
28. Manning BJ, Kristmundsson T, Sonesson B, Resch T. Abdominal aortic aneurysm diameter: a comparison of ultrasound measurements with those from standard and three-dimensional computed tomography reconstruction. J Vasc Surg 2009;50:263–8. [PubMed: 19631858]
29. Sprouse LR, Meier GH, Lesar CJ, Demasi RJ, Sood J, Parent FN, et al. Comparison of abdominal aortic aneurysm diameter measurements obtained with ultrasound and computed tomography: is there a difference? J Vasc Surg 2003;38:466–71; discussion: 471–2. [PubMed: 12947257]
30. Singh K, Jacobsen B, Solberg S, BØnaa KH, Kumar S, Bajic R, et al. Intra-and interobserver variability in the measurements of abdominal aortic and common iliac artery diameter with computed tomography. The Troms0 study. Eur J Vasc Endovasc Surg 2003;25:399–407. [PubMed: 12713777]
31. Chiu KW, Ling L, Tripathi V, Ahmed M, Shrivastava V. Ultrasound measurement for abdominal aortic aneurysm screening: a direct comparison of the three leading methods. Eur J Vasc Endovasc Surg 2014;47:367–73. [PubMed: 24491283]

ARTICLE HIGHLIGHTS

- Type of Research: Retrospective cohort study of patients treated in the Veterans Affairs Health Care System
- Key Findings: In 13,834 patients with abdominal aortic aneurysm (AAA) disease and diabetes treated from 2003 to 2013, metformin prescription in 39.7% was associated with a 20% decrease in yearly AAA growth rates.
- Take Home Message: The authors recommend prospective clinical trials to test the ability of metformin to suppress AAA disease in both diabetic and nondiabetic patients.

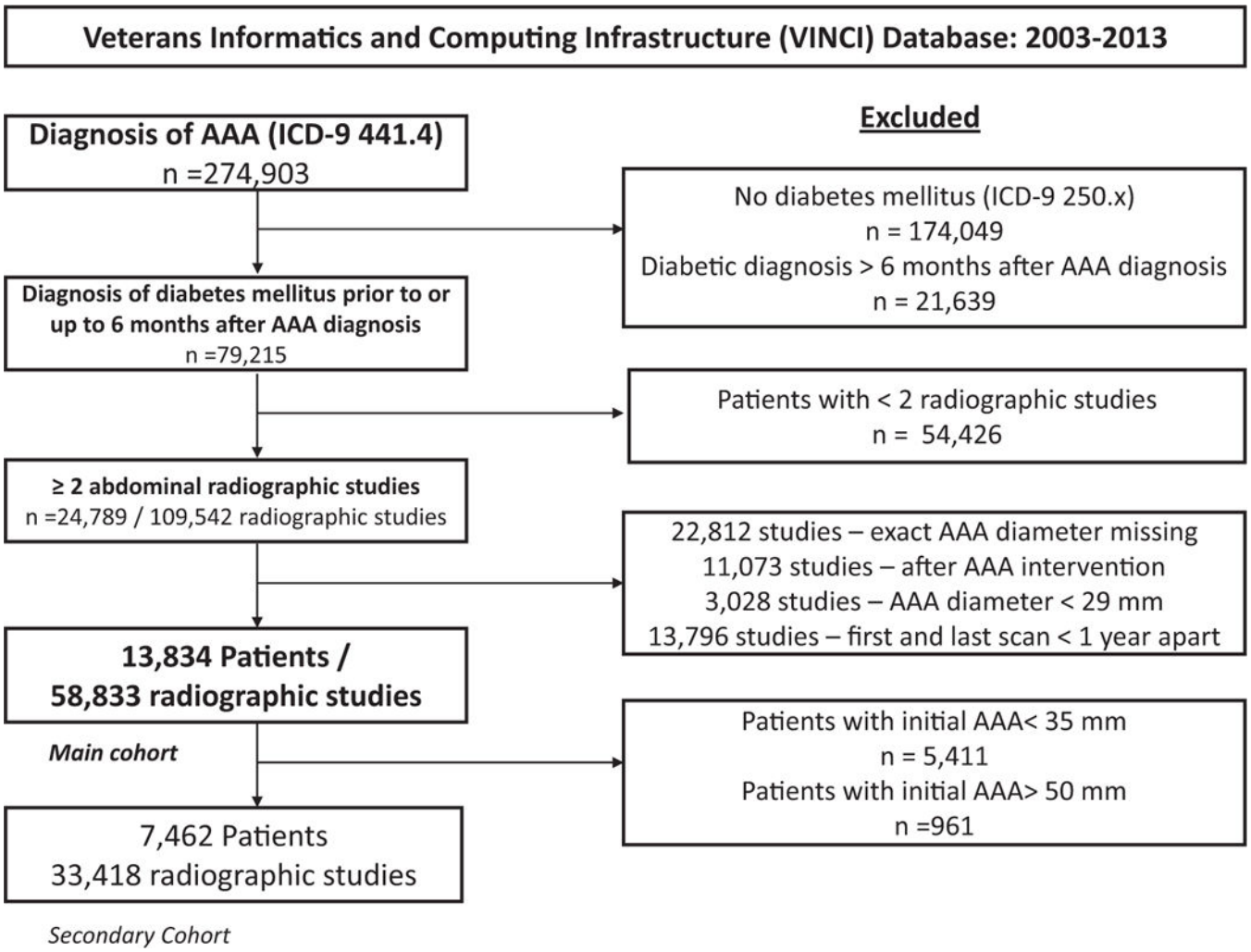

Fig 1.

Study design with inclusion and exclusion criteria for cohort identification. *AAA,* Abdominal aortic aneurysm; *ICD-9, International Classification of Diseases, Ninth Revision.*

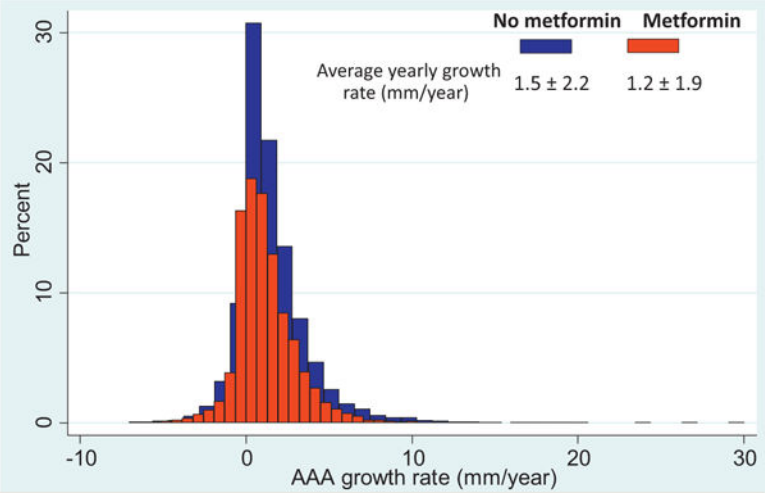

Fig 2.

Distribution of yearly abdominal aortic aneurysm (*AAA*) growth rates with and without a metformin prescription. Average yearly growth is expressed as mean ± standard deviation.

Table I.

Patients' demographics

Characteristic	Total (N = 13,834)
Age, years	69.8 ± 7.8
Male	99.4
Starting AAA size, mm	38.0 ± 7.1
Race	
American Indian	0.8
Asian	0.3
Black	6.6
White	87.2
Hispanic	3.2
Native Hawaiian	1.0
Smoking status	
Nonactive smoker	11.4
Active smoker	28.5
Unknown smoking status	60.1
Comorbidities	
COPD	31.9
Renal disease	14.9
Diabetes with complications	18.4
HIV infection	<0.2
Moderate or severe liver disease	0.7
Mild liver disease	5.2
Cancer	17.1
Metastatic solid tumor	1.1
Myocardial infarction	2.0
Hemiplegia or paraplegia	1.3
Cerebrovascular disease	17.4
Dementia	1.2
Rheumatologic disease	1.8
Peptic ulcer disease	2.4
Congestive heart failure	14.7

AAA, Abdominal aortic aneurysm; *COPD,* chronic obstructive pulmonary disease; *HIV,* human immunodeficiency virus.

Categorical variables are presented as percentages. Continuous variables are presented as mean ± standard deviation

Table II.

Patients' medication within a 6-month window of abdominal aortic aneurysm (AAA) diagnosis

Medication	Total (N = 13,834), %
Diabetic medication	
Metformin	39.7
Alpha glucose inhibitors	1.1
Thiazolidinediones	4.9
Sulfonylureas	36.7
Dipeptidyl peptidase 4 inhibitors	0.4
Other cardiovascular medication	
Alpha blocker	13.9
ARBs	12.3
Angiotensin-converting enzyme inhibitors	60.3
Beta blockers	64.6
Calcium channel blockers	32.1
Diuretics	47.7
Statins	68.4

ARBs, Angiotensin receptor blockers.

Table III.

Adjusted differences in expansion rate by significant predictor: Multivariate linear regression—Model 1; multivariate mixed-effects model—Model 2

Characteristic	Adjusted difference, mm/y	95% CI Model 1	*P* value	Adjusted difference, mm/y	95% CI Model 2	*P* value
Metformin	−0.23	−0.31 to −0.16	<.001	−0.20	−0.26 to −0.14	<.001
ARB	−0.23	−0.35 to −0.12	<.001	−0.15	−0.25 to −0.01	.001
Diabetes with complications[a]	−0.12	−0.21 to −0.03	.01	−0.12	−0.20 to −0.05	.001
Sulfonylureas	−0.10	−0.18 to −0.03	.006	−0.10	−0.15 to −0.04	.002
COPD	0.12	0.05–0.20	.002	0.11	0.044–0.17	.001
Renal disease	0.18	0.08–0.28	<0.001	0.10	0.01–0.02	.021
Active smoker	0.27	0.15–0.39	<.001	0.26	0.16–0.36	<.001
Metastatic solid tumor[b]	0.52	0.20–0.85	.002	0.36	0.07–0.65	.02
Baseline AAA size/10 mm	0.58	0.53–0.63	<.001	0.51	0.47–0.55	<.001

AAA Abdominal aortic aneurysm; *ARB,* angiotensin receptor blocker; *CI,* confidence interval; *COPD,* chronic obstructive pulmonary disease. Model 1 is based on average growth rate of 1.4 mm/y. Model 2 is based on average growth rate of 1.3 mm/y.

[a]Diabetes with renal, ophthalmic, or neurologic manifestations.

[b]Secondary malignant neoplasm of lymph nodes and other organs.