The Combined Effect of Renin Angiotensin System Blockade and Metformin on Abdominal Aortic Aneurysm Growth Rate in People with Diabetes Mellitus—A Propensity-Matched Retrospective Cohort Study

E.A.A.A. Otify,[1] I. Nunney,[2] K. Dhatariya,[1,3] and P.W. Stather,[1,4] Norwich, United Kingdom

Background: Identification of a safe and effective medical therapy for abdominal aortic aneurysm (AAA) remains a significant unmet clinical need. This study evaluated the associations between commonly prescribed medications in type 2 diabetes mellitus (T2DM), HbA_{1c} measurements, and AAA growth over a 14-year surveillance period.

Methods: A retrospective cohort study including all patients enrolled in the AAA screening and surveillance program at Norfolk and Norwich University Hospital NHS Foundation Trust. Records of AAA size, risk factors, medications, outcomes, complications, and mortality were analyzed. A 1:1 propensity matching was undertaken to validate results.

Results: The study comprised 986 patients (84.7% male), of whom 199 had T2DM. The mean initial AAA diameter did not differ significantly between groups (39.3 mm [standard deviation (SD) 7.2] in T2DM versus 39.4 mm [SD 6.9] in non-T2DM; $P = 0.68$). Patients with T2DM had a significantly lower mean AAA growth rate (2.2 mm/year [SD 3.1] vs. 2.7 mm/year [SD 2.9]; $P = 0.042$). The mean follow-up duration was longer in the T2DM group (5.2 years [SD 3.6] vs. 4.6 years [SD 3.3]; $P = 0.03$). Use of metformin and angiotensin-converting enzyme inhibitor/angiotensin II receptor type I blocker therapy was independently associated with reduced AAA growth rates (1.40 mm/year, 95% confidence interval [CI] 1.05−1.88; and 1.67 mm/year, 95% CI 1.52−1.83, respectively). Combined therapy was associated with the greatest reduction (1.19 mm/year, 95% CI 0.97−1.47) compared with neither medication (1.94 mm/year, 95% CI 1.78−2.12). These findings remained significant after 1:1 propensity score matching.

Conclusion: Metformin and ACEi/angiotensin II receptor type I blocker therapy are associated with reduced AAA growth rates, with the greatest protective effect observed in patients receiving combined therapy.

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Data availability: Digital input/output and hyperlinks are present; both original data generated within this research and secondary data used support the results and analyses.

[1]*Norwich Medical School, University of East Anglia, Norwich, United Kingdom.*

[2]*Norfolk and Norwich University Hospital NHS Trust, Norwich, United Kingdom.*

[3]*Department of Endocrinology, Norfolk and Norwich University Hospital NHS Trust, Norwich, United Kingdom.*

[4]*Department of Vascular Surgery, Norfolk and Norwich University Hospital NHS Trust, Norwich, United Kingdom.*

Correspondence to: Otify E.A.A.A., MBBS, MRes, Norwich Medical School, University of East Anglia, 28 Atherstone Avenue, Peterborough, Norwich PE3 9TX, United Kingdom; E-mail: eman.otify@nhs.net

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INTRODUCTION

Most abdominal aortic aneurysms (AAAs) are asymptomatic and are detected either incidentally or following rupture, which carries a mortality rate approaching 80% if not treated emergently.[1] Despite the NHS AAA National Screening Program, approximately 5,000 deaths annually in the United Kingdom are attributed to AAA rupture.[2]

A recent meta-analysis[3] demonstrated that metformin significantly reduces annual AAA growth rates compared with nonuse. Additionally, metformin was associated with lower rates of AAA development, rupture, and mortality. These promising findings have led to ongoing clinical trials evaluating metformin as a potential therapeutic strategy for AAA.[4]

Functional disturbances of the renin–angiotensin system are associated with many cardiovascular disorders, including a critical involvement in the pathogenesis and progression of AAA.[5] Although several studies have indicated that angiotensin-converting enzyme inhibitors (ACEis) and angiotensin II receptor type I blockers (ARBs) can inhibit the growth and rupture of AAAs,[6–8] there are other clinical and experimental data suggesting that ARB and ACEis may not offer comparable protection, and in contemporary clinical practice guidelines for medical management of AAAs, these 2 classes of renin–angiotensin system inhibitors have received a weak recommendation with a low level of evidence.[9–14] These conflicting data have led to the need for clinical trials in this area of research. Given these uncertainties, this study aimed to evaluate the combined effects of metformin and ACEi/ARB therapy on AAA growth rates.

AIMS AND OBJECTIVES

To determine the impact of medications on AAA growth rates in patients with and without type 2 diabetes mellitus (T2DM).

METHODS

A retrospective observational cohort study was conducted using the Norwich Aortic Aneurysm Database (NorAAD)[15] including patients who have been diagnosed with AAA at Norfolk and Norwich University Hospital (NNUH) between 2009 and 2023. AAA diameter measurements were obtained from ultrasound (majority) or computed tomography (CT) imaging. The database was held on the local trust network. Data fields were collected from local electronic systems at NNUH NHS Foundation Trust. Data collection was completed, anonymized, and stored on secure NHS trust–encrypted password-protected computers at NNUH. Data were collected from existing surgical reporting systems as well as the review of clinical notes.

The NorAAD database was analyzed for the impact of independent factors on AAA growth rates in patients with and without T2DM. Medication and comorbidity data were obtained from GP and NHS patients' records. Treatment with ACEIs or ARBs and metformin 500 mg to 2 g were evaluated to determine whether there is an association with a reduction of AAA growth and the possibility of a difference in treatment effects between these pharmacological regimens.

A general linear model was used, the outcome measure being the log of growth rate. The growth rate has been log-transformed because it had a skewed distribution and by log-transforming the values, it removes the skewness so that the data were normally distributed. When transforming back to the natural scale, we have the geometric mean not the arithmetic mean. This is because we are using log-transformed values, the effect sizes are no longer differences but a ratio. The geometric mean is similar to the median, so the median values are referenced. In addition, 2 models were produced one for T2DM and another for metformin. T2DM is defined as individuals whom HbA1C was $\geq$48 mmol/mol at diagnosis by a medical practitioner. Metformin use was limited to individuals with T2DM; therefore, diabetes status and metformin use were analyzed in separate multivariable models to avoid collinearity.

Eligibility Criteria

This research database includes patients, male or female over 18 years of age who have been diagnosed with an AAA, excluding any patients under the age of 18.

Sampling

The database hosts clinical data for approximately 3000 patients with sections for those on the surveillance program, those that have undergone surgical intervention, and those having postoperative surveillance. Only patients undergoing AAA surveillance were utilized for this study.

Screening and Enrollment

The clinical database has been collected as part of ongoing care. Regular updates are obtained as part of ongoing departmental audit processes. The database does not require patient contact or recruitment because data are already collected as part of routine clinical care.

Data Collection

Data were extracted from electronic hospital records and included:

- Demographics
- AAA diameter measurements
- Comorbidities
- Medication history
- Laboratory data (including HbA1c)
- Mortality

Data Handling and Management

The data have been collected into Microsoft Excel 2021 (Microsoft, Redmond, WA) database management program. The database is a standalone MS Excel file and does not require any server. There is no data interfacing or transfer between packages required; all data were entered into the MS Excel file. This contained identifiable data in order to create the database but was only accessible by the healthcare professionals involved in their clinical care. All data were anonymized prior to statistical analysis.

Data collected included date of birth, age, sex, aneurysm diameter, body mass index, past medical and drug history, date of death if applicable, blood results that included HbA1c. Data collection was undertaken through electronic program interrogation of hospital systems and manually as required.

Statistical Analysis

Fully anonymized data were analyzed. Cohorts with and without diabetes were initially compared, with patients with diabetes subcategorized into their use of ACEi/ARB and metformin use enabling in-group comparison.

AAA growth rate was calculated using initial and most recent diameter measurements divided by follow-up duration.

Statistical analyses were performed using Statistical Package for the Social Sciences and Statistical Analysis System software.

Comparisons between groups were performed using the following:

- *Chi*-squared test for categorical variables
- Independent *t*-test for continuous variables
- Wilcoxon rank-sum test where appropriate
- Multivariable general linear models
- 1:1 propensity score matching

Ethical Considerations

This is a retrospective observational cohort study. Ethical approval was granted by East of England—Essex research ethics committee for the NorAAD, IRAS project ID: 318930 to carry out this primary research from the NNUH information systems.

RESULTS

The cohort consisted of 986 patients, with a mean age of 80.2 years ± 6.9 and a clear prevalence of male gender (835; 84.7%), (Table I). People with T2DM had a lower mean growth rate (2.2 ± 3.1 mm/year) than those without T2DM (2.7 ± 2.8 mm/year), $P = 0.042$ (Table II). The mean follow-up is longer for those with T2DM (5.2 years) than non-T2DM (4.6 years), $P = 0.03$. Overall, median follow-up is 56.7 months and interquartile range (IQR) is 5.2 months.

Both metformin and ACEi/ARB are associated with a reduction in AAA growth rates. Metformin has a more profound effect than ACEi/ARB 1.40 mm/year, 95% CI [1.05—1.88]. However, the combination of both medications is superior, being associated with a reduction in AAA growth rates to 1.19 mm/year, 95% CI [0.97—1.47] compared to those on neither medication 1.94 mm/year, 95% CI [1.78—2.12], (Table III).

A 1:1 propensity score—matched cohort of 950 patients compared those with and without T2DM/metformin therapy; the model accounted for gender, age, whether having T2DM or receiving metformin, ACEi/ARB, and statin (Table IV). The growth rate is significantly higher for those with no T2DM than those with T2DM (ratio 1.44; 95% confidence interval [CI] [1.23—1.67]; $P < 0.0001$), and in the case of the metformin model, the growth rate is 1.40 times higher for those not on metformin than those on metformin (95% CI: 1.17—1.69; $P = 0.0003$). ACEi/ARB therapy was independently associated with a reduction in AAA growth rate ($P = 0.0111$) and combined use with metformin showed additive benefit ($P = 0.0129$). (Table IV).

Table I. Describes the baseline characteristics of people with and without type 2 diabetes mellitus of the first cohort study

Type 2 diabetes				
Baseline characteristics	No ($n = 787$)	Yes ($n = 199$)	Overall ($n = 986$)	*P* value
Gender				
Female	131 (16.6%)	20 (10.1%)	151 (15.3%)	0.021
Male	656 (83.4%)	179 (89.9%)	835 (84.7%)	
Age				
Median [Q1, Q3]	81.0 [76.0–85.0]	80.0 [75.0–84.0]	81.0 [76.0–85.0]	0.137
Peripheral neuropathy				
No	767 (97.5%)	186 (95.4%)	953 (97.0%)	0.126
Yes	20 (2.5%)	9 (4.6%)	29 (3.0%)	
Hypertension				
No	300 (38.2%)	60 (30.5%)	360 (36.6%)	0.045
Yes	486 (61.8%)	137 (69.5%)	623 (63.4%)	
Chronic lung disease				
No	531 (67.5%)	132 (67.3%)	663 (67.4%)	0.973
Yes	256 (32.5%)	64 (32.7%)	320 (32.6%)	
Ischemic heart disease				
No	465 (59.1%)	100 (50.8%)	565 (57.4%)	0.035
Yes	322 (40.9%)	97 (49.2%)	419 (42.6%)	
Heart failure				
No	694 (88.2%)	165 (84.6%)	859 (87.5%)	0.178
Yes	93 (11.8%)	30 (15.4%)	123 (12.5%)	
Chronic kidney disease				
No	650 (82.6%)	155 (79.5%)	805 (82.0%)	0.313
Yes	137 (17.4%)	40 (20.5%)	177 (18.0%)	
Cerebral vascular accident				
No	618 (78.5%)	152 (77.9%)	770 (78.4%)	0.861
Yes	169 (21.5%)	43 (22.1%)	212 (21.6%)	
Active cancer				
No	605 (76.9%)	141 (72.3%)	746 (76.0%)	0.182
Yes	182 (23.1%)	54 (27.7%)	236 (24.0%)	
Peripheral arterial disease				
No	657 (83.5%)	162 (83.1%)	819 (83.4%)	0.892
Yes	130 (16.5%)	33 (16.9%)	163 (16.6%)	
Medications				
Single antiplatelet				
No	247 (31.5%)	58 (29.7%)	305 (31.2%)	0.635
Yes	537 (68.5%)	137 (70.3%)	674 (68.8%)	
Dual antiplatelet				
No	733 (93.5%)	183 (93.8%)	916 (93.6%)	0.858
Yes	51 (6.5%)	12 (6.2%)	63 (6.4%)	
Statin				
No	152 (19.4%)	19 (9.7%)	171 (17.5%)	0.002
Yes	632 (80.6%)	176 (90.3%)	808 (82.5%)	
Beta-blocker				
No	453 (57.8%)	101 (51.8%)	554 (56.6%)	0.131
Yes	331 (42.2%)	94 (48.2%)	425 (43.4%)	
ACEi ARB				
No	404 (51.5%)	73 (37.4%)	477 (48.7%)	0.0004
Yes	380 (48.5%)	122 (62.6%)	502 (51.3%)	
Insulin				
No	784 (100%)	172 (88.2%)	956 (97.7%)	<0.00001
Yes	0 (0.0%)	23 (11.8%)	23 (2.3%)	

(*Continued*)

Table I. Continued

Type 2 diabetes				
Baseline characteristics	No (n = 787)	Yes (n = 199)	Overall (n = 986)	P value
Metformin				
No	782 (99.7%)	76 (39.0%)	858 (87.6%)	<0.00001
Yes	2 (0.3%)	119 (61.0%)	121 (12.4%)	
Direct oral anticoagulant/ warfarin				
No	577 (73.6%)	142 (72.8%)	719 (73.4%)	0.826
Yes	207 (26.4%)	53 (27.2%)	260 (26.6%)	
Sulfonylurea				
No	784 (100%)	141 (72.3%)	925 (94.5%)	<0.00001
Yes	0 (0.0%)	54 (27.7%)	54 (5.5%)	
Dipeptidyl peptidase-4				
No	783 (99.9%)	175 (89.7%)	958 (97.9%)	<0.00001
Yes	1 (0.1%)	20 (10.3%)	21 (2.1%)	
Glucagon-like peptide-1				
No	784 (100%)	193 (99.0%)	977 (99.8%)	0.004
Yes	0 (0.0%)	2 (1.0%)	2 (0.2%)	
Sodium-glucose co-transporter 2				
No	781 (99.6)	194 (99.5)	975 (99.6)	0.799
Yes	3 (0.4)	1 (0.5)	4 (0.4)	
Thiazolidinediones				
No	784 (100)	191 (97.9)	975 (99.6)	0.00005
Yes	0 (0.0)	4 (2.1)	4 (0.4)	
Mortality				
No	430 (54.7)	115 (57.8)	545 (55.3)	0.435
Yes	356 (45.3)	84 (42.2)	440 (44.7)	

P value is the *chi*-squared test comparing people with and without diabetes, except for age where t-test has been used.

Table II. Outcomes of people with and without diabetes mellitus type 2 diabetes

Type 2 diabetes			
Characteristic	No (n= 78)	Yes (n = 199)	P value
Growth rate (mm/year)			
Mean (SD)	2.7 (2.8)	2.2 (3.1)	0.042
Mean initial AAA diameter in mm (SD)	39.4 (6.9)	39.3 (7.2)	0.6845
Mean follow-up in years (SD)	4.6 (3.3)	5.2 (3.6)	0.03
Overall mean HbA_{1c} mmol/mol (SD)	40.5 (6.2)	54.2 (13.6)	<0.001

DISCUSSION

This retrospective cohort study has highlighted a significant association with lower AAA growth rates in people using metformin and/or ACEi/ARB. Also, people using both metformin and ACEi/ARB had greater protection against AAA growth rate than using a single agent alone. This is the first study to evaluate the impact of the combined use of metformin and ACEi/ARB on AAA growth rate, with long-term follow-up.

T2DM has consistently been associated with reduced AAA development and growth rate and when metformin has been evaluated separately, a similar pattern emerges. These results confirm previous reports of a considerably reduced AAA growth rate among people using metformin compared with

Table III. Subgroup analysis of metformin and ACEi/ARB use and AAA growth rate

Subgroups	Geometric mean growth rate (mm/year [95% CI])
No metformin and no ACEi/ARB	1.94 [1.78−2.12]
ACEi/ARB and no metformin	1.67 [1.52−1.83]
Metformin and no ACEi/ARB	1.40 [1.05−1.88]
GM, geometric mean	1.19 [0.97−1.47]

GM, geometric mean.

non-T2DM. This may in part be driven by broad anti-inflammatory effects of metformin[16,17] and reduction of extracellular matrix remodeling.[16] Due to the clinical benefits of metformin on AAA, there are ongoing clinical trials[4] testing the effect of metformin on AAA, one of which is a randomized controlled trial called the ''metformin aneurysm trial''[18] testing the effect of metformin on the complications of AAA.

Nephropathy is a known complication of T2DM,[19] and there is a strong clinical evidence that the progression of kidney disease in people with diabetes is slowed by treatment with ACEis.[20] Therefore, people with T2DM are more likely to be on ACEi/ARB compared to people without T2DM. Although some studies have indicated that ACEi/ARB can inhibit the growth and rupture of AAAs,[6−8] there are other clinical and experimental data suggesting that ACEi/ARB may not offer comparable protection, and in contemporary clinical practice guidelines for medical management of AAAs, these 2 classes of renin−angiotensin system inhibitors have received a weak recommendation with a low level of evidence.[9−14,21]

One of the studies that reported no protection of ACEi on AAA growth was a randomized placebo-controlled trial[21] which suggested no significant impact of perindopril compared with placebo or amlodipine on small AAA annual growth rate over a 2-year period; however, this 3-armed study has fewer than 100 patients in each arm, with a short duration of follow-up therefore had low power to detect small differences. This study looks at the effect of ACEi over a longer duration. A large trial with longer follow is likely required to determine the true effect of ACEi on AAA growth and thus inform clinical guidelines.

Kristensen et al.[22] conducted an observational study, reporting an inverse association between the growth rate of AAAs and the level of HbA_{1c}, which further supports our findings and indicates that long-lasting elevated blood glucose impairs aneurysmal progression in individuals with and without T2DM. Taimour et al.[23] found no correlation between HbA1c and aortic diameter in newly diagnosed patients with T2DM; however, the detection of AAA is often by chance, and they have not reported AAA growth rates.

Within our cohort, the mean follow-up was longer in those with DM (5.2 years) than in non-T2DM (4.6 years), $P = 0.03$. This is most likely related to the slower AAA growth rate; therefore, patients will take longer to reach the 55 mm threshold diameter for surgical intervention.

This study has several important strengths. It represents a large cohort of patients undergoing long-term AAA surveillance within a structured national screening program. The extended follow-up period (up to 14 years) enhances the reliability of growth rate estimation and allows meaningful assessment of longitudinal treatment effects. Detailed medication and laboratory data, including HbA1c measurements, enabled evaluation of both pharmacological exposure and glycemic control. Furthermore, the use of multivariable modeling and 1:1 propensity score matching strengthens the robustness of the findings by reducing confounding and selection bias. Importantly, this is the first study to evaluate the combined effect of metformin and ACEi/ARB therapy on AAA growth, providing novel insights with potential therapeutic implications.

This study was limited to the inability to retrieve missing records of patients that were not scanned and uploaded onto electronic hospital systems. Taking this into account, this study had ethical approval to only use hospital records to retrieve patients' records. This creates a risk of selection bias if those missing patients had different clinical trajectories (e.g., faster growth leading to early surgery). However, the 1:1 propensity matching was undertaken to mitigate this risk as much as possible.

The predominance of male participants in this study (84.7%) reflects the well-known epidemiology of AAA. However, this may limit the generalizability of the findings to female populations. Further studies including a higher proportion of female patients would be valuable to better evaluate potential sex-specific differences.

In addition, although ultrasound was used in the majority of individuals for surveillance, there were some CT scans usually as part of detection of incidental AAAs. The use of both ultrasound and CT imaging may introduce minor measurement variability and could potentially influence growth rate calculations.

As this is a retrospective cohort study, its findings can only establish association and that residual

Table IV. Baseline characteristics after 1:1 propensity score−matched cohort

Type 2 DM model ($N = 950$)			Type 2 DM model ($N = 950$)	
Category	Adj. GM [95% CI]	*P* value	GM, geometric mean [95% CI]	*P* value
Gender				
Female	1.56 [1.32−1.85]		1.55 [1.29−1.85]	
Male	1.53 [1.39−1.68]		1.50 [1.34−1.67]	
Ratio male:female	1.02 [0.87−1.21]	0.7877	1.03 [0.88−1.22]	0.6969
Diabetes or metformin				
No	1.85 [1.68−2.04]		1.80 [1.64−1.99]	
Yes	1.29 [1.1−1.52]		1.28 [1.05−1.56]	
Ratio no:yes	1.44 [1.23−1.67]	<0.0001	1.40 [1.17−1.69]	0.0003
ACEi/ARB				
No	1.67 [1.47−1.89]		1.65 [1.43−1.89]	
Yes	1.43 [1.26−1.63]		1.41 [1.22−1.62]	
Ratio no:yes	1.17 [1.03−1.3]	0.0129	1.17 [1.04−1.3]	0.0111
Statin				
No	1.52 [1.29−1.79]		1.50 [1.26−1.79]	
Yes	1.57 [1.42−1.73]		1.55 [1.38−1.73]	
Ratio no:yes	0.97 [0.83−1.1]	0.7074	0.97 [0.83−1.1]	0.7104
Age				
Ratio in growth rate (per unit change)	0.99 [0.98−1.0]	0.0698	0.99 [0.98−1.00]	0.0684

GM, geometric mean.

confounding, including confounding by indication, may remain despite the propensity-matching.

CONCLUSION

ACEi/ARB therapy is associated with reduced AAA growth rates. Metformin demonstrates a greater protective effect, and combined therapy appears to confer additive benefit.

Prospective randomized controlled trials are required to determine whether these therapies reduce AAA growth independently of T2DM status.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

E.A.A.A. Otify: Writing − review & editing, Writing − original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **I. Nunney:** Software, Formal analysis, Data curation. **K. Dhatariya:** Writing − review & editing, Validation, Supervision. **P.W. Stather:** Writing − review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Conceptualization.

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