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Editor's Choice – Metformin Prescription is Associated with a Reduction in the Combined Incidence of Surgical Repair and Rupture Related Mortality in Patients with Abdominal Aortic Aneurysm

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WHAT THIS PAPER ADDS

Currently there is no drug therapy for abdominal aortic aneurysm (AAA). This cohort study examined the association between metformin prescription and the combined incidence of AAA repair or AAA related mortality (AAA events). Patients with diabetes who were prescribed metformin, but not patients with diabetes who were not prescribed metformin, had a lower incidence of AAA events compared with those without diabetes. A randomised controlled trial is needed to definitively test whether metformin reduces AAA related clinical events in patients with small AAAs.

Objectives: Currently there is no drug therapy for abdominal aortic aneurysm (AAA) and most previous investigations have focused on imaging rather than clinical outcomes. The aim of this study was to assess whether AAA related clinical events were lower in patients prescribed metformin.

Methods: This was a prospective cohort observational study performed in three cities in Australia, which was designed to study risk factors for clinical events not simply to focus on metformin. Patients with an asymptomatic unrepaired AAA of any diameter $\geq$30 mm were recruited from hospital outpatient clinics and surveillance programs run at four centres. The main outcome was the requirement for AAA repair or AAA related mortality (AAA events). The association between metformin prescription and AAA events was assessed using Kaplan–Meier analysis and Cox proportional hazard analysis.

Results: Patients (1,080) with a mean (SD) initial AAA diameter of 46.1 (11.3) mm were followed for a mean (SD) of 2.5 (3.1) years until an AAA event ($n = 454$), death ($n = 176$), loss to follow up ($n = 128$), or completion of current follow up ($n = 322$). Patients with diabetes who were prescribed metformin (adjusted HR 0.63, 95% CI 0.44–0.93), but not patients with diabetes who were not prescribed metformin (adjusted HR 1.15, 95% CI 0.83–1.59), had a lower incidence of AAA events compared with those without diabetes. Findings were similar in sensitivity analyses restricted to patients with an initial AAA diameter $\leq$50 mm and patients with a minimum follow up of six months before an AAA event.

Conclusions: These findings suggest that clinically important AAA events may be reduced in patients with diabetes who are prescribed metformin, but not those with diabetes receiving other treatments. A randomised controlled trial is needed to definitively test whether metformin reduces AAA related clinical events in patients with small AAAs who do not have diabetes.

Keywords: Abdominal aortic aneurysm, Surgical repair, Metformin
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INTRODUCTION

Open or endovascular surgical repair are the only treatments for abdominal aortic aneurysm (AAA) and based on current guidelines are recommended for large asymptomatic ($\geq$55 mm in men and $\geq$50 mm in women), and symptomatic or ruptured AAAs.[1,2] Asymptomatic AAAs

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smaller than these diameters are simply monitored but approximately 50% eventually undergo surgical repair.[1,2] There is great current interest in discovering drug therapies which may be used to treat patients with screening or incidentally identified small asymptomatic AAAs to reduce the requirement for surgical repair.[3,4]

Diabetes has been consistently associated with reduced AAA prevalence and progression.[5] Two recent human association studies reported that metformin prescription was associated with reduced AAA growth as assessed by repeat measurement of AAA diameter during aneurysm surveillance.[6,7] These findings suggest that metformin may be partially or wholly responsible for the association of diabetes with reduced AAA prevalence and progression.[8] AAA diameter is associated with measurement error, and change in diameter during mid-term follow up is often within the limits of agreement of the reproducibility for its assessment.[4,9] Furthermore, to be valuable, any drug treatment for small AAAs ultimately needs to reduce clinically important events (i.e. requirement for AAA repair and AAA rupture). There has, however, been limited previous investigation of the association between concurrently prescribed medications and important AAA related clinical outcomes such as requirement for AAA repair or AAA related death caused by rupture. Assessment of the association of metformin prescription with AAA events in patients with unrepaired AAAs may provide further insight as to whether it is worth testing metformin in a large clinical trial. The aim of this study was to determine whether AAA related clinical events were lower in AAA patients who had been prescribed metformin.

METHODS

Study design and patients

This study was part of a prospectively established and ongoing cohort investigation which commenced in 2002 aimed at identifying predictors of outcomes for AAA patients.[10,11] The current study included patients with an asymptomatic unrepaired AAA of any diameter $\geq$30 mm recruited between February 2002 and June 2017. One of the aims of this cohort study at the outset was to examine the association between prescribed medications at the time of recruitment and outcomes, although there was no specific focus on metformin alone. Patients were recruited from hospital outpatient clinics and surveillance programs run in three cities and four centres in Australia including Brisbane (The Royal Brisbane and Women's Hospital), Gosford (Gosford Vascular Clinic), and Townsville (The Townsville Hospital and the Mater Hospital Townsville).[10–12] All centres followed patients as part of their standard care to record AAA events. There is no screening program for AAA in Australia and therefore all patients included had an AAA identified by incidental imaging. Infrarenal aortic diameter was measured from ultrasound or computed tomography imaging at one of the four centres using previously reported reproducible protocols.[12] At recruitment, patients were assessed by clinical interview and physical examination to collect risk factor and medication history, including age, sex, diabetes, hypertension, ischaemic heart disease, heart failure, smoking history, and medication prescriptions. Risk factors were defined by prior history or treatment.[10–12] This information was used to categorise patients into three groups: patients with no history or medically recorded diagnosis of diabetes; patients previously diagnosed with diabetes prescribed metformin at the time of recruitment; and patients previously diagnosed with diabetes but not prescribed metformin at the time of recruitment.

The study was approved by the relevant ethics committees and written informed consent was obtained from all participating patients. No formal sample size calculation was developed prior to commencing the study or analyses.

Follow up and outcome assessment

The main outcome for this study was the combined incidence of AAA repair (open or endovascular) or mortality as a result of AAA rupture (defined as AAA events). Outcome events were determined from follow up visits and linked hospital admission and death records.[10–12] Outpatient follow up was performed according to local clinical practice and protocols. Patients with AAAs measuring 30–44 mm were usually followed up annually, while those with AAAs $\geq$45 mm were usually seen every six months.[10–12] For patients not experiencing a primary outcome event, follow up was censored at the date of last in- or outpatient review or at the time of data linkage, whichever was most recent. AAA repair was at the discretion of the treating consultant vascular surgeon and not standardised for the purpose of this study. AAA repair was identified with patients during follow up at outpatient clinics, review of hospital records, and through linked hospital data recording surgery for the appropriate International Statistical Classification of Diseases and Related Health Problems (ICD) diagnostic codes (e.g. ICD-10-CM I71.4 or ICD-10-CM I71.3). Surgeons and participants understood that the ongoing cohort study aimed to identify factors associated with outcomes, but were unaware of the focus on metformin prescription specifically. Decisions to proceed to AAA repair were made at the discretion of the treating vascular consultant and were independent of any planned analysis. AAA deaths as a result of rupture were identified through medical records, death certificates, or linked hospital data recording cause of death as the appropriate ICD diagnostic code (i.e. ICD-10-CM I71.3, ICD-9441.3). Linked data were obtained in November 2017 from the Admitted Patient Data Collections and National Death Index, which are regularly audited for accuracy although data were not available on all patients. Loss to follow up was defined where a patient had failed to attend their last two follow up appointments and linked data were not available for that patient in November 2017.

Statistical analyses

Complete recruitment data were available for all patients. The risk factors and medications recorded at the time of recruitment were compared between groups using Student *t* test or chi-square test for continuous and categorical

variables, respectively. Continuous data were normally distributed based on the result of Q—Q plots and Shapiro—Wilk tests using the SPSS v.23 software package (IBM). The incidence of AAA events in patients in different groups was compared using Kaplan—Meier with log rank test and Cox proportional hazard analyses using the SPSS v.23 software package (IBM) and R. The reference group was patients without diabetes. These analyses were focused on the incidence of and risk factors for the first AAA event that occurred in each patient. In the Cox proportional hazard analyses a number of different models were tested based on including risk factors previously associated with AAA growth or events (specifically age, sex, smoking, initial AAA diameter, ischaemic heart disease, and hypertension), and risk factors identified to be disparate between groups in univariable analyses (based on $p < .100$ in univariable analysis comparing patients with and without diabetes).[13] For these models initial AAA diameters were classified into four groups (ranges 30—39 mm, 40—49 mm, 50—54 mm, and ≥55 mm) and the resulting variable was stratified to avoid violating the proportional hazard assumptions. Sensitivity analyses were performed focusing on two subgroups: (a) patients with smaller initial AAA diameter (≤50 mm); and (b) patients with a minimum of six months follow up before any event or loss to follow up.

These subgroups were further examined as it was envisaged they would have longer follow up prior to an AAA event. For all Cox proportional hazards models, the proportional hazards assumption was accepted to be upheld if a global p value $> .05$ was observed. All models presented conformed to the proportional hazards assumption. For all analyses, p values $< .05$ were considered to be statistically significant.

RESULTS

Characteristics of the overall cohort in relation to diabetes and metformin prescription

A total of 1080 patients were included, of whom 129 (11·9%) had diabetes and were prescribed metformin, and 105 (9·7%) had diabetes but were not prescribed metformin at baseline. The risk factors and medications of patients at recruitment in relation to diabetes and metformin prescription are shown in Table 1. Patients prescribed metformin had smaller initial AAA diameters and were more likely to be male, have hypertension and heart failure, and also be prescribed statins, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blocking (ARB) medications than those without diabetes. Patients with diabetes not prescribed metformin were more likely to be male, have heart failure, and be prescribed ARB medication, and less likely to be current smokers than those without diabetes. Differences in risk factors and medications between the two diabetes groups included more frequent current smoking,

Table 1. Characteristics of patients in relation to diabetes and metformin prescription

	No diabetes	Diabetes not prescribed metformin	*p* value[a]	Diabetes prescribed metformin	*p* value[a]	*p* value[b]
Number	846	105		129		
Age, years	73.6 ± 8.0	74.2 ± 7.2	.429	72.4 ± 6.5	.054	.037
AAA diameter, mm	46.6 ± 11.5	45.3 ± 10.0	.272	43.4 ± 10.3	.002	.172
Female	174 (20.6%)	12 (11.4%)	.026	13 (10.1%)	.005	.739
Smoking			.038		.241	.044
Current	226 (26.7%)	16 (15.2%)		35 (27.1%)		
Former	503 (59.5%)	73 (69.5%)		83 (64.3%)		
Never	117 (13.8%)	16 (15.2%)		11 (8.5%)		
Hypertension	626 (74.0%)	80 (76.2%)	.628	115 (89.1%)	<.001	.008
Ischaemic heart disease	412 (48.7%)	57 (54.3%)	.280	64 (49.6%)	.847	.477
Heart failure requiring furosemide prescription	62 (7.3%)	19 (18.1%)	<.001	17 (13.2%)	.023	.300
Aspirin	487 (57.6%)	58 (55.2%)	.649	86 (66.7%)	.050	.074
Other antiplatelet	130 (15.4%)	18 (17.1%)	.636	28 (21.7%)	.069	.382
Anticoagulation	74 (8.7%)	15 (14.3%)	.066	11 (8.5%)	.934	.163
Statin	531 (62.8%)	74 (70.5%)	.121	116 (89.9%)	<.001	<.001
Calcium channel blocker	231 (27.3%)	38 (36.2%)	.057	48 (37.2%)	.020	.872
Beta blockers	298 (35.2%)	42 (40.0%)	.336	42 (32.6%)	.554	.238
Angiotensin converting enzyme inhibitor	314 (37.1%)	44 (41.9%)	.339	70 (54.3%)	<.001	.060
Angiotensin receptor blocker	177 (20.9%)	34 (32.4%)	.008	41 (31.8%)	.006	.922
Follow up, years	2.5 ± 3.0	2.2 ± 2.9	.500	3.2 ± 3.3	.015	.018
AAA repair or AAA rupture related mortality	378 (44.7%)	44 (41.9%)	.589	32 (24.8%)	<.001	.005
Deaths from any cause	248 (29.3%)	37 (35.2%)	.211	36 (27.9%)	.743	.229
Lost to follow up	97 (11.5%)	12 (11.4%)	.991	19 (14.7%)	.286	.459

Compared with chi-square or t test to the no diabetes group[a] or between the diabetes groups[b]. Numbers represent numbers (%) or mean (± standard deviation). AAA = abdominal aortic aneurysm.

hypertension, and prescription of statins in diabetes patients prescribed metformin.

AAA events

During a mean (±standard deviation) follow up of 25 (±3.1) years (total patient years: 2724.6), 454 (42.0%) patients had at least one AAA event. The primary AAA event was endovascular repair in 238 (22.0%), open repair in 204 (18.9%), and death as a result of AAA rupture without repair in 12 (1.1%). For the 12 patients who died of AAA rupture without repair, they either failed to attend for follow up ($n = 6$), were deemed unfit for surgery ($n = 3$), or refused repair ($n = 3$), and their date of death was provided from linked data. Of the patients not having an AAA event ($n = 626$; 58.0%), 176 (16.3%) were followed up until they died from causes unrelated to their AAA, 322 (29.8%) had complete follow up, and 128 (11.9%) were lost to follow up (as defined in the Methods) prior to study completion. Table S1 illustrates the risk factors, and medications of patients at the time of recruitment in patients that did or did not later have an AAA event. Patients having an AAA event were less likely to have diabetes, or be prescribed anticoagulants, metformin, or a dipeptidyl peptidase-4 inhibitor at the time of recruitment. They also had larger initial AAA diameter and were younger than those who did not have an event. No sex differences were observed between the patient groups (Table S1).

Association between diabetes and metformin prescription with AAA events

AAA events were less common in patients with diabetes prescribed metformin (32 of 129; 24.8%) than in patients with diabetes not prescribed metformin (44 of 105; 41.9%; $p = .005$) or patients with no diabetes (378 of 846; 44.7%; $p < .001$; Table 1). By Kaplan–Meier analysis, the incidence of AAA events was 17.7%, 30.7%, and 32.6% after one year, and 22.1%, 42.2%, and 43.7% after three years, in patients with diabetes prescribed metformin, patients with diabetes not prescribed metformin, and patients with no diabetes, respectively (Fig. 1A and Table S2). All cause mortality was similar in the three patient groups (Table 1). Cox proportional hazard analyses were performed examining the association between diabetes with or without metformin prescription and AAA events (Table 2). These analyses included adjustment for potential confounding variables such as age, sex, initial AAA diameter, smoking, and prescribed medications. Patients with diabetes prescribed metformin had a significantly reduced incidence of AAA events (HR 0.46–0.63 in different models) compared with patients who did not have diabetes (Table 2). Patients with diabetes not prescribed metformin did not have a reduced incidence of AAA events (HR 0.96–1.15 in different models; Table 2).

Sensitivity analyses

Patients with initial AAA diameter ≤50 mm. There were 763 (70·6%) patients with an initial AAA

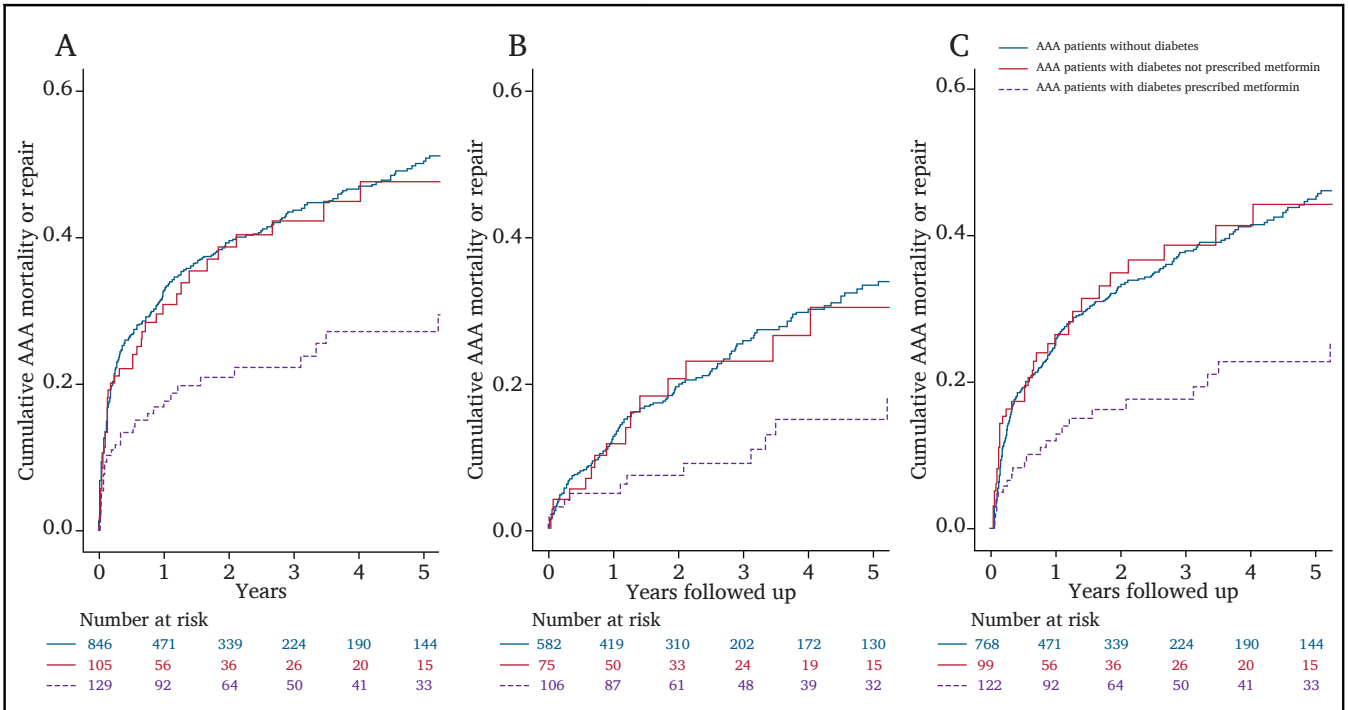

Figure 1. Combined incidence of abdominal aortic aneurysm (AAA) repair or mortality from AAA rupture (AAA events) in patients with diabetes prescribed metformin (purple dotted line), those with diabetes not prescribed metformin (red line), and those without diabetes (blue line). Graphs show cumulative proportion of events over five years for the whole cohort (A), patients with initial AAA diameter ≤ 50 mm (B), and patients with at least six months follow up (C). In the whole cohort, the incidence of AAA events was less in patients with diabetes prescribed metformin than in patients who had diabetes but were not prescribed metformin ($p = .003$) or patients who did not have diabetes ($p < .001$). The incidence of AAA events was similar in people who had diabetes but were not prescribed metformin and patients who did not have diabetes ($p = .839$). Findings in the two subgroups shown in (B) and (C) were similar (p values given in Table S2).

Table 2. Association between diabetes prescribed metformin and diabetes not prescribed metformin and requirement for AAA repair or AAA related mortality

Model	Diabetes prescribed metformin			Diabetes not prescribed metformin		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Unadjusted	0.47	0.33–0.68	<.001	0.97	0.71–1.32	.832
Model 1[a]	0.46	0.32–0.66	<.001	0.96	0.70–1.32	.815
Model 2[b]	0.63	0.43–0.91	.013	1.14	0.83–1.57	.410
Model 3[c]	0.63	0.44–0.93	.018	1.15	0.83–1.59	.396

The reference group was patients with no diabetes. HR = hazard ratio; CI = confidence interval. AAA = abdominal aortic aneurysm.
Adjusted for:
[a] Age and sex;
[b] Age, sex, smoking, initial AAA diameter, ischaemic heart disease, and statin prescription;
[c] Age, sex, smoking, initial AAA diameter, hypertension, ischaemic heart disease, statin, furosemide, angiotensin converting enzyme inhibitor, and angiotensin receptor blocker.

diameter ≤ 50 mm, including 106 with diabetes prescribed metformin, 75 with diabetes not prescribed metformin, and 582 who did not have diabetes. Table 3 shows the risk factors and medications at recruitment for these patient groups. As in the main analysis, AAA events were substantially and significantly lower in patients with diabetes prescribed metformin in comparison with patients with diabetes not prescribed metformin and those who did not have diabetes (Tables 3 and S2, and Fig. 1B). In Cox proportional hazard analysis models patients with diabetes prescribed metformin had approximately half the incidence of AAA events compared with those without diabetes (HR 0.44–0.49; Table 4). The incidence of AAA events was similar in patients with diabetes not prescribed metformin and those without diabetes (Fig. 1B, Tables 3,4 and S2).

Patients with at least 6 months follow up prior to an AAA event or loss to follow up. There were 989 patients (91.6%) with a follow up of at least 6 months before an AAA event, death, completion, or loss to follow up. Of these, 122 were prescribed metformin for diabetes, 99 had diabetes and were not prescribed metformin, and 768 did not have

Table 3. Characteristics of patients in relation to diabetes and metformin prescription for participants with initial AAA diameter ≤50 mm

	No diabetes	Diabetes not prescribed metformin	*p* value[a]	Diabetes prescribed metformin	*p* value[a]	*p* value[b]
Number	582	75		106		
Age, years	73.8 ± 8.0	74.2 ± 7.4	.621	72.6 ± 6.5	.098	.110
Initial AAA diameter, mm	40.5 ± 5.8	40.2 ± 5.3	.704	39.9 ± 5.9	.390	.763
Female	134 (23.0%)	8 (10.7%)	.014	12 (11.3%)	.007	.890
Smoking			.318		.292	.141
Current	147 (25.3%)	13 (17.3%)		30 (28.3%)		
Former	347 (59.6%)	50 (66.7%)		66 (62.3%)		
Never	88 (15.1%)	12 (16.0%)		10 (9.4%)		
Hypertension	428 (73.5%)	58 (77.3%)	.481	96 (90.6%)	<.001	.014
Ischaemic heart disease	282 (48.5%)	40 (53.3%)	.426	53 (50.0%)	.770	.658
Aspirin	342 (58.8%)	42 (56.0%)	.648	74 (69.8%)	.032	.056
Other antiplatelet	80 (13.7%)	11 (14.7%)	.828	25 (23.6%)	.010	.139
Anticoagulation	58 (10.0%)	11 (14.7%)	.211	9 (8.5%)	.638	.192
Statin	382 (65.6%)	50 (66.7%)	.859	95 (89.6%)	<.001	<.001
Calcium channel blocker	152 (26.1%)	27 (36.0%)	.070	39 (37.8%)	.024	.913
Beta blockers	209 (35.9%)	31 (41.3%)	.359	33 (31.1%)	.343	.157
Angiotensin converting enzyme inhibitor	204 (35.1%)	35 (46.7%)	.049	56 (52.8%)	.001	.414
Angiotensin receptor blocker	130 (22.3%)	23 (30.7%)	.108	34 (32.1%)	.030	.841
Furosemide prescribed for cardiac failure	40 (6.9%)	15 (20.0%)	<.001	12 (11.3%)	.111	.106
Follow up, years	3.2 ± 3.2	2.9 ± 3.2	.444	3.6 ± 3.2	.157	.112
AAA repair or AAA rupture related mortality	158 (27.1%)	19 (25.3%)	.739	14 (13.2%)	.002	.037
Deaths from any cause	155 (26.6%)	23 (30.7%)	.459	28 (26.4%)	.963	.531

Compared with chi-square or *t* test to the no diabetes group[a] or between the diabetes groups[b]. Numbers represent numbers (%) or mean (± standard deviation). AAA = abdominal aortic aneurysm.

Table 4. Association between diabetes prescribed metformin and diabetes not prescribed metformin and requirement for AAA repair or AAA related mortality in patients with initial AAA diameter ≤50 mm

Model	Diabetes prescribed metformin			Diabetes not prescribed metformin		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Unadjusted	0.44	0.25–0.75	.003	1.02	0.63–1.64	.939
Model 1[a]	0.44	0.26–0.77	.004	1.04	0.64–1.68	.866
Model 2[b]	0.49	0.27–0.87	.015	1.17	0.72–1.92	.529
Model 3[c]	0.48	0.27–0.87	.015	1.16	0.70–1.93	.557

Reference group comprised patients with no diabetes. HR = Hazard ratio; CI = Confidence interval. AAA = abdominal aortic aneurysm.
Adjusted for:
[a] Age and sex;
[b] Age, sex, smoking, initial AAA diameter, ischaemic heart disease, and statin prescription;
[c] Age, sex, smoking, initial AAA diameter, hypertension, ischaemic heart disease, statin, frusemide, angiotensin converting enzyme inhibitor, and angiotensin receptor blocker.

diabetes. The characteristics of these patients are detailed in Table S3. Kaplan–Meier analyses demonstrated that the incidence of AAA events was significantly lower in the patients prescribed metformin, compared with the other two groups (Fig. 1C, Table S2). In Cox proportional hazard models, patients with diabetes prescribed metformin had a significantly reduced incidence of AAA events (HR ranging from 0.43 to 0.57; Table S4). The incidence of AAA events did not differ significantly between patients with diabetes who were not prescribed metformin and those with no diabetes (Tables S2–4).

DISCUSSION

The main finding from this study was that among patients with AAAs, those with diabetes prescribed metformin had a significant and substantially lower incidence of clinically important AAA events in comparison with other patients. This association was independent of established risk factors for AAA growth such as initial AAA diameter and smoking, and also potential confounding factors associated with diabetes such as the prescription of statins, or angiotensin inhibitor or blocking medications.[4,13] Patients with diabetes not prescribed metformin had similar rates of AAA events to patients without diabetes. Sensitivity analyses suggested that the reduced rates of AAA events in patients with diabetes prescribed metformin were even more marked in patients with smaller AAAs and with longer follow up.

It has been proposed that metformin may inhibit progression of AAA pathology via multiple mechanisms including limiting aortic inflammation, and reducing extracellular matrix remodelling and oxidative stress based on findings within *in vitro* studies and animal models.[7,8,14–18] Recently it has been reported that activation of the master regulator of energy homeostasis adenosine-5′-monophosphate (AMP)-activated protein kinase (AMPK), which is thought to be the major mechanism by which metformin works, inhibits experimental AAA.[19] Similar animal and *in vitro* support has, however, been reported for other drugs, such as doxycycline, mast cell inhibitors, and angiotensin converting enzyme inhibitors, which have subsequently been unsuccessful in clinical trials.[4,20–22] Also the relevance of *in vitro* and rodent models to human AAA has been questioned.[3,4] The human observational evidence available to support these previously trialed medications has, however, been limited or inconsistent.[3,4] The observational data presented for metformin in this study and two previously reported studies would appear to be substantially stronger than has been reported for other drugs.[6–8] These data provide a strong rationale for a large clinical trial to test whether metformin limits AAA related clinical events in patients with small AAAs.

As far as the present authors are aware, there have been no previous studies examining the association between medication prescription and requirement for AAA repair. Instead, most investigations have studied risk factors for AAA growth. The largest reported analysis of predictors of small AAA growth, which included data on 15,475 patients, reported that larger initial AAA diameter, current smoking, and absence of diabetes were the only independent risk factors for more rapid AAA growth.[13] The study did not report risk factors for AAA repair, but did study AAA rupture rate in a smaller subset of patients. Older age, female sex, current smoking, lower body mass index, and higher blood pressure were all independently associated with AAA rupture risk.[13] None of the medications examined were associated with AAA rupture risk, although metformin prescription was not reported. One previous nested case control population study has examined the association between metformin and AAA rupture. The investigators reported reduced numbers of metformin users among patients with ruptured AAA, although this association was not significant after adjusting for other risk factors.[23]

The current study has a number of strengths and weaknesses. The study included one of the largest groups of patients in which clinically important AAA events have been studied. The patients in the current study were recruited from hospitals and therefore may not be representative of those with screening detected AAAs. Drug history was generally only collected at one time point and information was not routinely collected on the duration or changes to, or compliance with medications. The decision to perform AAA repair was at the discretion of the treating consultant vascular surgeon and was not standardised. Information on the control of diabetes, such as HbA1c, was not collected.

This further information would have been useful in adjusting for any differences in blood glucose control between groups. Event data were collected from multiple routes, including patient follow up and linked data and were not complete for all patients. It needs to be acknowledged that as independent adjudication of events was not performed it is possible that inaccuracies may have occurred. Moreover, although patients who did not experience an outcome event were censored at the date of last contact, or data linkage, the potential for attrition bias must be acknowledged. This was partly mitigated by conducting a sensitivity analysis that excluded patients with less than 6 months follow up. Furthermore, human association studies, as reported here, are subject to confounding and selection bias. Attempts were made to reduce the influence of confounding by adjusting for established risk factors for AAA growth and identified differences between patient groups. However, it remains impossible to exclude residual confounding. The number of patients with diabetes in this study was relatively small, meaning that the data analyses must be interpreted with caution. Taking account of all these caveats, it is imperative that metformin is assessed in a well designed randomised controlled trial to test if it has benefit before any conclusion can be drawn on its efficacy. Although metformin has recognised gastro-intestinal side effects and has rarely been associated with lactic acidosis, it has been successfully used in a range of patients without diabetes without an excess of major complications, suggesting that it will be well tolerated by those with AAAs.[24]

In conclusion, this study suggests that clinically important AAA related events are fewer in patients with diabetes prescribed metformin than those without diabetes. Patients with diabetes not receiving metformin did not have reduced AAA events. These findings, along with previous data reporting the association between metformin prescription and reduced AAA growth, provide a compelling case for a randomised controlled trial to investigate the efficacy of metformin as a medical treatment for AAA in patients without diabetes and one such trial has already started.[6–8,25]

CONFLICT OF INTEREST

No conflicts of interest.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejvs.2018.07.035.

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COUP D'OEIL

Type IIIB Endoleak 19 Years After Thoracic Endovascular Aneurysm Repair

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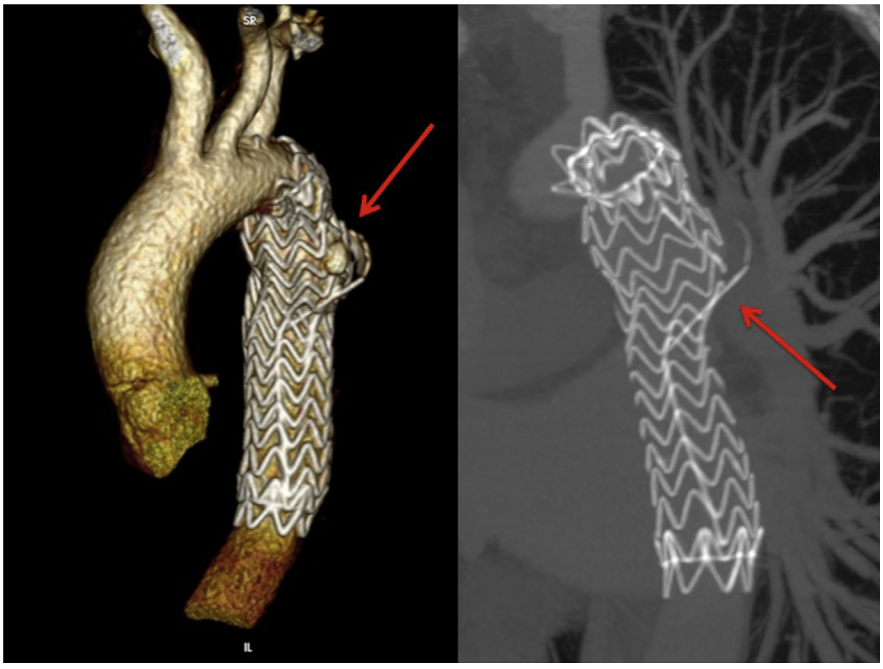

A 66 year old patient presented 19 years following a 26-26-125 TAG (W.L. Gore and Assoc, Flagstaff, AZ, USA) endograft owing to blunt thoracic trauma in 1999. During follow up, no problems were encountered until year 19, when a type IIIB endoleak appeared, caused by a fabric tear secondary to fracture of the longitudinal bar. Another 26-26-100 C-TAG device (W.L. Gore) was deployed inside the previous one, solving the endoleak. This case shows the importance of lifelong imaging and strict surveillance of patients with aortic trauma treated by thoracic endovascular aneurysm repair.

EDITOR'S COMMENT:

The journal is informed that the circumstances of the endoleak due to stent fracture had been reported to the manufacturer. Gore Medical responded mentioning that the TAG device underwent significant changes between 2001–2004 (keeping in mind the original deployment was circa 1999), including removal of the longitudinal bars that the authors feel were probably under additional mechanical stress when deployed along the typical thoracic aortic curves, and also the type of PTFE used. This is no doubt reflected in the modern versions including the new Conformable TAG thoracic endoprosthesis.

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