An analysis of drug modulation of abdominal aortic aneurysm growth through 25 years of surveillance

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Background: **A modest (41%) reduction in abdominal aortic aneurysm (AAA) growth rate is likely to delay AAA-related events (surgery or rupture) by 5 years, making the notion of AAA medical treatment very appealing. Randomized controlled trials of commonly used existing medications are expensive and ethically questionable. This study reviewed the independent associations of commonly used medications and AAA growth during a 25-year period of AAA surveillance.**
Methods: **The study included all patients monitored through an AAA screening and surveillance program. Records of AAA size, risk factors, outcomes, death, and medications were entered into a continually updated database. AAA growth rates were calculated using a flexible hierarchical model. A multivariate model was used to test for associations independent of confounders.**
Results: **The study comprised 1269 patients (94.1% men) who had a mean age of 67 years. The median starting diameter was 35 mm, the end diameter was 44 mm, and follow-up was 3.4 years. Drugs used in the treatment of diabetes were associated with a 56% reduction in AAA growth rate ($P = .01$) independent of confounding factors, including other therapeutic agents ($P = .003$). Angiotensin-receptor blockers and potassium-sparing diuretics were also associated with slower AAA growth rates, although these effects were not independent of all confounders.**
Conclusion: **Diabetes or its medications, or both, have a negative effect on AAA growth. Because of polypharmacy, demonstrating the independent effects of individual drugs affecting the renin-angiotensin system was not possible. In light of this analysis, however, strong associations between angiotensin-receptor blockers and aldosterone-receptor blockers and slowed AAA progression are credible. (J Vasc Surg 2010;52:55-61.)**

Abdominal aortic aneurysm (AAA) disease is a common life-threatening condition in the Western world with an increasing prevalence. The adoption of large-scale screening programs for men at risk (age ≥65 years), designed to identify and monitor small aneurysms, provides a window for medical therapy, which has yet to be fully explored. Less than one-third of all men identified with a small AAA through screening come to repair within a 4-year period,[1] and only half of those considered fit for surgery at diagnosis will have undergone repair at the end of a 5-year period.[2,3] This reflects an average time to intervention for screen detected AAA patients of between 4 and 6 years and provides an opportunity for therapies designed to slow AAA disease progression.

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Extrapolation of linear growth rates published by this unit demonstrate that a modest 41% reduction in growth rate could delay intervention for the median screened AAA of 35 mm by 5 years (mean linear growth rate of 2.81 mm/y).[4] At an average of 7.1 years to reach 55 mm from a 35-mm starting diameter, a growth rate of 1.66 mm/y (a 41% reduction) delays to 12.1 years the average time to reach 55 mm.

The two aims of medical therapies are to reduce comorbidity from concomitant cardiovascular disease and to modify AAA disease progression (ie, reduce the risk of AAA rupture).[5] The universally used measure of rupture risk is AAA diameter. It is generally assumed that therapies achieving slowed AAA growth or relative decreases in AAA diameter will result in a reduced rupture risk. The pathophysiology of AAA rupture is complicated, however, and it may be that some therapeutic effects on AAA rupture cannot be reported through AAA size alone.[6] Modelling AAA growth rate over time can predict AAA diameter and infer AAA rupture risk. If AAA growth rate can be modified by medical therapy, it implies that the risk of rupture will also be altered. If the time to AAA surgical intervention can be delayed sufficiently that the risks presented by other comorbidities begin to outweigh those of AAA rupture, an expensive and potentially dangerous intervention can be avoided.

Despite the enormous potential for disease-modifying drugs, evidence is lacking, and there is currently no ac-

cepted therapeutic agent for the management of AAA expansion. Expensive randomized controlled trials have struggled to obtain adequate numbers, whereas retrospective studies have yet to overcome difficulties of confounding factors. New randomized controlled trials looking at the effect of widely used medications such as statins and renin-angiotensin system modulators on AAA growth are likely to encounter difficulties in obtaining ethical approval. Currently, level B and C evidence from small studies suggests that roxithromycin, doxycycline, and statins reduce AAA expansion rates,[7] and evidence from a large linked administrative database suggests that angiotensin-converting enzyme (ACE) therapy may protect from AAA rupture.[8]

This study reviewed the independent associations of commonly used medications and AAA growth from a 25-year period of AAA surveillance. To overcome problems of confounding factors, a novel method of comparing AAA growth rates within a multivariate model was used.

METHODS

Ethics approval for the study was sought and obtained from the West Sussex local Research Ethics Committee (Ref 03/04/4b).

Inclusion criteria. All patients identified with an AAA through the Chichester AAA screening program between January 1984 and January 2007 were considered for the study. Although the program targets men, women who were incidentally found to have a small AAA by the local vascular service were offered surveillance within the program. Patients were excluded for not having more than one ultrasound scan measurement of aneurysm diameter or if the follow-up time was <3 months.

Patient follow-up. Patients were invited to attend AAA surveillance clinics where they would be asked to complete a detailed questionnaire of risk factors and current medications before having three separate automated blood pressure readings and a B-mode ultrasound (AP and transverse) measurement of their AAA diameter. The interval between follow-up was determined by the maximal AAA diameter at the previous visit (<4.5 cm yearly and ≥4.5 cm every 3 months).

Patient demographics. Cardiovascular risk factors for each AAA patient, including hypertension, age, gender, smoking history, diabetes, and ischemic heart disease, were obtained from the surveillance unit database.

Record of prescriptions. Starting in 1984, all patients identified with an AAA through screening or referred for AAA surveillance with a small AAA were asked to list all current medications. This was completed under supervision at the time of the ultrasound scan. Records of these prescriptions were updated at each surveillance visit through a questionnaire completed at the time and entered into a purpose-built database that estimated the start date of each prescription (the date the drug was first mentioned) and the end of each prescription (the date when the drug was first omitted from the questionnaires). Validation of prescriptions kept on the database was performed using repeat prescriptions provided from a single general practice surgery for the time period (Supplement Table A, online only). All categories of regular medication, categorized according to the British National Formulary (BNFno. 53, March 2007. Royal Pharmaceutical Society of Great Britain Publishing Group, UK) with potential relevance to AAA pathophysiology, and with a prescription frequency of ≥1% were included (Table I).

Table I. Drug categories recorded in database

Categories by pathophysiology	*BNF ID*	*Drug categories*
Lipid-regulating drugs	2.12	Statins
Anti-inflammatory drugs	10.1.1	Nonsteroidal anti-inflammatory drugs
	10.1.2	Drugs to suppress rheumatic disease
	10.1.3	Corticosteroids
	10.1.4	Drugs for treatment of gout
Antihypertensive drugs	2.5.4	α-Blockers
	2.5.5.1	Angiotensin-converting enzyme inhibitors
	2.5.5.2	Angiotensin-receptor blocker
	2.4	β-Blockers
	2.6.2	Calcium channel blockers
	2.2.1	Thiazides and related diuretics
Oral anticoagulants, antiplatelets	2.9	Antiplatelets
	2.8.2	Oral anticoagulants
Cardiac medications	2.1	Positive inotropic drugs
	2.3	Antiarrhythmic drugs
	2.6.1	Nitrates
	2.6.3	Potassium-channel activators
	2.7	Sympathomimetics
Diabetic medication	6.1	Drugs used in diabetes
Nonthiazide diuretics	2.2.2	Loop diuretics
	2.2.3	Potassium-sparing diuretics
	2.2.4	Potassium-sparing diuretics + other diuretics
COPD medication	3.1	Bronchodilators

BNF, British National Formulary; *COPD,* chronic obstructive pulmonary disease.

Statistical analysis of growth rates. AAA growth rates were modeled using a likelihood-based, multilevel model adapted from Brady et al.[9] The analysis of growth rates by this model can be thought of as having two distinct steps, although the model actually combines these steps in a single function. The first of these steps analyzes within-subject variation. Serial measurements are collated for each AAA patient. To adapt this for the purpose of measuring differences in growth rate by prescription, only AAA serial measurements that corresponded to the prescription period were selected (the remaining portions of the growth plot for that individual were excluded from that particular analysis). Linear and quadratic time effects and mean arterial pressure (MAP) measures during the same period were used as predictors of these serial measurements, and an adjusted linear growth rate was obtained.

The second level of analysis (between-subjects) compared growth rates between these two groups. Patients taking the drug under investigation were placed in the

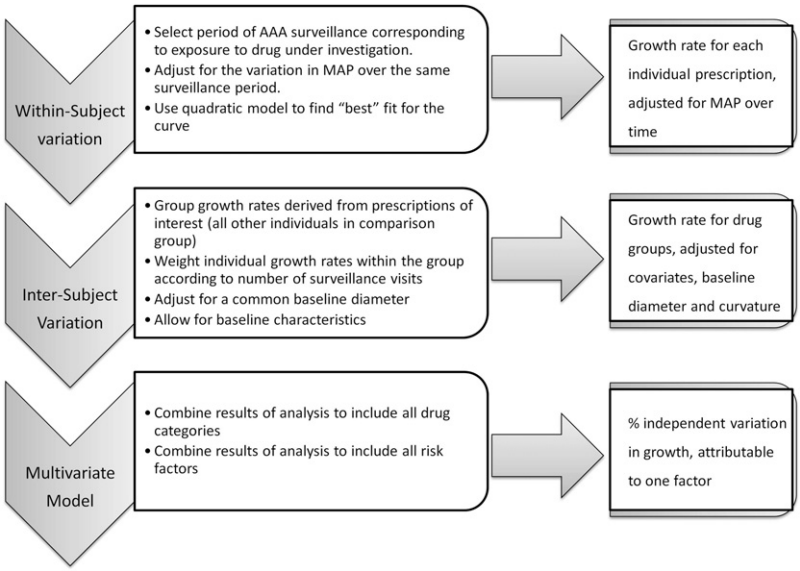

Fig 1. Summary of analytical process used in interpreting the data. *AAA*, Abdominal aortic aneurysm.

active group (growth rates for these patients only corresponded to the period they were exposed to the drug). All patients not taking the drug under investigation were placed in a comparison group. A further adjustment was made, so that each group reflected a common average baseline diameter, or start point, and adjustment was made for covariates (age at baseline, MAP, gender, and smoking history) between the groups.

The models were fitted using Markov Chain Monte Carlo methods as implemented in MLwin software.[10] Noninformative priors were used. Intercept, slope, and curvature terms were assumed to follow a multivariate normal distribution. Slope, curvature, and MAP effect were allowed to vary for each individual. Confounders were included as fixed-effect covariates and the cross-level interactions of drug category with time were tested to compare growth rates for these groups. Observations censored due to surgery were considered missing at random .The steps of analysis are summarized in Fig 1.

Multivariate analysis. A third level of analysis was added. A multivariate model was fitted to determine which categories of drug were independently associated with changes in growth rate. Terms for age, smoking, gender, and blood pressure were forced into the model to ensure that associations were independent of these factors. Variables for drug categories were then entered into the model one at a time, adding the variable most strongly associated with growth rate at each step, until there were no more variables that added significantly to the model. The *P* value for entry was .05. For these models, measurements during the entire follow-up period were used.

RESULTS

Of 1649 patients considered for the study, 380 patients were excluded (244 patients with <2 AAA measurements, 53 patients with AAA diameter of <3 cm, 83 patients with <3 months follow-up), leaving 1269 AAA patients. Of these, 335 underwent elective AAA repair, and the AAA in 88 patients ruptured, of whom 71 were considered unfit or had declined repair (Fig 2).

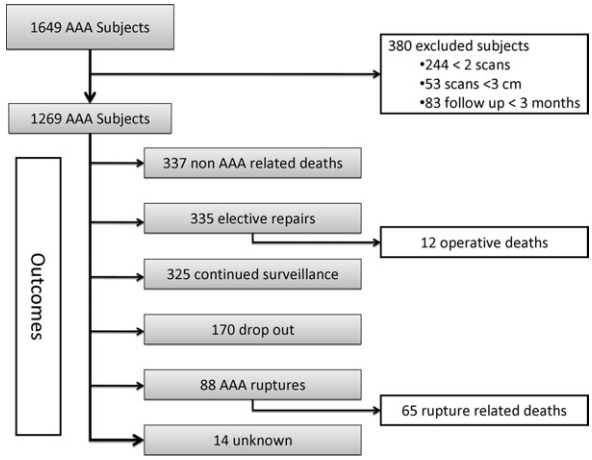

Fig 2. Schematic representation shows patients included in the study and outcomes.

The average adjusted growth rate for AAAs under surveillance was 1.97 mm/y, with the median AAA starting at 35 mm and growing to 44 mm during a 3.4-year period (Table II). Female gender was associated with a 42% lower AAA growth rate of −0.84 mm/y (95% confidence interval [CI], −1.37 to −0.31 mm/y; $P = .002$). Current smoking was associated with 24% higher AAA growth rate of 0.56 mm/y (95% CI, 0.29-0.83 mm/y) compared with nonsmokers (including ex-smokers; $P < .001$). No significant differences in AAA growth were detected between ages or

Table II. Patient characteristics

Variable	*Result*
Final AAA diameter, mean (IQR) mm	44 (35-56)
Start diameter, mean (IQR) mm	35 (31-42)
Follow-up time, mean (IQR) y	3.4 (2.0-6.5)
Age, mean (IQR) y	67 (65-71)
Female, No. (%)	75 (5.9)
Current smokers, No. (%)	403 (32.8)
Growth rate, mean (SE) mm/y [95% CI]	1.97 (0.11) [−1.60 to 5.54]

AAA, Abdominal aortic aneurysm; *CI,* confidence interval; *IQR,* interquartile range; *SE,* standard error.

for differences in the mean blood pressure for all surveillance visits combined.

In a multivariate model adjusting for curvature, baseline diameter, MAP, age at baseline, gender, and smoking history, patients taking hypoglycemic medications had a 56% slower AAA growth rate ($P = .01$), those treated with angiotensin-receptor blockers (ARBs) had a 47% slower AAA growth rate ($P = .04$), and those treated with potassium-sparing diuretics had a 71% slower AAA growth rate ($P = .05$; Table III). When all classes of therapeutic agent were added to the multivariate model, only diabetic medications were independently associated with AAA growth rate ($P = .003$), accounting for 2.7% of the variability. Smoking and female gender were the risk factors that showed an independent association with AAA growth rate.

DISCUSSION

This study used complex growth modeling and multivariate analysis to provide meaningful commentary on 25 years of prospectively collected data on 1269 AAA patients. To our knowledge, this is the longest reported continuous collection of AAA data and provides an opportunity for comparison of cardiovascular risk factors and >5000 prescriptions with AAA growth rates. Current prescribing guidelines would make it difficult to find a comparable group of AAA patients not taking, for example, statins, but because of the historical nature of this cohort, more than two-thirds of patients were not exposed to statin therapy during the course of the study. Although including 25 years of data does introduce the risk of temporal bias, we believe the nature of AAA pathophysiology is unlikely to have changed in this time frame, and risk factors of age, blood pressure, gender, and smoking history, which may have altered over time, were adjusted for in the analysis.

Advantages of this analysis over previously reported retrospective association studies include adjustment of AAA growth rates based on multilevel modeling, adjustment of MAP over time, and inclusion of AAA measurements for analysis related only to periods of exposure to the medication in question (reducing comparison of individual variation between patients). Although compliance is an issue in any therapeutic study because of the nature of the within-group comparison, any noncompliance in one group is likely to be balanced in another, resulting in a reduction of power to detect differences but not in false-positive results.

Smoking was associated with an increased AAA growth rate, but this was not true for serial MAP measurements or a history of hypertension, as has previously been reported.[9] Unexpectedly, female gender was associated with slowed adjusted AAA growth, although numbers of women were low (n = 75). This finding contradicts those of two other studies[11,12] and has been discussed by this group in more detail elsewhere.[4] In summary, AAA size, distribution, age, and gender fit the expectations of a screening program targeting men at 65 years.

Exposure to hypoglycemic medication was the single association with therapeutic agents to maintain significance through multivariate analysis ($P = .003$). This is supported by several studies that demonstrated a protective role for diabetes in AAA expansion.[9,13,14] No single subclass of diabetic therapeutic agent had a greater effect than any other ($P > .05$, Supplement Table B, online only), making it likely that diabetes has the protective role rather than the actions of its therapeutic agents. Almost all patients identified as diabetic through the questionnaires were receiving medication (17 were diet controlled); thus, it was not possible to confirm the effects of diabetes on AAA growth outside of those medicated patients.

ARBs and potassium-sparing diuretics demonstrated significant associations with slowed AAA growth rate separate of their effects on MAP. The actions of ARBs through the angiotensin-1 (AT1) receptor of the RAS are well reported. Potassium-sparing diuretics act by blocking aldosterone receptors, aldosterone being released through activation of the AT1 receptor. Several groups have reported on the effects of blocking the AT1 receptor and the effects of aldosterone in murine models of AAA disease,[15,16] but to our knowledge this is the first time that agents affecting these components of the RAS have been associated with altered AAA growth in a clinical study.

ACE inhibitors, in contrast with a previous large cohort study looking at rupture rates,[8] was not associated with slowed AAA growth rate. However, inclusion of ACE as a drug affecting the RAS (along with ARBs and potassium-sparing diuretics) strengthened the power of the association with slowed AAA growth rate (Supplement Table B, online only).

Demonstrating independent effects in these therapeutic agents through multivariate analysis was not possible due to the polypharmaceutical approach taken to address cardiac risk factors in many of these patients. However, in the context of existing evidence that the RAS plays a strong role in the pathophysiology of AAA disease,[17] this should be seen as evidence that drugs affecting the RAS are likely to slow AAA growth.

The overall trend for AAA exposed to categories of therapeutic agents is for slowed AAA growth, with the notable exception of drugs to suppress rheumatic disease, which includes methotrexate, azathioprine, and penicilla-

Table III. Abdominal aortic aneurysm growth rates and medication exposure adjusted for baseline diameter, curvature, mean arterial pressure, age at baseline, sex, and smoking history

Class of medication	*Patients No.*	*Surveillance visits No.*	*Growth rate per year (Mean SE) mm*	*Estimated difference in AAA growth rate (95% CI)*	P *value*
Statins					
No	840	6919	1.54 (0.14)	0	
Yes	357	3531	1.47 (0.20)	−0.07 (−0.45 to 0.32)	.73
NSAIDS					
No	1102	9181	1.53 (0.14)	0	
Yes	120	1269	1.03 (0.31)	−0.51 (−1.13 to 0.08)	.11
Rheumatic disease suppressants					
No	1231	10339	1.64 (0.23)	0	
Yes	13	111	3.93 (1.28)	2.29 (−0.20 to 4.78)	.07
Corticosteroids					
No	1165	9775	1.49 (0.13)	0	
Yes	74	675	1.73 (0.32)	0.24 (−0.38 to 0.87)	.45
Drugs to treat gout					
No	1175	9844	1.57 (0.13)	0	
Yes	63	606	1.14 (0.38)	−0.43 (−1.16 to 0.30)	.25
α-Blockers					
No	1030	9729	1.81 (0.23)	0	
Yes	69	721	2.27 (0.42)	0.45 (−0.28 to 1.18)	.23
ACE inhibitors					
No	834	7777	2.04 (0.24)	0	
Yes	265	2673	1.76 (0.27)	−0.28 (−0.67 to 0.12)	.17
ARBs					
No	1026	9869	1.94 (0.23)	0	
Yes	73	581	1.03 (0.48)	−0.91 (−1.78 to −0.03)	.04
β-blockers					
No	773	7138	1.96 (0.24)	0	
Yes	326	3312	1.77 (0.27)	−0.19 (−0.55 to 0.16)	.29
Calcium channel blockers					
No	808	7441	1.97 (0.24)	0	
Yes	291	3009	1.68 (0.27)	−0.29 (−0.66 to 0.08)	.12
Thiazides, related diuretics					
No	912	8559	1.95 (0.24)	0	
Yes	187	1891	2.03 (0.30)	0.09 (−0.37 to 0.54)	.71
Antiplatelet drugs					
No	757	6183	1.54 (0.15)	0	
Yes	443	4267	1.35 (0.83)	−0.19 (−0.53 to 0.12)	.26
Oral anticoagulants					
No	1168	9678	1.52 (0.14)	0	
Yes	68	772	1.27 (0.33)	−0.26 (−0.92 to 0.39)	.43
Positive inotropic drugs (cardiac glycosides)					
No	1182	9838	1.56 (0.14)	0	
Yes	54	612	1.34 (0.35)	−0.21 (−0.91 to 0.47)	.55
Antiarrhythmic drugs					
No	1210	10150	1.52 (0.13)	0	
Yes	30	300	1.09 (0.73)	−0.46 (−1.87 to 0.98)	.53
Nitrates					
No	1087	8943	1.49 (0.14)	0	
Yes	143	1507	1.27 (0.43)	−0.21 (−0.66 to 0.24)	.36
Potassium-channel activators					
No	1231	10306	1.47 (0.13)	0	
Yes	12	144	1.85 (1.13)	0.39 (−1.86 to 2.63)	.73
Diabetic medication					
No	1163	9928	1.70 (0.23)	0	
Yes	69	522	0.74 (0.40)	−0.95 (−1.66 to −0.25)	.01
Loop diuretics					
No	1096	9066	1.53 (0.13)	0	
Yes	130	1384	1.17 (0.26)	−0.36 (−0.87 to 0.25)	.16
Potassium-sparing diuretics					
No	1208	10111	1.58 (0.13)	0	
Yes	31	339	0.49 (0.55)	−1.09 (−2.17 to −0.06)	.05
Potassium-sparing diuretics + other diuretics					
No	1175	9759	1.52 (0.13)	0	
Yes	62	691	1.19 (0.37)	−0.33 (−1.03 to 0.37)	.36

Table III. Continued.

Class of medication	*Patients No.*	*Surveillance visits No.*	*Growth rate per year (Mean SE) mm*	*Estimated difference in AAA growth rate (95% CI)*	P *value*
Bronchodilators					
No	1219	10210	1.52 (0.13)	0	
Yes	25	240	1.51 (0.68)	−0.01 (−1.34 to 1.29)	.99
Drugs acting on the RAS[a]					
No	817	7382	1.93 (0.13)	0	
Yes	392	3068	1.60 (0.16)	−0.33 (−0.63 to −0.03)	.03

AAA, Abdominal aortic aneurysm; *RAS,* renin-angiotensin system; *SE,* standard error.
[a]Angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and potassium-sparing diuretics.

mine. Here we found a nonsignificant trend for a 140% increase in growth rate. This suggests that immunosuppressive drugs may destabilize the AAA wall, permitting further AAA expansion. A similar but less marked trend is seen with corticosteroids. In contrast to recent reports, no association was found with statins and altered growth rate.[18,19] Ideally the positive associations identified by this study would be confirmed by those discontinuing therapies (a retrospective cross-over study); however, the numbers of patients taken off medication once started were too small for meaningful analysis.

A criticism of observational studies has been the inability to exclude covariates as a causal factor when reporting an association. This study attempted to address this point by using a multivariate model to analyze all possible covariates (risk factors and categories of therapeutic agents). This exposed the study to errors of multiple testing; however, correction methods such as the Bonferroni method are very conservative and increase the likelihood of type II errors, meaning that important differences may be missed. Errors of interpretation are less when no adjustment is made.[20,21] For this reason all associations with a value of $P < .05$ have been reported as significant in this study but with a warning that some findings may be due to statistical chance rather than a true association. Multivariate analysis has provided a tool to assess the independence of associations; however, associations that cannot prove independence may still be true and should be considered within the context of all available evidence. The alternative to observational studies is controlled trials, but these are likely to be unpalatable to patients and ethics boards because many of the drugs in question have proven benefits for risk modification in these patients.

Embracing the approach put forward in this study of including all covariates requires very large numbers. Even this cohort of >1200 patients followed-up for 25 years was unable to demonstrate independence for several of the observed associations. With the advent of national AAA screening programs, an opportunity is available to compile databases that are large enough to demonstrate independent associations between current drug use and AAA progression (expansion and rupture).

CONCLUSIONS

In studying AAA growth modulation, the importance of historical observational data is paramount considering the difficult ethical implications of devising cohort studies using established treatments for coexisting pathologies. Although analysis of such data is complex and interpretation of results difficult, conclusions can still be drawn. This large study found diabetes and smoking were independently associated with altered AAA growth rate. Drugs influencing the RAS, in particular ARBs and aldosterone-receptor blockers, may reduce the rate of AAA growth, but these associations need confirmation from similar observational studies or prospective studies.

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AUTHOR CONTRIBUTIONS

Conception and design: AT, JC, HH
Analysis and interpretation: AT, JC, SH, HH
Data collection: AT, MF, HA, HH
Writing the article: AT, JC, HH
Critical revision of the article: AT, JC, HA, HH
Final approval of the article: AT, JC, MF, SH, HA, HH
Statistical analysis: AT, JC, HA, HH
Obtained funding: AT, HA, HH
Overall responsibility: HH

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Additional material for this article may be found online at www.jvascsurg.org.

Supplement Table A (online only). Sample population from a single general practitioner assessing questionnaire accuracy for hypertension medications[a]

	GP prescriptions	
Anti-HT prescriptions	*Present (104)*	*Absent*
Questionnaire		
Present (77)	75	2
Absent	29	Unknown

[a]If the general practitioner records are taken as the gold standard, then the positive-predictive value of the test (questionnaires) was 97% (75 of 77), with a sensitivity of 72% (75 of 104).

Supplement Table B (online only). Subgroups of diabetic medication

Drug	*No.*	*Mean growth rate per year (SE)*	*Estimated difference in AAA growth rate (95% CI)*	P[a]
Biguanides				
No	1190	1.55 (0.13)	0	
Yes	47	0.75 (0.40)	−0.80 (−1.60 to −0.008)	.05
Insulins				
No	1236	1.51 (0.13)	0	
Yes	8	0.18 (1.59)	−1.33 (−4.44 to 1.78)	.40
Sulfonylureas				
No	1193	1.59 (0.13)	0	
Yes	42	0.70 (0.41)	−0.89 (−1.71 to −0.07)	.03
Other anti-diabetic				
No	1231	1.52 (0.13)	0	
Yes	13	0.67 (1.15)	−0.85 (−3.11 to 1.41)	.46

[a]No significant difference in abdominal aortic aneurysm growth rates between subgroups of diabetic medication ($P > .05$).